Predictive and explanatory models of cigarette smoking: Computational approaches to understanding nicotine addiction

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Lee Kosel Jollans

Summary of the thesis

Smoking is the leading cause of preventable death worldwide, causing 6 million deaths every year (WHO, 2011). Most people try smoking for the first time in adolescence (O'Loughlin et al., 2014), making this a critical period for research regarding risk factors for progressing into nicotine addiction. As with other substance use disorders, much is known about how nicotine-induced changes in neurotransmitter systems and sensitivity to drug- and non-drug rewards lead from recreational to habitual and finally to compulsive use. Differences in personality, life history, environment, behavioural responding, and neurobiology between non-smokers, smokers, and smokers who manage to quit are also known. However, there is very little evidence as to what pre-existing neurobiological factors make adolescents vulnerable to smoking behaviour.

Using a large sample of 548 14-year old non-smokers, machine learning was used to predict smoking behaviour in the next four years. The analysis framework was chosen based on a rigorous empirical examination of 13 machine learning analysis pipelines for use with neuroimaging data. This revealed that the Elastic Net (Zou & Hastie, 2005), a form of regularized regression, allows use of large quantities of correlated variables in prediction models without the decline in accuracy seen with other approaches when large amounts of data are examined. Of the participants, 59 became regular smokers before age 16, and 33 became regular smokers before age 18. Using only MRI and fMRI data prediction accuracy was poor. Using personality, life history, psychopathology, substance use, and family/peer environment, classification into smoking trajectories was good with only a small reduction in accuracy when neuroimaging and non-imaging measures were combined. In line with previous research, behavioural and trait impulsivity were strong predictors of smoking. Extending previous knowledge, the ability of impulsivity metrics, particularly novelty-seeking, to predict smoking behaviour differed strongly by age of smoking onset. The absence of behavioural expressions of impulsivity such as conduct disorder was hypothesized to be a protective factor delaying onset of smoking.

Using fMRI measures of reward processing, inhibitory control, affective processing, and mathematical and semantic processing, a predictive phenotype indicating risk for smoking onset between the ages of 16 and 18 emerged. The presence of deficits in processing of facial affect indicated by altered activity in regions including the temporal pole was a predictor of future smoking, and is consistent with previous accounts linking similar deficits to future binge-drinking behaviour (Whelan et al., 2014). Grey matter volume in the temporo-parietal junction and function of associated networks including the default-mode-network were also observed as risk factors for smoking. The primary finding regarding atypical brain function putting adolescents at risk for smoking was seen in networks underlying reward processing and cognitive control. Reduced sensitivity to cues signalling non-drug rewards in regions involved in attribution of saliency –

including the orbitofrontal cortex (OFC) and anterior cingulate, and increased activity in these regions upon receipt of a reward were strong indicators for long-term smoking risk. To further examine this effect, functional connectivity patterns of the reward system were examined in a sample of 206 14-year old adolescents who had already begun smoking. A Psychophysiological Interaction analysis coupled with Elastic Net regression revealed patterns of altered ventral striatum functional connectivity associated with lifetime frequency of smoking. Adolescents who had smoked more showed stronger functional connectivity between reward system nodes including the OFC and the ventral striatum. In addition, heightened smoking frequency was associated with lower functional connectivity between reward system nodes and regions involved in cognitive control and inhibition, including the right inferior frontal gyrus.

To determine whether reward-related changes in cognitive control and sensitivity to rewarding stimuli would still be evident after adolescence and when using a different behavioural measure, a sample of adult smokers, non-smokers, and ex-smokers was recruited. Participants completed the Iowa Gambling Task (Bechara et al., 1994), which is known to engage the same brain regions for which smoking-related effects were found in the previous studies. Behavioural responses in this task indicate reinforcement learning, sensitivity to positive and negative feedback, and ability to anticipate future outcomes. These elements of task performance were quantified using computational models. As conclusively proving the validity of such models is challenging, EEG data from a separate sample was used to confirm the neurobiological validity of computational model calculations. Findings showed that both smokers and ex-smokers displayed strong preferences for immediate rewards with a disregard for the long-term negative consequences of choices.

A phenotype characterized by reduced anticipatory sensitivity to non-drug reinforcers and increased attribution of salience when receiving non-drug rewards is suggested. This phenotype appears to put adolescents at risk for future smoking, has an association with smoking frequency, and persists in adulthood and after smoking cessation. The use of predictive modelling was shown to be a valuable tool to extend knowledge of aetiology and pathophysiology of maladaptive behaviour. The combination of neuroimaging and psychometric data made it possible to create a holistic model of smoking risk that took into account diverse facets of psychological, neurobiological, and environmental vulnerabilities. The neurobiological insights and behavioural indicators of decision-making and executive function identified here as risk factors for smoking behaviour have the potential to be translated into cognitive training or neurofeedback tools to be used in prevention or intervention efforts. Given the demonstration of the neurobiological validity of computational models of cognitive mechanisms, such tools could be used as cost-effective means of approximating reward system function in risk assessment or progress monitoring.

Publications arising from the thesis

Journal papers

Jollans, L., & Whelan, R. (2016). The Clinical Added Value of Imaging: A Perspective from Outcome Prediction. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 1*(5), 423-432. DOI: 10.1016/j.bpsc.2016.04.005. (Chapter 1, Appendix D.1)

Jollans, L., & Whelan, R. (2018). Neuromarkers for mental disorders: Harnessing population neuroscience. *Frontiers in psychiatry, 9*. DOI: 10.3389/fpsyt.2018.00242. (Chapter 1, Appendix D.2)

Jollans, L., Zhipeng, C., Icke, I., Greene, C., Kelly, C., Banaschewski, T., ... & Conrod, P. J. (2016). Ventral Striatum Connectivity During Reward Anticipation in Adolescent Smokers. *Developmental Neuropsychology, 41*, 6-21. DOI: 10.1080/87565641.2016.1164172. (Chapter 4, Appendix D.3)

Jollans, L., Whelan, R., Venables, L., Turnbull, O. H., Cella, M., & Dymond, S. (2016). Computational EEG Modelling of Decision Making Under Ambiguity Reveals Spatio-Temporal Dynamics of Outcome Evaluation. *Behavioural Brain Research, 321*, 28-35. DOI: 10.1016/j.bbr.2016.12.033. (Chapter 5, Appendix D.4)

Conference papers and peer-reviewed abstracts

Jollans L, Whelan R, & The IMAGEN Consortium (2017, September). *Predicting adolescent smoking: Mental Health, life stressors, and environmental factors.* Poster presented at the International Association of Youth mental Health Conference, Dublin, Ireland. (Chapter 3)

Jollans L, Whelan R, & The IMAGEN Consortium (2017, September). *Predicting adolescent smoking using fMRI – A possible predisposing role for inhibitory control and reward processing in addictive behaviours.* Poster presented at the 30th ECNP Congress of Applied and Translational Neuroscience, Paris, France. (Chapter 3)

Jollans, L., Whelan, R., Venables, L., Turnbull, O. H., Cella, M., & Dymond, S. (2017, April). *Computational EEG Modelling of Decision Making Under Ambiguity Reveals Spatio-Temporal Dynamics of Outcome Evaluation*. Poster presented at the British Neuroscience Association Conference, Birmingham, UK. (Chapter 5)

Jollans, L., & Whelan, R. (2016, October). *A machine learning method for the interrogation of multimodal neuroimaging data.* Paper presented at the 'Multivariate Methods Applied to Imaging Genetics Data Workshop', Max Planck Institute of Psychiatry, Munich, Germany. (Chapter 2)

Whelan, R., Jollans, L., & The IMAGEN consortium (2016, August). *Predicting Alcohol Binging and Smoking in adolescents.* In K. Obermayer (Chair), In Silico Predictions for Alcohol Use and

Addiction. Symposium conducted at the ISBRA & ESBRA World Congress on Alcohol and Alcoholism, Berlin, Germany. (Chapter 3)

Jollans, L., Zhipeng, C., Icke, I., Greene, C., Kelly, C., Whelan, R., & The IMAGEN Consortium (2016, June). *Ventral Striatum Connectivity During Reward Anticipation in Adolescent Smokers.* Poster presented at the meeting of the Organization for Human Brain Mapping, Geneva, Switzerland. (Chapter 4)

Jollans, L., Watts, R.., Duffy, D., Spechler, P., Garavan, H., Whelan, R., & The IMAGEN Consortium (2015, June*). A Method for the Optimization of Feature Selection with Imaging Data.* Poster session presented at the meeting of the Organization for Human Brain Mapping, Honolulu, HI. (Chapter 2)

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Table of Contents

Abbreviations

Brain imaging terms

EEG	Electroencephalography
MRI	Magnetic resonance imaging
fMRI	Functional magnetic resonance imaging
rsFC	Resting-state functional connectivity

Brain regions

OFC	Orbitofrontal cortex
PFC	Prefrontal cortex
mPFC	Medial prefrontal cortex
vmPFC	Ventromedial prefrontal cortex
dlPFC	Dorsolateral prefrontal cortex
ACC	Anterior cingulate cortex
PCC	Posterior cingulate cortex
IPL	Inferior parietal lobule
TPJ	Temporo-parietal junction
SMG	Supramarginal gyrus
AG	Angular gyrus
IFG	Inferior frontal gyrus
MFG	Middle frontal gyrus
SFG	Superior frontal gyrus
TP	Temporal pole
SMA	Supplemental motor area
VS	Ventral striatum
NAcc	Nucleus accumbens
BLA	Basolateral amygdala
VTA	Ventral tegmental area

Neurotransmitter terms

DA	Dopamine
nAChR	Nicotinic acetylcholine receptor

Functional brain networks

DMN	Default mode network
vFAN	Ventral frontoparietal attention network

Psychiatric disorders

CD	Conduct disorder
ADHD	Attention deficit hyperactivity disorder

SU(D)	Substance use (disorder)
MDD	Major depressive disorder
ASD	Autism spectrum disorder
ODD	Oppositional defiant disorder

Machine learning terms

EN	Elastic Net
MR	Multiple Regression
RF	Random Forest
GPR	Gaussian Process Regression
MKL	Multiple Kernel Learning
KRR	Kernel Ridge Regression
FS	Feature selection

Model fit metrics

AUC	Area under the curve
AIC	Akaike information criterion
BIC	Bayesian information criterion

Behavioural/fMRI task paradigms

MID	Monetary incentive delay task
SST	Stop signal task
GCA	Global cognitive assessment task
IGT	Iowa gambling task

Computational models (chapter 5)

PVL-Decay model	Prospect valence learning model with decay reinforcement rule
PVL-Delta model	Prospect valence learning model with delta learning rule
VPP model	Value-Plus-Perseverance model

Smoking groups (chapter 3)

NS	Non-smokers
EOS	Early-onset smokers
LOS	Late-onset smokers

Chapter 1 – Introduction

Publications:

Jollans, L., & Whelan, R. (2016). The Clinical Added Value of Imaging: A Perspective from Outcome Prediction. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 1*(5), 423-432. DOI: 10.1016/j.bpsc.2016.04.005.

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1.1. Predictors and correlates of smoking behaviour

In Europe 16% of all deaths among individuals aged 30 years or older can be attributed to tobacco (WHO, 2012). On average 27.3% of people over the age of 15 in European countries smoke tobacco (WHO, 2015a). By age 24, about 75% of individuals have tried at least one cigarette, but the majority of young adults smoked their first cigarette before the age of 16 (O'Loughlin et al., 2014; von Ah et al., 2005). While figures vary, multiple reports estimate that at least a quarter of individuals who try smoking will go on to become regular smokers (Wellman et al., 2018; Von Ah et al., 2005). While large-scale smoking prevention and cessation efforts have resulted in a relative decrease in smoking rates over the last decade (WHO, 2015b), there is little evidence for the efficacy of smoking prevention strategies targeting children and adolescents (de Kleijn et al., 2015; Wiehe et al., 2005; Lantz et al., 2000; Thomas, McLellan & Perera, 2015). Given additional emergent risk in this group due to new substance-use related technologies such as e-cigarettes (Pearce et al., 2017; Perkins, Karelitz & Michael, 2015), substantial efforts to better understand adolescent smoking behaviour are warranted.

Smoking is a complex multi-stage behavioural phenomenon that is challenging to define and categorize. The cognitive-developmental model of smoking postulated by Leventhal et al. (Hirschman, Leventhal & Glynn, 1984; Leventhal & Cleary, 1980) suggests that there are four stages of smoking: A preparatory stage in which perceptions about smoking and smokers are formed, initiating smoking behaviour through smoking of the first one or two cigarettes, experimental or irregular smoking, and finally smoking maintenance (i.e. regular smoking behaviour). Although an understanding of how individuals progress through these stages is important to understanding the risk factors for becoming and staying a smoker, studies investigating smoking behaviour are overwhelmingly cross-sectional in design. While most studies define smoking behaviour based on established measures such as the Fagerström test for nicotine dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), there is nevertheless wide variety in the group inclusion parameters used across studies. While some studies include only smokers meeting criteria for nicotine addiction and individuals who never initiated smoking, other studies also include individuals who initiated smoking but never progressed to regular use. This diversity in populations allows for some exploration of differences between individuals at different stages of the smoking pathway. However, the unique set of risk factors and vulnerabilities leading to progression from one stage of smoking to the next can only be dissociated from any effect smoking itself may have on behaviour and brain function through longitudinal studies. Compared to cross-sectional studies the number of longitudinal studies in this area is very small. Nevertheless, there have been studies following the development of smoking behaviour from childhood to adolescence (Kellam, Ensminger & Simon, 1980; Burt et al., 2000), from childhood to adulthood (Stewart & Livson,

1966), over shorter periods during adolescence (Collins et al., 1987), from adolescence to young adulthood (Cherry & Kiernan, 1976; Sieber & Angst, 1990; O'Loughlin et al., 2014), and from young adulthood to later in life (Barefoot et al., 1989). These studies identify what factors are associated with progression and non-progression from one stage of smoking behaviour to the next, disentangling cause and effect of smoking behaviour. There have also been a number of studies specifically investigating the trajectories of smoking behaviour in adolescence and young adulthood (Chassin et al., 2000; Colder et al., 2001; Soldz & Cui, 2002; White et al., 2002; Audrain-McGovern et al., 2004a). Using various clustering methods these studies all identified at least three distinct groups of adolescent smoking trajectories: non-smokers, occasional or experimental smokers, and heavy regular smokers. Most studies also distinguished between those regular smokers who began smoking early in adolescence, and those who began at a later age. Colder et al. (2001) and Audrain-McGovern et al. (2004a) also differentiated between trajectories based on how quickly adolescents moved from initiation to regular use. These longitudinal assessments of smoking patterns indicate that not only is it possible to clearly separate individuals who progress from one stage of smoking behaviour to the next from those who do not, the age and speed at which progress from each stage to the next takes place is important in understanding pathways of adolescent smoking.

In the following, longitudinal and cross-sectional studies will be reviewed with regard to what factors associated with progressing from non-smoking to smoking initiation, to smoking a second cigarette, to becoming a regular smoker, and to smoking cessation are observed.

1.1.2. Smoking stage 1: Trying the first cigarette

1.1.2.1. Risk-taking and impulsivity

Smoking in adolescents motivated to engage in non-normative behaviours is facilitated through risk-taking or sensation-seeking and impulsivity. Risk-taking and "sensation seeking" are often used to refer to the same facet of impulsive behaviour. While these constructs are not well defined in the literature, studies using different tools to measure these or closely related traits generally find differences between smoking trajectories. In college-age adults, self-reported impulsivity and sensation-seeking as recorded using the Minnesota Multiphasic Personality Inventory (MMPI) were associated with higher risk of beginning to smoke at least one year later (Lipkus et al., 1994). Multiple studies have also found established smokers to score higher than never-smokers on the Zuckerman Sensation Seeking scale, with effects found for total scores, disinhibition, experience seeking, and thrill and adventure seeking (Rezvanfard et al., 2010; Mitchell, 1999; Balevich, Wein & Flory, 2013; Harmsen et al., 2006). A longitudinal study investigating smoking trajectories from adolescence to adulthood found that higher levels of disinhibition increased the risk not only of being a smoker, but also of being a regular compared to

an occasional smoker (White et al., 2002). Similar findings were made by Balevich et al. (2013), who found smokers, experimenters, and never-smokers to all significantly differ in their disinhibition scores. However, a cross-sectional study found no difference in disinhibition between light and never-smokers (Rezvanfard et al., 2010), which may mean that disinhibition plays a larger role in continued smoking than smoking initiation. In contrast to disinhibition and other facets of risk-taking and sensation seeking, studies have found that novelty seeking, as measured by the Temperament and Character Inventory (TCI, Cloninger et al., 1994) can distinguish between regular smokers and non-smokers but generally not between smoking trajectories, although regular adolescent smokers may have higher novelty seeking than experimenters (Audrain-McGovern et al., 2004a; 2009; Dinn, Aycicegi & Harris, 2004). Light and experimental young adult and adolescent smokers do not appear to differ from never-smokers on novelty seeking (Audrain-McGovern et al., 2004a; Rezvanfard et al., 2010).

Risk-taking, sensation-seeking, and novelty-seeking can all be considered aspects of trait impulsivity. Using the Barratt Impulsiveness Scale (BIS, Patton, Stanford & Barratt, 1995), multiple studies have found established smokers to score higher than non- or never-smokers on measures of impulsivity (Rezvanfard et al., 2010; Mitchell, 1999; Balevich, Wein & Flory, 2013; Skinner, Aubin & Berlin, 2004). When degree of smoking was evaluated, a number of studies have found that heavy smokers scored significantly higher on the BIS than light smokers or experimenters, with no difference in scores between light smokers and non- or never-smokers (Rezvanfard et al., 2010; Balevich, Wein & Flory, 2013). In a study evaluating abstinent individuals with alcohol use disorder, current smokers were more impulsive than ex-smokers, and there was some evidence to suggest that degree of smoking is associated with impulsivity (Skinner, Aubin & Berlin, 2004). Of the BIS subscales, only motor impulsivity has been frequently found to differentiate between heavy smokers and other smoking or non-smoking groups (Rezvanfard et al., 2010; Mitchell, 1999; Balevich, Wein & Flory, 2013). While scores on the BIS do not appear to be associated with smoking initiation, both heavy and light smokers show significantly higher scores on the venturesomeness subscale of the Eysenck Personality Inventory (Eysenck, Pearson, Easting & Allsopp, 1985) than never-smokers (Rezvanfard et al., 2010), indicating a relationship between this trait and smoking initiation. The same pattern was not found in an earlier study (Dinn, Aycicegi & Harris, 2004). However, both of these studies found that smokers scored significantly higher than never-smokers on the impulsiveness subscale, although Rezvanfard and colleagues (2010) found no effect for smokers scoring below 7 on the modifed Fagerström Tolerance Questionnaire (Prokhorov et al., 1998) compared to never-smokers, indicating a relationship between this trait and level of nicotine dependence. The degree to which trait impulsivity is a risk factor for smoking initiation

specifically is therefore unclear, but the evidence supports a strong role of trait impulsivity and risk-taking in continued smoking behaviour.

1.1.2.2. Environmental factors

Leventhal and Cleary (1980) propose that the perceived prevalence and social acceptability of smoking, the perceived characteristics of smokers, and the perceived consequences of smoking contribute to the preparatory set that puts youth at higher or lower risk of smoking initiation. In line with this theory, a longitudinal study by Collins and colleagues (1987) found that smoking initiation in the next 4 months in 7th graders was predicted by higher perceived prevalence of smoking and an assumption of social approval of smoking. Wellman and colleagues (2018) suggest that exposure to an environment where smoking is normative, such as presence of smokers in the home, may remove a sense of violation of social norms associated with smoking and therefore remove a large deterrent to smoking. In addition to normalizing cigarette smoking, the presence of smokers in a child's direct environment also leads to less negative attitudes toward smoking and less aversion or disgust of cigarette smoke (Cameron, 1972). These attitudes may in turn influence the choice of smoking or non-smoking peers, potentially reinforcing risk factors for future smoking behaviour. There is evidence that peer smoking (Hirschmann, Leventhal & Glynn, 1984 ; Pederson, 1997; Audrain-McGovern et al., 2004a/b, Mayhew et al., 2000; O'Loughlin et al., 2014), parental smoking (Pederson, 1997; Mayhew et al., 2000; Tyas & Pederson, 1998; Wellman et al., 2018), and sibling smoking (Pederson, 1997; Flay et al., 1994; Tyas & Pederson, 1998; Duncan et al., 1996) are associated with smoking initiation. While the effect of peer smoking on initiation appears to be robust, there have been variations in findings relating to family member smoking and smoking initiation. Hirschman, Leventhal and Glynn (1984) failed to find an effect of parental smoking on trying a cigarette, and a recent study by Wellman and colleagues (2018) reported that sibling smoking was only associated with smoking initiation for children of mothers with moderate to high education level. Findings from this study also indicate that lower socio-economic status and maternal education level are associated with higher incidence of risk factors such as family member smoking and absence of a smoking ban in the home, indicating that there may be some shared variance among the effect of parent or sibling smoking and other variables such as economic environment on risk for smoking initiation.

A robust link between smoking initiation and adolescent environmental stress factors has been uncovered. Adolescents who would subsequently initiate smoking in the next year reported significantly higher stress of school attendance, family conflict, parental control, and school performance than adolescents who remained non-smokers and adolescents who were already smokers (Byrne, Byrne & Reinhart, 1995). There is some evidence that smoking, along with other

substance use, may be used by adolescents as a coping response to deal with stress (Mates & Allison, 1992). The presence of so-called 'broken-home indicators' such as parental separation by age 19, not having lived with parents (particularly between ages 1 and 6 years old), and being adopted also predicted smoking behaviour (Sieber & Angst, 1990; Covey & Tam, 1990; Tyas & Pederson, 1998; Ellickson et al., 2001). However, there is no evidence that these 'broken-home indicators' pose a risk specifically for initiation of smoking, compared to experimentation or maintenance of smoking. On the other hand, low actual or perceived academic performance is associated specifically with risk of smoking initiation (Pederson, 1997; Audrain-McGovern et al., 2004a/b; Mayhew et al., 2000; Ellickson et al., 2001; Soldz & Cui, 2002; Wellman et al., 2018). Failure to succeed in normative patterns of behaviour (in school, work, or socially) has been linked to substance use in a theory put forward by Kaplan and colleagues (Kaplan, Martin & Robbins, 1984). The authors suggested that self-devaluing experiences in an individual's membership group would lead to a loss of motivation to conform to normative patterns of behaviour. A modest link observed between low self-esteem and likelihood of smoking is also consistent with this theory (Koval et al., 2000; Byrne & Mazanov, 2001). Motivation to engage in other patterns of behaviour that may reinforce a sense of self-worth may thus be increased in some adolescents. The low academic achievement and the higher tolerance for deviance observed in adolescents who begin smoking (Mayhew et al., 2000; Pederson, 1997; Chassin, 2000) may be factors contributing to a common developmental pathway leading toward substance use and smoking behaviour. Indeed, higher alcohol consumption in adolescence is associated with increased risk for smoking initiation, and vice versa (Pederson, 1997; Ellickson et al., 2001; Soldz & Cui, 2002), indicating that most adolescents who begin smoking have a generally more favourable attitude toward deviant or antisocial behaviour. In the same vein, hostility and antisocial behaviour have been linked to smoking initiation (Lipkus et al., 1994; Kellam, Enslinger & Simon, 1980), which is consistent with an account of adolescent smoking as an expression of rebellion. Longitudinal studies in adolescents (Collins et al., 1987; Burt et al., 2000) and young adults (Barefoot et al., 1989) have found that higher scores on measures of rebelliousness are associated with smoking initiation. The notion that rebelliousness is a predictor of smoking initiation (rather than level of smoking) is supported by a study by Mayhew et al. (2000), who found tolerance for deviance and antisocial behaviour to be associated only with smoking onset and not higher level of smoking. Pederson (1997) also found rebelliousness and low social conformity to meaningfully distinguish ever- from never-smokers.

1.1.2.3. The adolescent brain and risk for addiction

It is clear that impulsivity and a favourable attitude toward risk-taking are associated with increased risk for smoking behaviour. These traits are at their peak during adolescence (Brändström, Sigvardsson, Snylander & Richter, 2008; Steinberg, Graham, O'Brien, Woolard,

Cauffman & Banich, 2009). A number of neurobiological models have attributed this to a difference in the balance between different brain systems in adolescence. The dual-system model (e.g. Steinberg, Albert, Cauffman, Banich, Graham & Woolard, 2008), the triadic model (Ernst, Pine & Hardin, 2006) and the imbalance model (Casey, Jones & Hare, 2008) all explain the heightened impulsivity and risk-taking in adolescence with respect to the reward system and the cognitive control systems. Among the structures involved in cognitive control are the dorsolateral prefrontal cortex (dlPFC) which is one of the most important executive control regions (Alvarez & Emory, 2006), the orbitofrontal cortex (OFC) which has been attributed a role in saliency and value attribution (O'Doherty, 2004), the anterior cingulate cortex (ACC) which has been implicated in selective attention (Alvarez & Emory, 2006), and the right inferior frontal gyrus (IFG) which has been established as a central region in behavioral inhibition (Chikazoe, Konishi, Asari, Jimura & Miyashita, 2007; Aron et al., 2014). There are many interacting regions involved in reward processing (see Haber & Knutson, 2010). Among these regions, the ventral striatum (VS) is particularly important. The VS receives dopaminergic input from the ventral tegmental area (VTA) and is connected to frontal areas such as the orbitofrontal and ventromedial cortices. The VS is not only central to processing reward-related stimuli, but also plays a key role in integrating affective and cognitive information, and in action selection and motivation (Floresco, 2015). Along with decreases in impulsive choice from adolescence to adulthood, activation in the VS during reward-related decision making decreases and activations in prefrontal cognitive control regions have been shown to increase with age (Christakou, Brammer & Rubia, 2011). The functional connectivity between the VS and prefrontal cortex (PFC) during reward outcomes also increases over the course of adolescence (Van den Bos, Cohen, Kahnt & Crone, 2012).

The evidence supports a biologically based account of higher sensitivity to positive reinforcements and lower cognitive control over affective responding in adolescence. Furthermore, there is also evidence for an effect of the presence of peers on activity of the reward system in adolescents (Blakemore & Robbins, 2012), indicating that adolescents additionally show heightened vulnerability to peer pressure. Given these insights into the vulnerabilities specific to the adolescent developmental period it is unsurprising that adolescence is a time of increased risk for impulse-control disorders, including addiction (Chambers, Taylor & Potenza, 2003; Giedd, Keshavan & Paus, 2008), with the most common addiction in adolescence being nicotine (Young Corley, Stallings, Rhee Crowley & Hewitt, 2002). The biological insights into the mechanisms predisposing adolescents to initiate smoking and the mechanisms that contribute to continued smoking behaviour and addiction (see 1.1.4.) can be harnessed using modern neuroimaging technologies to establish high-risk profiles based on biological data. The neurocircuitry of addiction

is described further in 1.1.4.1, and concepts and opportunities in the area of creating biologically-based models of substance use risk will be explored further under point 1.2.

1.1.3. Smoking stage 2: Experimental smoking

Having a positive experience (e.g., experiencing relaxation) when first smoking a cigarette has been associated with an increased risk of current smoking, daily smoking, nicotine dependence, and cue-induced cravings for a cigarette (Ursprung, Savageau & Difranza, 2011). Klein, Sterk and Elifson (2013) found that more than half of their participants found the experience of smoking their first cigarette more negative than expected, and disliked the taste. However, three quarters reported feeling calm and relaxed after their first cigarette. Negative attitudes toward smoking and negative experiences trying the first cigarette are protective factors against trying a second cigarette (Hirschmann, Leventhal & Glynn, 1984). Audrain-McGovern, Nigg, and Perkins (2009) suggest the 'sensitivity model', which posits that innate higher sensitivity to the drug will be associated with a higher pleasurable response but also possibly with stronger adverse effects upon first exposure. Contrary to this hypothesis, Hughes, Rose and Callas (2000) found that former smokers, never-smokers, and current smokers did not differ on any subjective ratings of nicotine gum during a double-blind trial, although exposure to nicotine decreased tension in current smokers but not the other groups. Another theory proposes that the way in which adolescents respond to unfamiliar bodily sensations may influence their experience of cigarette smoking, with individuals who are more likely to interpret foreign physiological sensations as negative being less likely to enjoy their first smoking experience, and thus also being less likely to smoke again (Leventhal & Cleary, 1980).

Beside the influence of the subjective experience of first smoking a cigarette, the factors associated with further smoking experimentation are very similar to the risk factors outlined above for smoking initiation, although specific evidence for the factors associated with progressing from initiation to experimentation but not regular smoking is scarce. However, the available data confirms that peer and sibling smoking are predictive of trying a second cigarette (Hirschmann et al., 1984), and that risk-taking and rebelliousness are associated with higher cigarette use at short-term follow-up in adolescents who had recently initiated smoking (Collins et al., 1987). It is possible that the same preparatory set that leads adolescents to try smoking as a form of rebellion also encourages further involvement in behaviours that reinforce a self-image as someone who engages in rebellious and deviant activities. It is likely that this perspective is closely related to smoking in the peer environment, and that the subjective experience of smoking may play a lesser role in the decision to continue smoking for those adolescents for whom smoking serves the purpose of shaping how they see themselves. Indeed, Hirschman and colleagues (1984) provide some support

for the hypothesis that those who progress quickly from the first to the second cigarette are likely to smoke for reasons related to life stressors and the positive mood-related effects of smoking, while those who progressed more slowly were likely influenced more by peers and their smoking behaviour was less sensitive to negative sensations while smoking.

1.1.4. Smoking stage 3: Smoking maintenance

While research on reasons why adolescents move from the first to the second cigarette is scarce, there is an abundance of research investigating factors associated with regular smoking behaviour. Most important to understanding why individuals become addicted to nicotine is an understanding of how nicotine impacts the body and mind, and how the use of nicotine and other substances alter behavioural and brain mechanisms leading to dependence.

1.1.4.1. Neurocircuitry of nicotine addiction

In the brain, nicotine binds to nicotinic acetylcholine receptors (nAChRs). Receptors in the VTA are particularly important in the rewarding effect of nicotine (Corrigall et al., 1994). Rapid desensitization of GABA neurons and longterm potentiation of glutamatergic neurons caused by nicotine exposure act upon ventral tegmental area (VTA) dopamine (DA) neurons to cause a net increase in DA activity in the nucleus accumbens (NAcc) of the VS. This is known to be perceived as a rewarding sensation (Mansvelder, Keath & McGehee, 2002). Chronic treatment with nicotine in rats resulted in upregulation of nAChRs availability in the substantia nigra and VTA (Visanji et al., 2006; Ryan & Loiacono, 2000). Human smokers also show a significant upregulation of nAChRs compared to non-smokers (Wuellner et al., 2008). nAChRs have at least three specific states: (1) Non-conducting or resting in the absence of an agonist, (2) Active or open upon exposure to an agonist, and (3) desensitized upon sustained exposure to an agonist (Changeux, Devillers-Thiery & Chemouilli, 1984; Buisson & Bertrand, 2001; Wang & Sun, 2005). While the number of nAChRs increases with chronic exposure to nicotine, these receptors may not actually be functional. In line with the observation that chronic exposure to nicotine results in increased behavioural tolerance, studies have found that upregulation in nAChR availability was accompanied by the down-regulation of receptor function (Marks, Grady & Collins, 1993). Further studies also observed reduced binding potential of D1 receptors in the VS of smokers compared to non-smokers (Dagher et al., 2001). Dani and Heinemann (1996) suggested that smokers begin to experience withdrawal and craving when the desensitized nAChRs are unoccupied for extended periods of time (i.e. during abstinence) and thus recover to a state of responsivity again. They suggest that an abnormally high number of active and unoccupied nAChRs may cause the sense of discomfort and dysphoria experienced by smokers during withdrawal, which is mediated by smokers maintaining a near complete saturation (and thus desensitization) of nAChRs throughout the day (Brody et al., 2006;

Benowitz, 2008). Reports of the first cigarette after extended periods of abstinence, such as overnight, being the most pleasurable (Russell, 1989) are consistent with this hypothesis.

Smoking is thus associated with a rewarding sensation, and discontinuation of smoking after sufficiently consistent exposure to nicotine is associated with negative effects. The rewarding sensation associated with nicotine and other drugs is distinctly different from that associated with natural rewards, as the nicotine-induced dopaminergic input to the NAcc does not show a habituation or satiation effect in the same way that natural rewards such as food do (Di Chiara, 2002). Furthermore, animal studies have shown that DA transmission within the shell and core of the NAcc is differentially affected by exposure to drug (ethanol) compared to natural (sucrose) rewards (Bassareo et al., 2017). Learning theory accounts of addiction state that compulsive drug-seeking behaviours emerge as drug-using behaviours shift from being purely goal-directed (i.e. motivated by the positive effects of drug use) to being conditioned, habitual behaviours. That is, prolonged drug use will lead to the cues and behaviours that precede drug use becoming conditioned stimuli themselves, with drug use behaviours, rather than the effects of the drug, becoming the conditioned response (i.e. Pavlovian-instrumental transfer). The strong positive and negative reinforcing properties of drugs of abuse lead to acute drug administration greatly accelerating the process of habit learning when compared to natural rewards (Hogarth et al., 2013). The subregions of the NAcc play a crucial role in conditioned responding and habit learning. Animal studies have found that sensitization to nicotine is associated with reduced dopamine transmission in the NAcc shell and increased transmission in the NAcc core (Cadoni & Di Chiara, 2000). Findings relating to the distinct roles of NAcc core and shell confirm that this shift in DA activity within the NAcc is associated with the formation of drug-related stimulus-response associations. In rats, inactivation of the NAcc core reduced Pavlovian-instrumental transfer, i.e. the increased instrumental responding that takes place with exposure to a conditioned cue previously paired with a reward (Corbit et al., 2001; Hall et al., 2001). However, animals with NAcc shell lesions exhibit normal transfer. These findings are consistent with an account that suggests that the NAcc shell is crucial in establishing associations between reinforcers and learned goal-directed behaviours, while the NAcc core is involved in retrieval and expression of learned instrumental responding to primary and secondary reinforcers (Di Chiara, 2002; Everitt & Robbins, 2013). Increased DA transmission in the NAcc core in rats sensitized to nicotine can thus be interpreted as an expression of the shift from goal-directed, to habitual drug-seeking.

Hogarth and colleagues (2013) state that the transition of drug use from goal-directed to habitual behaviour reflects “a loss of intentional regulation of behaviour”, since the learned stimulus-response associations are no longer contingent upon the effect of the drug itself, and circumvent explicit motivation and choice. Animal studies have shown that nicotine (and other

drug) use moves from being a goal-directed activity that is sensitive to devaluation to being insensitive to devaluation with prolonged exposure (Zapata, Minney & Shippenberg, 2010; Corbit, Nie & Janak, 2012; Clemens et al., 2014). As drug-cues become conditioned stimuli they elicit anticipatory DA release that is expressed as drug craving (Volkow, Koob & McLellan, 2016). This effect was observed in smokers in a study that found that occasional smokers showed higher ventral and dorsal striatum reactivity to cues for monetary than cigarette rewards, while dependent smokers showed equivalent reactivity to both types of cues, linked to subsequent motivation to obtain a reward (Bühler et al., 2010). In humans, neuroimaging evidence points toward dissociable roles of the ventral and dorsal striatum in relation to reinforcement learning, with the VS being recruited in both instrumental and Pavlovian conditioning and the dorsal striatum playing a larger role in implementing behaviour based on instrumental learning (O'Doherty et al., 2004). These findings prompted the theory put forward by Everitt and Robbins (2005) that transition from goal-directed to habitual drug seeking behaviours is accompanied by a transition from more ventral to more dorsal striatal control over responding. Based on animal studies, a shift in involvement of the dorsomedial striatum to the dorsolateral striatum with the shift from goal-directed to stimulus-response behaviour has also been observed (Balleine, Delgado & Hikosaka, 2007; Zapata, Minney & Shippenberg, 2010; Corbit, Nie & Janak, 2012; Everitt & Robbins, 2013). Evidence of enlarged putamen in substance users and their biological siblings (but not recreational users) suggests that differences in the dorsal striatum may precede substance use and pose a vulnerability for developing an addiction (Ersche et al., 2012, 2013a). However, there is also evidence that prolonged smoking abstinence results in a recovery of DA synthesis capacity in the dorsal striatum, which is significantly lower in current than in non-smokers (Rademacher et al., 2016). Aspects of reward learning, while altered during addiction, may thus be recovered in abstinence.

In addition to the striatum, regions central in the rewarding effects of drugs of abuse include the basolateral amygdala (BLA) and the OFC. The BLA is thought to encode motivationally salient representations of reward-value, and sends unidirectional excitatory input to the NAcc and dorsomedial striatum, regulating DA activity in the NAcc (Wassum & Izquierdo, 2015). Specifically, projections from the BLA to NAcc appear to underlie the ability to use outcome value to guide instrumental actions, and are crucial in Pavlovian-Instrumental Transfer (Shiflett & Balleine, 2010). The OFC is thought to play a role in attribution of saliency and valuation (O'Doherty, 2004), and activity in ventromedial frontal regions including the OFC and ventral ACC has been interpreted to reflect drug craving (Volkow et al., 2011). There is considerable evidence that the OFC plays a role in affective value attribution to a wide range of primary and (abstract) secondary reinforcers, and codes both reward and punishment (Kringelbach & Rolls, 2004). Dependent smokers exhibited

significantly less OFC activation during anticipation of monetary rewards than occasional smokers, suggesting a reduction in sensitivity to non-drug rewards (Bühler et al., 2010). Substance dependent individuals also show a significant decrease in grey matter volume in this region (Ersche at al., 2013a). The OFC and ventromedial PFC project primarily to the rostral striatum, including the NAcc (Haber, 2016). Other regions that project to the striatum include the dorsal ACC (dACC) and the dlPFC (Haber, 2016). The ACC is thought to be associated with drug-related attentional bias (Goldstein & Volkow, 2011), and is activated for pain, negative affect, and cognitive control functions (Shackman et al., 2011). Furthermore, the anterior insula and ACC are part of the so-called 'salience network' (Menon & Udin, 2010) which integrates information from internal and external sources to guide behaviour. In substance dependent individuals, a significant decrease in grey matter volume in the ACC has been observed (Ersche et al., 2013b). The dACC has been suggested to play a role in high-level cognitive control functions (Heilbronner & Hayden, 2016), and to subserve inhibitory control functions (Luijten et al., 2014). Resting state functional connectivity (rsFC) between the dACC and striatum is negatively associated with nicotine addiction severity (Hong, Gu & Yang, 2009), underlining that reduced dACC involvement is central in progression toward increased nicotine addiction. Interestingly, there is evidence that rsFC in the dACC-VS and extended amygdala circuit is also associated with a gene variant associated with smoking (Hong et al., 2010), possibly making function of this system a vulnerability marker for nicotine addiction. The medial prefrontal cortex (mPFC) has also been highlighted as a key region involved in addictive behaviours. The mPFC encodes the subjective and actual value of rewards (Kable & Glimcher, 2009; Niv & Montague, 2009; Haber & Knutson, 2010; Chib et al., 2009), and biases healthy individuals toward more conservative choices when making decisions under risk (Clark et al., 2008). Animal studies have shown that stimulation of the mPFC reduced cocaine-seeking behaviour (Levy et al., 2007), while mPFC lesions increased cocaine-seeking behaviour (Weissenborn, Robbins & Everitt, 1997). Furthermore, higher rsFC of the mPFC is associated with craving in smokers (Janes et al., 2014).

A popular account of why some individuals are more likely to develop an addiction suggests that pre-existing structural or functional differences in brain regions associated with reward learning or cognitive control make certain individuals more sensitive to the pleasurable (or adverse) effects of drug use (Audrain-MvGovern, Nigg & Perkins, 2009). A series of studies carried out by Ersche and colleagues set out to investigate the existence of an intermediate phenotype, or 'endophenotype' that makes some individuals more susceptible to addiction and compulsive drug use than others. For these studies a group of largely cocaine dependent individuals was recruited, as well as their biological siblings who were not users, a group of non-addicted casual cocaine users, and non-using non-addicted control subjects. In line with findings regarding substance use

initiation, casual and addicted users showed significantly higher sensation seeking and disinhibition than non-using groups (Ersche et al., 2010; 2013a). However, both the addicted and non-addicted siblings showed significantly higher levels of trait impulsivity than controls, although impulsivity was significantly higher among the using than non-using siblings (Ersche et al., 2010; 2013). Simultaneously, siblings and users both showed impaired inhibitory control compared to controls, which was associated with reduced fiber tract density in regions adjacent to the right IFG (Ersche et al., 2012). Further studies have also shown reduced grey matter volume and density in smokers compared to controls in frontal regions including the PFC, ACC, and OFC, and in subcortical structures including the cerebellum (Brody et al., 2004; Gallinat et al., 2006; Kuhn, Schubert & Gallinat, 2010). Ersche and colleagues found that addicted and non-addicted siblings also showed significantly enlarged amygdala and putamen, and significantly reduced grey matter volume in the posterior insula and postcentral and superior temporal gyri compared to controls and recreational users (Ersche et al., 2012; 2013a). The insula has been implicated in interoceptive processing (Naqvi & Bechara, 2009), and there is evidence that damage to the insula disrupts nicotine addiction (Naqvi et al., 2007). Findings from these studies support an account of the etiology of addictive behaviours whereby those who have certain deficits in prefrontal cognitive control networks (such as the right IFG) and an increased sensitivity to reward (subserved in part by the striatum and extended amygdala) are at an increased risk of developing compulsive drug-seeking behaviour. While there is evidence of some dose-related structural brain differences in smokers (Gallinat et al., 2006), the brain regions described above are important targets for investigations into the neural basis of addiction, and may be promising biomarkers for substance use predictions (see point 1.2).

1.1.4.2. Smoking maintenance to manage mood and as a coping mechanism

As discussed previously, acute life stressors have a strong impact on smoking initiation. In a similar manner in which stress has been proposed to facilitate smoking as a coping behaviour, it has also been suggested that smoking may be used as self-medication to cope with mental ill health. Indeed, individuals with mental illness (including among others psychotic, anxiety and depressive disorders) are about twice as likely to smoke, and consume a disproportionately large percentage of all cigarettes smoked (Grant et al., 2004; Lasser et al., 2000; Lawrence, Mitrou & Zubrick, 2009). Furthermore, smokers with co-occurring mental illness appear to respond differently to cessation efforts than the general population (Le Cook et al., 2014). In adolescence, anxiety and depression are among the most common mental health issues. Research has shown that anxiety disorders are not associated with progression from initiation to daily smoking (Rohde et al., 2004), with daily smoking onset (Clark & Cornelius, 2004), or with current smoking (Upadhyaya et al., 2003) in adolescents. While there is little evidence for a link between anxiety

disorders and smoking, there is clear evidence for a relationship between depressive disorders and smoking. In adolescence, smoking is associated with increased rates of depression (Upadhyaya et al., 2003), and higher scores for depression in adolescents are associated with higher likelihood of smoking (Koval et al., 2000). To untangle the question of cause and effect there have been numerous longitudinal studies investigating smoking behaviour and depressive symptoms.

There is some evidence to suggest that adolescents with major depression are no more likely to initiate smoking than their non-depressed peers (Kandel, 1996, as cited in Breslau et al., 1998). However, adolescents who have ever smoked score higher for depression than never-smokers (Pederson, 1997). Furthermore, Patton et al. (2006) found that for individuals who had not been daily smokers as teens the presence of persisting symptoms of depression and anxiety was the clearest predictor of nicotine dependence in young adulthood, resulting in a 6-fold increase of risk. And more generally, depressiveness is associated with non-specific substance use 12 years later (Sieber & Angst, 1990). It must be noted that these studies do not specifically support a role of depressive symptoms in smoking initiation. Rather, it appears that the presence of major depressive disorder may be associated with the progression from smoking initiation to daily smoking (Breslau et al., 1998; Rohde et al., 2004). However multiple studies did not find depressive disorders to be predictive of future smoking (Clark & Cornelius, 2004; Goodman & Capitman, 2000). An interaction effect of dopamine transporter gene and depression with smoking progression has been identified (Audrain-McGovern et al., 2004c), and there is some evidence that a history of depression in smokers is associated with greater reduction in reward responsiveness upon acute nicotine withdrawal, which may contribute to increased risk for relapse in this population (Pergadia et al., 2014).

There is also considerable support for the notion that depression emerges subsequent to smoking behaviour (Luger, Suls & Vander Weg, 2014). Teenagers who are daily smokers have slightly higher rates of psychiatric morbidity than other adolescents (Patton et al., 2006). Adolescents who are smokers are also up to four times as likely to be depressed at 1-year follow-up, with some evidence for a dose-response relationship (Goodman & Capitman, 2000; Steuber & Danner, 2006; Covey & Tam, 1990; Rezvanfard et al., 2010). Breslau and colleagues (1998) found that from age 19, individuals who were daily smokers at baseline were significantly more likely to develop major depression for the first time. However, they report that part of this effect may be accounted for by baseline history of alcohol use disorder and early conduct problems, indicating that smoking itself was likely not causal in the development of major depressive disorder, but was rather a symptom of the same mechanism that produced other maladaptive behaviours and possibly resulted in psychopathology later in life. Rodriguez, Moss et al., (2005) found that the relationship between depressive symptoms and smoking behaviour in adolescence differs

depending on the severity of depressive symptoms. For adolescents with high depressive symptoms smoking may act to ammeliorate symptoms to a certain extent, while the reverse may be true for adolescents with moderate depressive symptoms. Rezvanfard et al. (2010) also found depressive symptoms to be a significant distinguishing feature between heavy and light smokers. There is some evidence that depressed smokers are more likely to smoke to reduce negative affect (Lerman et al., 1996), and that smokers with a history of depression do indeed show more reward sensitivity than non-smokers with a history of depression (Janes et al., 2015a). This fits with Mathew et al.'s (2017) theory that in depressed persons low positive affect and high negative affect each represent distinct states that are conducive to smoking maintenance.

Overall the evidence does not conclusively support a causal role of depressive symptoms in smoking behaviour, but it appears that smoking may be used to ameliorate negative affect, or that depressed smokers may be less likely to quit. Furthermore, there is evidence that the degree to which negative mood increases the rewarding effect of smoking is associated with certain DA and opioid genes, indicating that there is a genetic component in the susceptibility to the reinforcing effects of smoking to regulate mood (Perkins et al., 2008).

1.1.4.3. Behavioural impulsivity, inhibitory control, and craving in smokers

A facet of impulsivity which has been widely studied in addicted populations is impulsive action – i.e. behavioural impulsivity that is not governed strictly by conscious choice processes. A group of tasks which measure this type of impulsive responding includes the Stop Signal Task (SST) and the Go/No-Go Task (GNG). In these tasks, participants are asked to respond as quickly as possible to a standard stimulus and to withhold responding to a different and less common stimulus. Participants' ability to withhold responding to the less common stimulus is used as a measure of the ability to exert inhibitory control over automatic responding. In the case of the SST the ability to stop an already initiated behaviour is assessed. These tasks require both management of response conflict and processing of response errors. A review of studies using these inhibitory control paradigms to compare smokers and non-smokers found that in the absence of behavioural differences, smokers showed significantly lower activity in brain regions involved in inhibitory control, including the ACC and the right IFG (Luijten et al., 2014). Using EEG, differences between smokers and non-smokers were also found regarding the P3 and N2 potentials. Both the P3 and the N2 have been found to be measures of the unexpectedness of an outcome (Fuentemilla et al., 2013; Holroyd et al., 2004; Holroyd et al., 2011). While the N2 (which has its neural origin in the dACC) is lower in individuals with addictions, findings have been conflicting regarding the P3 (Luijten et al., 2014). The insula and putamen are also involved in inhibitory control during GNG in smokers. While connectivity between the putamen and ACC is increased during inhibitory control

in all individuals, smokers exhibit higher functional connectivity between the anterior putamen and right insula (Akkermans et al., 2016), which may indicate less efficient recruitment of this network, or use of alternative strategies. While longitudinal studies assessing whether deficits in impulsive action tasks and associated neural activity precede smoking onset are lacking, it is possible that individuals with structural or functional deficits in inhibitory control networks are more vulnerable to smoking initiation.

1.1.4.3.1. Delay Discounting

Choice impulsivity is another popular measure of behavioural impulsivity frequently used with smoking and substance-using populations. A widely used measure of choice impulsivity is delay (or temporal) discounting (DD). DD refers to the diminished value of a reward as a function of the temporal delay of its receipt. This is a measure of impulsivity that combines reward-processing, decision-making, and episodic future thinking. Typically participants are asked to choose between a smaller but immediate, or a larger but temporally delayed reward. Both monetary rewards, and rewards in the form of the drug of abuse are commonly used in DD tasks with substance users. DD is a trait-like characteristic that is fairly stable over time (Peters & Büchel, 2011). The medial OFC, VS, and posterior cingulate cortex are involved in processing of subjective rewards in this task (Kable & Glimcher, 2007). Multiple studies have found that DD can distinguish between smokers and non-smokers but not between smoking trajectories when smoking is defined based on quantity or frequency of smoking (Audrain-McGovern et al., 2009; Johnson, Bickel & Baker, 2007; Mitchell, 1999). On the other hand, at least two studies have also found that heavy smokers, defined based on level of dependence on cigarettes, show significantly higher temporal discounting than both light and never-smokers (Rezvanfard et al., 2010; Sweitzer et al., 2008). Sweitzer and colleagues (2008) found that DD only showed a relationship with level of nicotine dependence defined based on the Fagerström Test of Nicotine Dependence (Fagerström, 1978), but not with cigarettes smoked per day. As there is some evidence that DD may be an indicator of risk of fast progression into smoking behaviour once a regular habit is developed (Audrain-McGovern et al., 2004b), DD appears to be associated with level of dependence and compulsive use rather than quantity of use. Evidence that established adult smokers discount monetary and cigarette rewards significantly more than both never- and ex-smokers further confirms a role of DD in smoking maintenance (Bickel, Odum & Madden 1999; Sweitzer et al., 2008). Observations that light and heavy smokers discount cigarette rewards more than other outcomes (Johnson, Bickel & Baker, 2007), that elevations in DD in smokers are strongest for immediate rewards (Mitchell & Wilson, 2012), and that DD increases with acute abstinence (Field et al., 2006) also support the hypothesized role of this facet of impulsivity in the maintenance of smoking behaviour.

1.1.4.3.2. Iowa Gambling Task

A further highly relevant area of impulsivity that has been investigated with smoking and other substance using populations is decision making under risk and under uncertainty. The Iowa Gambling Task (IGT; Bechara et al. 1994) is a popular measure of decision making under ambiguous conditions. The IGT is an experience-based partial information paradigm that involves participants choosing among four decks of cards. Each deck yields an average monetary (or point) win and loss, with two of the four decks yielding a net gain over multiple trials (advantageous/good decks), and the other two decks yielding a net loss (disadvantageous/bad decks). Of the advantageous and disadvantageous decks respectively one deck results in less frequent but larger losses than the other deck. The participants' goal is to maximize monetary or point gain after 100 trials. Although not all studies found an effect of smoking on IGT performance (Buelow & Suhr, 2014; Businelle et al., 2009; Lejuez et al., 2003; Harmsen et al., 2006), adolescents who had smoked in the past week performed significantly worse on this task than never-smokers (Xiao et al., 2008). Furthermore, both non-smokers and ex-smokers outperformed current young adult smokers on a variation of the IGT (Briggs et al., 2014). There is also some evidence that nicotine dependence moderates poorer IGT performance in opiate addicts compared to control smokers and non-smokers (Rotheram-Fuller et al., 2004). Rather than failure to learn reward contingencies, differences in task performance between smokers and non-smokers may be due to an increased tendency to favour large rewards among smokers (Ert, Yechiam & Arshavsky, 2013). There is also evidence that awareness of reward and punishment contingencies is lower among current smokers (Briggs et al., 2014). Valuation of outcomes is central to IGT performance, and it is known that performance in the IGT relies strongly on the ventromedial PFC (vmPFC, Bechara et al., 1994), which is thought to underlie this process (Chib et al., 2009). In a study investigating the performance of individuals with substance use disorder (SUD) on the IGT compared to healthy controls and patients with vmPFC lesions, Bechara et al. (2001) found that performance of the SUD group was intermediate to the other two groups, indicating that deficits in vmPFC function in SUD may be an important factor in reduced IGT performance. Work by de Wit et al. (2009) has demonstrated that the vmPFC is activated more strongly during behaviours involving goal-directed action than during habitual responding, making altered vmPFC function a possible target for future investigations into risk for smoking behaviour.

1.1.4.3.3. Monetary Incentive Delay Task

Both DD and IGT measure not only impulsive responding, but also reward processing. Since addictions and compulsive behaviours are established primarily as a result of rewarding effects of substances like nicotine, reward processing is a central area of investigation in addiction research. In both DD and IGT participants make deliberate choices that will result in some type of rewarding

or non-rewarding outcome. While choice patterns in these tasks can reveal a lot about the altered nature of reward processing in smokers and other SUD populations, it is difficult to disentangle the stages of decision-making, anticipation, and receipt of the reward. A straightforward way to investigate participants' anticipatory processing and processing of outcomes in isolation from each other is made possible by the Monetary Incentive Delay Task (MID; Knutson, Westdorp, Kaiser & Hommer, 2000). In this task participants are presented with a cue signifying whether they will have the opportunity to receive a reward, lose points/money, or receive only visual feedback. After presentation of this informative cue, participants are asked to respond as fast as possible to a target stimulus, and feedback on what outcome was received is presented on the next screen. The task is designed in such a way that participants receive the more favourable outcome (a reward, positive feedback, or no loss) on two thirds of all trials. The paradigm has the distinct advantage of temporally separating anticipation and receipt of outcomes, making it possible to examine the activation patterns associated with each separately. VS activity is observed during the anticipation of rewards in the MID (Adcock, Thangavel, Whitfield-Gabrieli, Knutson & Gabrieli, 2006; Knutson, Fong, Bennett, Adams & Hommer, 2003). Other regions associated with reward anticipation in this task include the dorsal striatum, cuneus, thalamus, ACC, ventromedial PFC, OFC, insula, and midbrain (Haber & Knutson, 2010; Van Leijenhorst, Zanolie, Van Meel, Westenberg, Rombouts & Crone, 2010). Studies comparing performance of smokers to controls on the MID have found no significant behavioural differences between groups (Rose et al., 2013; van Hell et al., 2010; Luo et al., 2011). However, fMRI studies have found lower anticipatory activity in the dorsal striatum for gain compared to loss (or no reward) in smokers compared to non-smokers (van Hell et al., 2010). Lower dorsal striatum activation in anticipation of rewards has also been observed in a group of smokers acutely exposed to nicotine compared to placebo (Rose et al., 2013). Furthermore, both smokers and cannabis users showed attenuated NAcc activity during outcome anticipation (van Hell et al., 2010; Rose et al., 2013). A dose-response effect of even a small number of lifetime smoking occasions on VS activity during reward anticipation in adolescents has been shown (Peters et al., 2010). Taken together these findings indicate that exposure to nicotine mediates the involvement of the striatum in anticipatory reward processing. Differences in anticipatory striatal recruitment between smokers and non-smokers have also been shown to be associated with latency to reward receipt, with smokers showing significantly lower striatal responses in anticipation of delayed rewards, moreso than immediate rewards (Luo et al., 2011). Given the findings of increased temporal discounting in smokers, the observed differences in striatal function during the MID task may be part of the same mechanisms responsible for altered reward processing in smokers. Despite a wealth of studies investigating responses to positive and negative feedback, the outcome phase of the MID has not been as keenly studied with smokers as

anticipatory reward processing. However, there is evidence that both smokers and cannabis users exhibited increased activity in the caudate compared to controls during feedback (van Hell et al., 2010), and smokers exposed to acute nicotine show greater middle frontal gyrus and cingulate activity for successful compared to unsuccessful trials than controls (Rose et al., 2013). In the absence of studies comparing brain activity during the MID between smokers and ex-smokers, or longitudinally between individuals who will go on to become smokers or remain abstinent, it remains unclear whether the clear differences between smokers and non-smokers in striatal function during this task emerge before or after smoking initiation.

1.1.4.3.4. Smoking cue paradigms

A group of behavioural paradigms that investigates impulsivity and cognitive processes directly in relation to smoking employ stimuli or cues that are related to smoking behaviour. The level of self-reported craving when exposed to smoking cues is highest for smokers, and higher in ex-smokers than controls (Zanchi et al., 2015). Cue-elicited craving is associated both with the amount of money smokers are willing to pay to smoke, and duration of subsequent puffs from a cigarette (Gass & Tiffany, 2017). Despite a wealth of research assessing behavioural cue-reactivity in smokers in laboratory studies, it is possible that these studies have limited ecological validity (Shiffman et al., 2015). However, a subset of cue-reactivity studies in smokers examines not only behavioural responding, but also brain responses to smoking cues. Smokers show higher ACC, PFC, dorsal striatum, insula, and precuneus activity to smoking than neutral cues (Janes et al., 2015b; Engelmann et al., 2012). These regions are all known to play a role in the formation and maintenance of addictive behaviours. Resting-state and task-related functional connectivity research targeting these brain regions has revealed an association between smoking behaviour and connectivity of the anterior insula and ACC. When compared to non-smokers, smokers show higher activity in the ACC when exposed to smoking-cues (Zanchi et al., 2015) with activity here being associated with nicotine dependence severity (McClernon, Kozink & Rose, 2008). Furthermore, "real-time" neurofeedback to reduce ACC activity to smoking cues was associated with reduced self-reported craving (Li et al., 2013). Smoking-cue related functional connectivity between the right anterior insula and ACC is significantly lower in current and ex-smokers than in non-smokers (Zanchi et al., 2015), which signals that smoking may be preceded by or cause lasting dysfunction in the salience network. However, coupling of anterior insula and dACC during rest is also associated with greater smoking cue-related activity in the visual cortex, PFC, and putamen in smokers (Janes et al., 2015b), and abstinent smokers show higher rsFC of the insula with the ACC, dlPFC, vmPFC and precuneus than non-abstinent smokers (Yang et al., 2014). These finding show that a network of regions including the ACC, insula, and PFC plays a role in craving or inhibitory control of drug-seeking impulses, consistent with the suggested role of anterior insula and ACC in salience

attribution and behavioural control. A further brain region that has proven to be important in cue-elicited drug craving is the precuneus. The strength of smoking-cue induced craving is significantly associated with the strength of connectivity between the right anterior insula and precuneus (Moran et al., 2015), and precuneus activation to drug cues is significantly associated with severity of dependence for both nicotine and alcohol (Courtney et al., 2014). Findings of increased precuneus activity to drug-cues in multiple SUD populations have prompted the suggestion that the precuneus underlies exteroceptive processing which influences cue-elicited craving (De Witt et al., 2015), and therefore interacts with the network of anterior insula, ACC, and PFC.

1.1.5. Smoking cessation

A number of neuropsychosocial factors involved in smoking maintenance have been discussed. These include most notably mood-related benefits that may result in smoking being used by way of a coping or self-medication mechanism, a shift of smoking behaviour from being goal-directed to becoming habitual, and dysfunction in the ability of cognitive control mechanisms to prevent reward-oriented and impulsive responding. Given these factors that serve to maintain smoking behaviour, differences in psychological profiles, behaviour, and brain function between current and ex-smokers have the potential to illuminate what factors can aid in smoking cessation.

1.1.5.1. Behavioural correlates of smoking cessation

Studies employing the behavioural paradigms discussed above in relation to smokers have also been used to examine whether performance in these tasks is associated with successful smoking cessation. Evidence from the IGT shows that while performance on the task does not differ between current and former smokers, former and non-smokers' awareness of reward contingencies of decks in the IGT is higher than that of smokers, and their ability to adapt to altered reward contingencies is also significantly better (Briggs et al., 2014). Higher cognitive flexibility in former compared to current smokers has previously been demonstrated in a study using a Stroop colour-word naming task (Nooyens et al., 2008). However, findings from this study indicate that those adults that smoked at baseline but not at follow-up already had greater cognitive flexibility than continued smokers even before quitting, indicating that cognitive flexibility and adaptability may be factors that predispose smokers to have greater odds of successful smoking cessation. Differences between current and former smokers have also been observed in the DD task, where ex-smokers and non-smokers both discount delayed rewards less than current smokers (Bickel, Odum & Madden, 1999; Sweitzer et al., 2008). However, it is unclear whether differences in DD emerge after smoking cessation or precede a successful quit attempt. Surprisingly, these differences in DD do not extend to health outcomes, which may have implications for the effectiveness of health-education based interventions (Odum, Madden &

Bickel, 2002). Ex-smokers also perform differently from smokers on the GNG task. Ex-smokers are more successful at inhibiting responses than current smokers while simultaneously responding more slowly than current and non-smokers (Nestor et al., 2011). While, again, it is unclear whether this effect preceded smoking cessation, these findings indicate that ex-smokers may engage in inhibitory control in a more cautious or conservative manner. In contrast to other behavioural measures, differences between current and former smokers in reactivity to smoking cues are more clearly linked to successful smoking cessation. Munafo and colleagues (2003) found that current smokers showed significantly more interference than former smokers on a Stroop colour-naming task with smoking-related words. Interference on this task has also been used to successfully classify smokers who will remain abstinent from those who will relapse (Janes et al., 2010a), with attentional bias toward smoking-related words being associated with likelihood of relapse (Waters et al., 2003). Level of interference has been found to be associated with polymorphism in the serotonin transporter gene in former but not in current smokers (Munafo, Johnstone & Mackintosh, 2005), indicating that reactivity to smoking cues and likelihood of cessation (Munafo et al., 2004) may be associated to some degree with genotypic factors. Furthermore, level of interference among smokers was associated with their combined scores on the Eysenck Personality Questionnaire (Revised) (EPQ-R) (Eysenck and Eysenck, 1994) subscales for extraversion and neuroticism (Munafo et al., 2003). There is some evidence for a dose-dependent relationship between smoking and these personality dimensions (Cherry & Kiernan, 1976), which may indicate that sensitivity to smoking cues and certain personality characteristics reflect a shared state that can change with smoking cessation, or change in which may facilitate smoking cessation.

1.1.5.2. Psychological correlates of smoking cessation

Given that all ex-smokers were once smokers, there is substantial overlap in psychological and environmental traits between current and former smokers. However, those traits in which ex-smokers do differ from current smokers either predispose them to be more likely to successfully quit, or emerge after smoking cessation. A number of studies have highlighted significant differences between current and former smokers on measures of impulsiveness and inhibition. In a sample of alcoholics undergoing treatment, ex-smokers scored significantly lower than current smokers on the BIS, including the motor impulsivity, cognitive impulsivity, and non-planning subscales (Skinner, Aubin & Berlin, 2004). A study using data from adults who were part of British birth cohorts found that higher childhood self-control as reported by teachers was associated with lower likelihood of becoming a smoker, as well as greater likelihood of successful cessation (Daly et al., 2016). Furthermore, smoking status at 20-year follow-up was associated with measures of impulsivity in a large longitudinal cohort study, with those who quit smoking scoring significantly lower than current smokers on a measure of sensation-seeking at baseline (Lipkus et al., 1994).

Furthermore, ex-smokers in this sample also scored lower on a measure of hostility than current smokers at baseline. Given that hostility and sensation-seeking, as well as other measures of impulsivity are known to also predict smoking initiation, it seems that a certain psychological profile not only entails a heightened risk of becoming a smoker, but is also associated with subsequent higher risk of remaining a smoker and not quitting successfully. Other personality factors for which the relationship with smoking cessation is less clear include neuroticism and extraversion. Although both extraversion and neuroticism have been associated with smoking initiation and with current smoking (Cherry & Kiernan, 1976; Sieber & Angst, 1990; Eysenck et al., 1960; Eysenck, 1963; Munafo, Zettler & Clark, 2007; Hakulinen et al., 2015), these traits appear to be differentially associated with cessation and show a function of age. There is evidence that older adult smokers score higher on neuroticism but not on extraversion than older adult non-smokers (Terracciano & Costa, 2004). In a population sample, only neuroticism showed an association with likelihood of cessation and risk for relapse (Hakulinen et al., 2015). However, a longitudinal study investigating the relationship between personality, age, and smoking cessation found that while neuroticism was not associated with cessation, extraversion was associated with cessation only in older adults (Munafo & Black, 2007). Further studies evaluating neuroticism and extraversion alongside level of nicotine dependence and use in a longitudinal fashion across age groups will be necessary to illuminate the relationship of these variables to smoking cessation.

Psychopathology and life stressors may play a large role in failure to quit smoking if smoking is used at least in part to manage mood. While still showing higher rates of depression than non-smokers, ex-smokers nevertheless show reduced rates of depression compared to current smokers (Wiesbeck et al., 2007; Perez-Stable et al., 1990; Luger, Suls & Vander Weg, 2014). Based on findings that individuals with a history of depressive symptoms were more likely to attempt quitting but less likely to successfully quit (Green & Pope, 2000; Anda et al., 1990; Glassman et al., 1990) it can be concluded that depression is a significant barrier to smoking cessation. There is also evidence that smoking cessation is associated with a decrease in depressive symptomatology, whereas relapse is associated with an increase in symptoms (Rodriguez-Cano, et al., 2016). While the causality linking relapse and depressiveness is not clear, the treatment of depression alongside cessation efforts will likely have a positive effect on cessation success.

1.1.5.3. Neuroimaging correlates of smoking cessation

There is considerable neuroimaging evidence that reactivity to smoking cues and other types of stimuli is a strong indicator of smoking cessation success. A number of studies have used smoking cue paradigms to examine brain activity before participants attempted to quit. A study evaluating success during 8-week abstinence found that reactivity to smoking cues compared to

reactivity to neutral cues in the insula, ACC, amygdala and putamen among other regions was higher in participants who would relapse (Janes et al., 2010a). Another study found that abstinence over a 1-month period was associated with stronger amygdala and VS activity to smoking than neutral cues at baseline and the opposite effect after one-month abstinence (McClernon et al., 2007). This is consistent with findings of lower NAcc activity to smoking cues in ex-smokers than current smokers (Nestor et al., 2011) and evidence of a negative relationship between VS reactivity to smoking cues and craving (McClernon et al., 2008). Furthermore, those who successfully abstain for 4 months also show higher amygdala reactivity to smoking-cessation messages than relapsers (Jasinska et al., 2012), confirming that amygdala activity to both smoking and smoking-cessation stimuli is an important predictor of cessation success. Like smoking-related interference effects (Munafo, Johnstone & Mackintosh, 2005), amygdala activity to smoking cessation messages is mediated by a polymorphism in a serotonin transporter gene (Jasinka et al., 2012). The above studies suggest that those who remain abstinent over short periods show increased activity to smoking cues compared to neutral cues in a network including the amygdala and striatum, while those who relapse show a diminished difference in reactivity to smoking and other cues. Furthermore, amygdala reactivity to cessation messages is a predictor of cessation success, indicating that the emotional saliency of both smoking and cessation messages are key factors in whether smokers will be able to quit successfully. Mihov and Hurlemann (2012), in a review of studies investigating amygdala function in smokers, suggested that blunted amygdala reactivity may be a marker of reduced harm avoidance behaviours, which is consistent with accounts of increased amygdala activity to smoking cues being associated with abstinence success.

Versace and colleagues (2014) also investigated the relationship between smoking-cue reactivity and subsequent abstinence using a different analysis approach than prior studies. The authors clustered smokers into groups based on their brain activity in a network of regions in which activity was significantly stronger for smoking, pleasant, or unpleasant cues compared to neutral cues. This resulted in two groups with different levels of activity to evocative cues in regions including the cuneus and precuneus, as well as a number of parietal and occipital regions. The group that showed higher activity in this network to pleasant stimuli and lower activity to smoking stimuli had significantly higher rates of long-term (6 month) abstinence, and lower rates of depression, sadness, anxiety, or anger. Since the precuneus has been thought to underlie exteroceptive processing, this group may have had higher sensitivity to non-smoking rewards and may therefore have been less susceptible to smoking for mood-related benefits. Lower grey matter volume in the cuneus has also been shown in smokers who manage to remain abstinent for one month (Froeliger et al., 2010), indicating that differences in cuneus and precuneus between smokers who relapse and those who do not may predate uptake of smoking behaviour. Versace

and colleagues (2014) also found differences in dorsal striatum activity to smoking stimuli between groups, with the group with lower cessation rates showing higher activity in the dorsal striatum to cigarette compared to other stimuli, and the opposite effect being observed in the other group. Higher grey matter volume in the putamen was also observed in relapsers (Froeliger et al., 2010), again indicating a possible pre-existing vulnerability to smoking relapse.

As in current smokers, regions of the salience network have also been strongly implicated in studies of cue-reactivity investigating cessation success. In a smoking Stroop task subjects who relapsed showed more interference when presented with smoking-related words, and interference was associated with insula, dACC, hippocampus, and amygdala activity (Janes et al., 2010a/b). However, only insula activity remained significant in a model predicting cessation success (Janes et al., 2010a). In smokers who had successfully quit, significantly higher activity in the ACC and insula to smoking cues was observed (Nestor et al., 2011) which is consistent with findings that only ex-smokers and not current smokers show higher insula activity to smoking cues than non-smokers (Zanchi et al., 2015). While these findings point toward a possible role of the insula and ACC in compensatory processing in ex-smokers, they also appear to contrast with data indicating that insula and ACC activity to smoking cues is associated with relapse in smokers attempting to quit (Janes et al., 2010a). Further investigations show that rsFC between the (posterior) insula and precentral and postcentral gyri is greater in smokers who remain abstinent at 10-week follow-up compared to those who relapsed (Addicott et al., 2015), and that rsFC of the insula is greater in acute nicotine abstinence (Yang et al., 2014). These results indicate that more effective communication of interoceptive signals from the insula may facilitate management of abstinence and craving. However, the contrasting findings relating to activity of the salience network in smokers about to quit and in former smokers warrant further investigation.

When comparing current to former smokers, a study by Nestor et al. (2011) also highlights a role of frontal regions associated with cognitive control in successful smoking cessation. Established ex-smokers exhibit significantly higher PCC and dlPFC activity than current smokers during an attentional bias paradigm, which may indicate lower recruitment of prefrontal executive control regions to visual cues in current smokers. Furthermore, activity in the ACC during stop trials in the GNG task was significantly higher in ex-smokers than in current smokers, again pointing to differences in general inhibitory processing in ex-smokers compared to current smokers. In contrast, both current and former smokers showed lower activity than controls in the left IFG, right temporal regions, parahippocampal gyrus and anterior insula during stop trials in the GNG task. In the absence of longitudinal evidence it is unclear whether these functional deficits predated smoking.

Overall, the neuroimaging evidence paints a picture of some lasting deficits in inhibitory control functions in current and former smokers, alongside substantial differences in how smokers who will subsequently quit smoking, or have successfully quit, process smoking and other rewarding stimuli. The ACC, insula, and amygdala have been implicated consistently across studies as areas in which connectivity and function are indicators of cessation success. While the dorsal and ventral striatum have also been highlighted in many studies comparing current and former smokers, evidence as to how striatal function and striatal projections facilitate abstinence or are altered as a function of abstinence is as yet undetermined.

1.2. A role for neuroimaging biomarkers and predictive modelling in understanding nicotine addiction

Given sufficient knowledge about the predictors and causes of developing, maintaining, and failing to cease smoking, the targeted prevention of smoking in youth and the effective implementation of personalized cessation programs in current smokers is possible. Examples of predictive modelling to achieve improved preventative care and treatment for psychiatric and behavioural disorders are presented in Figure 1.1., with relevant examples for prevention of smoking and cessation treatments shown in panels 1 and 3 respectively. In this section the current approaches to smoking prevention are briefly reviewed, followed by a detailed examination of how predictive modelling can be used to improve patient care in psychiatry.

1.2.1. Studies evaluating adolescent smoking prevention strategies

The majority of smoking prevention programmes take place in schools, as this is the most convenient way to reach adolescents. Strategies to prevent or reduce adolescent smoking typically emphasize the health outcomes of smoking, attitudes toward smoking, or ability to recognize and resist social pressures to smoke. Among school-based smoking interventions, those focusing on social reinforcement and resisting social pressures appear to be most effective (Lantz et al., 2000). Peer-led interventions have also shown success in reducing rates of regular smoking onset in a Romanian sample (Lotrean et al., 2010) and in a Dutch sample (Dijkstra et al., 1999). Success has also been reported using an implementation intention intervention. Adolescents who signed an agreement detailing how they would respond to offers of cigarettes and committing not to smoke in certain locations and throughout a certain period of time smoked significantly less over the next two years than adolescents who completed a self-efficacy intervention (Conner & Higgins, 2010). A similar concept that is used in many European schools is the ‘smoke-free classroom’ program, in which students sign a contract committing themselves not to smoke and win prizes if successful. A meta-analysis by Isensee and Hanewinkel (2012) found this approach to be effective in smoking prevention.

Results from interventions that attempted to modify high-risk behaviours associated with smoking have also been reported. Kellam and Anthony (1998) employed a 'good behaviour' intervention targeting disruptive and aggressive classroom behaviour, and an intervention utilizing an enriched curriculum to improve low academic achievement in first and second grade students. Both interventions reduced smoking during follow-up (up to age 14). While the academic intervention showed a modest effect in reducing smoking behaviour at most subsequent data collection points, the 'good behaviour' intervention appeared to target an earlier antecedent of teenage smoking behaviour, with greater effects seen when youth were 10 years or older. Interestingly the greatest effect of the 'good behaviour' intervention was seen among boys who were already low in aggressive and disruptive behaviour, indicating that this group benefitted from reinforcement of positive behaviour at a young age. Similar interventions were found to only reduce the risk of being offered tobacco, not the risk or latency to smoking initiation (Wang et al., 2012). An interaction effect of this type of intervention and a polygenic risk score has also been found, with increasing intervention success in individuals with the presence of a polygenic marker (Musci et al., 2015). Despite the apparent effectiveness of prevention programs in childhood and adolescence, the effect of these prevention programs may only be a delay in smoking onset (Lantz et al., 2000).

There is evidence that school-based interventions show higher success when paired with mass media (radio and television) interventions (Flynn et al., 1992; 1994; Worden et al., 1996). However, media campaigns have a higher chance of being effective if they are large-scale and tailored to a specific target group (Lantz et al., 2000). There are examples of large-scale community interventions showing success in reducing tobacco use (Pentz et al., 1989; 1992; Biglan et al., 1999), and Saffer and Chaloupka (1999) report that comprehensive bans on tobacco advertising could reduce consumption by about 6%. Increased cigarette prices and restrictions on smoking in public places and schools also appear to be an effective deterrent to youth cigarette consumption, while limits on youth access to tobacco appears to have little impact (Chaloupka & Grossman, 1996). However, not all studies report significant reductions in smoking as a result of community-wide efforts (Kristjansson et al., 2010).

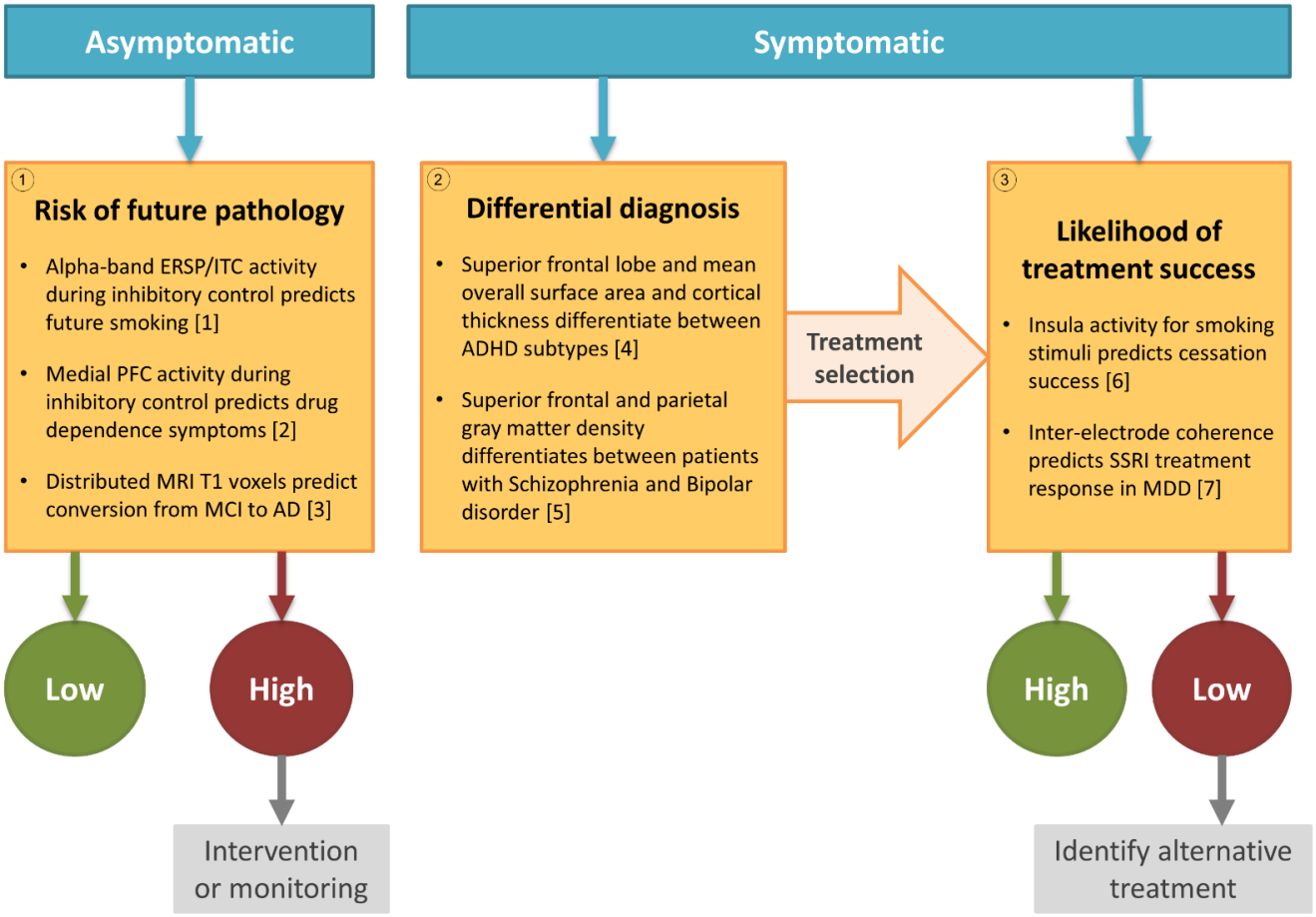

Figure 1.1. Schematic representation of applications for predictive modelling in psychiatry. ERSP: Event-related spectral perturbation; ITC: Inter-trial coherence; PFC: Prefrontal cortex; MRI: Magnetic resonance imaging; MCI: Mild cognitive impairment; AD: Alzheimer's Disease; ADHD: Attention deficit hyperactivity disorder; SSRI: Selective serotonin reuptake inhibitor; MDD: Major depressive disorder. [1] Anokhin & Golosheykin, 2016; [2] Mahmood et al., 2013; [3] Moradi et al., 2014; [4] Qureshi et al., 2016; [5] Nieuwenhuis et al., 2016; [6] Janes et al., 2010a; [7] Khodayari-Rostamabad et al., 2013.

1.2.2. Targeting smoking risk factors and identifying predictors

By attempting to target behavioural risk factors for smoking, Kellam and Anthony (1998) and subsequent studies removed the focus of their interventions from smoking behaviour itself. They observed that there are meaningful individual difference factors in how adolescents respond to such interventions. A similar approach has also been used to prevent or reduce adolescent alcohol use. In their study Conrod et al. (2013) administered interventions targeting anxiety sensitivity, hopelessness, impulsivity, and sensation seeking to students high in one of these traits, and subsequently found significantly lower alcohol use in these students compared to controls. Given the shared risk for substance use and other antisocial behaviour that is associated with traits such as sensation seeking and rebelliousness, interventions targeting these domains and other known predictors of future smoking and substance use is a promising avenue for reducing problem behaviours.

While many risk factors for smoking are well established, the majority of studies fail to confirm that these variables can predict future smoking. In an applied setting, only those variables that can generate some information about the outcome of interest for an individual are useful. This outcome may be the projected age of smoking onset or simply whether or not an individual is likely to try smoking. Without the knowledge that a personality trait or behavioural dimension has the ability to predict a future outcome, any intervention targeting this trait is based to a large extent on speculative inference.

The majority of studies in psychological, social, and health sciences fail to determine whether variables are truly predictive of outcomes. This is due to a number of factors in study design and analysis strategy. Among these are the use of cross-sectional study designs and inferential statistics (see glossary). By definition, cross-sectional studies cannot establish causation and therefore cannot identify whether variables are predictive of an outcome. However, even longitudinal studies may fail to establish predictive utility if their statistical analysis approach is inferential in nature. Most studies investigating smoking divide their sample into groups based on smoking status and then compare characteristics of these groups. Statistical significance between groups is quantified based on group means and within-group variance (see Lo et al., 2015 for a discussion). Differences will therefore be strongest between groups with high within-group homogeneity. Good predictors, on the other hand, capitalize on heterogeneity within the entire sample to generate an outcome estimate. While variables that significantly differ between groups may also be good predictors, this is not necessarily the case, and vice versa (Arbabshirani et al., 2017; Dubois & Adolphs, 2016; Lo et al., 2015; Moutoussis et al., 2016; Yahata et al., 2017).

Improvements and further developments in the area of smoking prevention will likely rely on research identifying predictors of smoking behaviour that can be addressed and targeted through interventions such as cognitive skill building or stress management. Furthermore, predictive modelling also has the potential to reveal what interventions and treatments are most likely to work for an individual (see Figure 1.1). Being able to estimate the likelihood that an individual will respond to a particular treatment or intervention is the basis for precision medicine, and for the integration of diagnosis and therapeutics, or 'theranostics' (Yahata et al., 2017). Based on predicted treatment response or disease course, clinicians can personalize treatment plans and avoid or delay costly, arduous, and possibly ineffective treatments. In the case of nicotine addiction, the cost of failing to identify and prevent or treat cigarette smoking is often death. Early identification of smoking risk and targeted treatment would therefore have a great impact on the quality of life of patients, and on the economic and personal cost of healthcare to the individual and society.

1.2.3. The potential of biological data to indicate smoking risk

In other domains of medicine, predictive models for estimation of treatment efficacy, risk assessment, and prognosis are routinely employed by medical professionals, and advocated by policymakers (Damen et al., 2016). Over the last decade, for example, cancer and heart disease are two specific areas in which biologically based (predictive) models, or *biomarkers*, have been used for purposes of screening, diagnosis, staging, prognosis, treatment selection, and monitoring (Ludwig & Weinstein, 2005; Jaffe, Babuin & Apple, 2006; Braunwald, 2008). Rather than replace the clinician, these biomarkers provide a measure that can supplement clinical decision-making (Steyerberger, 2009; Moons et al., 2012a). In order to be clinically useful, a biomarker needs to augment existing diagnostic/prognostic criteria. That is to say, the estimate of a future event (or current condition) based on the biomarker, or adding the biomarker to current methods, needs to be better than the estimate based on current methodology alone. A key element of why biomarkers are so desirable in medicine is that they provide an objective estimate. This has the potential to reduce bias in clinical decision making. In psychiatry, the incorporation of biological evidence into diagnosis, prognosis, and treatment selection could improve the quality of healthcare which patients receive (Gabrieli et al., 2015). The National Institute of Mental Health acknowledged this in their 'Research Domain Criteria' (RDoC; www.nimh.nih.gov/research-priorities/rdoc/index.shtml) almost a decade ago. The RDoC framework assumes that (1) mental disorders are disorders of brain circuits, (2) neuroscientific methods can identify these dysfunctions in vivo, and (3) genetic and imaging data will yield biomarkers that can augment clinical management (Insel et al., 2010). Some examples of how neuromarkers could be used in psychiatric healthcare are shown in Figure 1.1.

The behavioural deficits observed in smokers and SUD populations have been linked to structure and function of brain networks subserving inhibitory control, reward processing, attentional control, and executive function. Using neuroimaging it may be possible to highlight biological markers that make adolescents more or less likely to engage in risky behaviours such as smoking and other substance use. Knowledge of such biological risk factors would be the first step in establishing highly personalized preventative programs that aim to give adolescents the tools to compensate for their identified deficits in behavioural control. The field of biomarker research investigating behavioural and mental health outcomes is still young, but is becoming increasingly relevant as neuroimaging techniques improve and the shortcomings of preventative medicine in addressing addiction and other mental health issues become more apparent. Below a review of research into predictive biological markers of addiction and substance use disorder is provided, focusing on (1) what requirements biomarkers for psychiatric or behavioural outcomes must fulfill and how these requirements can be met, (2) what research into neuroimaging biomarkers (hereafter 'neuromarkers') of substance use disorders has been conducted to date, and (3) what the developmental pipeline of a neuromarker should look like.

1.2.3.1. Biomarkers for behavioural and mental health outcomes

A mechanistic approach to the search for clinically relevant neuromarkers in psychiatry posits that an understanding of the pathophysiology of a condition, such as addiction, is necessary to develop biological tests (Pine & Leibenluft, 2015), and priority should be given to neuromarkers that more closely describe mechanisms that cause psychopathology. Developing prognostic tests assessing the risk for future psychopathology would certainly be facilitated by a better understanding of the neurobiology of psychiatric disorders (Insel et al., 2010; Kapur, Phillips & Insel, 2012). However, one could argue that psychiatry is a special case: given the complexity of the human brain, mechanistic approaches may not be tractable. Therefore, a pragmatic approach, in which a neuromarker is justified by its utility, suggests that priority should be given to neuromarkers that are clinically useful rather than those that necessarily link brain structure or function to symptomatology (Paulus, 2015). Pragmatic and mechanistic approaches are to some extent complementary: discovery of a neuromarker (e.g., brain activity that predicts recovery), may lead to a new focus on proximal mechanisms, or possible pharmacological agents (Doyle, Mehta & Brammer, 2015).

Regardless of whether or not a mechanistic or pragmatic approach is used, psychiatric imaging prediction findings must be both accurate and generalizable in order to benefit individual-level psychiatric assessment (Kapur, Phillips & Insel, 2012). Studies that aim to predict outcomes require a particular set of statistical tools (Gabrieli, Ghosh & Whitfield-Gabrieli, 2015). There is a rich neuroimaging literature examining psychiatric pathology. Psychiatric neuroimaging research

typically involves a group of patients, and a group of healthy control participants (normally matched to the patient group in terms of various demographic characteristics). These are compared in terms of their brain structure or function. The typical sample size of a neuroimaging study from a single laboratory does not exceed 100 participants. In contrast, neuroimaging datasets typically include hundreds – if not thousands – of voxels (see glossary) or regions of interest (ROIs, see glossary), particularly when data from multiple modalities are used (such as MRI and electrophysiological recordings or positron emission tomography). MRI and fMRI data are usually analysed by carrying out statistical significance tests on each voxel. This type of analysis is referred to as mass-univariate analysis, as it involves conducting a massive number of tests for each analysis. When groups of patients and control participants are being compared, an ANOVA or *t*-test (see glossary: Inferential statistics) will usually be carried out at each voxel. To account for the high risk of false positive findings (see glossary), mass univariate analyses are ordinarily reported using corrected statistical significance thresholds. This approach has produced important insights into the neuropathology underlying many psychiatric conditions including addiction (e.g. Luijten et al., 2017); schizophrenia (e.g. Crossley et al., 2015); social anxiety disorder (e.g. Bruehl, Delsignore, Komossa & Weidt, 2014), Attention deficit hyperactivity disorder (ADHD; e.g., Plichta & Scheres, 2014), and anorexia nervosa (Gaudio et al., 2016). However, there are considerable issues in terms of reliability, generalizability, and reproducibility with this type of analysis framework in terms of identifying neuromarkers. Regression and machine learning methods are able to capture the complexity of neuroimaging data and are thus preferable statistical tools when identifying possible predictive variables (see Box 1, top panel, for a brief description of some commonly used methods).

Box 1. Tools and terminology for outcome prediction

Examples of Machine Learning Classifiers

Support Vector Machines (SVM) generate decision functions (or hyperplanes), which separate datapoints from separate classes in a multidimensional representation with the largest margin possible. These functions can be used to classify new datapoints.

Random Forests use large amounts of decision trees grown using random subsamples of the dataset to generate a decision function based on the most commonly used classification functions across decision trees.

Regularized Regression penalizes regression weights in a regression model to reduce overfitting. Examples are the Lasso method which favors sparse models, Ridge regression which shrinks coefficient values rather than excluding variables, and the Elastic Net (19), which combines these two approaches.

Quantifying Replicability: Common resampling procedures

Bootstrapping: Repeating an analysis by randomly sampling with replacement to estimate sample distributions or accuracy.

Cross-validation (CV): Division of a dataset into training and test sets. The training set is used to generate a model which is subsequently applied to the test data. The test set can be comprised of one observation (*Leave-one-out cross-validation*, *LOOCV*), or of one of *k* equal partitions of the dataset (*k-fold cross-validation*).

Nested cross-validation: Multiple layers of CV are used, making it possible to define model parameters or select input variables using CV on a portion of the data (the training data), and to carry out a generalizability test using the remainder of the data (the test data).

Feature Selection methods

Filter methods select variables based on factors such as their correlation with the outcome variable.

Wrapper methods evaluate the quality of subsets of features, thereby accounting for the importance of feature interaction effects.

Embedded methods combine feature selection and function optimization. Regularization methods such as the Elastic Net are the most common type of embedded feature selection algorithms.

Random Label Permutation quantifies the baseline classification level of a classifier by repeating the analysis with randomly assigned outcome labels. This provides an exact estimate of the effect size and significance of a model.

In practical terms, a good biomarker needs to be workable – it must be reasonably simple and quick to obtain the data necessary to compute the biomarker, so that clinicians can realistically implement the measures in assessments (Hahn et al., 2016). It is easiest to implement unimodal models (see glossary) in new settings, as they do not require multiple imaging protocols or modalities. A measure that is easy and practical to include in an assessment protocol should also be low in personal and economic cost. Paying for an MRI scan for the sake of a small improvement in diagnostic accuracy may not be worthwhile. Yet, as Gabrieli and colleagues (2015) point out, a neuromarker may provide sufficient improvement in diagnostic or prognostic accuracy to be a cost-effective option. If the human and economic cost associated with failing to provide an intervention, delaying treatment, or administering a treatment that is ineffective can be prevented or reduced, then administering an MRI may be more economical than the alternative. However, Gabrieli et al. (2015) also note that to be clinically useful the question that must be answered is not solely whether one particular intervention or treatment is likely to work, but which treatment out of a number of treatment options is likely to be the most beneficial for the patient. Another practical concern is that the imaging protocol necessary for calculation of the neuromarker must be robust to slight deviations in data collection or preprocessing procedure. That is to say, broadly similar results should be obtained when different clinicians or professional health-care providers administer the test, or when different participants view similar stimuli thought to engage the same sensory or cognitive processes (Dubois & Adolphs, 2016). Furthermore, a good biomarker must have good construct validity. A classifier which purports to identify individuals with Alzheimer's disease should also perform reasonably well identifying individuals with mild cognitive impairment, but should have no relevance when separating unipolar from bipolar depression.

The use of appropriate performance metrics alone is not sufficient to guarantee the reliability of findings. Insufficient sample size is a key issue associated with lack of reproducibility and low power (Button et al., 2013). Small samples, particularly when combined with a large number of predictors, can result in apparently accurate predictions reflecting the idiosyncrasies of the sample and failing to generalize to other cases from the same population (this is generally referred to as 'overfitting'; Whelan & Garavan, 2014). Large samples, possible through multi-site imaging initiatives like the Alzheimer's Disease Neuroimaging Initiative (ADNI, Jack et al., 2008), IMAGEN (Schumann et al., 2010), EU-AIMS (Murphy & Spooren, 2012; Loth et al., 2016), and the Adolescent Brain Cognitive Development Study (NIH) can help to guard against overfitting. However, collapsing data across multiple data collection sites is a non-trivial task that can add additional confounding factors into the dataset. Differences between different cohorts from the same population can have much larger effect sizes than differences between groups within the population (i.e., typically developing and individuals on the autism spectrum, Plitt et al., 2015). Testing prediction models either on an entirely new cohort or on 'held-over' data from within

the sample can quantify overfitting, as can resampling methods such as bootstrapping or cross-validation (see Box 1, lower panel, for a brief description of common resampling measures).

1.2.3.2. Review of biomarkers and predictive neuroimaging models used for substance use outcomes

The aim of this section is to provide an insight into the utility of imaging data as a prognostic tool for substance use outcomes. Studies are included if they used analysis frameworks appropriate for prediction (i.e. regression or machine learning procedures), and utilized functional or structural magnetic resonance imaging (MRI) data. Studies are reviewed if they evaluated treatment outcomes or disease trajectory. Details on the samples used, clinical outcome measures, and analysis procedures (including resampling techniques where available) are presented in Table 1.1. The metrics which are used to quantify the goodness-of-fit of the prediction models throughout the text are outlined in Box 2.

Box 2. Accuracy Metrics

	Elements in the positive class (generally the patient group)	**Elements in the negative class** (generally the non-patient group)	
Elements classified as positive	*True positive rate/Sensitivity/Recall:* Correctly classified positive elements	*False positive rate:* Incorrectly classified negative elements	*Positive Predictive Value (PPV)/Precision:* Proportion of elements classified as positive which were elements of the positive class.
Elements classified as negative	*False negative rate:* Incorrectly classified positive elements	*True negative rate/Specificity:* Correctly classified negative elements	*Negative Predictive Value (NPV):* Proportion of elements classified as negative which were elements of the negative class.

The *Receiver Operating Characteristic (ROC)* curve tracks true and false positives during classification, and the *area under the curve (AUC)* for this plot is the primary evaluation metric used for classification performance, with larger AUC values denoting better classification.

Accuracy refers to the percentage of cases which were correctly classified overall. If both classes contain the same amount of observations this value is the mean of sensitivity and specificity.

The *odds ratio (OR)* is a measure of how likely the outcome is given the presence or absence of a single predictor variable, with OR>1 indicating that the predictor is positively associated with the outcome and OR<1 indicating that the predictor is negatively associated with the outcome.

Table 1.1. Specifics of samples and outcome measures for all reported studies.

	Disorder	Modality	Resampling	Analysis method	Outcome measure	Prediction sample	Generalization sample
Mahmood et al., 2013	SU	fMRI during a behavioral inhibition task	none	Hierarchical multiple regression	CDDR scores at 18-month follow-up	n=41 baseline light substance users; n=39 baseline heavy substance users	none
Jacobus et al., 2013	SU (cannabis)	structural MRI	none	Hierarchical linear regression	CDDR scores at 18-month follow-up	n=47 baseline cannabis users; n=49 baseline non-users	none
Schuckit et al., 2016	SU (alcohol)	fMRI during viewing of affective faces	none	Backward elimination regression	Alcohol use and alcohol-related problems including DSM-IV abuse and dependence	n=114	none
Whelan et al., 2014	SU (alcohol)	structural MRI and fMRI during the Monetary Incentive Delay Task, Behavioral inhibition, and viewing of affective faces	nested 10-fold CV	Elastic Net Regression	European School Survey Project on Alcohol and Drugs scores regarding lifetime alcohol use and lifetime drunkenness episodes at age 16 (2 years after baseline)	n=121 future binge-drinkers; n=150 continuous abstainers	none
Falk et al., 2011	SU (nicotine)	fMRI during viewing of smoking-cessation ads	none	Multiple regression	Difference between baseline CO measurement and CO measurement after 1 month	n=28	none
Chua et al., 2011	SU (nicotine)	fMRI during tailored smoking-cessation messages	none	Logistic regression	Abstinence: absence of reported (7 day) smoking at 4-month follow-up	n=42 relapsers; n=45 quitters	none
Janes et al., 2010a	SU (nicotine)	fMRI during viewing of smoking-related and neutral stimuli	LOOCV	Discriminant function analysis	Smoking slip: any smoking for <7 consecutive days or once a week in non-consecutive weeks at any point for 8 weeks after smoking cessation	n=9 with slips, n=12 abstinent	none
Paulus et al., 2005	SU (metham-phetamine)	fMRI during a 2-choice prediction task	LOOCV	Linear discriminant analysis	Relapse: any use of methamphetamine after one year	n=18 relapsers, n=22 abstainers	none

LOOCV, Leave-one-out cross-validation; CV, cross-validation; SVM, Support Vector Machine; PCA, Principal Component analysis; CDDR, Customary Drinking and Drug Use Record

A number of studies have attempted to predict future SU, particularly in adolescence, which is a key risk period for substance misuse. BOLD activity during behavioral inhibition in 16- to 19-year olds was associated with drug use occasions and dependency symptoms at 18-month follow-up (Mahmood et al., 2013). However, these findings were only significant in adolescents who already exhibited heavy SU. Similarly, fractional anisotropy was only associated with SU in adolescents with high (but not low) baseline cannabis use (Jacobus et al., 2013). Future SU has also been examined in typical adult drinkers (Schuckit et al., 2016). Functional MRI data collected during viewing of emotional face stimuli was associated with alcohol problems 5 years later, while accounting for the level of responsiveness to alcohol established at baseline. However, none of these studies used any generalizability tests, limiting their utility in developing neuromarkers or gaining mechanistic insights.

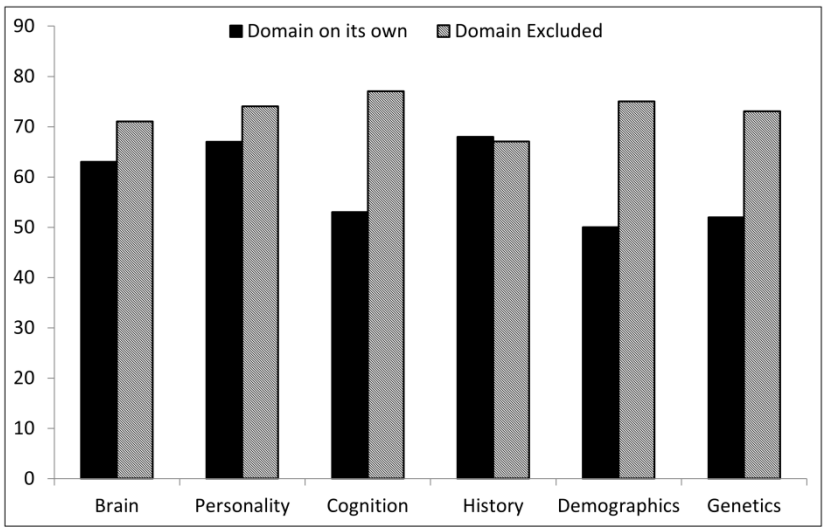

Figure 1.2. AUC values (in %) for each domain individually, and when each domain was excluded, as reported in Whelan et al. (2014).

The largest investigation of adolescent future substance use to date comes from the IMAGEN study (Schumann et al., 2010). MRI data from 14-year old non-drinkers, as well as life history, personality, cognitive, and demographic measures were used to predict binge-drinking at age 16 (Whelan et al., 2014). 73% of abstainers and 66% of future binge drinkers were correctly classified (64% precision, 93% recall, AUC=.75). Brain measures which predicted future binge drinking included markers of brain structure, as well as functional activation during reward processing, behavioral inhibition, and affective face processing. Repeating the analysis with each domain on its own yielded the highest AUC value for the history domain, followed closely by personality (see Figure 1.2). The brain-only prediction ranked third, reaching an AUC value of .63. Excluding each domain iteratively revealed that excluding life history resulted in the largest drop in accuracy, followed by that resulting from excluding all brain measures (see Figure 1.2). This is

currently one of the only studies which has examined the predictive value of different assessment domains in this manner, providing a clear quantification of the added value of each.

Two studies predicting smoking cessation outcomes used fMRI data gathered during viewing of smoking-cessation messages. The amount of variance in change of smoking behaviour after one month which was explained by self-reported intentions and self-efficacy was approximately 15%, which was increased to 35% by including activation of the medial PFC during viewing of video advertisements designed to encourage smokers to quit (Falk et al., 2011). A study that examined the efficacy of individually tailored messages using fMRI also implicated the medial PFC (Chua et al., 2011), activity in which predicted smoking cessation after 4 months, while controlling for the number of cigarettes smoked at baseline. Neither of these studies included generalization tests, making it difficult to draw conclusions from these findings. A further study used performance on an emotional Stroop task and fMRI recorded while viewing smoking-related and neutral images to evaluate the efficacy of various smoking interventions (Janes et al., 2010a). A model including Stroop interference reaction times and accuracy, as well as anterior insula and dorsal ACC activation predicted whether smokers remained abstinent over 8 weeks or had smoking slips with 79% accuracy. 74% accuracy was reached with only Stroop interference effects and insula activation. Results from a brain-only or behavioral-only analysis were not reported, but Stroop interference effect was significantly associated with insular and dorsal ACC activity, which suggests that the contribution of imaging measures may have been small.

Finally, one study examined relapse in methamphetamine users participating in a 28-day inpatient program using fMRI recorded during decision-making under uncertainty (Paulus, Tapert & Schuckit, 2005). Relapse after one year was predicted with 90% accuracy (94% sensitivity and 86% specificity). Sociodemographic characteristics, baseline symptoms, and substance use characteristics did not significantly differentiate between relapsers and abstainers, but the predictive power of these variables was not reported. The high prediction accuracy reached in this study is an indication of the potential of imaging data to contribute to clinical prognosis in SU treatment.

Of the eight studies predicting measures of SU reported here, only three used resampling procedures (Whelan et al., 2014; Janes et al., 2010a; Paulus, Tapert & Schuckit, 2005) and none used a generalization sample. Only one study included more than 20 participants in each group (Whelan et al., 2014). It is notable, however, that in the case of SU non-brain variables provided robust predictions, suggesting that neuroimaging may not have great potential to augment clinical prognoses. While mean prediction accuracy, where reported, was quite high (70% in Whelan et al., 2014 and 90% in Paulus et al., 2005), the utility of outcome prediction based on brain variables compared to prediction based on non-brain variables were not always evaluated. Where these

results were reported, they suggest that brain measures may account for up to 35% of the variance in SU outcomes (Falk et al., 2011), but it is unclear whether neuroimaging measures can explain some of the variance not accounted for by other measures. While some of these findings undoubtedly represent some degree of unwarranted optimism, studies that were able to successfully predict clinical outcomes using only brain variables (e.g.; Paulus, Tapert & Schuckit, 2005) support the conclusion that neuroimaging has the potential to be an important tool in psychiatric prognosis in the area of SU.

In contrast to quantitative prediction accuracy, the practical clinical utility of predictions depends on the cost of misclassification (or 'regret'). That is, the specificity of prognostic tools should be higher for invasive and/or risky interventions. Inaccurate prognoses can lead to waste of time and resources on treatments that result in little or no improvement and may entail adverse consequences (e.g., medication side-effects). Therefore, even prediction models with high accuracy may not be suitable for clinical use due to the magnitude of the regret. Predictions that do not benefit the clinician directly may nevertheless reveal information about mechanisms of disease and of recovery (Pine & Leibenluft, 2015). With increased understanding of the pathophysiology of a psychiatric disorder comes the possibility of developing tools that test behavioral or cognitive domains related to the disease mechanisms uncovered using neuroimaging, which would eliminate the heavy economic burden of conducting neuroimaging as part of psychiatric assessments (Gabrieli & Ghosh & Whitfield-Gabrieli, 2015; Boksa, 2013). The ability to translate domains assessed using functional neuroimaging to less costly tools should therefore be considered when designing a study. However, as illustrated by the example of adolescent SU initiation, other demographic variables are a much cheaper and more informative tool than neuroimaging in some cases (Whelan et al., 2014). A careful consideration of the relative added value of neuroimaging measures in comparison to other tools is therefore necessary when embarking on research intended to identify a biomarker. The value of adding neuroimaging to a predictive model also including other assessment domains should remain a key consideration when attempting to use neuroimaging for outcome prediction (see Figure 1.2.).

1.2.3.3. Neuromarkers – a recipe

The studies reviewed here sought to predict psychiatric outcomes rather than developing specific predictive neuromarkers. Many researchers and clinicians have discussed the reasons and possible solutions for the discrepancy between neuroscientific research and clinical applicability (Arabshirani et al., 2016; Dubois & Adolphs, 2016; Feldstein Ewing, Tapert & Molina, 2016; Gabrieli et al., 2015; Gillan & Whelan, 2017; Insel et al., 2010; Pich et al., 2014; Savitz, Rauch & Drevets, 2013; Stringaris, 2015; Kapur, Phillips & Insel, 2012; Yahata et al., 2017). Four areas are consistently identified as targets for improvement in translational neuroscientific research: (1) the statistical

approaches used in neuroscience, (2) the need for larger population-based samples, (3) a lack of mechanistic understanding of psychiatric neuropathology, and (4) the need for a move away from the often ill-defined phenomenological (see glossary) diagnostic criteria in psychiatry. In this section these issues will be addressed, outlining methods that imaging prediction studies can adopt to increase the generalizability and replicability of results. Each point will be addressed by describing methods which are already being used in the field to improve neuromarker research. This section will be structured to follow the lifecycle of neuromarker development, focusing on the following elements: Study design, analysis frameworks, statistical tools, and the extended development pipeline of a neuromarker.

1.2.3.3.1. Study designs

Dubois and Adolphs (2016) likened big data in neuroscience to accelerators in particle physics or telescopes in astronomy – a necessary tool for scientific progress (for a discussion of the role of big data in psychiatry see also Gillan & Whelan, 2017). Large samples are achievable through multi-site imaging initiatives and consortia like the Alzheimer's Disease Neuroimaging Initiative (ADNI, Jack et al., 2008), IMAGEN (Schumann et al., 2010), EU-AIMS (Murphy & Spooren, 2012; Loth et al., 2016), the Adolescent Brain Cognitive Development Study (NIH), the Human Connectome project (Van Essen et al., 2012), and ENIGMA (Thompson et al., 2014). However, not all data from these initiatives are publicly available. Another option to achieve large sample sizes is data-sharing, possible through data-sharing facilities such as NeuroVault (neurovault.org, Gorgolewski et al., 2015) and OpenfMRI (openfmri.org, Poldrack et al., 2013). Large studies like IMAGEN not only gather neuroimaging data, but also gather information on genetics, demographics, and life history. This makes it possible to examine psychopathology in a holistic manner (Paus, 2010), under the rubric of 'population neuroscience'. By taking into consideration information from other domains, neuromarkers can more meaningfully contribute to our understanding of the etiology of psychopathology.

Many large datasets include participants with a wide range of symptoms. Yet, studies using these data to identify neural signatures associated with mental disorders often select a fairly narrow subset of cases and matched controls. Although strictly controlling for variables such as age, socio-demographic circumstances, symptoms, or medication use gives the experimenter greater control and greater clarity over the source of an effect, restrictions on study inclusion also restrict the utility of findings. That is to say, stricter inclusion criteria also narrow the range of circumstances in which a model will be useful and applicable (Woo et al., 2017). Considering this restriction on how a model can be useful in practice, the models and neuromarkers that will have the highest clinical significance will be models that take into account the heterogeneity within the population (Moons et al., 2012a; Woo et al., 2017; Yahata et al., 2017). This is particularly

important when attempting to predict clinical outcomes such as future psychopathology. Large datasets make it possible to create neuromarkers that provide information about how an individual's brain activity differs from the population average. This provides insight into how linear variations in brain structure and function are associated with changes in a variable of interest on a spectrum which includes the population-mean and pathological manifestations. In comparison to case-control studies, this individual-difference approach would mark a move toward creating neuromarkers for certain symptom clusters or processing domains, rather than for specific diagnoses.

Attempting to identify neural signatures of individual types of processing or behaviour can be seen as a 'component process' approach (Woo et al., 2017, p.371). This would ideally result in a set of models which capture brain structure or function associated with a particular variable that linearly varies across the population. A number of such models could then be combined to identify specific populations. This approach would be very valuable in terms of risk assessment, such as early identification of adolescents at risk for future psychopathology. An example of this could be ADHD and substance use disorder. Both individuals with ADHD and individuals with substance use disorder often show poor inhibitory control. A neuromarker that measures inhibitory control should therefore provide similar estimates for these two groups. Identifying an adolescent's level of inhibitory control based on a neuromarker can therefore provide a measure of risk of maladaptive behaviours involving poor inhibitory control, but will not provide any information about how this may manifest. The component process approach is thus very well suited to addressing certain types of research questions, but not particularly useful for other questions, such as predicting response to treatment.

1.2.3.3.2. Statistical tools for neuromarker development

Recognition of the limitations of the typical univariate group-difference approaches to neuroimaging research has led a large number of authors in psychology and neuroscience to emphasize the importance of moving away from explanatory and univariate analysis procedures and towards multivariate outcome prediction (Gabrieli et al., 2015; Poldrack, 2011; Jollans & Whelan, 2016; Woo et al., 2017). In the past decade the number of neuroimaging studies using multivariate methods has grown rapidly (Woo et al., 2017), and there is a strong recognition of the importance of this approach (Bray et al., 2009; Wolfers et al., 2015; Jollans et al., 2016; Gillan & Whelan, 2017). The divergence of findings using classic univariate compared to multivariate methods is demonstrated by two recent meta-analyses summarizing neuroimaging studies of unipolar depression: There was a notable lack of significant differences in brain activity during emotional or cognitively challenging tasks associated with unipolar depression using traditional group comparison studies (Mueller et al., 2017); However, a meta-analysis of studies using a

multivariate approach to classify patients with major depressive disorder and healthy control subjects found an average classification accuracy of around 75% for functional MRI (Kambeitz et al., 2016).

When using multivariate analysis methods, it is of great importance that the analysis protocol include some measures to prevent overfitting. The most fundamental of these is that a model must be tested on a previously unseen sample in order to obtain a realistic estimate of model accuracy. This step is crucial, as it is the most effective way to gauge how well a model will perform with other individuals from the same population. Using a separate dataset is the gold standard in terms of assessing external validity. However, a more easily accessible method is cross-validation (CV). One of the most frequently used methods is leave-one-out CV (LOOCV; e.g. Clark et al., 2014; Duff et al., 2012; Niehaus et al., 2014), or leave-k-out CV (e.g. Wang, Goh, Resnick & Davatzikos, 2013). A somewhat less computationally expensive method is k-fold CV (e.g. Whelan et al., 2014). When using CV it is imperative to ensure that the observations used to validate the model (the test set) remain statistically pure and do not at any point overlap with the observations used to create the model (the training set; Cawley & Talbot, 2010). Another tool that is important in quantifying in-sample generalizability is bootstrapping. Bootstrapping improves the stability of a model by randomly sampling the dataset with replacement multiple times in order to minimize the effect of outliers and estimate the true population mean (Hall & Robinson, 2009). In particular, bootstrapping provides a measure of how reliable and consistent coefficient estimates or feature metrics are with datasets that have a low signal-to-noise ratio (see glossary) and high multicollinearity. Bootstrap aggregation (bagging) has previously been used with large genetic datasets, and showed significant improvements over standard (non-bagged) methods in terms of model accuracy and stability (Abeel, Helleputte, Peer, Dupont & Saeys, 2010). Both cross-validation and bootstrapping can be considered 'resampling' procedures, and are standard tools used in Machine Learning.

Another important step which should be implemented when working with high-dimensional neuroimaging data is dimensionality reduction. Dimensionality reduction simply refers to the reduction of the number of variables that will be used to create a model. Dimensionality reduction approaches can be broadly categorized into 'feature selection', and 'feature extraction' methods. Feature selection takes the existing input features and strategically removes those features that will, or are most likely to, contribute little to the accuracy of the model. Some of the most common feature selection approaches that integrate dimensionality reduction into the analysis framework are regularization methods, which penalize model complexity as a part of function optimization. Examples of these methods include Ridge, Lasso, and Elastic Net regularisation (Zou & Hastie, 2005). The Elastic Net has gained popularity among neuroimaging

researchers in recent years, and has been successfully used in a number of large studies (e.g. Chekroud et al., 2016; Whelan et al., 2014).

In contrast to feature selection, feature extraction methods such as principal component analysis (PCA) and independent component analysis (ICA) are very familiar to neuroimaging researchers. Data scientists in other domains routinely use feature extraction techniques to map features onto higher-level summary variables to reduce the dimensionality of the dataset. Feature extraction always involves creating a new set of features from the original input variables, which normally makes the model difficult to interpret. It is therefore very complicated to evaluate whether a model is neurophysiologically plausible when feature extraction methods are used. While feature extraction methods often results in an improvement in model accuracy, they have largely been avoided by neuroimaging researchers when seeking to identify neuromarkers.

Finally, despite efforts to guard against overfitting, there may nevertheless be a degree of unwarranted optimism in any model. Establishing whether a model produces results that are significantly better than chance is therefore not possible using traditional p-values. Rather, an empirical significance threshold should be established using a null model. To generate a null model, random data (that is to say random features, a random dependent variable, or both) are put through the exact same analysis procedure as the real, non-random data. The level of accuracy achieved by the analysis framework using random data is compared to the accuracy of the model with real data, and this acts as a measure of the optimism inherent in the analysis framework.

1.2.3.3.3. The neuromarker development pipeline

The developmental pipeline for neuromarkers in psychiatry should be very similar to the standard drug development pipeline. Woo et al., (2017) and Moons et al. (2012a/b) have laid out this developmental pipeline for biomarkers, making specific recommendations and providing a tangible way to evaluate how close to clinical applicability biomarkers are. The number of participants required increases the further along the road to clinical applicability a model is (Moons et al., 2012b; Woo et al., 2017). Initial exploratory studies typically have small sample sizes and modest resources, but the findings from these studies can be used to justify investing a higher amount of resources for further research and development (Gabrieli et al., 2015; Woo et al., 2017). At this stage it is advantageous to pursue many different avenues in terms of modalities and functional tasks in order to find the approach that best predicts the outcome. Generally, the most efficient approach to biomarker development will take into consideration what we already know at every stage of the development pipeline (Moons et al., 2012a). In the initial stages of neuomarker research this may take the shape of selecting functional imaging tasks to use based on previous research. When analysing the data, this may include the use of targeted feature engineering as suggested by Hahn et al. (2016). Woo et al (2017) estimated that around 450 models in the

exploratory stage of development had been published in January 2016 relating to mental disorders (excluding substance use).

After the initial creation of a biomarker, the next step is the application of the model to an independent sample. This serves the purpose of initial generalizability testing. Biomarker models should be treated as shareable research product, to be updated, validated, and amended by other research groups (Woo, et al., 2015; Hahn et al., 2016; Moons et al., 2012b). While unimodal models are easiest to test in other laboratories, generalization studies (see glossary) should also examine what additional measures can enhance a model (Moons et al., 2012b). Multiple unimodal models can effectively be integrated using strategies such as 'voting', 'boosting', or other ensemble methods (Hahn et al., 2016; see glossary). In fact, combining multiple modalities in a single model typically results in higher model accuracy. Despite being more difficult to implement in new settings than unimodal models, multimodal models (see glossary) are also preferable from a theoretical perspective when attempting to describe the neurobiology underlying a given outcome (Ahmed et al., 2017; Bray et al., 2009; Gabrieli et al., 2015; Woo et al., 2017).

Finally, the ultimate test of the clinical utility of a biomarker should be large-scale randomized control trials, evaluating outcomes for patients who were assessed using traditional methods and patients who were assessed with the help of the biomarker (Moons et al., 2012b). This step will serve as a measure of how much use of the biomarker actually contributes to patient care in an applied healthcare setting. At this point weighing up the cost and the benefits of the biomarker will determine whether it is suitable for integration into healthcare settings.

1.2.3.3.4. Summary

In this section the tools necessary to develop neuromarkers for mental disorders were discussed. Studies that seek to identify or test neuromarkers must take into consideration that the population from which their sample is drawn will also be the only population to which findings can be expected to generalize. Furthermore, it is imperative that researchers make use of freely available large datasets or collect data from large samples. Studies that include a large number of participants with a wide range of symptoms, and collect not only imaging data but also genetics, demographic data, and so on have the potential to produce the most clinically useful findings. Whether researchers use supervised or unsupervised analysis methods will depend on the question which they seek to answer. Supervised learning is preferable when a definitive outcome (such as relapse or disease course) is known, whereas unsupervised learning may be more beneficial when the outcome is not so clear (such as subtypes of diagnostic categories). For supervised learning approaches, rigorous generalization testing through resampling methods is crucial. Reducing the number of features included in the model through feature selection can help to prevent overfitting. Other dimensionality reduction strategies are available, but researchers

should be aware of the practical and theoretical implications of choosing them. Significance should be established using null models. To reach clinical applicability, neuromarkers must undergo extensive generalization testing in other laboratories, with other populations, in combination with other biomarkers, and finally in randomized controlled trials. Due to many researchers' reluctance to use neuromarkers established in other research groups, most neuromarkers have not undergone generalization tests using other samples.

1.3. The thesis

The aim of this thesis is to initiate development of a model identifying a high-risk phenotype for nicotine addiction. Taking into consideration the continued high prevalence of nicotine use among adolescents and young adults and the high mortality burden associated with smoking, the focus of the studies contained within this thesis is on adolescent smoking onset and smoking frequency. Using data from the IMAGEN project, a large longitudinal multi-site study (Schumann et al., 2010), predictors of future smoking in non-smoking adolescents, and alterations in brain function in current adolescent smokers are identified using machine learning techniques. As an empirical validation of various machine learning algorithms and analysis pipelines for neuroimaging data is lacking in the literature, a detailed examination of how analytical approaches borrowed from the field of machine learning can be used to ideally interrogated neuroimaging data is carried out in Chapter 2 – '*Quantifying performance of machine learning analysis pipelines for neuroimaging data*'. The analysis methods identified as most effective for use with neuroimaging data are used in the subsequent studies.

In Chapter 3 – '*Predicting adolescent smoking using neuropsychosocial risk indicators*', predictive models of future smoking behaviour are developed taking into consideration variables from the majority of domains discussed as factors thought to contribute to smoking behaviour in section 1.1. These included measures of personality with a strong focus on trait impulsivity, assessment of psychopathology including depression, ADHD, and CD, present and past alcohol and other drug use, family circumstances, and behavioural assessment of delay discounting, inhibitory control, and working memory. Grey matter volume and fMRI activity during the Stop Signal Task, the Monetary Incentive Delay Task, and measures of response to affective facial stimuli and processing of semantic and mathematical information are also used. In line with previous findings regarding the utility of neuroimaging measures compared to measures from domains such as life history and personality for prediction of future substance use (Whelan et al., 2014), the contribution of neuroimaging and psychometric predictors is evaluated separately and in combination.

In line with a strong role of reward sensitivity and altered reward processing identified as a factor associated with substance use in the literature, and as a predictor of smoking identified in

Chapter 3, change in reward system function associated with adolescent smoking frequency is evaluated using an analysis of ventral striatum functional connectivity and a machine learning protocol in Chapter 4 – *'Ventral striatum connectivity during reward anticipation in adolescent smokers'*. As in Chapter 3, the data used here is drawn from the IMAGEN study, allowing a direct comparison between studies in terms of the assessment protocol.

Based on the insights into predictors and correlates of adolescent smoking gained in Chapters 3 and 4, the final study reported in this thesis seeks to examine the extent to which the identified deficits in reward system function in future and current adolescent smokers can be observed in adult smokers and in ex-smokers. This final study: *'Altered reward sensitivity in current and former smokers: evidence from computational modelling of decision-making under uncertain conditions'* also examines alternative methods of assessing deficits in reward processing, applying cost-effective behavioural and EEG assessments. The task paradigm used in this study, the Iowa Gambling Task (IGT), is known to engage regions of the reward system identified as critical nodes associated with adolescent smoking in the previous studies, and is thus suitable as a behavioural tool to identify possible dysfunction in these regions. In addition to examining behavioural task performance of present and past smokers, the utility and neurobiological validity of computational models of the cognitive processes employed in the IGT is also assessed. Such alternative interpretations of behavioural data are a possible approach to identify component processes in pathological expressions of reward system abnormality.

Findings are discussed separately regarding development of predictive models and insights into the pathophysiology associated with smoking behaviour. The novel empirical perspective on use of machine learning approaches in neuroimaging research and the practical implementation of such tools is discussed in the context of their use in Chapter 3. Findings from Chapters 3, 4, and 5 are evaluated with consideration to how network-based deficits regarding reward processing and cognitive control predispose adolescents to begin smoking, are associated with current nicotine use, and are observable even after smoking cessation.

Chapter 2 - Quantifying performance of machine learning analysis pipelines for neuroimaging data

2.1. Introduction

An increasing number of projects and consortia are now collecting large neuroimaging datasets. These include IMAGEN (Schumann et al., 2010), the Alzheimer's Disease Neuroimaging Initiative (ADNI, Jack et al., 2008), the Human Connectome project (Van Essen et al., 2012), ENIGMA (Thompson et al., 2017), and the 1000 Functional Connectomes project (Biswal et al., 2010), in addition to data-sharing facilities such as NeuroVault (neurovault.org, Gorgolewski et al., 2015), OpenfMRI (openfmri.org, Poldrack et al., 2013), and the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC; Kennedy, Haselgrove, Riehl, Preuss, & Buccigrossi, 2016). These sources of high-dimensional imaging data offer exciting opportunities to produce generalizable and reproducible research findings in arenas such as predicting disease trajectories, or linking behavioural and personality factors to functional and structural imaging data. As large samples become more commonplace in neuroimaging, analytical tools developed for data science, such as machine learning, are more frequently applied to neuroimaging data (Woo et al., 2017). A wide variety of studies have used machine learning algorithms to classify individuals based on structural or functional imaging data, using among other algorithms Support Vector Machines (e.g. Costafreda et al., 2009; Davatzikos et al., 2011; Koutsouleris et al., 2012), Random Forest (e.g. Ball et al. 2014, Ramirez et al., 2010), and Naïve Bayes classifiers (e.g. Adar et al., 2016; Wang, Redmond, Bertoux, Hodges & Hornberger, 2016; Zhou et al., 2015). There have also been successful efforts to predict continuous outcome variables, mostly using Relevance or Support vector regression, in arenas such as predicting age (Dosenbach et al., 2010; Franke et al., 2010; Mwangi et al., 2013), cognitive ability (Stonnington et al.,2010), language ability (Formisano et al., 2008), and disease severity in patients with major depression (Mwangi et al., 2012). While they have been increasingly used in neuroimaging research, none of these algorithms were specifically developed for neuroimaging data, which have high dimensionality, inherent multicollinearity, and typically small signal-to-noise ratios. Below we briefly review important considerations when analysing large neuroimaging datasets, and how machine learning methods may address these issues.

2.1.1. Outcome prediction

Several authors have emphasized the importance of moving away from explanatory and univariate analysis procedures and towards multivariate outcome prediction in psychology and neuroscience (Gabrieli et al., 2015; Jollans & Whelan, 2016; Poldrack, 2011; Westfall & Yarkoni, 2016). Using regression approaches, effective outcome prediction requires that accurate outcome estimations can be achieved for new cases. Prediction models exploit between-subject heterogeneity to make individual-level predictions. Good predictors may thus not emerge as significantly different between groups (Lo et al., 2015). Embracing machine learning for outcome

prediction would significantly contribute to the generalizability and reproducibility of neuroimaging research, and improve the ability of neuroimaging to explore individual differences (Dubois & Adolphs, 2016). There are several methods used to estimate and improve the generalisability of a regression model. Most common among these is cross-validation (CV). Here, the dataset is split into a 'training set', and a 'test set'. Models are developed using only the training set, and model performance is assessed using the test set. The training and test set must be kept separate for all analysis steps (Cawley & Talbot, 2010). Typically this split is carried out multiple times, alternating which data points fall into the test set. While many neuroimaging studies use test sets comprised of only one observation (leave-one-out CV; e.g. Brown et al., 2012; Clark et al., 2014; Duff et al., 2012; Niehaus et al., 2014), larger test sets (leave-k-out; e.g. Wang et al., 2013; Whelan et al., 2014) are preferable as they provide more accurate model performance estimates (Kohavi, 1995). When CV is used to assess model performance it serves a purely descriptive purpose, producing a realistic estimate of out-of-sample model fit. However, CV can also be used to provide an out-of-sample estimate of model performance within the regression framework itself. This estimate can then be used to optimize parameters for the regression model. When multiple layers of CV are used for internal and external validation of model performance this is referred to as 'nested' CV.

2.1.2. Prediction with neuroimaging data

Depending on the resolution, single MRI images can contain from 100,000 to a million voxels. As sample sizes in neuroimaging are often modest, the number of variables ('features') entered into a regression model typically exceeds the sample size. A higher ratio of features to cases increases the tendency of the model to fit to noise in that sample (i.e. overfitting; see Whelan & Garavan, 2014 for a discussion specific to neuroimaging). Overfitting will result in the model fitting poorly when it is applied to a new dataset. Even when using a smaller number of regions of interest (ROIs) instead of voxels, combining multiple data sources (such as neuroimaging data and cognitive data or demographics), imaging modalities, or conditions will result in a large number of features. Two strategies are commonly adopted for dealing with high-dimensional data: dimension reduction and regularization. A further method useful for neuroimaging data is bootstrap aggregation (bagging).

2.1.2.1. Dimension reduction

Reducing the number of features in a regression model, i.e. dimension reduction, will almost always be beneficial for attenuating overfitting when working with neuroimaging data. A wide array of techniques to reduce the number of features in a dataset is available. Some of these methods, such as principal and independent component analysis, have long been standard tools in neuroscience. Mwangi, Tian, and Soares (2014) described many dimension reduction techniques,

and reviewed their application to neuroimaging data. Dimension reduction techniques can be separated by whether they preserve the original values of features, whether they consider each feature in isolation or not, and whether they are unsupervised (using only the feature values) or supervised (using the feature and dependent variable values). The dimension reduction techniques that are often favoured with machine learning approaches in neuroimaging studies are feature selection techniques (supervised methods that do not alter the original feature values). Feature selection methods can broadly be categorized into 'filter' methods, 'wrapper' methods, and embedded methods (see Chandrashekar and Sahin, 2014). Filter methods are unimodal, considering each feature individually. Wrapper methods are multimodal, considering subsets of features. In contrast to filter and wrapper approaches, embedded methods integrate feature selection directly into optimization of the regression model.

In neuroimaging, good outcome predictions may rely on large feature sets, as any cognitive or behavioural variable of interest will most likely be best explained by a network of spatially correlated brain regions. Good regression models with neuroimaging data may therefore include interaction effects between features. To account for this, the feature selection methods that should be used with neuroimaging data will consider feature sets rather than individual features. Accordingly, previous work has shown that both wrapper methods (Tangaro et al., 2015) and embedded methods (Tohka, Moradi, Huttunen & ADNI, 2016) are preferable to filter methods with neuroimaging data. Furthermore, as neuroimaging data have an inherently low signal-to-noise ratio, the individual predictive power of each voxel or ROI can be expected to be quite small. It may therefore be advantageous to consider complex regression models that allow for the inclusion of some predictors with low effect sizes.

2.1.2.2. Regularization

Regularization is a method that attenuates overfitting by penalizing the size of the regression weights as model complexity increases. Regularization is often achieved through the L1-norm or the L2-norm. The L1-norm, as implemented in the Least Absolute Shrinkage and Selection Operator (LASSO), penalizes regression weights based on their absolute size, and results in sparse models (i.e., some regression weights can be set to zero). The L2-norm (also known as Ridge Regression or Tikhonov Regularization) penalizes regression weights based on their squared size, and does not result in sparse models. However, with highly multicollinear data (such as neuroimaging data) neither L1- nor L2-norm regularization are ideal because the large number of non-zero coefficients in models using the L2-norm is unable to produce parsimonious solutions, and the L1-norm is inadequate in accounting for highly correlated groups of predictors (Ogutu, Schulz-Streeck & Piepho, 2012; Mwangi, Tian & Soares, 2014). The Elastic Net (EN; Zou & Hastie, 2005) combines L1-norm and L2-norm regularization, and has the advantage of being an

embedded feature selection algorithm, and thus produces a sparse solution in which groups of correlated features are included or excluded. The Elastic Net has gained popularity among neuroimaging researchers in recent years, and has been successfully used in several studies with large samples (e.g. Chekroud et al., 2016; Whelan et al., 2014).

2.1.2.3. Bootstrap aggregation (bagging)

The low signal-to-noise ratio of neuroimaging data calls for a tool to increase the stability of findings and reduce error in outcome estimates. Stability can be estimated using *bootstrapping* (Efron & Tibshirani, 1997), where the dataset is randomly sampled with replacement many times to minimize the effect of outliers and estimate the true population mean (Hall & Robinson, 2009). Like CV, bootstrapping serves a purely descriptive purpose when used to estimate population metrics. However, a related approach termed bootstrap aggregation (bagging; Breiman, 1996), uses bootstrapping to improve stability within the model optimization framework. Bagging uses bootstrapped samples to generate multiple estimates of a calculation or metric, and an aggregate of these estimates is created. These aggregated estimates can be used instead of singular outcome estimates at every step of the analysis. Bagging has previously been used for embedded feature selection with large genetic datasets and showed significant improvements over standard non-bagged embedded methods in terms of model accuracy and stability (Abeel, Helleputte, Peer, Dupont & Saeys, 2010). Bagging is an effective way to decrease error, particularly with datasets that have a low signal-to-noise ratio and high multicollinearity (Zahari, Ramli & Mokhtar, 2014).

2.1.3. Researcher degrees-of-freedom

Another important consideration when carrying out prediction analyses is the objectivity of findings. This issue is not confined to neuroimaging research, and has been an important concern in the psychological sciences over the past decade. Flexible or 'exploratory' analysis introduces a high risk of false positive results or overestimated effect sizes (Button et al., 2013). Predetermined analysis pipelines and analytical decisions aid in producing reproducible results. The tendency for researchers to screen data before data collection is completed, to carry out multiple iterations of analyses without reporting the findings (e.g., with and without covariates), or to tweak parameters for group inclusion to better represent the problem has been termed 'researcher degrees of freedom' (Simmons, Nelson, & Simonsohn, 2011; Loken & Gelman, 2017; Westfall & Yarkoni, 2016). In the case of machine learning frameworks, the researcher input can potentially be greatly reduced, limiting the room for subjectivity and reducing the researcher degrees of freedom. To enhance objectivity, the role of the researcher should be confined to collecting and preparing the best data possible to describe the problem of interest, based on domain knowledge (Dubois &

Adolphs, 2016). Dimension reduction, model building, and parameter optimization do not require researcher input, and should be data-driven.

2.1.4. This study

Here, the impact and efficacy of various machine learning tools for use with large neuroimaging datasets is assessed. An empirical evaluation of the extent to which feature selection and resampling procedures affect results is conducted. The effect that data dimensionality has on accuracy is quantified by varying both sample size and number of features. Using simulated neuroimaging data with varying predictor effect sizes as well as real neuroimaging data, this study first compares performance of the Elastic Net, standard multiple regression, a state-of-the-art Machine Learning Toolbox for imaging data (PRoNTo, Schrouff et al., 2013), and an implementation of the popular 'Random Forest' method available in Matlab. Furthermore, an assessment of how the addition of bagging and feature selection affects the accuracy of results from simulated and real data is carried out, using an embedded feature selection approach developed with the intention of minimizing researcher degrees of freedom. Based on previous work, it is anticipated that both feature selection and regularization will improve predictions for datasets with large feature sets by creating less complex models, and that bagging may reduce overfitting for small samples by reducing the effect of outliers.

2.2. Method

2.2.1. Machine Learning protocol

The following regression methods were tested: Multiple Regression (MR), Gaussian Process Regression (GPR), Multiple Kernel Learning (MKL), Kernel Ridge Regression (KRR), Elastic Net (EN), and Random Forest (RF). In MR it is assumed that the output variable is a linear combination of all input variables, and regression weights are determined for each variable based on this assumption. GPR is a non-parametric probabilistic Bayesian method that uses a predefined covariance function ('kernel') to optimize the function of input values describing the output. GPR and MR are non-sparse methods and may thus not be suitable for very high-dimensional data. Furthermore, choosing the kernel in GPR appropriately for neuroimaging data may prove challenging. The MKL approach implemented used here uses the L1 norm to create a sparse combination of multiple kernels (Rakotomamonjy et al., 2008). KRR uses a kernel to make ridge regression (regularization via the L2 norm) non-linear (Shawe-Taylor & Cristianini, 2004). KRR can be thought of as a specific case of GPR but lacks the ability to give confidence bounds. EN combines the L1 and L2 penalties to arrive at a linear solution. For MR, GPR, MKL, KRR, and EN each input feature is assigned a weight, which may be zero when regularization is used (EN and KRR). This is not the case for RF. Rather,

decision trees are grown based on the input features and the output, and the predicted outcomes from multiple trees are aggregated using bootstrap aggregation.

The analysis steps outlined below were implemented in MATLAB 2016b using custom analysis scripts for EN, MR, and RF, and the PRoNTo Toolbox for GPR, MKL, and KRR. Analysis scripts used are available at github.com/ljollans/RAFT.

2.2.1.1. Nested cross-validation

The dataset is initially divided into 10 CV folds. The entire analysis is performed 10 times, using 90% of the dataset (the training set) to create a regression model which is then tested on the remaining 10% of the data (the test set). Within the training set, additional 'nested' CV with 10 partitions is used for feature selection, and for optimization of model parameters. The final (optimized) model from each CV fold is used to make outcome predictions for the test set (10% of the data) and the accuracy of predictions for the entire dataset is used to quantify model fit (see Figure 2.1).

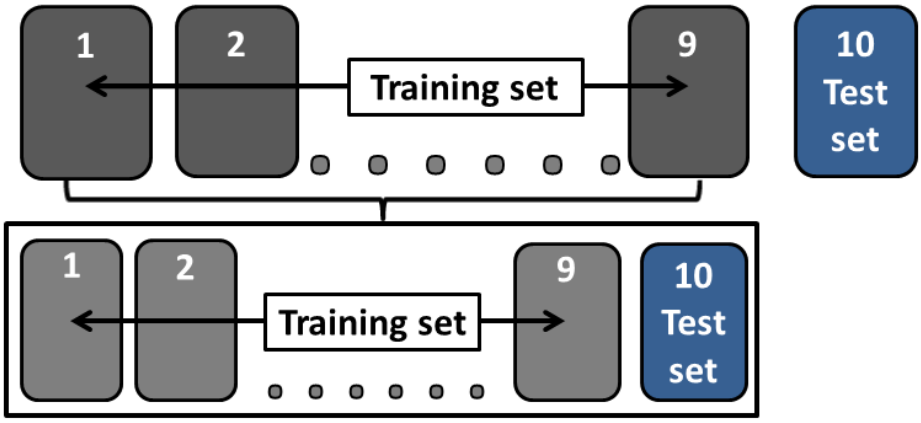

Figure 2.1. Representation of the nested cross-validation framework.

2.2.1.2. Feature selection

An embedded feature selection method that uses prediction accuracy and the stability of model performance across subsets of the sample to learn and to adapt the prediction model is used. Initial feature ranking is used to define feature subsets, and nested CV is used to assess how stable findings are when different subsets of the data are used to examine them. The key element of this method is an embedded thresholding step, which adjusts the criterion for feature selection according to the performance of feature subsets. A detailed explanation of this feature selection method is provided in Appendix A.

2.2.1.3. Bootstrap aggregation

All calculations other than the final outcome prediction are validated using 25-fold bootstrap aggregation (bagging, see Figure 2.2). Instead of performing the analysis once using all data, summary datasets are created by randomly sampling on average two thirds of the data in each iteration. Results from each iteration are aggregated using the median value.

2.2.1.4. Model Optimization

Of the algorithms that were tested (other than those in the PRoNTo toolbox) only the Elastic Net has model parameters to optimize. The Elastic Net uses two parameters: λ and α. Alpha represents the weight of lasso vs. ridge regularisation which the Elastic Net uses, and λ is the regularization coefficient. Both Lasso and Ridge regression apply a penalty for large regression coefficient values, but Lasso regularization favours models with fewer features, making it more prone to excluding features. Here, five values of λ and α are considered. For each model, the features that were excluded by the Elastic Net are noted, and features are removed after the model optimization step if the Elastic Net removed them in more than half of all bagging iterations.

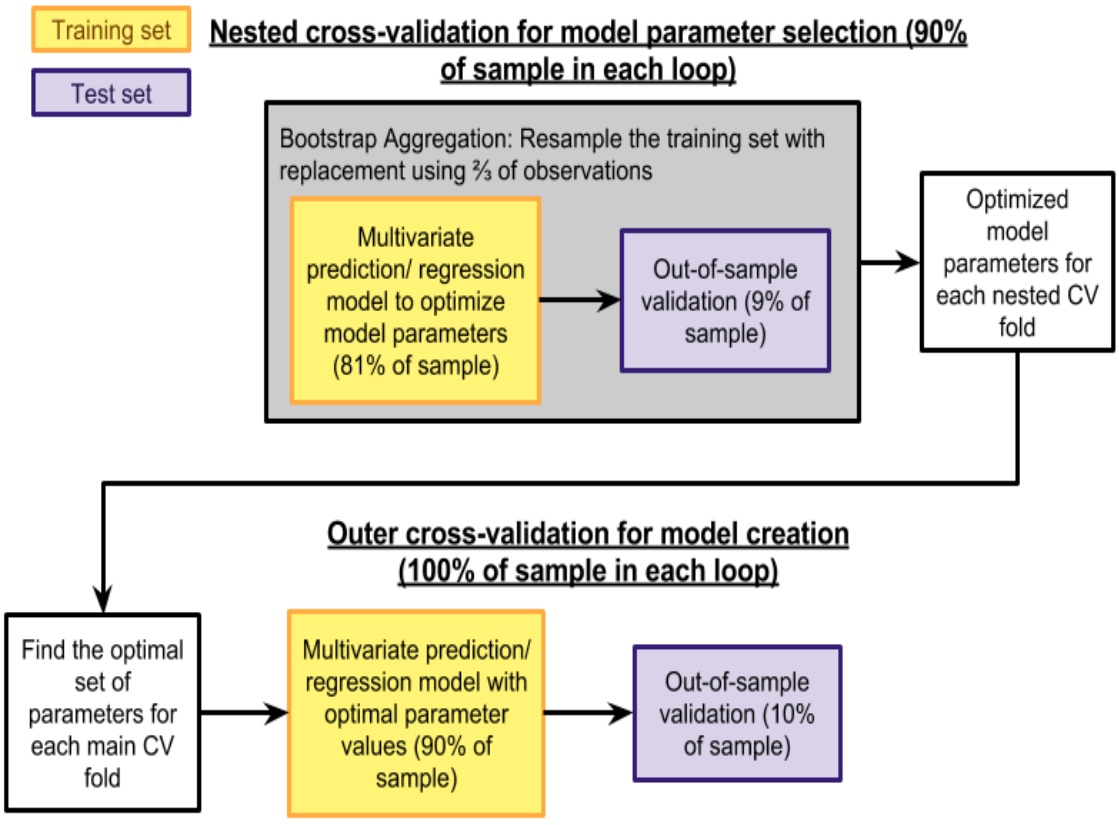

Figure 2.2. Analysis framework using bagging and nested cross-validation. CV: Cross-Validation.

2.2.1.5. Model validation

After the nested CV step, the combination of parameters (where applicable) that resulted in the model with the lowest prediction error is identified for each nested CV partition. Prediction error is quantified using root mean squared error. The optimal model parameters from each nested CV partition are used to identify what parameters will be used to create the final prediction model in each main CV fold, using the most frequently occurring values across nested CV folds. The evaluation of model fit is carried out using the complete vector of outcome predictions from all CV folds.

2.2.2. Data

2.2.2.1 Constructing simulated data

The analysis methods were tested on simulated datasets, built to resemble real neuroimaging datasets in terms of the between-feature correlations, and the range of correlations between features and the outcome variable. Data from the IMAGEN study (Schumann et al., 2010) were used to evaluate the range of between-feature correlations and predictive strength of imaging data for a psychometric variable (IQ measured using the WISC-IV; Wechsler, 2003). These neuroimaging data were extracted using 97 regions of interest (ROIs) based on the AAL atlas (Tzourio-Mazoyer et al., 2002). These ROIs included 90 masks from the standard 116 ROI AAL atlas excluding all masks for the cerebellum and vermis. An aggregated mask including the entire vermis, and a left and right aggregated mask for the cerebellum were used. Additional masks for the left and right subthalamic nuclei were also included, as well as masks for the left and right ventral striatum, with masks for the caudate and putamen altered to exclude the ventral striatum. The same data were also extracted using 278 ROIs from an atlas based on functional parcellation (Shen et al., 2013). Data from three functional tasks and grey matter volume were combined, resulting in 2224 ROIs (for the 278 ROI atlas) and 970 ROIs (for the 97 ROI atlas) for 1846 participants. The functional tasks were an affective face processing task (contrast images for affectively neutral and angry faces compared to a control stimulus, and angry compared to neutral faces), the stop signal task (contrast images for successful and unsuccessful response inhibition), and the Monetary Incentive Delay task (contrast images for anticipation and receipt of large compared to small or no reward). For each atlas these data were combined into one data matrix.

Correlation coefficients for correlations between features (within and between contrasts) and between features and the continuous outcome variable were determined in MATLAB (see Figure 2.3). Simulated data were constructed to mirror these correlation strengths as closely as possible, while achieving variation in predictor strength between data types. Simulated Data were constructed as follows:

1. Predictor and outcome creation. A random matrix *X* the size of the intended dataset was created (i.e. 2000 observations by 1000 features). A vector *b* representing beta weights, and a vector *Y* representing the continuous outcome variable were created such that *X*b=Y*.

2. Inter-ROI correlation clusters. A covariance matrix was created that was used to create a small number (ca. 33) features that were strongly correlated with each other using the *mvnrnd* function in MATLAB. The correlation coefficients for these Inter-ROI correlations were between *r*=.2 and *r*=.8, peaking at *r*=.6. This process was repeated 30 times, to create 30 'clusters' of features that were strongly correlated with other features in the same cluster and only weakly correlated with features outside the cluster.

3. Whole-brain correlations. The same process used in step 2 was used to create one matrix the size of *X* with features that were all correlated with each other at *r*=.25 on average.

4. Dataset creation. The layers of data created in step 1, 2, and 3 were combined using different weighting for each layer to achieve some variation in predictor strength (i.e. the final dataset was a weighted summation of all three data layers). The range of correlations between features and between features and the outcome was manipulated to produce datasets with small to moderate predictor effect sizes ($Simulated_{small}$), and datasets with strong predictor effect sizes ($Simulated_{Large}$; see Figure 2.3).

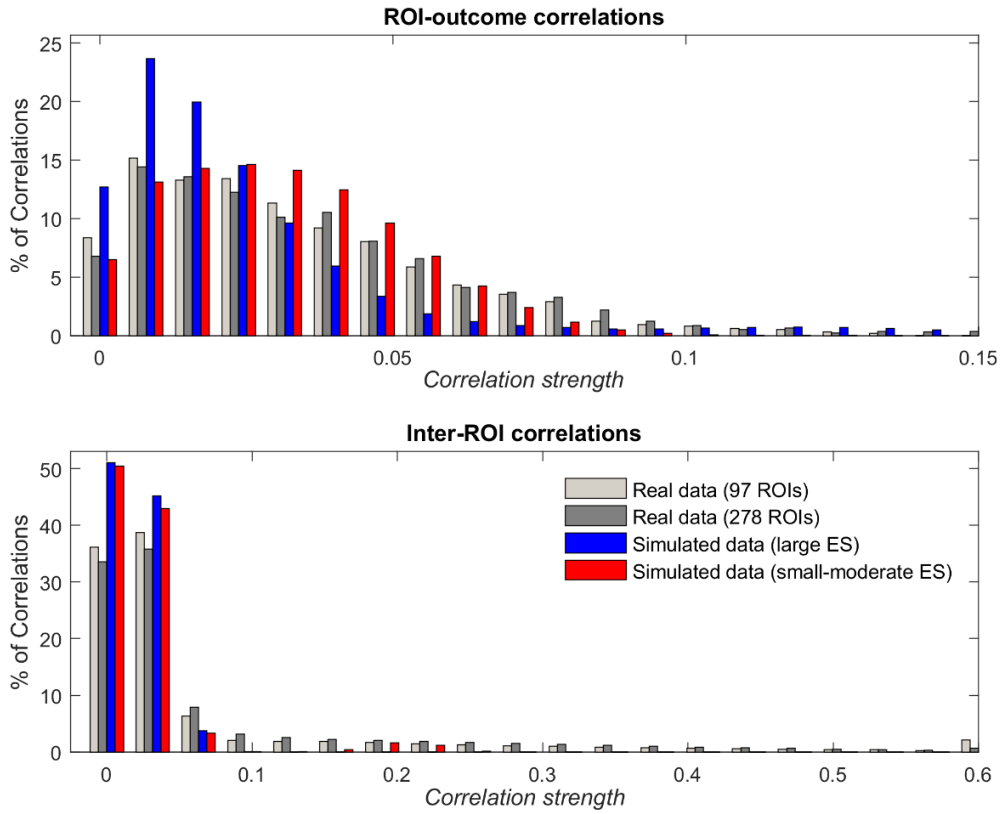

Figure 2.3. Correlation strength by percentage of features for correlations between features (Inter-ROI correlations) and between features and the outcome variable (ROI-outcome) for real and simulated datasets. ES: effect size.

2.2.2.2. Real MRI data.

To test whether findings transfer to real-world imaging data two real neuroimaging datasets were selected. First, a dataset from the IMAGEN study (Schumann et al., 2010) that included data from 967 participants was selected. The linear outcome variable used was the score on the block design subscale of the WISC-IV (Wechsler, 2003). Data drawn from Grey matter volume (GMV) and the Global Cognitive Assessment Task (GCA, Pinel et al., 2007) were used. In the GCA task participants were presented with visual and auditory stimuli for short sentences (e.g. '*We easily found a taxi in Paris'*), subtractions (e.g. '*Subtract nine from eleven'*), and motor instructions (e.g. '*Press the left button three times'*). Maps for subtractions and sentence presentations were used. Data from the two GCA contrasts and for GMV were extracted using the same functionally defined atlas used to create simulated data (Shen et al., 2013). A total of 834 ROIs were used. Note that the data from the GCA task were not used to establish the correlation coefficients to construct simulated datasets (see 2.2.2.1.). Based on previous work examining the relationship between intelligence and neuroimaging findings (Deary, Penke & Johnson, 2010) this dataset was presumed to have low-moderate effect sizes and was thus termed $\text{Imaging}_{\text{small}}$.

The second real neuroimaging dataset was comprised of 1360 structural T1 MRI images drawn from a number of sources: the Nathan Kline Institute Rockland Sample - Release 1 (NKI; Nooner et al., 2012), the Information eXtraction from Images dataset (IXI; http://www.brain-development.org), and the Southwest University Adult Lifespan Dataset (SALD; Wei et al., 2017). These data are freely available online through either NITRC.org or http://www.brain-development.org. Data from the same 97 grey matter ROIs based on the AAL atlas described above were extracted. The linear outcome variable used was participants' age, which has been shown to have a moderate-large effect size (Cole et al., 2017). This dataset was thus termed $\text{Imaging}_{\text{large}}$.

2.2.2.3. Evaluation of dataset size

For each analysis simulated datasets ($\text{Simulated}_{\text{small}}$ and $\text{Simulated}_{\text{large}}$) were generated with 2000 observations and 1000 features, and subsets of these data were randomly sampled. Simulated data were constructed with the following sample sizes: 75, 200, 400, 750, 1000, and 2000. The size of the input feature set (regions of interest) was varied using the following number of features: 75, 200, 400, 750, or 1000. Therefore, analyses were carried out across 30 dataset sizes. The maximum number of features and observations for simulated data was chosen to be comparable in dimensionality to the real neuroimaging data while also offering some insight into how an increase in sample size may affect findings.

For $Imaging_{small}$, random subsampling of the dataset (N=967 and 834 ROIs) at the following sample sizes was carried out: 75, 200, 400, 750, and 967. The features were subsampled at 75, 200, 400, 750 and 834 features. Therefore, analyses were carried out at 25 dataset sizes.

$Imaging_{large}$ (N=1360 and 97 ROIs) was subsampled only in the domain of sample size, using the following sample sizes: 75, 200, 400, 750, 1000, and 1360. This resulted in analyses being carried out at 6 dataset sizes.

2.2.3 Regression machine performance

Analyses for each approach at each cell (i.e. each sample and feature set size) and for each data type were carried out 10 times.

2.2.3.1. Comparison of regression machines

To directly compare performance of different machines for each data type, the results of all analysis iterations for all six algorithms within each cell were combined, and the quintiles of this distribution were calculated. Based on the median prediction accuracy of each algorithm within that cell it was determined into which quintile the performance of that algorithm fell, thereby determining a ranking of algorithms on a scale of 1 to 5 for each cell. For a clearer representation of rank, those algorithms that had negative median prediction accuracy (i.e., zero results) were assigned rank zero within each cell.

2.2.3.2. Bagging and Feature Selection

To evaluate whether performance of regression algorithms could be improved through the addition of bagging and/or embedded feature selection (FS), analyses for MR and EN were also carried out with bagging and/or FS, and RF was also carried out with FS. A series of t-test at each sample and feature set size was conducted to examine whether embedded FS and/or bagging significantly changed results. FS and bagging were not tested with GPR, KRR, and MKL, as these approaches were implemented through the PRoNTo toolbox.

2.2.3.3. Regularization

A series of Pearson's correlations between the strength of regularization used by EN (i.e. λ value) and prediction accuracy was carried out. For each analysis iteration the mean λ across CV folds was used as the regularization value for that analysis in the correlation. Correlations were carried out across all analysis iterations and within each cell. The mean rather than the median value was used since the median values for analyses with one of the real neuroimaging datasets ($Imaging_{Large}$) were equal for all analyses (at six sample size subsets) for analyses with feature selection. However, the patterns for mean and median values were similar across data types.

2.3. Results

2.3.1. Regression Machine performance

Median out-of-sample model performance (i.e., correlation between prediction for the test set and truth) for all regression algorithms is shown in Figure 2.4.

There was a clear effect of predictor effect sizes on prediction accuracy, with both *Simulated$_{Large}$, and Imaging$_{Large}$* predicting more accurately with all analysis methods than *Simulated$_{Small}$, and Imaging$_{Small}$*.

RF had the least amount of variation between data types, although it produced poorer predictions for datasets with large sample and feature set sizes relative to the other algorithms with all data types except Imaging$_{Large}$. The strongest variation in prediction accuracy between data types was observed for GPR, KRR, and MKL. These methods produced lower predictions than other approaches for Imaging$_{Large}$ and failed to produce significant results at any sample and feature set size for Simulated$_{Small}$ and Imaging$_{Small}$. However, KRR and GPR produced predictions similar to other approaches for Simulated$_{Large}$.

The degree to which increases in sample and feature set size affected accuracy varied by analysis method and data type, but except for MR and MKL the highest prediction accuracy was always achieved for datasets with the largest sample size and highest feature set sizes within each data type. For MR, the *'curse of dimensionality'* was observed for Simulated$_{Large}$, Simulated$_{Small}$, and Imaging$_{Small}$, such that models including a larger number of features than samples failed due to overfitting. This effect was also observed for feature sets up to 400 features with RF for Imaging$_{small}$. For MKL, Simulated$_{Large}$ data indicated that predictions declined when the sample size exceeded N=400 and more than 200 features were included.

While some predictions at small sample sizes reached significance with Simulated$_{Large}$ and Imaging$_{Large}$, predictions were generally most successful if the sample size was at least N=200, and ideally no less than N=400.

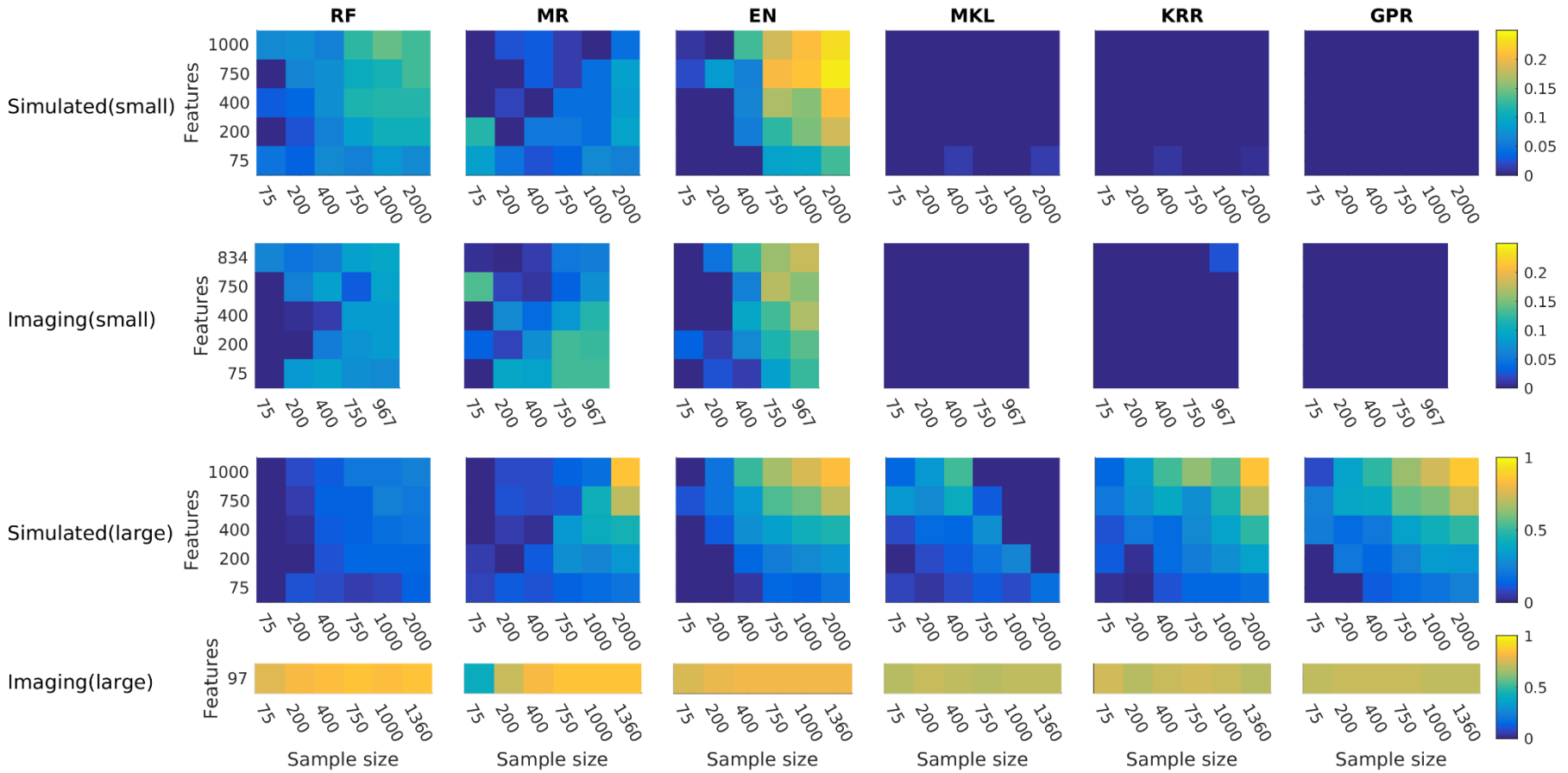

Figure 2.4. Median out-of-sample performance by sample size and analysis algorithm ($Simulated_{Large}$, $Simulated_{Small}$, $Imaging_{Large}$ and $Imaging_{Small}$). RF: Random Forest; MR: Multiple Regression; EN: Elastic Net; MKL: Multiple Kernel Learning; KRR: Kernel Ridge Regression; GPR: Gaussian Process Regression. Colour bars show the cross-validated Pearson's R value. Note that value ranges differ between plots for different data types.

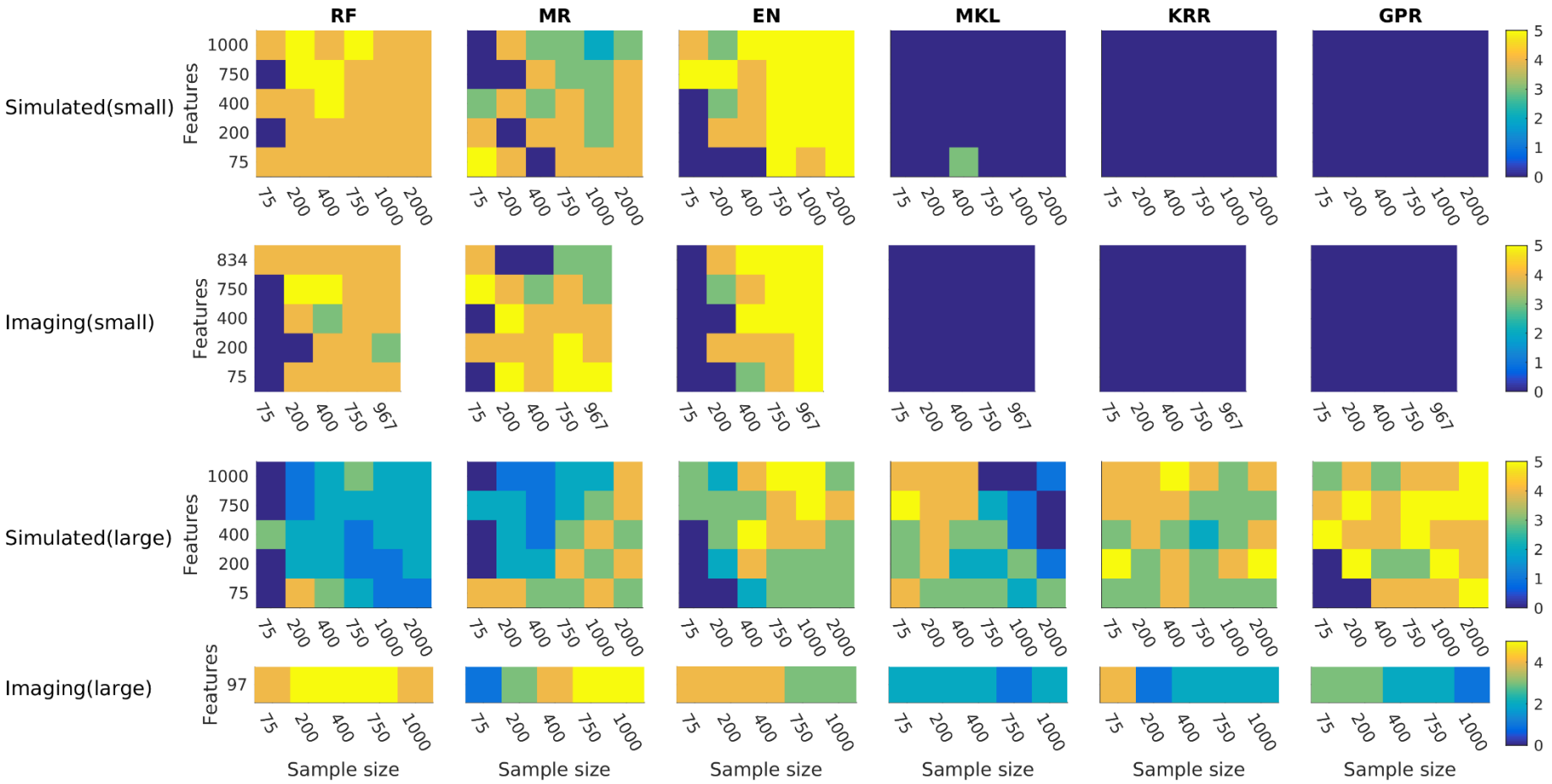

Figure 2.5. Quintile rank of prediction accuracy by sample size and analysis algorithm for Simulated$_{Large}$, Simulated$_{Small}$, Imaging$_{Small}$, and Imaging$_{Large}$. Shown ranks are the quintile into which the median prediction accuracy for each method within each data type and cell fell across the distribution of all analysis iteration for each data type and cell. RF: Random Forest; MR: Multiple Regression; EN: Elastic Net; MKL: Multiple Kernel Learning; KRR: Kernel Ridge Regression; GPR: Gaussian Process Regression. Colour bars and plot colouring show the rank from zero to five.

2.3.2. Comparison of Regression machines

Quintile ranks largely mirrored results observed in 2.3.1. (see Figure 2.5).

2.3.2.1. Dataset: Simulated$_{Small}$

RF had a high ranking across all cells with N≥200. EN ranked highest for datasets with N≥750. For datasets with 400 or more features and between 200 and 750 observations RF and EN performed similarly with somewhat better performance for RF. EN performed very poorly with small samples, particularly when the feature set was small. While MR ranked below RF and EN for almost all sample and feature set sizes, accuracy for ML for N=75 and up to 200 features was higher than for RF and EN. MKL, KRR, and GPR ranked below the other approaches in all cells, except for MKL at N=400 and 75 features.

2.3.2.2. Dataset: Imaging$_{Small}$

Quintile ranks for Imaging$_{Small}$ were very similar to results for Simulated$_{Small}$. EN ranked highest for N≥400, but performed poorly with small samples. Ranks for MKL, KRR, and GPR were zero for all dataset sizes. There was a trend toward higher performance of MR with smaller feature sets and higher performance of RF with larger feature sets.

2.3.2.3. Dataset: Simulated$_{Large}$

GPR showed the highest average ranking overall. In comparison to other methods, RF ranked lowest across cells. The *'curse of dimensionality'* effect was evident in the rankings for MR, which performed broadly similar to KRR and EN when the sample size exceeded the feature set size, but showed distinctly poor performance (comparable to RF) when the number of features exceeded the sample size. EN, KRR, and GPR ranked very similarly for datasets with N>400, but EN ranked lowest with small feature sets. KRR and MKL both ranked above other approaches for small datasets with more features than observations, and performed better with small sample sizes than EN. Both GPR and EN performed poorly for datasets with small samples and small feature sets. MKL performed very poorly for datasets with large samples, particularly when the number of features was also large.

2.3.2.4. Dataset: Imaging$_{Large}$

Despite lacking information about the effect of feature set size, data from Imaging$_{Large}$ repeated the finding of low performance of MKL, KRR and GPR compared to the other approaches. Unlike with other data types, both RF and MR outperformed EN at larger sample sizes. Given the similarity in median performance at larger sample sizes for EN, MR, and RF this was due to only very small differences in accuracy (see Figure 2.4). Furthermore, RF performed equal to or better

than all other algorithms for datasets with N<1000, while MR performed best for datasets with N=1000.

2.3.3. Change in prediction accuracy from Feature Selection and bagging

Changes in prediction accuracy from adding embedded FS, bagging, or both in combination were evaluated (see Figure 2.6). Mean performance of RF, MR and EN with FS and/or bagging (see Figure 2.7) and quintile ranks recalculated to include analyses with FS and/or bagging (see Figure 2.8) showed considerable effects of FS and bagging on algorithm performance. Ranks for the original six algorithms (see Figure 2.5) showed little change for $Imaging_{Small}$, $Simulated_{Large}$ and $Imaging_{Large}$. For $Simulated_{Small}$ ranks for RF, MR, and EN were reduced as MR and EN with bagging and/or FS ranked equal to or higher than the original approaches. Across data types the rank of RF improved as RF with FS ranked very low for all data types except $Imaging_{Large}$, and MR with FS and bagging ranked very low for $Simulated_{Large}$ and $Imaging_{Large}$.

2.3.3.1. Random Forest (RF)

The addition of embedded FS did not improve prediction accuracy of RF for any dataset size or data type. Significant decreases in prediction accuracy were observed for $Simulated_{Small}$ when at least 200 features and N≥750 were used, and for $Imaging_{Small}$ with 750 or more features and N≥400. In the quintile ranking of all analysis approaches RF with FS ranked very highly for $Imaging_{Large}$, in the absence of any significant changes in prediction accuracy. In contrast, RF with FS ranked very low for all other data types.

2.3.3.2. Multiple Regression (MR)

Feature selection. There were some small improvements in prediction accuracy for MR as a result of adding embedded FS with all data types. For $Simulated_{Small}$ and $Imaging_{Small}$ improvements occurred with N≥750, and for $Simulated_{Large}$ and $Imaging_{Large}$ improvements occurred with N=75 with additional small improvements up to N=400 for $Imaging_{Large}$. For $Simulated_{Small}$ MR with FS ranked higher than MR in the quintile ranking for almost all dataset sizes with more than 200 observations and features, and for most datasets with 400 or more features with $Imaging_{Small}$. Examination of the relationship between feature set size and accuracy at each sample size revealed that these differences in accuracy were due to a reduction of the *'curse of dimensionality'* effect observed with MR, evidenced by non-negative correlations between number of features and accuracy (see Figure 2.9). Quintile ranks for $Simulated_{Small}$ also showed that rank of MR with FS was higher than rank of MR for datasets with N=75 and more than 75 features. At larger sample sizes rankings and observed correlations between feature set size and accuracy were very similar,

indicating no effect of the feature selection step on performance. With $Imaging_{Large}$ ranking of MR with FS was higher than ranking for MR for N<400, and lower for larger samples.

Bagging. When bagging was used, prediction accuracy for MR also showed improvements for all data types except $Imaging_{Small}$. For $Simulated_{Small}$ there were some improvements for N≥400 and 1000 features and for N=400 and 75 features, and higher quintile ranks for MR with bagging compared to MR without bagging at almost all dataset sizes. For $Simulated_{Large}$ improvements occurred for datasets with N>75 and at least 400 features when the number of features was equal to or larger than the sample size. These cells overlap to a large extent with the dataset sizes for which the *'curse of dimensionality'* effect was observed (see Figure 2.7). Examination of the correlations between feature set size and accuracy revealed that bagging drastically increased this correlation for $Simulated_{Large}$, resulting in an almost complete disappearance of the *'curse of dimensionality'* effect when evaluating algorithm performance (see Figure 2.9). For $Imaging_{Large}$ improvements as a result of bagging occurred at N=75 and were thus similar to those seen for FS.

Feature selection and bagging. When both FS and bagging were used performance of MR for $Simulated_{Small}$ showed some small improvements for datasets with N=400 to N=1000 and 200 or more features, and quintile rank for MR with FS and bagging was higher than rank for MR at almost all dataset sizes with N>75. Performance of $Imaging_{Small}$ was also improved at the largest dataset size (N=967 and 834 features), while performance was reduced at N=750 and 75 features. As with $Simulated_{Small}$, quintile ranks for MR with FS and bagging were higher than ranks for MR for most cells with N>75, when 400 or more features were used. For $Simulated_{Large}$ performance was improved for N=400 and 400 to 750 features, but performance decreased for datasets for which the sample size was larger than the number of features with 200 or more features and N>400. Similarly, performance for $Imaging_{Large}$ was reduced for datasets with N>200, and quintile ranks for MR with FS and bagging were lower than those of MR in most cells for both $Simulated_{Large}$ and $Imaging_{Large}$, although ranks for datasets with N<400 were higher in some cells. For all data types the number of features showed a reduced correlation with prediction accuracy when MR was combined with both FS and bagging (see Figure 2.9). For $Simulated_{Large}$ and $Imaging_{Large}$ this caused reduced accuracy compared to MR alone when sample sizes exceeded feature set sizes.

2.3.3.3. Elastic Net (EN)

Feature selection. For $Simulated_{Small}$ and $Imaging_{Small}$ the addition of FS to EN resulted in significant reductions in accuracy for datasets with N>400 and 400 or more features. For $Simulated_{Small}$ there was a small improvement from FS at N=75 and 75 features. While quintile ranks for both $Simulated_{Small}$ and $Imaging_{Small}$ were reduced for EN with FS compared to EN for N>400, quintile ranks at small sample sizes were higher for EN with FS than for EN in some cells.

Examination of the relationship between feature set size and accuracy revealed that the addition of FS reduced the positive correlation between number of features and accuracy, which accounts for reduced EN performance with large datasets when FS was used (see Figure 2.9). For $Simulated_{Large}$ there was a small improvement in accuracy from FS at N=1000 and 750 features. Despite only a small significant change in prediction accuracy, quintile ranks indicated that EN with FS outperformed EN in almost all cells for $Simulated_{Large}$, with EN with FS ranking highest among all analysis approaches for almost all cells with N≥400 and 200 or more features. While FS also reduced the correlation between feature set size and accuracy for $Simulated_{Large}$, the correlation remained at r~.5 for N≥400, which is comparable to the correlations observed for $Simulated_{Small}$ and $Imaging_{Small}$ without FS. No significant differences were observed for $Imaging_{Large}$, and quintile ranks for EN with FS and EN were largely the same for this data type.

Bagging. The addition of bagging to EN only resulted in a significant change in accuracy for $Imaging_{Small}$ at N=967 and 400 features, where accuracy was reduced. While quintile ranks for EN with bagging were lower than ranks for EN in most cells for $Imaging_{Small}$, ranks for the other data types were similar between EN and EN with bagging. However, for both $Simulated_{Small}$ and $Imaging_{Small}$ EN with bagging ranked highest and equal to EN alone for N≥750 and large feature set sizes (400 or more for $Simulated_{Small}$ and 834 for $Imaging_{Small}$). Examination of the relationship between feature set size and accuracy revealed only a very small difference in correlations for EN and for EN with bagging (see Figure 2.9).

Feature selection and bagging. When both FS and bagging were used performance of EN with $Simulated_{Small}$ and $Imaging_{Small}$ was again significantly reduced for datasets with N>400 and 400 or more features, as was the case for EN with FS only. Similarly, the correlation between feature set size and accuracy was also reduced for $Simulated_{Small}$ and $Imaging_{Small}$ when both FS and bagging were used (see Figure 2.9). With $Simulated_{Small}$ quintile ranks for EN with bagging and FS were higher than for EN with just FS and lower than for EN alone. Ranks at large dataset sizes were higher for EN with only bagging than for EN with bagging and FS. For $Imaging_{Small}$ quintile ranks of EN with bagging and FS were lower than ranks for EN only and EN with FS. However, ranks for EN with bagging and FS were higher than for EN with only bagging in most cells. As with both bagging and FS individually, the combination of both bagging and FS did not result in any significant changes in accuracy for $Imaging_{Large}$. However, the quintile ranking showed that for $Imaging_{Large}$ EN with both bagging and FS ranked very poorly at the largest sample size (N=1000). While $Simulated_{Large}$ had shown a small improvement in accuracy for large datasets with FS, and no significant change for bagging, the addition of both bagging and FS resulted in a decrease in accuracy for the largest dataset sizes, i.e. N=2000 and 1000 features. The quintile ranking for $Simulated_{Large}$ indicated lower rank for EN with bagging and FS in almost all cells compared to EN

with FS, lower performance in some cells than EN with bagging, and some improvement at small feature set sizes compared to EN alone. Unlike FS alone, FS in combination with bagging did not result in a reduction of the correlation between feature set size and accuracy for $Simulated_{Large}$ (see Figure 2.9), which accounts for the higher quintile rank of analyses with FS in many cells with N≥400.

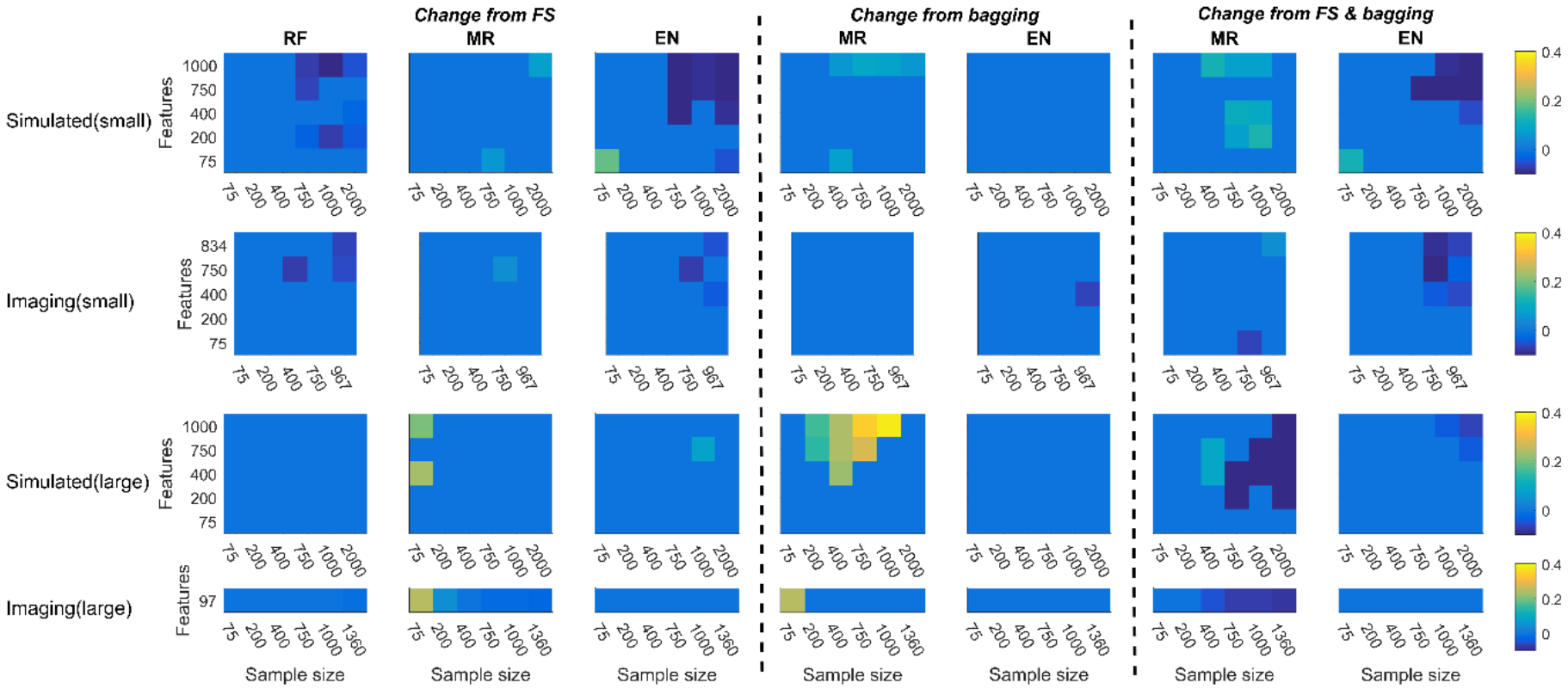

Figure 2.6. Significant improvement or decrease in median prediction accuracy (p<.005) from adding embedded Feature Selection (FS) and/or bagging to analyses with Random Forest (RF), Multiple Regression (MR), and Elastic Net (EN). Colour bars and plot colouring show the difference in median correlation between prediction and truth between standard analyses for each algorithm and analyses with FS and/or bagging.

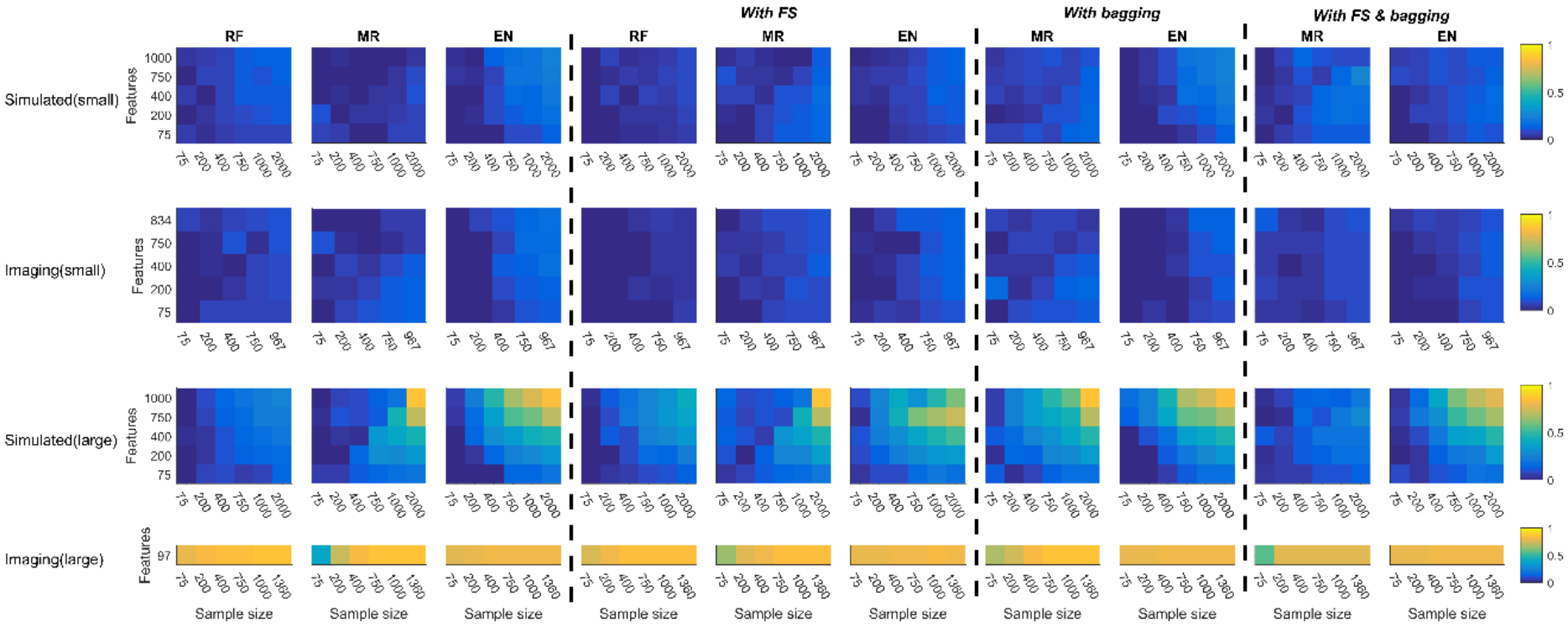

Figure 2.7. Mean out-of-sample performance by sample size and analysis algorithm for Random Forest (RF), Multiple regression (MR), and Elastic Net (EN) with and without bagging and embedded feature selection (FS). Colour bars show the cross-validated Pearson's R value.

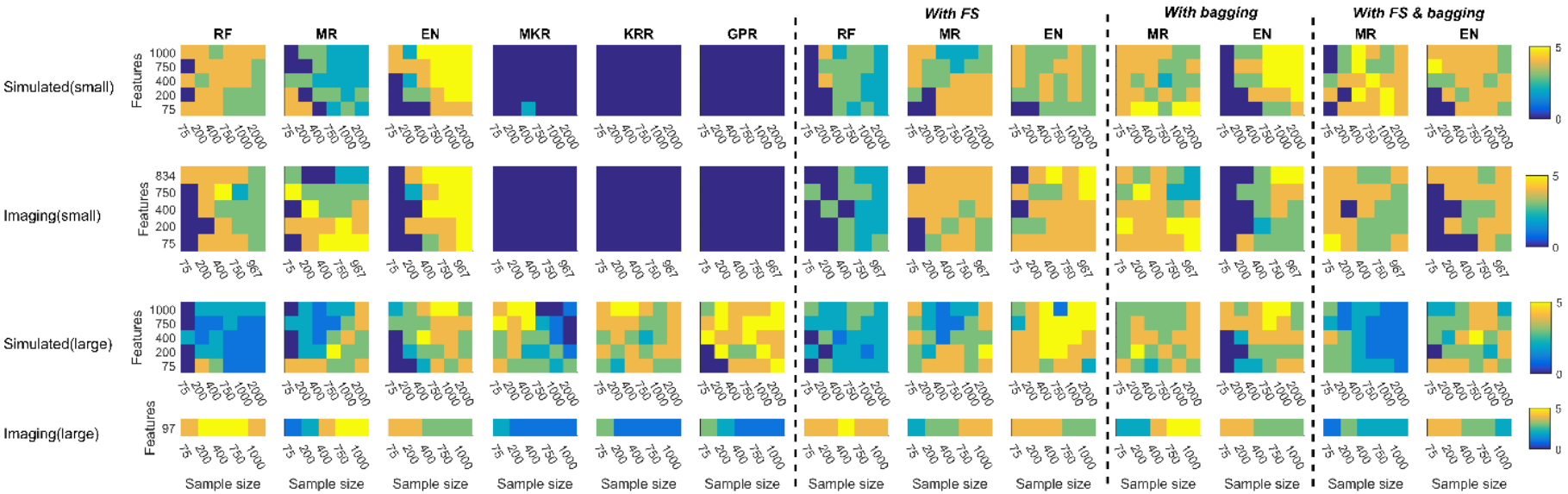

Figure 2.8. Quintile rank of prediction accuracy with and without embedded feature selection (FS) and/or bagging by sample size and analysis algorithm for $Simulated_{Small}$, $Imaging_{Small}$, $Simulated_{Large}$, and $Imaging_{Large}$. Shown ranks are the quintile into which the median prediction accuracy for each method within each data type and cell fell across the distribution of all analysis iteration for each data type and cell. RF: Random Forest; MR: Multiple Regression; EN: Elastic Net; MKL: Multiple Kernel Learning; KRR: Kernel Ridge Regression; GPR: Gaussian Process Regression. Colour bars and plot colouring show the rank from zero to five.

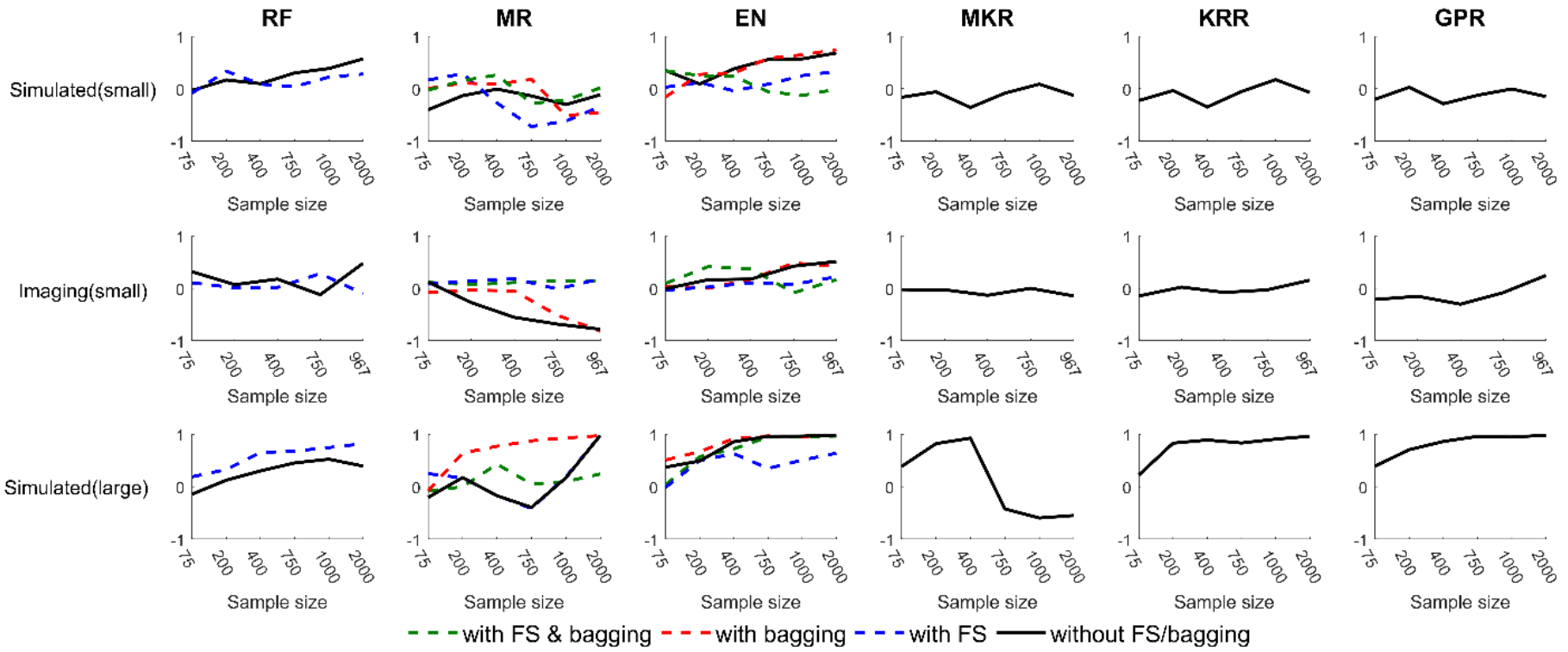

Figure 2.9. Correlation between feature set size and prediction accuracy for all analysis approaches and data types. RF: Random Forest; MR: Multiple Regression; EN: Elastic Net; MKL: Multiple Kernel Learning; KRR: Kernel Ridge Regression; GPR: Gaussian Process Regression; FS: Feature Selection.

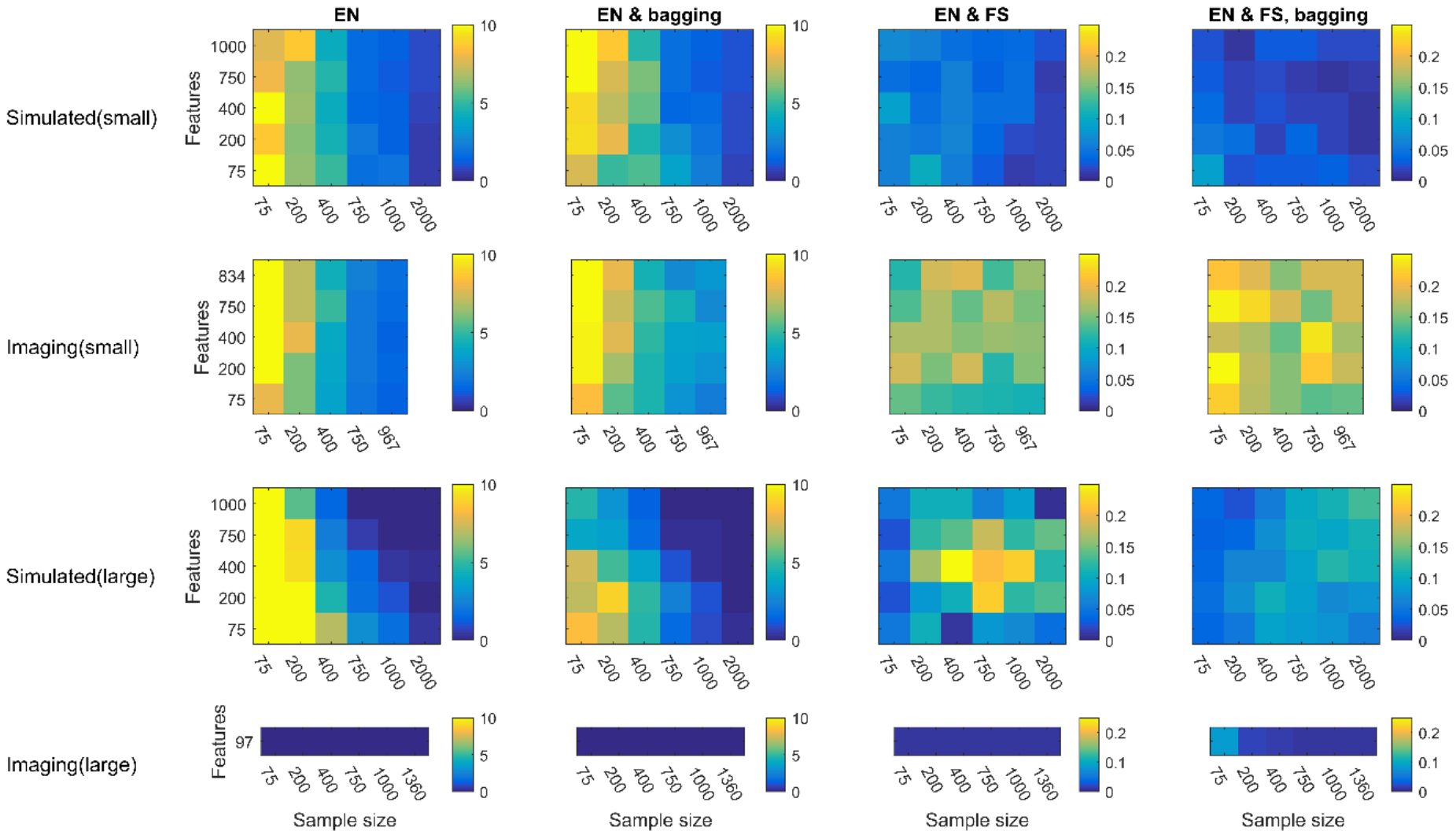

Figure 2.10. Mean regularization strength for the Elastic Net (EN) with and without bagging and/or embedded feature selection (FS).

2.3.3.3. Regularization weight

For all data types except $Imaging_{Large}$, when dataset size was not considered, there were negative associations between regularization weight and prediction accuracy for the standard EN and EN with bagging. That is, lower prediction accuracy was associated with higher regularization (see Table 2.1). For $Imaging_{Large}$ the lowest regularization strength was chosen for all analyses with the standard EN or EN with bagging (see Figure 2.10), and high prediction accuracy was achieved for all analyses. When FS was used the correlation strength for all data types was low, with a significant negative correlation for EN and FS only being observed for $Simulated_{Small}$. For EN with both FS and bagging $Simulated_{Small}$ and $Imaging_{Large}$ showed a significant negative correlation between regularization strength and prediction accuracy, while $Simulated_{Large}$ showed a significant positive correlation.

Table 2.1. Correlation coefficients between mean regularization weights across cross-validation folds and model performance for the Elastic Net including only non-zero models.

	$Simulated_{Small}$	$Imaging_{Small}$	$Simulated_{Large}$	$Imaging_{Large}$
Elastic Net	-.556*	-.785*	-.765*	.000
Elastic Net & bagging	-.587*	-.575*	-.722*	.000
Elastic Net & Feature Selection	-.259*	-.039	.174	-.274
Elastic Net & Feature Selection, bagging	-.278*	-.094	.314*	-.501*

*p<.001

Examination of regularization strength by sample size (see Figure 2.10) revealed that there was a clear effect of sample size on regularization strength for $Simulated_{Small}$ and $Imaging_{Small}$ when FS was not used, which is consistent with very low prediction accuracy at small sample sizes. For $Simulated_{Large}$ the pattern of higher regularization strength for cells that also showed low accuracy was also observed for EN without FS.

When FS was used the size of the regression weights was greatly reduced, as can be seen by the difference in scales for plots with and without FS in Figure 2.10. While there were some variations in regularization strength associated with dataset size and therefore also with prediction accuracy (see Table 2.1), variations in regularization strength for analyses with FS were minor compared to analyses without FS. Of note is an observed cluster of higher regularization strength for $Simulated_{Large}$ for EN with FS at N~750 and around 400 features. Evaluation of the percentage of

features that were selected by FS based on dataset size revealed that the median number of selected features for datasets with N≥400 and between 200 and 750 features was often approximately 100%, which effectively negates the FS procedure. Although it is not entirely clear why the percentage of selected features was higher in this cluster than in other cells with FS, the high regularization strength in these cells is in line with the higher regularization weights seen in analyses without FS than in analyses with FS.

2.4. Discussion

Analytical tools developed for data science have become frequently used in neuroimaging (Woo et al., 2017), but none of these tools were specifically developed for neuroimaging data. With the small samples, large feature sets, and low signal-to-noise that are characteristic of neuroimaging data, prediction models built using neuroimaging data are at a high risk of overfitting. In this paper, the merit of six different linear regression approaches for prediction analysis was empirically evaluated and compared using simulated and real neuroimaging data for the first time. Results showed that Gaussian Process Regression, Multiple Kernel Learning, and Kernel Ridge Regression implemented in the Pronto toolbox (Schrouff et al., 2013) could produce good predictions, but failed when effect sizes were small regardless of sample size. The Elastic Net on the other hand emerged as the most flexible and reliable regression machine. The Elastic Net created the most accurate prediction models independent of absolute predictor effect sizes, and across many sample and feature set sizes. Predictions were always improved when sample size was increased, but across all analyses an ideal minimum sample size of about 400 emerged as necessary to achieve reliable results. At smaller sample sizes and for datasets with weak effect sizes modest improvements in accuracy could be made using an embedded feature selection method. Another approach designed to increase model performance – bootstrap aggregation – could counteract the decline in standard Multiple Regression model accuracy with more predictor variables than observations. However, given adequate dataset sizes and using the Elastic Net, neither feature selection nor bootstrap aggregation improved findings significantly, and indeed resulted in substantially increased computational time for all analyses and reduced accuracy for some models.

The central observation of this study was that different types of linear regression approaches provide widely different results, and that these results are differently affected by sample size, number of predictors, and the ratio of signal to noise in the data. Previous meta-analyses by Kambeitz and colleagues (2015, 2016) have shown that not only the outcome to be predicted, but also the type of neuroimaging data that is used has a strong effect on the maximum performance of a model. Findings in the present study confirmed that when using multivariate regression methods, the expected size of the effect and effect sizes for individual predictor

variables are the most important criteria for selection not only of minimum sample size, but also selection of the analysis approach. However, across simulated and real neuroimaging data of varying effect sizes the Elastic Net had the highest median prediction accuracy for datasets with 400 or more features and observations. For smaller feature sets, variations of Multiple Regression resulted in better model fit.

When both the sample and feature set size were small, the MATLAB implementation of random forest also showed some promise. A key difference between Random Forest and many other regression methods is that the contribution of individual predictors is not easily, or at all, determinable from a completed model. While it has been debated in the literature whether the main goal of neuroimaging prediction should be predicting an outcome as accurately as possible, or identifying when and where data contain information about an outcome (Paulus, 2015; Pine & Leibenluft, 2015), the readability of neuroimaging prediction models is an important aspect of model development. The ability to scrutinize the contribution of individual neuroimaging predictors allows researchers to verify the neurophysiological plausibility of the model, while also enabling future research to consider which variables are strong or poor predictors of an outcome in the development of further experiments, studies, and prediction models (Woo et al., 2017; Jollans & Whelan, 2018). While some methods make it possible to gain insight into the contribution of individual predictors to the prediction model using random forest (Palczewska et al., 2014), these are computationally expensive, and present findings indicate that the scenarios in which Random Forest would substantially outperform the Elastic Net are very limited.

For the Elastic Net, which was found to show the most consistent performance across effect sizes and dataset sizes, an effect of a certain size could be retrieved with approximately equal accuracy at varying sample sizes by altering the number of input features. Given smaller sample sizes, inclusion of a larger feature set is thus one approach to improve model performance. Crucially, findings also indicated that preselection of variables for inclusion in the model did not improve performance and indeed resulted in lower model accuracy in some cases. It is therefore suggested that neuroimaging researchers refrain from preselecting regions of interest or contrasts of interest before implementing multivariate regression models. This will allow researchers to conduct analyses including variables that have not previously been linked to an outcome of interest, in the knowledge that the contribution of other predictors will not suffer from the inclusion of more *exploratory* variables. This possibility is of importance considering that most of the neuroimaging literature to date reports only univariate and frequentist findings which may not translate to predictive utility (Lo et al., 2015). An important note here is that, based on this study, the determination that dimensionality reduction (other than regularization) does not appear to be necessary for neuroimaging models can only be made when region of interest data are used, and

when sample sizes exceed a certain minimum threshold. Voxel-wise analyses and analyses with very small sample sizes are likely to benefit from some additional dimension reduction, as was shown by findings regarding accuracy for very small samples using the embedded feature selection approach.

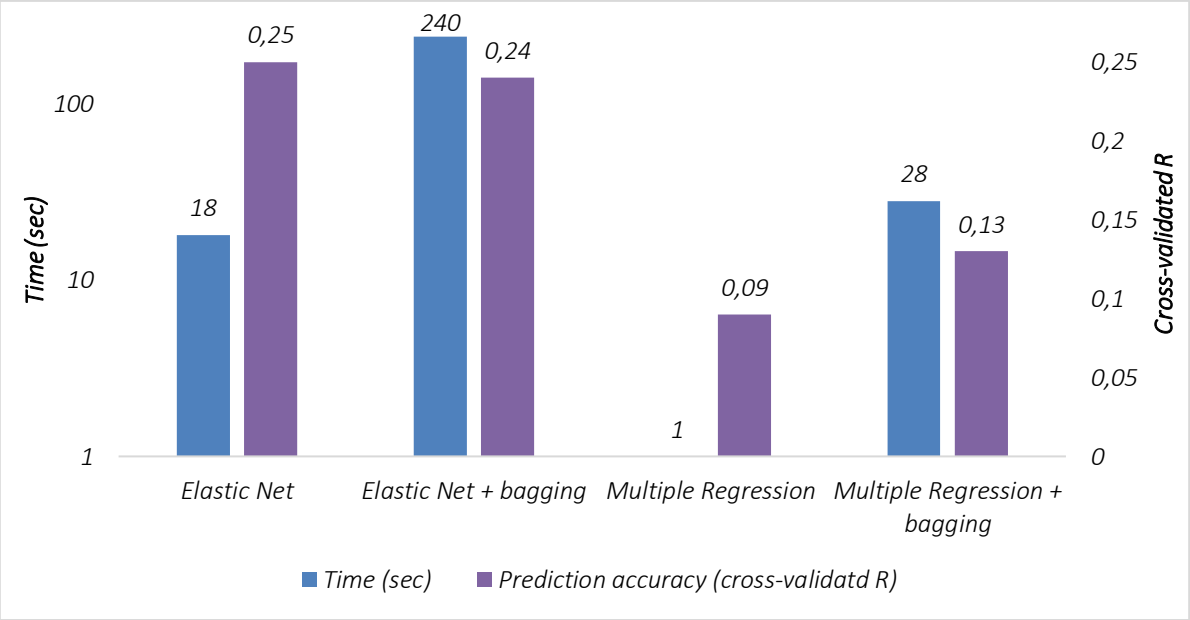

Figure 2.11. Example computational time and prediction accuracy for a sample simulated dataset from Simulated$_{Small}$ with N=400 and 1000 features.

There was evidence for a beneficial effect of embedded feature selection on results at small sample sizes for both the Elastic Net and Multiple Regression. Through feature selection the association between the number of features and model performance tended to shift toward zero, reducing the *'curse of dimensionality'* effect for Multiple Regression, but also counteracting the positive relationship between feature set size and model performance at large sample sizes for the Elastic Net. For the Elastic Net the feature felection step greatly reduced the need for regularization, as seen by very small regularization weights for analyses after feature selection. Any significant improvements in model performance because of embedded feature selection were not consistent or strong enough to recommend use of this approach, particularly considering the computational expense. Time needed to run Elastic Net analyses with N=400 and 1000 features was approximately 18 seconds (see Figure 2.11) for the standard Elastic Net (r=.25) compared to 225 minutes for the Elastic Net with the embedded feature selection approach (r=.15).

In contrast to embedded feature selection, there was strong evidence for the utility of bootstrap aggregation to improve prediction accuracy with Multiple Regression. This approach strongly counteracted the *'curse of dimensionality'* effect for Multiple Regression. Indeed, for half of all cells with fewer than 400 features or a sample size of N<400 Multiple Regression paired with 25-fold bootstrap aggregation performed in the highest quintile for the simulated and real

neuroimaging data with weak effect sizes. There was no significant effect of bootstrap aggregation on performance of the Elastic Net, and quintile ranks for analyses with and without this method were largely similar. Given the relatively small increase in time required for computations when bootstrap aggregation was used (see Figure 2.11) it may then be worthwhile including this method with a view to increasing model stability. However, given a robust cross-validation framework, as was used in the analyses presented here, it appears that bootstrap aggregation may not be a necessary addition to Elastic Net analyses.

There are some important limitations to the generalizability of findings in this study. While there were strong commonalities across results for the real neuroimaging dataset examined here and results achieved using data simulations, there was some indication that not all characteristics of real neuroimaging data were sufficiently accounted for in the simulations. In particular, there was higher accuracy for analyses with Random Forest for the real compared to the simulated datasets. Further examination of Random Forest and other regression methods such as Support Vector Machines for neuroimaging data are warranted. Furthermore, only ROI data rather than voxelwise analyses were considered in this study. While this decision was based on the intention of creating models that are easily interpretable, findings also do not necessarily translate to models with a strongly increased feature set size, and the characteristics of voxel as compared to ROI data are likely quite different in terms of the between-feature correlations and predictor strengths. Finally, based on previous findings that non-brain variables are much better predictors of phenotypic outcomes than neuroimaging data (Whelan et al., 2014), identifying the best methods to integrate imaging and non-imaging data in prediction analyses will be a crucial step in biomarker development.

2.5. Conclusions

Findings in this study have shown that the choice of analysis approach for linear regression analyses has a large impact on the accuracy of the resulting regression model. The size of the sample and number of predictors are important factors that determine which analysis approach will have the greatest success in extracting meaningful information from a neuroimaging dataset. Results in this study indicate that datasets with at least 400 observations have the highest likelihood of uncovering meaningful findings. Furthermore, increasing the number of ROI variables for inclusion in a model will improve results, eliminating the need for the researcher to preselect variables for inclusion. When at least 400 observations and 400 or more predictor variables are included in the analysis, regularized regression via the Elastic Net was shown to be the best analysis approach for ROI data. When the sample or feature set size is smaller, standard Multiple Regression supported by bootstrap aggregation showed the best performance in this study.

Chapter 3 - Predicting adolescent smoking using neuropsychosocial risk indicators

3.1. Introduction

The majority of adolescents will try smoking at some point (O'Loughlin et al., 2014). The crucial component important in understanding and possibly preventing, harmful cigarette use is the progression from initial experimentation to regular smoking behaviour. Known correlates of adolescent smoking include environmental factors, psychological factors, and aspects of brain function.

Adolescents are more likely to smoke again after their first cigarette if they had a positive experience smoking and are exposed to peers or siblings who smoke (Hirschmann, Leventhal & Glynn, 1984). Smoking has also been suggested to be a coping mechanism for adolescents dealing with life stressors such as family conflict or academic pressure (Byrne, Byrne & Reinhart, 1995; Mates & Allison, 1992; Pederson, 1997; Audrain-McGovern et al., 2004a/b; Mayhew et al., 2000; Ellickson et al., 2001; Soldz & Cui, 2002; Wellman et al., 2018). Depression and other mental health issues also show a strong association with smoking behaviour (Upadhyaya et al., 2003; Koval et al., 2000; Grant et al., 2004; Lasser et al., 2000; Lawrence, Mitrou & Zubrick, 2009).

There is a robust link between smoking behaviour and heightened trait impulsivity (Rezvanfard et al., 2010; Mitchell, 1999; Balevich, Wein & Flory, 2013; Skinner, Aubin & Berlin, 2004; Audrain-McGovern et al., 2004a; 2009; Dinn, Aycicegi & Harris, 2004), with some evidence that impulsivity precedes smoking behaviour (Lipkus et al., 1994; White et al., 2002). Smokers also differ from non-smokers on some measures of action impulsivity (Audrain-McGovern et al., 2009; Johnson, Bickel & Baker, 2007; Mitchell, 1999). During tasks measuring impulsive responding, smokers have lower recruitment of brain regions involved in inhibitory control (Luijten et al., 2014). Smokers also process rewards and punishments differently than non-smokers (van Hell et al., 2010; Rose et al., 2013; Luo et al., 2011). The brain regions that have been implicated most strongly in impulsivity and reward processing in relation to substance abuse are the anterior cingulate gyrus and insula (Akkermans et al., 2016; Zanchi et al., 2015), the ventral striatum (Peters & Büchel, 2010; Nestor et al., 2011; van Hell et al., 2010; Rose et al., 2013), the amygdala (Janes et al., 2010a/b; Mihov & Hurlemann, 2012), and the orbitofrontal cortex (Bühler et al., 2010; Gallinat et al., 2006; Kühn, Schubert & Gallinat, 2010).

The majority of studies examining factors associated with regular smoking are cross-sectional in nature, making it impossible to establish causation. Although there have been some longitudinal studies tracking adolescent smoking behaviour (Kellam, Ensminger & Simon, 1980; Burt et al., 2000; Stewart & Livson, 1966; Collins et al., 1987; Cherry & Kiernan, 1976; Sieber & Angst, 1990; O'Loughlin et al., 2014), the typical group comparisons employed in these studies are not necessarily able to identify factors that are predictive of future smoking (Lo et al., 2015). The knowledge of what risk factors increase the likelihood of future smoking behaviour is important in

developing prevention programs with a high chance of succeeding. Multivariate Regression and Machine learning tools are preferable to standard inferential statistics in outcome prediction (Bzdok, Altman & Krzywinski, 2018; Lo et al., 2015), and findings are most reliable with large samples (Woo et al., 2017; Jollans et al., 2016).

In this study, data from the IMAGEN study (Schumann et al., 2010), a large European multi-site neuroimaging initiative with more than 2000 participants in the first wave of data collection was used. At age 14 participants took part in a battery of neuroimaging and behavioural tasks, and completed a large number of measures assessing social context, personality, and psychological wellbeing. Data on substance use and smoking behaviour was also collected at age 14, 16, and 18. The Elastic Net (Zou & Hastie, 2005), a type of regularized regression previously successfully used to predict binge drinking behaviour in this population (Whelan et al., 2014), was used to predict future smoking behaviour based on baseline neuroimaging and psychometric data.

3.2. Method

3.2.1. Characteristics of the IMAGEN Study

A large sample of 14-year olds was recruited at eight recruitment sites. Adolescents completed an extensive battery of psychiatric and neuropsychological assessments, including magnetic resonance imaging (MRI). Participants completed follow-up assessments after two and four years. Details of the full study protocol and data acquisition are provided elsewhere (Schumann et al., 2010).

3.2.2. Participants

548 participants from the IMAGEN study were included. All participants had neuroimaging and psychometric data from baseline, as well as data on smoking behaviour and substance use from follow-up 1 (age 16) and follow-up 2 (age 18). Characteristics of the sample at baseline are provided in Table 3.1. Participants were classified into the following groups: continuous non-smokers (NS) who remained non-smokers at all three time points, early onset smokers (EOS) who were non-smokers at baseline but smokers at follow-up 1 and 2, and late onset smokers (LOS) who were non-smokers at baseline and the first follow-up but smokers at the second follow-up.

Table 3.1. Characteristics of the sample

	NS (n=456)	EOS (n=59)	LOS (n=33)
Age	14.46 (.43)	14.33 (.46)	14.39 (.34)
Sex	53.51% female	55.93% female	27.27% female*
Pubertal Development Status	3.56 (.76)	3.59 (.72)	3.42 (.75)
Socio-economic status	18.40 (3.53)	18.20 (3.57)	17.65 (3.24)

* significantly less than NS (p=.0035) and EOS (p=.0078)

3.2.3. MRI data collection

3.2.3.1. MRI Data Acquisition

Full details of the MRI acquisition protocols and quality checks have been described previously, including an extensive period of standardization across MRI scanners (Schumann et al., 2010). MRI acquisition was carried out at the eight assessment sites with 3T whole body MRI systems made by several manufacturers (Siemens: 4 sites, Philips: 2 sites, General Electric: 1 site, and Bruker: 1 site). To ensure comparability of MRI data acquired on these different scanners, image-acquisition techniques using a set of parameters that were held constant across sites and were compatible with all scanners were used.

Structural MRI. High-resolution anatomical MRI scans were acquired, including a 3D T1-weighted magnetization prepared gradient echo sequence (MPRAGE) based on the ADNI protocol (Jack et al., 2008). Structural MRI processing included data segmentation and normalization (to the Montreal Neurological Institute template) using the SPM 2 optimized normalization routine. Gray matter images were modulated, facilitating comparisons of volumetric, rather than tissue concentration differences. Overall values for total grey matter volume, total white matter volume, and ratio of grey to white matter volume were used as covariates in the prediction analyses.

Functional MRI. Standardized hardware for visual and auditory stimulus presentation (NordicNeurolabs, Bergen Norway, http://www.nordicneurolab.com) was used at all sites. BOLD functional images were acquired with a gradient-echo echoplanar imaging (EPI) sequence using a relatively short echo-time to optimize imaging of subcortical areas. Details of the fMRI task paradigms and resulting contrast images are provided below.

3.2.3.2. Stop Signal Task (SST)

The SST required participants to respond to regularly presented visual 'go' stimuli (arrows pointing left or right) but to withhold motor response when the go stimulus was followed by a

'stop'-signal (an arrow pointing upwards). Stopping difficulty was manipulated by varying the delay between the onset of the go arrow and the stop arrow (stop-signal delay, SSD) across trials using a previously described tracking algorithm (Rubia et al., 2005). A task block contained 400 go trials and 80 stop trials with variable delay. Stop trials occurred on average on 20% of trials. Stimulus duration in go trials was 1000 ms. In stop trials go stimulus presentation duration varied (0–900ms in 50 ms steps) in accordance with the tracking algorithm (initial delay for the stop signal was 250 ms). Contrast images for successful inhibitions ("stop success") and unsuccessful inhibitions ("stop fail") were calculated, both vs. an implicit baseline (i.e., they were compared to the successful Go trials; this method has previously been used in Whelan et al., 2012). SST behavioural task performance (number of correct and incorrect responses for GO and STOP trials) was also included in the analysis.

3.2.3.3. Monetary Incentive Delay (MID) Task

Participants completed a modified version of the MID task (Knutson, Westdorp, Kaiser & Hommer, 2000), involving small and large possible gains. Unlike in the original MID task this version did not include loss trials due to time constraints related to other assessments in this large-scale study. This modification was deemed appropriate since prior studies have shown the same pattern of ventral striatum response during reward anticipation and anticipation of loss avoidance (Bjork et al. 2008; Wrase et al. 2007; Beck et al. 2009; Yau et al. 2012). On each trial, the amount of points that could be won on that trial was signalled by a cue, displayed for 4 to 4.5 s. Participants could win a reward by responding as quickly as possible to a target stimulus presented after a random time interval. Responses were made by means of a button press, after which feedback was presented. The response and feedback phase lasted a total of 2 s. The response interval was dynamically adjusted so that subjects won on two thirds of all trials. Trials were separated by a 3.5 to 4.15 s inter-trial interval, during which a fixation cross was presented. The cue stimuli were a circle with two lines signalling a large reward (10 points), a circle with one line signalling a small reward (2 points), and a triangle signalling no reward. Contrast images were calculated from large minus small win, and large minus no win in the anticipation phase and in the feedback phase of the task.

3.2.3.4. Faces Task

The Faces task involved passive viewing of 2- to 5-s black-and-white video clips that displayed faces in movement with ambiguous (emotionally ''neutral'') or angry facial expressions, and control (non-biological motion) stimuli (Grosbras & Paus, 2006). The control stimuli consisted of black-and-white concentric circles of various contrasts, expanding and contracting at various speeds, roughly matching the contrast and motion characteristics of the face clips. The stimuli

were presented through goggles (Nordic Neurolabs, Bergen, Norway) in the scanner and subtended a visual angle of 10° by 7°. The video clips were arranged into 18 s blocks with each block including seven to eight video clips. Five blocks of each biological-motion condition (neutral and angry faces), and nine blocks of the control condition (circles) were intermixed and presented to the subject in a 6-minute run. Contrast images were calculated from angry and neutral faces vs. the control condition, and from angry faces vs. neutral faces. After the scanning session, participants completed a recognition task in which they were presented with three of the faces previously presented in the scanning session and two novel faces. Recognition success was included in the analysis.

3.2.3.5. Global Cognitive Assessment (GCA) Task

In the GCA task (Pinel et al., 2007) participants were presented with visual and auditory stimuli for short sentences (e.g. *'We easily found a taxi in Paris'*), subtractions (e.g. *'Subtract nine from eleven'*), and motor instructions (e.g. *'Press the left button three times'*). Over the 5-minute sequence each stimulus type was presented 10 times followed by 10 horizontal and 10 vertical flashing checkerboard patterns. Visual and auditory stimuli were each presented over the space of 1.2 to 1.7 sec. Maps for auditory and visual sentences and subtractions were calculated.

3.2.4. Self-report, parent-report, and experimenter measures

The majority of psychometric measures were administered to participants and/or a parent using the computerized assessment platform Psytools and were completed either at home or at the research institute. Psytools presented questionnaire items and response alternatives on a computer screen. The reliability of individual data was checked in a two-stage procedure: Before every task, adolescents were asked to report on the current testing context including questions about their attentional focus and the confidentiality of the setting. Potentially problematic testing situations were followed-up by research assistants face-to-face in a confidential setting.

Any missing data were imputed based on the mean for participants of the same sex at the same data collection site. Variables for which more than 150 participants were missing data were excluded. The 150 missing datapoint threshold was chosen based on inspection of the proportion of missing elements across all predictors. Variables in which all participants had the same value were excluded. These were mostly measures of psychopathology present in none of the participants (e.g. a diagnosis of PTSD), or items assessing use of illicit substances that were not applicable to any of the participants (e.g. heroin use). Variables that had no variation in the values for any two groups (e.g. EOS and LOS all had a score of zero on this variable) were also excluded to ensure that all variables could be used in all analyses, resulting in a total of 1105 variables (of 2008 variables originally considered for inclusion) being used in the subsequent analyses. The highest

proportion of missing data was among the parent-reported psychiatric symptoms and parent-reports for own substance use. An average of 60.19 variables were imputed for each participant ($mean_{NS}$=58.59, $mean_{EOS}$=73.69, $mean_{LOS}$=58.12).

3.2.4.1. Smoking and Substance use

Adolescent and parent smoking, alcohol, and cannabis use were measured using self-report on the 'European School Survey Project on Alcohol and Other Drugs' questionnaire (ESPAD, Hibell et al., 1997), the 'Fagerström Test for Nicotine Dependence' (FTND; Heatherton et al.,1991), and the 'Alcohol Use Disorders Identification Test' (AUDIT; Saunders et al., 1993). Substance use measures were excluded for participants who gave an indication to have known or taken the sham drug 'Relevin'. Parents also completed the 'Michigan Alcoholism Screening Test' (MAST; Selzer, 1971) and the 'Drug Abuse Screening Test' (DAST; Gavin et al., 1989, Skinner & Allen, 1982).

3.2.4.2. Personality

Adolescents and parents completed the 60-item 'Neuroticism-Extraversion-Openness Five-Factor Inventory' (NEO-FFI; Costa & McCrae, 1992), the novelty-seeking subscale of the 'Temperament and Character Inventory – Revised' (TCI-R; Cloninger, et al. 1999), and the 'Substance Use Risk Profile Scale' (SURPS; Woicik et al., 2009).

The NEO-FFI measures five broad dimensions of personality based on the Five-Factor Model of personality (Costa & McCrae, 1995): Extraversion, Agreeableness, Conscientiousness, Neuroticism, and Openness to Experience. Extraversion measures preference for engaging in social interaction. Agreeableness measures empathy, compassion and tendency for co-operation rather than self-interest. Conscientiousness measures tendency to exercise self-discipline and preference for planned over spontaneous behavior. Neuroticism mesures emotional lability and tendency to experience anxiety and low mood. Openness to experience measures creativity, intellectual curiosity, and tolerance for change.

The Novelty seeking scale of the TCI-R is composed of four sub-scales. Exploratory Excitability contrasts with 'stoic rigidity' and reflects sensation-seeking and novelty-seeking behaviors. Impulsiveness describes behavior on a dimension from impulsivity to reflection and captures elements of emotional reactivity and unreflective, careless behavior. The Extravagance subscale assesses overspending behavior and poor planning. Disorderliness reflects disorganized, uncontrolled, and antinormative behaviour.

The SURPS assesses personality traits that confer risk for substance misuse and psychopathology. This scale measures four distinct and independent personality dimensions : anxiety sensitivity, hopelessness, sensation seeking, and impulsivity. Anxiety sensitivity is

characterized by the fear of symptoms of physical arousal. Hopelessness is identified as a risk factor for the development of depression and characterized by dismal feelings. Sensation seeking is characterized by the desire for intense and novel experiences. Impulsivity involves difficulties in the regulation (controlling) of behavioral responses.

3.2.4.3. Life history and prenatal factors

Adolescents completed the 'Bully' Questionnaire (BULLY; Olweus, 1996), which assesses whether the participant has had any experiences of being bullied by peers or taking part in bullying someone else. In the research institute the researcher administered the Life-Events Questionnaire (LEQ; adapted from Newcomb et al., 1981) to adolescents. For each of 39 items the desirability (valence) and occurrence in the past year or over the participants' lifetime of a certain event was recorded. The items are categorized into the following domains: 'family', 'accident', 'distress', 'autonomy', 'deviance', 'sexuality' and 'other'.

Parents completed the 'Pregnancy and Birth' Questionnaire (PBQ, adapted from Pausova et al., 2007) in self-report. The PBQ assesses exposure of the child to potentially harmful conditions and substances before and during pregnancy. These include maternal substance use, medical/physical conditions of child and mother, and nutrition after birth.

3.2.4.4. Demographic measures

Sex, exact age, pubertal development status, handedness, and dummy-coded data collection site were used as covariates in all models.

Pubertal development status was self-reported by adolescents using the Puberty Development Scale (PDS, Petersen, Crockett, & Richards, 1988). This scale provides an eight-item self-report measure of physical development based on the Tanner stages with separate forms for males and females. For this scale, there are five categories of pubertal status: (1) prepubertal, (2) beginning pubertal, (3) midpubertal, (4) advanced pubertal, (5) postpubertal. Participants answered questions about their growth in stature and pubic hair, as well as menarche in females and voice changes in males.

A socioeconomic status score was calculated for each participant based on the sum of the following variables: Mother's Education Score, Father's Education Score, Family Stress Unemployment Score, Financial Difficulties Score, Home Inadequacy Score, Neighborhood Score, Financial Crisis Score, Mother Employed Score, Father Employed Score.

3.2.4.5. Psychopathology

Participants' psychopathology was assessed using the 'Development and Well-Being Assessment' Interview (DAWBA; Goodman et al., 2000) and the 'Strengths and Difficulties' Questionnaire (SDQ, Goodman, 1997; 1999), completed by both adolescents and their parents about the participant. The DAWBA assessment was based on ICD-10 and DSM-IV psychiatric diagnoses, and both computer prediction and assessments of responses by a clinician were completed for each participant. Individual symptoms such as behavioural tics or self-harm were also recorded based on parent report and included in the analysis.

3.2.4.6. Cognitive and behavioural measures

Participants completed the Monetary Choice Questionnaire (MCQ; Kirby, Petry, & Bickel, 1999), assessing temporal discounting of delayed rewards. Based on choices in the MCQ a value representing the degree to which delayed rewards are discounted by the participant was calculated.

Participants also completed the Passive Avoidance Learning Paradigm (PALP; Castellanos-Ryan, Rubia & Conrod, 2010). In this task subjects learn to respond to "good" numbers for monetary reward (point gain) and withhold responding to "bad" numbers to avoid punishment (point loss). A series of numbers is presented on screen, and participants must learn whether they should respond or not. The task is administered in the following three conditions: (1) Responding to a "good" number is rewarded and responding to a "bad" number is punished; (2) Responding to a "good" number is rewarded and not responding to a "bad" number is rewarded; (3) Not responding to a "good" number is punished and responding to a "bad" number is punished. After task practise participants completed 10 blocks of the task. In each block each of eight two-digit numbers (4 "good" and 4 "bad") were presented once for each condition.

Participants also completed the Cambridge Neuropsychological Test Automated Battery (CANTAB). The CANTAB battery has been described in detail in previous publications (Sahakian & Owen, 1992; Robbins et al. 1994). The CANTAB included the following games: the 'Pattern Recognition Memory' task, in which participants were required to identify whether they had previously been shown a particular pattern; the 'Spatial working memory' task, in which participants were required to touch a series of squares on a screen to find a hidden 'token' and avoid revisiting already examined boxes; the 'Rapid visual information processing' task, in which participants watched a series of digits on screen and were required to identify a particular pattern; and the 'Affective Go-no-Go' Task, in which participants were asked to respond only to words that belong to one of four categories: Positive, anxiety-related, depression-related, or neutral. For the CANTAB tasks measures of response time, errors, and task strategy were included.

3.2.5. MRI data processing

fMRI data from the following contrasts were used, resulting in a total of 1330 MRI and fMRI variables: SST (Stop success, stop failure), GCA (Auditory math, visual math, auditory sentences, reading sentences), Faces (neutral vs. control, angry vs. control, angry vs. neutral), MID (anticipation of large vs. small win, anticipation of large vs. no win, feedback large vs. small win, feedback large vs. no win).

Grey matter volume data and fMRI data from all contrasts were extracted for 95 regions of interest (ROIs). This included 86 masks from the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002), three aggregated masks based on the AAL masks for the entire vermis, and for the left and right cerebellum. Custom masks for the bilateral ventral striatum, and the caudate and putamen excluding the ventral striatum were also included.

Any missing data were imputed based on the mean for participants of the same sex at the same data collection site. Participants who were missing all data for any of the included contrasts (or grey matter) were excluded from further analysis.

3.2.6. Smoking behaviour classification

Scores on the ESPAD are ranked as follows: 0: no lifetime use, 1: 1 to 2 uses, 2: 3 to 5 uses, 3: 6 to 9 uses; 4: 10 to 19 uses, 5: 20 to 39 uses, 6:40 or more uses. Adolescents were defined as smokers at each timepoint if they scored 6 for the lifetime scale and at least 3 for the past month scale. Non-smoking was defined as a maximum score of 1 on the lifetime scale and 0 on the past month scale. Mean ESPAD scores for these measures for each group are reported in Table 3.2.

Table 3.2. ESPAD scores by group, mean (SD)

	Baseline smoking		Follow-up 1 smoking		Follow-up 2 smoking	
	Lifetime	Month	Lifetime	Month	Lifetime	Month
NS	0.028 (.16)	-	0.120 (.32)	-	0.250 (.43)	-
EOS	0.440 (.50)	-	6	3.661 (.90)	6	4.152 (.78)
LOS	0.121 (.33)	-	0.515 (.50)	-	6	3.636 (.82)

3.2.7. Elastic Net analysis

Prediction models were created for the following group comparisons: (1) NS vs. EOS, (2) NS vs. LOS, (3) NS vs. EOS/LOS, (4) EOS vs. LOS. Separate analyses were carried out using only neuroimaging data or psychometric data (*unimodal models*), or neuroimaging and psychometric data (*multimodal models*). All analyses were carried out using the Elastic Net (Zou & Hastie, 2005).

The Elastic Net is an implementation of regularized regression, which is used to attenuate overfitting by penalizing the size of the regression weights. In this study we combined the Elastic Net with nested cross-validation to determine the ideal parameters for each cross-validation fold. The optimal model parameters were identified based on the F1 score for analyses with balanced groups (EOS vs. LOS), and based on recall (i.e. percentage of smokers correctly classified) for all other analyses. The F1 score is a metric combining precision (i.e. percentage of smokers among participants classified as smokers) and recall.

For each comparison, 20 prediction models with different cross-validation fold allocations were created and results were aggregated across iterations. All analyses were carried out using actual group membership as the outcome variable, in addition to a random-label permutation of group membership to create a null-model. Findings were determined to be significant if F1 score and Area under the curve (AUC) obtained using the real group assignment were significantly higher than F1 score and AUC obtained using a random group assignment. Predictors for each model are said to pass the significance threshold and are reported if the frequency with which the predictor was selected by the Elastic Net across models and the mean absolute beta weight were larger than the 95^{th} percentile for the null models and actual models. For items with binary responses from the LEQ and DAWBA questionnaires (such as lifetime occurrence of an event or presence of a behaviour or symptom) the number of participants from each group who endorsed the item are reported to allow for a determination whether effects may have been driven by a small number of positive responses.

Cannabis use was identified as a strong predictor of future smoking. Of the 1833 participants included in the IMAGEN study who satisfied the smoking inclusion criterion at baseline, 34 had tried cannabis (of 165 participants who had tried cannabis overall). Of these 34 participants 12 did not return for follow-up assessments. The remaining 22 participants did not differ in reported lifetime smoking or cannabis use from the 12 participants who were lost to the study. After excluding participants due to missing datapoints four participants who had tried cannabis at baseline remained in the sample. Of these, three fell into the EOS group and one into the LOS group. As smoking cannabis often also involves use of tobacco, analyses were carried out with and without the inclusion of variables measuring cannabis use. The results with and without the inclusion of cannabis use as a predictor varied only very slightly, and all discrepancies are reported in Appendix B.

3.3. Results

The unimodal neuroimaging models only reached significance for the prediction of LOS compared to NS, with 57 significant predictors of which 6 were also seen in the multimodal model. Classification for the unimodal psychometric and for the multimodal models was significant for all

group comparisons (see Table 3.3, Appendix B.1 for models without cannabis predictors). Recall (the rate of correctly classified smokers) was above two thirds for all unimodal psychometric and multimodal analyses (see Figure 3.1).

Based on inspection of the number of features that passed the predictor significance threshold in all null models and actual models (mean .04% for null models and mean 2.7% for actual models) the approximate false discovery rate was ~1.5%. For both psychometric and neuroimaging data the predictors that were significant followed a similar pattern in the unimodal and multimodal models (see Table 3.4) and in the models with and without cannabis predictors (see Appendix B.2). For the models comparing NS and EOS no predictors survived the comparison with the null models, despite good performance of the models. For analyses excluding cannabis predictors there were significant psychometric predictors of EOS compared to NS, which are reported in Appendix B.4. The ten strongest predictors for each model are reported in Table 3.5 (see Appendix B.3 for analyses excluding cannabis predictors).

Table 3.3. Mean AUC and F1 score for all analyses

	Neuroimaging model		Psychometric model		Multimodal model	
	AUC	F1 score	AUC	F1 score	AUC	F1 score
EOS vs. NS	0.478	0.212	0.841**	0.485**	0.799**	0.461**
LOS vs. NS	0.557**	0.173**	0.715**	0.224**	0.706**	0.253**
EOS/LOS vs. NS	0.510	0.296	0.787**	0.489**	0.770**	0.491**
EOS vs. LOS	0.444	0.530	0.623**	0.590**	0.574*	0.567*

* p<.0005; **p<.00005

Table 3.4. Number of predictors of each type that were significant for each analysis

	Neuroimaging predictors	Psychometric predictors	
	Multimodal model	Multimodal model*	Unimodal model
EOS	0	0 (0)	0
LOS	8	15 (3)	27
EOS/LOS	3	80 (34)	34
EOS vs. LOS	26	59 (29)	34

**Number of psychometric predictors significant in both the unimodal psychometric and multimodal models in brackets*

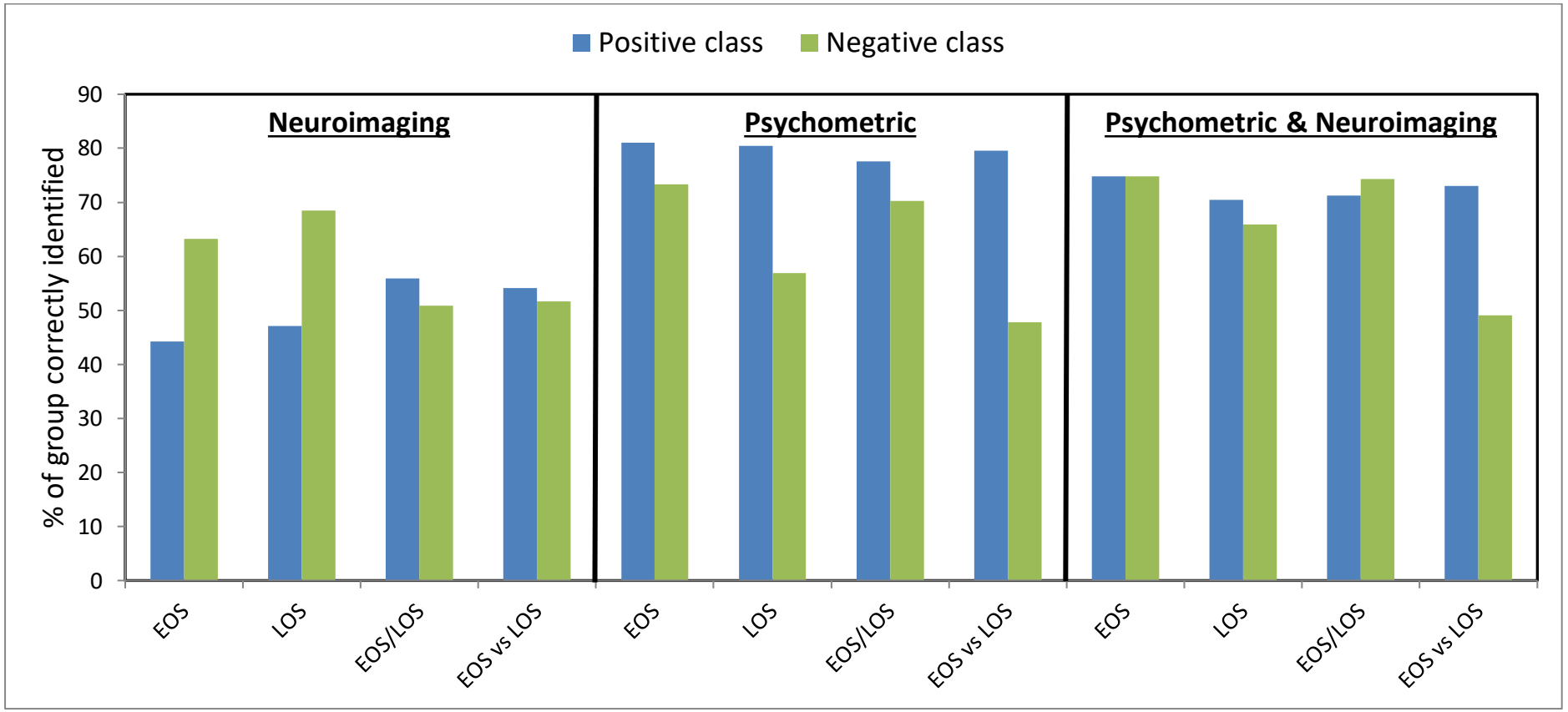

Figure 3.1. Recall (% of positive class correctly identified) and Specificity (% of negative class correctly identified) for all models. Positive class is the smoker group for analyses 'EOS', 'LOS', and 'EOS/LOS'. For analysis 'EOS vs LOS' positive class is LOS. EOS: Early-onset smokers; LOS: Late-onset smokers.

Table 3.5. Ten predictors with highest absolute regression weights for all significant models

	LOS	EOS/LOS	EOS vs. LOS
TCI-R			
Novelty-seeking	-	-	-.052
Disorderliness ('I am not very good at talking my way out of trouble when I am caught doing something wrong')	-	-	-.067
Exploratory excitability ('I am slower than most people to get excited about new ideas and activities')	-	-	-.049
DAWBA			
Parent: popularity	-	-	-.063
Parent: Recent deliberate self-harm	-	.030	-
Teacher: other psych. development concerns	-	-	.088
ADHD clinical rating	-.161	-	-
ADHD hyperactive-impulsive clinical rating	-.174	-	-
ESPAD			
Alcohol			
Lifetime drunkenness occasions	-	.031	-
Past month drunkenness occasions	-	.030	-
Cannabis			
First cannabis use	-	-.037	-
Lifetime cannabis use	-	.037	-
Past year cannabis use	-	.037	-
Past month cannabis use	-	.031	-
Past week cannabis use	-	.031	-
Inhalants			
Past year inhalant use	-	.028	-
Past month inhalant use	-	.055	-
Family variables			
Parent: 'Gets help and support when stressed'	.146	-	-
Parent lifetime cocaine use	-.126	-	-
Parent variables			
NEO-ffi parent: Neuroticism ('At times I have been so ashamed I just wanted to hide')	-	-	-.058
Neuroimaging variables			
GCA[1]: Heschl's gyrus, L	-.148	-	-
GCA[1]: Heschl's gyrus, R	-.123	-	-

GCA[1]: Superior temporal gyrus, L	-.143	-	-
GCA[1]: Rolandic operculum, L	-.133	-	-
SST (stop success): Cerebellum, R	-	-	.049
SST (stop failure): Amygdala, L	-.124	-	-
MID[1]: Medial orbitofrontal cortex, L	-	-	-.055
MID[1]: Inferior frontal gyrus, pars triangularis, L	-	-	-.051
MID[2]: Posterior cingulate cortex, L	-.135	-	-
Faces[1] : Posterior cingulate cortex, R	-	-	.058

The positive class for 'EOS', 'LOS', and 'EOS/LOS' is the smoker group and LOS for 'EOS vs. LOS'. GCA[1]: GCA auditory sentences; MID[1]: MID task anticipation of large win minus no win; MID[2]: MID task feedback large win minus small win; Faces[1]: Faces task, angry affective facial stimuli minus control stimuli.

3.3.1. Neuroimaging predictors

3.3.1.1. Grey matter volume

In the unimodal model only, lower volume in the right supramarginal gyrus predicted LOS compared to NS. LOS compared to EOS was predicted by lower volume in the left inferior parietal lobule in the multimodal model.

3.3.1.2. SST (see Table 3.6, Figure 3.2)

Stop success: In the unimodal model LOS compared to NS was predicted by higher activity in the right OFC. Higher activity in the orbital extension of the right MFG and SFG also predicted LOS compared to EOS in the multimodal model. LOS compared to EOS was also predicted by higher activity in the left calcarine fissure, cuneus, angular and lingual gyrus, superior occipital gyrus, and in the right cerebellum in the multimodal model.

Failed stopping: In both the unimodal and multimodal models LOS compared to NS was predicted by lower left amygdala activity. In the unimodal model only, LOS compared to NS was predicted by lower left superior temporal pole activity and higher left inferior occipital gyrus and right postcentral gyrus activity. Higher activity in the right paracentral lobule predicted EOS/LOS compared to NS in the multimodal model.

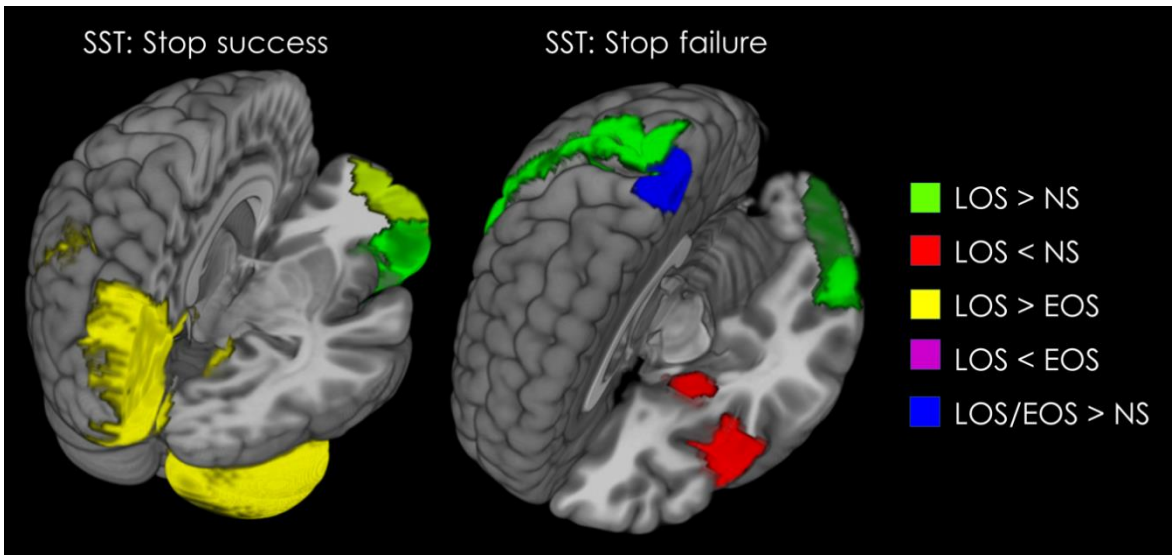

Figure 3.2. ROIs significantly predicting smoking status during successful and failed response inhibition in the SST.

Table 3.6. Significant neuroimaging predictors from the Stop Signal Task

Task contrast		LOS		EOS/LOS	LOS vs. EOS
		Unimodal	Multimodal	Multimodal	Multimodal
Failed stopping	Paracentral lobule, R			0.0092	
	Postcentral gyrus, R	0.0285			
	Amygdala, L	-0.0537	-0.1248		
	Superior temporal pole, L	-0.0282			
	Inferior occipital lobe, L	0.0337			
Stop success	Orbital extension of IFG, R	0.0292			
	Orbital extension of MFG, R	0.0404			0.0349
	Orbital extension of SFG, R	0.0367			0.0388
	Angular gyrus, L				0.0253
	Calcarine fissure, L				0.0288
	Cuneus, L				0.0373
	Lingual gyrus, L				0.0305
	Superior occipital lobe, L				0.0245
	Cerebellum, R				0.0491

3.3.1.3. MID task (see Table 3.7, Figure 3.3)

Anticipation of large vs. no win: In the unimodal model only, LOS compared to NS was predicted by lower activity in the right ACC, orbital extension of the MFG, superior temporal pole, and the vermis. Lower activity in the bilateral ACC and orbital extension of the MFG, left IFG pars triangularis and olfactory gyrus also predicted LOS compared to EOS in the multimodal model.

Anticipation of large vs. small win: In the unimodal model only, LOS compared to NS was predicted by lower activity in the left ACC, orbital extension of the MFG and medial SFG.

Feedback for large vs. no win: In the unimodal model only, LOS compared to NS was predicted by higher activity in the left paracentral lobule. Higher activity in this region also predicted EOS/LOS compared to NS in the multimodal model. In the unimodal model higher activity in the bilateral caudate and anterior and middle cingulum, and lower activity in the left PCC and bilateral middle temporal gyrus predicted LOS compared to NS. Further predictors of LOS compared to NS in the unimodal model were higher activity in the left medial SFG, right SFG, right paracentral lobule and bilateral SMA, and lower activity in the left calcarine fissure and Heschl's gyrus.

Feedback for large vs. small win: In both the unimodal and multimodal models LOS compared to NS was predicted by lower bilateral PCC activity. In the unimodal model, LOS compared to NS was also predicted by lower activity in the left SMA and higher activity in the right ACC, right inferior occipital gyrus, and the vermis. Higher activity in the vermis and left orbital extension of the MFG also predicted LOS compared to EOS in the multimodal model.

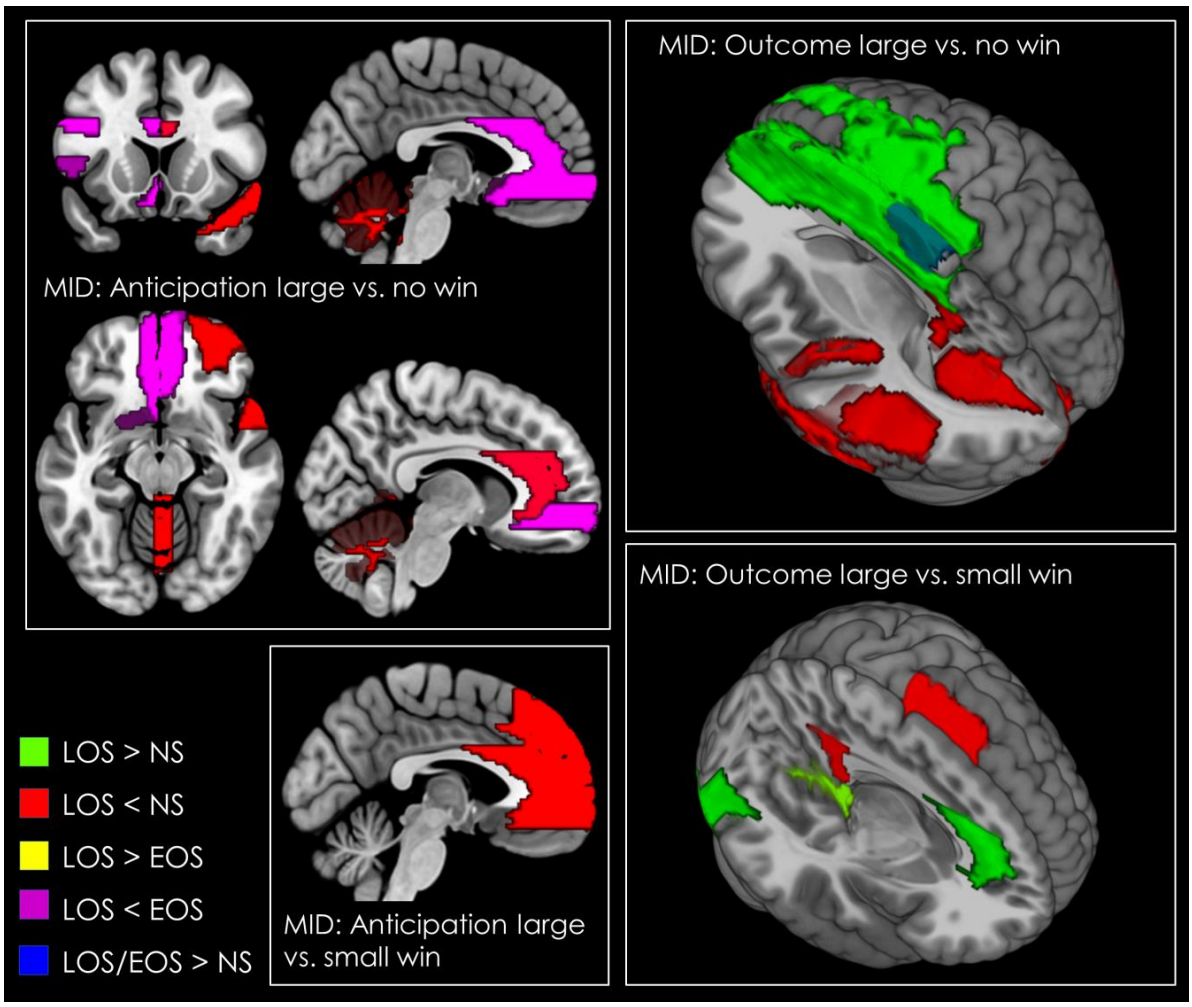

Figure 3.3. ROIs significantly predicting smoking status during anticipation and feedback for large compared to small reward and large compared to no reward in the MID task.

Table 3.7. Significant neuroimaging predictors from the Monetary Incentive Delay Task

Task contrast		LOS		EOS/LOS	LOS vs. EOS
		Unimodal	Multimodal	Multimodal	Multimodal
Anticipation: Large win vs. no win	Medial OFC, L				-0.0553
	Medial OFC, R				-0.0397
	Olfactory gyrus, L				-0.0299
	Orbital extension of the MFG, R	-0.0286			
	IFG, pars triangularis, L				-0.0512
	Anterior cingulate, L				-0.0337
	Anterior cingulate, R	-0.0276			-0.0332
	Superior temporal pole, R	-0.0262			
	Vermis	-0.0352			
Anticipation: Large win vs. small win	Medial SFG, L	-0.0281			
	Medial OFC, L	-0.0303			
	Anterior cingulate, L	-0.0365			
Feedback: Large win vs. no win	Medial SFG, L	0.0268			
	SFG, R	0.0330			
	Paracentral lobule, L	0.0318		0.0116	
	Paracentral lobule, R	0.0421			
	SMA, L	0.0318			
	SMA, R	0.0337			
	Anterior cingulate, L	0.0289			
	Anterior cingulate, R	0.0284			
	Middle cingulate, L	0.0258			
	Middle cingulate, R	0.0258			
	Posterior cingulate, L	-0.0300			
	Caudate, L	0.0311			
	Caudate, R	0.0368			
	Heschl's gyrus, L	-0.0260			
	Middle temporal gyrus, L	-0.0472			
	Middle temporal gyrus, R	-0.0328			
	Calcarine fissure, L	-0.0263			
Feedback: Large win vs. small win	Orbital extension of the MFG, L				-0.0236
	SMA, L	-0.0262			
	Anterior cingulate, R	0.0270			
	Posterior cingulate, L	-0.0444	-0.1359		
	Posterior cingulate, R	-0.0414	-0.1074		
	Inferior occipital lobe, R	0.0282			
	Vermis	0.0711			0.0397

3.3.1.4. Faces task (see Table 3.8, Figure 3.4)

Neutral faces vs. control: In the unimodal model only, LOS compared to NS was predicted by higher activity in the right PCC and left orbital extension of the SFG, and lower activity in the left inferior temporal gyrus.

Angry faces vs. control: In the unimodal model only, LOS compared to NS was predicted by higher activity in the right PCC. Higher activity in the bilateral PCC also predicted LOS compared to EOS in the multimodal model. In the unimodal model, LOS compared to NS was also predicted by higher activity in the right caudate and ventral striatum, and in the left gyrus rectus, and by lower activity in the left inferior parietal lobule and postcentral gyrus. LOS compared to EOS was predicted by lower activity in the left middle and superior temporal pole and middle temporal gyrus in the multimodal model.

Angry vs. neutral faces: In the unimodal model only, LOS compared to NS was predicted by lower activity in the right orbital extension of the SFG, and higher activity in the right ventral striatum, right middle occipital gyrus, bilateral parahippocampal gyri and right hippocampus. Higher activity in the left parahippocampal gyrus also predicted EOS/LOS compared to NS in the multimodal model.

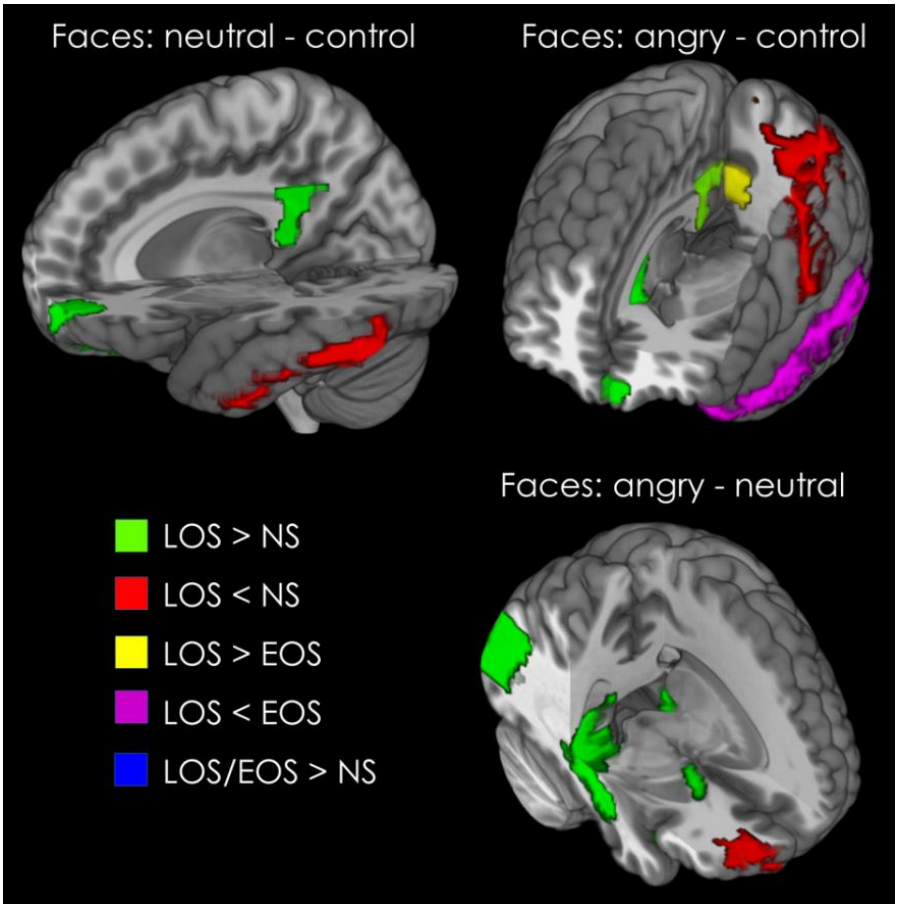

Figure 3.4. ROIs significantly predicting smoking status during the affective face viewing paradigm for affectively neutral or angry faces compared to control stimuli or for angry compared to neutral face stimuli.

Table 3.8. Significant neuroimaging predictors from the Affective Face processing Task

Task contrast		LOS		EOS/LOS	LOS vs. EOS
		Unimodal	Multimodal	Multimodal	Multimodal
Neutral faces vs. control stimuli	Posterior cingulate, R	0.0259			
	Orbital extension of the SFG, L	0.0263			
	Inferior temporal gyrus, L	-0.0253			
Angry faces vs. control stimuli	Posterior cingulate, L				0.0291
	Posterior cingulate, R	0.0292			0.0586
	Inferior parietal lobule, L	-0.0306			
	Postcentral gyrus, L	-0.0274			
	Caudate, R	0.0252			
	Gyrus rectus, L	0.0256			
	Ventral striatum, R	0.0269			
	Middle temporal gyrus, L				-0.0350
	Middle temporal pole, L				-0.0296
	Superior temporal pole, L				-0.0261
Angry faces vs. neutral faces	Orbital extension of the SFG, R	-0.0299			
	Hippocampus, R	0.0304			
	Middle occipital lobe, R	0.0364			
	Parahippocampal gyrus, L	0.0394			
	Parahippocampal gyrus, R	0.0485			
	Ventral striatum, R	0.0291			

3.3.1.5. GCA task (see Table 3.9, Figure 3.5)

Visual math: Activity in the insula was a significant predictor of LOS compared to NS in both the unimodal and multimodal models, but the direction of the effect differed such that lower left insula activity was predictive of LOS in the multimodal model, and higher bilateral insula activity was predictive of LOS in the unimodal model. In the unimodal model, higher activity in the right caudate and putamen also predicted LOS compared to NS. In the multimodal model differentiating smoking trajectories higher right putamen activity also predicted LOS compared to EOS.

Listening to sentences: In both the unimodal and multimodal models LOS compared to NS was predicted by lower activity in left Heschl's gyrus and the superior temporal gyrus. Lower activity in the right Heschl's gyrus and left Rolandic operculum were predictive of LOS compared to

NS in the multimodal model only. In the unimodal model higher activity in the left inferior occipital gyrus and lower activity in the right parahippocampal gyrus also predicted LOS compared to NS. LOS compared to EOS was predicted by lower activity in the left precentral gyrus in the multimodal model.

Reading sentences: In the unimodal model only, lower activity in the right olfactory and supramarginal gyri predicted LOS compared to NS. Lower activity in the right inferior parietal lobule and left orbital extension of the MFG predicted LOS compared to EOS in the multimodal model.

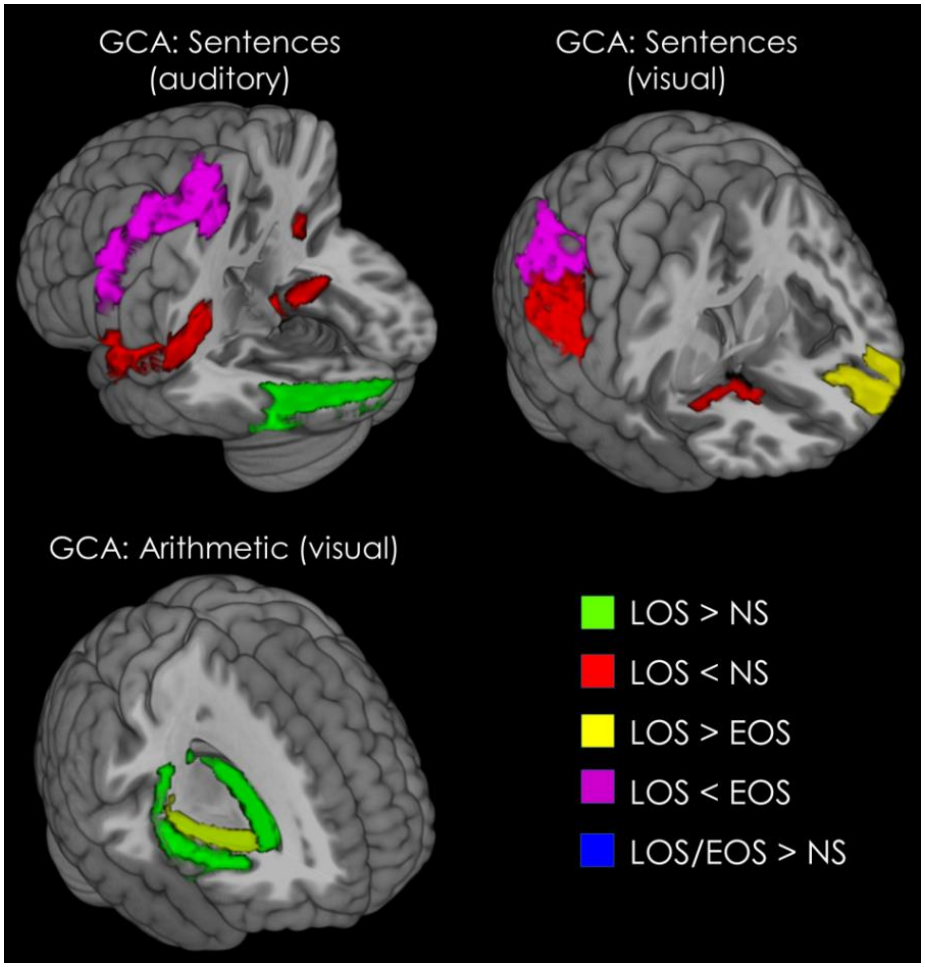

Figure 3.5. ROIs significantly predicting smoking status during visual and auditory presentation of sentences and visual presentation of mathematical stimuli during the GCA task.

Table 3.9. Significant neuroimaging predictors from the Global Cognitive Assessment Task

Task contrast			LOS		EOS/LOS	LOS vs. EOS
			Unimodal	Multimodal	Multimodal	Multimodal
Listening to sentences	Precentral gyrus, L					-0.0296
	Parahippocampal gyrus, R	-0.0270				
	Rolandic operculum, L		-0.1337			
	Heschl's gyrus, L	-0.0261	-0.1486			
	Heschl's gyrus, R		-0.1237			
	Superior temporal gyrus, L	-0.0259	-0.1430			
	Inferior occipital lobe, L	0.0328				
Reading sentences	Olfactory gyrus, R	-0.0264				
	Orbital extension of the MFG, L					0.0250
	Inferior Parietal lobule, R					-0.0270
	Supramarginal gyrus, R	-0.0276				
Visual arithmetic	Insula, L	0.0281	-0.1077			
	Insula, R	0.0256				
	Caudate, R	0.0292				
	Putamen, R	0.0293				0.0262

3.3.2. Substance use (ESPAD) (Appendix C.1)

3.3.2.1. Alcohol

EOS/LOS compared to NS was predicted by higher alcohol use in the unimodal and multimodal models. This included higher lifetime, past year, and past month drunkenness occasions, higher level of drunkenness at the last drunkenness occasion, and earlier first occasion of being drunk and of drinking spirits. In the multimodal model EOS/LOS compared to NS was also predicted by higher lifetime bingeing occasions, and by higher lifetime and past year drinking occasions.

Earlier first occasion of drinking wine predicted LOS compared to NS in the unimodal model and EOS/LOS compared to NS in the multimodal model. Higher number of drinks typically consumed when drinking predicted LOS compared to NS in the unimodal model and EOS/LOS compared to NS in the unimodal and multimodal models.

3.3.2.2. Cannabis

EOS/LOS compared to NS was predicted by earlier first use of cannabis and higher lifetime and past year cannabis use in the unimodal and multimodal models. In the multimodal model higher past month and past week cannabis use also predicted EOS/LOS compared to NS.

3.3.2.3. Drugs of abuse

Ever having heard of 'Coke', 'Heroin', 'MDMA', or 'Narcotics' predicted EOS compared to LOS in the multimodal model. However, self-report of ever having wanted to try any drugs of abuse predicted EOS/LOS compared to NS in the multimodal model.

Ever having heard of Inhalants predicted NS compared to LOS in the unimodal model and EOS compared to LOS in the unimodal and multimodal models. Past year and past month inhalant use predicted EOS/LOS compared to NS in the multimodal model. While inspection of the data revealed that participants in all groups had used inhalants in the past year, past month use was reported by only one participant each from the two smoker groups.

3.3.3. Personality (Appendix C.2)

In the multimodal model EOS/LOS compared to NS was predicted by parents describing their child as 'lively'.

3.3.3.1. TCI-R

Novelty-seeking: In both the unimodal and multimodal models higher scores on the TCI novelty-seeking scale predicted EOS/LOS compared to NS, and EOS compared to LOS. No effect for LOS compared to NS was observed. As novelty-seeking was one of the strongest predictors of EOS compared to LOS and is widely used in the literature a series of two-sample t-test were carried out to further evaluate this effect. Inspection of the data revealed that the EOS group had significantly higher values for novelty-seeking than the NS group (p=10*10^-12, t=6.96) and the LOS group (p=.0019, t=3.19), but the NS and LOS groups did not significantly differ (p=.0255, t=2.24).

Disorderliness: Higher scores on the disorderliness subscale of the TCI novelty-seeking scale predicted EOS/LOS compared to NS and EOS compared to LOS in unimodal and multimodal models. In both models, endorsement of the item 'I often break rules and regulations when I think I can get away with it' predicted EOS/LOS compared to NS, and in the multimodal model endorsement of the item 'I am not very good at talking my way out of trouble when I am caught doing something wrong' predicted NS compared to EOS/LOS. This latter item also predicted LOS compared to NS in the unimodal and multimodal models. In the multimodal model endorsement of the item 'I can usually do a good job of stretching the truth to tell a funnier story or to play a joke on someone'

and disagreement with the item 'Even when most people feel it is not important, I often insist on things being done in a strict and orderly way' also predicted EOS compared to LOS.

Exploratory excitability: In both the unimodal and multimodal models LOS compared to EOS was predicted by lower scores on the exploratory excitability scale, and endorsement of the item 'I am slower than most people to get excited about new ideas and activities'. In the multimodal model LOS compared to EOS was also predicted by endorsement of the item 'I conversations I am much better as a listener than as a talker'.

Extravagance: EOS/LOS compared to NS was predicted by higher scores on the extravagance scale, lower endorsement of the item 'I am better at saving money than most people', and higher endorsement of the item 'Because I so often spend too much money on impulse, it is hard for me to save money - even for special plans like a vacation' in the unimodal and multimodal models. Endorsement of the latter item also predicted LOS compared to NS in the unimodal model. In the multimodal model EOS/LOS compared to NS was also predicted by endorsement of the item 'I often spend money until I run out of cash or get into debt from using too much credit' and disagreement with the items 'I enjoy saving money more than spending it on entertainment or thrills' and 'Some people think I am too stingy or tight with my money'. LOS compared to EOS was predicted by endorsement of the item 'I am much more reserved and controlled than most people' and disagreement with the item 'It is fun for me to buy things for myself' in the multimodal model.

Impulsiveness: LOS compared to EOS was predicted by endorsement of the TCI impulsiveness subscale item 'I like to think about things for a long time before I make a decision' in the multimodal model.

3.3.3.2. NEO-ffi

Agreeableness: Lower scores on the NEO-ffi agreeableness scale predicted LOS compared to NS in the unimodal model and LOS compared to EOS in the unimodal and multimodal models. LOS compared to NS was also predicted in the unimodal model by lower parent-reported politeness in the DAWBA, and by lower endorsement of the NEO-ffi agreeableness item 'I try to be courteous to everyone I meet' and higher endorsement of the items 'If I don't like people, I let them know it' and 'If necessary, I am willing to manipulate people to get what I want'. EOS/LOS compared to NS was predicted by lower endorsement of the NEO-ffi item 'I generally try to be thoughtful and considerate' in the multimodal model.

Conscientiousness: EOS/LOS compared to NS was predicted by lower scores on the conscientiousness scale of the NEO-ffi and by lower endorsement of the following items in the

unimodal and multimodal models: 'I work hard to accomplish my goals', 'I am a productive person who always gets the job done', and 'I strive for excellence in everything I do'. In the multimodal model EOS/LOS compared to NS was also predicted by endorsement of the item 'I never seem to be able to get organized'. Parents' characterization of their child as 'Keen to learn' and 'Does homework without reminding' also predicted NS rather than EOS/LOS in the multimodal model. However, parents characterizing their child as taking care of their appearance predicted LOS compared to NS in the multimodal model.

Neuroticism: EOS compared to LOS was predicted by endorsement of the NEO-ffi neuroticism scale item 'I often feel helpless and want someone else to solve my problems' and disagreement with the item 'I am seldom sad or depressed' in the multimodal model.

Openness: In both the unimodal and multimodal model endorsement of the NEO-ffi openness scale item 'I am intrigued by pattern I find in art and nature' predicted EOS compared to LOS. Endorsement of the item 'I often try new and foreign foods' predicted EOS/LOS compared to NS in the multimodal model, while endorsement of the item 'I have a lot of intellectual curiosity' predicted LOS compared to EOS in the multimodal model.

3.3.3.3. SURPS

Sensation seeking: Summary scores for the SUPRS sensation seeking scale and endorsement of the item 'I would like to learn how to drive a motorcycle' predicted EOS/LOS compared to NS in the unimodal and multimodal models. Endorsement of the item 'I would like to skydive' predicted LOS compared to NS in the unimodal model and EOS/LOS compared to NS in the multimodal model. Endorsement of the item 'I enjoy new and exciting experiences even if they are unconventional' predicted EOS/LOS compared to NS in the multimodal model. Endorsement of the item 'I am interested in experience for its own sake even if it is illegal' predicted EOS/LOS compared to NS in the multimodal model, EOS compared to LOS in the unimodal and multimodal models.

Impulsiveness: EOS/LOS compared to NS was predicted by scores on the SURPS impulsiveness scale in the multimodal model.

Anxiety sensitivity: LOS compared to EOS was predicted by lower scores on the anxiety sensitivity scale of the SURPS in the unimodal and multimodal models. In the multimodal model LOS compared to EOS was also predicted by lower endorsement of the items 'I get scared when I'm too nervous' and 'I get scared when I experience unusual body sensations'. LOS compared to NS was also predicted by lower endorsement of the latter item in the unimodal model.

3.3.3. Life history (LEQ) (Appendix C.3)

The number of participants from each group who endorsed each of the significant LEQ predictors (for occurrence in the past year or lifetime), or rated the emotional valence of an event as neutral or positive are shown in table 3.10.

NS compared to LOS was predicted by adolescents reporting on the LEQ that they had ever 'found religion' in the multimodal model.

Table 3.10. Number of participants from each group who endorsed significant LEQ predictors

	NS (%)	EOS (%)	LOS (%)
Ever 'found religion'	168 (36.84)	21 (35.59)	7 (21.21)
Valence: family member accident/injury*	17 (3.72)	1 (1.69)	3 (9.09)
Valence: self accident/injury*	12 (2.63)	3 (5.08)	5 (15.15)
Ever: self accident/injury	63 (13.81)	9 (15.25)	10 (30.30)
Past year: Death in family	94 (20.61)	23 (38.98)	7 (21.21)
Ever: started going out with a boy/ girlfriend	193 (42.32)	39 (66.10)	26 (78.78)
Ever: broke up with with a boy/ girlfriend	147 (32.23)	32 (54.23)	23 (69.69)
Past year: started going out with a boy/ girlfriend	117 (25.65)	28 (47.45)	22 (66.66)
Past year: broke up with with a boy/ girlfriend	82 (17.98)	18 (30.50)	19 (57.57)
Valence: 'stole something valuable'*	106 (23.24)	11 (18.64)	15 (45.45)
Past year: Parent changed jobs	83 (18.20)	18 (30.50)	10 (30.30)
Valence: Parent changed jobs*	435 (95.39)	58 (98.30)	29 (87.87)
Past year: Parent remarried	2 (0.43)	0 (0.00)	2 (6.06)

**Figures for valence items refer to the number of participants who rated their feelings about the item as 'neutral', 'happy', or 'very happy'. Remaining participants rated their reponse as 'unhappy' or 'very unhappy'.*

3.3.3.1. Accident scale

LOS compared to EOS was predicted by more positive reported valence for the idea of a family member or the adolescent themselves sustaining a serious injury or being involved in a serious accident in both the unimodal and multimodal models. Valence of sustaining a serious injury or accident themselves also predicted LOS compared to NS in all models. Examination of the data revealed that a larger portion of the LOS group than in the other groups had selected that their emotional response to these events would be 'neutral' rather than negative. Ever having

sustained a serious accident or injury predicted LOS compared to EOS in the multimodal models and LOS compared to NS in the unimodal model.

Having experienced a death in the family in the past year predicted EOS/LOS compared to NS in the multimodal model.

3.3.3.2. Sexual and romantic experience scale

Summary scores on the sexuality scale of the LEQ for the past year predicted LOS compared to NS in the unimodal model and EOS/LOS compared to NS in the unimodal and multimodal models. The summary score for lifetime occurrence of items in this scale predicted EOS/LOS compared to NS in the multimodal model.

Having ever started going out with a boyfriend or girlfriend and ever having broken up predicted LOS compared to NS on the unimodal model and EOS/LOS compared to NS in the multimodal model. Having started going out with a boyfriend or girlfriend in the past year predicted LOS compared to NS in the unimodal model and EOS/LOS compared to NS in the unimodal and multimodal models. Having broken up with a boyfriend or girlfriend in the past year predicted LOS compared to NS in the unimodal model, EOS/LOS compared to NS in the multimodal model and LOS compared to EOS in the unimodal and multimodal models.

3.3.3.3. Deviance scale

Positive reported valence for the item 'stole something valuable' predicted LOS compared to EOS in the multimodal model. Valence for the item 'got in trouble at school' predicted EOS/LOS compared to NS in the multimodal model and LOS compared to NS in the unimodal model.

3.3.3.4. Relocation scale

Self-report that a parent changed jobs in the past year predicted EOS/LOS compared to NS in the multimodal model. More positive reported valence associated with the idea of a parent changing jobs predicted EOS compared to LOS in the unimodal and multimodal models.

3.3.4. Demographic measures

EOS/LOS compared to NS was predicted by lower self-reported academic performance in the past term in the unimodal and multimodal models. Self-report of ever having gotten poor grades in school predicted EOS compared to LOS in the multimodal model.

3.3.5. Behaviour and psychopathology (Appendix C.4)

The number of participants from each group who endorsed each of the significant DAWBA items relating to maladaptive behaviour or psychiatric symptoms is reported in table 3.11. This

includes only items that had binary 'Yes'/'No' response options or response options in the form of 'None'/'Somewhat'/'A lot' when referring to the presence of behaviours or symptoms.

Table 3.11. Number of participants from each group to whom significant DAWBA predictors applied

	NS (n=456)	EOS (n=59)	LOS (n=33)
Teacher expressed concerns about psychological development	13	1	3
Any report of 'I took part in bullying another student/ peer at school'	63	13	3
Any report of 'I hit, kicked, pushed, shoved around, or locked a student/ peer indoors.'	31	4	6
Any parent-report of past year lying	100	28	11
Any parent-report of past year staying out late	70	27	7
Any parent-report of often lying or cheating	116	32	13
Any parent-report of past year ignoring rules/ disobedience	57	20	5
Any parent-report of past year truancy	18	11	1
Any parent-report of past year starting fights	30	13	2
Any parent-report of past year starting stealing	28	10	1
Parent-reported past month sadness	119	30	7
Parent-report of recent deliberate self-harm	1	3	0
Parent-report of any deliberate self-harm	23	10	2
Computer prediction for separation anxiety (DSM-IV)	34	5	0
Parent-report of self-blame for overeating	40	7	1

LOS compared to EOS was predicted by parent-report that a teacher had expressed concerns about the child's psychological development that did not fall under the areas assessed by the DAWBA (phobias, anxiety disorders, mood disorders, ADHD, conduct disorders, eating disorders, tics) in the unimodal and multimodal models.

3.3.5.1. Antisocial behaviour and peer relationships

In both the unimodal and multimodal models EOS compared to LOS was predicted by computer predictions of conduct disorder based on self-report, and self-report of having taken part in bullying another student or peer. In the unimodal model EOS compared to LOS was also

predicted by self-report of having 'hit, kicked, pushed, showed around, or locked up a student/ peer indoors'.

In the multimodal and unimodal models EOS/LOS compared to NS was also predicted by computer predictions of conduct disorder based on parent report, and parent-report of staying out late and lying in the past year, as well as often lying or cheating. In the multimodal model EOS/LOS compared to NS was also predicted by parent-report of ignoring rules or being disobedient, lying, truancy, and starting fights in the past year. Self-reported truancy in the past month predicted EOS compared to LOS in the unimodal and multimodal models. LOS compared to NS was predicted by lower parent-report of stealing in the past year in the multimodal model.

The summary score for parent-reported peer problems on the SDQ predicted NS compared to EOS/LOS in the unimodal and multimodal models. Parent-report that the child 'related better to adults than peers' also predicted NS compared to EOS/LOS in the multimodal model. Parent-report that the child is popular predicted EOS compared to LOS in the unimodal and multimodal models. Self-report that they had ever 'found a new group of friends' predicted adolescents being NS compared to LOS in the unimodal model and EOS compared to LOS in the multimodal model.

3.3.5.2. Depression (DAWBA)

EOS compared to LOS was predicted by parent report of the child being sad in the past month. Any future smoking compared to NS was predicted by reports of the child recently or ever having engaged in deliberate self-harm.

3.3.5.3. ADHD (DAWBA)

In the multimodal model LOS compared to NS was predicted by lower clinical ratings for ADHD overall and for ADHD hyperactive-impulsive type symptoms.

3.3.5.4. Eating disorder symptoms (DAWBA)

In the unimodal model EOS compared to LOS was predicted by parent-report of the adolescent blaming themselves a lot for overeating.

3.3.6. Cognitive and behavioural measures

During the PALP, any future smoking was predicted by more omission errors during the third block using positive reinforcement for selection of correct numbers and avoidance of incorrect numbers in the multimodal model. LOS compared to EOS was predicted by more omission errors under the same reinforcement scheme in the second block in the multimodal model.

3.3.7. Parents and family environment

3.3.7.1. Family situation (Appendix C.4)

3.3.7.1.1. Broken home indicators. LOS compared to EOS was predicted by living with the biological father and with just one family rather than between homes or in alternative arrangements in the unimodal and multimodal models. In the unimodal model LOS compared to EOS was also predicted by not living with a stepfather. Compared to NS, LOS was also predicted by a parent having remarried in the past year, in both the unimodal and multimodal models.

3.3.7.1.2. Parenting. Parent-report that the child 'gets help and support when stressed' predicted LOS compared to NS in the unimodal and multimodal models, and predicted LOS compared to EOS in the unimodal model. Parent report that the child often 'gets blamed unfairly' by family members was predictive of EOS rather than LOS in the unimodal and multimodal models, and having consistently applied rules predicted LOS compared to EOS in the multimodal model and in the unimodal model when cannabis predictors were excluded.

3.3.7.1.3. Family relationships. Parent-report that the child likes being involved in family activities predicted NS compared to EOS/LOS in the multimodal model. However, self-report of having been bullied by a family member also predicted NS when compared to LOS in the multimodal model.

Computer predictions indicating the presence of separation anxiety based on self-reported symptoms predicted EOS compared to LOS in the unimodal and multimodal models.

3.3.7.1.4. Family life. In the model comparing EOS and LOS, EOS was predicted by self-report that the family had ever had money problems in the unimodal model, while LOS was predicted having gotten an own TV or computer in the past year in both the unimodal and multimodal models. However, in the same comparison parent-report of the financial difficulties being a family stressor predicted LOS compared to EOS in the multimodal model.

Parent report of family stress due to the neighbourhood or the neighbours predicted EOS compared to LOS in the multimodal model.

Parent report that their partner was stressed predicted LOS compared to EOS in the multimodal model, and report that the partner had shown a loss of interest in usually enjoyable activities predicted LOS compared to NS in the unimodal model and LOS compared to EOS in the unimodal and multimodal models.

3.3.7.2. Parent NEO-ffi (Appendix C.5)

Agreeableness: LOS compared to EOS was predicted by lower parent endorsement of the NEO-ffi agreeableness scale item 'I would rather cooperate with others than compete with them' in the multimodal model. EOS/LOS compared to NS was predicted by higher parental endorsement of the item 'Often, people aren't as nice as they seem to be' in the multimodal model.

Extraversion: LOS compared to EOS was predicted by parental endorsement of the NEO-ffi extraversion scale item 'I often feel as if I'm bursting with energy' in the multimodal model.

Neuroticism: Parental endorsement of the NEO-ffi neuroticism scale item 'at times I have been so ashamed I just wanted to hide' predicted EOS compared to LOS in the unimodal and multimodal models. In the multimodal model EOS compared to LOS was predicted by higher parental indication of feeling 'very sad, miserable, unhappy or tearful' in the previous 4 weeks.

3.3.7.3. Parent TCI-R (Appendix C.5)

Extravagance: EOS compared to LOS was predicted by parent endorsement of the TCI extravagance subscale item 'It is fun for me to buy things for myself' in the multimodal model.

Impulsiveness: LOS compared to EOS was predicted in both the unimodal and multimodal models by parental endorsement of the TCI impulsiveness subscale item 'I usually think about all the facts in detail before I make a decision'.

3.3.7.4. Parent SURPS (Appendix C.5)

In the multimodal model parental endorsement of the SUPRS item 'I often don't think things through before I speak' predicted EOS/LOS compared to NS.

3.3.7.5. Parent substance use (Appendix C.5)

Alcohol: Adolescent report that a parent had ever abused alcohol, and parent report that a member of the family had ever complained or worried about their drinking predicted LOS compared to NS in the multimodal model. Higher parent self-reported quantity of drinks consumed when drinking predicted EOS compared to LOS in both the unimodal and multimodal models.

Smoking: Parental smoking in the past month predicted LOS compared to NS in the unimodal model and EOS/LOS compared to NS in the multimodal model.

Higher current maternal smoking occasions and higher daily smoking predicted LOS compared to NS in the unimodal model. EOS/LOS compared to NS was predicted by higher maternal occasions of smoking, the mother ever having regularly smoked, and earlier maternal smoking initiation in the multimodal model. In the unimodal and multimodal models EOS/LOS

compared to NS was predicted by higher frequency of cigarettes smoked daily, more smoking occasions in the year before pregnancy, and higher daily smoking in the year before pregnancy.

Cocaine: In the multimodal model NS compared to LOS was predicted by parent-report of ever having used cocaine, lifetime use occasions, and self-report of being able to stop using or refrain from using cocaine. Inspection of the data revealed that parents of 15 participants in the NS group and of four participants in the EOS group had reported ever using cocaine.

3.3.7.6. Prenatal factors (Appendix C.5)

EOS/LOS compared to NS was predicted by the mother having been exposed to second-hand smoke at a later stage of pregnancy in the multimodal model.

LOS compared to EOS was predicted by the mother having been given leave from work because of her pregnancy in the unimodal and multimodal models.

3.4. Discussion

In this study, a machine learning algorithm capable of classifying groups based on a large number of variables was used to predict future smoking behaviour in adolescents, and to identify risk profiles for different adolescent smoking trajectories. Structural and functional neuroimaging data, personality, life history, psychopathology, behavioural factors, family environment, and parental predictors of future smoking onset were identified. The findings in this study show that neuroimaging data can be used as an indicator of risk for smoking behaviour at age 18 but show little utility for prediction of earlier smoking onset. A general risk profile for future smoking in adolescents was identified, as well as distinct risk profiles for adolescents who start smoking before or after age 16. Any future smoking was predicted by variables such as alcohol use, novelty seeking, and life stressors. Adolescents who self-reported antisocial behaviour and unstable family environments were more likely to commence smoking in the next two years, while initiating smoking more than two years later was predicted by brain activity in reward and inhibitory control networks, and by atypical affective processing and processing of auditory language stimuli.

Anxiety sensitivity distinguished between those likely to take up smoking at an earlier age compared to later in adolescence. This heightened negative reaction to unusual or unexpected physiological sensation was previously identified by Hirschman and colleagues (1984) as a possible factor differentiating adolescents who smoke because of external influences such as peer pressure from those who smoke due to factors such as mood-related effects of smoking. In this study, those who remained non-smokers and those who took up smoking at an earlier age had higher anxiety sensitivity. In line with the hypothesis put forward by Hirschmann and colleagues (1984) it is possible that early-onset smokers simply had a more positive experience when first smoking than

individuals with equal levels of anxiety sensitivity who did not take up regular smoking, or that their smoking behaviour was motivated more by external factors than by the physiological sensation of smoking. Those who became late-onset smokers, in contrast, are likely to represent a population for which the physiological sensations associated with cigarette smoking are a strong reason to engage in smoking behaviour.

A further factor differentiating early-onset smokers from late-onset smokers was higher parent-report of the child being sad or depressed in the past month at baseline. Self-report of 'often feeling helpless' and sad or depressed also predicted falling into the early- rather than the late-onset smoking trajectory. These variables specifically distinguished individuals as likely to have earlier onset of smoking behaviour, but parent-report of any deliberate self-harm was a strong predictor of any future smoking. While the link between depressive symptoms and smoking behaviour is not well understood, there is evidence that major depression is associated with progression to regular smoking (Breslau et al., 1998; Rohde et al., 2004), and that smokers with depressive symptoms are more likely to smoke to reduce negative affect (Lerman et al., 1996). A possible interpretation of this finding is that the presence of depressive symptoms plays a role in the progression to regular smoking behaviour. Based on the differences in depressive symptoms between smoking trajectories, depressiveness may play a larger role in early smoking onset than late smoking onset or be an acute risk factor for prompt onset of smoking behaviour. However, an important consideration given the findings of this study is that rather than depressiveness playing a role in the causation of smoking behaviour, deliberate self-harming behaviour may share an etiological pathway with smoking. While reasons for adolescent self-harm are varied (Scoliers et al., 2009), the presence of various possible life stressors as predictors of early-onset smoking in this study points toward the possibility that both self-harming behaviour and smoking arise as a result of life history and environmental stressors. Having recently experienced a death in the family predicted early-onset smoking. Any future smoking was also predicted by the frequency of recent notable life events in general as assessed by the LEQ, and specifically by a parent's recent change of jobs, and starting or ending romantic relationships. Life stressors are therefore an important predictor of becoming a smoker in the (near) future, and other stress-related maladaptive behaviours may emerge prior to smoking onset.

The pattern of results observed in this study suggests that many variables that predicted early-onset smoking may not have been indicators of earlier age of onset, but rather of sooner smoking onset. As such, many of the predictors specific to the early-onset smoking trajectory may be regarded as 'acute risk factors', while those specific to the late-onset trajectory can be thought of as 'long-term risk factors'. The higher prediction accuracy of a psychometric-only model for predicting early-onset than late-onset smoking can thus also be attributed to the temporal

dimension inherent in some of the measures employed at baseline in this study. Questions regarding events in the past year in the 'Life Events questionnaire', or recent psychopathology assessed using the DAWBA can be expected to have a larger effect size when predicting events in close temporal proximity. On the other hand, more stable environmental factors, such as family structure, are not subject to change with the passage of time in the same manner.

A set of predictors that can be characterized as 'broken home indicators', including whether the child lives in a traditional nuclear family environment with two biological parents rather than in other circumstances predicted early- compared to late-onset smoking. Broken home indicators have previously been linked to future adolescent smoking behaviour (Sieber & Angst, 1990; Covey & Tam, 1990; Tyas & Pederson, 1998; Ellickson et al., 2001). Becoming an early-onset smoker compared to a late-onset smoker was also predicted by lower levels of parent-support, which is consistent with previous research that found those adolescents who started smoking early and remained smokers to have lower levels of family support (Chassin et al., 2000). High parental support is a protective factor (Wills, Windle & Cleary, 1998). The importance of family relationships for smoking risk in adolescence was also underlined by any future smoking being predicted by parent-report that the child does not enjoy being involved in family activities. There was evidence in this study that various family stressors such as financial worries or increased stress and apathy in the parent's partner were associated with future smoking, but these factors will require further investigation.

Current parental (particularly maternal) smoking predicted any future smoking behaviour. While some studies have failed to find an effect of parent smoking on adolescent smoking and suggested that similarities in cigarette use between parents and children were likely to be accounted for by their genetic relatedness (Hirschman, Leventhal & Glynn, 1984; Boomsma et al., 1994), effects of parent smoking on adolescent smoking and substance use behaviour have been observed in several studies (Pederson, 1997; Mayhew et al., 2000; Tyas & Pederson, 1998; Wellman et al., 2018). Being exposed to smoking behaviour is likely to lead to a normalization of smoking and to reduce negative perceptions, thereby facilitating the initiation of smoking behaviour (Wellman et al., 2018; Cameron, 1972). Similarly, other substance use – particularly alcohol and cannabis – was strongly linked to future smoking in this and other studies (Audrain-McGovern et al., 2004a/b, 2009; Dinn et al., 2004; Rezvanfard et al., 2010). In this study parental alcohol use and self-reported curiosity about trying other drugs of abuse predicted smoking behaviour. Like environmental exposure to smoking, exposure to other substances may serve to reduce a sense of violation of social norms otherwise associated with smoking. Interestingly, falling into the late-onset smoking trajectory was predicted by lower exposure and awareness of illicit substances, which likely acts as a protective factor delaying onset of smoking behaviour. Late-onset

smoking was also predicted by problematic alcohol use by a parent, which may have acted as a deterrent to substance use.

Engaging in non-normative behaviours including substance use has been hypothesized to be linked to failure to succeed in normative patterns of behaviour (Kaplan, Martin & Robbins, 1984). Rebelliousness and low social conformity have been linked to elevated risk of smoking behaviour in adolescents across several studies (Pederson, 1997; Collins et al., 1987; Burt et al., 2000). As observed in many previous studies (Pederson, 1997; Audrain-McGovern et al., 2004a/b, 2009; Mayhew et al., 2000; Ellickson et al., 2001; Soldz & Cui, 2002; Wellman et al., 2018), low academic performance was predictive of future smoking. Additionally, more positive feelings about getting in trouble at school also predicted smoking, indicating low motivation to respect rules. A number of other self-reported statements indicating a high tolerance for deviant or even illegal behaviour also predicted smoking. In particular, short-term smoking risk was predicted by experiencing trouble with the law in the past year, and with reporting that illegality would not be a deterrent to engaging in behaviours for the sake of the sensation or experience. While measures of impulsive behaviour were predictive of all smoking in this study, novelty-seeking and antisocial behaviours were predictive specifically of early-onset smoking. This is a departure from previous studies using group-comparisons, in which novelty-seeking was found to be increased in early and late-onset adolescent smokers compared to non-smokers (Audrain-McGovern et al., 2004a; Dinn, Aycicegi & Harris, 2004), with no differences between different smoking groups (Audrain-McGovern et al., 2009). Both conduct disorder and high novelty-seeking in adolescence have been linked to young adult substance dependence (Palmer et al., 2013). Previous work in antisocial early-onset alcohol use disorder has identified that novelty-seeking appears to be associated with conduct disorder and antisocial behaviour rather than with substance use (Finn et al., 2002). This is consistent with the finding that novelty-seeking and antisocial behaviour appear to form a symptom cluster that is specific to the early-onset smoking trajectory. Novelty-seeking has also been linked to atypical reward processing and the dopamine system. Finn et al. (2002) suggested that novelty-seeking is associated with paying more attention to rewards, and research in individuals with Parkinson's disease has shown an effect of dopaminergic medication on novelty-seeking (Bodi et al., 2009). Furthermore, evidence of the functional basis of conduct disorder points to abnormalities in the orbitofrontal cortex and associated motivation networks (Rubia et al. 2009).

While novelty-seeking was more strongly associated with early-onset smoking, sensation-seeking showed a stronger effect for late-onset smoking. Sensation-seeking has previously been found not to be associated with conduct disorder, but with specific measures of pathological substance use such as binge drinking, with this relationship possibly being mediated by reward

response bias (Castellanos-Ryan, Rubia & Conrod, 2010). In this study, higher reward response bias in the passive avoidance learning paradigm predicted late-onset smoking. The fMRI predictors found for late-onset smoking during the MID task also point toward altered function of the frontostriatal reward pathway as signifying late-onset smoking risk. The frontostriatal reward pathway projects to the ventromedial PFC, including the ACC and OFC. These regions have been attributed a role in value attribution and value encoding (O'Doherty, 2004; Kable & Glimcher, 2009; Niv & Montague, 2009; Haber & Knutson, 2010; Chib et al., 2009), and reduced activity may reflect a disruption in the frontostriatal cortical network, and a deficit in the ability to generate outcome expectancies (Feil et al., 2010; Haber, 2016). Disruption of ACC and OFC activity is associated with impulsive responding (Volkow & Fowler, 2000). In this study, lower activity of the ACC, mPFC and OFC during anticipation of large compared to small and no reward predicted late-onset smoking compared to early-onset and non-smoking. Higher activity in these same areas during the outcome phase predicted late-onset smoking, which is in line with an account of higher sensitivity to rewards being a risk factor for addictive behaviours (Ersche et al., 2010; 2012; 2013a). During the outcome phase of the MID task, lower activity in the temporal cortex also predicted late-onset smoking. Activity in the middle temporal gyri is associated with cue-induced nicotine craving (Smolka et al., 2006), and reduced activity in this region may be an indicator of reduced valuation of natural reinforcers. A further pattern observed in the MID task was that late-onset smoking was predicted by increased activation in the paracentral lobule and SMA, and reduced activity of the posterior cingulate cortex (PCC, a node of the default-mode network) during reward outcomes, indicating increased activity of a task-positive attention network. This pattern was specific to the comparison of large rewards compared to no rewards, which reinforces a conclusion that higher attention paid to reward outcomes generally predicts late-onset smoking. Previous work has also found that during reward anticipation, functional connectivity of the nucleus accumbens with the paracentral lobule and SMA was increased in individuals with familial risk for alcoholism, and that this was associated with sensation-seeking (Weiland et al., 2013). Predictors assessing sensation-seeking, parent alcohol abuse and heightened activity in these regions for reward outcomes were all stronger for late- than early-onset smoking, making this cluster of predictors a possible target for future work identifying a high-risk phenotype specific to a late-adolescent onset smoking trajectory.

A facet of executive function that is closely related to reward sensitivity is inhibitory control. Late-onset compared to early-onset smoking was predicted by higher activity during successful response inhibition in the left cuneus, superior occipital gyrus, lingual gyrus, angular gyrus, and calcarine fissure. These regions were identified to show increased functional connectivity with the putamen during inhibitory control in a previous study (Akkermans et al.,

2016). In this study, lower volume in the angular gyrus and adjacent regions predicted late-onset smoking compared to early-onset smoking. Increased activity in the angular gyrus during an inhibitory control task has previously been found to predict future substance use and dependence symptoms, with an indication that this effect was driven by high-frequency rather than low-frequency users (Mahmood et al., 2013). It is therefore likely that lower angular gyrus volume alongside increased angular gyrus activity during inhibitory control is a marker of a phenotype that puts some adolescents at high risk for long-term substance use.

During the Stop signal task higher activity in the occipital lobe, PFC, and cerebellum also predicted late-onset smoking compared to early-onset smoking during successful inhibitory control, pointing toward a pattern of compensatory activity. Increased cerebellar activity during response inhibition has previously been observed in cocaine users (Hester & Garavan, 2004), and a similar compensatory mechanism has also been observed in alcoholics (Desmond et al., 2003) and in individuals with schizophrenia (Meyer-Lindenberg et al., 2001; Schlösser et al., 2003). Activity in the right vlPFC, including part of the right IFG also predicted late-onset smoking compared to non-smoking. The right vlPFC has been robustly linked to inhibitory control functions (Levy & Wagner, 2011). Previous work has shown greater engagement in regions overlapping with those that predicted smoking in this study for inhibitory control functions in individuals with high impulsivity (Horn, Dolan, Elliott, Deakin & Woodruff, 2003). Given the distinctions between facets of impulsivity that were predictive of different smoking trajectories, a more detailed exploration of how domains of impulsiveness are associated with brain activity during behaviour inhibition may be necessary. Notably, the same predictors seen for successful inhibition did not emerge for failed inhibition. However, increased activity in the paracentral lobule and postcentral gyrus during failed inhibition predicted any smoking compared to non-smoking. Activity in the postcentral gyrus has previously been found to be increased for active versus inactive trials (Menon, Adleman, White, Glover & Reiss, 2001) and for failed versus successful inhibitory control (Garavan, Ross, Murphy, Roche & Stein, 2002) in Go-NoGo task paradigms. Compared to non-smoking, smoking thus appears to be predicted by increased effort for successful response inhibition, and greater engagement of a response-active set during failed inhibitory control. Furthermore, a strong predictor of late-onset smoking was lower amygdala activity during failed stop trials. The amygdala is primarily linked to inhibition in the context of affective processing, but animal studies have also shown that amygdala lesions impair acquisition of learned associations and impact visual attention (Holland, Han & Gallagher, 2000). Lower activity of the amygdala may thus contribute to poor task performance and lower chance of successful inhibitory control. Further exploration of the link between amygdala function and non-affective inhibitory control is required.

Apparent deficits in affective processing were observed to predict late-onset smoking during affective face viewing. The PCC and temporo-parietal junction are known to be related to self-related attribution of emotion during affective face viewing (Schulte-Ruther, Markowitsch, Fink & Piefke, 2007), and activity in the temporo-parietal junction has been related to deficits representing mental states in autism spectrum conditions (Lombardo, et al., 2011). Lower activity in the left temporal lobe - including much of the temporal pole (TP), and higher activity in the PCC predicted late-onset smoking compared to early-onset smoking. The TP is known to play a role in emotional processing and facial recognition (Olson, Plotzker & Ezzyat, 2007), and TP activity is associated with both anger and anxiety (Lorberbaum et al., 2004). Reduced activity for angry facial expression in this region could therefore be associated with a deficit in emotion recognition. Reduced TP activity to angry face stimuli was previously found to predict future binge drinking in a sample drawn from the same population as this study (Whelan et al., 2014), and may thus be a general indicator of substance use risk. Furthermore, lower agreeableness – a facet of which is empathy – was also found to selectively predict late-onset smoking. Previous work has established that there is a link between fMRI activity to affective facial stimuli and agreeableness (Haas, Omura, Constable & Canli, 2007). Atypical processing of angry facial cues and low agreeableness may therefore both be facets of a specific developmental pathway putting individuals at risk for smoking and may be associated with parent-report that a teacher had expressed concerns about the child's psychological development, which predicted late-onset smoking. Higher activity during angry face viewing compared to affectively neutral and control stimuli in the right ventral striatum, caudate, and hippocampus, and in the parahippocampal gyri also predicted late-onset smoking. Damage to the ventral striatum is associated with impaired recognition of anger (Calder et al., 2004). Sensitization to angry facial cues occurs in the hippocampus (Strauss et al., 2005), and increased responding to emotional cues in the hippocampus and parahippocampal gyri has been observed in patients with anxiety disorders (Etkin & Wager, 2007). However, activity in the striatum and hippocampus did not differentiate significantly between smoking trajectories, making it possible that this effect is not unique to the late-onset trajectory.

A predictive effect of fMRI activity in language-processing regions during exposure to language stimuli was also found. During auditory presentation of sentences in the Global Cognitive Assessment task, late-onset smoking was predicted by lower activity in regions including Wernicke's area and the auditory cortex, as well as the parahippocampal gyrus. Findings relating parahippocampal activity to language processing have mostly focused on visual representations of language (Jouen et al., 2015), but there is also some evidence for an association between connectivity of the parahippocampal gyri and auditory hallucinations (Alderson-Day et al., 2015). Higher activity in occipital regions known to show task-related functional connectivity to the

anterior temporal lobe region which is central to semantic processing (Jackson et al., 2016) also predicted late-onset smoking. Taken together, these results suggest that abnormalities in the processing of auditory language stimuli may be a risk-factor for future smoking behaviour. The relatively strong effect seen for affective face processing and the lower fMRI activity seen for semantic processing may be part of a specific cluster of developmental traits that are associated with using nicotine as a form of self-medication or self-regulation later in adolescence.

3.4.1. Discussion of methodology

This is one of the first studies to show that combining neuroimaging data with data from another modality, specifically psychometric self-report and behavioural data in a machine learning framework is a viable and beneficial way to gain insight into the aetiology and developmental precursors of a maladaptive outcome. The neuroimaging predictors of the smoking outcome identified in this study largely expressed cognitive and developmental domains that could be linked to non-imaging predictor variables. In future studies of this nature an evaluation of variable clusters, correlation structures, or factors in the combined neuroimaging and non-imaging data may be beneficial to help examine the themes in resultant sets of predictor variables. However, such an analysis step should be incorporated into the analysis protocol as a variable creation or variable selection step to avoid post-hoc examination of the already analysed data.

An unusual analytical decision in this study was to include not only summary values for various personality and life-history questionnaires, but to also include responses to individual items. As scores for individual items and summary scores including these items are highly correlated, including both types of variables carries the risk of failing to discover an important effect because the variance of said effect was shared between multiple predictor variables. However, in this study only a minority of features and of significant predictors were summary scores, while a majority were responses to individual items. A notable example of how including individual questionnaire items was beneficial in this study comes from the NEO-ffi 'Openness' scale, where responses to individual items showed opposite effects when classifying early- and late-onset smokers. These facets of the 'Openness' trait would not have been discovered through inclusion of only the summary value, which itself was not significant in this study. However, to be consistent with previous research the inclusion of summary scale values nevertheless remained useful. The constructs of 'novelty-seeking' and 'sensation-seeking' for instance emerged as predictors alongside individual variables that formed part of these summary scores. This made it possible to compare results from this study to previous research using these constructs. Stratifying variables in a way that allows interpretation of 'main effects' may be a useful way to deal with this issue in the future. With similar large datasets that include many highly correlated variables use of an alternative dimension reduction approach to ensure model sparsity may be warranted. One

such method is sparse canonical correlation analysis (sCCA; Hardoon & Shawe-Taylor, 2011), which was shown to effectively select sparse feature projections that maximize correlations with the outcome of interest in large datasets. Further work determining whether sCCA can enhance Elastic net regularization or may even be a superior approach for large psychometric and neuroimaging datasets may be worthwhile.

Finally, while neuroimaging data alone were not able to achieve predictions with high accuracy, the inclusion of neuroimaging variables in multimodal models proved that neuroimaging variables contribute meaningfully to the prediction of smoking outcomes. However, the inclusion of neuroimaging variables alongside other predictors always resulted in a small decrease in AUC values. While broadly the same set of non-imaging predictors were identified in the unimodal and multimodal models in this study, the extension of the variable set through inclusion of additional data alters the composition of the variable space which the Elastic Net evaluates. As the majority of neuroimaging features were found not to be informative in predicting smoking outcomes, the inclusion of the entire neuroimaging data set resulted in the inclusion of many features not associated with the outcome in the model (i.e., effectively adding noise), which is the probable cause of the slight reduction in model performance. Examination of specificity and recall revealed that neuroimaging models had much poorer recall than non-imaging models, likely due to the combination of relatively small sample size of the smoking groups and lower signal-to-noise ratio in the neuroimaging compared to non-imaging data. When neuroimaging variables were included in multimodal models the recall values were also lowered, although specificity increased modestly in all models. The changes in specificity and recall are likely a direct result of the change in the proportion of predictors to noise in the feature space and would likely be counteracted by an increase in sample size. Further evaluation of the limits for variable inclusion with the Elastic Net and the consequences of combining data types or altering the amount of noise in Elastic Net models will be necessary.

3.5. Summary

The predictors of early-onset smoking and of late-onset smoking that emerged in this study point toward distinct etiological pathways toward smoking behaviour. A stronger effect of biological predisposition was observed in adolescents who began smoking in late adolescence than in those who took up smoking at an earlier age. At age 14, recent stressful life events, novelty-seeking, antisocial behaviour, and having engaged in other substance use were strong predictors of taking up smoking in the next two years. Living in a household with a non-traditional family structure was also predictive of starting to smoke regularly by age 16. Beginning to smoke after age 16 was predicted by variables suggesting disruption to the frontostriatal reward network, reliance on compensatory processes for behavioural inhibitory control, atypical language processing, and

deficits in affective processing. Alongside this functionally defined risk profile, late-onset smoking was predicted by what may act as a set of protective factors against smoking for at least two more years, including low exposure to illicit substances and a supportive family network. This study offers insights into how age of smoking onset is associated with environmental, psychological, and neurobiological risk factors. Furthermore, this study provides a demonstration of how machine learning can be used to combine neuroimaging and psychometric variables to allow for important mechanistic insights into the biological basis of adolescent cigarette smoking while also identifying and confirming indicators of smoking risk. The aspects of altered reward processing identified using fMRI in this study are a promising target for development of early risk-assessment tools capitalizing on insights from neuroimaging but utilizing more cost-effective cognitive testing. Paradigms such as the PALP task measuring reward response bias may prove to assess similar cognitive domains as those in which deficits were found to be associated with smoking risk. Based on further studies evaluating the similarity in risk estimates obtained from neuroimaging and non-imaging measures of the identified processing domain, the neurobiological insights from this study may form the basis of more easily administered self-report or behavioural tools.

In comparison to previous cross-sectional studies, this longitudinal examination of smoking risk identified a number of new risk factors associated with smoking onset, as well as confirming the importance of previously identified risk and protective factors. A key insight gained in this study relates to the relationship of novelty-seeking to smoking behaviour, which was previously thought to be associated with all adolescent smoking (Audrain-McGovern et al., 2004a; 2009 ; Dinn, Aycicegi & Harris, 2004), but was shown here to be a risk factor specific to one smoking trajectory over another. A further important behavioural indicator of smoking risk identified in this study but previously not observed in the literature was the presence of self-harm behaviours in adolescent future smokers. The neurobiological risk factors for smoking behaviour identified in this study gave a perspective on predisposing vulnerabilities in adolescents who would go on to become smokers, but also highlighted that the role of biological predisposition compared to acute environmental factors may be an important differentiation when examining the etiological pathways leading adolescents to smoke. The interplay between environmental and neurobiological factors in the development of smoking behaviours and changes in the influence of each domain requires further investigation using larger samples and additional follow-up assessments. However, as the first longitudinal study to evaluate a breadth of functional neuroimaging variables in relation to adolescent smoking outcomes, this study was able to identify a number of important associations between reward-related and inhibitory control related brain function and smoking risk. Based on the evidence for dysfunction in the reward system predicting adolescent smoking behaviour, further investigation of the link between adolescent smoking and reward system function is

warranted. In the following chapter reward processing in adolescents who have tried smoking is examined. As reward processing involves several interacting regions (see Haber & Knutson, 2010), a functional connectivity approach is adopted to investigate network-based changes in reward processing associated with smoking frequency.

Chapter 4 - Ventral striatum connectivity during reward anticipation in adolescent smokers

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Publications:

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4.1. Introduction

Adolescence is a period of substantial behavioral and brain changes and of heightened propensity for risk-taking. Adolescence is also a time of increased risk for impulse-control disorders, including addiction (Chambers, Taylor & Potenza, 2003; Paus, Keshavan & Giedd, 2010). The most common addiction in adolescence is nicotine (Young Corley, Stallings, Rhee Crowley & Hewitt, 2002). Smoking is the leading cause of preventable deaths in the U.S., and nearly one in five adults is a smoker (U.S. Department of Health and Human Services, 2014). Next to alcohol, nicotine is one of the most widely available addictive substances, meaning that it is much easier for adolescents to try cigarette smoking than other drugs. Adolescent smoking differs widely in its frequency and regularity, but can broadly be categorized into four smoking trajectories: 1) Adolescents who start smoking at an early age and go on to become regular smokers, 2) individuals who follow the same path but initiate smoking at a later age, 3) adolescents who experiment with smoking but don't become addicted or stop smoking, and 4) non-smokers (Audrain-McGovern et al., 2004a,; Chassin, Presson, Pitts & Sherman, 2000; Mayhew, Flay & Mott, 2000).

While the behavioral and personality differences between adolescents in different smoking trajectories are subtle and difficult to pinpoint, the differences between adolescent smokers and non-smokers are well established: Adolescent smokers show increased novelty seeking, reduced harm avoidance, and increased choice impulsivity (Audrain-McGovern et al., 2004a/b; Wills, Windle & Cleary, 1998). In the previous chapter novelty-seeking was also established as an important predictor of future smoking behaviour in adolescents. However, these traits are not only characteristic of adolescent smokers compared with non-smokers, but also of adolescents compared with adults (Brändström, Sigvardsson, Nylander & Richter, 2008; Steinberg, Graham, O'Brien, Woolard, Cauffman & Banich, 2009). A number of neurobiological models have attributed these characteristics of the adolescent developmental period to a difference in the balance between different brain systems in adolescence. The dual-system model (e.g. Steinberg, Albert, Cauffman, Banich, Graham & Woolard, 2008), the triadic model (Ernst, Pine & Hardin, 2005) and the imbalance model (Casey, Jones & Hare, 2008) all distinguish between the reward system and the cognitive control systems. Among the structures involved in cognitive control are the dorsolateral prefrontal cortex (dlPFC) which is one of the most important executive control regions (Alvarez & Emory, 2006), the orbitofrontal cortex (OFC) which has been attributed a role in saliency and value attribution (O'Doherty, 2004), the anterior cingulate cortex (ACC) which has been implicated in selective attention (Alvarez & Emory, 2006), and the right inferior frontal gyrus (IFG) which has been established as a central region in behavioral inhibition (Chikazoe, Konishi, Asari, Jimura & Miyashita, 2007; Aron et al., 2014).

In the previous chapter activity of the OFC and ACC during a reward processing paradigm were among the strongest predictors of future smoking behaviour in adolescence. Functional MRI activity during reward processing in adolescents is thus indicative of future smoking behaviour. Reward processing involves many interacting regions (see Haber & Knutson, 2010). Among these regions, the ventral striatum (VS) is particularly important. The VS receives dopaminergic input from the ventral tegmental area and is connected to frontal areas such as the orbitofrontal and ventromedial cortices. The VS is not only central to processing reward-related stimuli, but also plays a key role in integrating affective and cognitive information, and in action selection and motivation (Floresco, 2015). Along with decreases in impulsive choice from adolescence to adulthood, activation in the VS during reward-related decision making decreases, and activations in prefrontal cognitive control regions have been shown to increase with age (Christakou, Brammer & Rubia, 2011). The functional connectivity between the VS and prefrontal cortex (PFC) during reward outcomes also increases over the course of adolescence (Van den Bos, Cohen, Kahnt & Crone, 2012). Furthermore, ventral striatal dopamine D2 receptor availability was associated with alcohol cue-induced activation in the ACC and medial prefrontal cortex, confirming a role for dopamine in VS-medial prefrontal interactions (Heinz et al., 2004).

In adult smokers, lifetime tobacco use is associated with structural brain alterations in both the reward and cognitive control systems (Gallinat et al., 2006; Zhang, Salmeron, Ross, Geng, Yang, & Stein, 2011). Furthermore, adult smokers show reduced connectivity between the striatum and anterior cingulate cortex (ACC), associated with the severity of nicotine dependence (Hong et al., 2009). While these findings suggest a role of long-term chronic cigarette smoking in brain deficits in these systems, there is robust evidence linking the VS to adolescent impulsivity and smoking. VS hypoactivity during reward anticipation can be observed in adolescents with ADHD compared to control subjects (Scheres, Milham, Knutson & Castellanos, 2007), and is associated with risk-taking bias in typically developing adolescents (Schneider et al., 2012). It appears that VS activity is negatively associated with impulsivity, independent of age (Ripke et al., 2012). VS hypoactivity can be seen in dependent adult smokers compared to occasional smokers (Bühler et al. 2010) and is associated with level of nicotine use in adults (Rose et al., 2013). Importantly, a reduction in VS activation during reward anticipation has also been observed in adolescents prenatally exposed to nicotine (Müller et al., 2013) and in adolescent smokers (Peters et al., 2011). Furthermore, Peters et al. reported that ventral striatal activity during reward anticipation was negatively correlated with smoking frequency in adolescents. These findings point toward a possible deficit in the processing of rewarding stimuli in individuals who are at risk for developing nicotine dependence.

Whereas the majority of studies to date have used measures of regional changes in Blood Oxygen Level Dependent (i.e., BOLD) activation to examine differences between substance using

groups and non-users, a number of recent studies have used BOLD to evaluate differences in brain connectivity between these groups. However, the majority of these studies have focused on resting-state connectivity (Fedota & Stein, 2015). Compared with resting state measures of functional connectivity, examining differences in connectivity in relation to specific conditions, such as different reward cue types, has the potential to be more informative with regard to differences in reward processing. For instance, a study examining reward cue reactivity in smokers found greater functional connectivity between the left insula and a widespread network including the OFC, ACC, and dorsal striatum during smoking compared to food cues (Claus, Blaine, Filbey, Mayer & Hutchison, 2013). While examining smokers' reactivity to smoking cues is a valuable tool for understanding the mechanisms of craving and relapse in addicted smokers, the way in which non-smoking rewards are processed has the potential to offer more insight into factors associated with smoking initiation and smoking trajectories in adolescents.

A task which has widely been used to examine generalized reward processing in the context of functional magnetic resonance imaging (fMRI) is the Monetary Incentive Delay (MID) task (Knutson, Westdorp, Kaiser & Hommer, 2000). The paradigm has the distinct advantage of temporally separating anticipation and receipt of positive or negative outcomes, making it possible to examine the activation patterns associated with each separately. VS activity is observed during the anticipation of rewards in the MID (Adcock, Thangavel, Whitfield-Gabrieli, Knutson & Gabrieli, 2006; Knutson, Fong, Bennett, Adams & Hommer, 2003). Other regions associated with reward anticipation in this task include the dorsal striatum, cuneus, thalamus, ACC, ventromedial PFC, OFC, insula, and midbrain (Haber & Knutson, 2010; Van Leijenhorst, Zanolie, Van Meel, Westenberg, Rombouts & Crone, 2010).

Here, the association between adolescent smoking frequency and functional connectivity in the VS during anticipation of large rewards compared to no reward in the MID task is examined, using Psychophysiological Interaction (PPI) analysis (Friston et al., 1997). A powerful machine learning procedure is employed to examine the connectivity patterns associated with smoking. Such approaches have previously been used to investigate adolescent binge-drinking (Whelan et al., 2014) and intelligence (Jollans et al., 2015). This approach has the potential to detect relatively subtle differences, while guarding against spurious findings, using both cross-validation and random-label permutation. 206 adolescents from a large multisite study were included, with a wide spectrum of nicotine use. As the aim of this study was to identify effects associated with smoking frequency rather than with smoking initiation, only adolescents who had smoked on three or more occasions in their lifetime at the point of data collection were included. In line with a recent review examining resting state functional connectivity in nicotine addiction (Fedota & Stein, 2015), which concluded that disruptions in nicotine addiction appear to be focused on the salience

network as well as frontal cognitive control systems, it was hypothesized that frequency of smoking would be associated with reduced VS connectivity to fronto-parietal cognitive control regions (Garavan & Weierstall, 2012) and increased connectivity to regions associated with salience or valuation of stimuli, such as the anterior cingulate and orbitofrontal and insular cortices (Seeley et al., 2007).

4.2. Method

4.2.1. Characteristics of the IMAGEN Study

A large sample of 14-year old adolescents was recruited at eight recruitment sites. Adolescents completed an extensive battery of psychiatric and neuropsychological assessments, including fMRI. Details of the full study protocol and data acquisition are provided elsewhere (Schumann et al., 2010).

4.2.2. Participants

Participants were a subset of 206 adolescents from the multisite study (110 female). Further information on the distribution of smoking frequency is provided in Table 4.1, and other details about the sample are provided in Table 4.2.

4.2.3. Substance use

Lifetime smoking, alcohol, and cannabis use were measured using the European School Survey Project on Alcohol and Other Drugs questionnaire (ESPAD, Hibell et al., 1997), which was administered using the computerized assessment platform Psytools. Psytools presented questionnaire items and response alternatives on a computer screen. The reliability of individual data was checked in a two-stage procedure: Before every task, adolescents were asked to report on the current testing context including questions about their attentional focus and the confidentiality of the setting. Potentially problematic testing situations were followed-up by research assistants face-to-face in a confidential setting. Exclusion criteria for substance use measures included an indication that the participant was in a hurry, somebody was watching, or an indication to have known or taken the sham drug *Relevin*. Scores on the ESPAD are ranked as follows: 0: no lifetime use, 1: 1 to 2 uses, 2: 3 to 5 uses, 3: 6 to 9 uses; 4: 10 to 19 uses, 5: 20 to 39 uses, 6:40 or more uses. Participants were included if they had a score of 2 or higher on the ESPAD item measuring lifetime smoking. ESPAD scores for lifetime smoking are reported in Table 4.1.

Table 4.1. Distribution of smoking frequency across the sample.

Lifetime smoking occasions		n
ESPAD score	ESPAD range	
2	3 to 5	57
3	6 to 9	37
4	10 to 19	32
5	20 to 39	20
6	40+	60

Table 4.2. Characteristics of the sample

	Mean	SD	Correlation with nicotine use	
			r	p
Age	14.58	0.46	0.11	0.13
Socioeconomic Status	17.50	4.36	-0.16	0.025
Pubertal Development Status	3.66	0.70	0.13	0.065
WISC-IV Perceptual Reasoning	103.66	12.97	-0.01	0.92
WISC-IV Verbal Comprehension	107.80	13.79	-0.10	0.13
ESPAD Lifetime Alcohol use	3.21	1.63	0.26	0.0002*
ESPAD Lifetime Cannabis use	0.64	1.45	0.21	0.0029*
SURPS Anxiety Sensitivity	2.24	0.49	-0.14	0.045
SURPS Impulsivity	2.60	0.42	-0.05	0.44
SURPS Hopelessness	1.93	0.40	0.02	0.77
SURPS Sensation Seeking	2.80	0.54	-0.08	0.22
TCI-R Disorderliness	23.71	4.33	0.07	0.26
TCI-R Exploratory Excitability	33.44	4.74	0.03	0.70
TCI-R Extravagance	30.79	6.02	0.04	0.52
TCI-R Impulsivity	27.82	5.01	-0.06	0.41
TCI-R Novelty Seeking	115.77	14.43	0.05	0.47

*$p<0.003125$, p value corrected for multiple comparisons using Bonferroni correction

4.2.4. Psychometric Data

4.2.4.1. Wechsler Intelligence Scale for Children

Participants completed a version of the Wechsler Intelligence Scale for Children WISC-IV (Wechsler, 2003), of which the following subscales were included: Perceptual Reasoning, consisting of *Block Design* (arranging bi-colored blocks to duplicate a printed image) and *Matrix Reasoning* (a series of colored matrices are presented and the child is asked to select the consistent pattern from a range of options); and Verbal Comprehension, consisting of *Similarities* (two similar but different objects or concepts are presented and the child is asked to explain how they are alike or different) and *Vocabulary* (a picture is presented or a word is spoken aloud by the experimenter and the child is asked to provide the name of the depicted object or to define the word).

4.2.4.2. Substance Use Risk Profile Scale

The Substance Use Risk Profile Scale (SURPS; Woicik, Stewart, Pihl, & Conrod, 2009) assesses personality traits that confer risk for substance misuse and psychopathology. This scale measures four distinct and independent personality dimensions; anxiety sensitivity, hopelessness, sensation seeking, and impulsivity. The anxiety sensitivity dimension is characterized by the fear of symptoms of physical arousal. The hopelessness dimension is identified as a risk factor for the development of depression and characterized by dismal feelings. The sensation seeking dimension is characterized by the desire for intense and novel experiences. The impulsivity dimension involves difficulties in the regulation (controlling) of behavioral responses.

4.2.4.3. Temperament and Character Inventory

The novelty seeking scale of the Temperament and Character Inventory – Revised (TCI-R; Cloninger, 1999) was administered. The Novelty seeking scale is composed of four sub-scales. Exploratory Excitability contrasts with 'stoic rigidity' and reflects sensation-seeking and novelty-seeking behaviors. Impulsiveness describes behavior on a dimension from impulsivity to reflection and captures elements of emotional reactivity, and unreflective, careless behavior. The Extravagance subscale assesses overspending behavior and poor planning and is believed to reflect a tendency to approach reward cues. Disorderliness reflects disorganized, uncontrolled, and antinormative behavior.

4.2.4.4. Puberty Development Scale

The Puberty Development Scale (PDS; Petersen, Crockett & Richards, 1988) was used to assess the pubertal status of the adolescent sample. This scale provides an eight-item self-report measure of physical development based on the Tanner stages with separate forms for males and

females. For this scale, there are five categories of pubertal status: (1) prepubertal, (2) beginning pubertal, (3) midpubertal, (4) advanced pubertal, (5) postpubertal. Participants answered questions about their growth in stature and pubic hair, as well as menarche in females and voice changes in males.

4.2.5. Functional MRI

4.2.5.1. Monetary incentive Delay Task

Participants completed a modified version of the MID task, involving small and large possible gains. On each trial, the amount of points that could be won on that trial was signaled by a cue, displayed for 4-4.5 s. Participants could win a reward by responding as quickly as possible to a target stimulus presented after a random time interval, by means of a button press, after which feedback was presented. The response and feedback phase lasted a total of 2 s. The response interval was dynamically adjusted so that subjects won on 66% of all trials. Trials were separated by a 3.5-4.15 s inter-trial interval, during which a fixation cross was presented. The cue stimuli were a circle with two lines signaling a large reward (10 points), a circle with one line signaling a small reward (2 points), and a triangle signaling that no reward could be gained. 22 trials per condition were completed, resulting in 66 total trials. Task stimuli and timings are presented in Figure 4.1.

4.2.5.2. fMRI Data Acquisition

Full details of the magnetic resonance imaging (MRI) acquisition protocols and quality checks have been described previously, including an extensive period of standardization across MRI scanners (Schumann et al., 2010). MRI Acquisition Scanning was performed at the eight assessment sites with a 3T whole body MRI system made by several manufacturers (Siemens: 4 sites, Philips: 2 sites, General Electric: 1 site, and Bruker: 1 site). To ensure a comparison of MRI data acquired on these different scanners, image-acquisition techniques were implemented using a set of parameters compatible with all scanners that were held constant across sites, for example, those directly affecting image contrast or fMRI preprocessing. Standardized hardware for visual and auditory stimulus presentation (NordicNeurolabs, Bergen Norway, http://www.nordicneurolab.com) was used at all sites. BOLD functional images were acquired with a gradient-echo echoplanar imaging (EPI) sequence using a relatively short echo-time to optimize imaging of subcortical areas. For the MID, 300 volumes consisting of 40 slices were acquired for each subject. Scanning time for this task was a total of 11 minutes.

4.2.5.3. fMRI preprocessing and analysis

Briefly, the functional imaging processing was as follows: Time series data were first corrected for slice-timing, then corrected for movement, non-linearly warped onto MNI space

using a custom EPI template, and gaussian-smoothed at 5mm-full width half maximum. Nuisance variables were also added to the design matrix: estimated movement was added in the form of 6 additional regressors (3 translations, 3 rotations). These analysis steps were carried out in SPM8. All subsequent analyses were conducted in SPM12.

In a general linear model (GLM), three separate regressors were defined to estimate the neural activation associated with the monetary cue types: *No-win*, *Small-win*, and *Big-win*. Six movement parameters for each participant were also included in the individual models. Two contrasts were estimated using this GLM: A T-contrast between two conditions (*Big-win* minus *No-win*), and an F-contrast to identify the sources of signal of interested and remove noise.

Two spherical ROIs with 3mm radius were defined in the left and right VS, centered at MNI coordinates [-12, 10, -10] and [12, 10, -10]. The mean BOLD signal from these ROIs was extracted using the Volume of Interest (VOI) time series, and then adjusted by the F contrast (i.e. the effect of interest). For the right and left VS separately the extracted signal time series was defined as the physiological regressor, and the main effect of conditions (Big-win minus No-win) was defined as the psychological regressor. The PPI variable representing the regressors of interest was built using the PPI toolbox in SPM. After computing the PPI variable, a variable indicating the PPI interaction term and a variable indicating the original ROI time series were generated for each subject. Subsequently, the interaction term and the original ROI time series together with estimated movement parameters were specified in a GLM model. These were estimated to model the task-dependent interaction (changes of connectivity) between the VS and other voxels. Data from this PPI were extracted from predetermined ROIs and used in the machine learning analysis.

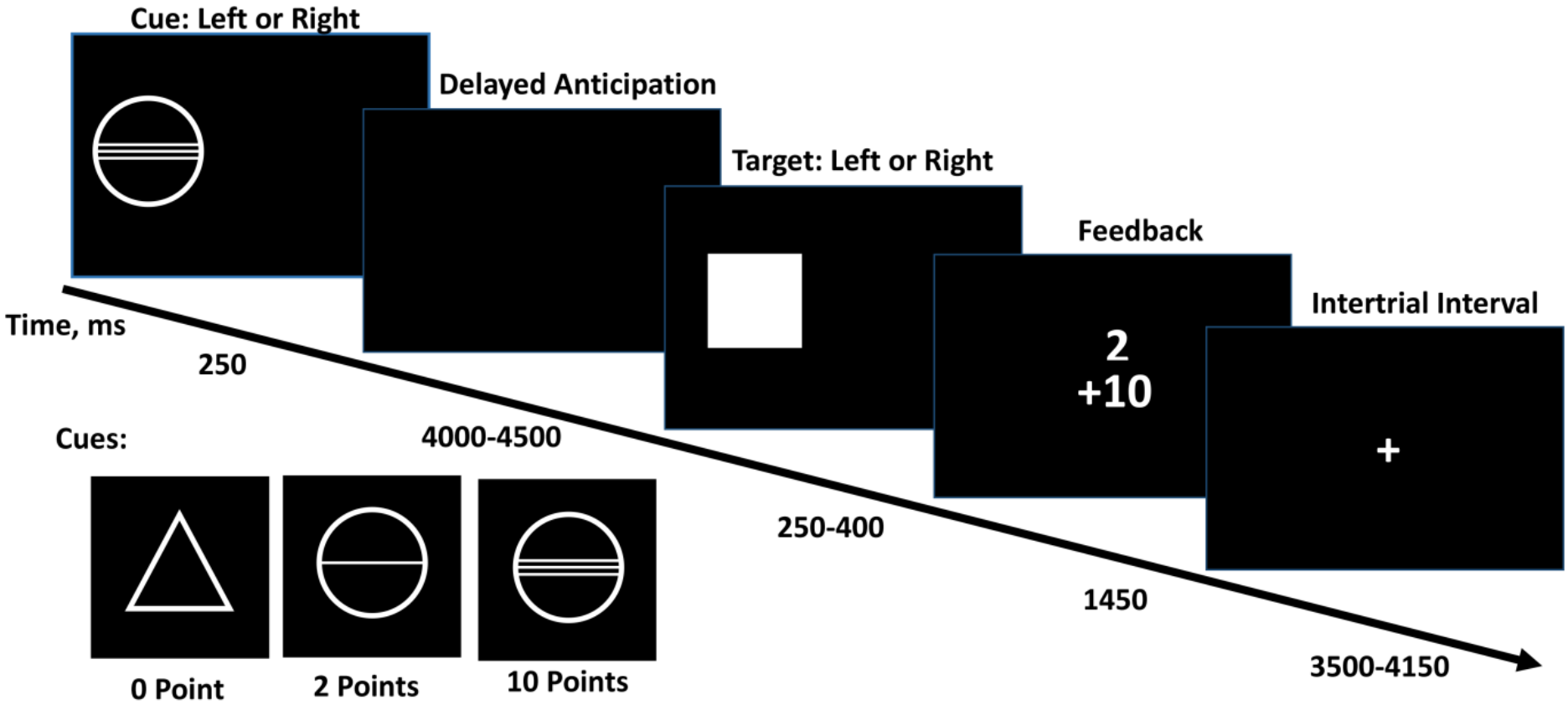

Figure 4.1. Stimuli and timings in the MID Task. Cues signaling the task condition (no reward, small reward, large reward) were displayed for 4-4.5 s. The response and feedback phase lasted a total of 2 s. Trials were separated by a 3.5 - 4.15 s inter-trial interval.

4.2.6. Functional connectivity analyses

4.2.6.1. Functional connectivity during reward anticipation

A one-sample t-test to identify clusters in which functional connectivity for reward anticipation differed significantly from zero was conducted in SPM12. Data acquisition site, sex, and PDS were also entered into the analysis as nuisance covariates. The family-wise error ($p<.05$) was corrected for by using an uncorrected p-value of 0.001 in combination with a minimum cluster extent of 14 contiguous voxels, calculated using SPM.

4.2.6.2. Functional connectivity associated with smoking frequency

Data from 92 ROIs based on the AAL atlas (Tzourio-Mazoyer et al., 2002) and two masks for the subthalamic nuclei (x=-12, y=-10, z=-5; x=12, y=-13, z=-5), as well as lifetime alcohol and cannabis use, data acquisition site, sex, and pubertal development status were entered into the analysis. Data were z-scored. The analysis procedure is a variation on that shown in Figure 2.2 in chapter 2 and can be seen in Figure 4.2. A similar approach has previously been used by Whelan et al. (2014) and Jollans et al. (2015). To assess the effect of lifetime smoking on VS connectivity, two regularized multiple regression analyses for the left and right VS seed were carried out in Matlab R2014a, via the Elastic Net (Zou & Hastie, 2005). Regression with Elastic Net regularization is an example of a sparse regression method, which imposes a hybrid of both L1- and L2-norm penalties (i.e., penalties on the absolute (L1 norm) and squared values of the β weights (L2 norm)). This allows relevant but correlated coefficients to coexist in a sparse model fit, by doing automatic variable selection and continuous shrinkage simultaneously, and selects or rejects groups of correlated variables. Least absolute shrinkage and selection operator (LASSO, Tibshirani, 1997) and ridge regression (Hoerl & Kennard, 1970) are special cases of the Elastic Net.

10-fold nested cross-validation was used, in which 10 separate regression models were generated, with the beta weights for all parameters being generated on 90% of the dataset (the training set), and tested on 10% of the dataset (the test set). Within the test set, additional 10-fold cross-validation was used to identify the optimal Elastic Net parameters α and λ. Alpha represents the weight of lasso vs. ridge regularization which the Elastic Net uses, and λ is the regularization coefficient.

Additionally, 50-fold bootstrap aggregation was applied to introduce an additional level of stability (Breiman, 1996). That is, parameter optimization was repeated 50 times, using sampling with replacement (i.e., on average two thirds of the data in each iteration). The results from all iterations within each training fold were then averaged. In addition to bootstrap aggregation this entire analysis procedure was repeated 50 times, and the results (correlation coefficients and beta

weights) were averaged across all 50 iterations of the analysis procedure. Overall, this yielded 500 sets of beta weights, from 10 cross-validation folds across 50 analysis iterations. Beta weights were averaged for each variable.

Two null models were also computed using the same method. For these, the same analysis procedure was carried out using random label permutations with the same dataset (i.e., subjects were randomly assigned to ESPAD scores). These null models yielded average beta weights of 0.018 and 0.016, and average correlation coefficients of r=-0.006 and r=-0.01. Based on the null models, the threshold for reporting ROIs was set at a minimum absolute beta weight of 0.048 this was the 95th percentile of the distribution of beta weights in the null models). The reporting thresholds for the minimum frequency with which ROIs should be included in the regression models across iterations was set at 84% (left) and 81% (right, this was the 95th percentile of the distribution of occurrence frequency across iterations in the null models).

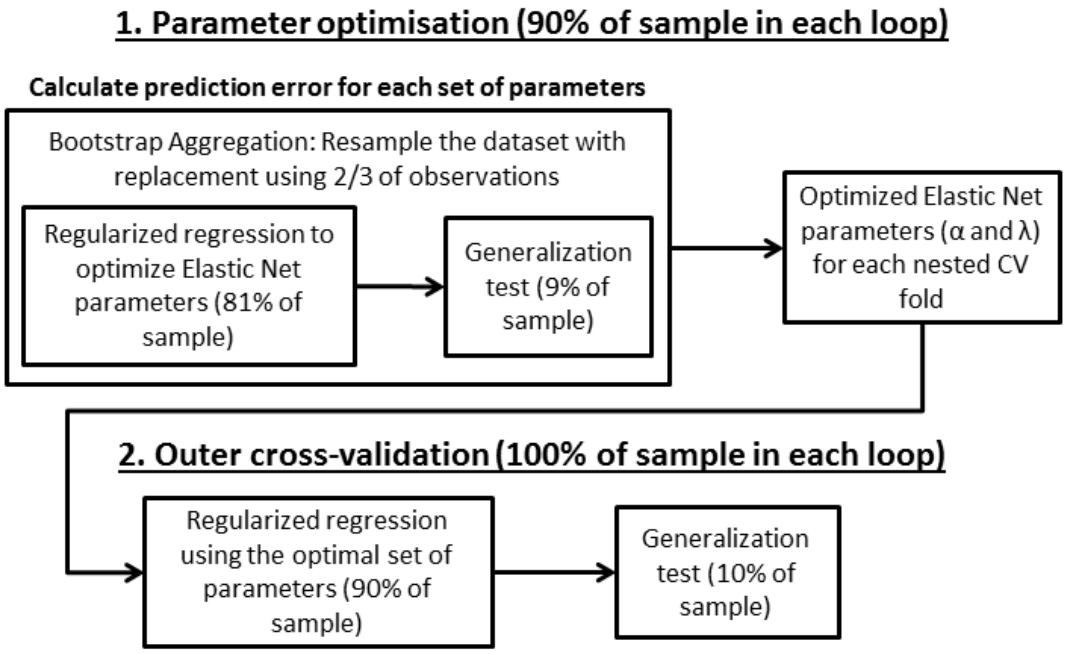

Figure 4.2. Machine Learning analysis procedure. The machine learning analysis was carried out in two stages: (1) The optimal Elastic Net parameters for each main cross-validation (CV) fold were identified using nested CV within each main CV fold. Bootstrap aggregation was used in this step. (2) The optimal Elastic Net parameters for each main CV fold were applied to the full training set (90% of the data) to generate beta weights for all input variables. These beta weights were then used to generate outcome predictions for the remaining, untouched 10% of the dataset in each main CV fold. The goodness-of-fit was estimated using the outcome predictions for the entire dataset.

4.3. Results

A series of Spearman's rank correlations were conducted (see Table 4.2). Using Bonferroni correction for multiple comparisons, lifetime smoking was significantly positively correlated with alcohol and cannabis use.

4.3.1. VS connectivity during reward anticipation

A number of cortical and subcortical clusters showed altered functional connectivity with the VS during anticipation of a large reward vs. no reward. Clusters with significantly increased or decreased functional connectivity are reported in Table 4.3 and shown in Figure 4.3.

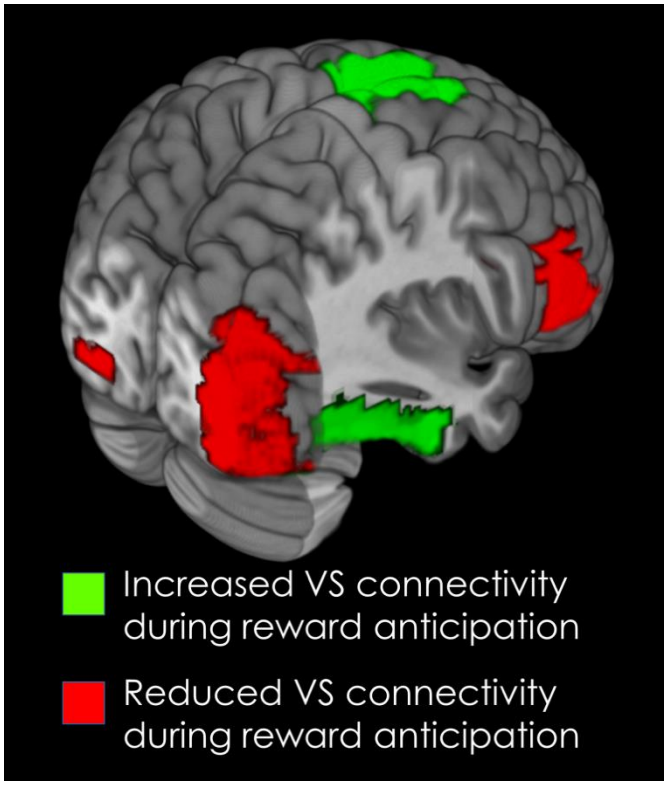

Figure 4.3. ROIs for which VS connectivity was altered during anticipation of large reward vs. no reward.

4.3.2. Changes in VS connectivity associated with lifetime smoking

There was a significant association between lifetime smoking and both right (mean r=.27) and left (mean r=.21) VS functional connectivity. ROIs which passed the thresholds for absolute beta weights and frequency of occurrence across cross-validation folds determined using the null models are reported (see Table 4.4. and Figure 4.4 for ROIs associated with lifetime smoking).

Table 4.3. Clusters which showed significant changes in functional connectivity with the VS during anticipation of a large reward vs. no reward

x	y	z	k	max t	
Clusters with increased functional connectivity					
Left VS					
-6	-1	64	27	4.27	Supplemental Motor Area (L)
12	20	37	15	4.15	Middle Cingulum (R)
6	11	61	22	4.15	Supplemental Motor Area (R)
Right VS					
24	-70	-11	16	4.12	Fusiform Gyrus (R)
Clusters with decreased functional connectivity					
Left VS					
-30	-91	-11	138	7.30	Inferior Occipital Gyrus (L)
27	-94	1	105	6.24	Middle Occipital Gyrus (R)
-42	26	25	16	3.80	IFG, triangular part (L)
Right VS					
-27	-91	-11	68	6.00	Inferior Occipital Gyrus (L)
33	-88	-11	59	4.98	Inferior Occipital Gyrus (R)

R: right; L: left; k; cluster extent; IFG: Inferior Frontal Gyrus

Table 4.4. ROIs for which functional connectivity with the VS during anticipation of a large reward vs. no reward was associated with lifetime nicotine use

	Left VS		Right VS	
	Beta weight	% of CV folds	Beta weight	% of CV folds
Gyrus Rectus (R)	0.105	93.2	0.305	100
SFG, orbital part (R)			0.191	93.6
MFG, orbital part (L)			0.077	84.6
SFG, medial part (L)			-0.251	86.6
Olfactory gyrus (L)			-0.325	93.4
IFG, opercular part (R)			-0.176	92.4
IFG, orbital part (R)	-0.099	91.8		
Amygdala (R)			0.323	90.4
Thalamus (R)			0.150	89.6
Caudate (R)			0.076	81.2
Posterior Cingulate (L)			0.184	88.0
Posterior Cingulate (R)	0.238	88.6		
Precentral gyrus (R)			0.337	93.6
Supramarginal Gyrus (L)	0.381	84.8		
Supramarginal Gyrus (R)			-0.311	95.4
Angular Gyrus (R)			-0.138	89.6
Inferior parietal lobule (L)	-0.201	84.0		
Superior occipital gyrus (R)			-0.245	83.0
Lingual gyrus (L)			-0.100	82.6
Middle Temporal Pole (L)	-0.281	85.0		
Middle Temporal Pole (R)			-0.146	84.4
Superior Temporal Pole (R)			-0.204	96.0
Cerebellum (R)			-0.144	92.8

CV: Cross-validation; R: right, L: left; SFG: Superior frontal gyrus; MFG: Middle frontal gyrus; IFG: Inferior Frontal Gyrus

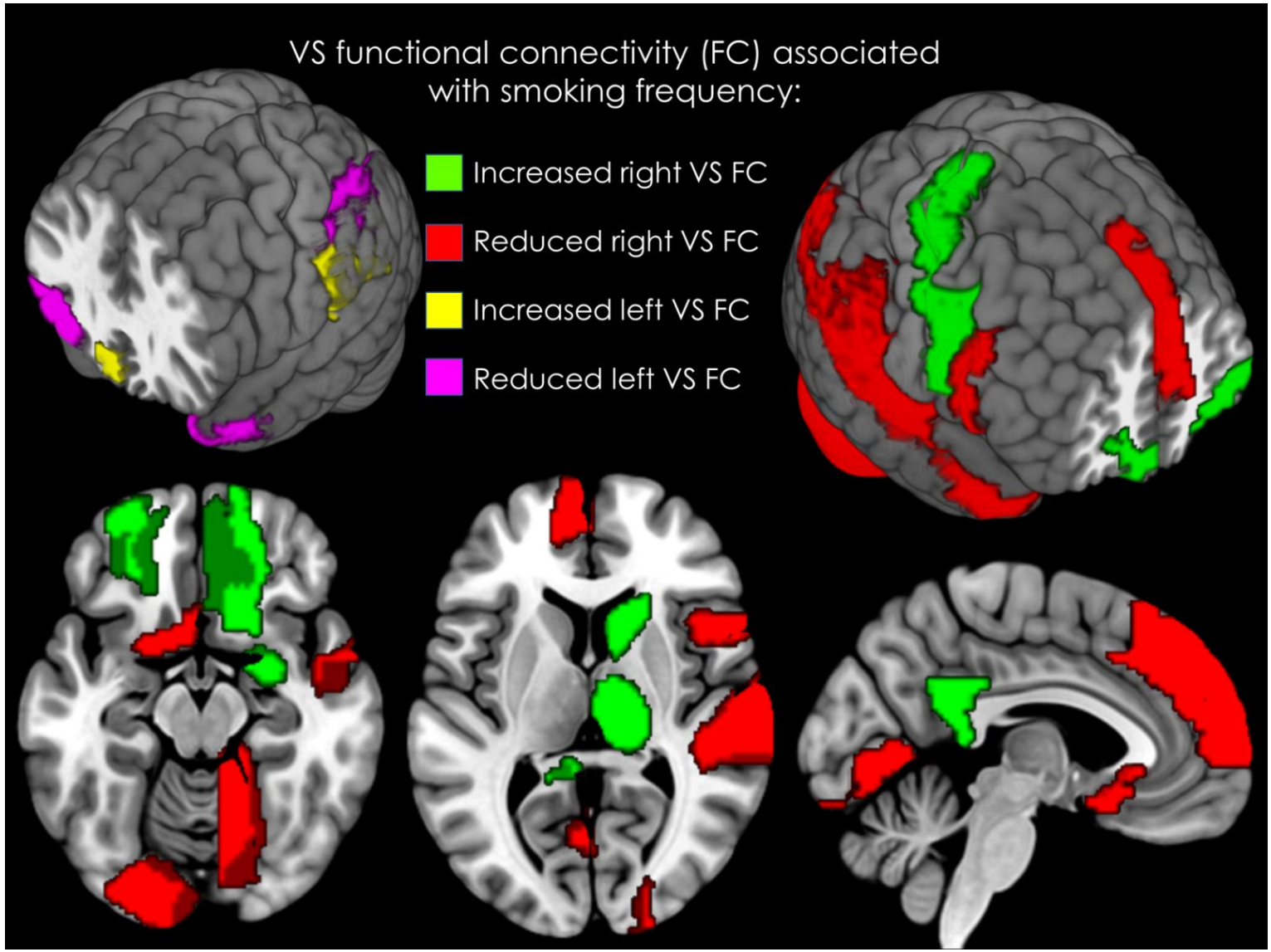

Figure 4.4. ROIs for which functional connectivity (FC) with the ventral striatum (VS) during anticipation of a large reward vs. no reward was associated with lifetime smoking.

4.4. Discussion

A Psychophysiological Interaction (PPI) analysis of a large (n=206) sample of adolescent smokers has produced two key findings with respect to adolescent smoking frequency and functional connectivity with the VS during anticipation of rewards: (1) a positive association within the reward system; specifically, between the VS and OFC and amygdala, (2) a negative correlation between the reward system and inhibitory control and attention networks; specifically, between VS and the right IFG, inferior parietal cortex, and medial PFC. Smoking frequency was also not significantly associated with measures of impulsivity or novelty seeking, which is in line with previous studies that were not able to distinguish between adolescent smokers in different smoking trajectories on the basis of novelty-seeking or choice impulsivity (Audrain-McGovern et al., 2004a; 2009).

Smoking frequency was associated with an increase in connectivity between the OFC and VS. The VS can indirectly modulate frontal cortical activity, by means of the thalamus. However, the ACC, mPFC and OFC also provide direct input to the VS (Cohen et al., 2011; Haber & Knutson, 2010). The OFC has previously been implicated in a study comparing occasional and dependent smokers (Bühler et al., 2010). This study found that dependent smokers exhibited significantly less orbitofrontal activation during anticipation of monetary rewards than occasional smokers, supporting the finding of altered function of this region associated with frequency of smoking. Interestingly, the same study also reported increased activity during reward anticipation in the right medial OFC and gyrus rectus in short-term abstinent compared to non-abstinent smokers, for monetary and cigarette rewards (Bühler et al., 2010). In line with the proposed role of the OFC in attribution of saliency and valuation (O'Doherty, 2004), the finding of increased striatal connectivity with these same medial orbitofrontal regions associated with smoking frequency suggest that adolescent smoking is associated with generalized increased reward valuation; similar to the pattern demonstrated during nicotine withdrawal by Bühler and colleagues.

Thalamus-VS connectivity was also positively associated with smoking frequency. The thalamus has been highlighted as an important region in incentive processing in adolescents and adults, along with the insula (Cho et al., 2013). Cho et al. (2013) suggest that interoceptive information from the insula, and alerting signals about opportunities for incentive processing from the thalamus converge in the nucleus accumbens (NAc), which forms part of the VS. Considering findings of increased activation in the thalamus during reward anticipation in alcoholics (Wrase et al., 2007), the finding of increased connectivity between the VS and thalamus points toward a heightened sensitivity toward salient external stimuli. Increased functional connectivity between the bilateral VS and the contralateral posterior cingulate cortex (PCC) was also observed, associated with smoking frequency. A general role for the PCC in directing the focus of attention

internally or externally, and in determining the width or breadth of the attentional focus has been proposed (Leech & Sharp, 2014), which is consistent with its role as a central node of the default-mode network (DMN, Buckner et al., 2008). In monkeys PCC activity was also found to be mediated by actual and expected reward value (McCoy et al., 2003), and in humans the PCC has been shown to play a role in integrating motivational information and spatial attention (Mohanty et al., 2008). Along with the OFC, the PCC showed heightened activation during motivationally salient cues in humans (Mohanty et al., 2008), which suggests that the heightened functional connectivity between the VS and PCC may reflect a similar effect of heightened attention to highly valued and motivationally salient events as the heightened connectivity with the OFC.

In line with previous research which found that smokers show less IFG activity than non-smokers to negative emotional images (Froeliger et al., 2013), functional connectivity between the VS and right IFG was negatively associated with smoking frequency. The right IFG is a central region for response inhibition (Chikazoe, Konishi, Asari, Jimura & Miyashita, 2007; Aron et al., 2014) and attentional control (Hampshire, Chamberlain, Monti, Duncan & Owen, 2010). The right IFG can also be considered part of a ventral frontoparietal attention network, which further includes the inferior parietal cortex and supramarginal gyri (Corbetta et al., 2008). This network plays a role in attentional shifting and filtering sensory input according to behavioral relevance. A strong negative association between smoking frequency and VS connectivity to regions in the medial PFC (mPFC) was also observed. Studies of patients with lesions to the mPFC have shown that this region is involved in decision-making under risk, biasing healthy individuals toward more conservative choices (Clark et al., 2008). Taken together with the finding of increased connectivity between the VS and OFC, the deficit in right IFG, inferior parietal (and superior occipital) cortex, and mPFC connectivity is consistent with the imbalance model's account of an over-active motivational system, receiving heightened input from regions central in the valuation of stimuli, and not being reigned in sufficiently by an underactive inhibitory control system and a deficit in directing attention toward behaviorally relevant stimuli.

In addition to the above-mentioned ROIs, there was a significant association between smoking frequency and functional connectivity between the VS and the amygdala. Connectivity between the right VS and the right amygdala has been found to be associated with the relevance of stimuli (Ousdal, Reckless, Server, Andreassen & Jensen, 2012). This is consistent with present findings of higher VS connectivity to regions associated with salience and valuation of stimuli. VS connectivity to the adjacent bilateral temporal poles on the other hand showed a strong negative association with smoking frequency. A previous study found that adult smokers' level of nicotine dependence was positively associated with activation in the temporal pole and insula during presentation of smoking compared to food cues (Claus et al., 2013). While the majority of studies

examining temporal pole function have focused on social cognition and emotion processing, there is some evidence that the temporal pole could serve as a hub integrating emotional and sensory cues (Fan et al., 2014; Pehrs et al., 2015; Olson et al., 2007). Furthermore, reduced grey matter volume in the temporal pole has been reported in cocaine users (Albein-Urios et al., 2013), making this region a promising target for further investigation in substance use.

While PPI analysis is a valuable tool for identifying functional differences in connectivity, it is not able to identify anatomical or structural alterations in connectivity. Conducting PPI in conjunction with tractography (e.g., Cohen, Elger & Weber, 2008) would allow the identification of structural differences associated with functional connectivity alterations in smokers. Furthermore, PPI analyses often suffer from a lack of power, particularly when event-related tasks are used (O'Reilly, Woolrich, Behrens, Smith & Johansen-Berg, 2012). However, low power is a chronic problem in neuroimaging research (Button et al., 2013). In this study this issue was addressed by using a large sample, and a very rigorous analysis protocol. Cross-validation and bootstrapping are valuable tools for guarding against false positives (Whelan & Garavan, 2014) and identifying true, but small, effects. In addition, the random-label permutation (null model) approach which was adopted is an effective means of quantifying the validity of results.

In conclusion, the use of a PPI analysis in conjunction with a robust machine learning approach identified differences in VS connectivity during reward anticipation associated with adolescent smoking frequency. The increased functional connectivity between the VS and OFC and PCC with increased cigarette use suggests that adolescent smoking may be associated with increased attribution of salience to reward-related stimuli. Furthermore, the finding of reduced functional connectivity between the VS and the right IFG, mPFC, and inferior parietal cortex with increased smoking indicates a deficit in inhibitory control and attentional orienting. Taken together, these findings paint a picture of increased valuation of rewards, alongside difficulties inhibiting behavior, and possibly a deficit in the integration of sensory and motivational cues in adolescent smokers. Notably, present findings extend the literature showing differences in the neural networks underpinning reward processing between adolescent smokers and non-smokers, showing that reward processing also differs between different adolescent smoking trajectories. While it is not possible to deduce whether these differences in VS connectivity preceded smoking initiation, the link between reward-related activity in the VS and adolescent impulsivity supports the conclusion that differences in VS connectivity may pose a risk for adolescent smoking. Future longitudinal studies should evaluate whether VS connectivity can be established as a predictive biomarker of substance use risk in adolescence.

Chapter 5 - Altered reward sensitivity in current and former smokers: evidence from computational modelling of decision-making under uncertain conditions.

Publications:

Jollans, L., Whelan, R., Venables, L., Turnbull, O. H., Cella, M., & Dymond, S. (2016). Computational EEG Modelling of Decision Making Under Ambiguity Reveals Spatio-Temporal Dynamics of Outcome Evaluation. *Behavioural Brain Research, 321*, 28-35. DOI: 10.1016/j.bbr.2016.12.033.

5.1. Introduction

Although it has been well established that smokers and non-smokers differ in various aspects of trait impulsivity (Audrain-McGovern et al., 2004a, 2009; Dinn, Aycicegi & Harris, 2004; Rezvanfard et al., 2010; Mitchell, 1999; Balevich, Wein & Flory, 2013; Skinner, Aubin & Berlin, 2004), many behavioural paradigms measuring aspects of impulsive responding and sensitivity to positive and negative outcomes fail to find significant differences between groups. However, although there appear to be no behavioural differences between smoking groups in paradigms including the Stop Signal task (SST) and Monetary Incentive Delay Task (MID), strong and consistent differences in brain activity during these paradigms have been recorded between groups (Luijten et al., 2014; Rose et al., 2013; van Hell et al., 2010; Luo et al., 2011). The previous chapters showed that these differences in fMRI activity during the SST and MID task are also associated with future smoking behaviour and can predict smoking in adolescents. Brain differences observed during such behavioural task paradigms are typically interpreted to reflect differences in intangible and qualitative aspects of cognition. Such features of cognitive processing can also be estimated using computational models of behavioural responding. These models conjecture determining factors in the response or decision-making process that are not apparent from objective measures. Computational models of choice behaviour have the potential to illuminate aspects of pathological behaviour, and give insight into maladaptive cognitive processes. A model which accurately reflects a cognitive process might be expected to show a relationship to measures of brain function during execution of this cognitive process. Should it be possible to prove a neurobiological basis of a computational models of cognitive processes based on only behavioural responding, use of such models may be a viable alternative to more costly imaging studies for certain applications.

Given the role of reinforcement learning and sensitivity to positive and negative outcomes in the development of substance use behaviours, a behavioural paradigm assessing these domains has the potential to give insight into abnormalities in reward-related decision making in smokers compared to non-smoking groups. In the two previous chapters the MID task was used to evaluate anticipation of, and response to rewarding outcomes. However, the MID task is not a good measure of how behaviour is adapted based on positive or negative outcomes, as the single behavioural measure of behaviour change in the MID is response time. Furthermore, the individual trial outcomes in the MID task are manipulated to ensure a sufficient amount of trials with each outcome type. An examination of reward- and punishment-related behaviour and reinforcement learning requires a different task framework. A measure that has been widely used to examine reinforcement learning and reward sensitivity in healthy and pathological populations is the Iowa Gambling Task (IGT; Bechara et al. 1994). The IGT relies on participants learning from reward and punishment to maximize rewards over the course of the task, and allows insight into how

participants respond to outcome valence and outcome magnitude. During the IGT participants choose among four decks of cards. Each deck yields an average monetary (or point) win and loss, with two of the four decks yielding a net gain over multiple trials (advantageous/good decks), and the other two decks yielding a net loss (disadvantageous/bad decks). Of the advantageous and disadvantageous decks respectively one deck results in less frequent but larger losses than the other deck. The participants' goal is to maximize monetary or point gain after 100 trials. Advantageous performance on the IGT is based on approximations of long-term consequences rather than exact calculations (Christakou et al., 2009), and choice behavior typically shifts across trials as participants learn to make more advantageous selections with increasing knowledge of the outcome contingencies (Gansler et al., 2011). Inferior performance on the IGT has been observed in several substance using groups (Petry, Bickel, & Arnett, 1998; Verdejo-Garcia et al., 2007; Mazas, Finn, & Steinmetz, 2000; Grant, Contoreggi, & London, 2000). Findings relating to the effect of smoking on IGT performance are unclear (Buelow & Suhr, 2014; Businelle et al., 2009; Lejuez et al., 2003; Harmsen et al., 2006). However, there is some evidence that adolescents who had smoked in the past week performed significantly worse on the IGT than never-smokers (Xiao et al., 2008), and that both non-smokers and ex-smokers outperformed current young adult smokers on a variation of the IGT (Briggs et al., 2014).

There exists a large and sophisticated literature using computational modelling to examine aspects of task performance in the IGT (e.g. Busemeyer and Stout, 2002; Ahn et al., 2008, 2011; Fridberg et al., 2010; Worthy et al., 2013). This is not the case for many other experimental measures of response to reward and punishment, including the MID task. Previous work has used computational modelling of IGT performance to examine characteristics of choice behaviour in substance using groups (Yechiam et al., 2005; Fridberg et al., 2010; Ahn et al. 2014), considering factors such as the attention given to outcome valence (i.e., to wins vs. losses), how the recency of feedback affects future decisions, and how choices are influenced by experience (i.e., to what extent choices are random). Models of behaviour in the IGT assume that the valence experienced on each trial informs a probabilistic choice mechanism, and shapes outcome expectation and prediction error on subsequent trials. Computational models of task behaviour thus estimate individuals' subjective experiences of the task and task-expectations, rather than objective task outcomes (Yechiam et al., 2005). Furthermore, the parameters used in the models of choice behaviour can be used to examine how populations differ in terms of their decision-making processes (Cella et al. 2010; Yechiam et al., 2005). Considering the inconsistent results across studies examining the effect of smoking on IGT performance, use of a computational modelling approach to identify qualitative elements of decision-making that differ between groups in this task may provide some insight into whether and how smokers, non-smokers, and ex-smokers differ in their approach to decision-making under ambiguous conditions. This may in turn provide some

insight into the processes guiding increased impulsive responding and differences in reinforcement learning between smoking and non-smoking groups.

In addition to behavioural and computational studies, the IGT has also been a target for neuroimaging studies investigating the neural underpinnings of adaptive decision-making (Christakou et al., 2009; Gansler et al., 2012). While both computational modelling and neuroimaging studies of the IGT endeavor to describe factors underlying task behaviour, the two approaches have not been combined to establish whether computational models of the IGT have an observable link to brain function. There is a large body of work investigating reinforcement learning using EEG (e.g. Sambrook & Goslin, 2015), and the high temporal resolution of event-related potentials (ERPs) is conducive to an examination of the temporal dynamics of decision-making. Previous work has shown that ERPs associated with the anticipation and processing of wins and losses are sensitive to the valence, magnitude, and likelihood of the outcome (Holroyd et al. 2004, 2011; Hajcak et al. 2005; Wu and Zhou 2009; Talmi et al. 2012; Fuentemilla et al. 2013). Given a model-based estimate of subjective choice and outcome value, aspects of the ERP associated with less objective trial outcomes could also be evaluated. For this, a trial-by-trial evaluation of ERPs is necessary, which departs from the typical procedure of averaging over trial types employed in most EEG studies (e.g., Hajcak et al. 2006; see Larsen and O'Doherty, 2014, for an exception).

This study contrasts the three most successful computational models of choice behaviour currently available for the IGT: The Prospect Valence Learning (PVL) model with a decay reinforcement learning rule (PVL-Decay), the PVL model with a delta learning rule (PVL-Delta), and the Value Plus Perseverance (VPP) model. The fit of these models to a group of non-smokers, a group of ex-smokers, and a group of current smokers is evaluated. Based on the best-fitting model the model parameters reflecting qualitative aspects of decision-making are extracted and compared between groups. To examine whether there is an observable neurobiological basis to these models, associations between model-based regressors and EEG data collected during the task are examined in a separate sample of control subjects. In this sample, participants' subjective appraisal of their chosen deck and prediction errors are estimated using the best-fitting model, and this subjective evaluation component is applied as a trial-by-trial regressor to each participant's EEG data with the goal of identifying elements in the ERP that are ostensibly associated with subjective outcome appraisal. Taken together these analyses will show (1) how IGT choice patterns differ between smoking and non-smoking groups, (2) what computational model can best account for these choice patterns, (3) whether the model that accounts best for behavioural data has a link to neurobiological activity during the task, and (4) how model-based quantifications of the cognitive processes utilized in the IGT differ between smoking and non-smoking groups.

5.2. Methods

5.2.1. Participants

5.2.1.1. Smoking, non-smoking, and ex-smoking groups

Participants were drawn from two separate data collection protocols with slight variations in demographic and smoking assessment. In both protocols participants self-identified as current smokers, former smokers, or non-smokers. For participants who classified themselves as current or former smokers, past month and lifetime smoking was assessed using the following scale to measure cigarette use: 0: no use, 1: 1 to 2 uses, 2: 3 to 5 uses, 3: 6 to 9 uses; 4: 10 to 19 uses, 5: 20 to 39 uses, 6:40 or more uses. Ex-smokers (n=22, 11 female, 11 male) reported a score of 6 for lifetime cigarette uses, having ever smoked daily, and a maximum score of 2 for past month smoking. Current smokers (n=51, 26 female, 1 genderqueer, 24 male) reported scores of 4 or higher for past month smoking. Lifetime smoking and daily smoking was assessed for only a subset of this group (n=24), for which scores for lifetime smoking were also 6. Of the remaining 27 participants for which lifetime use was not assessed, 21 said they sometimes chain-smoked, 26 said they sometimes smoked more than they intended, 26 said they sometimes felt they needed cigarettes to help them function, and 26 said they sometimes made special trips to get cigarettes. A group of non-smokers was also recruited (n=59, 36 female, 1 genderqueer, 22 male). All participants from the first data collection protocol (including all ex-smokers, 25 non-smokers and 24 smokers) were between the ages of 18 and 21. Participants from the second data collection protocol had a wider age range, with the 27 smokers varying in age from 18 to 61 (*mean age* = 26.4 years, *SD* = 8.2 years) and the 34 non-smokers varying in age from 18 to 37 (*mean age* = 24.4 years, *SD* = 6.6 years).

5.2.1.2. EEG sample

Twenty healthy, right-handed adults (9 female), 19 to 38 years old (*mean age* = 24.9 years, *SD* = 4.8 years) participated.

5.2.2. Iowa Gambling Task

A computerized variant of the original IGT (Bechara et al. 1994) was used, in which participants were instructed to select cards from four concurrently available decks (labeled A, B, C and D). Deck locations were randomly varied across participants. Trials were preceded by a 2-s choice appraisal interval, during which choices could not be made, as the four individual decks and the text, “Please consider your choice” appeared on screen. After this, choices were made using

the mouse (the cursor was centered at the start of every trial). An initial 'loan' of 1000 virtual money, ($ for the smokers, non-smoker, and ex-smoker groups, £ for the EEG sample) displayed at the bottom of the screen, was updated immediately following choices accompanied by text stating the amount of money gained and/or lost. Decks varied in their net outcome and frequency of loss outcomes (see Table 5.1). Decks that had a net positive outcome were termed 'advantageous' decks (Deck C and D), and decks with a net negative outcome were termed 'disadvantageous' decks (Deck A and B). Decks A and C resulted in frequent small losses while decks B and D resulted in infrequent larger losses. Onscreen feedback was displayed for 10s, before a 2s inter-trial interval. The task ended after 100 trials.

Table 5.1. Win and loss contingencies of all decks in the IGT

Deck	A	B	C	D
Win (per trial)	100	100	50	50
Loss (per 10 trials)	1250	1250	250	250
Loss frequency	5/10	1/10	5/10	1/10
Loss range	150-350	1250	25-75	250

5.2.3. Computational models of behavioural data

The deck chosen on trial *t* is denoted *D(t).* The reward received on each trial is denoted *R(t)*, and the loss on each trial is denoted *L(t)*, such that if deck B (a disadvantageous deck) were chosen on trial *t* = 9 (i.e. *D(9)* = D_2) then *R(D(9))* = 100 and *L(D(9))* = 1250. The total monetary outcome on each trial is denoted *X(t)*, such that *X(9)* = - 1150 in the example above.

An approximation of the subjective valence *u(t)* on trial *t* is calculated based on *X(t)* using the prospect utility function in the PVL-Decay model, the PVL-Delta model, and the VPP model:

$$u(t) = \begin{cases} X(t)^{\alpha} \; if \; X(t) \geq 0 \\ = -\lambda * |X(t)|^{\alpha} \; if \; X(t) < 0 \end{cases} \qquad [1]$$

Subjective valence *u(t)* is calculated using a shape parameter α, and a loss aversion parameter λ. High values of α indicate high sensitivity to feedback. Lower values of λ indicate less sensitivity to losses, with values smaller than 1 indicating lower sensitivity to losses than to gains. The subjective valence value *u(t)* is used to calculate the expected valence $Ev(t+1)_j$ for the selected deck *j* on the following trial using a learning rule. The PVL-Delta model and the VPP model use a Delta Learning rule to calculate expected valence:

$$Ev_j(t+1) = Ev_j(t) + A * \delta_j(t) * \Big(u(t) - Ev_j(t)\Big) \qquad [2]$$

Here, *A* is a *recency parameter* (or *learning rate*) that determines how previous experience with the chosen deck *j* is weighted in comparison to the most recent deck selection. Higher values of *A* indicate that the most recent outcome has a high influence on expectations for future outcomes with this deck, while low values indicate lower influence of the most recent outcome and higher influence of previous experience. The recency parameter can also be understood as a measure of how quickly or slowly past outcomes are forgotten. The Delta learning rule only updates the expected valence of the selected deck *j* on each trial, as expressed through the dummy variable $\delta_j(t)$ that is 1 if deck *j* is chosen on trial *t* and 0 otherwise. The decay reinforcement learning rule used in the PVL-Decay model updates expected valence values for each deck on every trial:

$$Ev_j(t+1) = A * Ev_j(t) + \delta_j(t) * u(t) \quad [3]$$

Here *A* is also a parameter accounting for the recency of past outcomes, but is better conceptualized as a *decay rate*. Low values of *A* indicate rapid decay of expected outcomes for the selected and unselected decks on each trial, while high values of *A* indicate a lower rate of discounting outcome expectancies, or slower forgetting. For the PVL-Decay and PVL-Delta models the expected valence value $Ev_j(t+1)$ for each deck *j* is used as input into a Softmax action-selection rule to calculate the probability $Pr[D(t+1)=j]$ that deck j will be selected on the next trial:

$$Pr[D(t+1) = j] = \frac{e^{\theta(t)Ev_j(t+1)}}{\sum_{k=1}^{4} e^{\theta(t)Ev_k(t+1)}} \quad [4]$$

The sensitivity θ is assumed to be trial-independent and set at 3^c-1. The consistency parameter *c* quantifies to what extent participants make choices in accordance with the expected valence for each deck. High values of *c* indicate more deterministic and consistent choice patterns, while low values of *c* indicate more random or exploratory choice behaviour.

Unlike the two PVL models, the VPP model includes a measure of perseverance P_j which considers the likelihood of selecting deck *j* again based on outcome valence:

Chosen deck: $$P_j(t+1) = \begin{cases} k * P_j(t) + \varepsilon_{pos} \; if \; X(t) \geq 0 \\ k * P_j(t) + \varepsilon_{neg} \; if \; X(t) < 0 \end{cases} \quad [5]$$

Unchosen decks: $$P_j(t+1) = k * P_j(t)$$

The parameter *k* is a decay rate parameter similar to the parameter *A* in [3]. Parameters ε_{pos} and ε_{neg} indicate likelihood to persevere in choosing deck *j* despite or because of positive or negative outcomes respectively. Negative values of $\varepsilon_{pos}/\varepsilon_{neg}$ indicate a tendency to switch to a different deck after receiving positive/negative feedback, while positive values of $\varepsilon_{pos}/\varepsilon_{neg}$ indicate that positive/negative feedback reinforces perseverance in choosing the same deck again on the

subsequent trial. Perseverance and expected valence values are combined to calculate the overall value V_j of each deck:

$$V_j(t+1) = \omega * Ev_j(t+1) + (1-\omega) * P_j(t+1) \qquad [6]$$

The reinforcement learning parameter ω indicates to what extent choice behaviour relies on reinforcement learning (*Ev*) rather than on the perseverance heuristic (*P*). High values of ω indicate higher reliance on reinforcement learning while lower values of ω indicate higher reliance on the perseverance heuristic and lower reliance on reinforcement learning. In the VPP model the overall deck value $V_j(t+1)$ is used as input into the same Softmax action-selection rule in the same way as $Ev_j(t+1)$ is used in the two PVL models:

$$Pr[D(t+1) = j] = \frac{e^{\theta(t)V_j(t+1)}}{\sum_{k=1}^{4} e^{\theta(t)V_k(t+1)}} \qquad [7]$$

Previous studies have found that the PVL-Delta model has the best post-hoc fit using the Bayesian Information criterion (BIC), while the PVL-Delta model shows the best simulation performance, being able to account for a variety of choice patterns, and the VPP model shows the best fit using a Bayesian factor (Steingroever et al., 2014; 2016; Ahn et al., 2014).

5.2.4. Model fitting

The hBayesDM package (Ahn, Haines & Zhang, 2017) was used to fit all models. hBayesDM is an R package designed to fit computational models of reinforcement learning and decision making using hierarchical Bayesian analysis. Markov Chain Monte Carlo (MCMC) sampling is used for posterior inference. Three simultaneously run MCMC chains were used for each parameter, and convergence was assessed visually and using the R̂ statistic (Gelman & Rubin, 1992). R̂ values close to 1.0 indicate that all chains have successfully converged to their stationary distributions, while values above 1.1 indicate inadequate convergence. MCMC chains were initialized randomly, and a total of 3000 samples including 2000 burn-in samples were collected. Models were fit separately for each group, as group-level parameter values are used in the hierarchical Bayesian model fitting framework. As suggested by Steingroever, Wetzels, and Wagenmakers (2016) performance of the models was assessed when making predictions for the next trial based on previous choices (post-hoc fit) as well as the performance of the models when making predictions about choice behaviour without information about previous deck selections (simulation). As this feature was not available in the hBayesDM package at the time of this study, simulation performance was assessed using custom MATLAB scripts and the parameter values extracted from the hBayesDM fit, and using the procedure described in Appendix B of Ahn, Busemeyer, Wagenmakers, and Stout (2008).

The PVL-Decay and PVL-Delta models often show convergence difficulties. In line with previous work (Steingroever et al., 2014) five chains instead of three were run when convergence difficulties were observed, and subsequently parameter values were extrapolated using the three chains with least deviance. This was done for the PVL-Decay models for all groups, and for the PVL-Delta models for the smoker and non-smoker groups.

5.2.5. Parameter comparison

Model parameters for the best-fitting model were compared between groups for the smoker, non-smoker, and ex-smoker groups by assessing overlap of the parameter distributions using the interval between the 5^{th} and 95^{th} percentile of group distributions as the criterion. A similar approach to establishing differences in value distributions based on Bayesian model fitting was used by Wiecki, Sofer and Frank (2013).

5.2.6. EEG recording

EEG data were recorded in a sound-attenuated room using the ActiveTwo Biosemi™ electrode system from 134 electrodes (128 scalp electrodes) organized according to the 10-5 system (Oostenveld and Praamstra 2001), digitized at 512 Hz.

5.2.7. EEG analysis

5.2.7.1. EEG data processing

EEG preprocessing and artifact rejection was performed using the Fully Automated Statistical Thresholding for EEG artifact Rejection toolbox (FASTER; http://sourceforge.net/projects/faster; Nolan et al. 2010), implemented in EEGLAB (Delorme and Makeig 2004) under Matlab 7.12. EEG data were filtered (1–95 Hz, with a notch filter at 50 Hz). Epoch length was initially set to -3 s to 2 s for the outcome evaluation phase (marker set to onset of outcome). EEG data from one participant was excluded due to poor data quality.

EEG data were processed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Data from each participant were transformed into two-dimensional sensor-space (interpolated from the 128 scalp channels), over peri-stimulus times from -100–600 ms for the feedback processing phase, thus producing a three-dimensional spatio-temporal characterization of the ERP. Baseline was corrected from 100 ms before cue presentation. The EEG timeseries data were subsequently parcellated based on both spatial and temporal domains. Data were averaged in 64 spatial bins, and across time segments of 25.4 ms (resulting in 23 time bins in the outcome phase).

5.2.7.2. Outcome measures

For each participant, three variables were used as regressors in a general linear model with the parcellated data from the phase of the same trials: the valence and the magnitude of the outcome (objective outcome measures), and the trial-by-trial choice probability for the selected deck calculated using the best-fitting model. The temporal and spatial properties of associations between regressors and the EEG timecourse across the whole outcome interval were examined. Associations between valence, magnitude and choice probability and two ERP components that consistently occur following feedback, the Feedback-related negativity (FRN) and the P3, were examined.

5.2.7.3. Significance testing

A linear regression was carried out for each regressor individually. This resulted in a beta weight being generated for each regressor and each bin. The same calculations were also carried out using a random permutation of the model regressors (i.e. the values of each regressor were shuffled), which resulted in a baseline, or 'null' distribution. For each regressor and each of the bins a one-sample t-test was carried out using the beta values for each participant, as well as the beta values from the random label permutations. For each regressor the bins in which the test statistic was larger than the 95th percentile of the distribution of test statistic values for the beta weights generated using random label permutations were deemed significantly associated with the regressor. A simplified representation of the analysis framework is shown in figure 5.1.

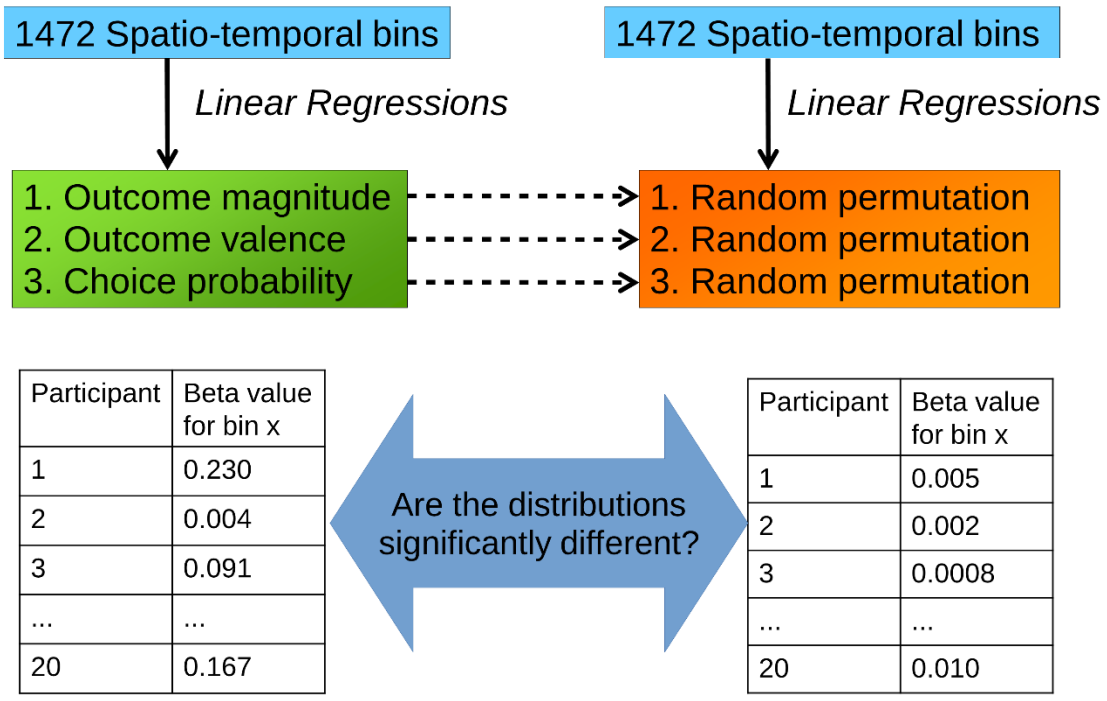

Figure 5.1. Simplified representation of the analysis framework used to determine which Spatio-temporal bins of the EEG were significantly associated with one of the trial-by-trial regressors.

5.3. Results

5.3.1. Behavioural task performance

Over the entire task the percentage of choices from disadvantageous decks was significantly higher than that of advantageous decks for both ex-smokers and smokers, but not non-smokers or the EEG sample (see Table 5.2, Figure 5.2). The percentage of selections from frequent loss decks was significantly lower than from infrequent loss decks for all groups except ex-smokers. Groups did not significantly differ (p<.005) in their percentage overall choices from frequent/infrequent loss decks, advantageous/disadvantageous decks, or from the four individual decks.

Table 5.2. Percentage of choices from disadvantageous and infrequent loss decks for all groups

	Disadvantageous deck Mean (Standard Deviation)	Infrequent loss decks Mean (Standard Deviation)
Ex-smokers	64.50 (28.70)*	54.86 (22.27)
Smokers	57.86 (26.04)*	56.98 (24.09)*
Non-smokers	52.22 (20.13)	57.49 (21.66)*
EEG sample	52.15 (13.09)	59.05 (9.66)*

*p<.005 for t-test comparison with other deck choice frequency

Ex-smokers made significantly more choices from disadvantageous decks than non-smokers in the fourth block of 20 trials ($Mean_{Ex}$=13.09, $Mean_{Non}$=9.20, p=.004). In the first task block the EEG sample chose deck A (disadvantageous with frequent losses) significantly less than the ex-smoker group (p=.0044, $Mean_{Ex}$=6.40, $Mean_{EEG}$=4.63) and deck B (disadvantageous with infrequent losses) significantly more than the smoker group (p=.0027, $Mean_{Smo}$=5.94, $Mean_{EEG}$=8.26). In the third task block ex-smokers chose deck D (advantageous with infrequent losses) significantly less than smokers (p=.0008, $Mean_{Ex}$=2.54, $Mean_{Smo}$=4.84), non-smokers (p=.0018, $Mean_{Non}$=4.62) and the EEG sample (p=.00008, $Mean_{Smo}$=6.10). No other significant differences emerged at the p<.005 level.

5.3.2. Post-hoc model fit

Across all participants post-hoc fit was best for the PVL-Delta model (see Table 5.3) although within the groups post-hoc fit for the PVL-Delta model was only better than fit of the VPP model in the smoker group.

Table 5.3. Post hoc and simulation fit and model comparison for all models in all groups

		Mean AIC	Mean BIC	AIC Comparison with PVL-Decay model	AIC Comparison with PVL-Delta model	Mean Square Deviation (MSD)	MSD Comparison with PVL-Decay model	MSD Comparison with PVL-Delta model
Smokers	*PVL-Decay*	738.74	750.16	-	-	.2055	-	-
(n=51)	*PVL-Delta*	560.30	570.72	*t*=3.23; *p*=.0021	-	.2002	*t*=1.04; *p*=.3087	-
	VPP	903.07	923.91	*t*=3.00; *p*=.0041	*t*=6.16; *p*=1*10^-7	.2009	*t*=0.64; *p*=.5233	*t*=1.62; *p*=.1191
Non-smokers	*PVL-Decay*	640.99	651.41	-	-	.2052	-	-
(n=59)	*PVL-Delta*	709.46	719.88	*t*=1.10; *p*=.2739	-	.2161	*t*=2.34; *p*=.0224	-
	VPP	618.96	639.80	*t*=0.36; *p*=.7183	*t*=2.24; *p*=.0289	.2032	*t*=0.53; *p*=.5977	*t*=2.55; *p*=.0132
Ex-smokers	*PVL-Decay*	778.44	788.86	-	-	.2123	-	-
(n=22)	*PVL-Delta*	812.54	822.96	*t*=0.47; *p*=.6428	-	.2063	*t*=1.43; *p*=.1569	-
	VPP	634.47	655.31	*t*=2.21; *p*=.0377	*t*=3.07; *p*=.0058	.2174	*t*=1.01; *p*=.3129	*t*=0.13; *p*=.8918
EEG data set	*PVL-Decay*	994.48	1004.90	-	-	.1946	-	-
(n=19)	*PVL-Delta*	701.20	711.62	*t*=4.77; *p*=.0001	-	.2263	*t*=3.12; *p*=.0059	-
	VPP	508.87	529.71	*t*=7.77; *p*=3*10^-7	*t*=4.48; *p*=.0002	.2046	*t*=1.67; *p*=.1112	*t*=2.53; *p*=.0206
All	*PVL-Decay*	738.85	749.27	-	-	.2050	-	-
participants	*PVL-Delta*	673.06	683.48	*t*=1.88; *p*=.0615	-	.2106	*t*=1.96, *p*=.0507	-
(n=151)	*VPP*	703.32	724.16	*t*=0.98; *p*=.3271	*t*=0.94; *p*=.3479	.2047	*t*=0.13, *p*=.8934	*t*=1.93, *p*=.0543

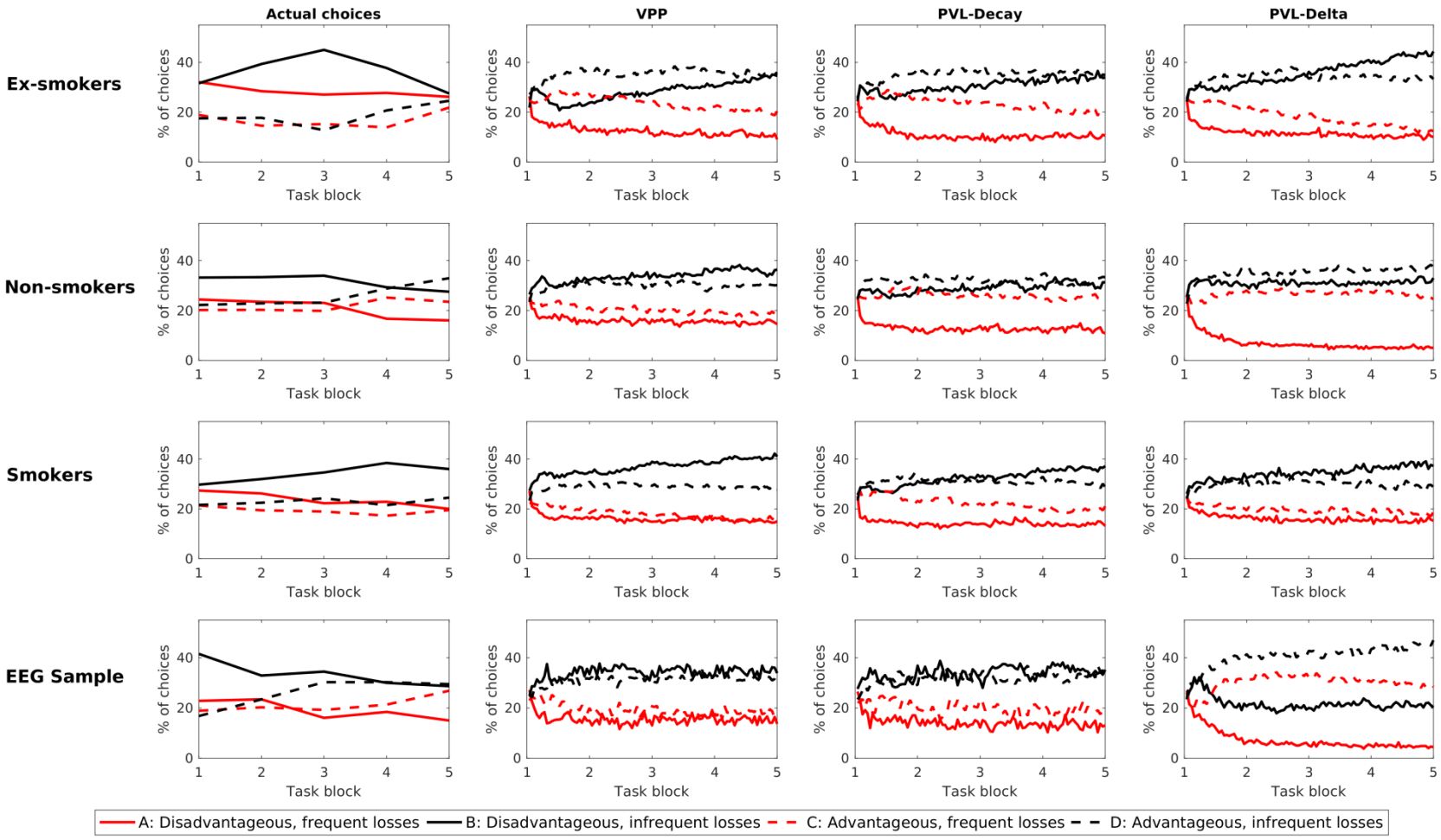

Figure 5.2. Deck choices and simulation performance of the VPP, PVL-Decay, and PVL-Delta models for the ex-smoker, non-smoker, current smoker, and EEG control participant group. Loss frequency is presented through line color, with black lines indicating infrequent loss decks. Mean reward value of the decks is presented through line style, with dashed lines indicating advantageous decks.

5.3.3. Simulation fit

As suggested by Steingroever, Wetzels, and Wagenmakers (2015), 100 iterations of the procedure to obtain simulated choice probabilities for each participant were completed (see Figure 5.2). Fit was determined based on Mean square deviation (see Figure 5.3, Table 5.3). Across all participants the VPP model had the best simulation fit although the PVL-Delta model had the best simulation fit in the smoker and ex-smoker group and MSD for the PVL-Decay model was lowest in the EEG sample.

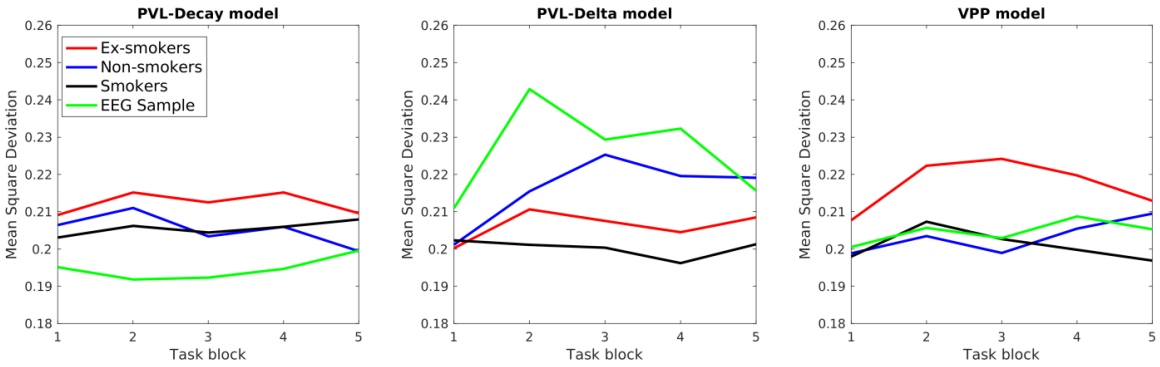

Figure 5.3. Mean square deviation indicating simulation error for all models by task block.

Based on the post-hoc and simulation fit, data from both the VPP and PVL-Delta models were used to carry out parameter value comparison between the ex-smoker, smoker, and non-smoker groups. The evaluation of the expression of model-based regressors in the EEG timecourse was also carried out using the VPP and PVL-Delta models.

5.3.4. Model Parameter comparison

5.3.4.1. PVL-Delta model parameters

There were no differences in the group-level distributions of model parameters for the PVL-Delta model (see Figure 5.4, Table 5.3).

5.3.4.2. VPP model parameters

Ex-smokers had higher values of α (outcome sensitivity) than non-smokers. Smokers had higher values of ω (reinforcement learning) than ex-smokers and non-smokers (see Figure 5.5, Table 5.3).

Table 5.3. VPP and PVL-Delta model parameter value medians (Interquartile range) by group

	Smokers (N=53)	Non-smokers (N=59)	Ex-smokers (N=25)
VPP model parameters			
α: outcome sensitivity	0.890 (0.640)	0.484 (0.194)	1.511 (0.130)
λ: Loss aversion	0.031 (0.013)	0.057 (0.022)	0.015 (0.003)
A: recency	0.130 (0.196)	0.389 (0.484)	0.484 (0.285)
K: Decay rate	0.430 (0.322)	0.434 (0.321)	0.479 (0.129)
ε_{pos}: Impact of gain	3.956 (14.312)	8.162 (21.832)	6.787 (5.639)
ε_{neg}: Impact of loss	-4.478 (20.961)	-0.141 (15.315)	4.170 (14.483)
ω: Reinforcement learning	0.913 (0.003)	0.852 (0.035)	0.872 (0.012)
c: Consistency	0.993 (0.027)	0.688 (0.222)	0.686 (0.047)
PVL-Delta model parameters			
α: outcome sensitivity	1.061 (1.779)	0.502 (0.336)	1.230 (0.899)
λ: Loss aversion	0.014 (0.016)	0.218 (0.249)	0.022 (0.016)
A: recency	0.134 (0.341)	0.271 (0.654)	0.265 (0.304)
c: Consistency	1.124 (0.328)	0.908 (0.704)	0.890 (0.583)

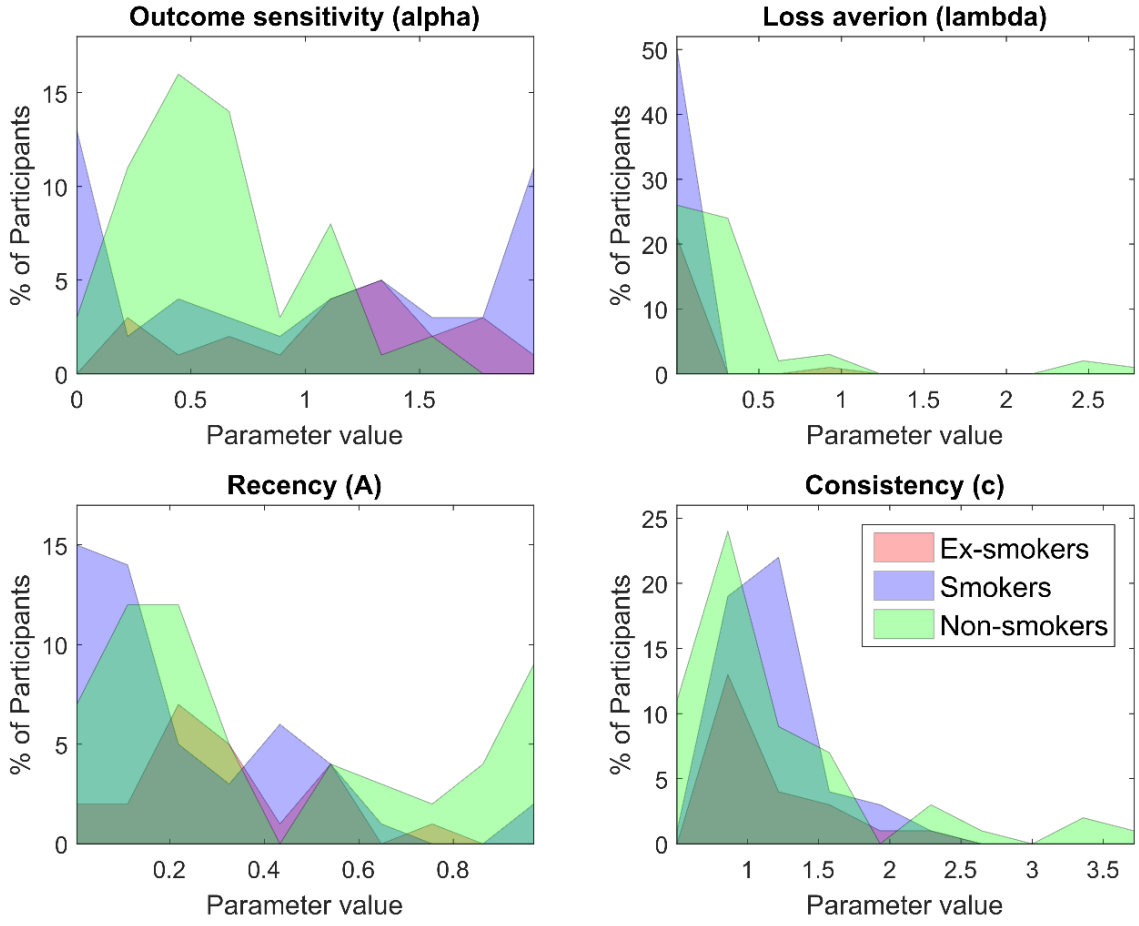

Figure 5.4. PVL-Delta model parameter value distributions for all groups.

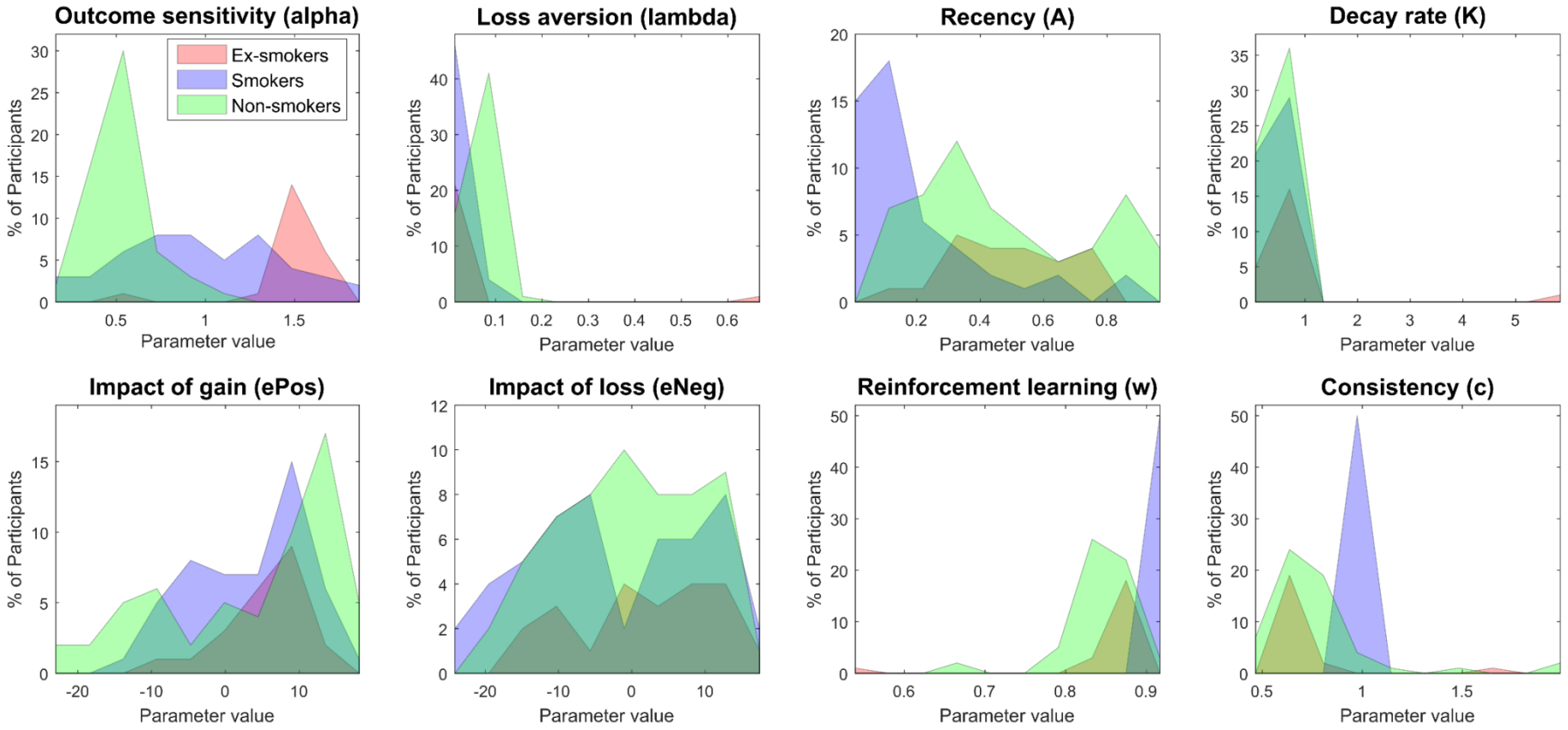

Figure 5.5. VPP model parameter value distributions for all groups.

5.3.2. Associations between outcome measures and the EEG timecourse

5.3.2.1. Bins associated with objective trial outcomes

Valence was significantly associated with the ERP in 201 bins throughout most of the outcome processing interval, up to approximately 500ms after feedback presentation (see Figure 5.6). The largest number of significant associations between the ERP and valence occurred between 279ms and 457ms after feedback presentation in central and anterior scalp locations, although there were also many significant associations between 102ms and 178ms after feedback presentation in right central and anterior scalp locations. The ERP was significantly associated with outcome magnitude in 53 bins, of which most fell within the first 150ms of feedback presentation. Outcome magnitude and valence were both associated with activity in 18 bins. These included two right posterior bins between 25ms and 102ms, six right anterior bins between 279ms and 356ms, three right and three left anterior bins between 356ms and 432ms, and four left posterior bins between 457ms and 483ms. Both outcome magnitude and outcome valence were also associated with activity in separate posterior scalp locations between 533ms and 559ms after feedback presentation.

5.3.2.2. Bins associated with choice probability

The VPP model choice probability was significantly associated with the ERP in 43 bins, with the majority of significant associations falling between 127ms and 279ms in left and midline scalp locations, and between 406ms and 533ms in central and anterior locations. The PVL-Delta model choice probability was significantly associated with the ERP in 38 bins in midline and right scalp locations between 25ms and 102ms, in midline and left scalp locations between 127ms and 279ms, and in similar central and anterior locations to VPP choice probability between 406ms and 533ms. There were 13 bins in common between the two choice probability variables. Two of these bins in a left anterior scalp location between 152ms and 178ms were shared by outcome valence. In addition, both probability variables were associated with activity in a left posterior bin between 254ms and 279ms, with three left anterior bins between 431ms and 483ms, with five right central bins between 431ms and 533ms, and with one left anterior bin between 558ms and 584ms. The non-shared bins for each probability variable fell within similar time ranges and scalp locations as the shared bins.

5.3.2.3. Bins associated with objective variables and choice probability

PVL-Delta choice probability and both objective outcome measures were significantly associated with the ERP in the first 100ms of the outcome phase in a right posterior bin. Both VPP and PVL-Delta choice probability and objective outcome valence were significantly associated with

two left anterior bins between 152 and 178ms. VPP choice probability and valence were also both associated with two additional left anterior bins in this time interval, and with three left anterior bins between 432 and 457ms. VPP choice probability and outcome magnitude were both associated with a left central bin between 381 and 406ms.

5.3.3. Associations between outcome measures and predefined ERPs

5.3.3.1. Feedback related Negativity (FRN)

Based on the observed EEG signal (see Figure 5.6, top panel), the FRN was defined as the interval between 178ms and 355ms. During the FRN time interval, outcome valence was associated with 77 bins, and outcome magnitude was associated with 7 bins (see Figure 5.7). VPP choice probability was associated with 9 bins, and PVL-Delta choice probability was associated with 7 bins. During this time interval, none of the bins with which PVL-Delta or VPP choice probability were associated were shared with bins associated with magnitude or valence, However, both choice probability variables were associated with activity in a left posterior bin between 254ms and 279ms.

5.3.3.2. P3

Based on the observed EEG signal (see Figure 5.6, top panel), the P3 was defined as the interval between 355ms and 482ms. During the P3 time interval, outcome valence was associated with 89 bins and outcome magnitude was associated with 15 bins (see Figure 5.7). VPP choice probability was associated with 15 bins, and PVL-Delta choice probability was associated with 12 bins. None of the bins associated with PVL-Delta choice probability during this time interval were shared by magnitude or valence, while activity in a left anterior bin between 381ms and 406ms was associated with VPP choice probability and magnitude, and activity in three left anterior bins between 431ms and 457ms was associated with VPP choice probability and valence. Furthermore, the majority of the shared associations of PVL-Delta and VPP choice probability fell within this time interval.

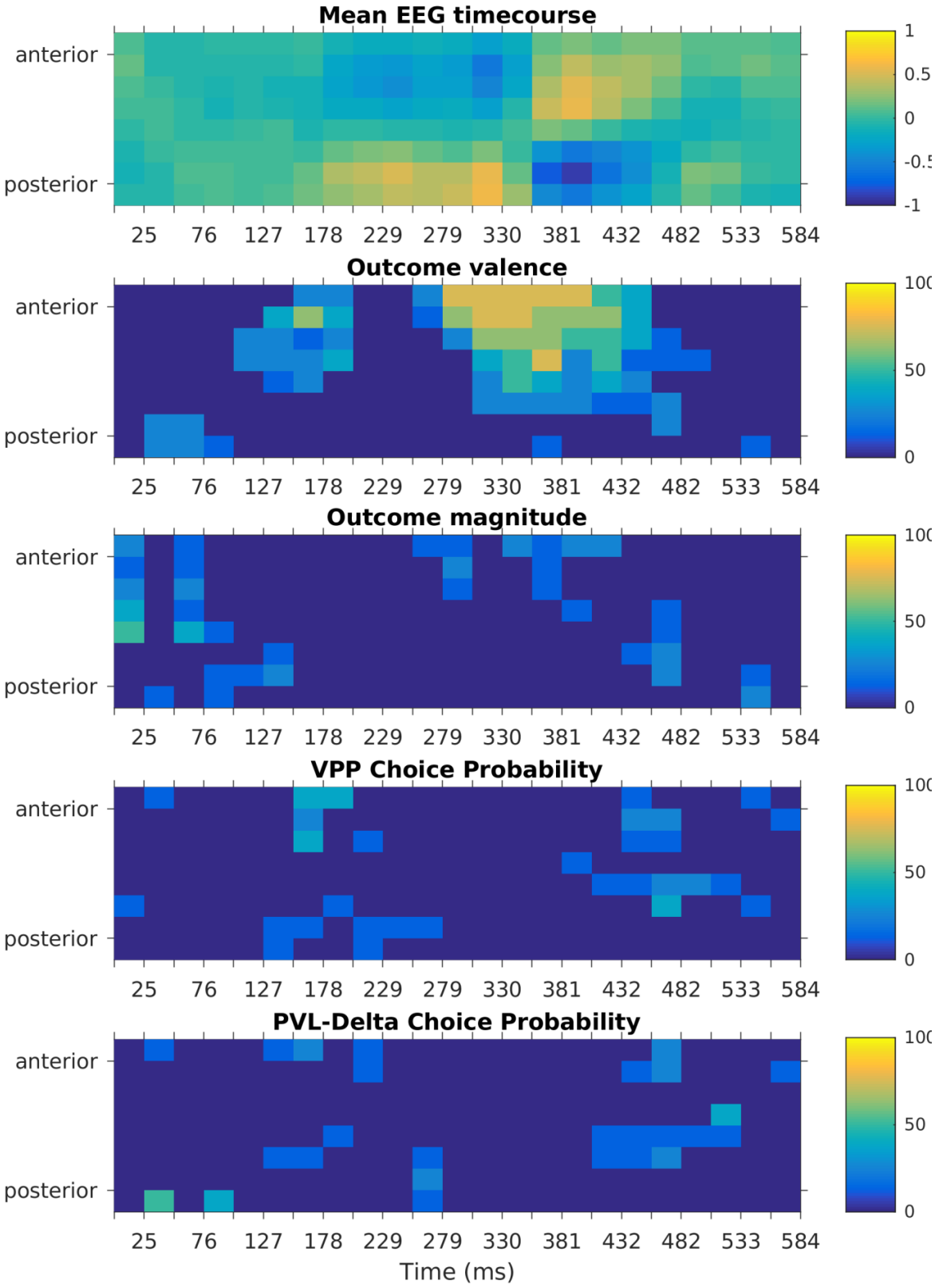

Figure 5.6. ERPs in each temporal bin from anterior to posterior, averaged over scalp bins from left to right and percentage of spatial bins from left to right in which each regressor was significantly associated with the ERP.

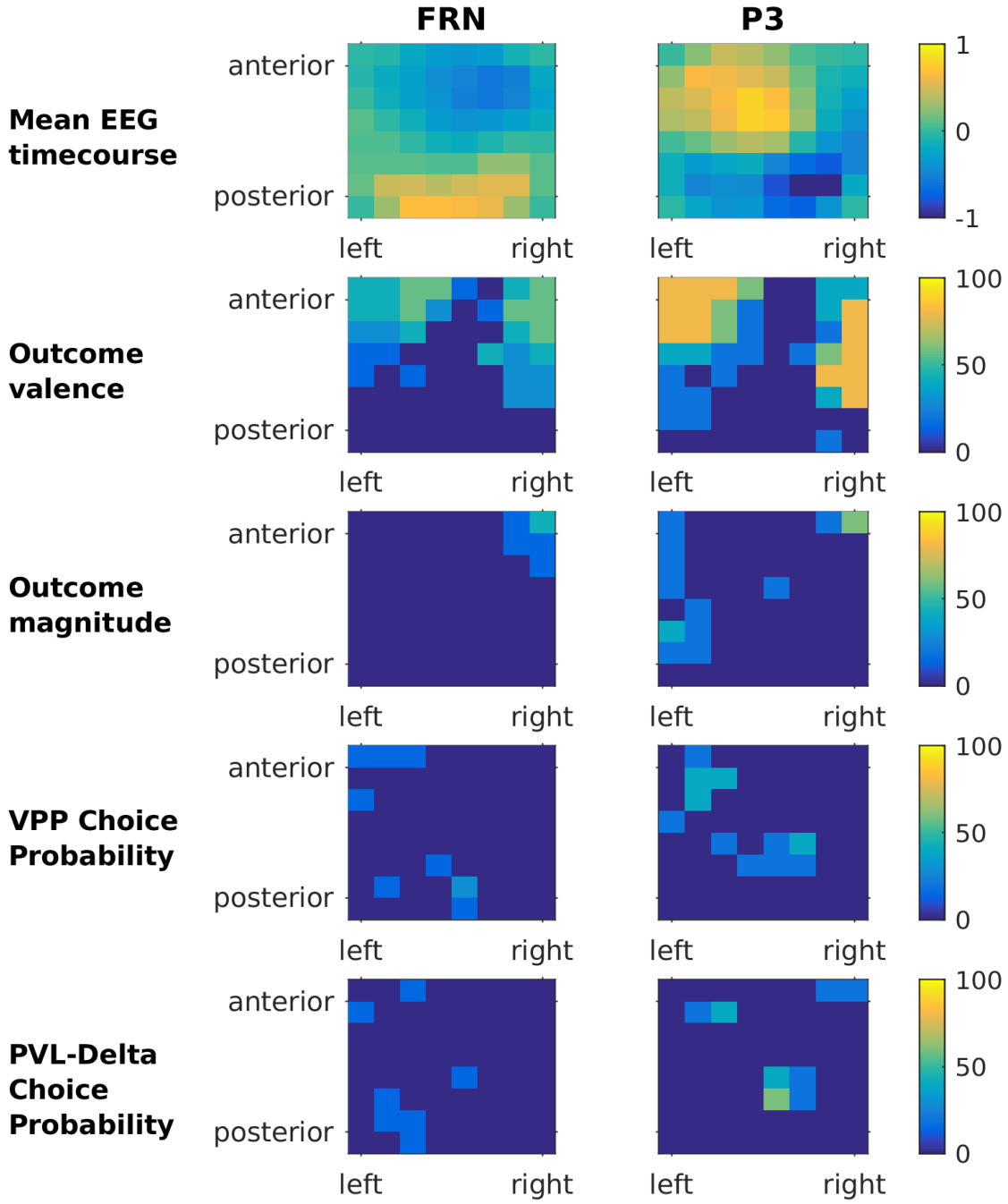

Figure 5.7. Feedback Related Negativity (FRN) ERP component with activation averaged across the FRN timecourse (178ms after feedback to 355ms after feedback) and P3 ERP component with activation averaged across the P3 timecourse (355ms after feedback to 482ms after feedback), and percentage of time bins during the FRN and P3 time intervals with which each regressor was significantly associated.

5.4. Discussion

In this study differences in choice behaviour between smokers, ex-smokers, and non-smokers in the IGT were observed. The different choice patterns between groups revealed variations in fit of computational models of IGT behaviour between groups. As reported in previous research, the PVL—Delta model provided good simulation-fit to atypical choice patterns (Steingroever, Wetzels & Wagenmakers, 2014) – in this case choice behaviour in the smoker and ex-smoker group. However, the VPP model fit better to choice behaviour in the healthy control samples. Despite superior fit of the VPP model to data from non-smoking groups, the expression of model-based regressors in the EEG of a control sample was similar for the PVL-Delta and VPP models, allowing conclusions about the validity of both models based on the observed shared effects. Examination of differences in parameter values of the PVL-Delta and VPP models supported an account of reward-based reinforcement learning as a trait that differs between current or former smokers and non-smokers.

Despite numerous studies showing no differences in IGT task performance between smoking and non-smoking groups (Buelow & Suhr, 2014; Businelle et al., 2009; Lejuez et al., 2003; Harmsen et al., 2006), this study revealed a clear pattern of atypical decision-making in both current and former smokers in this task. Unlike the non-smoking groups, both current and former smokers in this study showed a higher proportion of choices from disadvantageous decks than from advantageous decks throughout the task. Previous examinations of differences in performance of smokers and non-smokers on the IGT have indicated that differences in task performance may be due to an increased tendency to favour large rewards among smokers (Ert, Yechiam & Arshavsky, 2013). This study extends this conclusion to former smokers, suggesting that differences in reward-based feedback learning persist after smoking cessation. Furthermore, only former smokers showed no preference for decks with infrequent losses, indicating reduced sensitivity to negative outcomes. The three groups evaluated in this study thus show three distinct patterns of choice behaviour: Ex-smokers favor decks with large immediate gains with low sensitivity to frequency of losses; Current smokers favor decks with large immediate gains and avoid decks with frequent loss outcomes; Non-smokers do not favor decks with large immediate gains but avoid decks with frequent losses. Comparison with previous studies showed that the choice pattern of the ex-smoker group here was similar to that of cannabis users and the choice pattern of smokers showed similarities to that of abstinent heroin users, while the choice pattern of the non-smoker group was comparable to that observed in healthy controls in past studies (Fridberg et al., 2010; Ahn et al., 2014; Worthy et al., 2013).

Based on previous work, the PVL-Delta model shows the ability to generate good simulation performance, and to adapt to different choice strategies well (Ahn et al., 2008;

Steingroever et al., 2013; 2014). The best-fitting model based on post-hoc fit in this study was the PVL-Delta model, while the best-fitting model based on simulation fit was the VPP model. However, model fit varied across groups, with superior simulation fit of the VPP model for the non-smoking groups (showing the typical choice pattern seen in healthy control subjects), and superior fit of the PVL-Delta model for the smoker and ex-smoker group (showing atypical choice patterns). Although the prediction of choice patterns based on VPP simulations adequately recovered rank-order of decks for all but the ex-smoker group, PVL-Delta simulations provided somewhat better estimations of the change in choice patterns over the course of the task.

To determine whether there was any observable link between model-based value calculations and brain function during the task, the trial-by-trial values for choice probability calculated by the PVL-Delta and VPP models were used as regressors in a GLM of the EEG timecourse during the feedback processing interval alongside outcome valence and outcome magnitude. Of the 294 total bins for which significant effects were observed 257 were associated with only one regressor, indicating that the three elements of feedback processing evaluated here (outcome valence, outcome magnitude, and subjective outcome expectations) show distinctly different temporal properties in terms of their expression in the ERP. Furthermore, the ERPs associated with model-based estimations of subjective choice probability showed little overlap with the time interval of the FRN, which is generally considered to be associated with prediction error (Nieuwenhuis et al. 2004; Fuentemilla et al., 2013). However, the majority of bins associated with model-based regressors fell within the time interval of the P3 ERP. Previous research has found that the magnitude of the P3 ERP increases with the subjective unexpectedness of the task outcome (Fuentemilla et al., 2013; Mars et al., 2008). The findings in this study suggest that model-based outcome probability estimates reflect an aspect of subjective outcome likelihood processing that occurs during a later stage of the P3 time interval than processing associated with objective outcome variables. Previous work has also found that variations in P3 amplitude are associated with individual differences in risk attitudes (Fuentemilla et al., 2013). In the context of the IGT, risky deck choices (i.e. deck selections where the associated choice probability value was comparatively low) may have similarly resulted in higher P3 amplitudes. Overall, the finding of an association between the P3 and PVL-Delta/VPP model choice probability supports a link between the model-based choice predictions and neurobiological indicators of feedback processing, lending some biological validity to inferences made based on these models of choice behaviour.

The VPP and the PVL-Delta model showed very similar patterns of association with the ERP, indicating that the aspect of decision-making captured in trial-by-trial calculations by these models is largely the same. Despite the apparent similarity in the post-hoc choice probability estimates based on the ERP findings, the parameter values used to calculate the post-hoc choice probability

estimate were not entirely consistent. Most notably, the parameter α reflecting outcome sensitivity showed clear group differences in the VPP model but not in the PVL-Delta model. In the VPP model, ex-smokers had higher values of the outcome sensitivity parameter than non-smokers, suggesting higher sensitivity to feedback. In addition, both ex-smokers and non-smokers had lower values of the reinforcement learning parameter ω than smokers in the VPP model, indicating that the perseverance heuristic was incorporated into model calculations to a greater extent in the ex-smoker and non-smoker group than in the smoker group (see function [6]). Although the weighting of reinforcement learning was still a great deal higher than that of the perseverance heuristic in all groups, the greater incorporation of the additional perseverance calculation (function [5]) into VPP choice selection in the ex-smokers and non-smokers may account for the group differences in the outcome sensitivity parameter in the VPP but not in the PVL-Delta model despite similar trial-by-trial values for both models. Given strong evidence in favour of the VPP model over the PVL-Delta model when using a Bayes factor (Steingroever et al., 2016) and overall stronger evidence for the VPP model given simulation fit in this study, it is reasonable to conclude that the parameter values generated using this model better reflect actual aspects of choice behaviour in the IGT.

The group differences seen in VPP parameter values between smoking groups were consistent with a generally accepted account of smokers (and ex-smokers) as more driven by reward outcomes with less regard for negative consequences. The differences observed here clearly highlighted differences between non-smokers and former smokers in sensitivity to feedback. The absence of group-difference effects for the current smoker group suggests that this heightened sensitivity to feedback may be a general risk factor for smoking that is attenuated through smoking behaviour. Alternatively, this trait could in some way have facilitated successful cessation in the ex-smoker group. The conclusion that heightened sensitivity to feedback is a trait of both current and former smokers is supported by findings from neuroimaging studies investigating risk factors for compulsive drug-seeking behaviour that suggest that deficits in prefrontal cognitive control networks and increased sensitivity to reward put individuals at high risk for addictive behaviours (Ersche et al., 2010; 2012; 2013a/b).

While not statistically significant, values for the loss aversion parameter in the PVL-Delta and VPP models also appeared to be higher for non-smokers than ex-smokers and smokers, indicating that the increased sensitivity to feedback in the ex-smoker group may be stronger for gains than for losses. Worthy and colleagues (2013) previously observed that the number of choices from deck B was negatively associated with loss aversion. The high proportion of deck B choices among ex-smokers thus reinforces the conclusion that ex-smokers show heightened sensitivity to reward in this study. Using the same computational modelling approach used in this study, reduced loss aversion compared to control subjects has previously been found among a

heroin user group with similar choice patterns as the smoker group in this study (Ahn et al. 2014). Given the similarity in choice patterns and the suggested variations in loss aversion between current or former smoker and non-smokers it is possible that differences in loss aversion between substance using and non-using populations may be a general feature, and even a predisposing factor for some addictions.

A further aspect of decision-making in the IGT for which differences between the current smokers and non-smoking groups were found was the reliance on the perseverance heuristic. Based on this finding, the current smoker group relied almost entirely (or to a greater extent than the non-smoking groups) on the calculation of expected choice value $Ev(t+1)_j$ for each deck j to determine subsequent choices, whereas the other groups took into account the perseverative strength of each option to a greater extent. A possible account of the higher reliance on the expected choice value in smokers comes from a previous study using a subset of this data that found self-reported awareness of reward and punishment contingencies to be lower among current smokers than ex-smokers and non-smokers (Briggs et al., 2014). Employing the perseveration heuristic which determines whether the choice strategy should be changed or not based on outcome valence may require higher awareness of the long-term contingencies of the decks. Since the parameters used to calculate perseveration strength were not distinct between groups, reliance on the perseveration heuristic and its relationship to awareness of deck contingencies will require further investigation.

An important limitation of this study was that the variation in age ranges between groups and the use of self-reported smoking behaviour rather than breath CO monitoring limits the genaralizability of findings. As this study has shown that computational modelling of the IGT is a valid and informative approach to examining reward-related decision making in smokers and non-smokers, future work with larger samples and stricter inclusion criteria is warranted. A further limitation that should be addressed in future work is that differences in variables other than smoking behaviour, such as substance use or socioeconomic status were not considered in this study. As the IGT was created as an ecologically valid measure of decision-making these variables are likely associated with task performance. Bechara et al. (2001) found that the ability to hold gainful employment was the biggest predictor of IGT task performance in a substance using group (Bechara et al., 2001). In contrast to other substance use disorders, there is little support for the notion that smoking is causal to unemployment or absenteeism (Henkel, 2011), making this variable unlikely to confound findings in a study of IGT performance in smokers. However, as SUD populations have high smoking rates, and loss of functionality (such as inability to hold employment) is more commonly associated with SUD than smoking, the discrepancies in findings relating to IGT task performance of smokers between studies and differences between groups in

the present study could be related to differences in other substance use. In the absence of studies specifically examining whether there is a dissociable effect of smoking compared to other substance use on IGT performance it remains unclear to what extent smoking itself is associated with IGT performance in populations that also show other substance use. Future studies should consider possible differences between smoking and non-smoking groups in employment and other substance use when examining IGT performance.

Furthermore, the definition of smoking groups used in this study limits the inferences that can be drawn as to the differences between the smoker and ex-smoker group. Given the different measures used to assess smoking in the two different samples used here, there is a possibility that the ex-smoker group were all stronger smokers before quitting than the individuals in the current smoker group were at the time of the study. A further subdivision of smoking samples into heavy, casual, and ex-smokers or a longitudinal study design including attempted smoking cessation in future research would provide further insight into the possible interaction of nicotine dependence severity, cessation status and IGT performance.

This study showed that the currently available models of choice behaviour in the IGT still show some deficits in accounting for all possible choice patterns. However, this study also showed that it is possible to link regressors from computational models of the IGT to brain activity to identify neural representations of subjective choice appraisal, which fall in line with established accounts of outcome evaluation. Clear qualitative differences in how decision-making is influenced by reward and punishment were observed in current smokers, former smokers, and non-smokers. Results indicate that the heightened sensitivity to rewards in smokers that is routinely observed using neuroimaging measures is also evident for former smokers when using a computational modelling approach. Given the demonstrated link between ERPs during outcome evaluation and model-based calculations of choice probability, future work should consider incorporating trial-by-trial measures of physiological responding into assessment protocols using the IGT to further examine the correlates of model-based estimations of subjective decision-making components.

Chapter 6 – Discussion

6.1. Summary of empirical findings

The aim of this thesis was to explore precursors, risk factors, and correlates of smoking behaviour using a variety of populations and analysis approaches. Previous knowledge of neural, psychological and environmental factors associated with smoking was extensively reviewed in Chapter 1, followed by a detailed examination of how analytical approaches from the field of machine learning can benefit classification and prediction of psychiatric pathology. Chapters 1 and 2 addressed how neuroimaging data can be adequately interrogated using machine learning approaches. Utilizing these insights, a holistic model predicting future smoking in healthy adolescents was developed in Chapter 3. In line with a role of reward-related neuroimaging predictors of adolescent smoking identified in Chapter 3, the relationship between smoking behaviour and functional connectivity of the reward system was further examined in Chapter 4. Moving from adolescent to adult smoking behaviour, Chapter 5 examined the potential of computational models of reward-related decision making to further illuminate cognitive processes underlying complex choice behaviour, and compared outcomes of such cognitive models between smokers, non-smokers, and former smokers.

6.1.1. Summary of findings relating to machine learning analysis frameworks (Chapter 2, Chapter 3)

In Chapter 2 simulated and real neuroimaging data were used to evaluate which out of six selected linear regression algorithms provided the best fit to the data, and whether results could be improved through use of an embedded feature selection algorithm and/or bootstrap aggregation. The primary finding in Chapter 2 regarding the application of machine learning algorithms to neuroimaging data was that success largely depends on the amount of data available, with a sample size of N=400 emerging as a lower limit for necessary sample size. Across dataset sizes and evaluated data types the Elastic Net produced the best results. Gaussian Process Regression and Multiple Regression with embedded feature selection and/or bootstrap aggregation performed equally well or better than the Elastic Net in some cases (i.e. for some dataset sizes and data types) but produced much lower model fit for other cases. When used in Chapter 3 to predict group membership of adolescent smokers, the Elastic Net produced good predictions for data from psychometric and behavioural sources, but prediction accuracy using only neuroimaging data was poor despite both datasets having approximately equal size. When both neuroimaging and psychometric data were combined model fit was comparable to that of psychometric data alone, showing that data from different sources and modalities can be successfully combined in one model without compromising model fit.

6.1.2. Summary of findings relating to the prediction of adolescent smoking (Chapter 3)

The examination of smoking behaviour in a sample of 548 14-year old adolescents from the IMAGEN study (Schumann et al., 2010) revealed that psychological, environmental, and neuroimaging factors significantly contribute to risk of future smoking onset. Notably, neuroimaging variables were only identified as useful predictors of long-term smoking risk (i.e., between two and four years after baseline), while risk of becoming a regular smoker within the next two years was described best by a set of variables encompassing behaviour, personality, and psychopathology.

A set of core variables were predictive of any future smoking, regardless of when regular smoking commenced. These included alcohol and other substance use, as well as maternal smoking currently and before pregnancy. Low conscientiousness, high impulsiveness, and antisocial behaviour also predicted smoking. One of the strongest predictors of smoking was parent-report of deliberate self-harming behaviour over the adolescents' lifetime. Sensation-seeking and experience with romantic relationships had stronger predictive utility for late-onset smoking (LOS) than for early-onset smoking (EOS), while alcohol use, conduct disorder symptoms, self-harming behaviour and novelty-seeking had higher predictive utility for EOS. In addition, only LOS was predicted by low ADHD symptoms and low agreeableness. An unstable or unsupportive family environment was a risk factor for EOS. Adolescents who reported high 'anxiety sensitivity' reflecting fear or nervousness surrounding unfamiliar physiological sensations were more likely to be EOS or remain non-smokers (NS) than become LOS.

Low grey matter volume in the right IPL/TPJ was predictive of LOS compared to both NS and EOS. Adolescents who had low activity in this region while reading sentences and adolescents who had high activity in this region during successful response inhibition were more likely to become LOS than EOS. During failed response inhibition, low activity in the amygdala and TP among other regions predicted LOS compared to NS. High activity in the OFC during successful response inhibition also predicted LOS compared to EOS and NS. During reward anticipation in the MID task LOS compared to EOS and NS was predicted by low activity in the ACC and OFC. During the outcome interval of the task higher activity in the ACC and lower activity in the PCC, as well as higher activity in the paracentral lobule/SMA and caudate predicted LOS compared to NS. During affective face viewing LOS compared to EOS and NS was predicted by higher activity in the PCC. Low TP activity also predicted LOS compared to EOS, and high VS and hippocampal activity predicted LOS compared to NS. Low activity in the bilateral temporal lobe while listening to sentences, and high activity in the right dorsal striatum for visual arithmetic predicted LOS compared to NS.

6.1.3. Summary of findings relating to reward system connectivity and adolescent smoking (Chapter 4)

In a sample of 206 adolescents from the IMAGEN study (Schumann et al., 2010) who had smoked between two and more than forty times in their life, lifetime alcohol and cannabis use were significantly associated with smoking frequency, but demographic measures or measures of physiological anxiety sensitivity, impulsivity, or novelty-seeking were not.

During anticipation of large compared to no rewards in the MID task lifetime nicotine use was significantly correlated with functional connectivity between the VS and a number of cortical and subcortical regions. Connectivity of the VS with the contralateral PCC was positively associated with smoking, while connectivity with the contralateral TP was negatively associated with smoking. Connectivity of the bilateral VS with the right IFG and of the right VS with the left medial SFG and olfactory gyrus was negatively associated with smoking. Connectivity of the bilateral VS with the OFC was also positively associated with smoking. For the left VS connectivity with the ipsilateral SMG was positively associated with smoking, while connectivity of the right VS with the ipsilateral SMG/AG and of the left VS with the ipsilateral IPL was negatively associated with smoking. For the right VS, connectivity with the right amygdala, thalamus, caudate, and cerebellum was positively associated with smoking, and connectivity with the right superior occipital lobe and left lingual gyrus was negatively associated with smoking.

6.1.3. Summary of findings relating to differences in model-based characterization of reward related decision-making in current, former, and non-smokers (Chapter 5)

During reward/loss-based decision making under uncertain conditions in the IGT adult smokers, non-smokers, and ex-smokers showed distinctly different choice strategies. Both current and former smokers favoured choices that resulted in immediate large rewards, and both smokers and non-smokers avoided choices that resulted in frequent loss outcomes. While choice behaviour in all participants changed as they gained knowledge of the long-term consequences of their choices, only the non-smokers adapted their choice behaviour to prioritize long-term positive outcomes during the task.

Fitting three computational models of the IGT to participants' choice patterns showed that the ability of these models to capture change in choice strategies over the course of the task was limited. Nevertheless, examination of the electrophysiological correlates of model-based estimations of trial-by-trial choice likelihood showed that both the VPP and the PVL-Delta model capture aspects of decision-making that can be observed in EEG recordings. The expression of the model-based choice likelihood value overlapped with the well-known P3 ERP and was seen later in the outcome evaluation interval than the expression of objective outcome characteristics.

Based on the confirmation of the biological relevance of the PVL-Delta and VPP models and their objective fit to the data, individual model parameters were evaluated and compared between groups. Based on the distribution of parameter values between groups, ex-smokers were more sensitive to the magnitude of outcomes than non-smokers, while smokers placed higher importance on the direct reinforcement value of outcomes than ex-smokers and non-smokers. In the context of differences in choice behaviour between groups these differences in model parameters confirm lower sensitivity to losses and higher importance placed on high rewards in ex-smokers (and possibly current smokers) compared to non-smokers. Findings also indicate that smokers' choice behaviour was less influences by awareness of long-term outcomes than that of ex-smokers and non-smokers.

6.2. General Discussion

6.2.1. Discussion of findings concerning predictors and correlates of smoking behaviour

The brain undergoes profound changes during adolescence, resulting in altered behaviour and cognition (Dahl & Forbes, 2010; Crews, He & Hodge, 2007). While adolescents do not suffer from a deficit in the logical ability to weigh risks and benefits of behaviours, their decisions are motivated to a larger extent by the urge for immediate gratification, pleasure, and reward than those of adults (Reyna & Farley, 2006; Beyth-Marom et al., 1993; Steinberg, 2008). A measurable expression of this is increased novelty seeking, reduced harm avoidance, and increased choice impulsivity in adolescence (Brändström, Sigvardsson, Nylander & Richter, 2008; Steinberg, Graham, O'Brien, Woolard, Cauffman & Banich, 2009). Models of adolescent brain development attribute these characteristics to a deficit in the regulatory ability of cognitive control regions over reward-based motivational drives in adolescence (Steinberg, Albert, Cauffman, Banich, Graham & Woolard, 2008; Ernst, Pine & Hardin, 2005; Casey, Jones & Hare, 2008; Casey, 2015). The result of the developmental imbalance between these brain systems has been characterized as an inability to pay attention to stimuli that are not salient when salient or emotionally evocative stimuli are present (Blakemore, 2008). Findings from the studies contained within this thesis pointed toward development of smoking behaviour being closely associated with altered function of cognitive control and reward networks, differences in which may persist after smoking cessation.

Altered structure and function of the reward systems is associated with initiation, maintenance, and cessation of smoking, as discussed in 1.1.4.1. The reward processing paradigm used to examine alterations in reward system function and possible deficits in reward processing evident before smoking onset was the MID task, discussed in 1.1.4.3. During anticipation of rewards in this task activity is observed in the ventral and dorsal striatum, the ACC, mPFC, OFC, and the thalamus among other regions (Adcock, Thangavel, Whitfield-Gabrieli, Knutson & Gabrieli,

2006; Knutson, Fong, Bennett, Adams & Hommer, 2003; Haber & Knutson, 2010; Van Leijenhorst, Zanolie, Van Meel, Westenberg, Rombouts & Crone, 2010). Consistent with the known dose-response relationship between VS function during reward anticipation and smoking (Peters et al., 2011; van Hell et al., 2010; Rose et al., 2013), differences in functional connectivity of the VS during reward anticipation were associated with current smoking, but striatal activity during reward anticipation was not predictive of future smoking behaviour.

In contrast, findings from the anticipation phase of the MID task showed that reduced activity in the ACC and OFC was predictive of future smoking behaviour, indicating not only that adolescents will begin smoking but also at which age regular smoking will begin. The ACC and OFC have both been shown to be sensitive to the motivational salience of stimuli and are thought to be involved in the development and maintenance of drug-seeking behaviour (Dom, Sabbe, Hulstijn & van den Brink, 2005). Reduced grey matter volume has been found in the ACC and medial OFC in smokers compared to non-smokers (Brody et al., 2004; Kuhn, Schubert & Gallinat, 2010). Furthermore, smokers show increased ACC activity to smoking cues compared to non-drug cues and associated with nicotine dependence severity (Janes et al., 2013, 2015b; Engelmann et al., 2012, Zanchi et al., 2015; McClernon, Kozink & Rose, 2008). Dependent compared to occasional smokers also show reduced OFC activity to non-drug rewards (Bühler et al., 2010). Engagement of the ACC and OFC to reward cues can thus be interpreted as reflecting sensitivity to a reward, in line with a role of the ACC in salience attribution (Menon & Udin, 2010) and attentional bias (Goldstein & Volkow, 2011), and of the OFC in encoding value and saliency (O'Doherty, 2004; Kringelbach & Rolls, 2004). In line with evidence for changes in the OFC associated with nicotine use (Kuhn, Schubert & Gallinat, 2010) functional connectivity of the VS with OFC regions during reward anticipation was also associated with smoking frequency.

Some evidence suggests a genetic component in connectivity of the VS and ACC to the amygdala and in associated smoking risk (Hong et al., 2010). While no effect of smoking frequency on VS connectivity with the ACC was found, increased functional connectivity of the VS with the amygdala was associated with smoking frequency. The VS receives input from the BLA, which is known to be involved in encoding motivational salience and guiding instrumental action (Wassum & Izquierdo, 2015; Shiflett & Balleine, 2010). Altered amygdala function in smokers has not been extensively studied, with the majority of studies investigating amygdala function in association with smoking cues (Mihov & Hurleman, 2012). However, significantly enlarged amygdala volume has been found in dependent substance users and their biological siblings but not in casual recreational users (Ersche et al., 2012; 2013a), suggesting that the amygdala is implicated in a high-risk phenotype for substance use. Considering the known role of the amygdala, OFC, and ACC in attribution of salience to drug and non-drug stimuli, atypical activity during the anticipation of non-

drug reward cues in these regions can be interpreted as a deficit in reward sensitivity. As this effect was observed as a pre-existing risk factor and in adolescents the majority of which were likely not yet nicotine dependent, this extends a previous understanding of reduced sensitivity to natural reinforcers occurring as a result of substance use (Koob & LeMoal, 2005) to show that such deficits are also a pre-existing vulnerability for substance use.

Since altered ACC function was observed only as a predictor of future smoking with no effect of current smoking frequency, ACC function may be a specific risk factor for smoking initiation. The ACC is one of the cortical areas with the densest dopaminergic innervations (Gaspar, Berger, Febvret, Vigny & Henry, 1989). Reduced activity in the ACC for anticipation of non-drug rewards in non-addicted individuals may therefore be associated with altered dopaminergic activity. Dopamine D2 receptor availability has previously been linked to impulsivity (Trifilieff & Martinez, 2014) and the reinforcing effects of drugs of abuse (Volkow et al., 1999; Nader & Czoty, 2005; Thanos et al., 2005; Yoder et al., 2005). Furthermore, high D2 receptor availability in the ACC and OFC in individuals with high familial alcoholism levels have been interpreted as a protective factor against substance use disorders (Volkow et al., 2006). Further longitudinal examinations of DA activity and D2 receptor availability in adolescents who will go on to become smokers will be necessary to fully examine this effect.

DA release in the striatum and associated changes in reward-related behaviour have been observed as a result of transcranial magnetic stimulation of the mPFC (Cho et al., 2015). Effects seen for both future smokers and current smokers showed that the OFC and mPFC have dissociable roles in reward anticipation. While functional connectivity of the VS with the OFC was increased in association with smoking frequency, connectivity with the mPFC was decreased. Furthermore, a predictive effect of mPFC activation that was specific to anticipation of rewards of different magnitudes was observed, with reduced mPFC activity to large compared to small reward cues predicting late-onset smoking. The mPFC is known to bias individuals toward less risky choices, as shown in a lesion study using a gambling task (Clark et al., 2008). Furthermore, repetitive transcranial magnetic stimulation of the mPFC was shown to influence preference for large and delayed rather than immediate and small rewards in a temporal discounting task (Cho et al., 2015). Reduced mPFC engagement and reduced mPFC functional connectivity with the VS may thus reflect reduced cognitive control over reward system function for motivationally salient cues in present and future adolescent smokers.

Further evidence for reduced cognitive control over reward system response to reward cues associated with adolescent smoking can be seen in altered connectivity between the VS and the ventral frontoparietal attention network (vFPAN; Corbetta et al., 2008; Corbetta & Shurman, 2002). During anticipation of rewards in the MID task reduced functional connectivity of the VS and

the IPL, cerebellum, and right IFG associated with smoking frequency was observed. Activity in none of these generally right-lateralized regions thought to be part of the vFPAN (Vossel, Geng & Fink, 2014) predicted smoking during reward anticipation. However, reduced activity in the left IFG, which has been attributed a similar role in inhibitory control as the right IFG (Swick, Ashley & Turken, 2008; Chikazoe, Konishi, Asari, Jimura & Miyashita, 2007; Aron et al., 2014) predicted late-onset smoking compared to early-onset smoking. Lacking evidence for reduced engagement of a frontoparietal attention network in reward anticipation as a marker of future smoking risk, and previous research showing altered IPL function to natural and drug cues in substance dependent individuals (Garavan et al., 2000) indicate that altered reward-related function of the IPL and attention networks may emerge subsequent to substance use initiation.

A further region which has been found to show changes associated with substance use and for which a reward-related predictive effect was also indicated is the TP. The TP is an important region involved in social cognition and emotion processing but is also suggested to serve as a hub integrating emotional and sensory cues (Fan et al., 2014; Pehrs et al., 2015; Olson et al., 2007). Increased TP activity associated with nicotine dependence has previously been found for smoking cues (Claus et al., 2013). Reduced activity of the right superior TP for anticipation of large compared to no reward predicted late-onset smoking, and smoking frequency was associated with reduced VS functional connectivity to the same region and the bilateral middle TP during reward anticipation. The relationships between smoking behaviour and TP activity to drug- and non-drug reward cues established in the studies presented here and in previous research, and findings of altered TP structure in substance users (Albein-Urios et al., 2013) indicate that TP changes are partially a result of substance use. However, the observed predictive effect of right superior TP function during reward anticipation and the identification of the same region as showing changes in functional connectivity associated with smoking frequency indicates that pre-existing differences in TP recruitment are also a vulnerability for smoking behaviour.

In addition to the breadth of findings regarding anticipation of reward outcomes in the MID task, several findings regarding activity in response to receiving reward outcomes emerged. Adolescents who displayed increased task-related attention and outcome valuation were more likely to become late-onset smokers than to remain non-smokers. Compared to non-smoking, late-onset smoking was predicted by reduced bilateral PCC and middle temporal gyrus activity, indicating reduced default-mode network (DMN; Buckner, Andrews-Hanna & Schacter, 2008) recruitment. Furthermore, late-onset smoking was predicted by increased paracentral lobule and SMA activity when receiving rewarding outcomes, indicating higher recruitment of a task-active network. Increased ACC activity also predicted late-onset smoking compared to non-smoking,

indicating that reduced valuation of stimuli in the anticipation phase was followed by increased attention and valuation of stimuli when receiving reward outcomes.

Findings in Chapter 5 indicate that elements of the reward system dysfunction identified as a predictor of future smoking are still evident after smoking cessation. In the IGT, smokers and ex-smokers failed to learn to avoid choices that would result in large loss outcomes, and favoured choices with large immediate gains. Advantageous performance in the IGT is known to depend on vmPFC function (Bechara et al., 2001). The ACC and VS are also engaged in IGT performance (Li et al., 2010). The failure of smokers and ex-smokers to learn from disadvantageous choices may therefore reflect persistence of deficits in reward system function and continued heightened valuation of large positive non-drug outcomes after smoking cessation. Ex-smokers in particular were characterized by increased sensitivity to positive outcomes and an apparent insensitivity to negative outcomes. Examination of model parameters and results from a past study using a subset of the same data (Briggs et al., 2015) indicated that current smokers have a reduced awareness of the likely future reward or punishment outcomes of their choices, which may reflect a similar effect of dysfunction in reward anticipation as was observed during the MID task in adolescent current and future smokers.

The phenotype of altered reward sensitivity associated with smoking behaviour suggested by these results may be common to multiple impulse control disorders. A strong overlap between risk for future substance use and CD is suggested. In line with previous research showing that CD is a strong risk factor for adolescent substance use (Disney et al., 1999; Fergusson, Horwood & Ridder, 2007) adolescents for whom the presence of CD was indicated were also at high risk of becoming smokers before age 16. CD is associated with increased risky decision-making and insensitivity to negative consequences (Fairchild et al., 2009a; Sonuga-Barke et al., 2016). CD and antisocial behaviour can therefore be conceptualized as a set of traits that fall at the extreme end of the typical increase in risk-taking and insensitivity to negative consequences that is seen in adolescence. The choice patterns of smokers and ex-smokers in Chapter 5 were also similar to those seen in adolescents with CD/ODD (Schutter et al., 2011), and the apparent reduction in sensitivity to negative outcomes in ex-smokers is similar to patterns of outcome valuation seen in children with ODD (Humphreys & Lee, 2011). Along with other maladaptive behaviours and symptoms, CD and substance use may thus be an expression of a common high-risk phenotype characterized by deficits in cognitive control over motivational impulses. Based on findings regarding temporal discounting in adolescents with CD (White et al., 2014), Sonuga-Barke and colleagues (2016) suggested that CD/ODD may be characterized by a "present-oriented motivational style". Given findings of deficits in anticipating future reward outcomes as a predictor and correlate of smoking this conclusion may be adapted and extended to characterize individuals

at risk for smoking and possibly other impulse control disorders as having a "present-oriented and reward focussed motivational style". Despite the apparent overlap in the adolescent phenotypes associated with CD and risk for substance use, an evaluation of factors associated with externalizing disorders in adolescents from the IMAGEN study found that substance use and CD/ADHD show dissociable associations with facets of impulsivity and reward sensitivity (Castellanos-Ryan et al., 2014). The link between CD in adolescence and subsequent substance use disorders will require further investigation.

Based on the known link between disordered conduct and smoking, interventions targeting disruptive and aggressive classroom behaviour have previously reduced rates of smoking in adolescents who were already low in this type of behaviour (Kellam & Anthony, 1998). However, such interventions have been suggested to only reduce environmental exposure to smoking (Wang et al., 2012) and to delay smoking onset (Lantz et al., 2000) rather than eliminate a causal risk factor for adolescent smoking. The evidence suggests that antisocial behaviour and the associated tolerance for deviance seen here as risk factors for early-onset smoking are predominantly risk factors for smoking initiation (Mayhew et al. 2000). Present findings also indicate that novelty-seeking - like antisocial behaviour and CD - is a risk factor for initiating smoking behaviour rather than risk for becoming dependent. Previous research has shown that while non-smokers and light or experimental smokers do not appear to differ on novelty seeking, regular adolescent smokers have higher levels of novelty seeking than non-smokers and experimenters (Audrain-McGovern et al., 2004a; 2009; Dinn, Aycicegi & Harris, 2004; Rezvanfard et al., 2010). Findings from Chapter 3 and Chapter 4 extend this knowledge to show that frequency of smoking in 14-year-olds is not associated with novelty-seeking when a spectrum of smoking including relatively low levels is examined, but that novelty seeking at age 14 is predictive of adolescents becoming regular smokers before age 16. Notably this trait also differentiated between smoking trajectories, and is thus not a universal predictor of adolescent smoking, but rather a specific indicator of early adolescent smoking risk. Similarly, many of the variables differentiating between adolescents who would take up smoking before or after age 16, such as the identified 'broken home' indicators could be conceptualized as catalysts triggering earlier initiation of a maladaptive behaviour. Like the absence of antisocial behaviour and CD, the presence of a stable home environment and lack of exposure to illicit substances are likely protective factors that contribute to the delay of smoking onset. Interestingly another strong predictor of late-onset smoking was the absence of ADHD symptoms, which can also be interpreted as a protective factor given the high rate of co-occurrence of smoking and ADHD (McClernon & Kollins, 2008).

ADHD and CD have been shown to have dissociable underlying neurobiology, with deficits in ADHD lying predominantly in the area of inhibitory control and attention, and deficits in CD more

so in the domain of affect regulation and motivation (Rubia, 2011). However, the presence of both ADHD and CD symptoms predicted onset of regular smoking before the age of 16 rather than later smoking-onset. While the neurobiological evidence did not allow any conclusions about neurobiological factors predicting early-onset smoking compared to non-smoking, predictors of late- compared to early-onset smoking allowed some insight into deficits in brain function that may be related to these other impulse control disorders. The previously discussed negative relationship between anticipatory OFC and ACC activity and age of smoking onset is in line with disorder-specific reward-related hypoactivation of the OFC in individuals with CD (Rubia et al., 2009). In addition, an ADHD-specific hypoactivation of the PCC for rewards was observed in the same study (Rubia et al., 2009), which is similar to the predictive effect of PCC hypoactivation for reward outcomes in the MID task for late-onset smoking compared to non-smoking. Despite the presence of ADHD symptoms being counter-indicative of late-onset smoking risk, some of the underlying deficits of these disorders may thus nevertheless be shared.

Individuals with ADHD symptoms show deficits in inhibitory control, as measured using paradigms such as the SST (O'Halloran et al., 2018; Whelan et al., 2012). While the regions identified as predictors of smoking status during the SST did not overlap with those previously identified to differ in adolescents with or without ADHD from the IMAGEN study, there was substantial overlap between predictors of smoking behaviour in the SST and networks found to differ in adolescents with or without substance use experience (Whelan et al., 2012). Whelan and colleagues (2012) found that increased substance use experience was associated with reduced activity in the OFC during successful response inhibition. High activity in a corresponding set of OFC regions during successful inhibitory control predicted initiating regular smoking more than two years later compared to not smoking or beginning to smoke at an earlier age. Given the known relationship between activity in the OFC during successful response inhibition and substance use, increased OFC activity may be considered a protective factor associated with delay of smoking behaviour.

Predictors of late-onset smoking during the SST also further indicate that altered activity of the vFPAN is a risk-factor for future smoking behaviour. Increased activity during successful behavioural inhibition in the AG and cerebellum was predictive of becoming a late-onset rather than an early-onset smoker, and increased activity in the right IFG was predictive of becoming a late-onset smoker rather than remaining a non-smoker. This is in line with an account of the vFPAN responding to unexpected changes in sensory input and infrequent target stimuli (Vossel, Geng & Fink, 2014; Igelström et al., 2017). The heightened recruitment of the vFPAN during successful inhibitory control suggests reliance on compensatory mechanisms during behavioural inhibition as a risk factor for smoking behaviour two to four years later. A specific node of the vFPAN and DMN

for which structure and function emerged as particularly informative with regards to prediction of smoking behaviour was the IPL/TPJ including the SMG and AG. The IPL/TPJ was the only region for which grey matter volume predicted future smoking, with lower volume predicting late-onset smoking compared to both early-onset smoking and remaining a non-smoker.

Atypical recruitment of regions forming part of the DMN predicted smoking during processing of semantic stimuli in the GCA task. The core regions of the DMN are the IPL, mPFC, PCC, hippocampal formation and lateral temporal cortex (Buckner, Andrews-Hanna & Schacter, 2008). Late-onset smoking compared to both early-onset and non-smoking was predicted by low activity of the IPL while reading sentences, and reduced activity of the parahippocampal and superior temporal gyri predicted late-onset smoking compared to non-smoking while listening to sentences. These findings appear in line with an account of reduced DMN activity (i.e. increased task-based attention) during semantic processing as predictor of future smoking behaviour. It should be considered though that the temporal region in which lower activity predicted smoking overlapped with the auditory cortex and Wernicke's area. This may indicate lower reliance on, or lower recruitment of these regions. Further investigation of the relationship between semantic processing in early adolescence and subsequent substance use will be necessary to fully determine the nature of this effect.

While viewing affective facial stimuli, activity in DMN nodes also predicted future smoking. However, these differences in activation may have reflected processes other than DMN recruitment. During viewing of angry faces compared to control stimuli the IPL, PCC, hippocampal formation and lateral temporal cortex all showed a predictive effect for late-onset smoking. Activity in the IPL has previously been linked to evaluation of emotional expressions in a similar face processing paradigm, and postcentral gyrus activity has been linked to valence and intensity of emotional expressions (Sarkheil, Goebel, Schneider & Mathiak, 2013). The observed predictive effect of low activity in these regions for late-onset smoking thus suggests a deficit in emotion recognition and processing of affective facial stimuli consistent with the effects seen in the striatum and hippocampus for this task. Activity in the PCC and left temporal region including the temporal pole were the only predictors of late- compared to early-onset smoking in the face processing paradigm, with increased PCC activity and reduced left temporal activity predicting late-onset smoking. The role of the PCC in internally focussed attention (Schulte-Ruther, Markowitsch, Fink & Piefke, 2007) and the role of the TP in affect processing (Lorberbaum et al., 2004) suggest that atypical processing of angry affect is not only indicative of future smoking risk but also of future smoking trajectory. Furthermore, impaired recognition of facial expressions has also been observed in adolescents with CD (Fairchild et al., 2009b) and altered TP activity during this task also predicted adolescent binge-drinking (Whelan et al., 2014; albeit also in the IMAGEN sample),

allowing the conclusion that altered affect processing may be a general characteristic of adolescent impulse control disorders and risk factor for future adolescent substance use.

6.2.2. Discussion of findings relating to machine learning analysis frameworks

In addition to revealing factors associated with smoking behaviour, the studies contained within this thesis also provided a demonstration of the utility of machine learning approaches for psychological and neuroimaging applications. While both Chapter 4 and Chapter 5 used variations of multivariate regression approaches as part of data analysis, Chapter 3 provides a large-scale example of the potential for machine learning applications for use in the psychological sciences. The empirical evaluation of machine learning analysis frameworks for neuroimaging applications in Chapter 2 showed that, in line with calls for larger sample sizes in neuroimaging research, success of machine learning methods in neuroimaging largely depends on the amount of data available. Increasing sample size is an effective step to increase power in neuroimaging research (Button et al., 2013), and this also holds true for machine learning applications. Crucially, the findings in Chapter 2 also revealed that the number of predictor variables has an equally large impact on the ability of a machine learning model to retrieve an effect in a neuroimaging dataset. Increases in both the number of observations (i.e. sample size) and the number of features resulted in improved prediction accuracy when an imbalance in the number of features compared to the sample size was adequately addressed through dimension reduction. In a standard multiple regression framework this was achieved using an embedded preselection of features. However, solutions that were equal to and better than those achieved using this modified multiple regression framework were achieved by using a regularized regression approach: The Elastic Net (Zou & Hastie, 2005). The suitability of the Elastic Net to neuroimaging data can be attributed to its constituent regularization approaches: LASSO and Ridge Regression. While LASSO serves to reduce the size of the feature set, Ridge Regression is able to accommodate multicollinearity in the dataset. Theoretically, the Elastic Net can retrieve the features that best describe the optimization problem regardless of the size of the feature set (de Mol, de Vito & Rosasco, 2009). Chapter 2 confirmed that larger feature sets do indeed result in better predictions, but the generalizability of this finding to voxel-wise neuroimaging data or datasets with many more features should be further explored.

Table 6.1. Elastic Net Parameters and Correlation (Pearson's R) with AUC and F1 values by data type

	Neuroimaging data (1330 variables)	Psychometric data (1105 variables)	Neuroimaging & Psychometric data (2435 variables)
Mean λ	0.914	1.096	1.187
Mean α	0.378	0.130	0.220
Correlation between AUC value and λ *(r)*	-0.238	0.305	0.432*
Correlation between AUC value and α *(r)*	-0.542**	-0.277	-0.399*
Correlation between F1 score and λ *(r)*	0.109	0.296	0.291
Correlation between F1 score and α *(r)*	0.680**	0.196	0.197

*p<.0005 **p<.00005

Following findings in Chapter 2, Chapter 3 included both a large sample size (N>500) and more than 1000 features in every analysis. However, results in Chapter 2 and Chapter 3 confirmed that effect sizes determine prediction accuracy more so than dataset size. Nevertheless, as shown in Chapter 3, combining data from different modalities – such as MRI and psychometric data – and with different effect sizes does not necessarily result in less precise models. In fact, including MRI data alongside psychometric measures in Chapter 3 made it possible to determine what MRI predictors contributed most strongly to the outcome while maintaining a high level of prediction accuracy. Findings from simulated and real neuroimaging parameters in Chapter 2 showed that higher regularization (λ) in the Elastic Net was associated with lower model accuracy. This is supported to a limited extent when examining the regularization strength and associated AUC values for neuroimaging data in Chapter 3, where a negative but non-significant correlation between λ and AUC was observed (see Table 6.1). Based on these findings, data with weak effects result in larger λ values being chosen by the Elastic Net. In contrast, when examining λ values and correlations between λ values and AUC values for the analyses including psychometric data, a different pattern was observed. Larger λ values were in fact associated with higher AUC values for the multimodal models, and λ values had no significant relationship to the more informative F1 scores for any data type. These findings show that the regularization strength selected by the Elastic Net is dependent not only on the feature effect size and size of the effect discoverable in the data, but also on the type of data that is used to create the model. In Chapter 3 the psychometric and multimodal datasets, unlike the neuroimaging dataset, combined features drawn from sources that are minimally dependent (e.g. parent report of stressors in their romantic relationship and child reaction times in a behavioural paradigm). The correlation strength between features in the datasets used in Chapter 3 are shown in Figure 6.1., demonstrating that the degree of intercorrelation in the neuroimaging dataset was higher than in the datasets including

psychometric data. Low inter-correlation among features implies possible large variation in the utility of individual features. This may account for higher regularization and a positive relationship between regularization strength and model performance.

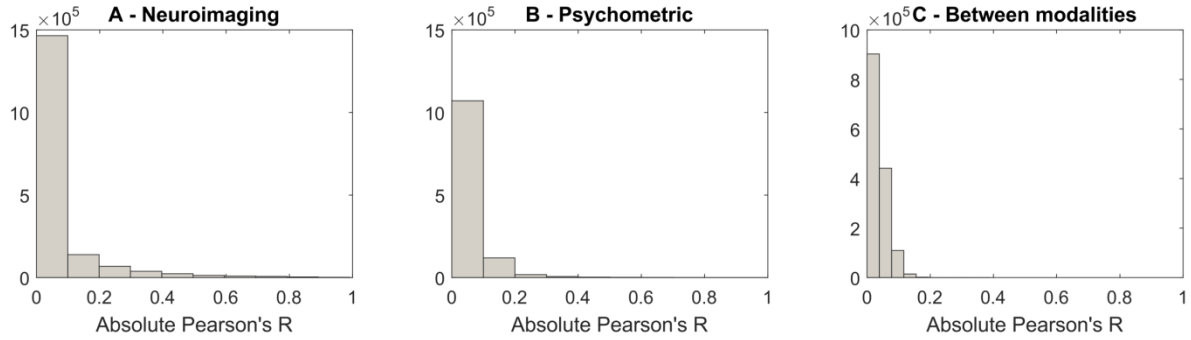

Figure 6.1. Histogram of Pearson's R values for correlations between variables of the same or different data type used in Chapter 3. A: Inter-correlations between all neuroimaging variables; B: Inter-correlations between all psychometric variables; C: Correlations between all neuroimaging variables and all psychometric variables.

Examination of the α values (extent to which LASSO compared to Ridge regression is used) can also shed some light on the differences in how the Elastic Net handles different data types. Higher values of α correspond to LASSO regression being used to a greater extent, and models thus being sparser. As can be noted by the average α values for the different data types (see Table 6.1), the proportion of LASSO regularization was highest for neuroimaging data and lowest for psychometric data. Furthermore, higher α values were associated with lower AUC values for all analyses including neuroimaging data, and with higher F1 scores for the neuroimaging-only models. Unlike trends observed for regularization strength, the relationship of α values to AUC values is thus independent of data type. The strong positive relationship between α values and F1 score for neuroimaging data appeared to be driven by higher α values for analyses comparing the two smoking groups, which were more balanced in size than other groups and therefore also had substantially higher F1 scores.

6.2.3. Limitations

The studies reported in this thesis were limited in the amount of demographic variabels that were assessed. While there was a measure of socio-economic status in the IMAGEN study, race or ethnicity was not assessed. There is some evidence that ethnicity has an effect on likelihood of initiating smoking, with Whites being more likely to start and maintain smoking than Black, Hispanic, Asian, or multiracial individuals (Tyas & Pederson, 1998; Mayhew et al., 2000; Ellickson et al., 2001). Of students in an American university, Asian students were most likely to never smoke, Latino/Hispanic students were most likely to try cigarettes, and White students were equally likely to be never-smokers, triers, and regular smokers (Balevich, Wein & Flory, 2013).

Whites have also been found to be more likely than other ethnic groups to smoke regularly in adolescence (Kollins et al., 2005; Upadhyaya et al., 2003). While these effects appear somewhat consistent across studies, it must be stressed that the degree to which these findings may be expected to translate to other contexts and communities is limited, as the intersection between ethnicity and other factors and their effect on likelihood of smoking is unclear. Furthermore, race effects have not been observed in all studies (Hirschmann, Leventhal & Glynn, 1984). Nevertheless, since race effects were not examined in the studies reported here, findings can only be expected to generalize well to European majority white populations.

Another facet of smoking risk among adolescents that was not accounted for here was peer smoking. There is strong evidence that peer smoking is a risk factor for smoking onset (Hirschmann, Leventhal & Glynn, 1984 ; Pederson, 1997; Audrain-McGovern et al., 2004a/b, Mayhew et al., 2000; O'Loughlin et al., 2014). In smoking and other substance use prevention the importance of peer pressure is often given substantial emphasis and school-based programs aiming to prevent youth smoking coach youth to recognize and resist external pressures to smoke (Thomas, McLellan & Perera, 2015). While peer pressure is a powerful factor associated with smoking, unsuccessful interventions targeting peer pressure point toward a more complex set of circumstances surrounding initial experiences with smoking (Onrust et al., 2015). Further studies examining adolescent smoking trajectories using predictive modelling should include an assessment of peer smoking and peer substance use, as these variables may be specific risk factors for early-onset smoking compared to late-onset smoking.

Finally, a set demographic variable that was not examined in depth in the studies reported here was sex and gender. Although being female emerged as a predictor of EOS compared to LOS in models without cannabis predictors in line with some previous findings (Mayhew et al., 2000; White et al., 2002), the assessment and definition of sex and gender in the IMAGEN study made inference based on this dimension challenging. Unlike in the study reported in Chapter 5 where participants self-reported their gender identity, the IMAGEN study (used in Chapter 3 and 4) only assessed apparent gender at baseline. Both self-identified gender and genetic sex (including the possible presence of intersex participants) were only accounted for at a later point during IMAGEN data collection and IMAGEN data processing and could therefore not be incorporated into the studies contained within this thesis. In addition to capturing the domain of gender rather than sex, the assessment of the sex/gender dimension in Chapter 5 differed from that used in the IMAGEN study in that multiple participants listed a gender identity other than female or male. Biological sex, gender of upbringing, and gender identity may have a strong impact on smoking and other substance use behaviour, but these domains should be accounted for separately and consistently in future research to ensure broad validity of findings.

6.2.4. Summary

The neuroimaging, psychological, behavioural, and environmental factors determined to be predictors or correlates of smoking behaviour painted a picture of adolescent smoking that partially overlaps with established accounts of adolescent smoking but also extended previous knowledge of factors associated with age of smoking onset. The primary insight into the etiology of smoking behaviour gained through the studies contained within this thesis came from the area of non-drug reward processing. Overall, a phenotype of reward system dysfunction is suggested whereby those at risk for smoking show reduced valuation of cues signalling natural reinforcers, indicated by ACC, OFC, and mPFC function. Reduced functional connectivity of reward system nodes with cognitive control regions is also associated with smoking frequency and may predate smoking onset. Reduced valuation or awareness of future reward outcomes and increased sensitivity to rewards is seen before smoking onset and persists until after smoking cessation. It is suggested that this phenotype may be part of a common etiological pathway of adolescent impulse control disorders that also includes CD. The presence of a number of protective factors that delay onset of smoking behaviour in adolescents in the late smoking onset trajectory despite presence of this high-risk phenotype is indicated. Structure and function of the IPL/TPJ and function of the associated vFPAN was found to predict smoking trajectory. Cognitive training designed to address deficits in inhibitory control and cognitive control over motivational impulses is a plausible avenue for preventative measures, similar to suggested uses in treatment of substance addiction (Garavan & Weierstall, 2012).

6.3. Conclusion

The search for biomarkers of behavioural and psychiatric outcomes has been accompanied by debate over what the primary focus of such biological models should be. A call for pragmatism and maximization of the practical utility of biological models of psychiatric outcomes (Paulus, 2015) stands opposite the perspective that mechanistic insight into pathophysiology gained through biological models has the greatest benefit for improvement of clinical care (Pine & Leibenluft, 2015). Given the correct analytical framework, these goals can be unified. With this purpose in mind, Elastic Net regression was identified as the method best suited for development of neuroimaging regression models among the approaches tested here. Using the use-case example of identifying those at risk for future substance use, this and previous projects (Whelan et al., 2014) revealed that despite appropriate study design, sample size, and analysis approach, neuroimaging data alone has as yet limited ability to improve judgements of risk for future pathology. However, modelling neuroimaging data in combination with self-report and behavioural testing revealed mechanistic insights into a neurobiologically defined high-risk phenotype that was shown to be consistent with deficits in currently and previously substance using individuals. As highlighted in

chapter 1, biomarkers of any outcome are only useful if they can augment current methods of assessing risk or of preventing and dealing with maladaptive or pathological outcomes. The example of smoking outcome prediction demonstrated clearly that functional and structural MRI do not contribute to a significant improvement in the accuracy of estimating smoking outcomes. However, the additional goal of improving assessment, treatment, and prevention through improved understanding of the neurobiological and cognitive mechanisms underlying development of psychopathology inherent in psychiatric biomarker research was well served with the approach used here. While not presently a reliable risk marker in isolation, highly informative structural and functional neuroimaging indicators of risk for future pathology can be identified in multimodal studies. Identification of component processes known to be risk indicators (Woo et al., 2018) and translation of these known vulnerabilities into cost-effective psychometric measures or cognitive models based on behavioural observation is a viable pathway to capitalize on results from multimodal predictive studies using neuroimaging measures.

The insights into neuroimaging and psychometric predictors of adolescent smoking and correlates of smoking frequency gained using the Elastic Net fall at the early end of development of a useful predictive model. Despite abundant literature on adolescent smoking, there is a lack of previous studies using predictive modelling and machine learning with regard to adolescent substance use. This makes further research validating findings from the studies presented here imperative. By using data from the same population as a previous study examining a similar outcome (Whelan et al., 2014) present findings have already revealed areas of commonality between predictors of smoking and binge drinking. The next step toward developing a viable tool for smoking and substance use risk assessment is the replication of effects seen in the studies presented here in a different sample. The predictive utility of a subset of the most informative variables including the IPL/TPJ, OFC, mPFC, ACC, and TP should be evaluated in a different sample, and variables should be added or removed to improve model performance in subsequent studies.

The research reported in this thesis used a wide lense to examine the cognitive neuroscience of cigarette smoking: Beginning with a prospective view of psychological, behavioural and neurobiological risk profiles for smoking in adolescence, including an examination of the relationship between function of the reward system and adolescent frequency of smoking, and concluding with an exploration of the cognitive aspects of reward-related reinforcement learning in adult current, ex-, and non-smokers using a computational approach to the interrogation of behavioural data. A central focus of this work was the validation and empirical evaluation of the analytical tools used in each study. A thorough investigation of the merits of the machine learning method chosen for the prediction of future smoking behaviour was carried out, and the computational modelling approach used to describe differences in reinforcement learning between

smoking groups was validated using a separate dataset and EEG recording. The use of multiple neuroimaging modalities, a diverse set of behavioural paradigms and psychological measures, and the choice of populations representing specific stages of progression into smoking behaviour in this work has made it possible to gain a well-rounded perspective of deficits associated with cigarette smoking.

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Glossary

Neuromarker: A neuromarker is a biomarker based on neuroscientific data, such as neuroimaging. Neuromarkers are biological indicators of the presence or progression of a disease or condition. They are generally statistical models that provide an objective estimate of how likely it is that a given condition is present. Neuromarkers can consist of a single variable, or be complex multivariate models.

Brain imaging terms

Voxel: A voxel can be thought of as a three-dimensional pixel. Voxels are the smallest units in three-dimensional brain images obtained using MRI.

Region of interest (ROI): ROI is a term used in neuroimaging to describe data which contain information about a specific area of the MRI image. ROIs will often correspond to predefined regions within the brain, such as the amygdala or the hippocampus. Data within an ROI are typically averaged for inclusion in statistical tests.

Signal to noise ratio (SNR): In imaging, SNR refers to the ratio of signal within the data to the background 'noise'. In brain imaging terms this represents the strength of the signal coming from the brain itself, such as from the BOLD signal, compared to the (random) background noise which is of no interest. SNR is normally low in neuroimaging.

Psychological terms

Symptomatology: For mental disorders, symptomatology refers to observable and self-reported symptoms which an individual experiences. This may include physiological and psychological symptoms.

Phenomenology: In psychology, phenomenology refers to the description of an individual's experience, and is dissociated from objective reality.

Neurotype: A neurotype or biological subtype of a disorder or condition is a subset of the population that shows particular characteristics of brain structure or function.

Statistical and machine learning terms

Inferential statistics: The *t-test* is a test of the statistical hypothesis that two samples are drawn from the same population. The underlying assumption of the t-test is that data from the same population would follow a normal distribution. T-tests are often used to test whether there are statistically significant differences between two groups. Generally, an Analysis of variance (*ANOVA*) is the extension of the t-test to multiple groups. ANOVAs test for differences in group means.

Model (Statistical model): A statistical model refers to the formal description of the generation of data. Statistical models can be thought of as mathematical representations of theories. Statistical models usually describe the relationship between one or more independent variables (such as neuroimaging data), and some dependent variable of interest (such as symptomatology). The multivariate models referred to throughout the thesis typically have multiple input variables that are weighted depending on how strongly they contribute to the description of the dependent variable. The weighted input variables are then

combined in a mathematical equation that results in an estimate of the outcome variable. Variable weigths are referred to as β (beta) weigths.

Unimodal and multimodal models: Unimodal models include only data from one modality, such as a single type of neuroimaging data. Multimodal models include data from more than one modality.

Ensemble methods: Ensemble methods make it possible to use multiple statistical models to create a summary model. Examples of this approach are 'voting', and 'boosting'. Ensemble methods often combine results from multiple models into a new model, weighting inputs to create a superior estimate than would have been achievable using each model on its own.

False positive: False positive results are findings which indicate that something is true, when it is in fact not true. False positives are often used to describe the results of classification studies, where a member of the negative class (typically control participants) may be erroneously classified as a member of the positive class (typically patients).

Sensitivity & Specificity: Sensitivity refers to the number of cases from the positive class (typically patients) that were correctly identified by the model, and specificity refers to the number of cases from the negative class (typically control participants) that were correctly identified.

Area under the curve of the receiver operating characteristic curve (AROC/AUC): The AROC refers to the integral of the receiver operating characteristic curve (ROC). The AROC is a frequently used metric of model fit for classification models and logistic regression. The ROC curve tracks the rate of true and false positive classification of the model. The true and false positive values are on a continuum where the extremes are the instances when all cases are classified as elements of one class. Higher AROC values denote better model fit, and a higher rate of true than false positive classification. The maximum AROC value is 1, with .5 representing chance performance.

Generalization study/test: A generalization study uses a sample that is independent of the dataset that was used to create a model. The generalization study is used to test how well a model performs when it is applied to a different sample.

Referenced model parameters

Elastic Net	λ	Regularization strength
	α	Extent of LASSO compared to ridge regularization being used. Alpha=1 corresponds to just LASSO being used, α=0 corresponds to just ridge being used.
Prospect utility function (all IGT models)	λ	Loss aversion
	α	Sensitivity to feedback
Delta learning rule (PVL-Delta and VPP model)	A	Recency parameter
Decay reinforcement rule (PVL-Decay model)	A	Decay rate
Perseveration function (VPP model)	k	Decay rate
	ε_{pos}	Perseverance value of positive outcomes
	ε_{neg}	Perseverance value of negative outcomes
	ω	Reinforcement learning parameter
Softmax action-selection rule (all IGT models)	c	Consistency parameter

Appendices

Appendix A. Feature Selection protocol

The feature selection method used in Chapter 2 is termed 'Adaptive feature thresholding', or Regularized Adaptive Feature Thresholding (RAFT) when used with the Elastic Net (see Figure D.1). The code for all analyses described here is available at github.com/ljollans/RAFT. Below the analysis steps involved in RAFT are described.

Appendix A.1. Nested cross-validation

The dataset is initially divided into 10 cross-validation (CV) folds. The entire analysis is performed 10 times, using 90% of the dataset (the training set) to create a regression model which is then tested on the remaining 10% of the data (the test set). Within the training set, additional 'nested' cross-validation with 10 partitions is used to support the analyses at the feature selection and model optimization level. Subsequently, results from all 10 CV folds are aggregated. The frequency with which a variable is found in models from different CV folds is used as a measure of its robustness.

Appendix A.2. Threshold creation

Each feature of the dataset is individually evaluated to assess its utility in predicting the target variable. A simple linear or logistic regression model is applied to the nested training set (81% of the total data) for that feature and the target variable, and the resulting regression weight is used to make outcome predictions for the nested test set (9% of the total data). The prediction error is quantified using root mean squared error for linear regression, and the F1 score for logistic regression. These values are referred to as feature *merit*.

Based on the range of merit values, a set of ten *feature merit thresholds* is created separately for each CV fold. These thresholds serve the purpose of ranking the features. The highest and lowest thresholds are determined based on the feature merit distribution of each CV fold, and the remaining eight thresholds are evenly distributed between them. The thresholds were chosen as follows:

At each merit threshold (t_{merit}) and for each nested CV partition *n* (within main CV partition *m*) there is a subset $s_{m,n}$ of features f which have smaller feature merit than that threshold.

$$s_{m,n}(t_{merit}) = \{f | merit_{m,n}(f) < t_{merit}\}$$

A set of ten *stability* (or 'occurrence') *thresholds* ($t_{stability}$) is also used to determine the stability of merit values for each feature across nested CV partitions (within the main CV fold). Feature stability $stability_{m,t_{merit}}(f)$ is quantified as the number of nested CV partitions *n* in which the feature's merit value is lower than a given merit threshold.

$$stability_{m,t_{merit}}(f) = \left|\{n|f \in s_{m,n}(t_{merit})\}\right|$$

The ten prediction error thresholds and ten stability thresholds jointly define 100 new summary datasets $D_m(t_{merit}, t_{stability})$ for each CV fold *m*. These summary datasets include all features that had a smaller prediction error value than t_{merit} in the number of CV partitions specified by $t_{stability}$.

$$D_m(t_{merit}, t_{stability}) = \{f|stability_{m,t_{merit}}(f) \geq t_{stability}\}$$

The merit thresholds are chosen separately for each main CV fold based on the range of merit and feature stability across the sample. The most liberal merit threshold $t_{merit}(min)$ is chosen such that in each main CV fold *m* there remains at least one feature which is common to all nested CV partitions, i.e. t_{merit}(min) is the smallest prediction error value (i.e. highest merit) at which the following is true:

$$D_m(t_{merit}(min), 10) \neq \emptyset$$

The strictest merit threshold $t_{merit}(max)$ is set as the lowest possible prediction error value (i.e. the highest merit) at which every nested CV partition *n* of the main CV fold *m* still contains at least one feature that has a smaller prediction error value (i.e. higher merit) than that threshold. That is, $t_{merit}(max)$ is the smallest prediction error value at which the following is true:

$$\left|\{n|s_{m,n}(t_{merit}(max)) \neq \emptyset\}\right| = 10$$

Taken together t_{merit} and $t_{stability}$ define how high the individual predictive power of each feature in the knowledge base is, and how sTable 2.the results with each feature are across different subsets of the sample. The creation of these thresholds serves the purpose of integrating the choice of the criterion used to select features from the filtering step into model selection, eliminating researcher input at this point.

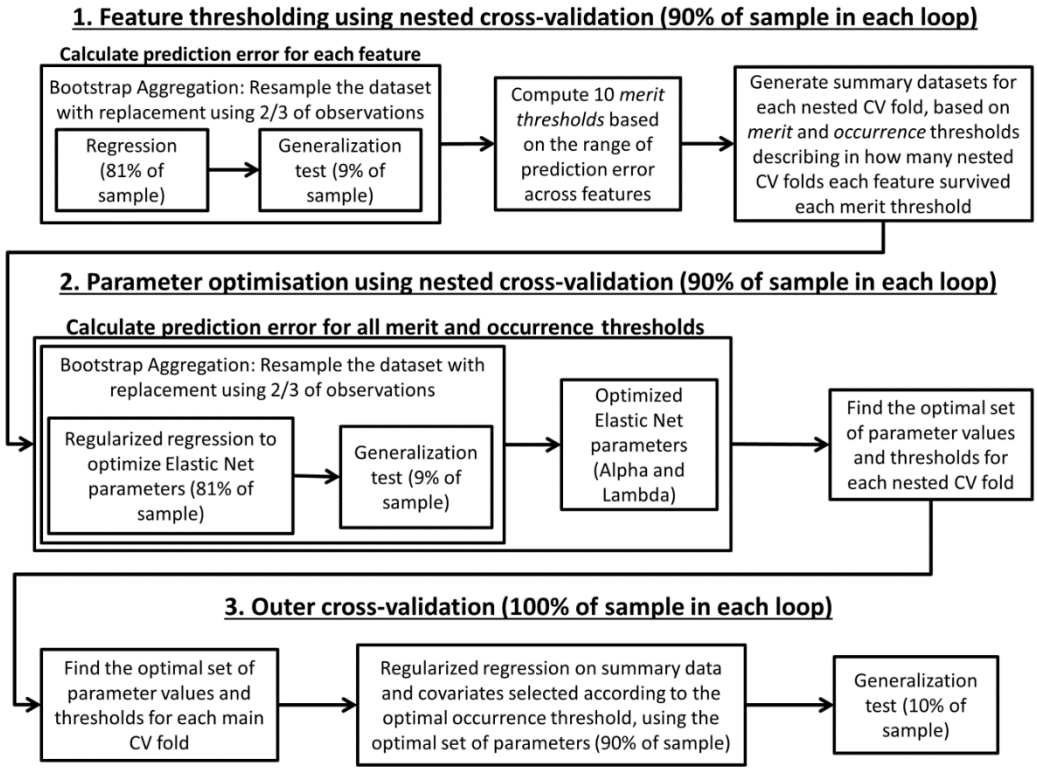

Figure D.1. Analysis protocol for the Elastic net with embedded feature selection and bootstrap aggregation.

Appendix A.3. Threshold Optimization

The 100 feature sets that are created in the first analysis step (from 10 stability thresholds and 10 merit thresholds) are used as inputs into the selected algorithm. This approach was tested using Multiple Regression, Random Forest, and the Elastic Net. In the following section, the model optimization and validation process is described for the Elastic Net.

The Elastic Net uses two parameters: λ and α. Here, five values of λ and α each are considered, resulting in the creation of 25 models with each feature set, for a total of 2500 models. For each of these models, the prediction error is quantified using root mean squared error for linear regression and the F1 score for logistic regression. For each model, an updated feature set *d* is saved, which excludes any features that were excluded by the Elastic Net.

$$d_{m,n}\left(t_{merit}, t_{stability}, \alpha, \lambda\right) \subseteq D_m\left(t_{merit}, t_{stability}\right)$$

Appendix A.4. Bootstrap aggregation

Calculations in the thresholding and model optimization step are validated using 25-fold bootstrap aggregation (bagging). Instead of performing the analysis once using all data, summary datasets are created by randomly sampling on average two thirds of the data in each iteration. Results from each iteration are aggregated using the median value. A feature is removed after the

model optimization step if the Elastic Net removed the feature in more than half of all bagging iterations.

Appendix A.5. Model validation

After the model optimization step, the combination of model parameters and thresholds which resulted in the model with the lowest prediction error is identified for each nested CV partition *n*. The optimal model parameters and thresholds from each nested CV partition are used to identify what parameters will be used to create the final prediction model in each main CV fold *m*, using the most frequently occurring values of α, λ, t_{merit} and $t_{stability}$. To select the features to include in the final model for each CV fold, the stability of all features that were included in the updated feature sets at the optimal prediction error and stability thresholds is re-calculated.

$$stability_m(f) = \left|\{n | f \in d_{m,n}(t_{merit}, t_{stability}, \alpha, \lambda)\}\right|$$

Only the features that were included in at least as many of the ten models with optimal parameters as specified by the optimal stability threshold are used to create the feature set for the final model.

$$FeatureSet_m = \{f | stability_m(f) \geq t_{stability,final(m)}\}$$

It is possible that this implementation of the stability threshold does not leave any features for inclusion in the model (i.e. the addition of the stability threshold restriction to the other parameters rules out all potential features). Should this be the case the closest possible parameter combination is used to create the feature set.

This feature set is used as input into the Elastic Net, using the optimal values for α and λ, and the entire training set (90% of the data). The beta weights generated by the Elastic Net are subsequently used to make outcome predictions for the final unseen portion of the data (10%). Each CV fold *m* is used to make outcome predictions for 10% of the data, and the evaluation of overall model fit is carried out using the complete vector of outcome predictions from all CV folds.

Appendix B. Smoking group classification results without inclusion of cannabis predictors

Appendix B.1. Classification performance

Table B.1. Mean AUC and F1 score for all analyses

	Psychometric model		Multimodal model	
	AUC	F1 score	AUC	F1 score
EOS	0.840**	0.489**	0.809**	0.469**
LOS	0.714**	0.223**	0.695**	0.253**
EOS/LOS	0.784**	0.487**	0.771**	0.489**
EOS vs. LOS	0.630**	0.600**	0.571*	0.564*

* p<.0005; **p<.00005

Appendix B.2. Significant predictors and predictor overlap with analyses including cannabis predictors

Table B.2. Number of predictors of each type that were significant for each analysis

	Neuroimaging predictors, joint model			Psychometric predictors, multimodal model (shared with unimodal model)			Psychometric predictors		
	With cannabis	Shared between models	Without Cannabis	With cannabis	Shared between models	Without Cannabis	With cannabis	Shared between models	Without Cannabis
EOS	0	0	0	0 (0)	0	0 (0)	0	0	30
LOS	8	0	0	15 (3)	0	0 (0)	27	19	20
EOS/LOS	3	3	3	80 (34)	75 (33)	80 (33)	34	31	33
EOS vs. LOS	26	24	26	59 (29)	56 (25)	59 (25)	34	26	29

Appendix B.3. Ten predictors with highest absolute regression weights for models with and without cannabis predictors

Table B.3. Ten predictors with highest absolute regression weights for all models

	EOS	LOS		EOS/LOS		EOS vs. LOS	
	NC*	C	NC*	C	NC	C	NC
TCI-R							
Novelty-seeking	.046	-	-	-	.027	-.052	-.060
Disorderliness ('I am not very good at talking my way out of trouble when I am caught doing something wrong')	-	-	-	-	-	-.067	-.075
Exploratory excitability ('I am slower than most people to get excited about new ideas and activities')	-	-	-	-	-	-.049	-
NEO-ffi							
Agreeableness ('If necessary, I am willing to manipulate people to get what I want')	-	-	-.043	-	-	-	-
SURPS							
Anxiety sensitivity	-	-	-	-	-	-	-.051
Anxiety sensitivity ('I get scared when I experience unusual body sensations')	-	-	-.037	-	-	-	-
DAWBA							
Parent: polite	-	-	-.036	-	-	-	-
Parent: popularity	-	-	-	-	-	-.063	-.067
Parent: Recent deliberate self-harm	-	-	-	.030	.030	-	-
Parent: Lifetime deliberate self-harm	.048	-	-	-	.023	-	-
Teacher: other psych. development concerns	-	-	-	-	-	.088	.071
Parent: 12-month truancy	.048	-	-	-	-	-	-
Parent: 12-month starting fights	.044	-	-	-	-	-	-
Parent: 12-month staying out late	.042	-	-	-	-	-	-
ADHD clinical rating	-	-.161	-	-	-	-	-
ADHD hyperactive-impulsive clinical rating	-	-.174	-	-	-	-	-
ESPAD							
Alcohol							
Age of first getting drunk	-	-	-	-	-.024	-	-
Lifetime drunkenness occasions	.052	-	-	.031	.032	-	-
Past month drunkenness occasions	.065	-	-	.030	.032	-	-
Degree of drunkenness at last occasion	.050	-	-	-	.028	-	-
Number of drinks needed to get drunk	.047	-	-	-	.027	-	-
Cannabis use							
First cannabis use	-	-	-	-.037	-	-	-

Lifetime cannabis use	-	-	-	.037	-	-	-
Past year cannabis use	-	-	-	.037	-	-	-
Past month cannabis use	-	-	-	.031	-	-	-
Past week cannabis use	-	-	-	.031	-	-	-
Inhalant use							
Has heard of inhalants	-	-	-.041	-	-	-	-
Past year inhalant use	.059	-	-	.028	.030	-	-
Past month inhalant use	-	-	-	.055	.053	-	-
LEQ							
Sexual/Romantic events scale, past year	-	-	.041	-	-	-	-
Broke up with boy/girlfriend in past year	-	-	.050	-	-	-	-
Started relationship in past year	-	-	.046	-	-	-	-
Valence: sustaining a serious injury or accident	-	-	.055	-	-	-	-
Family variables							
Parent: 'Gets help and support when stressed'	-	.146	-	-	-	-	-
Parent: Parents' partner has shown loss of interest in usually enjoyable activities	-	-	.035	-	-	-	-
Parent variables							
Current maternal daily smoking quantity	-	-	.037	-	-	-	-
Parent lifetime cocaine use	-	-.126	-	-	-	-	-
NEO-ffi parent: Neuroticism ('At times I have been so ashamed I just wanted to hide')	-	-	-	-	-	-.058	-.067
Neuroimaging variables							
GCA[1]: Heschl's gyrus, L	-	-.148	-	-	-	-	-
GCA[1]: Heschl's gyrus, R	-	-.123	-	-	-	-	-
GCA[1]: Superior temporal gyrus, L	-	-.143	-	-	-	-	-
GCA[1]: Rolandic operculum, L	-	-.133	-	-	-	-	-
SST (stop success): Cerebellum, R	-	-	-	-	-	.049	.054
SST (stop failure): Amygdala, L	-	-.124	-	-	-	-	-
MID[1]: Medial orbitofrontal cortex, L	-	-	-	-	-	-.055	-.051
MID[1]: Inferior frontal gyrus, pars triangularis, L	-	-	-	-	-	-.051	-.052
MID[2]: Posterior cingulate cortex, L	-	-.135	-	-	-	-	-
Faces[1] : Posterior cingulate cortex, R	-	-	-	-	-	.058	.059

*The positive class for 'EOS', 'LOS', and 'EOS/LOS' is the smoker group and LOS for 'EOS vs. LOS'. C: with cannabis predictors; NC: without cannabis predictors; GCA[1]: GCA auditory sentences; MID[1]: MID task anticipation of large win minus no win; MID[2]: MID task feedback large win minus small win; Faces[1]: Faces task, angry affective facial stimuli minus control stimuli. *Results from unimodal model.*

Appendix B.4. Discrepancies between significant predictors in models with and without cannabis predictors

The predictors reported in this section cover all discrepancies between predictors in models with and without cannabis predictors. Effects for all predictors not mentioned here were the same for the models with and without cannabis.

B.4.1. Neuroimaging predictors

B.4.1.1. Grey matter volume

LOS compared to EOS was predicted by lower volume in the left inferior parietal lobule in the multimodal model with cannabis predictors and by lower volume in the right angular gyrus in the multimodal model without cannabis predictors.

B.4.1.2. Monetary Incentive Delay Task

Activity in the orbital part of the left MFG during feedback for large vs. small wins was no longer a significant predictor of LOS compared to EOS in the model without cannabis predictors.

B.4.1.3. GCA task

In addition to the predictors identified in the models with cannabis predictors, higher activity in the right middle temporal pole while reading sentences predicted LOS compared to EOS in the analysis without cannabis predictors.

B.4.2. Substance use (ESPAD) (Appendix C.1)

In the unimodal model without cannabis predictors EOS compared to NS was predicted by lifetime, past year and past month drunkenness occasions, higher level of drunkenness, higher drunkenness threshold, higher quantity of alcohol consumption when drinking, and earlier first drunkenness and first drinking spirits.

When cannabis predictors were excluded from the model, higher lifetime inhalant use and earlier first use of inhalants were significant predictors of EOS/LOS compared to NS in the multimodal model, while higher past year inhalant use predicted EOS compared to NS in the unimodal model. EOS/LOS compared to NS was also predicted by higher past year inhalant use in the unimodal model without cannabis predictors.

B.4.3. Personality (Appendix C.2)

B.4.3.1. TCI-R

Novelty-seeking: In the unimodal model without cannabis predictors EOS compared to NS was predicted by higher scores on the novelty seeking scale.

Disorderliness: Higher scores on the disorderliness subscale of the TCI novelty-seeking scale and the items 'I often break rules and regulations when I think I can get away with it' and 'I am not very good at talking my way out of trouble when I am caught doing something wrong' predicted EOS compared to NS in the unimodal model without cannabis predictors.

Exploratory excitability: When cannabis predictors were excluded responses to the item 'I am slower than most people to get excited about new ideas and activities' were no longer significant predictors in the

unimodal model predicting EOS compared to LOS. When cannabis predictors were excluded EOS compared to LOS was no longer predicted by the exploratory excitability summary score in the unimodal model.

Extravagance: EOS compared to NS was predicted by higher scores on the extravagance scale, lower endorsement of the item 'I am better at saving money than most people', and higher endorsement of the item 'Because I so often spend too much money on impulse, it is hard for me to save money - even for special plans like a vacation' in the unimodal model without cannabis predictors.

B.4.3.2. NEO-ffi

Agreeableness: When cannabis predictors were excluded the item 'If I don't like people, I let them know it' was no longer a significant predictor of LOS compared to NS.

Conscientiousness: EOS compared to NS was predicted by lower scores on the conscientiousness scale of the NEO-ffi and by lower endorsement of the following items in the unimodal and multimodal models: 'I work hard to accomplish my goals', 'I am a productive person who always gets the job done', and 'I strive for excellence in everything I do'.

B.4.3.3. SURPS

Sensation seeking: Summary scores for the SUPRS sensation seeking scale and endorsement of the item 'I would like to learn how to drive a motorcycle' predicted LOS compared to NS in the unimodal model when cannabis predictors were included. Endorsement of the item 'I am interested in experience for its own sake even if it is illegal' predicted EOS compared to NS in the unimodal model without cannabis predictors.

B.4.4. Life history (LEQ) (Appendix C.3)

When cannabis predictors were excluded EOS/LOS compared to NS was predicted by the overall summary score for events in the past year on the LEQ.

When cannabis predictors were excluded valence for a family member experiencing an accident or illness was no longer a significant predictor of LOS compared to EOS. Ever having sustained a serious accident or injury was no longer a significant predictor in the unimodal model predicting LOS compared to NS when cannabis predictors were excluded. In the unimodal model without cannabis predictors EOS compared to NS was predicted by having experiences a death in the family in the past year.

When cannabis predictors were excluded ever having broken up with a boyfriend/girlfriend predicted EOS/LOS compared to NS in the unimodal model.

In the unimodal model without cannabis predictors EOS compared to NS was predicted by having gotten in trouble with the law in the past year and more positive valence for getting poor grades in school.

B.4.5. Demographic measures

In line with the gender differences between groups, being female predicted EOS compared to LOS in the unimodal and multimodal models and in the multimodal model when cannabis predictors were excluded.

B.4.6. Behaviour and psychopathology (Appendix C.4)

Parent-report that a teacher had expressed concerns about the child's psychological development that did not fall under the areas assessed by the DAWBA (phobias, anxiety disorders, mood disorders, ADHD, conduct disorders, eating disorders, tics) was no longer a significant predictor of LOS compared to EOS in the unimodal model when cannabis predictors were excluded.

B.4.6.1. Antisocial behaviour and peer relationships

Self-reported bullying in the multimodal model for EOS and LOS was no longer a significant predictor when cannabis variables were excluded, and hitting, kicking or otherwise physically attacking or injuring a peer was also no longer a significant predictor of EOS compared to LOS in the unimodal model. However, computer predictions of conduct disorder and parent-report of starting fights, staying out late, and truancy in the past year predicted EOS compared to NS in the unimodal model without cannabis variables.

In the multimodal model without cannabis predictors parent-reported truancy in the past year predicted EOS compared to LOS.

Self-report that they had ever 'found a new group of friends' predicted adolescents being NS compared to LOS in the unimodal model without cannabis predictors.

B.4.6.2. Depression (DAWBA)

Ever having engaged in deliberate self-harm predicted EOS compared to NS in the model without cannabis predictors.

B.4.6.3. ADHD (DAWBA)

In the multimodal model without cannabis predictors EOS compared to LOS was predicted by higher parental report of the adolescent losing 'things s/he needs for school or games' in the past 6 months. In the unimodal model without cannabis predictors EOS compared to LOS was also predicted by the clinical rating for any indication of ADHD.

B.4.7. Parents and family environment

B.4.7.1. Family situation (Appendix C.4)

Broken home indicators. Compared to NS, LOS was no longer predicted by a parent having remarried in the past year in the unimodal model without cannabis predictors.

When cannabis predictors were excluded EOS compared to LOS was also no longer predicted by whether the adolescent was living with just one family and whether they were living with a stepfather in the unimodal model.

Parenting. In the unimodal model without cannabis predictors parent-report that the child 'gets help and support when stressed' was no longer a significant predictor of LOS compared to NS. In the multimodal model without cannabis predictors EOS compared to LOS was predicted by higher parent report that the child would be likely to seek help from family and friends.

Family life. Parent report of family stress due to the neighbourhood or the neighbours no longer predicted EOS compared to LOS in the multimodal model without cannabis predictors.

B.4.7.2. Parent TCI-R (Appendix C.5)

Extravagance: EOS compared to LOS was no longer predicted by parent endorsement of the TCI extravagance subscale item 'It is fun for me to buy things for myself' in the multimodal model when cannabis variables were excluded.

B.4.7.3. Parent SURPS (Appendix C.5)

In the unimodal model without cannabis predictors parental endorsement of the SUPRS item 'I often don't think things through before I speak' predicted EOS compared to NS.

B.4.7.4. Parent substance use (Appendix C.5)

Alcohol: When cannabis predictors were excluded EOS/LOS compared to NS was predicted by parent-reported frequency of alcohol use in the multimodal model. When cannabis predictors were excluded NS compared to LOS was also predicted by parents reporting that they had never 'been arrested, even for a few hours, because of drunken behaviour (other than driving)' in the unimodal model.

Smoking: When cannabis predictors were excluded parental past month smoking no longer predicted LOS compared to NS. In the unimodal without cannabis predictors maternal smoking occasions no longer predicted LOS compared to NS.

B.4.7.5. Prenatal factors (Appendix C.5)

In the multimodal model without cannabis predictors EOS/LOS compared to NS was predicted by the variable assessing whether the mother had been exposed to second-hand smoke at all during pregnancy.

Appendix C. Regression weigths, Chapter 3

Appendix C.1. Regression weights for ESPAD items, Chapter 3

		With cannabis predictors						Without cannabis predictors					
		Multimodal model			Unimodal model			Multimodal model			Unimodal model		
		LOS	EOS/ LOS	EOS vs. LOS	LOS	EOS/ LOS	EOS vs. LOS	EOS/ LOS	EOS vs. LOS	EOS	LOS	EOS/ LOS	EOS vs. LOS
ESPAD alcohol	How many *times IN YOUR WHOLE LIFETIME have you had five or more drinks in a row?*	-	0.010	-	-	-	-	0.012	-	-	-	-	-
	'On how many occasions IN YOUR WHOLE LIFETIME have you been drunk from drinking alcoholic beverages?	-	0.031	-	-	0.034	-	0.033	-	0.052	-	0.036	-
	On how many occasions OVER THE LAST 12 MONTHS have you been drunk from drinking alcoholic beverages?	-	0.020	-	-	0.019	-	0.022	-	0.036	-	0.022	-
	'On how many occasions OVER THE LAST 30 DAYS have you been drunk from drinking alcoholic beverages?	-	0.030	-	-	0.034	-	0.033	-	0.066	-	0.038	-
	'Please indicate on this scale from 1 to 10 how drunk you would say you were the last time you were drunk	-	0.026	-	-	0.028	-	0.028	-	0.051	-	0.031	-
	'How many drinks do you usually need to	-	0.026	-	-	0.028	-	0.027	-	0.047	-	0.030	-

	get drunk?												
	'When did you FIRST get drunk from drinking alcoholic beverages?'	-	-0.023	-	-	-0.026	-	-0.025	-	-0.039	-	-0.027	-
	'When did you FIRST drink spirits (at least one glass)?		-0.020	-	-	-0.022	-	-0.019	-	-0.025	-	-0.023	-
	When did you FIRST drink wine (at least one glass)?	-	-0.009	-	-0.034	-	-	-0.010	-	-	-0.035	-	-
	'On how many occasions IN YOUR WHOLE LIFETIME have you had any alcoholic beverage to drink?	-	0.011	-	-	-	-	0.012	-	-	-	-	-
	'On how many occasions OVER THE LAST 12 MONTHS have you had any alcoholic beverage to drink?	-	0.010	-	-	-	-	0.011	-	-	-	-	-
	'How many drinks containing alcohol do you have on a TYPICAL DAY when you are drinking?	-	0.022	-	0.030	0.025	-	0.022	-	0.025	0.032	0.026	-
ESPAD cannabis	First cannabis use	-	-0.037	-	-	-0.046	-	-	-	-	-	-	-
	Life cannabis use	-	0.037	-	-	0.046	-	-	-	-	-	-	-
	Month cannabis use	-	0.031	-	-	-	-	-	-	-	-	-	-
	Week cannabis use	-	0.031	-	-	-	-	-	-	-	-	-	-
	Year cannabis use	-	0.037	-	-	0.046	-	-	-	-	-	-	-
ESPAD inhalants	Have you ever heard of inhalants?	-	-	-0.040	-0.042	-	-0.042	-	-0.037	-	-0.042	-	-0.042
	First inhalant use	-	-	-	-	-	-	-0.010	-	-	-	-	-
	Life inhalant use	-	-	-	-	-	-	0.010	-	-	-	-	-

	Month inhalant use	-	0.056	-	-	-	-	0.053	-	-	-	-	-
	Year inhalant use	-	0.028	-	-	-	-	0.031	-	0.060	-	0.040	-
ESPAD drugs of abuse	“Have you ever heard of coke”	-	-	-0.029	-	-	-	-	-0.031	-	-	-	-
	“Have you ever heard of heroin”	-	-	-0.029	-	-	-	-	-0.029	-	-	-	-
	“Have you ever heard of MDMA”	-	-	-0.028	-	-	-	-	-0.029	-	-	-	-
	“Have you ever heard of narcotics”	-	-	-0.032	-	-	-	-	-0.033	-	-	-	-
	'Have you ever wanted to try any of the drugs mentioned in the previous questions?	-	0.015	-	-	-	-	0.017	-	-	-	-	-
ESPAD other	'Which of the following best describes your average grade in the end of the last term?	-	0.016	-	-	0.019	-	0.016	-	-	-	0.020	-
	I took part in bullying another student/ peer at school.	-	-	-0.033	-	-	-0.046	-	-	-	-	-	-0.052
	'I hit, kicked, pushed, shoved around, or locked a student/ peer indoors	-	-	-	-	-	0.040	-	-	-	-	-	-
	'I have been bullied by a family member	0.111	-	-	-	-	-	-	-	-	-	-	-
	'During the LAST 30 DAYS how many whole days of school have you missed because you skipped or ”cut”?	-	-	-0.041	-	-	-0.047	-	-0.039	-	-	-	-0.046

Appendix C.2. Regression weights for TCI-R, NEO-ffi and SURPS items, Chapter 3

		With cannabis predictors					Without cannabis predictors					
		Multimodal model			Unimodal model		Multimodal model			Unimodal model		
		EOS/LOS	EOS vs. LOS	LOS	EOS/LOS	EOS vs. LOS	EOS/LOS	EOS vs. LOS	EOS	LOS	EOS/LOS	EOS vs. LOS
TCI-R summary scores	Disorderliness	0.017	-0.047	-	0.019	-0.040	0.017	-0.042	0.036	-	0.019	-0.043
	Exploratory excitability	-	-0.046	-	-	-0.051	-	-0.045	-	-	-	-
	Extravagance	0.022	-	-	0.026	-	0.022	-	0.032	-	0.027	-
	Novelty seeking	0.027	-0.053	-	0.031	-0.043	0.027	-0.061	0.047	-	0.031	-0.047
TCI-R items	'I am much more reserved and controlled than most people	-	-0.030	-	-	-	-	-0.031	-	-	-	-
	I often spend money until I run out of cash or get into debt from using too much credit.	0.011	-	-	-	-	0.012	-	-	-	-	-
	I enjoy saving money more than spending it on entertainment or thrills.	0.009	-	-	-	-	0.009	-	-	-	-	-
	'I often break rules and regulations when I think I can get away with it.'	0.020	-	-	0.023	-	0.020	-	0.026	-	0.024	-
	'I like to think about things for a long time before I make a decision.	-	-0.031	-	-	-	-	-0.030	-	-	-	-
	'I can usually do a good job of stretching the truth to tell a funnier story or to play a joke on someone.	-	-0.027	-	-	-	-	-0.027	-	-	-	-
	I am better at saving money than most people.	0.021	-	-	0.026	-	0.021	-	0.030	-	0.027	-
	I am slower than most people to get excited about new ideas and activities.	-	-0.049	-	-	-0.046	-	-0.047	-	-	-	-

	Some people think I am too stingy or tight with my money.	0.013	-	-	-	-	0.013	-	-	-	-	-
	'I am not very good at talking my way out of trouble when I am caught doing something wrong.	0.011	-0.067	-	-	-0.069	0.011	-0.076	0.035	-	-	-0.072
	Because I so often spend too much money on impulse, it is hard for me to save money - even for special plans like a vacation.	0.021	-	0.032	0.025	-	0.020	-	0.027	0.034	0.026	-
	'It is fun for me to buy things for myself	-	-0.026	-	-	-	-	-0.027	-	-	-	-
NEO-ffi summary scores	Agreeableness	-	-0.027	- 0.033	-	-0.042	-	-0.027	-	-0.032	-	-0.046
	Conscientiousness	-0.016	-	-	-0.020	-	-0.017	-	-0.026	-	-0.020	-
NEO-ffi items	'I am intrigued by the patterns I find in art and nature'	-	-0.030	-	-	-0.042	-	-0.034	-	-	-	-0.046
	'I often try new and foreign foods'	0.014	-	-	-	-	0.013	-	-	-	-	-
	'I work hard to accomplish my goals'	-0.020	-	-	-0.024	-	-0.018	-	-0.029	-	-0.024	-
	'I try to be courteous to everyone I meet'	-	-	- 0.032	-	-	-	-	-	-0.032	-	-
	'I am seldom sad or depressed'	-	-0.024	-	-	-	-	-0.027	-	-	-	-
	'I generally try to be thoughtful and considerate'	-0.012	-	-	-	-	-0.012	-	-	-	-	-
	'I am a productive person who always gets the job done'	-0.015	-	-	-0.018	-	-0.015	-	-0.029	-	-0.018	-
	'I often feel helpless and want someone else to solve my problems'	-	-0.026	-	-	-	-	-0.027	-	-	-	-
	'I have a lot of intellectual curiosity'	-	0.024	-	-	-	-	0.024	-	-	-	-

	'If I don't like people, I let them know it'	-	-	- 0.027	-	-	-	-	-	-	-	-
	'I never seem to be able to get organized'	-0.014	-	-	-	-	-0.013	-	-	-	-	-
	'If necessary, I am willing to manipulate people to get what I want	-0.017	-	- 0.045	-0.022	-	-0.016	-	-	-0.043	-0.022	-
	'I strive for excellence in everything I do	-0.017	-	-	-0.023	-	-0.017	-	-0.029	-	-0.023	-
SURPS summary scores	Anxiety sensitivity	-	-0.041	-	-	-0.047	-	-0.051	-	-	-	-0.051
	Impulsiveness	0.009	-	-	-	-	0.009	-	-	-	-	-
	Sensation seeking	0.019	-	0.028	0.024	-	0.019	-	-	-	0.025	-
SUPRS items	I would like to learn to drive a motorcycle	0.022	-	0.035	0.026	-	0.021	-	-	0.034	0.027	-
	'I get scared when I'm too nervous	-	-0.027	-	-	-	-	-0.026	-	-	-	-
	I am interested in experience for its own sake even if it is illegal.	0.011	-0.031	-	-	-0.039	0.012	-0.029	0.032	-	-	-0.040
	'I get scared when I experience unusual body sensations	-	-0.027	- 0.038	-	-	-	-0.026	-	-0.038	-	-
	'I would like to skydive	0.010	-	0.028	-	-	0.011	-	-	-	-	-
	I enjoy new and exciting experiences even if they are unconventional	0.010	-	-	-	-	0.010	-	-	-	-	-

Appendix C.3. Regression weights for LEQ items, Chapter 3

		With cannabis predictors						Without cannabis predictors					
		Multimodal model			Unimodal model			Multimodal model			Unimodal model		
		LOS	EOS/LOS	EOS vs. LOS	LOS	EOS/LOS	EOS vs. LOS	EOS/LOS	EOS vs. LOS	EOS	LOS	EOS/LOS	EOS vs. LOS
LEQ summary scores	All past year life events	-	-	-	-	-	-	0.009	-	-	-	-	-
	Lifetime sexuality	-	0.015	-	-	-	-	0.016	-	-	-	-	-
	Past year sexuality	-	0.016	-	0.042	0.018	-	0.017	-	-	0.042	0.019	-
LEQ past year experiences	'Got in trouble with the law'	-	-	-	-	-	-	-	-	0.026	-	-	-
	'Death in family'	-	0.011	-	-	-	-	0.011	-	0.028	-	-	-
	'Parent changed jobs'	-	0.011	-	-	-	-	0.010	-	-	-	-	-
	'Got own TV or computer'	-	-	0.045	-	-	0.042	-	0.047	-	-	-	0.042
	'Started going out with a girlfriend/boyfriend'	-	0.018	-	0.046	0.021	-	0.018	-	-	0.047	0.022	-
	'Broke up with boy/ girl-friend'	-	0.013	0.042	0.049	-	0.044	0.014	0.043	-	0.050	-	0.044
	'Parent remarried'	0.095	-	-	0.155	-	-	-	-	-	-	-	-
LEQ lifetime experiences	Found a new group of friends'	-	-	-0.044	-	-	-	-	-0.045	-	-	-	-0.037
	Family had money problems'	-	-	-	-	-	-0.037	-	-	-	-	-	-0.036
	'Started going out with a girlfriend/boyfriend'	-	0.015	-	0.033	-	-	0.015	-	-	0.033	-	-
	Got poor grades in school'	-	-	-0.024	-	-	-	-	-0.027	-	-	-	-
	'Broke up with boy/ girl-friend'	-	0.016	-	0.034	-	-	0.016	-	-	0.035	0.017	-
	Found religion'	- 0.102	-	-	-	-	-	-	-	-	-	-	-

	'Serious accident or illness'	-	-	0.025	0.028	-	-	-	0.026	-	-	-	-
	'Parent abused alcohol'	0.107	-	-	-	-	-	-	-	-	-	-	-
LEQ valence	'Family accident or illness'	-	-	0.033	-	-	0.037	-	0.031	-	-	-	-
	'Stole something valuable'	-	-	0.047	-	-	-	-	0.046	-	-	-	-
	'Parent changed jobs'	-	-	-0.034	-	-	-0.040	-	-0.035	-	-	-	-0.041
	'Got in trouble at school'	-	0.009	-	0.034	-	-	0.010	-	-	0.034	-	-
	Got poor grades in school'	-	-	-	-	-	-	-	-	0.027	-	-	-
	Serious accident or illness'	0.096	-	0.047	0.054	-	0.055	-	0.045	-	0.055	-	0.059

Appendix C.4. Regression weights for DAWBA items, Chapter 3

		With cannabis predictors						Without cannabis predictors					
		Multimodal model			Unimodal model			Multimodal model			Unimodal model		
		LOS	EOS/LOS	EOS vs. LOS	LOS	EOS/LOS	EOS vs. LOS	EOS/LOS	EOS vs. LOS	EOS	LOS	EOS/LOS	EOS vs. LOS
ADHD	ADHD (Clinical rating, DSM-IV)	-0.162	-	-	-	-	-	-	-	-	-	-	-0.081
	ADHD hyp-imp (Clinical rating, DSM-IV)	-0.175	-	-	-	-	-	-	-	-	-	-	-
	ADHD: Loses things	-	-	-	-	-	-	-	-0.024	-	-	-	-
Conduct disorder / ODD / Antisocial behaviour	Conduct disorder (Computer prediction, DSM-IV & ICD-10)	-	-	-0.032	-	-	-0.037	-	-0.035	-	-	-	-0.036
	Conduct disorder	-	0.016	-	-	0.019	-	0.017	-	0.031	-	0.020	-
	Ignores rules/disobedient (past 6 months)	-	0.011	-	-	-	-	0.011	-	-	-	-	-
	Lies (past year)	-	0.009	-	-	-	-	0.009	-	-	-	-	-
	Fights (past year)	-	0.014	-	-	-	-	0.014	-	0.044	-	-	-
	Stays out (past year)	-	0.024	-	-	0.030	-	0.023	-	0.042	-	0.031	-
	Steals (past year)	-0.097	-	-	-	-	-	-	-	-	-	-	-
	Truancy (past year)	-	0.020	-	-	-	-	0.021	-0.024	0.048	-	-	-
	SDQ: Lies, cheats	-	0.017	-	-	0.020	-	0.017	-	-	-	0.021	-
Depressive symptoms	Sad (past 4 weeks)	-	-	-0.027	-	-	-	-	-0.030	-	-	-	-
	Deliberate self-harm recently	-	0.031	-	-	-	-	0.031	-	-	-	-	-
	Deliberate self-harm ever	-	0.023	-	-	-	-	0.024	-	0.048	-	-	-
Family environment	About respondents partner:	-	-	0.029	-	-	-	-	0.027	-	-	-	-

	Stressed												
	About respondents partner: Loss of interest	-	-	0.037	0.033	-	0.040	-	0.037	-	0.036	-	0.041
	Child gets help and support when stressed	0.146	-	0.028	0.028	-	-	-	0.028	-	-	-	-
	Child gets blamed unfairly	-	-	-0.043	-	-	-0.049	-	-0.044	-	-	-	-0.052
	Child has consistently applied rules	-	-	0.041	-	-	-	-	0.041	-	-	-	0.037
	Family stresses: Financial difficulties	-	-	0.037	-	-	-	-	0.038	-	-	-	-
	Family stresses: Neighbours or neighbourhood	-	-	-0.024	-	-	-	-	-	-	-	-	-
	Likely to seek help from family and friends	-	-	-	-	-	-	-	-0.025	-	-	-	-
	Living with parents	-	-	-0.044	-	-	-0.046	-	-0.048	-	-	-	-
	Adults in household 1: Biological father	-	-	0.036	-	-	0.037	-	0.035	-	-	-	0.037
	Adults in household 1: Stepfather	-	-	-	-	-	-0.044	-	-	-	-	-	-
Parent rating of child's positive attributes	Lively	-	0.009	-	-	-	-	0.010	-	-	-	-	-
	Keen to learn	-	-0.012	-	-	-	-	-0.012	-	-	-	-	-
	Does homework without reminding	-	-0.012	-	-	-	-	-0.013	-	-	-	-	-
	Likes to be involved in family	-	-0.009	-	-	-	-	-0.009	-	-	-	-	-

	activities												
	Takes care of appearance	0.100	-	-	-	-	-	-	-	-	-	-	-
	Polite	-	-	-	-	-	-	-	-	-	-	-	-
					0.036						0.036		
Parent rating of child's peer relationships (SDQ)	Relates better to adults than peers	-	-0.014	-	-	-	-	-0.014	-	-	-	-	-
	Peer problems score	-	-0.019	-	-	-0.023	-	-0.018	-	-	-	-0.024	-
	Popular	-	-	-0.063	-	-	-0.045	-	-0.068	-	-	-	-0.044
Anxiety	Separation anxiety (Computer prediction, DSM-IV)	-	-	-0.044	-	-	-0.057	-	-0.045	-	-	-	-0.062
Eating disorder	Blames self a lot for overeating	-	-	-	-	-	-0.036	-	-	-	-	-	-0.038
Other developmental concerns	Teacher has complained to parent of other concerns	-	-	0.088	-	-	0.141	-	0.072	-	-	-	-

Appendix C.5. Regression weights for all items completed by parents about themselves, Chapter 3

		With cannabis predictors						Without cannabis predictors					
		Multimodal model			Unimodal model			Multimodal model			Unimodal model		
		LOS	EOS/LOS	EOS vs. LOS	LOS	EOS/LOS	EOS vs. LOS	LOS	EOS/LOS	EOS vs. LOS	LOS	EOS/LOS	EOS vs. LOS
AUDIT	'How often do you have a drink containing alcohol?	-	-	-	-	-	-	-	0.009	-	-	-	-
	'How many drinks containing alcohol do you have on a typical day when you are drinking?	-	-	-0.038	-	-	-0.046	-	-	-0.036	-	-	-0.047
ESPAD	'Have you ever used cocaine?	- 0.115	-	-	-	-	-	-	-	-	-	-	-
	'On how many occasions in your lifetime have you used cocaine ?	- 0.126	-	-	-	-	-	-	-	-	-	-	-
	'Can you get through the week without using cocaine (unless you require it for medical reasons)?	- 0.115	-	-	-	-	-	-	-	-	-	-	-
	'Are you always able to stop using cocaine when you want?	- 0.115	-	-	-	-	-	-	-	-	-	-	-
	Past month smoking	-	0.013	-	0.027	-	-	-	0.013	-	-	-	-
MAST	'Does any member of your family ever worry or complain about your drinking?	0.103	-	-	-	-	-	-	-	-	-	-	-
	'Have you ever been arrested, even for a few hours, because of drunken behaviour (other than driving)?	-	-	-	-	-	-	-	-	-	- 0.033	-	-
PBQ	'Has the MOTHER ever smoked a cigarette on occasion or on a regular basis?	-	0.012	-	-	-	-	-	0.013	-	-	-	-
	'At the present time, does the MOTHER smoke	-	0.015	-	0.029	-	-	-	0.014	-	-	-	-

	every day, on occasion, or not at all?												
	'At what age did the MOTHER start smoking cigarettes?	-	0.010	-	-	-	-	-	0.010	-	-	-	-
	'How many cigarettes does the MOTHER smoke per day?	-	0.015	-	0.038	0.018	-	-	0.016	-	0.038	0.018	-
	'Before pregnancy, i.e. 12 MONTHS beforehand, did the MOTHER smoke every day, on occasion, or not at all?	-	0.017	-	-	0.021	-	-	0.017	-	-	0.022	-
	'How many cigarettes did the MOTHER smoke per day before pregnancy?	-	0.014	-	-	0.018	-	-	0.015	-	-	0.019	-
	'Was the father or other person living with the MOTHER smoking during her pregnancy IN THE PRESENCE of the MOTHER?	-	-	-	-	-	-	-	0.009	-	-	-	-
	At which stage of the pregnancy did they smoke this number of cigarettes?	-	0.009	-	-	-	-	-	0.009	-	-	-	-
	'During pregnancy, was the MOTHER granted leave from work because of pregnancy?	-	-	0.025	-	-	0.043	-	-	0.026	-	-	0.044
NEO-ffi	'I would rather cooperate with others than compete with them'	-	-	-0.030	-	-	-	-	-	-0.032	-	-	-
	Often people aren't as nice as they seem	-	-0.013	-	-	-	-	-	-0.012	-	-	-	-
	'I often feel as if Im bursting with energy'	-	-	0.025	-	-	-	-	-	-	-	-	-
	'At times I have been so ashamed I just wanted to hide	-	-	-0.058	-	-	-0.055	-	-	-0.068	-	-	-0.058
TCI-R	'I usually think about all the facts in detail before I	-	-	-0.041	-	-	-0.037	-	-	-0.041	-	-	-0.038

	make a decision.												
	Even when most people feel it is not important, I often insist on things being done in a strict and orderly way.	-	-	-0.030	-	-	-	-	-	-0.036	-	-	-
	'In conversations I am much better as a listener than as a talker	-	-	0.026	-	-	-	-	-	0.026	-	-	-
	'It is fun for me to buy things for myself	-	-	-0.028	-	-	-	-	-	-0.025	-	-	-
SURPS	I often don’t think things through before I speak.	-	0.011	-	-	-	-	-	0.011	-	-	-	-

Appendix D. Journal papers

Appendix D.1. Journal review paper about use of neuroimaging machine learning models for psychiatric applications

Review

Biological Psychiatry: CNNI

The Clinical Added Value of Imaging: A Perspective From Outcome Prediction

Lee Jollans and Robert Whelan

ABSTRACT

Objective measures of psychiatric health would be of benefit in clinical practice. Despite considerable research in the area of psychiatric neuroimaging outcome prediction, translating putative neuroimaging markers (neuromarkers) of a disorder into clinical practice has proven challenging. We reviewed studies that used neuroimaging measures to predict treatment response and disease outcomes in major depressive disorder, substance use, autism spectrum disorder, psychosis, and dementia. The majority of studies sought to predict psychiatric outcomes rather than develop a specific biological index of future disease trajectory. Studies varied widely with respect to sample size and quantification of out-of-sample prediction model performance. Many studies were able to predict psychiatric outcomes with moderate accuracy, with neuroimaging data often augmenting the prediction compared to clinical or psychometric data alone. We make recommendations for future research with respect to methods that can increase the generalizability and reproducibility of predictions. Large sample sizes in conjunction with machine learning methods, such as feature selection, cross-validation, and random label permutation, provide significant improvement to and quantification of generalizability. Further refinement of neuroimaging protocols and analysis methods will likely facilitate the clinical applicability of predictive imaging markers in psychiatry. Such clinically relevant neuromarkers need not necessarily be grounded in the pathophysiology of the disease, but identifying these neuromarkers may suggest targets for future research into disease mechanisms. The ability of imaging prediction models to augment clinical judgments will ultimately depend on the personal and economic costs and benefits to the patient.

Keywords: Machine learning, Neuroimaging, Nosology, Prediction, Psychiatry, Reproducibility

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It would be highly desirable if objective measures of diagnosis and prognosis for psychiatric disorders were available to the clinician, as is the case in other branches of medicine. The ability to tailor personalized treatment plans or early interventions based on predictions of disease trajectory would have considerable implications for the economic cost of health care and for the lives of patients. In contrast to current nosologic criteria in psychiatry, which are based on patient self-report and clinical observations, objective neuroimaging indicators (hereafter, "neuromarkers") would be unaffected by clinical bias, social desirability effects, or physical limitations, and therefore have the potential to be an important clinical tool. Hundreds of papers have been published reporting possible predictive neuromarkers, but these have yet to translate into clinical practice. The reasons and possible solutions for this gap between neuroscientific research and clinical applicability have long been discussed by both researchers and clinicians (1–4). We review some of the literature to date.

A mechanistic approach to the search for clinically relevant neuromarkers in psychiatry posits that an understanding of the pathophysiology of an illness is necessary to develop biological tests (5), and priority should be given to neuromarkers that are closer to the mechanisms that cause psychopathology. Developing prognostic tests assessing the risk for future psychopathology would certainly be facilitated by a better understanding of the neurobiology of psychiatric disorders (2,6). However, one could argue that psychiatry is a special case: given the complexity of the human brain, mechanistic approaches may not be tractable. Therefore, a pragmatic approach, in which a neuromarker is justified by its utility, suggests that priority should be given to neuromarkers that are clinically useful rather than those that necessarily link brain structure or function to symptomatology (7). Pragmatic and mechanistic approaches are to some extent complementary: discovery of a neuromarker (e.g., brain activity in a certain condition that predicts treatment recovery) may lead to a new focus on proximal mechanisms, or possible pharmacologic agents (8).

Regardless of whether a mechanistic or pragmatic approach is used, psychiatric imaging prediction findings must be both accurate and generalizable in order to benefit individual-level psychiatric assessment (6). Studies that aim to predict outcomes require a particular set of statistical tools (9). That is, factors associated with the likelihood of outcomes harness heterogeneity within the sample, whereas significant group differences (detected via *t* tests) are more likely to occur

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when there is greater within-group homogeneity. Indeed, variables that significantly differentiate between groups are often weak predictors (10). The inherent multicollinearity in neuroimaging data means that good prediction models often include interaction effects. Regression and machine learning methods are able to incorporate such interaction effects and are therefore able to capture the complexity of neuroimaging data (see Box 1, top panel, for a brief description of some commonly used methods).

The use of appropriate performance metrics alone is not sufficient to guarantee the reliability of findings. Insufficient sample size is a key issue associated with a lack of reproducibility and low power (11). Small samples, particularly when combined with a large number of predictors, can result in apparently accurate predictions reflecting the idiosyncrasies of the sample and failing to generalize to other cases from the same population [this is generally referred to as "overfitting" (8)]. Large samples, possible through multisite imaging initiatives like the Alzheimer's Disease Neuroimaging Initiative [ADNI (13)], IMAGEN (14), European Autism Interventions (15,16), and the Adolescent Brain Cognitive Development Study (17) can help to guard against overfitting. However, collapsing data across multiple data collection sites is a nontrivial task that can add additional confounding factors into the dataset. Differences between different cohorts from the same population can have much larger effect sizes than differences between groups within the population (i.e., typically developing individuals and individuals with autism spectrum disorder [ASD]) (18). Testing prediction models either on an entirely new cohort or on "held-over" data from within the sample can quantify overfitting, as can resampling methods, such as bootstrapping or cross-validation (see Box 1, middle panel, for a brief description of common resampling measures).

The aim of this review is to provide an insight into the use of imaging data as a prognostic tool in psychiatry. We included studies that used analysis frameworks appropriate for prediction (i.e., regression or machine learning procedures) and used functional or structural magnetic resonance imaging (MRI) data. We reviewed studies evaluating treatment outcomes in patients with major depressive disorder (MDD) and substance use (SU), as well as studies predicting disease trajectory in patients with SU, ASD, psychosis, and dementia. Details on the samples used, clinical outcome measures, and analysis procedures (including resampling techniques, where available) are presented in Table 1. The metrics used to quantify the goodness-of-fit of the prediction models throughout the text are outlined in Table 2. The following metrics are used to quantify the goodness-of-fit of the prediction models throughout the text: *Accuracy* refers to the percentage of cases that were classified correctly. The *odds ratio* (*OR*) is a measure of how likely the outcome is, given the presence or absence of a single predictor variable, with OR >1 indicating that the predictor is positively associated with the outcome and OR <1 indicating that the predictor is negatively associated with the outcome. The *receiver operating characteristic* curve tracks correct and incorrect classification frequency, and the *area under the curve* (*AUC*) for this plot is the primary evaluation metric used for classifier performance, with larger AUC values denoting better classification. More specific commonly used metrics are outlined in Table 2.

Box 1. Tools and Terminology for Outcome Prediction

Examples of Machine Learning Classifiers

Support vector machines generate decision functions (or hyperplanes), which separate data points from separate classes in a multidimensional representation with the largest margin possible. These functions can be used to classify new data points.

Random forests use large amounts of decision trees grown using random subsamples of the dataset to generate a decision function based on the most commonly used classification functions across decision trees.

Regularized regression penalizes regression weights in a regression model to reduce overfitting. Examples are the Lasso method, which favors sparse models; Ridge regression, which shrinks coefficient values rather than excluding variables; and the Elastic Net (19), which combines these two approaches.

Quantifying Replicability: Common Resampling Procedures

Bootstrapping. Repeating an analysis by randomly sampling with replacement to estimate sample distributions or accuracy.

Cross-validation. Division of a dataset into training and test sets. The training set is used to generate a model that is subsequently applied to the test data. The test set can be comprised of one observation (leave one out cross-validation [LOOCV]) or of one of *n* equal partitions of the dataset (*n*-fold CV).

Nested cross-validation. Multiple layers of CV are used, making it possible to define model parameters or select input variables using CV on a portion of the data (i.e., the training data), and to carry out a generalizability test using the remainder of the data (i.e., the test data).

Feature Selection Methods

Filter methods select variables based on factors such as their correlation with the outcome variable.

Wrapper methods evaluate the quality of subsets of features, thereby accounting for the importance of feature interaction effects.

Embedded methods combine feature selection and function optimization. Regularization methods, such as the Elastic Net, are the most common type of embedded feature selection algorithms.

Random Label Permutation

Random Label Permutation quantifies the baseline classification level of a classifier by repeating the analysis with randomly assigned outcome labels. This provides an exact estimate of the effect size and significance of a model.

MAJOR DEPRESSIVE DISORDER

Two studies used functional MRI (fMRI) data to predict disease course in patients with MDD. One study found that clinical variables, such as the number of previous episodes, depression severity, and time in remission, did not alone predict whether patients remained in remission after 14 months, but outcome predictions reached 75% accuracy (74% positive predictive value, 76% negative predictive value) on the basis of fMRI data gathered during a self- versus other-blaming task (20). A further study examined the onset of MDD in patients 14 to 16 years of age using fMRI data gathered during a monetary reward task (21). Ventral striatum activity during reward anticipation predicted transition to subthreshold depression (OR = 0.81). Right ventral striatum (OR = 0.66) and left middle superior frontal gyrus (OR = 0.71) activity predicted transition to clinical depression. These results did not change substantially after accounting for depressive symptoms at baseline. No generalizability tests were applied, and these findings have unknown external validity.

Response to cognitive therapy has been evaluated using fMRI data collected during a personal relevance rating task

Table 1. Specifics of Samples and Outcome Measures for All Reported Studies

Study, Year	Disorder	Modality	Resampling	Analysis Method	Outcome Measure	Prediction Sample	Generalization Sample
Lythe *et al.*, 2015 (20)	MDD	fMRI during a self- vs. other-blaming task	LOOCV and bootstrapping	Linear discriminant analysis	Remission: no recurrent major depressive episode and no other significant symptoms after 14 months	n = 25 in nonremission n = 31 in remission	None
Stringaris *et al.*, 2015 (21)	MDD	fMRI during the MID	None	Logistic regression	Clinical depression: scores of 4 or 5 on the Development and Well-Being Assessment depression band, and ≥5 depressive symptoms including ≥1 core symptom at 16 years of age (2 years after baseline)	n = 29 developed clinical depression n = 68 developed subthreshold depression n = 906 remained healthy	None
Siegle *et al.*, 2012 (22)	MDD	fMRI during a personal relevance rating task	Bootstrap aggregation	Random forests and random permutation tests	Clinical remission: 50% reduction in BDI score after 12 weeks of cognitive therapy	n = 8 in remission and nonremission	n = 14 in remission n = 13 in nonremission
Sämann *et al.*, 2013 (23)	MDD	Structural MRI	None	Multiple linear regression	Early response: >25% HRSD score reduction after 2 weeks antidepressant treatment; response: >50% HRSD score reduction at 5 weeks; remission: HRSD score <10 at week 5	n = 100 early responders n = 77 responders n = 39 remitters	None
Costafreda *et al.*, 2009 (24)	MDD	Structural MRI	LOOCV	SVM and random permutation tests	Clinical remission: HRSD score ≤7 after 8 weeks of treatment with fluoxetine or 16 weeks of treatment with cognitive behavioral therapy	n = 9 in remission and nonremission for fluoxetine n = 6 in remission and nonremission for CBT	None
Gong *et al.*, 2011 (25)	MDD	Structural MRI	LOOCV	SVM and random permutation tests	Refractory depressive disorder (RDD): <50% improvement in HRSD score after 6 weeks treatment each with ≥2 antidepressants from different pharmacologic classes	n = 23 RDD n = 38 nonrefractory depressive disorder	None
Mahmood *et al.*, 2013 (26)	SU	fMRI during a behavioral inhibition task	None	Hierarchical multiple regression	CDDR scores at 18-month follow-up	n = 41 baseline light substance users n = 39 baseline heavy substance users	None
Jacobus *et al.*, 2013 (27)	SU (cannabis)	Structural MRI	None	Hierarchical linear regression	CDDR scores at 18-month follow-up	n = 47 baseline cannabis users n = 49 baseline nonusers	None
Schuckit *et al.*, 2016 (28)	SU (alcohol)	fMRI during viewing of affective faces	None	Backward elimination regression	Alcohol use and alcohol-related problems including DSM-IV abuse and dependence	n = 114	None
Whelan *et al.*, 2014 (29)	SU (alcohol)	Structural MRI and fMRI during the monetary incentive delay task, behavioral inhibition, and viewing of affective faces	Nested 10-fold CV	Elastic net regression	European School Survey Project on Alcohol and Drugs scores regarding lifetime alcohol use and lifetime drunkenness episodes at 16 years of age (2 years after baseline)	n = 121 future binge-drinkers n = 150 continuous abstainers	n = 55 future binge-drinkers n = 66 continuous nonbinge-drinkers

Biological Psychiatry: CNNI

Table 1. Continued

Study, Year	Disorder	Modality	Resampling	Analysis Method	Outcome Measure	Prediction Sample	Generalization Sample
Falk *et al.*, 2011 (30)	SU (nicotine)	fMRI during viewing of smoking-cessation ads	None	Multiple regression	Difference between baseline CO measurement and CO measurement after 1 month	n = 28	None
Chua *et al.*, 2011 (31)	SU (nicotine)	fMRI during tailored smoking-cessation messages	None	Logistic regression	Abstinence: absence of reported (7 day) smoking at 4-month follow-up	n = 42 relapsers n = 45 quitters	None
Janes *et al.*, 2010 (32)	SU (nicotine)	fMRI during viewing of smoking-related and neutral stimuli	LOOCV	Discriminant function analysis	Smoking slip: any smoking for <7 consecutive days or once a week in nonconsecutive weeks at any point for 8 weeks after smoking cessation	n = 9 with slips n = 12 abstinent	None
Paulus *et al.*, 2005 (33)	SU (meth)	fMRI during a 2-choice prediction task	LOOCV	Linear discriminant analysis	Relapse: any use of methamphetamine after 1 year	n = 18 relapsers n = 22 abstainers	None
Akshoomoff *et al.*, 2004 (34)	ASD	Structural MRI	None	Discriminate function analysis	ASD diagnosis at age 5: ADI-R, ADOS, and DSM-IV criteria for autism; PDD-NOS: under ADI-R and ADOS cutoffs for autism	n = 26 low-functioning ASD n = 12 high-functioning ASD n = 10 PDD-NOS n = 13 healthy controls	None
Lombardo *et al.*, 2015 (35)	ASD	fMRI during a natural sleep language paradigm	5-fold CV	Partial least-squares linear discriminant analysis	Receptive and expressive language level on the Mullen Scales of Early Learning by age 3–4, about 1 year after testing	n = 36 with good language outcomes n = 24 with poor language outcomes	None
Plitt *et al.*, 2015 (18)	ASD	Resting state fMRI (functional connectivity)	Nested LOOCV and 5-fold CV	Ridge regression	Social autistic traits and adaptive functioning (change) scores after at least 1 year (mean 2 years, 10/11 months)	n = 31	None
Sarpal *et al.*, 2015 (36)	Psychosis	Resting state fMRI (functional connectivity)	None	Principal component analysis	Response: BPRS-A rating ≤3 for conceptual disorganization, grandiosity, hallucinatory behavior and unusual thought content, and two consecutive assessment visits with CGI improvement scores of 1 or 2 after 12 weeks treatment with risperidone or aripiprazole	n = 24 responders n = 17 nonresponders	n = 20 responders n = 20 nonresponders
Mourao-Miranda *et al.*, 2012 (37)	Psychosis	Structural MRI	LOOCV	SVM and random permutation tests	Continuous disease trajectory: no periods of remission >6 months after approximately 6 years; episodic trajectory: ≥1 period of remission ≥6 months and no episode of psychosis lasting >6 months	n = 28 continuous n = 28 episodic	n = 32 patients with no sustained periods of remission or psychosis
Koutsouleris *et al.*, 2012 (38)	Psychosis	Structural MRI	Nested 10-fold CV	SVM	Conversion: BPRS scores ≥4 for hallucination or ≥5 for unusual thought content, suspiciousness, or conceptual disorganization with symptoms occurring daily for >1 week by the end of the follow-up interval (maximum 7 years)	n = 21 nonconverters n = 16 converters	n = 17 converters and nonconverters
Fan *et al.*, 2008 (39)	Dementia	Structural MRI	LOOCV	High-dimensional pattern classification	Cognitive decline in MCI: change in MMSE scores over 3 years; optimal classification at the threshold of MMSE score change of −1 per year	n = 56 patients with AD n = 66 healthy control participants	n = 88 MCI patients
Davatzikos *et al.*, 2011 (40)	Dementia	Structural MRI	5-fold CV	SVM	Conversion from MCI to dementia: change in CDR score from 0.5 to 1	n = 69 converters n = 170 nonconverters	None

Added Value of Imaging in Psychiatric Prediction

Table 1. Continued

Study, Year	Disorder	Modality	Resampling	Analysis Method	Outcome Measure	Prediction Sample	Generalization Sample
Ewers *et al.*, 2012 (41)	Dementia	Structural MRI	Bootstrapping	Logistic regression	Conversion from MCI to AD: MMSE scores between 20–26, CDR score of 0.5 or 1, and subjective memory complaints after ca. 2 years	n = 81 patients with AD n = 101 healthy control participants	n = 58 converters n = 72 nonconverters
Plant *et al.*, 2010 (42)	Dementia	Structural MRI	LOOCV	SVM, Bayesian classifier, and voting feature intervals	Conversion from MCI to AD: defined by clinical examination and neuropsychologic testing after 2.5 years	n = 32 patients with AD n = 18 healthy control participants	n = 9 MCI converters n = 15 nonconverters

AD, Alzheimer's disease; ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule-Generic; ASD, autism spectrum disorder; BDI, Beck Depression Inventory; BPRS-A, Brief Psychiatric Rating Scale-Anchored; CDDR, Customary Drinking and Drug Use Record; CDR, clinical dementia rating; CGI, Clinical Global Impressions Scale; CO, carbon monoxide; CV, cross-validation; fMRI, functional magnetic resonance imaging; HRSD, Hamilton Rating Scale for Depression; LOOCV, leave one out cross-validation; MCI, mild cognitive impairment; MDD, major depressive disorder; meth, methamphetamine; MID, monetary incentive delay; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; PDD-NOS, pervasive developmental disorder-not otherwise specified; SU, substance use; SVM, support vector machine.

(22). Activity in the subgenual anterior cingulate cortex (ACC), in combination with baseline depression severity, was able to predict remission after 12 weeks with 78% accuracy (86% sensitivity and 69% specificity). The inclusion of multiple brain measures explained >40% of the variance in depression severity change, with subgenual ACC activation alone explaining 29% of the variance. Adding nonbrain variables to the analysis, such as scanner manufacturer and demographic data, did not significantly increase the explained variance. Despite use of a generalization sample, the overall small sample size in this study (n = 8 in the training set in each group) will likely result in limited generalizability.

Three studies evaluated treatment outcomes for antidepressant medications using structural MRI. One study reported that including gray matter volume with sex in a prediction model of treatment outcome increased the explained variance by 12% (23). This study included >200 participants but did not apply any kind of generalization tests or resampling procedures. Treatment response to an antidepressant, but not to cognitive behavioral therapy, could be predicted by neuroanatomic features with 89% accuracy (89% sensitivity and 89% specificity) (24). Because of the small sample size (n < 10 in each group) and lack of generalization cohort, the high prediction accuracy in this study likely reflects overfitting. A further study evaluated whether patients could be classified as having refractory or nonrefractory depressive disorder (25). The prediction reached 70% accuracy (70% sensitivity and 70% specificity) when only gray matter images were used; adding white matter images did not improve the prediction. While the refractory group had significantly longer disease duration than the nonrefractory group, the predictive value of this variable was not reported.

Of the six studies investigating future disease course in patients with MDD, four used resampling techniques (20,22,24,25), one of which also used a generalization cohort (22). Three of these studies determined the significance of their prediction models using random label permutation (22,24,25), which provides a superior estimate of the likelihood of a particular feature's appearing predictive by chance. Only two of the studies reported here included >20 participants in each group (20,25). These studies reached 70% (25) and 75% (20) prediction accuracy using only brain variables, which offers hope that brain imaging may ultimately be useful for clinical outcome prediction.

SUBSTANCE USE

A number of studies have attempted to predict future SU, particularly in adolescence, which is a key risk period for substance misuse. Blood oxygen level–dependent activity during behavioral inhibition in 16- to 19-year olds was associated with drug use occasions and dependency symptoms at 18-month follow-up assessments (26). However, these findings were significant only in adolescents who already exhibited heavy SU. Similarly, fractional anisotropy was only associated with SU in adolescents with high (but not low) baseline cannabis use (27). Future SU has also been examined in typical adult drinkers (28). fMRI data collected during viewing of emotional face stimuli was associated with alcohol problems 5 years later, while accounting for the level of

Table 2. Accuracy Metrics

	Elements in the Positive Class (Generally the Patient Group)	Elements in the Negative Class (Generally the Nonpatient Group)	Predictive Value
Elements Classified as Positive	True positive rate/sensitivity/recall: Correctly classified positive elements	False positive rate: Incorrectly classified negative elements	Positive predictive value/precision: Proportion of elements classified as positive that were elements of the positive class
Elements Classified as Negative	False negative rate: Incorrectly classified negative elements	True negative rate/specificity: Correctly classified negative elements	Negative predictive value: Proportion of elements classified as negative that were elements of the negative class

responsiveness to alcohol established at baseline. However, none of these studies used any generalizability tests, limiting their use in developing neuromarkers or gaining mechanistic insights.

The largest investigation of adolescent future substance use to date comes from the IMAGEN study (14). MRI data from 14-year-old nondrinkers and their life history, personality, cognitive, and demographic measures were used to predict binge drinking at 16 years of age (29). Seventy-three percent of abstainers and 66% of future binge drinkers were correctly classified (64% precision, 93% recall, AUC = 0.75). Brain measures that predicted future binge drinking included markers of brain structure and functional activation during reward processing, behavioral inhibition, and affective face processing. Repeating the analysis with each domain on its own yielded the highest AUC value for the history domain, followed closely by personality (Figure 1). The brain-only prediction ranked third, reaching an AUC value of 0.63. Excluding each domain iteratively revealed that excluding life history resulted in the largest drop in accuracy, followed by that resulting from excluding all brain measures (see Figure 1). To our knowledge, this is the only study that has examined the predictive value of different assessment domains in this manner, providing a clear quantification of the added value of each.

Two studies predicting smoking cessation outcomes used fMRI data gathered during viewing of smoking cessation messages. The amount of variance in change of smoking behavior after 1 month—as explained by self-reported intentions and self-efficacy—was approximately 15%, which was increased to 35% by including activation of the medial prefrontal cortex during viewing of video advertisements designed to encourage smokers to quit (30). A study that examined the efficacy of individually tailored messages using fMRI also implicated the medial prefrontal cortex (31); activity in the medial prefrontal cortex predicted smoking cessation after 4 months, while controlling for the number of cigarettes smoked at baseline. Neither of these studies included generalization tests, making it difficult to draw conclusions from these findings. A further study used performance on an emotional Stroop task and fMRI recorded while viewing smoking-related and neutral images to evaluate the efficacy of various smoking interventions (32). A model including Stroop interference reaction times and accuracy, as well as anterior insula and dorsal ACC activation, predicted whether smokers remained abstinent over 8 weeks or had smoking slips with 79% accuracy. Seventy-four percent accuracy was reached with only Stroop interference effects and insula activation. Results from brain- or behavioral-only analyses were not reported, but the Stroop interference effect was significantly associated with

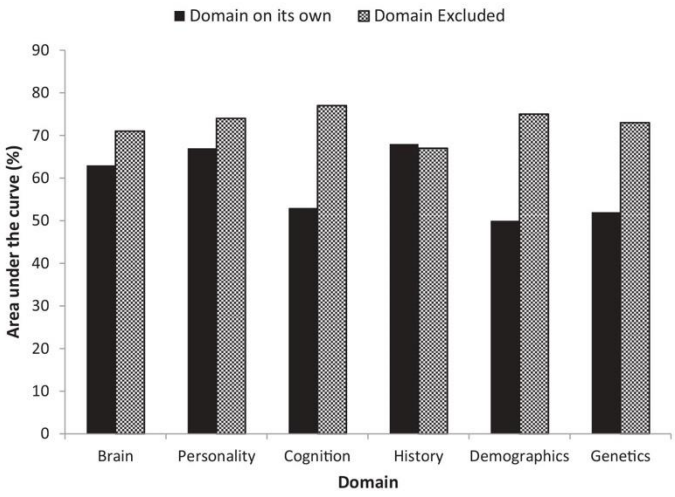

Figure 1. Area under the curve values (in %) for each domain individually, and when each domain was excluded, as reported by Whelan *et al.* (12).

insular and dorsal ACC activity, which suggests that the contribution of imaging measures may have been small.

Finally, one study examined relapse in methamphetamine users participating in a 28-day inpatient program using fMRI recorded during decision-making under uncertainty (33). Relapse after 1 year was predicted with 90% accuracy (94% sensitivity and 86% specificity). Sociodemographic characteristics, baseline symptoms, and substance use characteristics did not significantly differentiate between relapsers and abstainers, but the predictive power of these variables was not reported. The high prediction accuracy reached in this study is an indication of the potential of imaging data to contribute to clinical prognosis in SU treatment.

Of the eight studies predicting measures of SU reported here, only three used resampling procedures (29,32,33). Only one study included >20 participants in each group (29). It is notable, however, that in the case of SU, nonbrain variables provided robust predictions, suggesting that neuroimaging may not have great potential to augment clinical prognoses.

AUTISM SPECTRUM DISORDERS

Neuroanatomy in young children (2–5 years of age) was used to predict a diagnosis of ASD at 5 years of age (34). A classifier including white and gray matter volume correctly classified all but one of the healthy participants, and classified all children with low functioning autism and all but two children with high functioning autism as ASD. However, all but two of the children with other pervasive developmental disorders were misclassified as having ASD. This study did not use any generalizability tests, and inherent model optimism was therefore not quantified. Another study used fMRI data gathered during a natural sleep language paradigm to predict language level at 3 to 4 years of age in a sample of young children (12–48 months) at risk for ASD (35). Performance of classifiers using only baseline autism symptom severity (AUC = 0.67; 67% accuracy, 71% sensitivity, and 64% specificity), a combination of behavioral measures assessing language, adaptive functioning, and symptom severity (AUC = 0.70; 68% accuracy, 79% sensitivity, and 61% specificity), or only fMRI data (AUC = 0.69; 68% accuracy, 71% sensitivity, and 67% specificity) was similar. However, when all behavioral measures were entered into a classifier along with the fMRI data, classification accuracy showed a clear increase (AUC = 0.81; 80% accuracy, 88% sensitivity, and 75% specificity).

A study in young adults and adolescents with ASD used resting state connectivity to predict social and adaptive functioning (18). Connectivity within the frontoparietal task control (FPTC) network predicted changes in social responsiveness after ≥1 year with only 44% sensitivity (80% precision; 95% specificity). Changes in adaptive functioning were significantly explained by connectivity within the salience network (100% sensitivity, 71% precision, and 67% specificity), between the default and salience networks (100% sensitivity, 63% precision, and 53% specificity), and between the default and FPTC networks (83% sensitivity, 63% precision, and 60% specificity). Overall, resting state connectivity data could account for 20% of the total variance in social responsiveness change, and for 23.5% of the variance in adaptive functioning change after accounting for age and follow-up latency. The inclusion of variables measuring IQ or comorbid anxiety, depression, or attention-deficit/hyperactivity disorder did not improve any of the predictions.

While 2 of the studies reported here showed poor differentiation between groups in terms of future diagnosis and symptom change (18,34), a study of infants and toddlers with ASD was able to successfully predict future language level on the basis of behavioral and fMRI data (35). This study also found that combining behavioral and fMRI predictors resulted in the highest prediction accuracy. In addition, resting state connectivity measures could explain >20% of the total variance in ASD symptom change in adults (18). While none of the studies reported here used a generalization cohort, these findings nevertheless suggest that brain measures are a promising tool for prognosis in ASD.

PSYCHOSIS

A number of studies have evaluated illness course in patients presenting with first-episode psychosis or psychotic-like symptoms. The efficacy of treatment with antipsychotic medication was examined using striatal resting state connectivity in patients experiencing first-episode schizophrenia (36). A single connectivity index associated with treatment response after 12 weeks was developed and applied to an independent cohort of patients with acute psychotic symptoms. The model was able to predict treatment outcome with 80% sensitivity and 75% specificity in the generalization sample (AUC = 0.78, 76% positive predictive value, and 79% negative predictive value). While this study did not use resampling measures, the results from testing the model on a generalization sample suggest that the connectivity index is a promising potential neuromarker of psychosis. In a similar study, future disease course in patients with first-episode psychosis was evaluated after approximately 6 years (37). A classifier was able to distinguish between patients with an episodic and continuous disease course with 70% accuracy. Applying this classifier to a group of patients with an intermediate disease course resulted in 78% of patients who did not develop another episode being classified as episodic, and 65% of patients who did develop additional episodes being classified as continuous. Although this study used an exemplary analysis framework, the somewhat poor classification of the patient group will hinder the applicability of these findings in clinical decision-making. A further study was able to classify between at-risk patients who went on to develop further symptoms over 3 years and patients who remained stable with 84% accuracy (81% sensitivity and 88% specificity) using structural brain data (38). Classification in the generalization sample reached 88% accuracy (82% sensitivity and 94% specificity). This high classification accuracy is a promising finding that may well be the precursor to establishing a predictive anatomic neuromarker.

An already established connectivity index (36) and predictive structural markers (38) appear to have potential as future neuromarkers. The consistency with which prediction models generalized to novel data can be taken as evidence of the strong utility of neuroanatomic features in predicting future disease course in psychosis.

DEMENTIA

A number of studies have used classifiers trained to differentiate between patients with Alzheimer's disease and healthy participants to predict cognitive decline in patients with mild cognitive impairment (MCI), using structural brain data from the ADNI cohort (13). One study (39) reached 87% accuracy (AUC = 0.86) when comparing classification results to the rate of change in MCI patients' mental state over 3 years. The classifier trained in this study was subsequently applied to a different sample of MCI patients from the ADNI cohort (40). While the classification reached 90% sensitivity, only 37% of patients with MCI who remained stable within the time frame of the study were correctly classified. Prediction models that included the output from the previously trained classifier and cerebrospinal fluid biomarkers never reached specificity significantly above chance. Specificity for sparse regression models (41) also remained low for a model including only brain measures (63% accuracy, 80% sensitivity, and 49% specificity) and a model including both neuropsychologic and brain variables (64.1% accuracy, 80.4% sensitivity, and 51.4% specificity). Moderate model performance was also observed when applying this analysis approach to data from a different cohort (42) (75% accuracy, 56% sensitivity, and 87% specificity).

Models predicting future cognitive decline in MCI patients showed poor classification results for patients who would not transition from MCI to dementia. All studies used generalizability checks and reasonably large samples, and therefore the low differentiation between groups was likely caused by discrepancies between the population used to generate the prediction models (i.e., patients with Alzheimer's disease and healthy participants) and the population used to test the models (i.e., patients with MCI).

THE CONTRIBUTION OF NEUROIMAGING

Of the 24 studies reported here, 16 used a form of generalization test, and 13 of the 16 studies included >30 participants in the training set. Across these studies, the mean prediction accuracy was approximately 75% (Table 3). However, many studies did not evaluate how outcome prediction based on brain variables compared to prediction based on nonbrain variables. Where these results were reported, they suggest that brain measures may account for up to 40% of the variance in clinical outcomes (18,22,23,30) and can explain some of the variance where clinical variables fail to do so (22). While some of these findings undoubtedly represent some degree of unwarranted optimism, studies that were able to successfully predict clinical outcomes using only brain variables (20,25,33) support the conclusion that neuroimaging has the potential to be an important tool in psychiatric prognosis.

Table 3. Model Performance for Studies That Used Resampling Procedures and More Than 30 Participants

	Accuracy (%)	Sensitivity (%)	Specificity (%)
Gong *et al.*, 2011 (25)	70	70	70
Lythe *et al.*, 2015 (20)	75	—	—
Whelan *et al.*, 2014 (29)	70	66	73
Paulus *et al.*, 2005 (33)	90	94	86
Plitt *et al.*, 2015 (18)	81	100	67
Lombardo *et al.*, 2015 (35)	80	88	75
Sarpal *et al.*, 2015 (36)	78	80	75
Mourao-Miranda *et al.*, 2012 (37)	72	65	78
Koutsouleris *et al.*, 2011 (38)	88	82	94
Fan *et al.*, 2008 (39)	87	—	—
Davatzikos *et al.*, 2011 (40)	52	90	37
Plant *et al.*, 2010 (42)	75	56	87
Ewers *et al.*, 2012 (41)	63	80	49

In contrast to quantitative prediction accuracy, the practical clinical utility of predictions depends on the cost of misclassification (or "regret"). That is, the specificity of prognostic tools should be higher for invasive or risky interventions. Inaccurate prognoses can lead to a waste of both time and resources on treatments that result in little or no improvement and may entail adverse consequences (e.g., medication side effects). Therefore, even prediction models with high accuracy may not be suitable for clinical use because of the magnitude of the regret. Predictions that do not benefit the clinician directly may nevertheless reveal information about mechanisms of disease and recovery (5). With increased understanding of the pathophysiology of a psychiatric disorder comes the possibility of developing tools that test behavioral or cognitive domains related to the disease mechanisms uncovered using neuroimaging, which would eliminate the heavy economic burden of conducting neuroimaging as part of psychiatric assessments (9,43). However, as illustrated by the example of adolescent SU initiation, other demographic variables are a much cheaper and more informative tool in some cases (29).

IMPROVING GENERALIZABILITY AND REPLICABILITY OF RESULTS

With the exception of two studies (36,39), the studies reported here sought to predict psychiatric outcomes rather than developing specific predictive neuromarkers. In order to reach the level of external validity (i.e., predicting out-of-sample outcomes) necessary to create clinically useful neuromarkers, imaging prediction studies can adopt a number of methods that increase the generalizability and replicability of results. Neuroimaging studies typically have many more potential predictors than participants, which increases the tendency to overfit. One obvious aid would be to increase the sample size, a known element in ensuring the replicability of findings (11). Second, it is desirable to use "feature selection" to produce a model that is based on only a subset of the original predictors, both for interpretability of the final model and to facilitate generalizability. Many methods of feature selection exist (see Box 1, lower panel), but it is important to note that neuroimaging data are inherently multicolinear (i.e., data from one voxel tends to be similar to that from a neighboring voxel), and therefore the feature selection method chosen should account for this. Third, cross-validation is an established and powerful method for quantifying generalizability. One of the most popular methods used to quantify the degree of unwarranted optimism in imaging prediction studies is leave-one-out cross-validation (CV). However, leave-one-out CV is recognized to produce idiosyncratic estimates of the prediction error, and

methods such as 10-fold CV are preferable. Within each CV fold, nested CV or bootstrapping can provide an additional layer of stability by attenuating the effect of outliers. Bootstrapping the confidence intervals of coefficient estimates also allows for an additional measure of the effect size of each predictor. Fourth, using random label permutation tests (see Box 1) rather than traditional *p* values to establish the significance of a prediction model is an effective tool to quantify the baseline rate of variation in the coefficient estimates. Fifth, the population definition is another important consideration when designing a prediction study. A prediction model can only be expected to generalize well to a cohort drawn from the same population as the sample used to create the model (38), with differences in age, sex, demographic variables, and comorbidities likely being important factors. Finally, researchers should report a variety of performance metrics in order to provide a comprehensive picture of classifier performance. These include summary measures of sensitivity and specificity such as the receiver-operating characteristic and precision-recall curves (see Table 2).

CONCLUSIONS

The development of neuromarkers that improve the current clinical prognostic ability would represent a great leap forward in the ability to provide early interventions and to realize the ideal of "personalized medicine" that tailors treatment plans to individual patients. Whether or not the potential improvement in prognosis outweighs the high economic cost of neuroimaging will determine whether neuromarkers are integrated into clinical practice. Although clinical practice would benefit from neuromarkers that predict outcomes, regardless of the underlying mechanisms, identifying robust predictors using neuroimaging can highlight targets for future research. This would ultimately enable our understanding of many psychiatric disorders to move beyond symptomatically defined syndromes and toward biologically defined diseases. Considering the literature to date in the area of outcome prediction, neuroimaging for prediction of clinical outcomes has potential utility but remains a medium- to long-term goal.

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REVIEW
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Neuromarkers for Mental Disorders: Harnessing Population Neuroscience

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Despite abundant research into the neurobiology of mental disorders, to date neurobiological insights have had very little impact on psychiatric diagnosis or treatment. In this review, we contend that the search for neuroimaging biomarkers—neuromarkers—of mental disorders is a highly promising avenue toward improved psychiatric healthcare. However, many of the traditional tools used for psychiatric neuroimaging are inadequate for the identification of neuromarkers. Specifically, we highlight the need for larger samples and for multivariate analysis. Approaches such as machine learning are likely to be beneficial for interrogating high-dimensional neuroimaging data. We suggest that broad, population-based study designs will be important for developing neuromarkers of mental disorders, and will facilitate a move away from a phenomenological definition of mental disorder categories and toward psychiatric nosology based on biological evidence. We provide an outline of how the development of neuromarkers should occur, emphasizing the need for tests of external and construct validity, and for collaborative research efforts. Finally, we highlight some concerns regarding the development, and use of, neuromarkers in psychiatric healthcare.

Keywords: biomarker, neuromarker, machine learning, nosology, population neuroscience, big data, research domain criteria, neuroimaging

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INTRODUCTION

According to figures from the World Health Organization, the projected risk for developing some form of mental disorder across the lifetime is between 18 and 55% (1). Globally, mental disorders are the leading cause of years lived with disability (2). Thirty-eight percent of the EU population is estimated to suffer from a mental disorder each year (3). In 2010, the estimated average cost of addictive, anxiety, mood, and psychotic disorders was more than €3,500 per affected individual in Europe (4). The corresponding figure for dementia was as high as €16,500 per individual. The staggering economic cost and disability burden of mental disorders indicate that research into improved prevention and treatment is imperative. Unlike most other areas of medicine, prolific research in psychiatry throughout the past half century has not led to any substantial changes in treatment approaches or in the conceptualization of diagnostic categories. The last major shift in how mental disorders are treated occurred in the 1960's with the introduction of psychoactive medications, following the growing recognition that mental disorders have a basis in biology. However, the neuropathological underpinnings of psychiatric conditions have little influence on current healthcare practice, with both diagnosis and prognosis relying primarily on observed symptoms or self-report.

In this review we will explore this gap between neuropsychiatric research and psychiatric healthcare. First we will provide a general overview of how neuropsychiatric research is conducted, in order to familiarize the reader with the concepts referenced in later parts of the text. Second, we will detail the criteria that must be fulfilled for neuropsychiatric research to be clinically useful, introducing the concept of neuroimaging biomarkers. Third, we will highlight the key issues that have impeded the application of insights gained from neuropsychiatric research into applied psychiatric settings. Fourth, we will address these issues and offer solutions. Fifth, we will discuss some of the considerations which researchers and clinicians should take into account when carrying out research with, or when using biological models of mental disorders. Finally, we will provide a summary and a set of recommendations for neuropsychiatric research, to make it more clinically useful. A glossary explaining some of the terms used in this review is provided.

THE BRAIN AND MENTAL DISORDERS—AN OVERVIEW OF NEUROPSYCHIATRIC RESEARCH METHODS

From the fallacious discipline of phrenology to modern neuroimaging, researchers have hoped that understanding the brain would provide explanations or justifications for behavior, personality traits, cognition, and affect. The earliest knowledge of the connection between brain and behavior comes from post mortem examinations and studies of patients with brain lesions. A famous example is the case of Phineas Gage, whose personality changed dramatically after an iron rod passed through his skull and destroyed much of his frontal lobe. Cases of dramatic changes in patients who experienced brain lesions were the first evidence that some brain functions rely on specific brain areas. With the advent of non-invasive imaging technology, neuroscientists have no longer had to rely on lesion studies to explore the neurophysiological basis of cognitive functions, behavior, and pathology. Magnetic Resonance Imaging (MRI) is a non-invasive imaging technology which provides clinically useful images of internal tissue and organs. MRI scanners have been used since the 1980s and are available in almost all hospitals in the developed world. MRI can be used to examine brain structure and to measure gray and white matter volume in the brain. Functional MRI (fMRI) has been used for brain imaging since the early 1990's, and has provided many valuable insights into psychopathology, cognition, and behavior (5–7). fMRI utilizes regional blood-flow in the brain to infer neuronal activity via the blood-oxygen-level dependent (BOLD) signal. Most fMRI studies manipulate some variable of interest, such as the visual or auditory stimuli individuals are exposed to, and examine the difference in BOLD signal specifically associated with that variable. These studies can reveal how activations in specific brain regions are associated with certain types of sensory or cognitive processing.

There is a rich neuroimaging literature examining psychiatric pathology. Psychiatric neuroimaging research typically involves a group of patients, and a group of healthy control participants (normally matched to the patient group in terms of various demographic characteristics). These are compared in terms of their brain structure or function. The typical sample size of a neuroimaging study from a single laboratory does not exceed 100 participants. In contrast, neuroimaging datasets typically include hundreds—if not thousands—of voxels (see Glossary) or regions of interest (ROIs, see Glossary), particularly when data from multiple modalities are used (such as MRI and electrophysiological recordings or positron emission tomography). MRI and fMRI data are usually analyzed by carrying out statistical significance tests on each voxel. This type of analysis is referred to as mass-univariate analysis, as it involves conducting a massive amount of tests for each analysis. When groups of patients and control participants are being compared, an ANOVA or *t*-test (see Glossary: Inferential Statistics) will usually be carried out at each voxel. To account for the high risk of false positive findings (see Glossary), mass univariate analyses are ordinarily reported using corrected statistical significance thresholds. This approach has produced important insights into the neuropathology underlying many psychiatric conditions including addiction [e.g., (8)]; schizophrenia [e.g., (9)]; social anxiety disorder [e.g., (10)], Attention deficit hyperactivity disorder [ADHD; e.g., (11)], and anorexia nervosa [e.g., (12)]. However, there are considerable issues in terms of reliability, generalizability, and reproducibility with this type of analysis framework in terms of identifying neuromarkers (see Glossary). We outline the problematic elements of this approach in the section Barriers to the Use of Neuromarkers in Applied Psychiatry.

Summary

In this section we provided a brief outline of how neuropsychiatric research investigating mental disorders is often carried out. In the past two decades MRI has become the main tool used to investigate brain structure and function. Mental disorders are usually studied by comparing a group of individuals diagnosed with the mental disorder to a group of healthy control participants. Groups are then compared using mass-univariate analyses to investigate possible group differences.

BIOLOGICAL MODELS IN PSYCHIATRY—WHAT THEY SHOULD LOOK LIKE

In this section we will first outline why biological models (see Glossary) would be beneficial in psychiatry, introducing the concept of biomarkers. Subsequently we will describe some of the key characteristics which a useful biomarker must have.

Biomarkers and Why Psychiatry Needs Them

As previously noted, diagnoses of mental disorders are based on observed and/or self-reported symptoms, which are highly heterogeneous within, and often common across disorders (13). The absence of clear and distinct disorder phenotypes and a high rate of comorbidity of psychiatric disorders pose a considerable challenge to clinicians when it comes to selecting a treatment pathway from which the patient is most likely to benefit. In other domains of medicine, predictive models for estimation of treatment efficacy, risk assessment, and prognosis are routinely employed by medical professionals, and advocated by policymakers (14). Over the last decade, for example, cancer and heart disease are two specific areas in which biologically based (predictive) models, or *biomarkers*, have been used for purposes of screening, diagnosis, staging, prognosis, treatment selection, and monitoring (15–17). Rather than replace the clinician, these biomarkers provide a measure that can supplement clinical decision-making (18, 19). This affords patients and healthcare providers the opportunity to implement preventative measures in high-risk patients, to identify a disease in its early stages, aid differential diagnosis, select treatment pathways that are most likely to benefit the patient, and to make a well-informed prognosis about treatment outcome and disease course. Being able to estimate the likelihood that a patient will respond to a particular treatment is the basis for precision medicine, and for the integration of diagnosis and therapeutics ["theranostics," (20)]. Based on predicted treatment response or disease course, clinicians can personalize treatment plans and avoid or delay costly, arduous, and possibly ineffective treatments. This would have a great impact on the quality of life of patients, and on the economic and personal cost of healthcare to the individual and society.

In order to be clinically useful, a biomarker needs to augment existing diagnostic/prognostic criteria. That is to say, the estimate of a future event (or current condition) based on the biomarker, or adding the biomarker to current methods, needs to be better than the estimate based on current methodology alone. A key element of why biomarkers are so desirable in medicine is that they provide an objective estimate. This has the potential to reduce bias in clinical decision making. In psychiatry, the incorporation of biological evidence into diagnosis, prognosis, and treatment selection could improve the quality of healthcare which patients receive (21). The National Institute of Mental Health acknowledged this in their "Research Domain Criteria" (RDoC; www.nimh.nih.gov/research-priorities/rdoc/index.shtml) almost a decade ago. The RDoC framework assumes that (1) mental disorders are disorders of brain circuits, (2) neuroscientific methods can identify these dysfunctions *in vivo*, and (3) genetic and imaging data will yield biomarkers that can augment clinical management (22).

What a Biomarker Should Look Like

In practical terms, a good biomarker needs to be workable—it must be reasonably simple and quick to obtain the data necessary to compute the biomarker, so that clinicians can realistically implement the measures in assessments (13). It is easiest to implement unimodal models (see Glossary) in new settings, as they do not require multiple imaging protocols or modalities. A measure that is easy and practical to include in an assessment protocol should also be low in personal and economic cost. Paying for an MRI scan for the sake of a small improvement in diagnostic accuracy may not be worthwhile. Yet, as Gabrieli et al. (21) point out, a neuromarker may provide sufficient improvement in diagnostic or prognostic accuracy to be a cost-effective option. If the human and economic cost associated with delaying treatment or administering a treatment that is ineffective can be prevented or reduced, then administering an MRI may be more economical than the alternative. However, Gabrieli et al. (21) also note that to be clinically useful the question that must be answered is not solely whether one particular treatment is likely to work, but which treatment out of a number of treatment options is likely to be the most beneficial for the patient. Another practical concern is that the imaging protocol necessary for calculation of the neuromarker must be robust to slight deviations in data collection or preprocessing procedure. That is to say, broadly similar results should be obtained when different clinicians or professional health-care providers administer the test, or when different participants view similar stimuli thought to engage the same sensory or cognitive processes (23). Furthermore, a good biomarker must have good construct validity. A classifier which purports to identify individuals with Alzheimer's disease should also perform reasonably well identifying individuals with mild cognitive impairment, but should have no relevance when separating unipolar from bipolar depression.

Summary

In this section we have contended that the integration of neuromarkers into the diagnosis and treatment of mental disorders would be of great benefit to both patients and clinicians. Considering the high economic and personal cost of mental disorders, neuroimaging biomarkers may prove to be valuable and cost-effective. Useful biomarkers must be easy to implement in new settings, and have good external validity.

BARRIERS TO THE USE OF NEUROMARKERS IN APPLIED PSYCHIATRY

Reasons and possible solutions for the discrepancy between neuroscientific research and clinical applicability have been discussed by many researchers and clinicians (20–30). Four areas are consistently identified as targets for improvement in translational neuroscientific research: (1) the statistical approaches used in neuroscience, (2) the need for larger population-based samples, (3) a lack of mechanistic understanding of psychiatric neuropathology, and (4) the need for a move away from the often ill-defined phenomenological (see Glossary) diagnostic criteria in psychiatry. In this section we will address each of these areas, outlining why they pose a threat to the clinical applicability of neuroimaging research.

Solutions to these issues will be put forward in the subsequent section.

Statistics and Study Design

Most neuroimaging studies use group differences to infer characteristics of neuropathology. While the knowledge of how brain structure and function differs between patient populations and control subjects is valuable in terms of understanding disease mechanisms, making inferences about cognitive or affective processes based on observations of brain structure or function (i.e., reverse inference) is problematic (31). However, a key reason for the inability of neuroscientific insights to translate into clinical practice is the reliance on the results of inferential statistics (see Glossary) to determine the relevance of results, which does not necessarily translate into clinical relevance. In an applied setting only those variables that can generate some information about the outcome of interest for an individual patient—whether this is the projected disease course or simply whether or not a patient fits into a specific diagnostic category—are useful. Statistical significance between groups is quantified based on group means and within-group variance [see (32) for a discussion]. Differences will therefore be strongest between groups with high within-group homogeneity. Good predictors, on the other hand, capitalize on heterogeneity within the entire sample to generate an outcome estimate. While variables that significantly differ between groups may also be good predictors, this is not necessarily the case, and vice versa (20, 23, 32, 33).

Another concern regarding current statistical standards in neuroscience is the reliance on mass-univariate analyses to determine statistical significance of results. Considering each voxel in isolation assumes a level of extreme localized functional specialization that does not reflect the network-based neurophysiological underpinnings of cognitive functions and clinically relevant outcomes (34). The inherent connectedness of neuroimaging data necessitates that determining the predictors of a cognitive, behavioral, or clinical outcome should examine any interaction effects between brain regions. Examining a single cluster of voxels or a single brain region is rarely very informative. Multivariate, as opposed to univariate analysis procedures encompass the simultaneous analysis of more than one independent variable. In the context of neuroimaging research this typically takes the shape of multivariate (or multi-voxel) pattern analysis or regression analyses embedded within a machine learning approach. Most of these can be grouped into (1) classifiers or logistic regression approaches, and (2) linear regression approaches. Multivariate statistical tools have been incorporated into neuroimaging research more and more in the past decade (34). However, there is an additional concern when using multivariate methods. Neuroimaging data are expensive to acquire (approximately €750 per hour) and consequently sample sizes in neuroimaging research are generally quite small. The number of input variables in a neuroimaging datasets often exceeds the number of observations (i.e., sample size). When this is the case, predictions are at a high risk of being overly optimistic (35). This occurs when a model fits to the idiosyncrasies of the sample rather than factors that are common to the population from which the sample is drawn. This is generally referred to as "overfitting" [see (36) for an overview of this issue in neuroimaging]. Overfitting leads to models producing very good predictions on the sample they were created with, but that then generalize poorly to other samples from the same population.

Understanding Mechanisms

Besides improving the accuracy of clinical judgements, biological models of psychiatric illness have the potential to illuminate the neurobiological mechanisms of disease etiology and recovery. However, at least some understanding of neuropathology is necessary to create good neuromarkers (34). In the psychological tradition, most mental disorders are associated with at least one theoretical model of the component processes and functions associated with maladaptive behavior, cognition, or affect. Such models can be applied to neuroimaging data to examine associations between brain structure or function and theoretical components of the model [e.g., (37)]. This approach has the potential to illuminate certain aspects of neurobiology in the light of the psychological model, but rests on the assumption that the model reflects a cognitive process accurately (38). The majority of theories about maladaptive behavior or psychiatric pathology combine neuroscientific evidence with assumptions about the psychological processes that they influence or support. Theoretical models can emerge from neuroscientific evidence, or neuroscientific evidence can lead to the confirmation or reconsideration of already established psychological models. An example of neuroscientific evidence leading to a reconsideration of a theoretical model comes from the field of addiction, where increased availability of neuroimaging research led to an alteration in how the role of reward processing was viewed (39). This example shows that the state of understanding disorder mechanisms depends both on the available neuroscientific evidence, and on the available theoretical models of a condition.

Another issue regarding the understanding of disorder mechanisms emerges with the use of multivariate statistics. While the variables ("features") which are included in the model may be determined by the current understanding of disorder mechanisms, the model building process itself will be divorced from the theoretical understanding of the condition. This makes it important that neuromarker models be interpretable. That is to say, it must be possible to determine whether a neuromarker model is neurophysiologically plausible (34). As Woo et al. (34) put it, it is difficult to know when and why a model will fail if it is not understood why it works in the first place. However, constructing good interpretable models from neuroimaging data is not an easy feat. The machine learning tools which have been adopted by neuroimaging researchers typically come from fields such as computer science or engineering, where the importance that is placed on model interpretability is much lower.

Psychiatric Nosology

Nosology in psychiatry does not have a biological basis, and incorporates no knowledge about neuropathology. Evidence-based efforts to redefine diagnostic categories have been made using cluster analysis (see Glossary). Leaning on the psychological history of clustering psychiatric populations based on neurocognitive and affective symptoms, a phenomenological

subclassification of a population can be achieved. This can then be linked to neuroimaging data to reveal possible biological subtypes of the disorder. An example where neuromarkers could be useful is the case of bipolar disorder and schizophrenia. These disorders are distinct in terms of their diagnoses (40) but may in fact have a shared etiological pathway (41, 42). Both these disorders pose a considerable challenge in terms of differential diagnosis, as they have substantial commonality in their symptomatology (see Glossary). There is considerable evidence that biological subtypes of mental disorders may not necessarily correspond to diagnostic categories [see also (43, 44) for a discussion of biological subtypes in ADHD]. However, this knowledge alone has limited clinical applicability because no relationship to disorder etiology, treatment outcome, or disorder trajectory was established. Nevertheless, it is crucial to consider that neuromarkers may be unattainable when working with disorders based on phenomenology and current diagnostic categories [RDoC; (45)]. Therefore, the goal of the RDoC is a diagnostic system in psychiatry which is based on an understanding of the biological and psychosocial basis of mental illness (45). Many researchers have asserted that the unreliable (46) symptom-based stratification of mental disorders has prevented progress in determining the etiology and pathophysiology of mental disorders (20), and that nosology should be recast in more biologically meaningful terms, based on neuroscientific evidence (20, 47). An important consideration is that any categorization of disorder subtypes based on biological data will likely impose artificial boundaries upon the spectrum of disease pathology and symptomatology. Therefore, a biological redefinition of disorders must reflect the concept that biological indicators of pathology are likely to exist on a continuum.

Summary

In this section we have outlined the central problems which have led to neuroimaging research largely failing to generalize to clinical psychiatric practice. A fundamental issue in neuroimaging research is the mass-univariate analysis framework often used. When moving to multivariate approaches it is important to remain mindful of the danger of overfitting. Overfitting is more likely to occur when sample sizes are too small or when the number of variables is too large. Furthermore, neuroimaging models should be interpretable, to ensure their neurophysiological plausibility. Lastly, it is problematic to rely on current diagnostic categories when creating neuroimaging models of mental disorders, as these categories are often ill defined.

NEUROMARKERS—A RECIPE

In this section we will address the challenges raised in the previous section. We will address each point by describing methods which are already being used in the field to improve neuromarker research. This section will be structured to follow the lifecycle of neuromarker development, focusing on the following elements: Study design, analysis frameworks, statistical tools, the extended development pipeline of a neuromarker, and an example of a neuromarker which has already progressed through much of this developmental pipeline.

Study Approaches

Dubois and Adolphs (23) likened big data in neuroscience to accelerators in particle physics or telescopes in astronomy—a necessary tool for scientific progress [for a discussion of the role of big data in psychiatry see also (30)]. Large samples are achievable through multi-site imaging initiatives and consortia like the Alzheimer's Disease Neuroimaging Initiative [ADNI, (48)], IMAGEN (49), EU-AIMS (50, 51), the Adolescent Brain Cognitive Development Study (NIH), the Human Connectome project (52), and ENIGMA (53). However, not all data from these initiatives are publicly available. Another option to achieve large sample sizes is data-sharing, possible through data-sharing facilities such as NeuroVault [neurovault.org, (54)] and OpenfMRI [openfmri.org, (55)]. While utilizing data from multiple laboratories and multiple geographic locations contributes to the validity and generalizability of models, collapsing data across multiple data collection sites is a non-trivial task that can introduce additional confounding factors (24). While complex, it is possible to combine data from multiple data collection sites into a well-performing model (56). Large datasets facilitate a population-based approach to neuromarker research. Large studies like IMAGEN not only gather neuroimaging data, but also gather information on genetics, demographics, and life history. This makes it possible to examine psychopathology in a holistic manner (57), under the rubric of "population neuroscience." By taking into consideration information from other domains, neuromarkers can more meaningfully contribute to our understanding of the etiology of psychopathology.

Many large datasets include participants with a wide range of symptoms. Yet, studies using these data to identify neural signatures associated with mental disorders often select a fairly narrow subset of cases and matched controls. Studies using well-defined and clearly distinct groups are able to classify between patients and controls or between patient groups. However, the context in which knowledge gained from such classification studies is useful must be carefully considered at the outset of designing such a study. For example, a classifier which can differentiate between patients with schizophrenia and patients with bipolar depression with high accuracy only has clinical utility when it is applied to a patient who is already known to fall into either of those groups. If however the individual were suffering from unipolar depression the outcome of the classifier would have little meaning. Although strictly controlling for variables such as age, socio-demographic circumstances, symptoms, or medication use gives the experimenter greater control and greater clarity over the source of an effect, restrictions on study inclusion also restrict the utility of findings. That is to say, stricter inclusion criteria also narrow the range of circumstances in which a model will be useful and applicable (34). Considering this restriction on how a model can be useful in practice, the models and neuromarkers that will have the highest clinical significance will be models that take into account the heterogeneity within the population, and ideally define pathology

in a continuous rather than binary fashion (19, 20, 34). This is particularly important when attempting to predict clinical outcomes such as future psychopathology. Large datasets make it possible to create neuromarkers that provide information about how an individual's brain activity differs from the population average. This provides insight into how linear variations in brain structure and function are associated with changes in a variable of interest on a spectrum which includes the population-mean and pathological manifestations. In comparison to case-control studies, this individual-difference approach would mark a move toward creating neuromarkers for certain symptom clusters or processing domains, rather than for specific diagnoses.

Attempting to identify neural signatures of individual types of processing or behavior can be seen as a "component process" approach [(34), p. 371]. This would ideally result in a set of models which capture brain structure or function associated with a particular variable that linearly varies across the population. A number of such models could then be combined to identify specific populations. This approach would be very valuable in terms of risk assessment, such as early identification of adolescents at risk for future psychopathology. An example of this could be ADHD and substance use disorder. Both individuals with ADHD, and individuals with substance use disorder often show poor inhibitory control. A neuromarker that measures inhibitory control should therefore provide similar estimates for these two groups. Identifying an adolescent's level of inhibitory control based on a neuromarker can therefore provide a measure of risk of maladaptive behaviors involving poor inhibitory control. The component process approach is thus very well-suited to addressing certain types of research questions, such as general risk for maladaptive behavior. Applying the component process approach to other questions, such as predicting response to treatment, may however prove challenging.

Analysis Frameworks and Statistical Tools

To be valuable in an applied context, neuromarkers need to provide information about a variable of interest. Such models necessitate knowledge of an outcome category or score corresponding to each dataset. In machine learning terms, this type of analysis is known as *supervised* learning. As previously noted, the metrics that we currently use to delineate and define mental disorders may not be ideal. A true redefenition of diagnostic categories and disease entities based on biological data, as advocated by the RDoC, requires a different approach. In machine learning, *unsupervised*, or *data mining* approaches work independently of outcome categories or dependent variables, attempting to cluster the data into coherent groups based on the information provided. In the case of psychiatric neuroimaging this takes the form of grouping participants into sub-categories based on their brain structure or function, independent of symptomatology. An example of this approach comes from the field of ADHD: Costa Dias et al. (58) examined resting state functional connectivity in a sample of 106 children, 43 of which were diagnosed with ADHD. This study identified three ADHD neurotypes (see Glossary) characterized by differences in functional network structure. It is feasible that the neurotypes identified in this study might represent distinct etiological pathways. Since the neurotype groups also differed with regard to impulsivity and activity level, the core deficits in these groups appear to be at least partially distinct, making it likely that treatment approaches may differ in terms of success between neurotypes. Clustering studies that have direct clinical utility link neurotypes to clinically relevant outcomes. An early series of studies combined cluster analysis with prediction of treatment outcome in a group of cocaine users (59, 60). These studies found that unsupervised clustering of resting-state electroencephalography data could group cocaine users into groups which differed in terms of the length of their stay in a treatment facility. The neurotypes discovered in this study have no ability to reveal etiological pathways, but they do provide some evidence of neurobiological characteristics associated with recovery, which is an equally important aspect of psychiatric neuropathology. In contrast, a more recent study linked treatment outcomes in depression to neurotypes (61). This study was able to identify clear differences in likelihood of certain symptoms presenting and overall disorder severity between neurotypes, thereby creating a link between the biological disorder subtypes and clinical presentation.

Given a known outcome variable, such as treatment success, neuroimaging research has typically employed group-difference analyses to identify factors associated with this outcome. Recognition of the limitations of this approach has led a large number of authors in psychology and neuroscience to emphasize the importance of moving away from explanatory and univariate analysis procedures and toward multivariate outcome prediction (21, 31, 34, 62). In the past decade the number of neuroimaging studies using multivariate methods has grown rapidly (34), and there is a strong recognition of the importance of this approach [(30, 62–64)]. The divergence of findings using classic univariate compared to multivariate methods is demonstrated by two recent meta-analyses summarizing neuroimaging studies of unipolar depression: There was a notable lack of significant differences in brain activity during emotional or cognitively challenging tasks associated with unipolar depression using traditional group comparison studies (65); However, a meta-analysis of studies using a multivariate approach to classify patients with major depressive disorder and healthy control subjects found an average classification accuracy of around 75% for functional MRI (66).

Supervised learning using multivariate models requires a particular set of statistical tools that departs strongly from the traditional group-difference approach. When using multivariate analysis methods, it is of great importance that the analysis protocol include some measures to prevent overfitting. The most fundamental of these is that a model must be tested on a previously unseen sample in order to obtain a realistic estimate of model accuracy. This step is crucial, as it is the most effective way to gauge how well a model will perform with other individuals from the same population. Using a separate dataset is the gold standard in terms of assessing external validity. However, a more easily accessible method is cross-validation (CV). One of the most frequently used methods is leave-one-out CV [LOOCV; e.g., (67–69)], or leave-k-out CV [e.g., (70)]. A somewhat less computationally expensive method is k-fold CV (e.g., (71)]. When using CV it is imperative to ensure that the observations

used to validate the model (the test set) remain statistically pure and do not at any point overlap with the observations used to create the model [the training set; (72)]. Another tool that is important in quantifying in-sample generalizability is bootstrapping. Bootstrapping improves the stability of a model by randomly sampling the dataset with replacement multiple times in order to minimize the effect of outliers and estimate the true population mean (73). In particular, bootstrapping provides a measure of how reliable and consistent coefficient estimates or feature metrics are with datasets that have a low signal-to-noise ratio (see Glossary) and high multicollinearity. Bootstrap aggregation (bagging) has previously been used with large genetic datasets, and showed significant improvements over standard (non-bagged) methods in terms of model accuracy and stability (74). Both cross-validation and bootstrapping can be considered "resampling" procedures, and are standard tools used in Machine Learning.

Another important step which should be implemented when working with high-dimensional neuroimaging data is dimensionality reduction. Dimensionality reduction simply refers to the reduction of the number of variables that will be used to create a model. Dimensionality reduction approaches can be broadly categorized into "feature selection," and "feature extraction" methods. Feature selection takes the existing input features and strategically removes those features that will, or are most likely to, contribute little to the accuracy of the model. Feature selection methods can be categorized into *filter* methods, *wrapper* methods, and *embedded* methods. These differ in terms of how the selection of features included in the regression model and model optimization (or learning) interact. Filter methods rank all brain inputs by factors such as their correlation with the target variable (i.e., prediction accuracy), and the most informative variables are selected. This is often used to initially reduce the size of datasets before other feature selection methods are used. Wrapper methods (75) use a learning machine (e.g., sequential search algorithms) to evaluate the quality of subsets of features [see (70)], thereby accounting for the importance of feature interaction effects. In contrast to filter and wrapper approaches, model building and feature selection cannot be separated in embedded methods. Some of the most common embedded feature selection algorithms are regularization methods, which penalize model complexity as a part of function optimization. Examples of these methods include Ridge, Lasso, and Elastic Net regularization (76). The Elastic Net has gained popularity among neuroimaging researchers in recent years, and has been successfully used in a number of large studies [e.g., (71, 77)]. While the method of feature selection does not seem to make a difference for large genetic datasets (78), embedded methods have been shown to be more effective than filter methods with certain neuroimaging classification problems (79). A more in-depth discussion of filter and wrapper methods can be found in Chandrashekar and Sahin (80), and Mwangi et al. (81) provide a review of feature selection techniques and their application to neuroimaging data.

In contrast to feature selection, feature extraction methods such as principal component analysis (PCA) and independent component analysis (ICA) are very familiar to neuroimaging researchers. Data scientists in other domains routinely use feature extraction techniques to map features onto higher-level summary variables to reduce the dimensionality of the dataset. Feature extraction always involves creating a new set of features from the original input variables, which normally makes the model difficult to interpret. It is therefore very complicated to evaluate whether a model is neurophysiologically plausible when feature extraction methods are used. While feature extraction methods often results in an improvement in model accuracy, they have largely been avoided by neuroimaging researchers when seeking to identify neuromarkers. However, there have been some advances that capitalize on the improvement in accuracy which can be gained from feature extraction methods, while also mapping results back onto the original feature space (82).

In addition to feature selection and feature extraction, it is also possible to manually create summary variables based on domain knowledge. This is referred to by Hahn et al. (13) as "feature engineering." Feature engineering is a supervised form of feature extraction that capitalizes on the researchers' domain knowledge to create features that represent the underlying problem in a superior way. While this approach holds promise in that it makes it possible to integrate previous knowledge and theoretical understanding of a disorder directly into the model building process, we believe that some caution is warranted. In the same way that our current understanding of the neurobiological and psychological processes underlying mental disorders depends both on the state of the neuroscientific evidence and on the available theoretical frameworks, there is a danger that feature engineering may bias findings toward results that support a particular theoretical model of neurobiological processes. At the very least researchers should be aware of this caveat, and clearly communicate that their analysis framework is not purely data-driven, but incorporates at least some elements of theory-driven analysis (83).

Finally, despite efforts to guard against overfitting, there may nevertheless be a degree of unwarranted optimism in any model. Establishing whether a model produces results that are significantly better than chance is therefore not possible using traditional p-values. Rather, an empirical significance threshold should be established using a null model (i.e., a model against which the observed data can be compared to determine the likelihood that any observed effect could have occurred by chance). A commonly used approach to generating null model data is a simple randomization of the dependent variable across participants (random label permutation). Other approaches to constructing null models and null data include randomizing input data, and use of only nuisance covariates (23). The level of accuracy achieved by the analysis framework using this null data is compared to the accuracy of the model with real data, and this acts as a measure of the optimism inherent in the analysis framework.

The Neuromarker Development Pipeline

The developmental pipeline for neuromarkers in psychiatry should be very similar to the standard drug development pipeline. Woo et al. (34) and Moons et al. (19, 84) have laid out this developmental pipeline for biomarkers, making specific

recommendations and providing a tangible way to evaluate how close to clinical applicability biomarkers are. The number of participants required increases the further along the road to clinical applicability a model is (34, 84). Initial exploratory studies typically have small sample sizes and modest resources, but the findings from these studies can be used to justify investing a higher amount of resources for further research and development (21, 34). At this stage it is advantageous to pursue many different avenues in terms of modalities and functional tasks in order to find the approach that best predicts the outcome. Generally, the most efficient approach to biomarker development will take into consideration what we already know at every stage of the development pipeline (19). In the initial stages of neuomarker research this may take the shape of selecting functional imaging tasks to use based on previous research. When analyzing the data, this may include the use of targeted feature engineering as suggested by Hahn et al. (13), taking into account the caveats of this approach. Woo et al. (34) estimated that around 450 models in the exploratory stage of development had been published in January 2016 relating to mental disorders (excluding substance use).

After the initial creation of a biomarker, the next step is the application of the model to an independent sample. This serves the purpose of initial generalizability testing. Woo and colleagues estimate that only around 40 neuromarkers have been validated using independent samples. Jollans and Whelan (62) provide a summary of some of these studies from the domains of major depressive disorder (85), psychosis (86–88), and dementia (89–91). Only two neuromarkers were identified by Woo et al. (34) that had also been validated using data from another data collection site. One of these is the SPARE-AD classifier (89), an overview of which is given below. Biomarker models should be treated as shareable research product, to be updated, validated, and amended by other research groups (13, 34, 84). Testing in other laboratories is an important measure of model performance because differences between a variety of cohorts from the same population on occasion have much larger effect sizes than differences between groups within the population [for example, typically developing and ASD individuals, (92)]. While unimodal models are easiest to test in other laboratories, generalization studies (see Glossary) should also examine what additional measures can enhance a model (84). Examples of such an expansion of an existing neuromarker are given in a study by Davatzikos et al. (93), who included additional predictors alongside the SPARE-AD value (described further below), and in a study by Drysdale et al. (61) who found that an index of depression neurotype used in conjunction with a connectivity index was most successful in predicting treatment response. Multiple unimodal models can effectively be integrated using strategies such as "voting," "boosting," or other ensemble methods [(13); see Glossary]. In fact, combining multiple modalities in a single model typically results in higher model accuracy. Multimodal models (see Glossary) are also preferable from a theoretical perspective when attempting to describe the neurobiology underlying a given outcome (21, 34, 63, 94).

An essential element of model validation is testing for construct validity. That is to say, a good neuromarker must actually measure the concept that it is assumed to measure. This seems straightforward, but in many cases the substantial phenotypic overlap between disorders may make it difficult to pinpoint what aspect of a disorder a biomarker is measuring, and in what context it will perform poorly. An example of this could be a classifier that supposedly separates control subjects from individuals with substance use disorder. It is conceivable that such a biomarker may in fact tap into externalizing symptoms common to ADHD and substance use disorder, or inadvertently identify individuals with ADHD symptoms, since they have higher substance use risk than those without ADHD symptoms (95). A biomarker assumed to measure a particular concept should therefore also be tested using populations which it should not have any relevance to, as well as populations to which it is assumed to generalize well. Ideally, biomarkers should be tested on very large, population-level samples that include a range of "confounds."

Validating neuromarkers developed to differentiate among disorder subtypes is a specific challenge. For example, a study may identify a neurotype indicative of treatment outcome and provide a characterization of the neurotype based on symptomatology. However, given the difficulty (or indeed impossibility) of defining discrete disorder subtypes, indicators of neurotype could be integrated into models that predict other clinical outcomes such as treatment success [see (61)].

Finally, the ultimate test of the clinical utility of a biomarker should be large-scale randomized control trials, evaluating outcomes for patients who were assessed using traditional methods and patients who were assessed with the help of the biomarker (84). This step will serve as a measure of how much use of the biomarker actually contributes to patient care in an applied healthcare setting. At this point weighing up the cost and the benefits of the biomarker will determine whether it is suitable for integration into healthcare settings.

Not So Far Off After All: A Neuromarker for Alzheimer's Disease

The psychiatric domain which has seen the largest amount of neuromarker research and for which some of the most promising neuromarkers have been developed is Alzheimer's disease (34). This is largely due to the freely available ADNI database. ADNI includes data from older adults who are cognitively normal (CN), diagnosed with mild cognitive impairment (MCI), or with Alzheimer's Disease (AD). This stratification of participants along what can be regarded as a continuum of cognitive impairment and dementia represents a more ecologically valid sampling scheme (i.e., better represents the population) than many psychiatric neuroimaging studies. The ADNI study collected longitudinal data from older adults, capturing cognitive decline and transition from CN to MCI and from MCI to AD. Due to the large sample size and range of impairment present in this sample, researchers were able to use subsets of participants to develop and validate a neuromarker. The SPARE-AD classifier was originally developed using 66 CN and 56 AD

participants (89). The classifier generates a score which separated the AD and CN group in this sample with 94% accuracy. To validate the classifier, data from a group of 88 MCI participants were used. The classifier separated the MCI and CN group with 82% accuracy. Accuracy was 74% when separating the MCI and AD group. While confirming that the classifier has strong validity in detecting characteristics unique to AD, these results also show that the classifier detects factors associated with cognitive decline more generally. The next step in terms of model validation in this study was the classification of MCI patients according to their SPARE-AD score into a group likely to develop AD and a group likely not to develop AD. Based on participants' cognitive decline over the next 3 years the classification accuracy of MCI individuals ($n = 38$) was 87%. The classifier trained in this study was subsequently applied to a different sample of MCI patients from the ADNI cohort (93). This represents the first stage of generalization tests for this model. While the classification reached 90% sensitivity ($n = 69$ patients transitioned to dementia), only 37% of the MCI patients who remained stable within the timeframe of the study ($n = 170$) were correctly classified (56% classification accuracy). This result demonstrates the importance of generalization tests to obtain a realistic estimate of how well the neuromarker performs.

SPARE-AD has also been applied to data from the Baltimore Longitudinal Study of Aging (BLSA). Validating the classifier on a sample drawn from a different geographical location is an important step in determining external validity. Davatzikos et al. (96) used data from 109 CN participants who did not transition to MCI over a 14 year period and data from 15 individuals who transitioned from CN to MCI. They were able to predict whether or not individuals would transition to MCI based on the rate of change of their SPARE-AD score (AROC = 0.89; see Glossary). Davatzikos et al. (93) integrated the SPARE-AD classifier and a cerebrospinal fluid marker, which improved classification accuracy from 56 to 62% (84% sensitivity, 51.2% specificity). Further evidence from a study comparing various AD classifiers found that SPARE-AD in combination with a measure of cognitive performance and genotype information provided the highest classification accuracy (97). Integrating multiple classifiers to improve accuracy is another important step toward developing a clinically useful biomarker.

Both studies using the ADNI database used samples including more than 200 participants, and in total the SPARE-AD classifier has been tested on more than 550 individuals between the studies described here. Using larger than average samples from multiple data collection sites made it possible to develop a neuromarker of cognitive decline in older adults, which has been shown to reliably identify individuals at risk for future cognitive decline. While the rate of false positive identification was shown to be quite high for this classifier, it is a validated tool that could feasibly be applied in clinical contexts to make a reasonable estimate of risk of cognitive decline in older adults. Based on the encouraging results obtained in these studies, SPARE-AD should continue to be tested across laboratories and scanners to reach the final phase of the model development pipeline: population-level generalization (34).

Summary

In this section we discussed the tools necessary to develop neuromarkers for mental disorders. Studies that seek to identify or test neuromarkers must take into consideration that the population from which their sample is drawn will also be the only population to which findings can be expected to generalize. Furthermore, it is imperative that researchers make use of freely available large datasets or collect data from large samples. Studies that include a large number of participants with a wide range of symptoms, and collect not only imaging data but also genetics, demographic data, and so on have the potential to produce the most clinically useful findings. Whether researchers use supervised or unsupervised analysis methods will depend on the question which they seek to answer. Supervised learning is preferable when a definitive outcome (such as relapse or disease course) is known, whereas unsupervised learning may be more beneficial when the outcome is not so clear (such as subtypes of diagnostic categories). For supervised learning approaches, rigorous generalization testing through resampling methods is crucial. Reducing the number of features included in the model through feature selection can help to prevent overfitting. Other dimensionality reduction strategies are available, but researchers should be aware of the practical and theoretical implications of choosing them. Significance should be established using null models. To reach clinical applicability, neuromarkers must undergo extensive generalization testing in other laboratories, with other populations, in combination with other biomarkers, and finally in randomized controlled trials. Due to many researchers' reluctance to use neuromarkers established in other research groups, most neuromarkers have not undergone generalization tests using other samples. An exception to this is the SPARE-AD classifier of Alzheimer's disease.

WHAT TO WATCH OUT FOR WITH NEUROMARKERS—PRACTICAL AND ETHICAL CONSIDERATIONS

With the goal of using reliable neuromarkers in psychiatry come a number of ethical considerations that should be kept in mind by researchers and clinicians who are working toward integrating neuromarkers into clinical assessments. The most immediately relevant consideration concerning research in this field is resource allocation. Resource allocation for neuromarkers research should be based on the effectiveness of treatment using current standard tools. That is to say, groups that are not well-served by current diagnostic, prognostic, or treatment approaches should be the primary target of psychiatric neuromarker research (33). Furthermore, rather than continuing to develop new potential neuromarkers in domains which have already identified potential biological models, research efforts should go toward validating and updating or expanding the most promising existing models. Adopting a component process approach may contribute to the re-use of models across laboratories.

With increased focus on brain-based measures of psychiatric conditions also comes the challenge of maintaining a holistic view of psychiatric disorders as being caused by multiple diverse etiological factors (98). While there may be a temptation to prioritize brain-based methods of explanation and treatment, there is an important balance to be struck between undervaluing advances based on neuroimaging, and scientific reductionism which discounts treatments and modes of interpretation based on the mind in favor of the brain. To what extent psychiatric science based on domains other than biology will continue to be useful will remain to be seen. As noted by Kendler [(98), p. 385], "having a realistic view of the causal landscapes of psychiatric disorders can only help."

Another caveat to consider is that predictions are not deterministic. In the area of healthcare this is of particular importance, as risk assessments and prognoses based on biological measures may well go on to inform the cost of health insurance. On the other hand, neuromarkers indicating the most promising treatment pathway should be seen as objective support for the clinician's choice of treatment, and should therefore factor into the level of contribution from health insurance providers to the cost of treatment. Finding satisfactory middle ground will be complex in this area, and will require that both researchers and clinicians engaged in neuromarker development are aware of the possible implications of their work for the patients they aim to benefit.

Summary

Researchers and clinicians should remain aware that moving from the phenomenological framework in psychiatry to a more biologically defined approach has implications for how mental disorders will be approached by stakeholders in the healthcare industry. Furthermore, the goal of neuromarker research should be to improve upon current diagnostic and prognostic capabilities as much as possible, which means that resources should be allocated where neuromarkers are most promising and where they are already in development.

SUMMARY AND CONCLUSION

In this review we have discussed why neuroimaging research has not had a substantial influence on psychiatric practice to date, and what is required to work toward identifying truly useful neuromarkers—neuroimaging biomarkers—of mental disorders. We provided an outline of the tools that are typically used in neuropsychiatric research investigating mental disorders, and argued that research should be focused toward developing neuromarkers for use in applied psychiatric settings. We presented problems inherent in the traditional group comparison approach used in psychiatric neuroimaging research, and suggested that broader, more population-based study designs will be likely to have greater clinical utility. To move toward an approach that places higher emphasis on individual differences, it is necessary to work with large samples. It is also advantageous not to rely on current diagnostic criteria for mental disorders when working toward neuroimaging biomarkers, as these may not correspond to biological subtypes of mental disorders. Identifying neuroimaging biomarkers will only be possible if researchers adopt multivariate regression-type approaches, and machine learning analysis frameworks. The generalizability of findings should be given highest priority. Therefore, resampling methods such as cross-validation must be used at a minimum, with external validation as the "gold standard." Furthermore, neuroimaging data calls for the use of dimensionality reduction approaches such as feature selection. In order to determine the validity of a model it is necessary to be able to examine whether it is neurophysiologically plausible, making interpretability an important concern when constructing models. Before they can be implemented in healthcare settings, neuromarkers must be tested using large diverse samples, across a range of geographical locations and research groups.

We believe that a fundamental shift in how research in neuropsychiatry is conducted is necessary in order to produce viable neuromarkers. First, it is essential that researchers not rely solely on current diagnostic criteria when developing neuromarkers. These criteria are unreliable, based only on behavioral and self-reported symptoms, and they misrepresent the etiology and underlying neuropathology of many mental disorders. While we believe that it would be advantageous for psychiatric nosology to be redefined based on neuroscientific evidence, the most efficient approach to neuromarker development will likely include a move toward component-process based models, and a focus on individual differences across populations. This will require a significant shift in how researchers approach study design and analysis. The focus of neuromarker research must be on external validity, on the accurate representation of a model's performance, and on the attainment of clinically useful neuromarkers. This will require the cooperation of publishers and funding bodies to gather and distribute knowledge about what approaches appear promising and what approaches do not, and to prompt and support replication and generalizability studies. Specifically, a population neuroscience approach including samples with a wide range of symptoms, and data from multiple neuroimaging and non-imaging modalities will be necessary to create far-reaching and effective neuromarkers.

In conclusion, we believe that the field of neuromarker research offers exciting prospects for the future of psychiatric healthcare. As was shown with the example of the SPARE-AD classifier, it is possible to create well-validated neuroimaging biomarkers that augment existing prognostic capabilities. Biological models of mental disorders have the potential to identify individuals at risk of developing psychiatric illness, or those in the early stages of neurodevelopmental and neurodegenerative disorders. This knowledge would be a valuable tool to identify those individuals who would most benefit from early interventions or from periodic monitoring. Psychiatry is currently decades behind most other areas of medicine when it comes to the use of objective assessments of disorder status or risk. However, we believe that the integration

of big data and machine learning, which is already taking place in neuroscience and psychology, will allow us to not only improve healthcare through the integration of neuromarkers, but to also gain a much better understanding of the neurobiology associated with the development of, and recovery from, mental disorders.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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GLOSSARY

Neuromarker: A neuromarker is a biomarker based on neuroscientific data, such as neuroimaging. Neuromarkers are biological indicators of the presence or progression of a disease or condition. They are generally statistical models that provide an objective estimate of how likely it is that a given condition is present. Neuromarkers can consist of a single variable, or be complex multivariate models.

Brain imaging terms:

Voxel: A voxel can be thought of as a three-dimensional pixel. Voxels are the smallest units in three-dimensional brain images obtained using MRI.

Region of interest (ROI): ROI is a term used in neuroimaging to describe data which contain information about a specific area of the MRI image. ROIs will often correspond to predefined regions within the brain, such as the amygdala or the hippocampus. Data within an ROI are typically averaged to include in statistical tests.

Signal to noise ratio (SNR): In imaging, SNR refers to the ratio of signal within the data to the background "noise." In brain imaging terms this represents the strength of the signal coming from the brain itself, such as from the BOLD signal, compared to the (random) background noise which is of no interest. SNR is normally low in neuroimaging.

Psychological terms:

Symptomatology: For mental disorders, symptomatology refers to observable and self-reported symptoms which an individual experiences. This may include physiological and psychological symptoms.

Phenomenology: In psychology, phenomenology refers to the description of an individual's experience, and is dissociated from objective reality.

Neurotype: A neurotype, or biological subtype of a disorder or condition is a subset of the population that shows particular characteristics of brain structure or function.

Statistical and machine learning terms:

Inferential statistics: The *t*-test is a test of the statistical hypothesis that two samples are drawn from the same population. The underlying assumption of the *t*-test is that data from the same population would follow a normal distribution. *T*-tests are often used to test whether there are statistically significant differences between two groups., Generally, an Analysis of variance (ANOVA) is the extension of the *t*-test to multiple groups. ANOVAs test for differences in group means.

Model (Statistical model): A statistical model refers to the formal description of the generation of data. Statistical models can be thought of as mathematical representations of theories. Statistical models usually describe the relationship between one or more independent variables (such as neuroimaging data), and some dependent variable of interest (such as symptomatology). The multivariate models referred to throughout the text typically have multiple input variables that are weighted depending on how strongly they contribute to the description of the dependent variable. The weighted input variables are then combined in a mathematical equation that results in an estimate of the outcome variable.

Unimodal and multimodal models: Unimodal models include only data from one domain, such as a single type of neuroimaging data. Multimodal models include data from more than one modality.

Ensemble methods: Ensemble methods make it possible to use multiple statistical models to create a summary model. Examples of this approach are "voting," and "boosting." Ensemble methods often combine results from multiple models into a new model, weighting inputs to create a superior estimate than would have been achievable using each model on its own.

False positive: False positive results are findings which indicate that something is true, when it is in fact not true., False positives are often used to describe the results of classification studies where a member of the negative class (typically control participants) may be erroneously classified as a member of the positive class (typically patients).

Sensitivity and Specificity: Sensitivity refers to the number of cases from the positive class (typically patients) that were correctly identified by the model, and specificity refers to the number of cases from the negative class (typically control participants) that were correctly identified.

Area under the curve of the receiver operating characteristic curve (AROC): The AROC refers to the integral of the receiver operating characteristic curve (ROC). The AROC is a frequently used metric of model fit for classification models and logistic regression. The ROC curve tracks the rate of true and false positive classification of the model. The true and false positive values are on a continuum where the extremes are the instances when all cases are classified as elements of one class. Higher AROC values denote better model fit, and a higher rate of true than false positive classification. The maximum AROC value is 1, with .5 representing chance performance.

Generalization study/test: A generalization study uses a sample that is independent of the dataset that was used to create a model. The generalization study is used to test how well a model performs when it is applied to a different sample.

Clustering: Clustering or cluster analysis is a data-driven approach which groups datapoints such that datapoints within the same group (cluster) are more similar to each other than to datapoints outside the group.

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Ventral Striatum Connectivity During Reward Anticipation in Adolescent Smokers

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ABSTRACT

Substance misusers, including adolescent smokers, often have reduced reward system activity during processing of non-drug rewards. Using a psychophysiological interaction approach, we examined functional connectivity with the ventral striatum during reward anticipation in a large (N = 206) sample of adolescent smokers. Increased smoking frequency was associated with (1) increased connectivity with regions involved in saliency and valuation, including the orbitofrontal cortex and (2) reduced connectivity between the ventral striatum and regions associated with inhibition and risk aversion, including the right inferior frontal gyrus. These results demonstrate that functional connectivity during reward processing is relevant to adolescent addiction.

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Adolescence is a period of substantial behavioral and brain changes and of heightened propensity for risk-taking. Adolescence is also a time of increased risk for impulse-control disorders, including addiction (Chambers, Taylor, & Potenza, 2014; Paus, Keshavan, & Giedd, 2008). The most common addiction in adolescence is nicotine (Young et al., 2002). Smoking is the leading cause of preventable deaths in the United States, and nearly one in five adults is a smoker (U.S. Department of Health and Human Services, 2014). Next to alcohol, cigarettes are one of the most widely available addictive substances, meaning that it is much easier for adolescents to try cigarettes than other drugs. Adolescent smoking differs widely in its frequency and regularity, but can broadly be categorized into four smoking trajectories: (1) Adolescents who start smoking at an early age and go on to become regular smokers, (2) individuals who follow the same path but initiate smoking at a later age, (3) adolescents who experiment with smoking but do not become addicted or stop smoking, and (4) non-smokers (Audrain-McGovern et al., 2004a; Chassin, Presson, Pitts, & Sherman, 2000; Mayhew, Flay, & Mott, 2000).

While the behavioral and personality differences between adolescents in different smoking trajectories are subtle and difficult to pinpoint, the differences between adolescent smokers and non-smokers are well established: Adolescent smokers show increased novelty-seeking, reduced harm avoidance, and increased choice impulsivity (Audrain-McGovern et al., 2004a, 2004b; Wills, Windle, & Cleary, 1998). However, these traits are not only characteristic of adolescent smokers compared with non-smokers, but also of adolescents compared with adults (Brändström, Sigvardsson, Nylander, & Richter, 2008; Steinberg et al., 2009). A number of neurobiological models have attributed these characteristics of the adolescent developmental period to a difference in the balance between different brain systems in adolescence. The dual-system model (e.g. Steinberg et al., 2008), the triadic model (Ernst, Pine, & Hardin, 2006) and the imbalance model (Casey, Jones, & Hare, 2008) all distinguish between the reward system and the cognitive control system. Among the structures involved in cognitive control are the dorsolateral prefrontal cortex (dlPFC), which is one of the most important executive control regions (Alvarez & Emory, 2006), the orbitofrontal cortex (OFC), which has been attributed a role in saliency and value attribution (O'Doherty, 2004), the anterior cingulate cortex (ACC), which has been implicated in selective attention (Alvarez & Emory, 2006), and the right inferior frontal gyrus (IFG), which has been established as a central region in behavioral inhibition (Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Jacobson et al., 2003).

There are many interacting regions involved in reward processing (see Haber & Knutson, 2010). Among these regions the ventral striatum (VS) is particularly important. The VS receives dopaminergic input from the ventral tegmental area and is connected to frontal areas such as the orbitofrontal and ventromedial cortices. The VS is not only central to processing reward-related stimuli, but also plays a key role in integrating affective and cognitive information, and in action selection and motivation (Floresco, 2015). Along with decreases in impulsive choice from adolescence to adulthood, activation in the VS during reward-related decision making decreases, and activations in prefrontal cognitive control regions have been shown to increase with age (Christakou, Brammer, & Rubia, 2011). The functional connectivity between the VS and prefrontal cortex (PFC) during reward outcomes also increases over the course of adolescence (Van Den Bos, Cohen, Kahnt, & Crone, 2012). Furthermore, ventral striatal dopamine D2 receptor availability is associated with alcohol cue-induced activation in the ACC and medial prefrontal cortex, confirming a role for dopamine in VS-medial prefrontal interactions (Heinz et al., 2004).

In adult smokers, lifetime tobacco use is associated with structural brain alterations in both the reward and cognitive control systems (Gallinat et al., 2006; Zhang et al., 2011). Furthermore, adult smokers show reduced connectivity between the striatum and ACC, associated with the severity of nicotine dependence (Hong et al., 2009). While these findings suggest a role of long-term chronic cigarette smoking in brain deficits in these systems, there is robust evidence linking the VS to adolescent impulsivity and smoking. VS hypoactivity during reward anticipation can be observed in adolescents with attention deficit hyperactivity disorder (ADHD) compared to control subjects (Scheres, Milham, Knutson, & Castellanos, 2007), and is associated with risk-

taking bias in typically developing adolescents (Schneider et al., 2012). It appears that VS activity is negatively associated with impulsivity, independent of age (Ripke et al., 2012). VS hypoactivity can be seen in dependent adult smokers compared to occasional smokers (Bühler et al., 2010), and is associated with level of nicotine use in adults (Rose, Ross, Salmeron, & Lee, 2012). Importantly, a reduction in VS activation during reward anticipation has also been observed in adolescents prenatally exposed to nicotine (Müller et al., 2013) and in adolescent smokers (Peters et al., 2011). Furthermore, Peters et al. reported that ventral striatal activity during reward anticipation was negatively correlated with smoking frequency in adolescents. These findings point toward a possible deficit in the processing of rewarding stimuli in individuals who are at risk for developing nicotine dependence.

Whereas the majority of studies to date have used measures of regional changes in Blood Oxygen Level Dependent (i.e., BOLD) activation to examine differences between substance using groups and non-users, a number of recent studies have used BOLD activation to evaluate differences in brain connectivity between these groups. However, the majority of these studies have focused on resting-state connectivity (Fedota & Stein, 2015). Compared with resting state measures of functional connectivity, examining differences in connectivity in relation to specific conditions, such as different reward cue types, has the potential to be more informative with regard to differences in reward processing. For instance, a study examining reward cue reactivity in smokers found greater functional connectivity between the left insula and a widespread network including the OFC, ACC, and dorsal striatum during smoking compared to food cues (Claus, Blaine, Filbey, Mayer, & Hutchison, 2013). While examining smokers' reactivity to smoking cues is a valuable tool for understanding the mechanisms of craving and relapse in addicted smokers, the way in which non-smoking rewards are processed has the potential to offer more insight into factors associated with smoking initiation and smoking trajectories in adolescents.

A task that has widely been used to examine generalized reward processing in the context of functional magnetic resonance imaging (fMRI) is the Monetary Incentive Delay (MID) task (Knutson, Westdorp, Kaiser, & Hommer, 2000). The paradigm has the distinct advantage of temporally separating anticipation and receipt of positive or negative outcomes, making it possible to examine the activation patterns associated with each separately. VS activity is observed during the anticipation of rewards in the MID (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Knutson, Fong, Bennett, Adams, & Hommer, 2003). Other regions associated with reward anticipation in this task include the dorsal striatum, cuneus, thalamus, ACC, ventromedial PFC, OFC, insula, and midbrain (Haber & Knutson, 2010; Van Leijenhorst et al., 2010).

Here, we examine the association between adolescent smoking frequency and functional connectivity in the VS during anticipation of large rewards compared to no reward in the MID task, using Psychophysiological Interaction (PPI) analysis (Friston et al., 1997). We employed a powerful machine learning procedure to examine the connectivity patterns associated with smoking. Such approaches have previously been used to investigate adolescent binge-drinking (Whelan et al., 2014) and intelligence (Jollans et al., 2015). This approach has the potential to detect relatively subtle differences, while guarding against spurious findings, using both cross-validation and random-label permutation. We included 206 adolescents from a large multisite study, with a wide spectrum of nicotine use. As our aim was to identify effects associated with smoking frequency, rather than with smoking initiation, we included only adolescents who had smoked on three or more occasions in their lifetime at the point of data collection. In line with a recent review examining resting state functional connectivity in nicotine addiction (Fedota & Stein, 2015), which concluded that disruptions in nicotine addiction appear to be focused on the salience network as well as frontal cognitive control systems, we hypothesized that frequency of smoking would be associated with reduced VS connectivity to fronto-parietal cognitive control regions (Garavan & Weierstall, 2012) and increased connectivity to regions associated with salience or valuation of stimuli, such as the anterior cingulate and orbitofrontal and insular cortices (Seeley et al., 2007).

Method

Characteristics of the IMAGEN Study

A large sample of 14-year-olds was recruited at eight recruitment sites. Adolescents completed an extensive battery of psychiatric and neuropsychological assessments, including fMRI. Details of the full study protocol and data acquisition are provided elsewhere (Schumann et al., 2010).

Participants

Participants were a subset of 206 adolescents from the multisite study (110 female). Further information on the distribution of smoking frequency is provided in Table 1, and other details about the sample are provided in Table 2.

Substance use questionnaire

Lifetime smoking, alcohol, and cannabis use were measured using the European School Survey Project on Alcohol and Other Drugs questionnaire (ESPAD, Hibell et al., 1997), which was administered using the computerized assessment platform Psytools. Psytools presented questionnaire items and response alternatives on a computer screen. The reliability of individual data was checked in a two-stage procedure: Before every task, adolescents were asked to report on the current testing context including questions about their attentional focus and the confidentiality of the setting. Potentially problematic testing situations were followed-up by research assistants face-to-face in a confidential setting. Exclusion criteria for substance use measures included an indication that the participant was in a hurry, somebody was watching, or an indication to have known or taken the

Table 1. Distribution of smoking frequency across the sample.

Lifetime smoking occasions		*n*
ESPAD score	ESPAD range	
2	3–5	57
3	6–9	37
4	10–19	32
5	20–39	20
6	40+	60

Table 2. Characteristics of the sample.

			Correlation with nicotine use	
	Mean	*SD*	*r*	*P*
Age	14.58	0.46	0.11	0.13
Socioeconomic Status	17.50	4.36	−0.16	0.025
Pubertal Development Status	3.66	0.70	0.13	0.065
WISC-IV Perceptual Reasoning	103.66	12.97	−0.01	0.92
WISC-IV Verbal Comprehension	107.80	13.79	−0.10	0.13
ESPAD Lifetime Alcohol use	3.21	1.63	0.26	0.0002*
ESPAD Lifetime Cannabis use	0.64	1.45	0.21	0.0029*
SURPS Anxiety Sensitivity	2.24	0.49	−0.14	0.045
SURPS Impulsivity	2.60	0.42	−0.05	0.44
SURPS Hopelessness	1.93	0.40	0.02	0.77
SURPS Sensation Seeking	2.80	0.54	−0.08	0.22
TCI-R Disorderliness	23.71	4.33	0.07	0.26
TCI-R Exploratory Excitability	33.44	4.74	0.03	0.70
TCI-R Extravagance	30.79	6.02	0.04	0.52
TCI-R Impulsivity	27.82	5.01	−0.06	0.41
TCI-R Novelty-Seeking	115.77	14.43	0.05	0.47

*$p < .003125$, p value corrected for multiple comparisons.

sham drug *Relevin*. Scores on the ESPAD are ranked as follows: 0: no lifetime use, 1: 1–2 uses, 2: 3–5 uses, 3: 6–9 uses; 4: 10–19 uses, 5: 20–39 uses, 6: 40 or more uses. Participants were included if they had a score of 2 or higher on the ESPAD item measuring lifetime smoking. ESPAD scores for lifetime smoking are reported in Table 1.

Wechsler Intelligence Scale for Children

Participants completed a version of the Wechsler Intelligence Scale for Children (WISC-IV) (Wechsler, 2003), of which we included the following subscales: Perceptual Reasoning, consisting of Block Design (arranging bi-colored blocks to duplicate a printed image) and Matrix Reasoning (a series of colored matrices are presented and the child is asked to select the consistent pattern from a range of options); and Verbal Comprehension, consisting of Similarities (two similar but different objects or concepts are presented and the child is asked to explain how they are alike or different) and Vocabulary (a picture is presented or a word is spoken aloud by the experimenter and the child is asked to provide the name of the depicted object or to define the word).

Substance Use Risk Profile Scale

The Substance Use Risk Profile Scale (SURPS; Woicik, Stewart, Pihl, & Conrod, 2009) assesses personality traits that confer risk for substance misuse and psychopathology. This scale measures four distinct and independent personality dimensions; anxiety sensitivity, hopelessness, sensation seeking, and impulsivity. The anxiety sensitivity dimension is characterized by the fear of symptoms of physical arousal. The hopelessness dimension is identified as a risk factor for the development of depression and characterized by dismal feelings. The sensation seeking dimension is characterized by the desire for intense and novel experiences. The impulsivity dimension involves difficulties in the regulation (controlling) of behavioral responses.

Temperament and Character Inventory

The novelty-seeking scale of the Temperament and Character Inventory–Revised (TCI-R; Cloninger, 1999) was administered. The "Novelty Seeking" scale is composed of four subscales. "Exploratory Excitability" contrasts with "Stoic Rigidity," and reflects sensation-seeking and novelty-seeking behaviors. "Impulsiveness" describes behavior on a dimension from impulsivity to reflection and captures elements of emotional reactivity, and unreflective, careless behavior. The "Extravagance" subscale assesses overspending behavior and poor planning and is believed to reflect a tendency to approach reward cues. "Disorderliness" reflects disorganized, uncontrolled, and antinormative behavior.

Puberty Development Scale

The Puberty Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988) was used to assess the pubertal status of our adolescent sample. This scale provides an eight-item self-report measure of physical development based on the Tanner stages with separate forms for males and females. For this scale, there are five categories of pubertal status: (1) prepubertal, (2) beginning pubertal, (3) midpubertal, (4) advanced pubertal, (5) postpubertal. Participants answered questions about their growth in stature and pubic hair, as well as menarche in females and voice changes in males.

Monetary Incentive Delay task

Participants completed a modified version of the MID task, involving small and large possible gains. On each trial, the amount of points that could be won on that trial was signaled by a cue, displayed

for 4–4.5 sec. Participants could win a reward by responding as quickly as possible to a target stimulus presented after a random time interval, by means of a button press, after which feedback was presented. The response and feedback phase lasted a total of 2 sec. The response interval was dynamically adjusted so that subjects won on 66% of all trials. Trials were separated by a 3.5–4.15 sec inter-trial interval, during which a fixation cross was presented. The cue stimuli were a circle with two lines signaling a large reward (10 points), a circle with one line signaling a small reward (2 points), and a triangle signaling that no reward could be gained. 22 trials per condition were completed, resulting in 66 total trials. Task stimuli and timings are presented in Figure 1.

fMRI data acquisition

Full details of the magnetic resonance imaging (MRI) acquisition protocols and quality checks have been described previously, including an extensive period of standardization across MRI scanners (Schumann et al., 2010). MRI Acquisition Scanning was performed at the eight assessment sites with a 3T whole body MRI system made by several manufacturers (Siemens: four sites, Philips: two sites, General Electric: one site, and Bruker: one site). To ensure a comparison of MRI data acquired on these different scanners, we implemented image-acquisition techniques using a set of parameters compatible with all scanners that were held constant across sites, for example, those directly affecting image contrast or fMRI preprocessing. Standardized hardware for visual and auditory stimulus presentation (NordicNeurolabs, Bergen Norway, http://www.nordicneurolab.com) was used at all sites. BOLD functional images were acquired with a gradient-echo echoplanar imaging (EPI) sequence using a relatively short echo-time to optimize imaging of subcortical areas. For the MID, 300 volumes consisting of 40 slices were acquired for each subject. Scanning time for this task was a total of 11 minutes.

fMRI preprocessing and analysis

Briefly, the functional imaging processing was as follows: Time series data were first corrected for slice-timing, then corrected for movement, non-linearly warped onto Montreal Neurological Institute Coordinate System (MNI) space using a custom EPI template, and Gaussian-smoothed at 5 mm-full width half maximum. Nuisance variables were also added to the design matrix: estimated

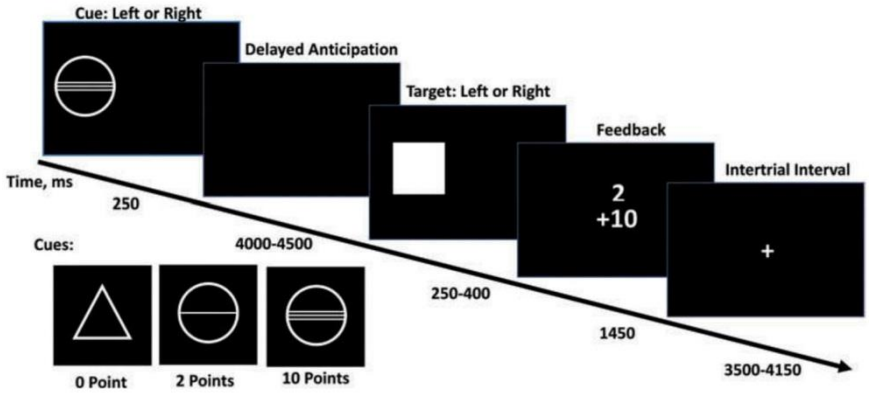

Figure 1. Stimuli and timings in the Monetary Incentive Delay (MID) task. Cues signaling the task condition (no reward, small reward, large reward) were displayed for 4–4.5 sec. The response and feedback phase lasted a total of 2 sec. Trials were separated by a 3.5–4.15 sec inter-trial interval.

movement was added in the form of six additional regressors (three translations, three rotations). These analysis steps were carried out in SPM8. All subsequent analyses were conducted in SPM12.

Three conditions (No-win, Small-win, Big-win) in addition to individual movement parameters were specified in a general linear model. An F contrast for effects of interest was conducted after model estimation. Subsequently, BOLD signals from 3-mm radius spherical regions of interest (ROIs) in the left ventral striatum (MNI coordinates: [−12, 10, −10]) and right ventral striatum (MNI coordinates: [12, 10, −10]) were adjusted by effects of interest and extracted. These extracted signal time series were used as the physiological regressors, and the effect of condition (Big-win versus No-win) was used as the psychological regressor. The PPI term was computed using the PPI toolbox in SPM12. For further details on the PPI analysis, see Supplementary Materials.

Functional connectivity during reward anticipation

A one-sample *t*-test to identify clusters in which functional connectivity for reward anticipation differed significantly from zero was conducted in SPM12. Data acquisition site, sex, and PDS were also entered into the analysis as nuisance covariates. The family-wise error ($p < .05$) was corrected for by using an uncorrected *p*-value of .001 in combination with a minimum cluster extent of 14 contiguous voxels, calculated using SPM.

Functional connectivity associated with smoking frequency

Data from 92 ROIs based on the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) and two masks for the subthalamic nuclei (x = −12, y = −10, z = −5; x = 12, y = −13, z = −5), as well as lifetime alcohol and cannabis use, data acquisition site, sex, and pubertal development status were entered into the analysis. Data were *z*-scored. The analysis procedure is shown in Figure 2. A similar approach has previously been used by Whelan et al. (2014) and Jollans et al. (2015). To assess the effect of lifetime smoking on VS connectivity, two ROI regularized multiple regression analyses for the left and right VS seed were carried out in Matlab R2014a, via the Elastic Net (Zou & Hastie, 2005). Regression with Elastic Net regularization is an example of a sparse regression method, which imposes a hybrid of both L1- and L2-norm penalties (i.e., penalties on the absolute (L1 norm) and squared values of the β weights (L2 norm)). This allows relevant but

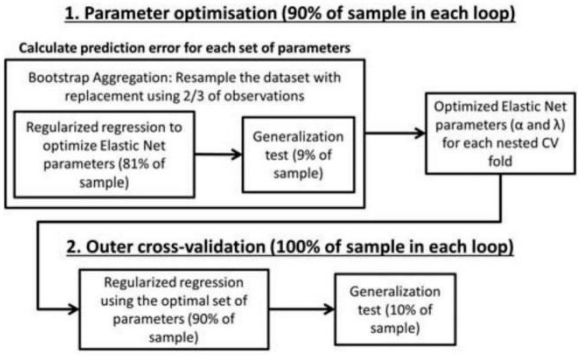

Figure 2. Machine learning analysis procedure. The machine learning analysis was carried out in two stages: (1) The optimal Elastic Net parameters for each main cross-validation (CV) fold were identified using nested CV within each main CV fold. Bootstrap aggregation was used in this step. (2) The optimal Elastic Net parameters for each main CV fold were applied to the full training set (90% of the data) to generate beta weights for all input variables. These beta weights were then used to generate outcome predictions for the remaining, untouched 10% of the dataset in each main CV fold. The goodness-of-fit was estimated using the outcome predictions for the entire dataset.

correlated coefficients to coexist in a sparse model fit, by doing automatic variable selection and continuous shrinkage simultaneously, and selects or rejects groups of correlated variables. Least absolute shrinkage and selection operator (LASSO, Tibshirani, 1996) and ridge regression (Hoerl & Kennard, 1970) are special cases of the Elastic Net.

We used 10-fold nested cross-validation, in which 10 separate regression models were generated, with the beta weights for all parameters being generated on 90% of the dataset (the training set), and tested on 10% of the dataset (the test set). Within the test set, additional 10-fold cross-validation was used to identify the optimal Elastic Net parameters α and λ. Alpha represents the weight of LASSO versus ridge regularization that the Elastic Net uses, and λ is the regularization coefficient.

We additionally applied 50-fold bootstrap aggregation to introduce an additional level of stability (Breiman, 1996). That is, parameter optimization was repeated 50 times, using sampling with replacement (i.e., on average two thirds of the data in each iteration). The results from all iterations within each training fold were then averaged. In addition to bootstrap aggregation this entire analysis procedure was repeated 50 times, and the results (correlation coefficients and beta weights) were averaged across all 50 iterations of the analysis procedure. Overall, this yielded 500 sets of beta weights, from 10 cross-validation folds across 50 analysis iterations. Beta weights were averaged for each variable.

Two null models were also computed using the same method. For these, the same analysis procedure was carried out using random label permutations with the same dataset (i.e., subjects were randomly assigned to ESPAD scores). These null models yielded average beta weights of 0.018 and 0.016, and average correlation coefficients of r = −0.006 and r = −0.01. Based on the null models, the threshold for reporting ROIs was set at a minimum absolute beta weight of 0.048 (this was the 95th percentile of the distribution of beta weights in the null models). The reporting thresholds for the minimum frequency with which ROIs should be included in the regression models across iterations was set at 84% (left) and 81% (right, this was the 95th percentile of the distribution of occurrence frequency across iterations in the null models).

Results

A series of Spearman's rank correlations were conducted (see Table 2). Using Bonferroni correction for multiple comparisons, lifetime smoking was significantly positively correlated with alcohol and cannabis use.

VS connectivity during reward anticipation

A number of cortical and subcortical clusters showed altered functional connectivity with the VS during anticipation of a large reward versus no reward. Clusters with significantly increased or decreased functional connectivity are reported in Table 3.

Changes in VS connectivity associated with lifetime smoking

There was a significant association between lifetime smoking and both right (mean r = .27) and left (mean r = .21) VS functional connectivity. ROIs that passed the thresholds for absolute beta weights and frequency of occurrence across cross-validation folds determined using the null models are reported (see Table 4 and Figure 3 for ROIs associated with lifetime smoking).

Discussion

A PPI analysis of a large (N = 206) sample of adolescent smokers has produced two key findings with respect to adolescent smoking frequency and functional connectivity with the VS during anticipation of rewards: (1) a positive association within the reward system; specifically, between the VS and OFC

Table 3. Clusters that showed significant changes in functional connectivity with the VS during anticipation of a large reward versus no reward.

x	y	z	k	max t	
Clusters with increased functional connectivity					
Left VS					
−6	−1	64	27	4.27	Supplemental Motor Area (L)
12	20	37	15	4.15	Middle Cingulum (R)
6	11	61	22	4.15	Supplemental Motor Area (R)
Right VS					
24	−70	−11	16	4.12	Fusiform Gyrus (R)
Clusters with decreased functional connectivity					
Left VS					
−30	−91	−11	138	7.30	Inferior Occipital Gyrus (L)
27	−94	1	105	6.24	Middle Occipital Gyrus (R)
−42	26	25	16	3.80	IFG, triangular part (L)
Right VS					
−27	−91	−11	68	6.00	Inferior Occipital Gyrus (L)
33	−88	−11	59	4.98	Inferior Occipital Gyrus (R)

Note. R = right; L = left; k = cluster extent; IFG = Inferior Frontal Gyrus.

Table 4. ROIs for which functional connectivity with the VS during anticipation of a large reward versus no reward was associated with lifetime nicotine use.

	Left VS		Right VS	
	Beta weight	% of CV folds	Beta weight	% of CV folds
Gyrus Rectus (R)	0.105	93.2	0.305	100
SFG, orbital part (R)			0.191	93.6
MFG, orbital part (L)			0.077	84.6
SFG, medial part (L)			−0.251	86.6
Olfactory gyrus (L)			−0.325	93.4
IFG, opercular part (R)			−0.176	92.4
IFG, orbital part (R)	−0.099	91.8		
Amygdala (R)			0.323	90.4
Thalamus (R)			0.150	89.6
Caudate (R)			0.076	81.2
Posterior Cingulate (L)			0.184	88.0
Posterior Cingulate (R)	0.238	88.6		
Precentral gyrus (R)			0.337	93.6
Supramarginal Gyrus (L)	0.381	84.8		
Supramarginal Gyrus (R)			−0.311	95.4
Angular Gyrus (R)			−0.138	89.6
Inferior parietal lobule (L)	−0.201	84.0		
Superior occipital gyrus (R)			−0.245	83.0
Lingual gyrus (L)			−0.100	82.6
Middle Temporal Pole (L)	−0.281	85.0		
Middle Temporal Pole (R)			−0.146	84.4
Superior Temporal Pole (R)			−0.204	96.0
Cerebellum (R)			−0.144	92.8

Note. ROI = region of interest; VS = ventral striatum; CV = cross-validation; R = right; L = left; SFG = Superior frontal gyrus; MFG = Middle frontal gyrus; IFG = Inferior Frontal Gyrus.

and amygdala, (2) a negative correlation between the reward system and inhibitory control and attention networks; specifically, between VS and the right IFG, inferior parietal cortex, and medial PFC (mPFC). We also found that smoking frequency was not significantly associated with measures of impulsivity or novelty-seeking, which is in line with previous studies that were not able to distinguish between adolescent smokers in different smoking trajectories on the basis of novelty-seeking or choice impulsivity (Audrain-McGovern et al., 2004a; 2009).

Smoking frequency was associated with an increase in connectivity between the OFC and VS. The VS can indirectly modulate frontal cortical activity, by means of the thalamus. However, the ACC, mPFC, and OFC also provide direct input to the VS (Cohen et al., 2012; Haber & Knutson, 2010).

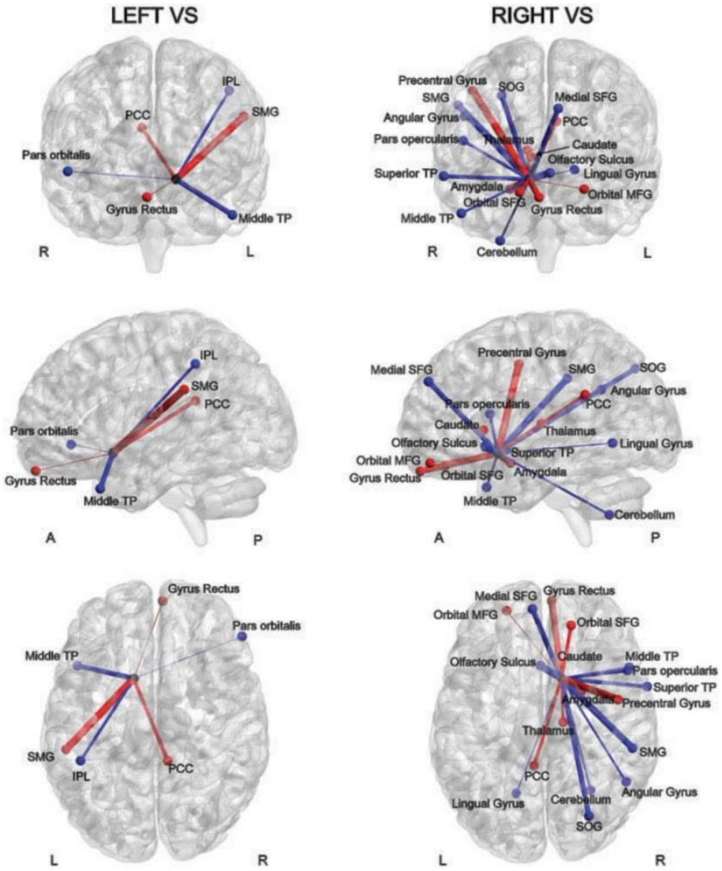

Figure 3. ROIs for which functional connectivity with the VS during anticipation of a large reward versus no reward was associated with lifetime smoking. *Note*. L = Left; R = Right; A = Anterior; P = Posterior; PCC = Posterior Cingulate; IPL = Inferior Parietal Lobule; TP = Temporal Pole; SMG = Supramarginal Gyrus; SOG = Superior Occipital Gyrus; SFG = Superior Frontal Gyrus; MFG = Middle Frontal Gyrus. Functional connectivity between the VS and nodes drawn in red was positively associated with smoking frequency. Functional connectivity between the VS and nodes drawn in blue was negatively associated with smoking frequency. This figure was generated using BrainNet Viewer (Xia, Wang, & He, 2013).

The OFC has previously been implicated in a study comparing occasional and dependent smokers (Bühler et al., 2010). This study found that dependent smokers exhibited significantly less orbitofrontal activation during anticipation of monetary rewards than occasional smokers, supporting our finding of altered function of this region associated with frequency of smoking. Interestingly, the same study also reported increased activity during reward anticipation in the right medial OFC and gyrus rectus in short-term abstinent compared to non-abstinent smokers, for monetary and cigarette rewards (Bühler et al., 2010). In line with the proposed role of the OFC in attribution of saliency and valuation (O'Doherty, 2004), our finding of increased striatal connectivity with these same medial orbitofrontal regions associated with smoking frequency suggests that adolescent smoking is associated with generalized increased reward valuation, similar to the pattern demonstrated during nicotine withdrawal by Bühler and colleagues.

Thalamus–VS connectivity was also positively associated with smoking frequency. The thalamus has been highlighted as an important region in incentive processing in adolescents and adults, along

with the insula (Cho et al., 2013). Cho et al. (2013) suggest that interoceptive information from the insula, and alerting signals about opportunities for incentive processing from the thalamus converge in the nucleus accumbens (NAc), which forms part of the VS. Considering findings of increased activation in the thalamus during reward anticipation in alcoholics (Wrase et al., 2007), our finding of increased connectivity between the VS and thalamus points toward a heightened sensitivity toward salient external stimuli. We also observed increased functional connectivity between the bilateral VS and the contralateral posterior cingulate cortex (PPC), associated with smoking frequency. A general role for the PPC in directing the focus of attention internally or externally, and in determining the width or breadth of the attentional focus has been proposed (Leech & Sharp, 2014), which is consistent with its role as a central node of the default-mode network (DMN, Buckner, Andrews-Hanna, & Schacter, 2008). In monkeys PPC activity was also found to be mediated by actual and expected reward value (McCoy, Crowley, Haghighian, Dean, & Platt, 2003), and in humans the PPC has been shown to play a role in integrating motivational information and spatial attention (Mohanty, Gitelman, Small, & Mesulam, 2008). Along with the OFC, the PPC showed heightened activation during motivationally salient cues in humans (Mohanty et al., 2008), which suggests that the heightened functional connectivity between the VS and PPC may reflect a similar effect of heightened attention to highly valued and motivationally salient events as the heightened connectivity with the OFC.

In line with previous research which found that smokers show less IFG activity than non-smokers to negative emotional images (Froeliger et al., 2013), we found that functional connectivity between the VS and right IFG was negatively associated with smoking frequency. The right IFG is a central region for response inhibition (Chikazoe et al., 2007; Jacobson et al., 2003) and attentional control (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). The right IFG can also be considered part of a ventral frontoparietal attention network, which further includes the inferior parietal cortex and supramarginal gyri (Corbetta, Patel, & Shulman, 2008). This network plays a role in attentional shifting and filtering sensory input according to behavioral relevance. We also observed a strong negative association between smoking frequency and VS connectivity to regions in the mPFC. Studies of patients with lesions to the mPFC have shown that this region is involved in decision making under risk, biasing healthy individuals toward more conservative choices (Clark et al., 2008). Taken together with the finding of increased connectivity between the VS and OFC, the deficit in right IFG, inferior parietal (and superior occipital) cortex, and mPFC connectivity is consistent with the imbalance model's account of an over-active motivational system, receiving heightened input from regions central in the valuation of stimuli, and not being reigned in sufficiently by an under-active inhibitory control system and a deficit in directing attention toward behaviorally relevant stimuli.

In addition to the aforementioned ROIs, we also observed a significant association between smoking frequency and functional connectivity between the VS and the amygdala. Connectivity between the right VS and the right amygdala has been found to be associated with the relevance of stimuli (Ousdal, Reckless, Server, Andreassen, & Jensen, 2012). This is consistent with our findings of higher VS connectivity to regions associated with salience and valuation of stimuli. VS connectivity to the adjacent bilateral temporal poles on the other hand showed a strong negative association with smoking frequency. A previous study found that adult smokers' level of nicotine dependence was positively associated with activation in the temporal pole and insula during presentation of smoking compared to food cues (Claus et al., 2013). While the majority of studies examining temporal pole function have focused on social cognition and emotion processing, there is some evidence that the temporal pole could serve as a hub integrating emotional and sensory cues (Fan et al., 2014; Olson, Plotzker, & Ezzyat, 2007; Pehr et al., 2015). Furthermore, reduced grey matter volume in the temporal pole has been reported in cocaine users (Albein-Urios et al., 2013), making this region a promising target for further investigation in substance use.

While PPI analysis is a valuable tool for identifying functional differences in connectivity, it is not able to identify anatomical or structural alterations in connectivity. Conducting PPI in conjunction

with tractography (e.g., Cohen, Elger, & Weber, 2008) would allow the identification of structural differences associated with functional connectivity alterations in smokers. Furthermore, PPI analyses often suffer from a lack of power, particularly when event-related tasks are used (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). However, low power is a chronic problem in neuroimaging research (Button et al., 2013). In this study we addressed this issue by using a large sample, and a very rigorous analysis protocol. Cross-validation and bootstrapping are valuable tools for guarding against false positives (Whelan & Garavan, 2014) and identifying true, but small, effects. In addition, the random label permutation (null model) approach that we adopted is an effective means of quantifying the validity of our results.

In conclusion, the use of a PPI analysis in conjunction with a robust machine learning approach identified differences in VS connectivity during reward anticipation associated with adolescent smoking frequency. The increased functional connectivity between the VS and OFC and PPC with increased cigarette use suggests that adolescent smoking may be associated with increased attribution of salience to reward-related stimuli. Furthermore, the finding of reduced functional connectivity between the VS and the right IFG, mPFC, and inferior parietal cortex with increased smoking indicates a deficit in inhibitory control and attentional orienting. Taken together, these findings paint a picture of increased valuation of rewards, alongside difficulties inhibiting behavior, and possibly a deficit in the integration of sensory and motivational cues in adolescent smokers. Notably, our findings extend the literature showing differences in the neural networks underpinning reward processing between adolescent smokers and non-smokers, showing that reward processing also differs between different adolescent smoking trajectories. While it is not possible to deduce whether these differences in VS connectivity preceded smoking initiation, the link between reward-related activity in the VS and adolescent impulsivity supports the conclusion that differences in VS connectivity may pose a risk for adolescent smoking. Future longitudinal studies should evaluate whether VS connectivity can be established as a predictive biomarker of substance use risk in adolescence.

Confict-of-interest statement

Dr. Banaschewski has served as an advisor or consultant to Bristol-Myers Squibb, Desitin Arzneimittel, Eli Lilly, Medice, Novartis, Pfizer, Shire, UCB, and Vifor Pharma; he has received conference attendance support, conference support, or speaking fees from Eli Lilly, Janssen McNeil, Medice, Novartis, Shire, and UCB; and he is involved in clinical trials conducted by Eli Lilly, Novartis, and Shire; the present work is unrelated to these relationships. Dr. Gallinat has received research funding from the German Federal Ministry of Education and Research, AstraZeneca, Eli Lilly, Janssen-Cilag, and Bristol-Myers Squibb; he has received speaking fees from AstraZeneca, Janssen-Cilag, and Bristol-Myers Squibb. The other authors report no biomedical financial interests or potential conflicts of interest.

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Appendix D.4. Journal paper investigating EEG signal corresponding to elements of computational models of the Iowa Gambling Task.

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Research report

Computational EEG modelling of decision making under ambiguity reveals spatio-temporal dynamics of outcome evaluation

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HIGHLIGHTS

- Complex human cognition is reflected in dynamic spatio-temporal activity.
- We combined event-related potentials with computational modelling.
- A general linear model created a three-dimensional map of neural dynamics.

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ABSTRACT

Complex human cognition, such as decision-making under ambiguity, is reflected in dynamic spatio-temporal activity in the brain. Here, we combined event-related potentials with computational modelling of the time course of decision-making and outcome evaluation during the Iowa Gambling Task. Measures of choice probability generated using the Prospect Valence Learning Delta (PVL-Delta) model, in addition to objective trial outcomes (outcome magnitude and valence), were applied as regressors in a general linear model of the EEG signal. The resulting three-dimensional spatio-temporal characterization of task-related neural dynamics demonstrated that outcome valence, outcome magnitude, and PVL-Delta choice probability were expressed in distinctly separate event related potentials. Our findings showed that the P3 component was associated with an experience-based measure of outcome expectancy.

1. Introduction

The Iowa Gambling Task (IGT; [1] is a popular measure of decision making under ambiguous conditions. The IGT is an experience-based partial information paradigm that involves participants choosing among four decks of cards. Each deck yields an average monetary (or point) win and loss, with two of the four decks yielding a net gain over multiple trials (advantageous/good decks), and the other two decks yielding a net loss (disadvantageous/bad decks). Of the advantageous and disadvantageous decks respectively one deck results in less frequent but larger losses than the other deck. The participants' goal is to maximize monetary or point gain after 100 trials. Advantageous performance on the IGT is therefore based on approximations of long-term consequences rather than exact calculations [2], and choice behaviour typically shifts across trials as participants learn to make more advantageous selections with increasing knowledge of the outcome contingencies [3].

The structure of the IGT allows for the examination of a number of questions relating to decision-making, including the role of memory, value updating, economic outcomes, and long-term calculations in choice selection [4]. As well as extensive research with healthy populations, decision-making deficits have been examined in a number of clinical populations using the IGT, including patients with frontal lobe damage [5], pathological gamblers [6], and people with schizophrenia [7]. Decision-making behaviour during the IGT is well suited to studying how task outcomes and prediction

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errors (i.e. unexpected outcomes) guide future behaviour, and has become a popular subject of reinforcement learning and heuristic computational models (e.g. [8–12,42,43]. These models consider factors such as the attention given to outcome valence (i.e., to wins vs. losses), how the recency of feedback affects future decisions, and how choices are influenced by experience (i.e., to what extent choices are random). Such parameter values have been used to examine how populations differ in terms of their decision-making processes [13,14].

One of the earliest models of choice behaviour in the IGT was the Expectancy Valence (EV) model [8]. However, this model often shows inadequate fit, and is consistently outperformed by other reinforcement-learning models such as the Prospect Valence Learning (PVL) Model [10]. The PVL-Delta model [9–11], a hybrid model combining elements of the EV and PVL models generates less accurate one step ahead predictions than the PVL model [15], but shows better simulation performance than other models [9]. Furthermore, the PVL-Delta model is able to account for most empirical choice patterns which tend to be observed in healthy decision makers [16,17]. This lends support to inferences about psychological processes underlying decision-making which are based on this model [18,40].

The nature of the IGT has also made it a target for neuroimaging studies investigating the neural underpinnings of adaptive decision-making [2,19]. While there is a large body of work investigating reinforcement learning using EEG (e.g. [20], the IGT has almost exclusively been examined using fMRI. Functional MRI offers greater spatial resolution, but the high temporal resolution of event-related potentials (ERPs) extracted from the ongoing EEG signal is conducive to an examination of the temporal dynamics of decision-making. Indeed, ERPs associated with the anticipation and processing of wins and losses are sensitive to a number of parameters relevant to computational modelling of decision-making such as the valence, magnitude, and likelihood of the outcome [21–26]. However, EEG studies of feedback learning typically contrast average ERPs over different trial types (e.g., [27] rather than modelling values on a trial-by-trial basis (see Larsen and O' Doherty [41]; for an exception). Evaluating ERPs on a trial-by-trial basis makes it possible to capture outcome expectation and response to prediction error, thus permitting a more detailed analysis of the neural dynamics underlying complex decision-making.

In this study we used the PVL-Delta model to approximate participants' subjective appraisal of their chosen deck and prediction errors. We then applied this subjective evaluation component as a trial-by-trial regressor to each participant's EEG data with the goal of identifying elements in the ERP that are ostensibly associated with subjective outcome appraisal. We further evaluated whether this subjective element of outcome evaluation is associated with two ERPs which are well established markers of prediction error and choice evaluation: the Feedback related negativity (FRN) and the P3 potential. Our objective was to identify subjective components of decision making under ambiguity, and to identify if and how their neural signature differs from that of absolute task outcomes and trial characteristics. This analysis may therefore provide insight into the nature and time course of the interplay between key cognitive processes and task experience during decision making.

2. Materials and methods

2.1. Participants

Twenty healthy, right-handed adults (9 female), 19–38 years old (mean age = 24.9 years, *SD* = 4.8 years) participated and were reimbursed with £10 that was not contingent on performance. The Department of Psychology Ethics Committee, Swansea University, approved all procedures. One participant was excluded due to insufficient EEG data quality.

2.2. Iowa gambling task

We used a computerized variant of the original IGT [1] in which participants were instructed to select cards from four concurrently available decks (labeled A, B, C and D). Deck locations were randomly varied across participants. Trials were preceded by a 2 s choice appraisal interval, during which choices could not be made, as the four individual decks and the text, "Please consider your choice" appeared on screen. After this, choices were made using the mouse (the cursor was centred at the start of every trial). An initial 'loan' of £1000 virtual money, displayed at the bottom of the screen, was updated immediately following choices accompanied by text stating the amount of money gained and/or lost. Decks A and B (termed 'disadvantageous') resulted in long-term loss (£250 loss per 10 trials), whereas decks C and D (termed 'advantageous') resulted in long-term gain (£250 gain per 10 trials). Participants always won £100 if they selected a card from the disadvantageous decks, and £50 if they selected a card from the advantageous decks. Losses varied between £150 and £350 for deck A; £1250 for deck B; £25 to £75 for deck C; and £250 for deck D. Decks A and C resulted in frequent losses (on 50% of trials), whereas decks B and D resulted in infrequent losses (on 10% of trials). Onscreen feedback was displayed for 10 s, before a 2-s inter-trial interval. The task ended after 100 trials. After every block of 20 choices, subjective awareness ratings were made of the relative "goodness" or "badness" of each deck [28,29] using a slider-scale from 0 ('*very bad*') to 10 ('*very good*').

2.3. Behavioural performance during the IGT

The effect of task block on awareness ratings, selection of advantageous vs. disadvantageous decks, and selection of frequent vs. infrequent loss decks was investigated using a chi squared goodness-of-fit tests and a series of one-way repeated ANOVA. Furthermore, two Pearson's correlations were carried out between the number of choices from advantageous and disadvantageous decks over each of the five task blocks and subjective awareness ratings.

2.4. The PVL-Delta model

The deck chosen on trial t is denoted $D(t)$. The reward received on each trial is denoted $R(t)$, and the loss on each trial is denoted $L(t)$, such that if deck D_3 (a disadvantageous deck) was chosen on trial $t = 9$ (i.e. $D(9) = D_3$) then $R(9) =$ £100 and $L(9) =$ £1250. The absolute monetary outcome on each trial is denoted $X(t)$.

An approximation of the subjective valence $u(t)$ on trial t is calculated using the prospect utility function, based on $X(t)$.

$$u(t) = \begin{cases} X(t)^{\alpha} & \text{if } X(t) \geq 0 \\ = -\lambda * |X(t)|^{\alpha} & \text{if } X(t) < 0 \end{cases} \quad (1)$$

Subjective valence is calculated using a shape parameter α, and a loss aversion parameter λ.

The subjective valence value is then used to calculate the expected valence $Ev(t+1)_j$ for the selected deck j on the following trial.

$$Ev_j(t+1) = Ev_j(t) + \phi * \left(u(t) - Ev_j(t)\right) \quad (2)$$

Ev is calculated using the delta learning rule, which includes the recency parameter ϕ.

$$\theta(t) = 3^c - 1 \quad (3)$$

Finally, the probability $Pr[D(t+1) = j]$ that deck j will be selected on the next trial is calculated using a Softmax action-selection rule

in conjunction with a trial-independent sensitivity function, which includes the consistency parameter c quantifying to what extent participants make choices in accordance with the expected valence for each deck.

$$Pr\left[D\left(t+1\right)=j\right]=\frac{e^{\theta(t)Ev_j(t)}}{\sum_{k=1}^{4}e^{\theta(t)Ev_k(t)}} \quad (4)$$

2.5. Model fitting

The hBayesDM package [30] was used to fit the PVL Delta, model. hBayesDM is an R package which uses hierarchical Bayesian analysis to fit computational models of reinforcement learning and decision making. The package utilizes a Markov Chain Monte Carlo (MCMC) sampling scheme to perform posterior inference. For each model parameter we used three MCMC chains, which were run simultaneously. Convergence of the MCMC chains was assessed visually, as well as using the $\hat{R}$ statistic [31]. $\hat{R}$ values close to 1.0 indicate that all chains have converged successfully to their stationary distributions, whereas values above 1.1 indicate inadequate convergence. We initialized MCMC chains randomly, and collected 1000 samples as well as 9000 burn-in samples. As the hBayesDM package did not include the modality of extracting model regressors, we employed a custom Matlab script (Supplementary materials), which calculated post hoc model fit for each participant using the parameters determined using hBayesDM.

As suggested by Steingroever et al. [18] we assessed the performance of the model when making predictions for the next trial based on previous choices (post-hoc fit) as well as the performance of the model when making predictions about choice behaviour without information about previous deck selections (simulation).

Based on one-step-ahead predictions the PVL-Delta model did not perform better than chance for either all deck predictions, or for both good vs. bad deck and frequent vs. infrequent loss deck predictions for five participants. The analysis of EEG data was therefore carried out both with the full sample (n = 19), and with only the participants for which the PVL-Delta model outperformed a baseline model (n = 14), and only findings which remained significant in the reduced sample are reported.

To evaluate whether the choice probability value captured an element of subjective awareness of deck contingencies two Pearson's correlations were carried out between the mean choice probability assigned to advantageous and disadvantageous decks over each of the five task blocks and subjective awareness ratings.

2.6. EEG acquisition and analysis

2.6.1. EEG recording

EEG data were recorded in a soundproofed room using the ActiveTwo Biosemi™ electrode system from 134 electrodes (128 scalp electrodes) organized according to the 10-5 system [32], digitized at 512 Hz.

2.6.2. EEG analysis

EEG preprocessing and artifact rejection was performed using the Fully Automated Statistical Thresholding for EEG artifact Rejection toolbox (FASTER; http://sourceforge.net/projects/faster [33], implemented in EEGLAB [34] under Matlab 7.12. EEG data were filtered (1–95 Hz, with a notch filter at 50 Hz). Epoch length was initially set to −3 s to 2 s for the choice appraisal interval (marker set to onset of appraisal interval) and the outcome evaluation phase (marker set to onset of outcome). EEG data from one participant was excluded due to poor data quality.

EEG data were processed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Data from each participant were transformed into two-dimensional sensor-space (interpolated from the 128 scalp channels), over *peri*-stimulus times from −100–600 ms for the feedback processing phase, thus producing a three-dimensional spatio-temporal characterization of the ERP. Baseline was corrected from 100 ms before cue presentation. The EEG timeseries data were subsequently parcellated based on both spatial and temporal domains. Data were averaged in 64 spatial bins, and across time segments of 25.4 ms (resulting in 23 time bins in the outcome phase).

2.6.3. Outcome measures

For each participant, three variables were used as regressors in a GLM with the parcellated outcome data from the same trials: the valence (whether there was a net win or loss) and the absolute magnitude of the outcome (objective outcome measures), and the trial-by-trial choice probability for the selected deck calculated using the PVL-Delta model. The temporal and spatial properties of associations between regressors and the EEG timecourse across the whole outcome interval were examined. Associations between valence, magnitude and choice probability and two ERP components that consistently occur following feedback, the FRN and the P3, were examined.

2.6.4. Significance testing

A linear regression was carried out for each regressor individually. This resulted in a beta weight being generated for each regressor and each bin. The same calculations were also carried out using a random permutation of the model regressors (i.e. the values of each regressor were shuffled), which resulted in a baseline, or 'null' distribution. For each regressor and each of the bins a one-sample t-test was carried out using the beta values for each participant, as well as the beta values from the random label permutations. For each regressor the bins in which the test statistic was larger than the 95th percentile of the distribution of test statistic values for the beta weights generated using random label permutations were deemed significantly associated with the regressor.

3. Results

3.1. Behavioural data and awareness ratings

The mean number of times advantageous (C and D) and disadvantageous decks (A and B), as well as frequent (A and C) and infrequent (B and D) loss decks were selected per block of 20 trials was calculated for each participant. Task choices for good (advantageous) and bad (disadvantageous) decks across task blocks are presented in the left panel of Fig. 1. Task choices for all four decks across task blocks are presented in the left panel of Fig. 2.

The chi-square statistic was calculated for each task block to examine whether there were significant deck preferences. The test was found to be statistically significant ($p < 0.01$) in every task block (see Supplementary Table 1). The results indicate that the percentage of choices from deck B (a disadvantageous deck with infrequent losses) was higher in all task blocks than expected. From the third task block onward choices from deck D (i.e., an advantageous deck with infrequent losses) were also higher than expected, and in the final task block only deck A (i.e., a disadvantageous deck with frequent losses) was chosen less frequently than expected.

Two, one-way, repeated ANOVA found a significant ($p < 0.025$) effect of task block on awareness ratings for disadvantageous decks ($F = 12.21$, $df = 2.5$, $p < 0.001$, $\eta_p^2 = 0.404$; see middle panel, Fig. 1) but not for advantageous decks ($F = 1.72$, $df = 1.8$, $p = 0.197$, $\eta_p^2 = 0.087$). The number of choices was also only significantly associated with deck ratings for disadvantageous decks (see Table 1).

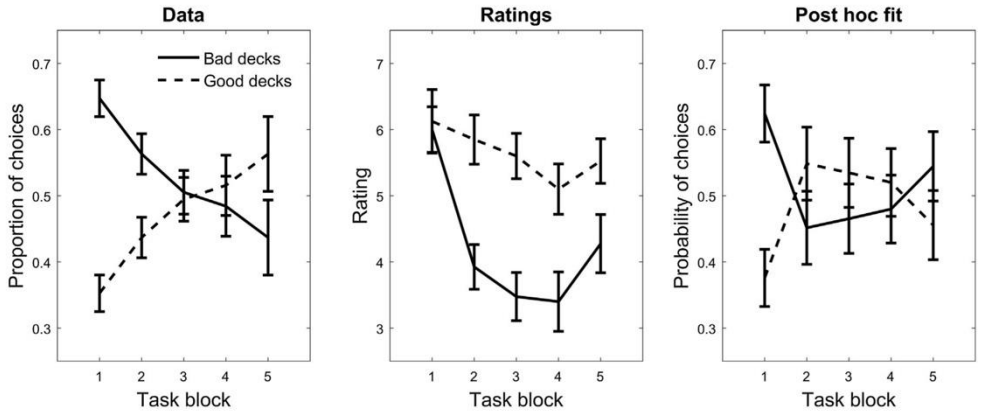

Fig. 1. Deck choice frequency, subjective awareness ratings, and PVL-Delta model choice probability (i.e. post hoc fit) for advantageous and disadvantageous decks. Error bars represent the standard error of the mean.

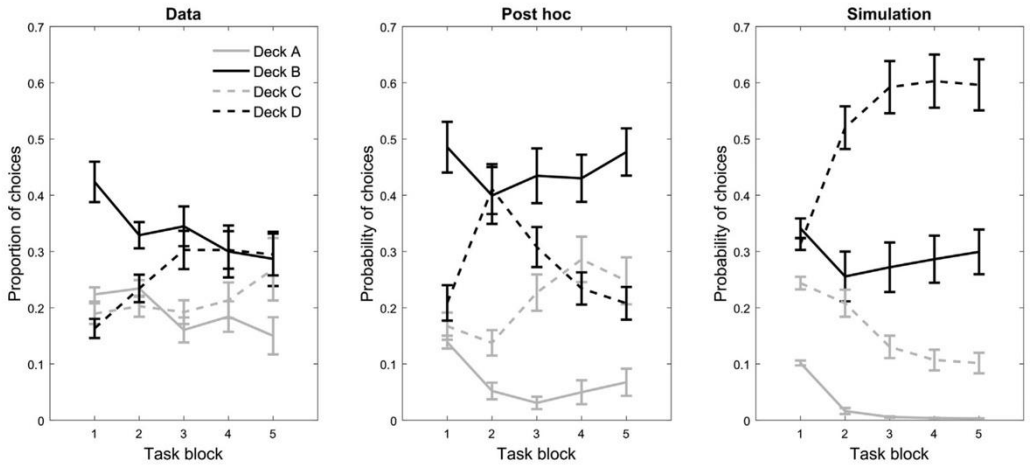

Fig. 2. Deck choice frequency, PVL-Delta model post hoc fit (i.e. choice probability), and simulation performance for all decks. Error bars represent the standard error of the mean.

Table 1
Speaman's rank correlations between choices, post hoc fit, and deck ratings for advantageous (good) and disadvantageous (bad) decks across task blocks (p values in brackets).

	Post hoc fit		Ratings	
	Good decks	Bad decks	Good decks	Bad decks
Choices	0.058 (0.58)	0.058 (0.58)	0.150 (0.17)	0.246 (0.01)
Ratings	0.209 (0.04)	0.141 (0.17)		

3.2. PVL-Delta model fit

The one-step-ahead predictions of the PVL-Delta model correctly predicted whether a good or bad deck would be selected 51.36% of the time, whether a frequent or infrequent loss deck would be selected 61.35% of the time, and which of the four decks would be selected 34.82% of the time. Both post hoc fit and simulation performance were best for decks A and D (see Fig. 2).

A series of Spearman's rank correlations revealed that post hoc fit averaged within task blocks (i.e. Pr) was not significantly associated with number of deck choices for good and bad decks ($r.058 = 0.058$, $p = 0.57$), or for frequent and infrequent loss decks ($r = -0.011$, $p = 0.91$). Post hoc fit was also not significantly ($p < 0.008$) associated with awareness ratings for good or bad decks (see Table 1).

The distribution of the optimal values for each parameter from the PVL-Delta model across all participants is reported in Supplementary Table 2.

3.3. Associations between outcome measures and the EEG timecourse

Of the 1472 (64 spatial by 23 temporal) bins, 148 bins (10.05%) showed a significant association with at least one of the regressors, with almost all (140 bins, 9.51%) uniquely associated with one

Table 2
Percentage of all 1472 bins that were significantly associated with each regressor.

Regressor	Bins associated with the regressor (%)	Bins uniquely associated with regressor (%)
Outcome magnitude	2.04	1.63
Outcome valence	7.61	7.07
PVL-Delta Choice Probability	0.95	0.82

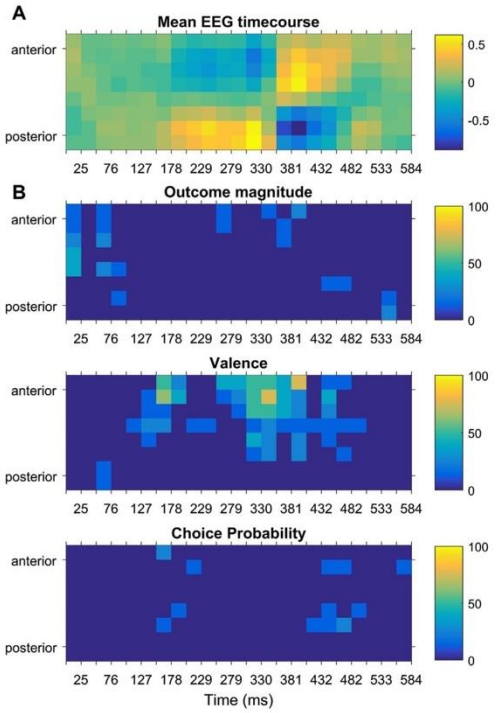

Fig. 3. (A) ERPs in each temporal bin from anterior to posterior, averaged over left and right. (B) Percentage of spatial bins from left to right in which each regressor (outcome magnitude, valence, and choice probability) was significantly associated with the ERP in each time bin at each of eight spatial locations from anterior to posterior.

regressor. Eight bins (0.54%) were associated with two regressors, and no bins were associated with all three regressors. The number of bins each regressor was significantly associated with is presented in Table 2 (see also Supplementary Table 3 for all bins which were significantly associated with a regressor).

3.4. Bins associated with objective task outcomes

ERPs associated with outcome magnitude occurred most strongly in the first 76 ms after feedback presentation (see Fig. 3B). Magnitude also showed some association with the ERP between 254 ms and 558 ms after feedback.

Valence was significantly associated with the ERP throughout most of the outcome processing interval, up to approximately 500 ms after feedback presentation (see Fig. 3B). The largest cluster of ERP activity associated with valence occurred between approximately 250 ms and 500 ms after feedback in a left anterior location. During this interval, there was also a large cluster of activation in a right central location which was associated with valence. Similar clusters previously showed associations with valence between about 100 ms and 250 ms.

The ERP in 6 bins was significantly associated with both magnitude and valence, with most of these associations occurring between about 330 ms and 480 ms after feedback presentation (Supplementary Table 3).

3.5. Bins associated with PVL-Delta choice probability

Associations between choice probability and the ERP occurred in a number of left anterior and central midline locations. Choice probability was associated with the ERP between about 150 ms and 230 ms after feedback presentation, as well as from approximately 400 ms after feedback until the end of the feedback interval (see Fig. 3B). The largest cluster of activation associated with choice probability occurred between about 400 ms and 480 ms in a central/posterior midline location.

3.6. Bins associated with objective variables and PVL-Delta choice probability

Choice probability and valence were significantly associated with the ERP between about 150 ms and 180 ms after feedback presentation in a left anterior location (Supplementary Table 3).

3.7. Associations between outcome measures and predefined ERPs

3.7.1. Feedback related negativity (FRN)

Based on the observed EEG signal (Fig. 3A) the FRN was defined as the interval between 178 ms and 355 ms. During the FRN time interval, choice probability was associated with 2 bins, valence was associated with 54 bins, and outcome magnitude was associated with 3 bins of which one was shared by valence (Fig. 4A).

3.7.2. P3

Based on the observed EEG signal (Fig. 3A), the P3 was defined as the interval between 355 ms and 482 ms. During the P3 time interval, choice probability was associated with 8 bins, valence was associated with 86 bins, and outcome magnitude was associated with 9 bins of which 6 were shared by valence (Fig. 4B).

4. Discussion

We used a computational model approach of decision making during the IGT to reveal for the first time the electrophysiological dynamics of feedback processing in a spatio-temporal characterization of the ERP. The choice patterns generated using the PVL-Delta model and the best-fit parameters for each participant mapped closely onto choice frequency for decks A and D. The trial-by-trial values for choice probability calculated by the PVL-Delta model were subsequently used as regressors in a GLM of the EEG timecourse during the feedback processing interval alongside outcome valence and outcome magnitude. This revealed that the ERPs associated with subjective choice probability do not overlap with the time interval of the FRN, which is generally considered to be associated with prediction error. However, in line with previous findings, subjective choice probability was associated with the ERP during the P3 time interval.

Across the entire outcome interval, valence was significantly associated with more than four times as many spatiotemporal bins of the ERP as the other model regressors. The PVL-Delta model choice probability variable was uniquely associated with 12 spatiotemporal bins. There was surprisingly little overlap between spatiotemporal bins associated with particular regressors, with

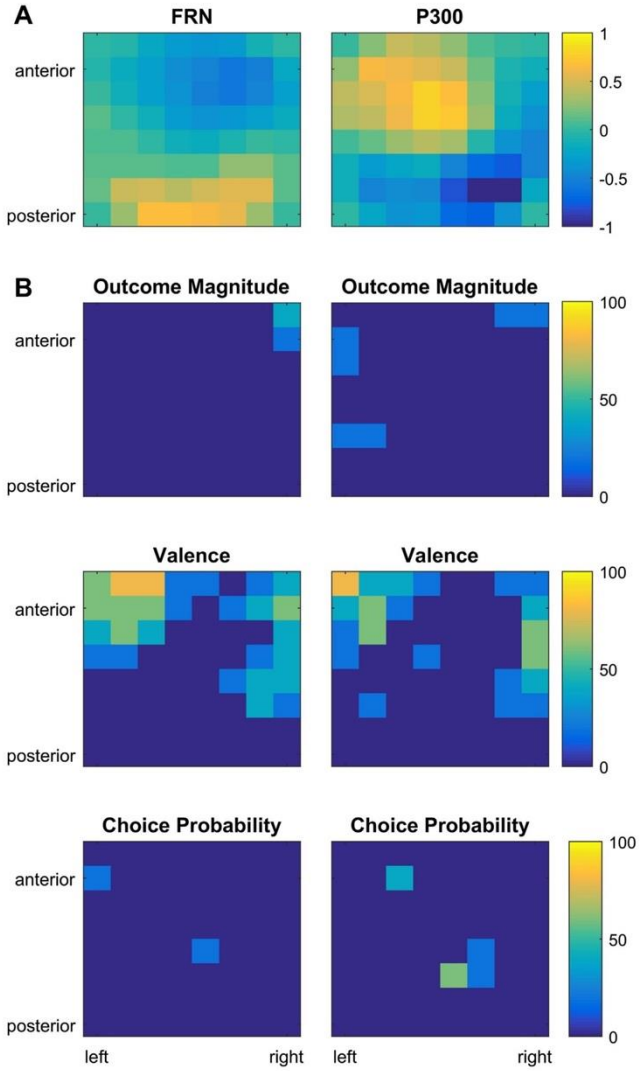

Fig. 4. (A) Feedback Related Negativity (FRN) ERP component with activation averaged across the FRN timecourse (178 ms after feedback to 355 ms after feedback), with percentage of time bins during the FRN time interval for which each regressor (outcome magnitude, valence, and choice probability) was significantly associated with the ERP. (B) P300 ERP component with activation averaged across the P3 timecourse (355 ms after feedback to 482 ms after feedback), with percentage of time bins during the P3 time interval for which each regressor (outcome magnitude, valence, and choice probability) was significantly associated with the ERP.

only eight bins in total showing significant associations with more than one regressor. This indicates that the three elements of feedback processing evaluated here (outcome valence, outcome magnitude, and subjective outcome expectations) show distinctly different temporal properties in terms of their expression in the ERP.

Past research has found that the FRN is associated with outcome valence [35,27], whereas the P3 appears not to be associated with valence [35]. This clear dissociation between the FRN and P3 is inconsistent with our findings relating to the expression of valence in the ERP. Valence was strongly associated with the ERP between 250 ms and 500 ms after feedback presentation, which includes both a late component of the FRN, as well as the P3 ERP. Outcome magnitude showed only a small number of significant associations with the EEG timecourse across the entire outcome interval. While there were some significant association between outcome magnitude and both the FRN and the P3, the quantity of these associations was much smaller than those observed for valence. While previous research suggests that the P3 is sensitive to magnitude [35], there have been conflicting findings with regard to the effect of magni-

tude on the FRN. A recent meta-analysis suggested that the FRN does show a strong main effect of reward magnitude [20], while other studies suggest that the FRN is not associated with magnitude [35,27,36].

The choice probability value generated using the PVL-Delta model had, compared to valence, a relatively weak association with the ERP during the FRN time interval. The FRN is thought to be related to the probability of an outcome. For example, Holroyd and colleagues [21] have proposed that the FRN is a manifestation of an evaluative process which reflects the degree to which the experienced outcome was better or worse than expected. This so-called 'prediction error' signal is context dependent, and depends on which task dimension is made salient to the participant Nieuwenhuis et al. [44]. In line with this hypothesis, Fuentemilla et al. [26] found that FRN amplitude differed between task blocks in which outcome probabilities were manipulated, reaching a maximum when rewards were highly improbable. The FRN can be thought of as reflecting a reappraisal or updating of expectations about future task outcomes [22]. Fuentemilla and colleagues [26] also investigated to what extent an estimation of subjective outcome expectations incorporating a measure of learning from past trials is associated with the same components of the ERP as simple outcome probabilities. Mirroring previous findings by Mars et al. [37], Fuentemilla et al. observed that the magnitude of the P3 ERP increased with the subjective unexpectedness of the task outcome. While these studies used simple stimulus response tasks, our finding shows that a measure of 'subjective' expectedness of an outcome is also associated with the P3 ERP in more complicated decision situations. Interestingly, Fuentemilla et al. [26] also observed that variations in P3 amplitude were associated with individual differences in risk attitudes. In the context of the IGT a similar effect may have occurred whereby risky deck choices (i.e. deck selections where the associated choice probability value was comparatively low) were associated with higher P3 amplitudes. Overall, the finding of an association between the P3 and PVL-Delta choice probability supports a theory of the P3 as reflecting decision formation, incorporating awareness of a mistake having been made [38].

In conclusion, the present study used a well-validated model of choice behaviour in the IGT to map the spatiotemporal expression of subjective choice certainty in the ERP during outcome processing. This revealed that participants' subjective choice valuations were associated with the P3, expanding our understanding of how the P3 relates to decision-making and outcome evaluation. The degree to which objective measures of trial feedback such as outcome valence and magnitude are reflected in the well-established P3 component warrants further investigation. Our participants made choices for hypothetical rewards, which behavioural findings show, are like those on tasks presenting real rewards [39]. However, using hypothetical task outcomes may have resulted in a decrease in model fit; thus, an extension to money-earning variant IGTs may be helpful. It should also be noted that the choice probability values generated by the PVL-Delta model were not significantly correlated with awareness ratings. A replication of our EEG and computational modelling approach utilizing a larger sample, and seeking to predict trial-by-trial choices based on EEG data, would lend additional support to our conclusions and further elucidate the neural dynamics of complex choice behaviour.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2016.12.033.

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