Examining the Relationship Between Alcohol and Multiple Impulsivity Endophenotypes

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Declaration

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This thesis is dedicated to my Mom & Dad.

Summary

Alcohol misuse is a leading global health concern, and its occurrence is rising among adolescents and young adults. Associations between different aspects of impulsivity and alcohol-related outcomes have been the focus of much research, yet precise relations remain elusive. Machine learning (ML) can harness large complex data by examining statistical relationships between variables that span across domains (brain, behaviour and traits) of impulsivity to predict different patterns of alcohol use.

Chapter 2 explored the potential predictive utility of self-report and task-based impulsivity endophenotypes for identifying individual differences in two orthogonal latent factors of alcohol use - alcohol intoxication and consumption frequency. Machine-learning with penalised regression was used to generate the model, and out-of-sample validation quantified model performance. Results indicated self-report and task-based impulsivity significantly predicted alcohol intoxication frequency but not consumption frequency. Elevated trait impulsivity (attentional, non-planning, disinhibition, and experience seeking), choice impulsivity (delay discounting), and cognitive impulsivity (sustained attention), but not motor impulsivity (inhibitory control), supported a tendency toward more frequent intoxication.

Extending these findings, *Chapter 3* applied a novel machine-learning method with penalised regression to ERP data indexing inhibitory control, and with other risk factor variables, to predict alcohol use. Results showed that inhibitory control ERPs can robustly predict individual differences in alcohol use.

One aspect of cognitive impulsivity – lapses in sustained attention – emerged as an important predictor of alcohol misuse. Although extensively examined in relation to

ADHD, the brain correlates of sustained attention in healthy adolescents had not yet been comprehensively characterised. *Chapter 4* is the largest population-based functional imaging study to date, to examine both average fMRI activity and functional connectivity as it relates to sustained attention in healthy adolescents. The findings indicated that sustained attentional processes are facilitated by an array of neural networks, including cerebellar crus I/II with motor, prefrontal and occipital cortices. Atypically strong connectivity within motor network was a signature of poor sustained attention, a finding that was also observed in a separate sample of adolescents exhibiting elevated ADHD symptoms, compared to asymptomatic adolescents. No significant brain connectivity correlates of alcohol use were identified in this relatively substance-naïve young adolescent cohort.

Overall, the findings support the view that different impulsivity endophenotypes contribute to different patterns of alcohol misuse. Machine learning is a useful method for analysing large amounts of data and it provides more nuanced insights into the relationship between alcohol use and psychological characteristics such as impulsivity. The EEG findings gleaned from *Chapter 3* underscore the potential ERPs can offer for improving objective screening and assessment of alcohol misuse. Functional connections spanning an array of brain networks also appear to underlie cognitive impulsivity, via sustained attention. Combining neuroimaging with other data modalities offers a possibility to bridge levels of analysis, linking neural phenotype and behaviour in understanding alcohol misuse. Ultimately, a *multivariate endophenotype*, based on a weighted combination of diverse variables, including brain, personality and psychological factors, may provide an increased power and greater predictive accuracy than any single endophenotype.

Published Work

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List of Abbreviations

Sx-5CRTT:	Five-Choice Serial Reaction Time Task
ACC	Anterior Cingulate Cortex
ADHD	Attention Deficit Hyperactivity Disorder
APA	American Psychiatric Association
API	Alcohol Problems Index
AU	Alcohol Use
AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorders Identification Test
AUQ	Alcohol Use Questionnaire
BART	Balloon Analogue Risk Task
BD	Binge-Drinking
BIS-11	Barratt Impulsiveness Scale – 11 Item version
BOLD	Blood Oxygenation Level Dependant
CANTAB	Cambridge Neuropsychological Test Automated Batter
CCPT	Conners' Continuous Performance Test
CDDR	Customary Drinking and Drug Use Record
CPT	Continuous Performance Test
CV	Cross-validation
D2	DBA/2J
DA	Dopamine
DAN	Dorsal attention network
DASS	Depression, Anxiety and Stress Scale
DAWBA	Development and Well Being Assessment
DDHx	Drinking and Drug History Questionnaire
DDQ	Delay Discounting Questionnaire
DDT	Delay Discounting Task
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DMQ	Drinking Motives Questionnaire
DSM-IV	Diagnostics and Statistics Manual 4th Edition

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DSM-V	Diagnostics and Statistics Manual 5th Edition
EEG	Electroencephalography
ERN	Error-related Negativity
ERP	Event-related potential
ESPAD	European school survey project on alcohol and other drugs
FH	Family History of Alcoholism
fMRI	Functional Magnetic Resonance Imaging
FrSBE	Frontal System Behaviour Scale;
GBD	Global Burden of Diseases
GNG	Go/No-Go task
IFC	Inferior Frontal Cortex
IGT	Iowa Gambling Task
IPL	Inferior parietal lobe
IPS	Intraparietal sulcus
IRV	Individual Response Variability
ITI	Inter-trial interval
KMO	Kaiser-Meyer-Olkin
PCA	Principal component analysis
PDHQ	Personal Drinking Habits Questionnaire
Pe	Evoked Potentials
PFC	Prefrontal cortex
LASSO	Least absolute shrinkage and selection operator
MRI	Magnetic Resonance Imaging
MCQ	Monetary Choice Questionnaire
MFG	Middle Frontal Gyrus;
mFWD	Mean framewise displacement
MID	Monetary Incentive Delay Task;
MINI	Mini International Neuropsychiatric Interview
ML	Machine Learning
MS	Millisecond
NEO-FFI	Neuroticism-Extraversion-Openness Five Factor Inventory

OFC	Orbitofrontal Cortex
QFV	Quantity Frequency-Variability Index
RAFT	Regularized Adaptive Feature Thresholding algorithm
RAPI	Rutgers Alcohol Problem Index
rIFC	right Inferior Frontal Cortex
RT	Reaction Time
SCID	Structured Clinical Interview for DSM-IV
SD	Standard deviation
SE	Standard Error of Mean
SFG	Superior Frontal Gyrus
SMA	Supplementary Motor Area
S-MAST	Short-Michigan Alcoholism Screening Test
SME	Standard Mean Error
SPSRQ	Sensitivity of Punishment and Sensitivity of Reward Questionnaire
SSAGA	Semi Structured Assessment for the Genetics of Alcoholism
SSS	Sensation Seeking Scale
SST	Stop Signal Task
SU	Substance use
SUD	Substance Use Disorder
SURPS	Substance Use Risk Profile Scale
TCIP	Two Choice Impulsivity Paradigm;
TCI-R	Temperament and Character Inventory-Revised;
TLFB	TimeLine Follow-Back
TRAILS	Tracking Adolescents' Individual Lives Survey;
UPPS	Impulsive Behaviour Scale
vmPFC	ventromedial prefrontal cortex
WISC-IV	Wechsler Intelligence Scale for Children
WOF	Wheel-of-Fortune Task
WHO	World Health Organisation
YAAPST	Young Adult Alcohol Problems Screening Test

Abstract

Alcohol use is the most significant worldwide risk factor for mortality and morbidity among young people, with consumption rates peaking in college years and highest in student populations. Impulsivity, broadly characterised as the tendency to act prematurely without foresight, is linked to alcohol misuse in college students. However, impulsivity is a multidimensional construct and different subdomains likely underlie different patterns of alcohol misuse. Furthermore, the relationship between certain impulsivity endophenotypes, such as cognitive impulsivity, i.e., lapses in sustained attention, and alcohol use is relatively unknown in young people, and the neural mappings underlying sustained attention in adolescents have yet to be identified. Machine learning methods can harness large complex data by examining statistical relationships between variables that span across domains (brain, behaviour and traits) of impulsivity to predict different patterns of alcohol use. Using this method, this thesis sought to quantify the association between different patterns of alcohol use and various impulsivity endophenotypes, including trait, motor, choice, and cognitive impulsivity, in student samples. A data-driven, multi-step analysis approach was also used to identify neural correlates of sustained attentional processes, an important aspect of cognitive impulsivity.

Results indicated different impulsivity endophenotypes predicted different aspects of alcohol use, such as elevated scores on the Alcohol Use Disorders Identification Test and a tendency towards alcohol intoxication, but not consumption frequency. Impulsive personality traits of disinhibition and poorer planning skills, and behavioural indicators of difficulties sustaining attention, appear to be the most important markers across different alcohol use patterns. Results also showed that inhibitory control ERPs can robustly predict individual differences in alcohol use. Cognitive impulsivity emerged as an important predictor of alcohol misuse in student samples, but not for relatively low alcohol use in adolescents. Sustained attentional processes were facilitated by an array of neural networks, including cerebellar crus I/II with motor, prefrontal and occipital cortices. Atypically strong connectivity within motor network was a signature of poor sustained attention, a finding that was also observed in a separate sample of adolescents exhibiting elevated ADHD symptoms, compared to asymptomatic adolescents. However, no significant brain connectivity correlates of alcohol use were identified in this relatively substance-naïve young adolescent cohort.

Overall, the findings support the view that different impulsivity endophenotypes contribute to different patterns of alcohol misuse. Machine learning is a useful method for analysing large amounts of data and it provides more nuanced insights into the relationship between alcohol use and psychological characteristics such as impulsivity. The EEG findings underscore the potential ERPs can offer for improving objective screening and assessment of alcohol misuse. Functional connections spanning an array of brain networks also appear to underlie cognitive impulsivity, via sustained attention. Combining neuroimaging with other data modalities offers a possibility to bridge levels of analysis, linking neural phenotype and behaviour in understanding alcohol misuse. Ultimately, a *multivariate endophenotype*, based on a weighted combination of diverse variables, including brain, personality and psychological factors, may provide an

increased power, greater predictive accuracy and more valuable clinical utility than any single   endophenotype.

1   Chapter 1: An Introduction to Impulsivity and Alcohol Use

GENERAL OVERVIEW AND AIMS OF RESEARCH[1]

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[1] *Sections of Chapter 1 have been published in Addiction (2017) and Current Addiction Reports (2017)*

1.1   Overview

Alcohol use is a leading risk factor for disease burden worldwide, and it contributes to serious ramifications for population health across the lifespan, according to the Global Burden of Diseases (GBD; Adhikari, 2018). The pattern of alcohol misuse in the form of binge-drinking (BD) or heavy episodic drinking has increased, especially among adolescents and young adults in recent years (Kuntsch, Kuntsche, Thrul, & Gmel, 2017). Alcohol misuse is often used as an omnibus term for underage alcohol use, alcohol abuse, alcohol dependence or alcohol use disorder (AUD), and is operationalized according to a wide range of overt symptoms. For example, an individual can be deemed to have an alcohol use disorder (AUD) by having any 2 of 11 symptoms during a 12-month period, based on DSM-V diagnostic criteria (American Psychiatric Association, 2013). This approach to phenotyping may hinder the search for biological mechanisms underlying alcohol misuse because individuals with no symptom overlap can be classified together, despite heterogeneity in symptoms. Therefore, an enhanced approach for ultimately understanding the pathophysiology of alcohol misuse will require focusing on endophenotypes (also known as intermediate phenotypes; Gottesman, & Gould, 2003).

Endophenotypes are neurocognitive, behavioural or cognitive processes associated with discrete deficits in defined neural systems (Robbins, Gillan, Smith, de Wit, & Ersche, 2012). One endophenotype – impulsivity – is well-characterised for its association with alcohol use, abuse and dependence (Dick et al, 2010; Lejuez et al., 2010; Perry & Carroll, 2008; Yip & Potenza, 2016). Impulsivity is a multifaceted, multidimensional construct (Evenden, 1999a; 1999b), and can be characterised by disinhibited thoughts and behaviours, difficulty sustaining attention and delaying gratification, despite negative consequences

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(Robbins & Dalley, 2017). Different aspects of impulsivity are likely to be derived from different neural systems that are, at least partially, independent (Bari & Robbins, 2013; Caswell, Bond, Duka, & Morgan, 2015a; Dalley & Robbins, 2017). As such, it is likely that different impulsivity endophenotypes underlie different patterns of alcohol misuse. However, the precise nature of those associations continues to remain unclear, elucidating upon this will be an important tenet of this thesis. Accurately characterising alcohol misusers in terms of impulsivity endophenotypes would identify target brain systems for future psychosocial or pharmacological intervention. This is important because alcohol misuse is associated with numerous adverse psychological and health-related outcomes, such as poorer health-related quality of life (Luquiens, Falissard, & Aubin, 2016) mental illness (Rehm, 2011), injuries, and even death (Hingson et al., 2005). Adolescents and young adults are particularly vulnerable to the adverse psychological effects of alcohol misuse, and a broad range of detrimental alcohol-related consequences (White & Hingson, 2013). Focusing on these populations is motivated by the particularly high levels of alcohol misuse among student populations (Lyvers, Duff, Basch, & Edwards, 2012), as well as the need to identify important neurocognitive brain networks prior to substance misuse in adolescents.

The aetiology and trajectory of addiction is complex: caused and moderated by individual differences in cognition, and related to neurobiological and environmental factors. Neuroimaging has the potential to detect subtle predictors of alcohol-use, however, the identification of neural predictors of alcohol initiation and misuse are underrepresented in addiction literature to date. Alcohol research has generally been conducted using methods developed within the natural sciences; that is, hypothesis-driven research typically based on assays of single cognitive functions, and the use of statistical inference to quantify the likelihood of an observed effect occurring by chance. However, a multi-domain approach

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could shed light on the precise correlates of alcohol misuse. A multi-domain approach is primarily data driven, using algorithms that search for patterns within data, with accurate prediction on previously unseen data as the metric of success. Basic principles and techniques developed within the field of machine learning are well suited for this approach. Later in this Chapter, some recent advances in neuroimaging will be outlined, with a focus on prediction of alcohol use through the use of machine-learning methods

1.1.1 Alcohol consumption trends.

Globally, 2.4 billion people are current drinkers; the global burden of alcohol use to date is substantial, and larger than previously estimated, in terms of its contribution to death, disability, and ill health, according to the GBD report (Adhikari, 2018). According to this comprehensive systematic analysis from the GBD for 195 countries and territories between 1990–2016, alcohol ranks as the global leading cause of both deaths and disability-adjusted life-years (DALYs) among 15–49-year-olds, whilst Ireland ranks fourth among European countries. Global research focusing on alcohol consumption and the incidence of BD highlights that significant quantities of alcohol are consumed worldwide, particularly, in single episodes. The standard BD definition is the consumption of large amounts of alcohol in a short period of time, with blood alcohol concentrations reaching up to 0.08 g/dl (NIAAA, 2004), often defined as greater than 5/4 drinks in men/women per occasion (Wechsler & Nelson, 2001; Wechsler et al., 1996). Prevalence rates of BD vary widely across countries; although, separating cultural variations from BD variations is difficult due to different measurements, time frames and restriction of age groups etc. (Kuntsche et al., 2017). In an effort to harmonise BD estimates (60 g on an occasion at least once in the past 30 days) the World Health Organization (WHO, 2014) has identified a different classification, which

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estimated that 7.5% of the worldwide population of 15 years and older, binge drink at least weekly.

In Ireland, 76% percent of the Irish population (15 years and older) identify as drinkers, and approximately 4 in 10 drinkers self-reported engaging in BD behaviour on a typical drinking occasion, according to the Healthy Ireland Survey (2015) conducted by the Irish Department of Health. This includes almost a quarter reporting BD at least once per week. The National Alcohol Diary Survey (2014) in Ireland reported that almost two thirds (64.3%) of young adult drinkers (18-24 years old) engaged in BD (6 or more standard drinks) in a typical drinking episode. In particular, higher levels of alcohol consumption and BD in Ireland have placed an increased burden on the health system, criminal justice system and society in general (O'Connell, Chin, & Lawlor, 2003). With recent estimates indicating that the prevalence of alcohol use is increasing at a relative rate (0.3% per year), as well as rates of BD (0.7% per year) in the United States, it is perhaps unsurprising that this reflects sharp increases in alcohol-related problems over the last decade (Grucza et al., 2018).

1.1.2   Alcohol consumption among young people.

Alcohol use often begins during adolescence, a time when risk-taking behaviours such as substance use are coming to the fore (Bava & Tapert, 2010). Early alcohol initiation in adolescents has detrimental effects in terms of an increase in risk-taking behaviour, neurotoxic effects on brain development and on future mental health (Guerri & Pascual, 2010; Zeigler et al., 2005). The social transitions and neuropsychological changes that occur during adolescence and continue into adulthood, make this a critical developmental period where adolescents are vulnerable to initiating alcohol misuse (Crews, He, & Hodge, 2007; Hall et al., 2016; Stone, et al., 2012). This vulnerability is characterised by

neuropsychological development underpinning cognitive functions implicated in social cognition and cognitive control (Blakemore & Choudhury, 2006). During puberty, young people experience significant increases in emotional arousal, impulsivity, and reward sensitivity (Steinberg, 2005), and this in turn can result in adolescents making choices that are oriented towards short-term outcomes, which potentially lead to adverse consequences (Ochsner & Gross, 2005; Todd, Cunningham, Anderson, & Thompson, 2012).

Age-of-onset of alcohol consumption is considered one of the most influential risk factors of dependence later in adulthood (Hawkins, Catalano, & Miller, 1992; Hingson, Heeren & Winter, 2006; Behrendt, Wittchen, Hofler, Lieb, & Beesdo, 2009). Although BD often starts during late adolescence, a large proportion of students seem to acquire this unhealthy pattern of consumption during their first years at university. A study of 1,894 first-year university students found that 1 in 4 first initiated BD at university in the United States (Weitzman, Nelson & Wechsler, 2003). Moreover, recent research has highlighted that BD that is evident at aged 18 in university students, is a significant predictor of whether young adults will continue to engage in problematic drinking behaviours at age 27 (Moure-Rodriguez et al., 2018).

Alcohol misuse among adult university students continues to be a significant health concern (Davoren, Dahly, Shiely, & Perry, 2017). University students are often classified as the most hazardous of drinkers (Lyvers, Duff, Basch, & Edwards, 2012), with students reporting to drink more than both adults and young adults who do not attend university (Balodis et al., 2009). Similarly, the prevalence of hazardous alcohol consumption in Ireland has been found to be considerably higher in students than that of the general population; 18–29-year-old students report elevated levels of consumption, compared with the general population (Health Research Board, 2014). Similarly, research indicates that there has been

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an increase in heavy episodic drinking and related problems among students in the United States (Hingson, Zha, & Smyth, 2017). Repeated misuse of alcohol in university students can contribute to numerous adverse consequences (Perkins, 2002), such as academic difficulties, unplanned and unprotected sexual activity, problems with authorities (Vik et al., 2000), injuries, and even death (Hingson et al., 2005).

1.2   Phenotyping alcohol misuse

One challenge in studying alcohol misuse is that there are many different methods of quantifying alcohol consumption (e.g. definitions of heavy versus light alcohol use) and alcohol-related consequences. Firstly, BD definitions have been difficult to unify; the definition of a standard drink (i.e., ethanol grams in a standard drink) is variable across different countries (Kalinowski & Humphreys, 2016), as are cut-off scores for BD (International Centre for Alcohol Policies, 2010). Indeed, research focusing on BD has been criticised for lacking "*empirical cohesion and definitional precision*" (Courtney & Polich, 2009, p.142). Single consumption-based measures of alcohol use are particularly problematic and are argued to lack predictive validity, are susceptible to ecological biases and appropriate group dichotomisation (Havard, 2016; Pearson, Kirouac, & Witkiewitz, 2016). Such differences limit our ability to accurately identify the risk factors that are associated with alcohol misuse, as well as the severity or types of alcohol-related consequences (Kuntsche et al., 2017). Focusing on standardised measures of alcohol use in research is one way to overcome the issues associated with single-consumption cut-off scores. For example, the Alcohol Use Disorders Identification Test (AUDIT) is one of the most widely used self-report instruments to assess alcohol-related risk, with a focus on hazardous alcohol consumption (Higgins-Biddle & Babor, 2018).

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Secondly, different alcohol consumption behaviours may be attributable to individual differences. For example, with regards to the consequences of alcohol use, drunkenness in young adolescents, not drinking *per se*, is a stronger risk factor for later problems (Kuntsche et al., 2013). Sanchez-Roige and colleagues (2014) suggest that a "binge score" focusing on patterns of drinking (including drunkenness) rather than a typical quantity measurement "drinks in a row," may provide better predictors of potential dependency on alcohol. However, memory heuristics can render the accuracy and validity of retrospective self-reported alcohol consumption as unrealiable (Patrick & Lee, 2010). Indeed, high drinkers have been found to underestimate consumption and drinking behaviour, and despite intercorrelation among alcohol-related indices, no one particular measure or term may adequately capture or describe the risky drinking patterns that young people engage in (Townshend & Duka, 2002). This problem can be mitigated using similar questions relating to multiple time points as a memory cue, which increases recall accuracy (Eisenhower, Mathiowetz, & Morganstein, 1991). For example, the European School Survey Project on Alcohol and Other Drugs questionnaire (ESPAD; Hibell et al., 2009) assesses alcohol use across lifetime, past 12-months and past 30-days, as well as items regarding expected personal consequences of alcohol use.

Thirdly, between-group comparison (e.g., heavy drinkers vs. controls), is common in the addiction literature, as will be evidenced later in this Chapter. Drawing control samples from groups with differing levels of substance use (SU) and failing to adequately control for possible variations in alcohol-use phenotypes may explain a sizeable portion of the differences in effects observed in the studies discussed below. It is likely that there are different phenotypes of alcohol-users, and the extent to which variation in processes associated with alcohol use represents dimensions versus homogenous groups has

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implications for our understanding of the aetiology of addiction. Conceptualising the traits of alcohol users as existing along a continuum suggests a change in focus from particular diagnostic groups to community samples, and the inclusion of individuals with intermediate levels of substance use (SU). Therefore, by considering a range of usages, it is possible to harness the potential of population-based cohort studies that have already been collected and that contain phenotypic data on multiple quantitative dimensions.

1.3   Measuring brain activity non-invasively

Neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), have enhanced researchers' prospects of linking discrete cognitive functions to specific brain regions and neuronal networks. Over the past three decades, researchers have utilised magnetic resonance imaging (MRI) as a non-invasive technique to characterise anatomical, physiological, and metabolic changes in the human brain in order to better understand the underlying mechanisms of impulsivity, as well as alcohol's deleterious effects on the brain.

MRI measures detectable radio signals emitted from hydrogen atoms, that are emitted when they are placed in a magnetic field and perturbed by radio waves. The signal can then be extrapolated to generate a structural image of the brain. In fMRI, a different method is utilised that measures the change in the relative concentration of oxygenated haemoglobin to deoxygenated haemoglobin in the blood, otherwise known as the blood-oxygen-level-dependent (BOLD) signal. fMRI allows us to observe functional brain activity in vivo during performance of a given cognitive task and has proven highly valuable in mapping higher order cognitive processes.

fMRI has the capacity to detect hemodynamic responses evoked by single events, based on block design tasks, as well as transient hemodynamic responses evoked by changing stimuli or task conditions during event-related tasks (i.e., stimulus randomisation). In event-related experiments, long inter-stimulus interval (ISI) enables recovery of the hemodynamic response, however this can be fatiguing and time-inefficient. Separation of signals from rapid event-related designs assumes that the hemodynamic responds to sequential events summate in a roughly linear fashion (Boynton et al., 1996; Dale and Buckner, 1997), although unwanted variance associated with the lower limit of the average response elicited by conditions of interest must be accounted for. There are two widely-used approaches to analyse spatiotemporal information of fMRI data. The first approach includes model-based methods, such as general linear model (GLM; Friston et al., 1994), which indicates how well a certain model fits to the fMRI data. The second approach includes data-driven methods, which are based on feature extraction from fMRI data (Calhoun et al., 2003, Shen et al., 2017). Using the GLM, neurophysiological responses can be partitioned into components of interest, as well as confounds and errors; evoked hemodynamic responses corresponding to the timing of the stimulus presentation are convolved with a canonical hemodynamic response function for each participant, to determine the activated brain areas. Data-driven methods, on the other hand, are more flexible and are useful for identifying features from the data, including unanticipated unexpected regional activation, which can later be used in model-based approaches.

Data-driven methods have emerged as being particularly useful for examining task-based functional connectivity – associations of synchronous fluctuations in brain signals – improving our understanding of how task-evoked regions fit within large-scale neural networks. For example, Rosenberg and colleagues (2016) highlighted the importance of

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data-driven fMRI analyses in their research, finding that sustained attentional processes emerged from an array of large-scale functional connectivity across different brain networks.

The temporal resolution (i.e., the precision of measurement with respect to time) for fMRI is typically in the order of seconds, whereas its spatial resolution is in the order of millimetres. Under most conditions there is a trade-off between temporal and spatial resolution, and harnessing measures with higher temporal resolution to identify exact timings of cognitive processes may outweigh the benefits associated with using fMRI. For example, due to its high temporal resolution, electroencephalography (EEG) is well-suited to study dynamic changes and the connectivity of brain networks underlying response inhibition (Huster, Plis, Lavallee, Calhoun, & Herrmann, 2014). EEG measures are typically used to examine event-related potentials (ERPs). ERPs provide an instantaneous, continuous, millisecond-resolution measure of cognitive processes, which can be used to isolate inhibitory control mechanisms. ERPs are voltage fluctuations that occur as a consequence of an external or internal event (e.g., presentation of a stimulus (sensory), or preparation of a movement (motor); arising from postsynaptic potentials in cortical neurons. This produces opposite polarities on either side of the active tissue, with polarity depending on whether the postsynaptic potential is excitatory or inhibitory (Buzsáki, Anastassiou, & Koch, 2012). If many neurons (in the order of thousands to millions) are active simultaneously and are spatially aligned, their electric fields summate, and the summed voltage can be recorded on the surface of scalp (Kappenman & Luck, 2016).

Although it is evident that these neuroimaging techniques come with a set of specific advantages, as well as limitations (e.g., Henson, 2005; Dietrich & Kanso, 2010), the use of each of them separately to infer functional brain organisation and human cognition so far has failed to provide a complete picture, as will be explored in this Chapter. Therefore, not

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surprisingly a multi-domain approach combining brain, behaviour and trait domains are increasingly gaining popularity among neuroscientists and psychologists striving to understand the neuropsychosocial profiles of alcohol misuse.

1.4   Defining Impulsivity

Impulsivity has long been recognised for its importance both in everyday life. Impulsivity is considered to exist along a continuum, with individual variation in impulsive tendencies contributing to alcohol use, as well as more severe behaviours, characterised by an impulsive urge towards alcohol consumption and an inability to inhibit consumption, regardless of negative consequences (Holmes, Hollinshead, Roffman, Smoller, & Buckner, 2016). Although the construct of impulsivity has been described as a "*a useful heuristic*" (Dalley et al., 2011), there are many definitions of this construct (Evenden, 1999a, 1999b; Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). Impulsivity can be defined as a predisposition for rapid, unplanned actions in response to internal or external stimuli without consideration for the negative consequences of these actions (Moeller et al., 2001). By this definition, impulsivity is an automatic process, driven by quick decision-making and a lack of foresight, thus impeding appropriate evaluation of the consequences. Similarly, Eysenck (Eysenck & Eysenck, 1978) disassociates impulsiveness and "*venturesomeness*", which is related to conscious risk-taking.

The above definitions characterise impulsivity as a maladaptive and a pathological feature; however, it is widely accepted that impulsivity is part of human nature, and individual differences can be adaptive in different contexts. Indeed, every person can be characterised on their impulsive tendencies and as such, impulsivity can be perceived as a personality trait (Herman, Critchley, & Duka, 2018). Eysenck and Eysenck (1978) first

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theorised that personality consists of two dimensions of higher-order traits; that is, extraversion vs introversion and neuroticism vs emotional stability, whereby impulsivity was a combination of high Extraversion and Neuroticism and Psychoticism. In a revised model, however, impulsivity is regarded as a part of third dimension items, i.e. psychoticism vs impulse control, whereby impulsivity is related to risk-taking and lack of planning and Extraversion is primarily defined by its sociability content (Eysenck & Eysenck, 1985). Although discriminating impulsivity from sociability helped to clarify the current conceptualisation of Extraversion, aspects of sociability from Eysenck's original proposal remain intertwined with the concept of impulsivity. For example, the Barratt Impulsiveness Scale (BIS; Barratt, 1959), a commonly used self-report measure of trait impulsivity, measures content related to extraversion (Sharma et al., 2014). Other ways to conceptualise impulsivity also emerged, including Zuckerman's (1984) concept of "sensation seeking", describing high sensation seekers as individuals who show a need for stimulation and novel experiences, regardless of the risks (Zuckerman, 1984).

Difficulties in establishing an unequivocal definition of impulsivity and situating it within personality models gave rise to conceptualising impulsivity as a multidimensional construct, where facets can be both distinct and overlapping, and reflect different aspects of behaviour (Congdon & Canli, 2008; Evenden, 1999a; Moeller et al., 2001). For example, the Barratt Impulsiveness Scale 11th version (BIS-11; Patton & Stanford, 1995) a questionnaire that is often used in both clinical and research settings, assesses three factors of impulsivity, including: Motor (inability to withhold responses or acting on the spur of the moment); and Non-planning (lack of consideration or not planning tasks carefully); and Inattention (difficulty focusing on the task at hand). Zuckerman's Sensation Seeking Scale (SSS; Zuckerman, Eysenck, & Eysenck, 1978), consists of four factors: Thrill and Adventure

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Seeking (engaging in risky and exciting activities), Disinhibition (a desire for social stimulation and disinhibited behaviour), experience seeking (a desire for experience a non-conforming lifestyle through unplanned activities or drugs), and boredom susceptibility (an aversion to repetition and routine).

The behavioural approach to impulsivity predominantly comprises at least two major dimensions. The first is *motor impulsivity* (or impulsive action) and reflects disinhibition, and can be divided into action cancellation and action restraint. The second, labelled *choice impulsivity* by some (e.g., Paloyelis, Asherson, Mehta, Faraone, & Kuntsi, 2010), reflects impulsive decision-making, and can be separated into risk or uncertainty-based choice and delay-based choice (Winstanley, Olausson, Taylor, & Jentsch, 2010). De Wit (2009) suggested a third dimension of impulsivity, such as attention lapses on a simple reaction time task, proposing that sustained attention is crucial for tempering drug-seeking behaviours in addicts. Furthermore, subtypes within impulsive action have been distinguished, at different stages of the process (Caswell et al., 2015a; Evenden, 1999a): impulsive preparation (i.e. reflection—responding before all necessary information is obtained; Kagan, 1965); motor impulsivity (failure to follow instruction and inhibit motor responses); and an outcome stage of impulsivity (failure to delay gratification). Other notable definitions have arisen, for example, temporal impulsivity encompasses both delay gratification and decision-making under conditions of risk or uncertainty (Fineberg et al., 2010; 2014; Winstanley et al., 2010).

Here, a review of the literature on endophenotypes of impulsivity in the context of alcohol misuse will be outlined, including: trait, choice impulsivity (delay discounting) and motor and cognitive impulsivity (sustained attention).

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1.4.1 Trait impulsivity and alcohol.

 Increased trait impulsivity is sensitive to different patterns of use among adolescents and young adults (Adan, Forero, & Navarro, 2017; Stautz & Cooper, 2013). Across various studies, binge-drinkers show higher scores for both impulsivity (Adan, Navarro & Forero, 2016; Leeman, Hoff, Krishnan-Sarin, Patock-Peckham, & Potenza, 2014; Mackie, Castellanos-Ryan, & Conrod, 2011; Motos Sellés, Cortés Tomás, Giménez Costa, & Cadaveira Mahía, 2015) and sensation seeking (Bø, Billieux, & Landrø, 2016; Lac, & Donaldson, 2016; Leeman, Fenton, & Volpicelli, 2006; Leeman, Hoff, Krishnan-Sarin, Patock-Peckham, & Potenza, 2014; Shin, Hong & Jeon, 2012), compared to non-binge-drinkers. Higher trait impulsivity and sensation seeking scores are also associated with increased numbers of drinks consumed per episode (Balodis, Potenza, & Olmstead, 2009; Doumas, Miller, & Esp, 2017; Lang et al., 2012) and the frequency of BD (Carlson & Johnson, 2012; Castellanos-Ryan, Rubia, & Conrod, 2011; Lang et al., 2012).

The BIS-11 is one of the most widely used measures of trait impulsivity to be examined in relation to alcohol use. BIS-11 total scores have been linked to alcohol use and alcohol status (Henges, & Marczinski, 2012; Papachristou, Nederkoorn, Havermans, van der Horst & Jansen, 2012), alcohol-related problems (Bjork et al., 2004; Rubio et al., 2008), and early-onset AUD symptomatology (Dom, Hulstijn, & Sabbe, 2006). Group differences between heavy and lighter drinkers are also reported. For example, heavier drinkers (AUDIT scores ≥11) have reported significantly higher BIS-11 total scores than light drinkers (AUDIT scores <11; Papachristou et al. 2012). However, BIS-11 total scores are associated with different patterns of alcohol use. For example, in 109 undergraduate students (Henges, & Marczinski, 2012), BIS-11 scores predicted number of drunk days, but not the number of drinking days or the highest number of drinks consumed on one occasion in a month.

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Differentiation between BIS-11 subscales and various aspects of alcohol misuse have also been found. Using a binge score of alcohol consumption, Sanchez-Roige and colleagues (2014) found that binge-drinkers displayed significantly higher scores for Motor and Non-planning subscales of the BIS-11, compared to non-binge drinkers. Unlike the BIS-11, researchers typically report facet-level scores of the UPPS and UPPS-P, rather than total scores (Stevens, Blanchard & Littlefield, 2018). Despite a strength of the BIS-11 measurement tool being its ability to assess different aspects of impulsive traits, researchers often report a total score when using the BIS-11 (Stevens, Blanchard & Littlefield, 2018), which assumes impulsivity to be a unidimensional construct (Stanford et al., 2009). Given that different aspects of alcohol use (e.g. drunkenness vs. frequency) appear to be related to total BIS-11 scores, it will be important to examine this further using the subscales.

Some researchers have combined self-report impulsivity measures to generate higher-order factors that may better explain alcohol-use behaviour. For example, Wardell and colleagues (2016) combined UPPS-P and BIS-11 scores in order to assess self-reported control over alcohol (Impaired Control Scale) in 300 18–25-year-old heavy drinkers, using a Timeline Follow-back measure (Sobell & Sobell, 1992) for alcohol frequency and RAPI for alcohol-related problems. The first higher-order factor – *response impulsivity* – describes difficulties inhibiting thoughts and behaviours, especially in the context of reinforcement. The second – *reflection impulsivity* – is the tendency to make quick decisions without sufficiently gathering or evaluating relevant information. Response impulsivity accounted for unique variance in impaired control over alcohol and in alcohol problems, whereas reflection impulsivity accounted for unique variance in heavy drinking frequency only. Further, indirect associations were observed from response and reflection impulsivity to alcohol problems, mediated via impaired control and heavy drinking frequency, respectively. The results

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suggest that impaired control may play a specific role in the pathway to alcohol problems from response impulsivity, but not from reflection impulsivity.

The Substance Use Risk Profile Scale (SURPS; Woicik, Stewart, Pihl & Conrod, 2009) was developed to examines impulsive traits that are directly related to substance misuse risk, including Sensation seeking, Impulsivity, Anxiety sensitivity, and Hopelessness. An examination of the SURPS in approximately 2000 14-year-olds found that Impulsivity and Sensation seeking dimensions predicted alcohol use two years later (Jurk et al. 2015). Other studies using the SURPS also showed that binge-drinkers had higher Sensation seeking, Impulsivity and Hopelessness scores than non-binging adolescents (Mackie, Castellanos-Ryan & Conrod, 2011; Whelan et al., 2014).

Examining which specific aspects of trait impulsivity are most closely related to alcohol misuse, as well as which measures can be used to asses personality, is difficult (Adan et al., 2017). Furthermore, other broad personality traits not directly related to impulsivity, such as the Big Five model (Extraversion, Neuroticism/Emotional stability, Conscientiousness, Openness (to new experiences)/Intellect, and Agreeableness) are considered to be important variables in determining BD trajectories (Sharma et al., 2014; Whelan *et al*., 2014; Zhang, Bray, Zhang & Lanza, 2015). However, cross-sectional studies using the Big Five model to examine the relationship between personality and BD have been inconclusive, and trait impulsivity in conjunction with more broader personality measures have rarely been examined (Adan et al., 2017).

1.4.2 Choice impulsivity and alcohol

Choice impulsivity (also referred to as temporal impulsivity), encompasses decision making based on evaluations of delayed consequences of behaviour. That is, an impulsive choice can

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be characterised by the tendency to choose a smaller immediate reward rather than waiting for a larger, but delayed, reward. Choice impulsivity can be measured via a questionnaire, such as the Delay Discounting Questionnaire (DDQ) and Monetary Incentive Questionnaire (MCQ; Kirby, Petry & Bickel, 1999), or via a task, such as the Two-Choice Impulsivity paradigm (TCIP Dougherty, Mathias, Marsh & Jagar, 2005) or the Delay Discounting Task (DDT; Kirby & Maraković, 1996; Kirby, Petry & Bickel, 1999).

The DDT is an established behavioural forced-choice measure of impulsive choice, quantifying the decline in the subjective value of a reward as the delay to its receipt increases (e.g., "Would you prefer €5 now or €10 in one month?"). Steeper discounting rates indicate increased choice impulsivity (Bickel, Odum & Madden, 1999). Steeper discounting is robustly associated with addictive behaviours in general, including nicotine (Reynolds et al., 2007), cocaine (Petry, 2003; Heil, Johnson, Higgins, & Bickel, 2006) and heroin (Petry, 2003), as well as severity and quantity-frequency of substance misuse (Amlung, Vedelago, Acker, Balodis & MacKillop, 2017). Studies have used other tasks to assess impulsive choices in the context of reward and punishment, such as the Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994), which assesses an individual's preference for disadvantageous deck cards (yield greater immediate gains but greater long-term losses) over advantageous decks (yield lower gains but lower long-term losses). During an IGT, 16-18-year-old binge-drinkers displayed poorer decision-making (a tendency to consistently select disadvantageous decks), as well as increased emotion-related brain activation in the amygdala and insula, compared to matched never-drinkers (Xiao et al., 2013). However, there is relatively less literature on the DDT in non-dependent samples in relation to alcohol misuse. Further exploration of task-based versus questionnaire-based measures of choice impulsivity and how they relate to different aspects of alcohol use is also required.

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1.4.3   Motor impulsivity and alcohol

Motor impulsivity, otherwise known as response inhibition, refers to the inability to inhibit certain unwanted behaviours or to quickly cancel an already-initiated response, and relies on effective and rapid inhibitory control in the brain. Various behavioural tasks have been developed to measure motor impulsivity. In both the Stop Signal Task (SST; Logan, 1994) and Go/No Go (GNG) task (Hogg, Evans, & Adrian, 1975) participants are required to respond to go-signals, and to inhibit their responses to stop signals. Evidence indicates that these tasks are not equivalent and probe distinct processes–the SST assesses 'action cancellation' (i.e., inhibition of an already initiated response), while the GNG assesses 'action selection and restraint' (i.e., inhibition of a response before it has started; Dalley, Everitt, & Robbins, 2011; Eagle, Bari, & Robbins, 2008). fMRI studies implicate dominant "stopping" brain activation patterns for both tasks, including the inferior and right MFG, ACC, pre-supplementary motor area, right inferior parietal lobe, and left middle temporal cortex (Rubia et al., 2001). However, the SST primarily shows activation in the right hemisphere, while the GNG task shows bilateral, but more left-hemisphere activation (D'Alberto, Funnell, Potter, & Garavan, 2017; Nikolaou, Critchley, & Duka, 2013; Rubia et al., 2001). Yet, these tasks are often used indiscriminately under the assumption that both measures are very similar at "stopping" abilities (Robinson et al., 2009; Dalley et al., 2011). Nevertheless, several studies have shown that both action cancellation and restraint are impaired in substance misusers, including alcohol misusers (Petit, Kornreich, Noël, Verbanck & Campanella, 2012; Czapla et al., 2017).

The SST can assay inhibitory control by requiring participants to respond as quickly as possible to frequent 'Go' cues, but to inhibit their ongoing motor response following

intermittent and unexpected 'Stop' cues (Verbruggen & Logan, 2008). On trials with a stop stimulus, the 'horse race model' (Band, Van Der Molen & Logan, 2003) posits a race between two separate processes that are each triggered by the Go and Stop signal. If the stop process is completed before the Go process, subjects will successfully inhibit their responses (Verbruggen & Logan, 2008) and vice-versa. The stop-signal reaction time (SSRT) indexes the time needed to successfully inhibit a response during the SST (Congdon et al., 2012), and is a reliable measure of deficits in inhibitory control. The SSRT is a measure of a covert mental process, and can be calculated by subtracting the average stop signal delay from the participant's Go reaction time. Shorter SSRTs indicate better inhibitory control. In neurologically healthy adults, SSRTs are approximately 200 ms (Dimoska et al., 2006; Hoptman et al., 2018; van Boxtel et al., 2001; Wessel & Aron, 2015; Wessel et al., 2016), but longer in adults with ADHD (Lijffijt et al., 2005) and in individuals with addictions (Luijten et al., 2011).

1.4.3.1 *Behavioural correlates of motor impulsivity.*

Longer SSRTs have been observed for disordered alcohol-use (Mole et al., 2015) and acute alcohol dosages (Caswell et al., 2013a). However, SSRT differences are not always found when comparing non-dependent drinkers to controls. For example, 19-year-old binge-drinkers (mean of 6.18 drinks on the last drinking episode) showed no SSRT differences compared to both cannabis-using and non-drug-using groups (Moreno et al., 2012). Similarly, SSRTs were not found to be related to the number of weekly alcohol units in heavy drinking 18-45-year-old students (Caswell et al., 2015b), or to binge drinking scores in 18-25-year-old drinkers (Sanchez-Roige et al., 2014). It is possible that non-dependent alcohol users have not yet experienced the neurotoxic effects of repeated alcohol abuse, which is thought to weaken

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top-down cognitive control (Robbins & Dalley, 2017; López-Caneda et al., 2013). However, differences in brain activity related to response inhibition have been observed in young adolescent drinkers, even in the absence of behavioural differences (Whelan et al., 2012; Wetherill, Squeglia, Yang & Tapert, 2013b; Worhunsky et al., 2016). This suggests that neural measures of inhibitory control have some potential to better characterise individual differences in alcohol misuse than behavioural metrics alone.

1.4.3.2 *fMRI: Brain correlates of motor impulsivity.*

Tasks assaying motor impulsivity, combined with neuroimaging, have the potential to detect subtle neurobehavioural vulnerabilities and predictive factors associated with alcohol-use (Heitzeg, Cope, Martz & Hardee, 2015). For example, a cross-sectional study of 1,896 healthy 14-year-olds (Whelan et al., 2012), found no SSRT differences between adolescent alcohol misusers (with only 1-4 lifetime uses of alcohol) and non-drinkers. However, Whelan and colleagues (2012) identified seven stop success and six stop-fail brain networks on an SST (see *Figure 1.1*), and found that the alcohol misusers had reduced lateral orbitofrontal cortex activity during response inhibition, as well as differences in orbito-frontal and pre-SMA networks, compared to the non-drinkers. Furthermore, the right frontal network was also associated with severity of substance use (Whelan et al., 2012). The findings indicated that the lateral orbitofrontal cortex may underlie impulsivity associated with alcohol initiation in young adolescents. Importantly, and given the low volume alcohol intake, these neural markers are less likely to be a consequence of alcohol use.
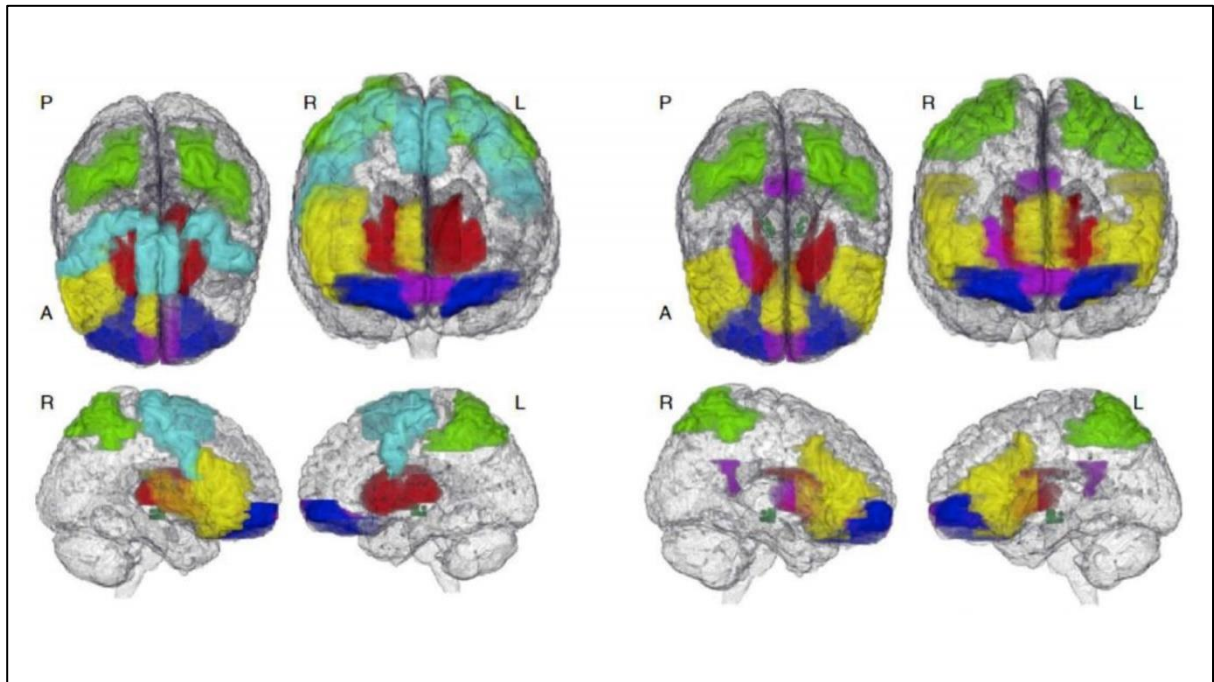
Figure 1.1. Stop success and stop fail networks characterised using factor analysis of the brain activation during the SSRT in 1896 14-year-olds from the IMAGEN sample (Whelan et al., 2012). Left side —seven stop success networks including: Basal Ganglia network (red); right Inferior frontal network (yellow); bilateral substantia nigra/subthalamic nucleus (STN) network (grey); Orbital network (dark blue); pre-supplementary motor/ precentral gyrus (cyan), parietal network (dark green) and the medial orbital network (magenta). Right side — six stop failure networks. The anterior cingulate network (yellow); the substantia nigra/STN network (grey); basal ganglia network (red), the parietal network (dark green); the PCC/medial orbital network (magenta) and the orbital network (dark blue). A: anterior; P: posterior; L: left; R: right.

Hypoactivation in frontoparietal, temporal and subcortical brain regions was also observed in college drinkers who binged in over 50% of the weeks in the past 6 months, when compared to light drinkers who binged fewer than 50% of weeks in the past 6 months, on a GNG task (Ahmadi et al., 2013), with longer reaction times (RTs) reported for heavy drinkers. Another study (Ames et al., 2014), however, has found increased activity in the right dorsolateral prefrontal cortex and cingulate cortex, as well as significantly longer RTs, during a GNG task in 18–22-year-olds classified as very heavy drinkers (≥15 drinks/week for males and ≥8 drinks/week for females when compared to light drinkers (<3 drinks/week and ≤2drinks during any drinking episode). The disparity between the findings may be related to

alcohol use differences; it is possible that in the latter study, the amount of alcohol consumed regularly was sufficient to impair brain function, leading the drinking group to recruit additional brain resources in response to cognitive demands.

Turning to prospective studies, a series of longitudinal fMRI studies have tracked individuals' neural changes underlying motor impulsivity over time, along with their drinking patterns, in order to determine consequences of alcohol-use. Two studies have shown that frontoparietal hypoactivation during response inhibition on GNG tasks predicted subsequent heavy drinking in 11-16-year-old drinkers (1-2 drinks daily or >4 drinks/month) versus continuous non-drinkers 3 years later (Wetherill, Squeglia, Yang & Tapert, 2013b) and 18-year-old college student heavy drinkers (number of drinks >4 on an occasion; mean drinks = 10.3), versus lighter drinkers (maximum of 3 drinks per occasion) 1 year later (Worhunsky et al., 2016), respectively. In both studies, behavioural differences between groups were absent at baseline. Supporting evidence for hyperactivation as a compensatory mechanism comes from an fMRI GNG task with alcoholic and non-alcoholic drinks as response cues (Beltz et al., 2013), in which 18-19-year-olds whose alcohol exposure increased during college had greater connectivity between prefrontal and anterior cingulate regions one year later. Behaviourally, participants' performance improved over time, showing faster reaction times and improved response accuracy from baseline for the alcohol condition one year later. A pattern of hypoactivation prior to very alcohol heavy use is, however, not uniform across studies. For example, a 5-year prospective study (Wetherill et al., 2013a) compared non-drinkers to 12-14-year-olds who were substance-naive at baseline but transitioned to problematic drinking at aged 18 (subdivided into adolescent who experience alcohol-induced blackouts and those that did not experience blackouts). At baseline, hypoactivation in parietal regions remained a significant predictor of future heavy alcohol-use for both groups, but

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adolescents who would subsequently experience blackouts had increased frontal hyperactivation at baseline.

1.4.3.3   EEG: brain correlates of motor impulsivity.

ERPs obtained using EEG are modulated by performance during the SST (e.g. Kenemans, 2015). Two ERPs, the P3 and N2, are predominately associated with response inhibition. The N2 is a fronto-lateral negative component peaking around 200-250ms. The N2 is thought to reflect conflict monitoring and effortful processing, predominantly through activity of the anterior cingulate cortex (ACC; Pandey et al., 2012). The P3 is a fronto-central positive component peaking around 300-350ms. Larger N2 amplitudes are sometimes observed for failed versus successful stop trials (Kok et al., 2004), while larger P3 amplitudes have been consistently observed for successful versus failed stop trials in healthy participants (Kok et al., 2004; Lansbergen et al., 2007).

A reduction in P3 amplitude during response inhibition is considered a vulnerability marker for alcoholism (Campanella et al., 2018; Luijten et al., 2014; Mumtaz et el., 2017a). However, ERP findings in non-dependent alcohol users are not always consistent. For example, no P3 or N2 amplitude differences were found between 48 young adult heavy drinkers and 49 lighter drinkers during successful response inhibition on a GNG task (Franken et al., 2017). Conversely, in a sample of 40 student drinkers performing the same task, heavy drinkers had reduced N2 and P3 amplitudes, compared to light drinkers on successful trials (Oddy & Barry, 2009). In a longitudinal study (López-Caneda et al., 2012) of 48 18-19-year-old light (n=25) and heavy (n=23) drinking students, no P3 amplitude differences were observed at baseline during a GNG task. However, those who binged (at least 6 drinks per occasion once per month) for 2 years exhibited larger P3 amplitudes during

a GNG task at follow-up. There is also some evidence that alterations in earlier ERP components (e.g., P1) are linked to alcohol misuse, as has been found among an alcoholic dependent sample (Maurage et al., 2007; 2012). Yet, these early components have surprisingly received little attention. It is important to establish whether the link between ERPs and alcohol misuse is specific to later N2/P3 components, or if deficits are already present earlier in the cognitive processing stream.

Mixed findings, such as potential ERP correlates of alcohol use, are common in cognitive neuroscience. Firstly, as outlined earlier in this Chapter, studies typically test the statistical significance of between-group comparison (e.g., heavy drinkers vs. controls), and cut-off scores used to define alcohol misusers are varied. Secondly, the discrepancies in the neuroimaging findings are likely to be related to methodological challenges that are associated with examining highly dimensional data, a point which will be discussed in more detail later in this Chapter. Notably, these EEG studies, as well as the aforementioned neuroimaging studies, used GNG tasks to examine the relationship between inhibitory control and alcohol use, with one exception (Whelan et al., 2012). However, these tasks are dissociable (Littman & Takács, 2017), and although the SST has not been widely used to determine the ERP-alcohol relationship, the SST may be sensitive to detecting alcohol-induced changes in the P3 during inhibition control (Plawecki et al., 2018).

1.4.4 Cognitive impulsivity and alcohol

The ability to efficiently and consistently maintain attentional resources on a moment-to-moment basis is central to our navigation of everyday life. Cognitive impulsivity, i.e., lapses in sustained attention, is linked with risky behaviours, such as drug-taking (Sharma et al., 2014). Attentional impairments have been observed in 18-25-year-old binge-drinkers, in

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the form of higher response omissions and lower accuracy during variable trials on a human version of the Five-Choice Serial Reaction Time Task (Sx-5CSRTT), compared to non-bingers (Sanchez-Roige et al., 2014). Attentional impairment has also been found for abstinent alcohol-dependent patients, in the form of increased commission errors during a Continuous Performance Test (CPT), compared to healthy controls (Bjork, Hommer, Grant & Danube, 2004; Rodriguez-Jimenez et al., 2006). However, the relationship between attentional abilities and alcohol is not straightforward. For example, some studies have found that the Attentional subscale on the BIS-11 (e.g., "I don't "pay attention") predicts BD trajectories (Carbia et al., 2018) and is associated with higher alcohol use (Mackillop et al., 2016), while others have not found this association (Caswell et al., 2015b; Sanchez-Roige et al., 2014). In a meta-analytic study that used principal-component analysis (PCA) to generate factors of impulsivity, Sharma and colleagues (2014) posited that inattention (based on the Stroop and a version of the CPT) may not be significantly associated with problematic alcohol use.

Sustained attention can also be assessed by examining trial-to-trial intra-individual response variability (IRV) on a given cognitive task (Hultsch, MacDonald & Dixon, 2002). The IRV can be examined using the SST and calculated using the intra-individual coefficient of variation formula (dividing the standard deviation of Go RTs by mean Go RTs), which controls for differences in an individual's overall speed of responding (Bellgrove et al., 2004). The IRV may yield insights into deficits associated with sustaining attention to top-down cognitive control demands (Bellgrove et al., 2004; Hervey et al., 2006), additional to those afforded by standardised cognitive or psychomotor tasks (Balota et al., 2010; Cherbuin, Sachdev & Anstey, 2010; Haynes, Bauermeister & Bunce, 2017) or simple RT (Dixon et al., 2007). For instance, higher IRV (i.e., worse sustained attention) is commonly reported in

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ADHD (Bellgrove, Hawi, Kirley, Gill & Robertson, 2005; Castellanos et al., 2005; Castellanos, Sonuga-Barke, Milham & Tannock, 2006; Kofler et al., 2013; Kuntsi & Klein, 2011; Mullins, Bellgrove, Gill & Robertson, 2005; Vaurio, Simmonds & Mostofsky, 2009). Yet, despite associations between BD and impaired attentional function and executive function (Scaife & Duka, 2009; Townshend & Duka, 2005), the IRV measure has yet to be examined in relation alcohol use.

1.4.4.1   *Brain correlates of IRV.*

Several fMRI studies have examined the relationship between IRV and whole brain task-related activation during response inhibition tasks. In healthy adults, higher IRV on GNG task has been associated with increased stop-related activation in prefrontal regions [middle frontal gyrus (MFG), inferior frontal gyrus (IFG)], motor-related regions (precentral gyrus and pre-SMA), the anterior cingulate cortex (ACC), inferior parietal lobe (IPL) and thalamus (Hervey et al., 2006). Similar brain activation patterns have been observed in healthy children, with higher IRV associated with increased activation in the MFG and thalamus, while lower IRV was associated with activation in postcentral gyrus, medial frontal gyrus, culmen, IPL and cerebellum (Simmonds et al., 2007). However, there are conflicting findings within the literature. For example, in healthy adults, lower IRV was found to be associated with greater activation of ACC (Esterman, Noonan, Rosenberg & DeGutis, 2012), and in the left pregenual anterior cingulate in healthy male adults (Johnson et al., 2015). Discrepancies in findings relating to frontal lobe activation patterns and IRV remain unresolved (Tamm et al., 2012), and there is growing interest into the characterisation of sustained attention within large-scale neural networks (Fortenbaugh, DeGutis & Esterman, 2017).

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Research posits that sustained attentional processes may emerge from an array of large-scale functional connectivity networks (Castellanos, Kelly & Milham, 2009; Kessler, Angstadt & Sripada, 2016), rather than single brain regions (Rosenberg, Finn, Scheinost, Constable & Chun, 2017). Although BOLD activation can yield insight into brain activity associated with IRV, functional connectivity – associations of synchronous fluctuations in brain signals – can identify brain regions that are engaged at the same time during a cognitive task. Sustained attention has been shown to involve the dorsal attention network (DAN; comprising intraparietal sulcus (IPS), superior parietal lobule; primate frontal eye fields, and inferior pre-central sulcus) and frontoparietal networks (Petersen & Posner, 2012; Szczepanski, Konen & Kastner, 2010). Lower IRV (i.e., better sustained attention) is associated with stronger anticorrelations between the default mode network (DMN; including medial prefrontal cortex, posterior cingulate, anterior temporal and precuneus) and task-positive networks (Kelly, Uddin, Biswal, Castellanos & Milham, 2008). The extent to which other networks outside these attentional networks contribute to sustaining attention is less well understood (Fortenbaugh et al., 2017; Glickstein, 2007), although studies examining a broader range of network connectivity have identified connectivity in regions such as the cerebellum, as being important for sustaining attention (Rosenberg et al., 2016). To date, however, the brain correlates of sustained attention in healthy adolescents, as indexed by IRV, have not been comprehensively characterised.

1.4.4.2   *ADHD and IRV.*

Neurodevelopmental disorders of impulsivity such as childhood attention-deficit/hyperactivity disorder (ADHD; American Psychiatric Association. 2013) are associated with increased risk for heavy alcohol use (Vogel et al., 2016) and the development

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of alcohol use disorders (Lee, Humphreys, Flory, Liu, & Glass, 2011; Wilens & Morrison, 2011) in adulthood. ADHD, characterised by an early onset of persistent and impairing levels of inattention-disorganisation and hyperactivity-impulsivity (APA, 2000), is one of the most frequently encountered disorders during childhood and adolescence in the U.S. (Barkley, 1998), with high prevalence rates (5-10%) in children (Scahill & Schwab-Stone, 2000). ADHD during childhood or adolescence increases the risk for developing AUD or other SUDs (Lee, Humphreys, Flory, Liu, & Glass, 2011; Wilens & Morrison, 2011), and is also a risk factor for heavy alcohol use and illicit drug-use initiation in young adults (Vogel et al., 2016). Neuroimaging studies have also implicated similar neural circuits and pathways in the pathophysiology of both ADHD and SUD. For example, one review found that the comorbidity between ADHD and SUD aetiologically overlapped in relation to impairment in motivational system and inhibitory control, indicated by blunted striatal dopamine (DA) release, as well as disturbance of neural circuits between the striatum and prefrontal cortex (Frodl, 2010). Furthermore, the functional connections between brain regions that are implicated in inattention for healthy adults may also be disrupted in individuals with ADHD (Rosenberg et al., 2016).

Numerous studies have demonstrated behavioural and neural deficits in sustained attentional processes in ADHD (Kofler et al., 2013). Children with ADHD have shown greater IRV-related activation in parietal and posterior frontal lobes during Go trials and in prefrontal and parietal regions during No-go trials on a GNG task, compared to controls (Suskauer et al., 2008). In adults with ADHD, greater inattention (high IRV) associated with impaired cerebellar DMN coupling with widespread cortical networks has been evidenced, in comparison to healthy controls (Kucyi, Hove, Biederman, Van Dijk, & Valera, 2015). However, neurological and psychopathological research is increasingly revealing a

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dimensionality aspect to developmental disorders such as ADHD (Hudziak, Achenbach, Althoff & Pine, 2007). For example, in adolescents with just symptoms of ADHD (i.e., no diagnosis), structural differences in the brain were found to be associated with increased IRV (Albaugh et al., 2017). It is possible that similar patterns of functional impairment related to IRV that have been observed in ADHD patients, may also be found for individuals with attentional difficulties. However, this has yet to be examined. Furthermore, given the comorbidity of early ADHD and substance abuse in later life, examining neural pathways associated with attention in young adolescent samples who are relatively substance-naïve, may be important for delineating future risk.

1.4.5 Multiple measures of impulsivity

Given that impulsivity is multifaceted (Sharma, Markon & Clark, 2014), the within-subject recording of multiple behavioural and self-report measures can potentially disentangle the overlap between alcohol-use and impulsivity endophenotypes. Generally, parallel measures have shown that increased trait and choice impulsivity tend to be consistently associated with alcohol misuse, whereas the relationship between action impulsivity and alcohol misuse is mixed. For example, 19-year-old binge-drinkers (mean of 6.18 drinks on the last drinking episode) made poorer decisions on an IGT and had higher trait impulsivity (BIS-11), compared to both cannabis-using and non-drug-using groups, but the binge drinkers did not show behavioural differences on an SST relative to controls (Moreno et al., 2012). A broadly similar result was reported in 44 18-25-year-old bingers (a binge score calculated using the Alcohol Use Questionnaire (AUQ; Horn, Skinner, Wanberg, & Foster, 1984), based on average of drinks consumed per hour, number of times being drunk in 6 months and percentage of times getting drunk while drinking) when compared to non-binge

drinkers (Sanchez-Roige et al., 2014). Trait impulsivity (BIS-11) and waiting impulsivity (5-choice serial reaction time task) were associated with binging, whereas neither action impulsivity (SST) nor choice impulsivity (DD) differences were observed between groups. Similarly, Caswell and colleagues (2015b) examined different aspects of trait, choice and motor impulsivity in 18-25-year-old student drinkers, and found that in heavier drinkers, the number of weekly alcohol units was characterised by higher trait impulsivity (Non-planning; BIS-11), but not by motor (SST) or choice impulsivity (MCQ).

As an alternative to comparing drinking and non-drinking groups on individual measures of impulsivity, factor analysis of multiple impulsivity measures in 1,252 18-30-year-olds with low levels of addiction (Mackillop et al., 2016) revealed three factors of impulsivity: trait (UPPS-P, BIS-11), choice (Monetary Choice Questionnaire, DD task), and action (GNG, SST, Conner's Continuous Performance Test) impulsivity. Impulsive traits were not strongly related to choice ($r = 0.10$) or to action ($r = 0.16$), with choice and action *unrelated ($r = 0.01$).* Alcohol Use Disorder Identification Test (AUDIT; Saunders, Aasland, Babor, De la Fuente, & Grant, 1993) scores were significantly associated with trait and choice impulsivity, but not with action impulsivity. However, contrary findings have also been reported with respect to action impulsivity. In 109 18-21-year-old social drinkers, trait (BIS-11) and action (GNG) impulsivity predicted various aspects of drinking (Henges & Marczinski, 2012). Both trait and action impulsivity were significantly associated with total number of drinks consumed and number of heavy drinking days. However, trait impulsivity was only significant for number of drunk days whereas action impulsivity was significant only for highest number of drinks consumed on one occasion in a month. In a prospective design (Fernie et al., 2013), action impulsivity (SST) and choice impulsivity (DD and Balloon Analogue Risk Task: BART) each predicted frequency and severity of alcohol

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problems 6 months later in 287 12-13-year-olds. The mixed findings across studies may reflect differences in the age range of the samples. Alcohol misuse in early adolescence often focuses on the initiation of alcohol consumption, and perhaps the willingness to experiment, whereas research on college-age alcohol misuse tends to orient towards episodic heavy use. It is likely that different impulsivity endophenotypes underlie different patterns of alcohol misuse.

In general, increased trait impulsivity is consistently associated with alcohol-use, particularly in studies using the BIS-11 (Henges & Marczinski, 2012; Mackillop et al., 2016; Sanchez-Roige et al., 2014). However, it is difficult to reach firm conclusions on this conjecture, perhaps partly due to variations in measures used across studies and definitions of groups based on alcohol intake. Furthermore, debate continues as to how these particular endophenotypes are related to each other, and which precise domains are most relevant in generating a risk profile for alcohol misuse (Gullo et al., 2014). For example, the study from MacKillop et al. (2016) found that associations between the self-report and task-based measures were low-to-moderate, and assessment modality varied substantially across three structures. Furthermore, although sensation seeking was initially included in trait impulsivity, it did not load onto this impulsive domain (i.e., $\lambda < .2$) and its removal results in adequate fit for the three-factor model. Whether or not impulsivity and sensation seeking are dissociable constructs remains unclear, with some researchers labelling their joint presence as "disinhibited personality" (Castellanos-Ryan, Rubia & Conrod, 2011).

The ability to sustain attention could be considered as part of the first phase of response inhibition, given that important part of an individual's capacity to inhibit a response is related to their capacity to attend to stimuli (Aragues, Jurado, Quinto & Rubio, 2011). Indeed, the SST requires sustained attention to monitor for the Stop signal in order to initiate

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response inhibition, as well as engagement of attention for both correct go and stop responses (Li & Sinha, 2008). It is suggested that behavioural inhibition requires suppression of a rapid, prepotent response, in order to allow for slower top-down cognitive processes that guide decisions and behaviour to lead to successful inhibitory control (Barkley, 1997; Jentsch & Taylor, 1999). Others argue that these forms of impulsivity are not overlapping, and may be mutually exclusive both at a behavioural or neurobiological level (De Wit & Richards, 2004; Winstanley, Theobald, Cardinal, & Robbins, 2004). Furthermore, another study showed that increasing task difficulty by challenging inhibitory control had a negative effect on inhibitory control (i.e., longer SSRTs), however challenging inhibitory control on other aspects of impulsivity, including reflection (decision making under conditions of uncertainty) and choice (delay of gratification) impulsivity did not adversely impact task performance (Caswell, Morgan, & Duka, 2013b). These findings further emphasise the importance of including impulsivity endophenotypes and measurements in order to establish its relationship with alcohol use.

Measures of inattention, such as the IRV and the Stroop, are often used to assess impulsivity, however inattention is sometimes (e.g., Barkley, Edwards, Laneri, Fletcher & Metevia, 2001) but not always (e.g., Miyake & Friedman, 2012) considered a part of executive functioning. In broad terms, executive functioning includes working memory, attention, and decision-making (Bechara et al., 2001; Koob & Volkow, 2016; Volkow, Wang, Fowler, Tomasi & Telang, 2011). Sharma and colleagues (2014) argue that attentional-related measures that are embedded in impulsivity-specific tasks may be considered more relevant to impulsivity than measures of intelligence or working memory (Sharma et al., 2014). Despite various impulsivity endophenotypes existing under one umbrella term, convergent validity between impulsivity domains (self-report and task-based measures) varies considerably,

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ranging from moderate to no associations (Sharma et al., 2014; MacKillop et al., 2016). This may be attributable to the measures assessing slightly different constructs, or self-report measures providing a subjective interpretation of personal impulsive behaviours (Moeller et al., 2001). Indeed, it has been suggested that task-based measures of impulsivity may yield better predictors of state impulsivity than self-report questionnaires (Caswell et al., 2013a). Ideally, a multi-domain approach that includes multiple impulsivity endophenotypes as well different assessments of similar constructs (e.g., task-based DDT and self-report MCQ for choice impulsivity) would be beneficial for identifying the most pertinent predictors of alcohol misuse.

An array of demographic, psychological and social functions subtend different alcohol-related trajectories. Ultimately, a comprehensive understanding of the factors that contribute towards individual differences in alcohol use will require a broad scope that incorporates everything from brain, cognitive, social and individual determinants. The findings from Whelan et al. (2014) demonstrates the potential of brain data to generate intermediate endophenotypes of alcohol misuse, as well as highlighting the importance of combining brain and personality data to delineate biological processes underpinning alcohol misuse.

Table 1.1

Summary of reviewed studies on impulsivity endophenotypes in alcohol misuse

Author (year)	Age (years) Mean (SD)/ Range (where available)	N	Sample Characteristics	Substance-Use Measure	Endophenotype measure	Main Results
Trait Impulsivity						
Papachristou et al. (2012)	26 (9.66)		29 Light Drinkers & 13 Heavy drinkers	AUDIT	BIS-11	Heavy drinkers had higher BIS-11 total scores than light drinkers
Wardell et al. (2016)	19.75(1.02)/18–25	300	Range of alcohol-users	TLFB, RAPI	BIS-11& UPPS-P	Response & Reflection impulsivity predicted variance in impaired control over alcohol & heavy drinking frequency
Motor Impulsivity						
fMRI						
Ahmadi et al. (2013)	18.9(0.7)/18–20	92	36 Light Drinkers & 56 Heavy drinkers	DSM-IV, SCID	GNG	Heavy drinkers had ↑ RTs & ↓ motor, prefrontal, BOLD responses
Ames et al. (2014)	20.5 (1.2)/ 18-22	41	21 heavy drinkers vs. 20 light drinkers	AUDIT	GNG with alcohol cues	Heavy drinkers had ↑ prefrontal, insula & cingulate activation, & poorer behavioural response inhibition
Beltz et al., (2013)	18-19 (first year students)	11	Range of Alcohol-Related Behaviours	YAAPST	GNG	Consequences of alcohol-use related to ↑ DLPFC & ACC connectivity
Wetherill et al., (2013a)	13.4(0.7)/12-14	60	40 Heavy drinkers (20 blackout+ & 20 blackout-)	The Customary Drinking & Drug Use Record	GNG	Blackout+ had ↑ frontal & cerebellar brain activation during response inhibition. MFG activation predicted future blackouts experience 5 years later

Wetherill et al. (2013b)	14.4(1.2)/11.7-16.7	40	20 heavy drinkers vs. 20 non-drinkers	DSM-IV, CDDR, TLFB	GNG	Heavy drinkers had ↓ baseline frontoparietal, putamen, & cerebellar activation
Worhunsky et al. (2016)	18.4(0.5)/18-19	36	18 escalating drinkers vs. 18 constant drinkers	SCID, SSAGA, MINI	GNG	Escalating drinkers had ↑ impulsivity & frontoparietal activation
Whelan et al. (2012)	14.5 (.45)		1-4 lifetime uses of alcohol vs. non-drinkers	ESPAD	SST	↓lateral OFC activity during successful response inhibition

EEG

Franken et al., (2017)	23.2(9.3)	97	48 Heavy drinkers vs. 49 Light drinkers	QFV	GNG	No behavioural or response inhibition ERP differences, with the exception of ↓ ERN/Pe amplitude in heavy drinkers
López-Caneda et al. (2012)	18.7(0.5)/18-19	48	23 Binge-drinkers & 23 Controls	AUDIT	GNG	Bingers had ↑ NoGo-P3 amplitude at follow-up

Choice Impulsivity

Schneider et al. (2014)	14.3(0.8)/13-15	48	Healthy adolescents	ESPAD alcohol use questions (30 days, past year, lifetime)	DD	Steeper DD associated with ↑ alcohol-use & ↓reward-related activation in the nucleus accumbens & vmPFC.

Multiple Impulsivity Endophenotypes

Moreno et al. (2012)	20(1.8)18–24	66	22 Binge-drinkers, 20 Cannabis users, 26 Non-drug users	CAGE	BIS-11, SSS-V, GNG, SST, IGT, 2-choice task	Bingers had ↑ trait impulsivity & sensation-seeking & impulsive decision-making, but no SST difference
Caswell et al. (2015b)	20.85 (3.79)	160	Range of alcohol-	AUQ	BIS-11, SST,	In heavier drinkers, the number of weekly

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	students		users: 17 units of alcohol/week (range 0–72)		GNG, MCQ, TCIP, SKIP	alcohol units was characterised by higher trait impulsivity (Non-planning; BIS-11), but not by motor (SST) or choice impulsivity (MCQ),
Sanchez-Roige et al. (2014)	21.18(1.89)/18-25	44	22 Binge-drinkers vs. 22 Non-binge-drinkers	AUQ	BIS-11, Sx-5CSRTT, SST, TCIP	BIS-11 5x-5CSRTT ↑ associated with binging; no differences in SST & DD between groups
Mackillop et al. (2016)	21.5/18-30	1,252	Young adults with low levels of addictive behaviour	AUDIT	DD, MCQ, CCPT, GNG, SST, BIS-11, UPPS-P	AUDIT scores ↑ associated with trait impulsivity & choice impulsivity, but not action impulsivity.
Henges & Marczinski (2012)	19.6(1.1)/18-21	109	Range of alcohol-users	TLFB, PDHQ	BIS-11, GNG	↑ trait impulsivity significant for number of drunk days; ↑ action impulsivity was significant for highest number of drinks consumed on one occasion in a month
Fernie et al. (2013)	13.3(0.3)/12-13	287	Range of alcohol-users	AUQ, API	DD, BART, SST	All impulsivity tasks predicted alcohol involvement 6 months later, but not vice versa

AU: Alcohol Use; API: Alcohol Problems Index; AUD: Alcohol Use Disorder; UPPS: Impulsive Behaviour Scale; TLFB: Alcohol Timeline Followback; DMQ: Drinking Motives Questionnaire; S-MAST: The Short-Form Michigan Alcoholism Screening Test; BIS-11: Barratt Impulsiveness Scale; AUDIT: Alcohol Use Disorders Identification Test; FrSBE: Frontal System Behaviour Scale; OFC: Orbitofrontal Cortex; VmPFC: Ventromedial Prefrontal Cortex; SPSRQ: Sensitivity of Punishment and Sensitivity of Reward Questionnaire; YAAPST: Young Adult Alcohol Problems Screening Test; GNG: Go/No Go Task; DLPFC: Dorsolateral Prefrontal Cortex; ACC: Anterior Cingulate Cortex; MFG: Middle Frontal Gyrus; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; SCID: Structured Clinical Interview for DSM-IV; RT: Reaction Time; SSAGA: Semi Structured Assessment for the Genetics of Alcoholism; MINI: Mini International Neuropsychiatric Interview; CDDR: Customary Drinking and Drug Use Record; BART: Balloon Analogue Risk Task; QFV: Quantity Frequency-Variability Index; SKIP: Single Key Impulsivity Paradigm; IMT; Immediate Memory Task; ERP: Event-Related Potentials; Pe: Evoked Potentials; RAPI: Rutgers Alcohol Problem Index; BD: Binge-drinkers; TRAILS: Tracking Adolescents' Individual Lives Survey; MID: Monetary Incentive Delay Task; DDHx: Drinking and Drug History Questionnaire; FH: Family History of Alcoholism; fMRI: Functional Magnetic Resonance Imaging; M: Mean; SST: Stop Signal Task; CAGE: CAGE Questionnaire; SU: Substance use; PDHQ: Personal Drinking Habits Questionnaire; IST: Information Sampling

Task; SSS-V: Sensation-Seeking Scale form V; ESPAD: European school survey project on alcohol and other drugs; Sx-5CRTT: Five-Choice Serial Reaction Time Task; TCIP: Two Choice Impulsivity Paradigm; IGT: Iowa Gambling Task; AUQ: Alcohol Use Questionnaire; MCQ: Monetary Choice Questionnaire; CCPT: Conners' Continuous Performance Test; SURPS: Substance Use Risk Profile Scale; CANTAB: Cambridge Neuropsychological Test Automated Battery; WISC-IV: Wechsler Intelligence Scale for Children; SFG: Superior Frontal Gyrus; DD: Delay Discounting Task; TCI-R: Temperament and Character Inventory-Revised; ERN=Error-related Negativity (*Pe* amplitude reflects the perception of the error); ↑ = increase; ↓ = decrease; + = symptom present; - = symptom absent. *No study to date has examined the IRV on the SST in relation to cognitive impulsivity with alcohol use, and therefore it was not included in this table.

1.5   Other risk factors and alcohol

1.5.1   Reward and punishment learning

The choice impulsivity findings indicate that maladaptive decision-making process are related to increased alcohol misuse. The ability to update reward and punishment contingencies is another aspect of decision-making, which requires the ability to successfully adapt to a changing environment. The probabilistic selection task (PST; Frank, Seeberger, & O'Reilly, 2004) quantifies individual differences in learning from reinforcement relative to learning from punishment (i.e., from positive relative to negative feedback). The PST has demonstrated the ability to predict smoking status in students; with lower rates of learning from rewards associated with an increased likelihood of being a smoker or ex-smoker, compared with being a non-smoker, and higher rates of learning from punishment associated with an increased likelihood of being a smoker, compared to non-smokers (Rai et al., 2018). Substance misusers (e.g., alcohol, cannabis, and nicotine use) are poorer at learning both from rewards and from punishment relative to non-dependent groups (Baker, Stockwell, Barnes & Holroyd, 2011; Baker, Stockwell & Holroyd, 2013), supporting addiction models that involve desensitisation of reward circuits over time (Volkow, Koob, & McLellan, 2016). Examining reward and punishment learning in alcohol misusers would shed further light on addictive risk factors.

1.5.2   Psychological health

Alcohol abuse is implicated in a variety of physical health issues across the lifespan, for example, liver disease (Louvet & Mathurin, 2015); specific cancers (Bagnardi et al., 2015); and cardiovascular disease (Roerecke & Rehm, 2014). However, the psychological impact of alcohol can occur from both acute and chronic abuse, with alcohol consumption

consistently linked to increased levels of depressive disorders (Boden & Fergusson, 2011; Schuckit, Smith & Kalmijn, 2013) and anxiety disorders, particularly, social anxiety (Gilles, Turk & Fresco, 2006; Ham, Zamboanga, Bacon & Garcia, 2009). Alcohol misuse is often associated with increased symptoms of depression, anxiety and stress in both the general population (Wiener et al., 2017) and among university students (Walters, Bulmer, Troiano, Obiaka & Bonhomme, 2018). The My World Survey (Dooley & Fitzgerald, 2012), the first Irish national study of youth mental health (12-25-year olds) found a strong relationship between problematic levels of alcohol consumption and psychological distress (stress, depression and anxiety, based on the DASS in adolescents and young adults. However, while some studies suggest anxiety is a risk factor for alcohol use in university students (DeMartini & Carey, 2011; Stewart, Zvolensky & Eifert, 2001), others have failed to identify a significant link (Armeli, Todd, Conner & Tennen, 2008; Ham et al., 2007; Novak et al., 2003). It is possible that these inconsistencies are due to differences in anxiety measures or constructs (social anxiety versus anxiety sensitivity).

1.5.3 Social Support

Specific contextual factors promote, hinder, or intensify individual risk factors for alcohol misuse (e.g., peers, family, and cultural norms for drinking; Kaiser et al., 2016; Schneider et al., 2014). Alcohol misuse is largely recognised as being influenced by multiple social factors, including family, peers and neighbourhoods. Social support, defined as an accessible social network that provides emotional and instrumental support (Cohen, 2004). is a risk factor for, and protective factor against, problematic behaviours. For example, college students with lower social support were found to have a higher tendency to engage in drinking after a negative event than their peers with higher levels of social support (Hussong,

Hicks, Levy & Curran, 2001). In young adulthood, being in a committed romantic relationship has been found to be a protective factor against heavy and frequent drinking (Fischer & Wiersma, 2012; Fleming, White, & Catalano, 2010), while relationship dissolution is a risk factor (Fleming, White, Oesterle, Haggerty, & Catalano, 2010; Salvatore, Kendler, & Dick, 2014).

Cumulative risk factors are associated with higher binge-drinking rates (Gowin et al., 2017), and there are numerous other risk factors for alcohol misuse, such as gender, cannabis and nicotine (Squeglia et al., 2016; Whelan et al., 2014) and executive functioning (Peeters et al., 2015). Facilitating the inclusion of a large number of variables will provide a more nuanced insight into the relationship between impulsivity endophenotypes, as well as other pertinent psychological constructs, and alcohol use.

1.6   Multi-domain analyses

There are likely to be thousands of potentially informative predictors of alcohol-related outcomes, such as demographic, personality, behavioural, neurobiological, and genetic variables. One of the challenges this presents is how best to utilise methods that can interrogate large, multivariable datasets. Firstly, acquiring neuroimaging data is expensive, and neuroimaging studies often use small sample sizes (typically less than 50 participants), which increases the probability of false positive findings –Type I errors (Button et al., 2013). Secondly, neuroimaging data are highly dimensional and highly collinear by nature. In the case of fMRI data, there are usually hundreds or thousands of voxels, whilst for EEG, there are typically more than 64 channels, acquired at a sampling rate of over 256 Hz. When generating predictive models using neuroimaging data using standard methods, the high ratio of predictors to participants will result in 'overfitting' even in relatively large samples (see

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Whelan & Garavan, 2014). Overfitting occurs because a model derived from a sample will partly reflect the unique data structure of that particular sample—including noise in the data. In other words, the model fits to the idiosyncrasies of the sample, as opposed to factors that are common to the population from which the sample is drawn. Overfitting leads to models producing seemingly very good prediction, however, they then generalise poorly to other samples from the same population. Fortunately, principles and techniques developed within the field of machine learning are well suited for neuroimaging data.

1.7   Interrogating large, multi-domain data

Addiction research has traditionally been conducted using methods developed within the natural sciences; that is, hypothesis-driven research typically based on assays of single cognitive functions and the use of statistical inference to quantify the likelihood of the observed effect occurring by chance. However, data driven approaches, using algorithms that search for patterns in data are gaining increasing traction in the field of psychology and neuroscience. In contrast to traditional approaches (Bzdok, Altman & Krzywinski, 2018), many different types of data can be included in a model and there are usually more data points than there are participants. This is borne out of the arrival of the 'Big Data' era, which typically denotes datasets that cannot be acquired or processed in a reasonable time frame on standard computers (Chen, Mao, & Liu, 2014; Cheung & Jak, 2016). Rather than statistical inference, accurate prediction on previously unseen data is the metric of success. Statistical significance between groups is quantified based on group means and within-group variance, and differences are strengthened by higher within-group homogeneity (Lo, Chernoff, Zheng, & Lo, 2015). Good predictors, conversely, harness individual differences (i.e. heterogeneity within the entire sample) to generate an outcome estimate (Jollans & Whelan, 2018).

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Therefore, variables that significantly differ between groups may (or may not) be good predictors, and vice versa ((Dubois & Adolphs, 2016; Westfall & Yarkoni, 2017). Machine learning methods can offer a substantially different perspective on addiction.

1.7.1 Machine Learning

Machine learning (ML) is a useful method for interrogating complex datasets, particularly when the number of variables exceeds the number of participants (Bzdok, Krzywinski & Altman, 2018). ML searches for patterns in the data and selects the most important variables, termed 'feature selection', in a principled way that also attenuates overfitting. Unlike null hypothesis significance testing, from a machine-learning perspective the ability of a model to accurately predict previously unseen data quantifies success (Bzdok, Krzywinski & Altman, 2018): often termed 'out-of-sample' validation. Using a separate dataset is the gold standard in terms of assessing out-of-sample validation. However, a more cost-effective method can be implemented by resampling the data— cross-validation (CV), which involves the division of a dataset into multiple 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), which will be discussed below.

Different methods for feature selection exist (e.g., random forests, support vector machines), or some form of linear or logistic regression. Not every method is suitable for data that are inherently multicollinear (e.g., timings for ERPs in EEG data – often in the order of ms, or neighbouring voxels in neuroimaging data), and this needs to be accounted for when choosing a feature selection method. In regression methods, typically, the outcome variable is used to train an algorithm to identify some combination of features (e.g., brain, behavioural,

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trait, environmental, and/or genetic) that are associated with that outcome. The outcome variable can be categorical measures (e.g., addicted versus non-addicted groups), wherein the objective is to identify the features that accurately classify the groups – a logistic analysis. Model performance can be evaluated using the area under the curve (AUC) of the receiver-operating characteristic (ROC) curve (AROC), which quantifies the ability of the model to correctly classify groups by tracking the rate of true and false positive classification of the model. Alternatively, the outcome being predicted can be dimensional measures (e.g. SU severity across a group of individuals), wherein the outcome is a weighted linear combination of predictive features – a linear regression analysis.

In traditional multiple-linear regression models (i.e., ordinary least squares for linear regression) the estimates are optimised for the sample of data in which the model is fitted. Therefore, the model fit statistics will increase as the number of estimated parameters increases, and/or the number of participants decreases. This results in an overfit, and leads to overoptimistic interpretations of the results (Whelan & Garavan, 2014). A consequence of this overfitting, however, is that the model will poorly predict the outcome of new, previously unseen observations. Crucially, the goal for predictive modelling is to ensure that a model can accurately make predictions about novel observations. The tendency to overfit (whilst retaining the variables to participants ratio) can be attenuated using two methods in tandem: cross-validation, and regularisation.

Penalised regression is a regularization method that involves adding a penalty on the complexity of the model. Three types of penalized regression (LASSO, ridge or elastic nets) vary in their variance/bias trade-offs, depending on the characteristics of a given dataset. LASSO (Least Absolute Shrinkage And Selection Operator; Tibshirani, 1996) regulariation imposes an L1 penalty, which constrains the sum of absolute values of coefficients and

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encourages parameters to be 0. This ensures a parsimonious solution; selecting only variables that are important and eliminating coefficients of unimportant variables. This solution may not be appropriate for a dataset of correlated variables, especially if the number of variables is small compared to the number of participants. On the other hand, ridge regularization (Hoerl & Kennard, 1970) encourages parameters to be small, avoiding overfitting (Murphy, 2012), but rather than excluding variables, ridge regression will keep all variables in the final. Machine learning using the Elastic Net (Zou & Hastie, 2005) is a regularization method for generalised linear models, which provides some balance between LASSO and the ridge regressions.

The Elastic Net includes both L1 regularization (i.e., LASSO regularization - penalties on the absolute) and L2 regularization (i.e., ridge regularization – penalties on squared values of the β weights)). This allows relevant but correlated coefficients to coexist in a sparse model fit, by doing automatic variable selection and continuous shrinkage simultaneously (Jollans et al., 2016). The Elastic Net uses two parameters: λ and α. Alpha represents the weight of LASSO versus ridge regularization, and λ is the regularization coefficient.

Cross-validation involves the partitioning of the original dataset into multiple training and test sets. A model is created with 90% of the data (training set), and the model is then evaluated on the remaining 10% of the data (test data). Importantly, the test set is not used during model estimation, which allows a researcher to establish how well the model generalises to out-of-sample data. This is referred to as the outer CV stage, where feature selection occurs.

Within the test set, an additional CV fold (nested CV) is created with the model building on 81% of the data and evaluated on the 9%, which is used to identify the optimal

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Elastic Net parameters α and λ. k-fold cross-validation, where k=number of partitions (folds) from the original dataset. Each fold contains an equal number of unique samples from the original dataset (i.e., when k= 10 and N=100, each kth fold will have n=10 observations). k-fold cross-validation then becomes an iterative process whereby a single fold is set aside as the test sample ("test fold"), and a model is estimated on the remaining k-1 folds. The model estimated on the k-1 folds is then evaluated on the set aside test fold, thereby insuring the independence of the final test sample. This process is repeated k times, resulting in k final models. In doing so, each observation is tested exactly once, and used in model estimation k-1 times. Ten-fold cross-validation with nested cross-validation for tuning and validating the model is recommended for datasets that include a large number of variables and have relatively smaller sample sizes (Jollans et al., 2015). See *Figure 1.2*. for an example of the procedure for nested cross-validation.
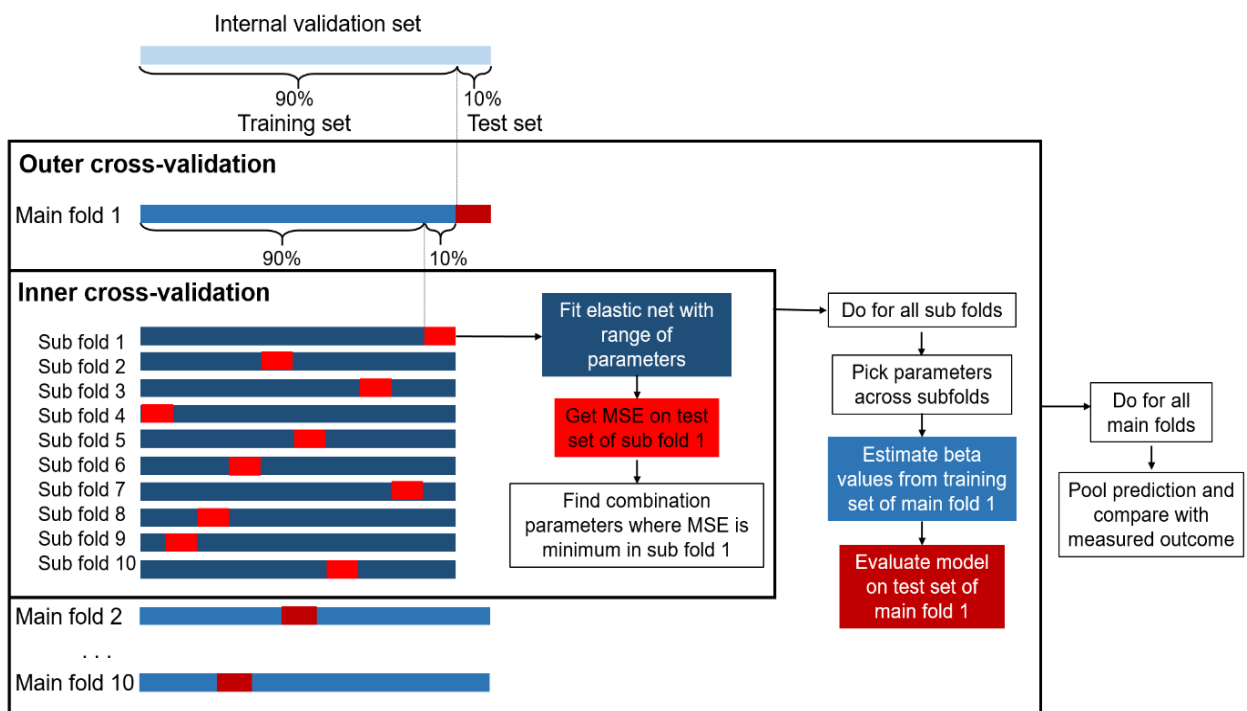
Figure 1.2. Example of procedure for nested cross-validation. MSE=mean squared error.

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Bootstrap aggregation can also be introduced as an additional level of stability (Breiman, 1996), whereby parameter optimisation is repeated a number of times (e.g. 25), using sampling with replacement. The results from all iterations within each training fold are then averaged. This analysis on the internal validation set can be repeated numerous times (e.g., 10 times) and the results (correlation coefficients and beta weights) can be averaged across the 10 iterations of the analysis procedure, which would yield 100 sets of beta weights, from 10 cross-validation folds across 10 analysis iterations, with beta weights averaged for each variable.

Despite efforts made to guard against overfitting, there may nevertheless still be a degree of inherent optimism in any model. Ensuring that a model produces results that are significantly better than chance is not possible using traditional p-values (Jollans & Whelan, 2016). Instead, 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 randomisation of the dependent variable across participants (random label permutation). 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 performance of the model can be quantified using typical model performance statistic, such as cross-validated r, which is the best combination of parameters.

1.7.2 Machine learning studies examining alcohol

Several studies of substance use have already applied machine learning methods to large neuroimaging datasets. For example, a 2-year prospective MRI study in the IMAGEN cohort (total n = 692; Whelan et al., 2014) showed that a combination of factors (demographic, life history, personality, cognitive, and brain data) could accurately predict BD at 16 years-old, based on data collected at 14 years-old, with 73% of abstainers and 66% of future binge-drinkers correctly classified. Predictors of future binge drinking included neuroimaging data from tasks assaying reward processing, behavioural inhibition and affective face processing. By iteratively omitting each domain (e.g., brain, personality, or life history) from the model and repeating the analysis, insights were gained into the relative contributions of different factors for binge drinking. Life history was most important predictor, followed by personality, with brain data ranking third. Similarly, Squeglia and colleagues (2016) collected neuroimaging data, both structural (cortical thickness) and functional (a visual working memory task) from 137 12–14-year-old substance-naive adolescents. A machine-learning approach, using a method called Random Forest, was able predict alcohol-use initiation by age 18, with 74% sensitivity and 73% specificity. Adolescents with lower performance on tests of executive functioning tests and who were faster on sustained attention tests were more likely to initiate alcohol use. One other longitudinal fMRI study from the IMAGEN project showed that decreased activity in the mesolimbic (ventral striatal and midbrain) and prefrontal cortical (dorsolateral prefrontal cortex) regions to anticipated rewards (measured using the Monetary Incentive Delay Task) predicted whether novelty-seeking adolescents (N = 144) would later develop problematic drug use (Büchel et al., 2017). Machine learning analysis revealed that out-of-sample

prediction accuracy was higher for a model including brain measures compared to a model with only behavioural measures (Büchel et al., 2017).

Although the above studies show the potential utility of neuroimaging for predicting substance use, neuroimaging predictors of alcohol use have shown modest utility to date. It is worth noting that, first, a wide range of data were collected and second, that no single type of predictor was very accurate on its own. These findings underscore the need for a wide range of data to be obtained. Future research should use out-of-sample performance as a quantitative measure of a predictor's utility. Neuroimaging data should be combined across multiple modalities, including structural information such as volumetrics and cortical thickness, in conjunction with white-matter tractography. A number of relevant neurocognitive systems should be assayed; particularly, inhibitory control, reward processing and executive functioning

1.7.3   Predicting alcohol outcomes using EEG data

Electroencephalography (EEG) measures may improve screening and assessment of alcohol misuse, as they offer high temporal resolution, are relatively convenient to use and are objective (Mumtaz, Vuong, Malik, & Rashid 2017a). In order to identify neural indicators of alcohol misuse, meaningful individual ERP parameters are needed (Campanella et al., 2018). However, as described earlier, EEG datasets are highly dimensional. To reduce the likelihood of Type I errors, data from high density EEG arrays are reduced in dimension by selecting a specific time interval and a minimal set of channels to define ERPs. As a result, EEG studies examining alcohol use have typically focused on 'single ERP components' (i.e., P3, N2) for a specific brain region, and several neurofunctional components are still unexplored.

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A multivariable approach, based on a weighted combination of diverse electrophysiological features, will likely be more useful for predicting outcomes than any single endophenotype. Machine learning may be particularly useful for finding new relationships among variables because analyses are not restricted to specific time intervals or electrodes, and nested cross-validation ensures that parameter optimisation is done automatically and is independent from the data upon which the model with selected parameters will be tested. EEG-based ML methods to predict alcohol-related outcomes show promising results (Kuncheva & Rodrıguez, 2013; Lopes et al., 2004; Mumtaz et al., 2017b). Mumtaz and colleagues (2017b) applied a ML approach to resting-state EEG data, and found that EEG features (spectral power and inter-hemispheric coherences) accurately classified 30 patients with AUD from 15 healthy controls (Accuracy=89.3%, sensitivity=88.5%, specificity=91%). However, ML has been rarely used to interrogate ERPs (but cf Johannesen et al., 2016; Kiiski et al., 2018; Stock et al., 2015), although the use of a task probing specific cognitive systems markedly improves performance (Greene, Gao, Scheinost, & Constable, 2018).

This thesis will investigate this further, however, a better approach for ultimately understanding the pathophysiology of alcohol misuse is to focus on endophenotypes, such as impulsivity, to indicate markers of alcohol consumption, as well as evidence provided by neuroimaging data.

1.8   Specific aims of the research

Based on the evidence compiled in **Chapter 1**, impulsivity endophenotypes are strongly related to different patterns of alcohol use, although the precise nature of these associations remains unclear. A multi-domain approach that includes impulsivity endophenotypes, as well other risk factors, would help identify the most pertinent predictors of alcohol use. Machine learning can harness large complex data with heterogeneous distributions, determine relationships from complex conditional dependencies between variables, and test the reliability of results through repeated cross-validation. Using this framework, an avenue for research is to investigate which impulsivity endophenotypes are most closely related to patterns of alcohol use. Secondly, neuroimaging indexing inhibitory control can characterise individual differences in alcohol use - yet, the potential for ERPs to predict alcohol use is relatively underexplored. Thirdly, cognitive impulsivity (i.e., lapses in sustained attention), has been relatively under--researched, compared to trait, motor and choice impulsivity, and the brain networks supporting cognitive impulsivity indexing sustained attention have yet to be mapped in healthy adolescents.

Chapter 2 applied machine learning to test the hypothesis that different facets of impulsivity were related to different alcohol use patterns. A factor analysis was conducted to generate two orthogonal latent factors of alcohol use. ML with penalized regression and feature selection was applied to impulsivity endophenotypes to predict different alcohol-related outcomes. A second model combining impulsivity endophenotypes with other risk factors (gender, nicotine-, cannabis- and other drug-use, executive functioning and learning processes) was also tested with the alcohol use factors, and its performance was compared to the model comprising of impulsivity alone. Out-of-sample validation was used to quantify model performance. This Chapter identified neuroimaging as a useful tool for identifying

vulnerability markers of alcoholism.

However, as introduced in **Chapter 3**, machine learning studies using event-related potentials (ERPs) to predict alcohol use remain scarce, and research on the relationship between alcohol use and SSRT, and between alcohol use and ERPs, is mixed. Chapter 3 applies a ML method with penalised linear regression to ERPs indexing inhibitory control on an SST, in order to predict a wide range of scores on the Alcohol Use Disorders Identification Test. Extending the findings from Chapter 2, four separate models are also tested, including demographic, self-report and task-based measures of impulsivity, personality and psychological factors, with out-of-sample validation used to quantify performance.

Based on the findings of Chapters 2 and 3, it became evident that cognitive impulsivity, i.e., lapses of attention, was an important predictor of different patterns of alcohol use. Despite important implications of individual variability in sustained attentional abilities, we know relatively little about its neurobiological underpinnings in healthy adolescents, as indexed by the intra-individual response variability (IRV) on an SST. Using fMRI, **Chapter 4** examined the brain regions and functional connections underlying IRV in a large population-based sample of adolescents, as well as the relationship between IRV with alcohol use and with symptoms of ADHD. A data-driven, multi-step analysis approach was used to identify networks associated with low IRV (i.e., good sustained attention) and high IRV (i.e., poorer sustained attention).

In the final Chapter, **Chapter 5**, the main findings of this thesis were summarised and integrated into a wider context. This Chapter considered how the research informs theory, as well as potential directions for studying the relationship between impulsivity endophenotypes and alcohol-related outcomes, methodological limitations, and explored clinical implications.

2 Chapter 2: A Combination of Impulsivity Endophenotypes Predict Alcohol Intoxication Frequency[2]

2.1   Introduction

As described in Chapter 1, impulsivity, broadly characterised as the tendency to act prematurely without foresight, is known to be related to alcohol misuse. However, impulsivity is a broad concept and has been subdivided into various domains by different researchers (Robbins & Dalley, 2017). One possible way to fractionate impulsivity is as follows. *Trait* impulsivity relates to traits such as non-planning or boredom susceptibility, and can be quantified using self-report scales. *Choice* impulsivity involves the tendency to choose immediate smaller rewards over larger delayed rewards – quantified by individual differences in delay discounting – and can be measured via a questionnaire or via a task. *Motor* impulsivity is the tendency towards prepotent, disinhibited motor responses and can be assayed using Go/No-Go (GNG) or Stop Signal (SST) tasks. Finally, *cognitive* impulsivity can refer to impaired sustained attention (Sharma et al., 2014), and it can also be measured using the SST by examining behavioural variability in task performance (i.e., greater variance in response times on Go response trials; Bellgrove *et al*., 2004). Other impulsivity domains have been proposed (e.g., *reflection impulsivity* – insufficient accumulation of information prior to making a decision), and some have suggested that sensation seeking represents a different construct from impulsivity (see MacKillop et al., 2016).

Debate continues as to the precise domains that are most relevant to generating a risk profile for alcohol misuse (Gullo et al., 2014). Moreover, despite various facets of impulsivity existing under one umbrella term, convergent validity between impulsivity domains (self-report and task-based measures) varies considerably, ranging from moderate to no associations (Sharma et al., 2014; MacKillop et al., 2016). For example, in a cross-sectional study of 1,252 light drinkers (MacKillop et al., 2016), associations between self-report and task-based measures of impulsivity, including trait (UPPS-P and Barratt

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Impulsiveness Scale 11th version; BIS-11), choice (delay discounting task; DDT) and action impulsivity (including GNG and SST), were low-to-moderate.

Different impulsivity endophenotypes may be differentially related to patterns of alcohol consumption. Indeed, the lack of shared variance among impulsivity measures presents an opportunity to combine impulsivity endophenotypes into a single model to predict individual differences in alcohol use. Using structural equation modelling for impulsivity domains, Mackillop and colleagues (2016) found that trait (Attentional, Motor, and Non-planning BIS-11 second-order factors) and choice impulsivity, but not action impulsivity, were significantly associated with lighter levels of alcohol use in student drinkers (mean of 4 on the Alcohol Use Disorder Identification Test; AUDIT). In heavier drinking 18-25-year-old students (Caswell *et al*., 2015b), the number of weekly alcohol units was characterised by increased trait impulsivity (Non-planning; BIS-11), but not by action (SST) or choice impulsivity (measured using a *Monetary Choice Questionnaire). Similarly,* binge drinking scores (Sanchez-Roige *et al*., 2014) were associated with higher trait impulsivity (Non-planning and Motor; BIS-11), but not by action (SST) or choice impulsivity (DDT).

The relationship between impulsivity and alcohol may also depend on the type of alcohol use measurements that are employed. For example, Henges and Marczinski (2012) evaluated how trait (BIS-11) and action (Go/No-Go; GNG) impulsivity, as well as gender and drinking history, would predict various aspects of alcohol consumption (total number of drinks consumed; highest number of drinks consumed; number of heavy drinking days; number of drunk days in past 30 days on a Timeline Followback Interview) in 109 18–21-year-old student drinkers using multiple regression. Although gender and history were significantly associated with all alcohol outcomes, only trait impulsivity was significant for

number of drunk days, and only action impulsivity was significant for highest number of drinks consumed.

Given the variability in findings relating to alcohol use and impulsivity, incorporating several predictor variables to better characterise alcohol use patterns may be advantageous. However, including several highly correlated measures in regression models is challenging, due to multicollinearity and overfitting (see Whelan & Garavan, 2014). Penalized regression, often employed within machine-learning approaches, can overcome these difficulties (Gillan & Whelan, 2017; Yarkoni & Westfall, 2017). For example, a machine learning study that used a combination of neuroimaging, executive functioning, demographic and behavioural factors (e.g., sex, socioeconomic status, early dating, externalizing behaviours, and positive alcohol expectancies) from 12–14-year-olds, predicted alcohol-use initiation at age 18 with 74% accuracy and 73% specificity (Squeglia *et al*., 2016). Similarly, a study of 14-year-olds (Whelan *et al*., 2014) also demonstrated the ability to predict binge-drinking two years later with approximately 70% accuracy, utilising measures of trait impulsivity, choice impulsivity (delay discounting) and cognitive impulsivity (standard deviation of go reaction time (RT) from the SST). It is plausible that trait impulsivity but not choice or action impulsivity predict alcohol use in middle adolescence, as some have previously suggested (Chapter 1). However, the self-report and task-based impulsivity measures that are associated with heavier college-age drinking patterns remain to be delineated. Furthermore, including other risk factors associated with adolescent alcohol misuse, such as executive functioning and reward processing, may shed light into cumulative risk factors associated with higher binge-drinking rates (Gowin et al., 2017).

Executive dysfunction (e.g., poor performance on the Stroop task; see Day et al., 2015) and reward processing are closely related to impulse control and increased substance

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use in young adults (Yip & Potenza, 2016). One aspect of reward processing – learning from reinforcement relative to learning from punishment (i.e., from positive relative to negative feedback) – can be examined using the Probabilistic Selection Task (PST; Frank et al., 2004). Learning from reward and from punishment during the PST was attenuated in a polysubstance-dependent sample (alcohol, cannabis, and nicotine use) compared to a non-dependent group (Baker et al., 2013), supporting the theory that reward circuits become desensitised over time in addiction (e.g., Rose et al., 2012; Volkow et al., 2016). However, another study examining alcohol-dependent patients compared to healthy controls found no group differences in reward learning (Rustemeier et al., 2012). It therefore remains unclear how individual differences in reward and punishment learning are related to non-dependent alcohol use.

Defining alcohol misuse in university students is difficult. Memory heuristics render the accuracy and validity of widely used self-reported alcohol consumption as questionable (Patrick & Lee, 2010). However, this problem can be mitigated by using similar questions relating to multiple time points as a memory cue, which increases recall accuracy (Eisenhower et al., 1991). Secondly, the standard binge drinking definition (i.e., Wechsler & Nelson, 2001) employs a single consumption-based measure, which may not necessarily reflect the effects of alcohol that contribute to severity and alcohol-related harm (Pearson et al., 2016). Some research indicates that alcohol cut-off scores do not provide particularly strong levels of sensitivity and specificity for predicting adverse consequences of alcohol use, and that model optimisation is also dependent on the measure used (e.g., number of drinks per drinking day or highest number of drinks consumed during a given time period; Pearson *et al*., 2017). Furthermore, countries differ in the average amount of alcohol per unit or standard drink (Kuntsche *et al*., 2017), limiting our understanding of the severity or types of

alcohol-related consequences and the development of effective treatments (Kuntsche *et al*., 2017). In contrast, drunkenness in adolescence, rather than alcohol quantity *per se*, has been linked to persisting problem behaviours (e.g., smoking and cannabis use) by age 15 (Kuntsche *et al*., 2013). Therefore, rather than solely focusing on quantity of alcohol, incorporating patterns of drinking (including intoxication frequency) may provide better predictors of problem behaviours. A composite alcohol-use score may also provide a better metric for examining alcohol-related consequences and underlying factors, including impulsivity. Here, alcohol-use patterns were examined, (i.e., alcohol composite scores based on frequency of alcohol use, binge-drinking frequency and perceived intoxication levels) in university student drinkers by applying machine-learning to trait, choice, motor and cognitive measures of impulsivity.

2.2 Materials & Methods

2.2.1 Sample

Students (N=106) from two universities (age range 18-21-years-old; 47 females) participated and all reported alcohol use in the past 12 months. Exclusion criteria included having current substance dependence (other than nicotine), or a history of traumatic brain injury. As expected, the majority of the sample reported having tried cigarettes (90%), cannabis (79%) and other drugs (44%) at some time in their lives, and excluding these participants might have led to a non-representative sample.

2.2.2 Procedure

Participants were recruited at two universities via direct e-mail and campus flyers. Following completion of informed consent forms, participants began the experimental tasks alone in a sound-attenuated booth (see Measures for task order). Questionnaires were
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completed immediately after the testing session, or at home via an online survey platform. Participants were provided with €10 (approximately $12) compensation, in addition to travel expenses up to the value of €10, or with course credit. The study procedure was approved by the University College Dublin School of Psychology Ethics Committee and the Trinity College Dublin School of Psychology Ethics Committee.

2.2.3 Measures

Substance Use. A portion of the European School Survey Project on Alcohol and Other Drugs questionnaire (ESPAD; Hibell *et al*., 2009) was used to assess personal use of alcohol, nicotine, cannabis, and other drug-use, as well as items regarding expected personal consequences of alcohol use (See Supplemental, Table S2.2 for items included). Frequency of alcohol use was assessed across lifetime, past 12-months and past 30-days (see Table 2.1). Nine adverse consequences ("Because of your own alcohol-use, how often during the last 12 months have you experienced the following?") and eleven expectations ("How likely is it that each of the following things would happen to you personally, if you drink alcohol?") of alcohol-use were also assessed.

Table 2.1

ESPAD Substance Use Sample Characteristics

Title	Females (n=47)	Males (n=59)	Total Mean (SD)	p
Alcohol				
Age of first Drunkenness	2.40 (1.03)	3.05(1.36)	2.76 (1.26)	.26
Frequency >5 Drinks per occasion in past 30 Days	3.21 (1.67)	3.15 (1.57)	3.18 (1.61)	.85
Intoxication Frequency				
(1) lifetime	5.04 (1.98)	4.95 (1.68)	4.99 (1.81)	.54
(2) past 12 months	3.51 (2.04)	2.93 (1.86)	3.19 (1.96)	.12
(3) past 30 days	1.64 (0.87)	1.54 (.86)	2.58 (0.86)	.43
Drinking Frequency				
(1) lifetime	5.94 (1.01)	6.34 (0.58)	6.16 (0.82)	.004*
(2) past 12 months	5.49 (1.53)	6.00 (1.27)	5.77 (1.41)	.01*
(3) past 30 days	3.98 (2.05)	4.31 (1.72)	4.16 (1.87)	.34
Cannabis				
Cannabis Frequency				
(1) lifetime	3.66 (2.20)	4.93 (2.39)	4.37 (2.38)	.005*
(2) past 12 months	2.72 (2.14)	3.78 (2.69)	3.31 (2.51)	.07
(3) past 30 days	1.47 (1.28)	2.61 (2.17)	2.10 (1.91)	.003*
Drugs				
Drugs Frequency (amphetamines, tranquillizers / sedatives, ecstasy, LSD, crack, cocaine, heroin, magic mushrooms" GHB, anabolic-steroids)				
(1) lifetime	2.19 (1.93)	3.19 (2.21)	2.75 (2.14)	.01*
(2) past 12 months	1.77 (1.49)	2.37 (1.76)	2.10 (1.67)	.03*
(3) past 30 days	1.30 (0.83)	1.34 (0.66)	1.32 (0.74)	.32
Nicotine				
Nicotine Frequency				
(1) lifetime	5.36 (2.34)	6.00 (1.88)	5.72 (2.11)	.13
(2) past 30 days	2.32 (1.71)	2.54 (1.86)	2.44 (1.79)	.51

Note: Scoring of items are as follows: Age of first Drunkenness 1=Never, 2=16yrs, 3=15yrs, 4=14yrs, 5=13yrs, 6=12yrs, 7=11yrs, 8=3-10yrs, 9=<9yrs); Frequency >5 Drinks per occasion in past 30 Days (1=0, 2=1, 3=2, 4=3-5, 5=6-9, 6=>10); Intoxication/Drinking / Cannabis/Drugs / Nicotine Frequency (1=0, 2=1-2, 3=3-5, 4=6-9 5=10-19, 6=20-39, 7=>40). *Significant differences between females and males, using Mann-Whitney U tests.

Self-reported Impulsivity. The Barratt Impulsiveness Scale 11th version (BIS-11; Patton & Stanford, 1995), a 30-item questionnaire measuring impulsivity on a five-point Likert scale (ranging from disagree strongly to agree strongly), yields three second-order factors – Motor, Attentional and Non-planning impulsivity. The scale has strong internal consistency and reliability (Stanford et al., 2009).

Self-reported Sensation Seeking. The Sensation Seeking Scale Form V (SSS-V; Zuckerman et al., 1978) consists of 40 dichotomous questions probing individual differences in one's tendency to pursue feelings and experiences that are more novel, diverse, complex and/or intense, which are divided into four 10-item subscales – Boredom Susceptibility, Disinhibition, Experience Seeking, and Thrill and Adventure Seeking. The SSS-V has good psychometric properties (Zuckerman, 2007).

Choice Impulsivity. Delay discounting rates (K) were assessed using Mazur's (1987) hyperbolic discounting model (See Supplemental for further details). The Monetary Choice Questionnaire (MCQ; Kirby et al., 1999) is a 27-item measure assessing choice impulsivity. Participants choose between a fixed sequence of sooner, immediate rewards (SIR; ranging from \$11-\$80) or later, delayed rewards (LDR; ranging from \$20-\$85, in delays from 7-186 days). This scale has good internal reliability (Duckworth & Seligman, 2005). Kirby's automatic scoring tool (Kaplan et al., 2014) was used to generate a geometric mean k score for each participant. In addition, an adaptive Delay-Discounting Task (DDT) was used (74 trials in total in a 6-minute run). This required participants to choose between a series of choices between SIR and LDR, and adapted to the participant's own k value. See Supplemental and *Figure S2.1* for further task details.

Motor impulsivity. An adaptive Stop Signal Task (SST; 120 trials in total in a 9-minute run) assessed impulsive action, whereby a tracking algorithm was used to adjust task difficulty. The Stop Signal Reaction Time (SSRT), an index of inhibitory function, was calculated for each participant. Participants with an SSRT below 75 ms were excluded. See Supplemental and *Figure S2.2* for further task details.

Cognitive impulsivity. Cognitive impulsivity, i.e., lapses in sustained attention, was assessed by examining trial-to-trial individual response variability (IRV) on the SST for each participant, and calculated using the intra-individual coefficient of variation formula (dividing the standard deviation of Go RTs by mean Go RTs), which controls for differences in an individual's overall speed of responding.

Executive Functioning. The Stroop Colour–Word Test assessed cognitive conflict (MacLeod, 1991). Participants were presented with the name of a colour and were required to name the colour when the word name was printed in either a congruent (e.g., blue) or incongruent colour (e.g., the word red printed in blue ink). Reaction time on incongruent trials is typically slower than for congruent trials, known as the "Interference Effect" (MacLeod, 1991), which was calculated by subtracting incongruent from congruent trials. Lower Interference effect indicates better performance.

Reinforcement and punishment learning. The Probabilistic Selection Task (PST; Frank et al., 2004) was employed to measure individual differences in learning from reinforcement and from punishment. The PST included a training phase (120 trials) and a subsequent test phase (120 trials), in which ability to learn from positive feedback (reward sensitivity) and negative feedback learning (punishment sensitivity) was assessed for each participant. See Supplemental and *Figure S2.3* for further task details.

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2.2.4 Data Analysis

Spearman's Rho correlations among impulsivity domains were calculated. A factor analysis, with principal component analysis for extraction followed by VARIMAX Rotation, was conducted to generate orthogonal latent factors of alcohol use. The two groups were then compared (presence or absence of harmful consequences of alcohol-use) on these latent factors, in order to demonstrate validity of these factors. Non-significant results were further analysed by estimating the corresponding Bayes factor, with <0.3 indicating that the null hypothesis could be accepted, using the JASP software package (Version 0.8.5 Beta 1; https://jasp-stats.org).

Machine-learning analysis. I employed the same method as that reported in Kiiski et al. (2018; see Appendix 1 for details). Alcohol composite scores, self-report and task-based composite scores were first z-transformed. Penalized linear regression with the Elastic Net (Zou & Hastie, 2005) was used to predict alcohol-use composite sores for: measures of impulsivity only; and measures of impulsivity, demographic, reinforcement vs. punishment learning and executive functioning. The dataset was then divided into 10 cross-validation (CV) folds. Next, 90% of the dataset (the training set) was used to create a regression model that was then tested on the remaining 10% of the data (the out-of-sample test, or holdout, set). Within each CV fold I used nested CV to set the Elastic Net parameters: *lambda*, the degree of regularization applied, and *alpha*, the weight of ridge versus LASSO regression. All analysis steps up to this point were conducted using 25-fold bootstrap aggregation (i.e., bagging). The combination of model parameters that resulted in the model with the lowest

prediction error was identified for each nested CV partition. The optimal model parameters from each nested CV partition were used to determine the lambda and alpha parameters to create the final prediction model in the holdout set. This analysis was repeated 10 times, using different CV fold allocations each time (i.e., until each holdout test set had been used). See Supplemental and *Figure S2.4* for a more detailed description of this analysis.

The entire analysis was repeated 10 times in order to attenuate idiosyncrasies of any given partitioning of the dataset. Results are median values across all iterations of the analysis. The performance of each model was further validated by creating a null model, which was generated by a random-label permutation (i.e., randomly assigning the outcome variable across subjects). Using this permuted outcome variable, the entire analysis was performed again. The accuracy achieved using the null model was then compared to the accuracy of the model with real data (i.e., the actual model) by ranking the cross-validated r values from iterations of both actual and null models. The actual model was deemed to have performed better than the null model in 100% of iterations (i.e., 10/10 of the highest cross-validated r values were from actual models). Cross-validated r is the most appropriate measure to use with linear regression conducted using machine learning (see for example Jollans & Whelan, 2016).

To ensure that results of these models were not driven by factors influencing the outcome variable (i.e. intoxication frequency), a separate analysis with the same impulsivity variables for intoxication, excluding variables relating to alcohol or drug use from the SSS-V subscales was conducted (see Supplemental - Machine Learning Results).

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2.3 Results

2.3.1 Participants

Participants (N = 106) were 44% female (see Table 2.2 for descriptive statistics). The majority of the sample reported at least one episode of alcohol use in the past 30 days (90.6%; 56/59 males, 40/47 females), drinking 5 drinks or more at least once in the past 30 days (75.5%; 45/59 males, 35/47 females). A minority of the sample and being intoxicated at least once in the past 30 days (39.6%; 21/59 males, 21/47 females), reported smoking at least one cigarette per day in the past 30 days (32.1%; 21/59 males, 13/47 females), at least one episode of cannabis use in the past 30 days (33%; 26/59 males, 9/47 females) and at least one episode of other drug use in the past 30 days (19.8%; 14/59 males, 7/47 females).

Substance use varied by gender (Table 2.2): males had significantly increased frequency of past-year alcohol ($p = 0.004$), past-month alcohol ($p = 0.01$), past-year cannabis ($p = 0.005$) and past-month cannabis use ($p = 0.003$), compared to females. Gender differences were also observed for some aspects of impulsivity (Table 2.2): males showed significantly increased self-reported Thrill & Adventure Seeking (SSS-V; $p = 0.01$), Boredom Susceptibility (SSS-V; $p = 0.003$), Disinhibition (SSS-V; $p = 0.02$), Experience Seeking (SSS-V; $p < 0.001$), as well as task-based punishment sensitivity (PST; $p = 0.05$).

2.3.2 Relationship among impulsivity domains

There were no significant correlations between self-report and task-based impulsivity domains, with the exception of Non-planning (BIS-11) correlating with the Interference effect (Stoop; $r = 0.22$, $p = 0.02$), and MCQ correlating with DDT ($r = 0.67$, $p<0.001$), using Spearman's Rho analysis. Supplemental Table S2.1 reports all correlations, including

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significant correlations that did not survive Bonferroni correction (which is likely too conservative given non-independence of measures). See Table 2.2 for sample characteristics on each measure.

Table 2.2

Self-report and Task-based Measures Sample Characteristics

	Males	Females	Total	p
Self-report Impulsivity				
BIS-11 Attentional	17.56 (3.63)	18.13 (3.66)	17.81 (3.64)	.57
BIS-11 Motor	23.80 (4.16)	24.00 (4.92)	23.89 (4.49)	.89
BIS-11 Non-planning	25.25 (4.38)	26.11 (4.68)	25.63 (4.52)	.26
SSS-V Thrill & Adventure Seeking	7.68 (2.29)	6.47 (2.54)	7.14 (2.47)	.01
SSS-V Boredom Susceptibility	3.42 (2.28)	2.17 (1.51)	2.87 (2.06)	.003*
SSS-V Disinhibition	6.53 (2.44)	5.45 (2.41)	6.05 (2.48)	.02
SSS-V Experience Seeking	7.24 (1.78)	5.91 (1.95)	6.65 (1.97)	<.001*
MCQ Kirby Geomean k	0.03 (0.05)	0.04 (0.06)	0.04 (0.05)	.32
Task-based Impulsivity (index)				
DD k (choice)	-4.25 (2.91)	-3.81.06 (1.66)	-4.25 (2.91)	.68
Stop Signal Reaction Time (motor)	161.60 (46.44)	163.66 (44.79)	162.51 (45.51)	.85
Individual response variation (IRV; cognitive)	0.211 (0.04)	0.21 (0.03)	0.21 (0.04)	.77
Other Variables				
Stroop (Interference)	166.18 (554.7)	401.95 (925.0)	270.72 (747.5)	.38
PST approach A (Reward sensitivity)	75.36 (21.38)	72.12 (22.69)	73.93 (22.25)	.39
PST avoid B (Punishment sensitivity)	70.58 (18.67)	63.28 (20.58)	67.34 (19.78)	.05

*Significant differences between females and males, using Mann-Whitney U tests (using $p <$ 0.003, which is the Bonferroni-corrected threshold for statistical significance).

2.3.3   Factor analysis results

The participant-to-item ratio (106:9), KMO (.672) and Bartlett's test of sphericity ($\chi 2$ [36] = 341.081, $p<.001$) indicated that the data were suitable for factor analysis. Although

three components had Eigenvalues > 1 (see *Figure S2.5* in Supplemental for scree plot), a two-factor solution produced a simple structure with only one cross-loading item. Two orthogonal factors were extracted, explaining 61% of the common variance (see Table 2.3). I labelled these factors *Intoxication Frequency* (Factor 1) and *Alcohol Consumption Frequency* (Factor 2).

Table 2.3

Varimax-Rotated Exploratory Principal Components Factor Analysis

Alcohol-use Item	Intoxication Frequency	Consumption Frequency
Intoxication (in past 12 months)	0.911	
Intoxication (in past 30 days)	0.875	
≥5 Drinks (in past 30 days)	0.745	
Intoxication (lifetime)	0.691	
Frequency of drinks (lifetime)		0.818
Frequency of drinks (in last 12 months)		0.793
First Drunkenness (age)		0.645
Frequency of drinks (in last 30 days)	.359	0.469

Note. Loadings >.30 are shown.

For subsequent analysis, I created dichotomous variables of zero experiences / expectations versus any experiences / expectations. Groups who experienced negative consequences of alcohol-use had higher intoxication frequency scores, whereas those who expected positive outcomes from alcohol-use had lower intoxication frequency scores (see Table 2.4). Group differences were not observed for consumption frequency scores, with the exception of physical fighting.

Table 2.4. Groups with and without experience of consequences & expectations of alcohol-use compared on each latent factor (intoxication frequency and consumption frequency)

	n	Intoxication Frequency				Consumption Frequency		
		Median	Mean Rank	p	Cohen's d	Median	Mean Rank	p
Experience of consequences of alcohol-use	*(no/yes)*	*(no/yes)*	*(no/yes)*			*(no/yes)*	*(no/yes)*	
Physical fight	96/10	-.24/.75	51.26/75.00	0.02		.10/.67	50.64/81.00	0.003
Accident/ injury	66/40	-.49/.56	42.80/71.15	<.001	.42	.12/.13	54.74/51.45	0.59
Serious problems with your parents	90/16	-.37/-.04	50.74/69.00	0.02		.12/20	54.26/49.25	0.58
Serious problems with your friends	78/28	-.44/.23	47.09/71.36	<.001	.35	.16/.01	54.90/49.61	0.47
Performed poorly as school/ work	58/48	-.42/.03	46.72/61.69	0.01	.23	.18/.10	56.43/49.96	0.28
Victimised by robbery/ theft[‡]	99/7	-.25/1.52	-	-		.18/-.07	-	-
Trouble with the police[‡]	100/6	-.24/1.79	-	-		.12/25	-	-
Hospitalized/admitted to ER	94/12	-.37/.31	50.55/76.58	<.006		.12/.20	54.98/41.92	0.16
Engaged in unprotected sex	66/40	-.38/-.05	46.77/64.60	0.004	.23	.12/.15	53.95/52.75	0.85
Engaged in sex you regretted	75/31	-.44/.58	45.11/73.81	<.001	.38	.12/.13	53.73/52.93	0.90
Experience of expectations of alcohol-use	*(no/yes)*	*(no/yes)*	*(no/yes)*			*(no/yes)*	*(no/yes)*	
Feel relaxed	37/69	-.13/-.37	58.74/50.69	0.19		.11/.12	56.88/51.69	0.40
Get into trouble with police	84/22	-.33/-.10	51.79/60.05	0.26		.11/.21	52.63/56.82	0.57

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Harm my health	29/77	-.49/-.18	48.62/55.34	0.31		-.01/.19	48.28/55.47	0.28
Feel happy	30/70	.22/-.51	72.88/45.85	<.001	.37	.12/.13	51.88/54.14	0.73
Forget my problems	15/91	.58/-.31	69.27/50.90	0.03		-.04/.13	49.13/54.22	0.55
Not be able to stop drinking	40/66	-.65/-.02	39.10/62.23	<.001	.40	.20/.01	556.28/51.82	0.46
Get a hangover	8/98	-.77/-.20	-	-		-.50/.12	-	-
Feel friendlier and more outgoing	33/73	.24/-.44	68.77/46.60	0.001	.37	.11/.13	53.83/53.35	0.94
Do something I regret	9/97	-.80/-.18	22.89/56.34	0.002		.10/.13	38.56/54.89	0.12
Have a lot of fun	30/76	.59/-.45	73.12/45.76	<.001	.38	.06/.16	53.45/53.52	0.99
Feel sick	23/83	-.76/-.14	36.61/58.18	0.003	.29	.52/.11	61.52/51.28	0.15

Table depicts groups who reported the presence or absence of consequences & expectation of alcohol-use were compared on the two factors of alcohol-use (i.e., intoxication frequency and consumption frequency). Mean rank and probability values are based on the intoxication frequency and consumption frequency scores, according to group allocation (i.e., presence/absence of each consequence & expectation of alcohol-use). Mann-Whitney U tests were used for group comparisons. Values are for drunkenness scores from factor 1 (PCA). ‡Only descriptive statistics presented because one group had n<12.

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2.3.4 Machine Learning Results

Intoxication frequency was significantly predicted by the impulsivity variables (Model 1; median cross-validated r=0.38, median p=.0003), including self-report trait Attentional (BIS-11), Non-planning (BIS-11), Disinhibition (SSS-V), Experience Seeking (SSS-V) and choice impulsivity (MCQ), and by task-based cognitive impulsivity (sustained attention operationalised as IRV on the SST). Intoxication frequency was also significantly predicted by the same impulsivity variables plus other, non-impulsivity, variables (Model 2; median cross-validated r=0.40, median p=.0004), including executive functioning (Stroop Interference), learning from punishment (PST), gender, and lifetime nicotine and cannabis.

Consumption frequency was not significantly predicted by impulsivity variables (Model 3; median cross-validated r=0.15, median p=.14). However, consumption frequency was significantly predicted by impulsivity plus other, non-impulsivity, variables (Model 4; median cross-validated r=0.38, median p=.0002), including Disinhibition (SSS-V), steeper discounting (DDT), gender, and lifetime drugs and cannabis.

Each actual model outperformed null models 100% of the time. Variables that passed the thresholds for absolute beta weights and frequency of occurrence across cross-validation folds determined using the null models are reported in Table 2.5.

Table 2.5

Machine-learning results

	Intoxication Frequency				Consumption Frequency	
	Impulsivity Only 0.38 (0.0003)		Impulsivity + Other 0.40 (<0.001)		Impulsivity + Other 0.38 (<0.001)	
CV median *r* value (p value)						
	Beta Weight	% of CV folds	Beta Weight	% of CV folds	Beta Weight	% of CV folds
BIS-11 Attentional	0.05	88	0.07	95	-	-
BIS-11 Non-planning	0.09	89	0.08	92	-	-
BIS-11 Motor	-	-	-	-	-	-
SSS-V Thrill & Adventure Seeking	-	-	-	-	-	-
SSS-V Boredom Susceptibility	-	-	-	-	-	-
SSS-V Disinhibition	0.23	100	0.20	100	0.06	89
SSS-V Experience Seeking	-0.12	85	-0.13	93	-	-
MCQ k	0.05	80	0.06	91	-	-
DDT k	-	-	-	-	0.09	82
SST Stop signal reaction time	-	-	-	-	-	-
SST IRV	0.06	88	0.07	93	-	-
Stroop Interference			0.12	95	-	-
PST approach A			-	-	-	-
PST avoid B			-0.06	93	-	-
Gender			-0.04	89	0.08	87
Drugs Lifetime			-	-	0.07	92
Smoking Lifetime			-0.07	87	-	-
Cannabis Lifetime			0.12	92	0.12	100

CV: cross-validated; BIS-11: Barratt Impulsiveness Scale 11th version; SSS-V: Sensation Seeking Scale Form V; MCQ: Monetary Choice Questionnaire; DDT: Delay Discounting Task; SST: Stop Signal Task; PST: Probabilistic Selection Task. Higher beta values denote better accuracy in predicting intoxication scores. Predictors that were accurate in 100% of CV folds are reported.

2.4   Discussion

Here, I created two orthogonal latent factor scores for alcohol use, which I labelled intoxication frequency and consumption frequency. Intoxication frequency was predicted by self-reported trait impulsivity (Attentional, Non-planning, Disinhibition and Experience Seeking), task-based choice impulsivity (delay discounting) and cognitive impulsivity (sustained attention). However, the impulsivity traits Boredom Susceptibility and Thrill and Adventure seeking, as well as Motor impulsivity were not significant predictors. In contrast, impulsivity endophenotypes did not predict alcohol consumption frequency. The finding that impulsivity domains predicted intoxication but not consumption frequency lends further support to the idea that different components of impulsivity contribute to different patterns of alcohol misuse (Henges & Marczinski, 2012), and is consistent with observations of increased impulsivity associated with heavier drinking for trait (Henges & Marczinski, 2012; Moreno et al., 2012; Sanchez-Roige et al., 2014), motor (Ahmadi et al., 2013; Ames et al., 2014; Henges & Marczinski, 2012), and choice impulsivity (Schneider et al., 2014).

The current study was motivated by previous findings that impulsivity consists of non-overlapping and distinct constructs (Mackillop et al., 2016; Sharma et al., 2014). There was no significant relationship among different measures of impulsivity, yet distinct aspects of impulsivity combined to significantly predict intoxication frequency. Concordant with previous studies (Caswell et al., 2015b; Mackillop et al., 2016; Sanchez-Roige et al., 2014), some of the strongest predictors of intoxication frequency were trait impulsivity measures. However, important distinctions between types of impulsive traits associated with alcohol use patterns were highlighted. Specifically, intoxication frequency was characterised by trait

Disinhibition (SSS-V), Attentional and Non-planning impulsivity (BIS-11) and steeper discounting (MCQ). However, Disinhibition was the only trait predictor of consumption frequency. Trait Disinhibition (SSS-V) underpins the loss of control component of impulsivity, and has been previously linked to student binge drinking (+6 drinks threshold; Moreno et al., 2012). However, sensation seeking may be conceptually different from impulsivity *per se* –Mackillop et al. (2016) showed that the exclusion of sensation seeking significantly improved impulsive trait loading coefficients and model fit. Here, although Experience Seeking was positively correlated with other impulsivity measures on the SSS-V, it was negatively associated with intoxication frequency. Experience Seeking is defined as the pursuit of an unconventional lifestyle (Zuckerman et al., 1978), and its associated behaviours (e.g., travelling, parachuting) may actually require foresight and careful planning, yet it is often grouped without distinction with other risky behaviours. Non-planning (BIS-11), in contrast, was a predictor of higher intoxication frequency scores. One possibility is that Non-planning incorporates more short-term aspects of behavioural (dys)control (e.g., "*I say things without thinking*"), while Experience Seeking assesses more long-term behaviours that implicate impulsive tendencies (e.g., tasting new foods). Therefore, it is plausible that propensity for intoxication is inversely correlated with the ability to plan into the future.

Choice impulsivity, operationalised here as delay discounting, has previously been found to be robustly associated with disordered alcohol use (Amlung et al., 2017), and to be steeper in young adolescent binge drinkers (Whelan *et al*., 2014). However, findings are mixed in student samples, with some studies reporting latent domains of choice impulsivity (MCQ and DDT) to be associated with alcohol use (Mackillop *et al*., 2016), and others

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finding no association (MCQ - Caswell *et al*., 2015b; delay discounting questionnaire, Sanchez-Roige *et al*., 2014). Although Sanchez-Roige and colleagues (2014) did find increased impulsive choice in binge-drinkers on their behavioural task (the Two-Choice Impulsivity paradigm), task-based measures of delay discounting have not been extensively utilised to explore the relationship between choice impulsivity and student drinking. Here, DDT choice impulsivity was a weak-to-moderate predictor of intoxication frequency (70% of CV folds), and it was a significant predictor of consumption frequency when combined with other risk factors. Further exploration of various task-based measures of choice impulsivity, compared to questionnaire-based measures, and how they relate to various types of substance use will require further investigation. Importantly however, the findings indicate that different discounting paradigms may yield different results, but also that there are distinctions between choice impulsivity and patterns of alcohol use.

Self-reported Motor impulsivity (a second order factor of the BIS-11) was not a predictor of either intoxication frequency or consumption frequency, despite previous findings linking self-reported motor impulsivity to increased alcohol use (Carlson *et al.*, 2010; Mackillop *et al*., 2016; Sanchez-Roige *et al*., 2014). However, a study that followed a cohort of 63 students during an eleven-year period (18–29 years old) found that while Attentional and Non-planning impulsivity factors significant predicted binge-drinking trajectories, self-reported Motor impulsivity did not (Carbia *et al*., 2018). Furthermore, task-based motor impulsivity (operationalised here as the SSRT) was not a significant predictor of intoxication frequency. Previous studies have also failed to observe SSRT differences across samples of drinkers (Sanchez-Roige *et al*., 2014; Caswell *et al*., 2015b). However, longer

SSRTs have been associated with disordered alcohol-use (Mole *et al*., 2015) and acute alcohol dosages (Caswell *et al.*, 2013a). One potential explanation for these results is that the neurotoxic effects of chronic alcohol exposure weakens top-down cognitive control, which in turn can lead to further risk for substance abuse (Robbins & Dalley, 2017; López-Caneda et al., 2013). Furthermore, SSRT findings among non-dependent alcohol users are less clear (Weafer et al., 2014), and it could be speculated that heavier drinkers in the current sample (consuming alcohol at least once a week on average, greater than 5 drinks at least twice a month, and being intoxicated at least once in the past 30 days) are at increased risk of developing disordered alcohol use. Therefore, this thesis tentatively suggests that aberrant SSRTs are more likely to be observed in chronic alcohol misusers.

Sustained attention, an aspect of cognitive impulsivity that was operationalised here by IRV, attentional trait impulsivity (BIS-11) and executive functioning (Stroop Interference) were strong predictors of intoxication frequency, but not consumption frequency. The findings are concordant with previous research describing binge drinkers with greater attentional deficits in tasks relating to cognitive impulsivity (Sanchez-Roige et al., 2014). Reaction time variability may be more strongly related to impulsivity than inattention (Epstein et al., 2003; Kofler et al., 2013). This study considered IRV an impulsivity-related measure, as it was embedded in an impulsivity-specific task (see Sharma et al., 2014 for a discussion). Sharma and colleagues (2014) who, in a hypothetical demonstration of results that might be obtained if a battery of impulsivity measures were administered jointly along with alcohol use, indicated that tasks assaying inattention alone would not significantly predict problematic alcohol use, but would when combined with other impulsive measures.

The current findings suggest that cognitive impulsivity predicts alcohol use via poorer sustained attention, and raises the question of the extent of overlap between aspects of impulsivity and executive functioning measures, which, at least originally, were considered separate constructs.

Binge drinking thresholds (+4/5 drinks per occasion for females/males, respectively) have failed to optimally predict clinically meaningful outcomes (Pearson et al., 2017). The intoxication frequency scores were derived from several self-report items – including intoxication (lifetime, past 12 months and 30 days), excessive consumption ($\geq$5 Drinks per occasion) and frequency of drinks in the past 30 days). These latent factors were associated with negative experiences due to alcohol use. Students who experienced injury, negative sexual experiences, as well as problems with friends and academic performance, had significantly higher intoxication frequency latent factor scores, compared to groups without these experiences. Conversely, groups who had positive expectations of alcohol-use had lower intoxication frequency scores. Moreover, alcohol consumption frequency scores did not differ between groups with or without experiences of negative consequences of alcohol use, or expectations of positive outcomes from alcohol use. This result lends support to previous findings that intoxication, rather than drinking frequency *per se*, is a risk factor for adverse consequences of alcohol use (Kuntsche et al., 2013; Prince et al., 2018). Endeavors to evaluate prevention and treatment efficacy may be better served using cut-offs relating to alcohol-related consequences.

Cumulative risk factors are associated with higher binge-drinking rates (Gowin et al., 2017), and I show that other risk factors observed in adolescents, such as gender, cannabis

and nicotine (Squeglia et al., 2016; Whelan et al., 2014) and executive functioning (Peeters et al., 2015), also hold for heavier college-age drinkers. The gender gap between male and female university students is narrowing with regard to excessive alcohol consumption (Davoren et al., 2016), and establishing which impulsivity predictors diverge or overlap according to gender will be an important future consideration for prevention and treatment. Early adolescent drunkenness was more predictive of problem behaviours, including cannabis and nicotine use, than frequency of alcohol use (Kuntsche et al., 2013). Here, cannabis use was a predictor of both intoxication frequency and consumption frequency, while smoking predicted intoxication frequency only. Impulsivity differences have been found between cannabis and alcohol users. For example, 19-year-old binge-drinkers had higher trait impulsivity (total BIS-11 scores), compared to both cannabis-using and non-drug-using groups, but cannabis users had increased motor impulsivity (stop reaction times on SST; Moreno et al., 2012). Future studies could apply machine learning to identify the impulsivity variables that uniquely contribute to the prediction of different types of substance use.

The PST (Frank et al., 2004) also showed that intoxication frequency was associated with a decrease in learning from punishment (negative feedback). To the author's knowledge, no other study has examined the PST in non-dependent drinkers, and this finding suggests that alcohol users may be less sensitive to negative outcomes. This lends support to addiction models that suggest that outcome desensitisation (to punishment, in this case) occurs following repeated substance use (Baker et al., 2013; Volkow et al., 2016). Given that impulsivity is characterised by a disregard for future consequences, this finding warrants further exploration.

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There are some other limitations to this study. Although a comprehensive battery of measures was employed, other impulsivity domains (e.g., reflection impulsivity) were not assessed. Secondly, despite moderate-to-high test-retest of impulsivity tasks, differential mood-related stability effects have been noted (Weafer et al., 2013), and previous studies show that affect underlying trait impulsivity is strongly related to heavy student drinking (Carlson et al., 2010). Given that higher intoxication was associated with negative alcohol-related experiences, anxiety and/or stress could be included in future models to improve predictive value. Traditional personality measures, such as extraversion, are among the strongest predictors of binge-drinking in adolescents (Whelan et al., 2014). However, whether impulsivity-specific or broad traditional trait measures are the best predictors of alcohol use remains unclear. With respect to the measurement of alcohol use, self-reported alcohol consumption questions based on absolute quantities do not account for dose-specific variability in absorption and metabolism (Ramchandani et al., 1999). The current measures included questions about drunkenness (i.e., perceived intoxication, regardless of absolute alcohol consumed), which may account somewhat for individual differences in alcohol absorption rates, approximate alcohol absorption rates can be estimated from body weight and biological sex. Therefore, including measures such as body mass index and socio-economic status would be beneficial for future research.

Machine learning is a useful method for interrogating complex datasets and has previously been shown to produce high classification accuracy for binge-drinking versus non-binge-drinking groups (e.g., Squeglia et al., 2016; Whelan et al., 2014). As has been demonstrated here, such methods have the potential to facilitate the inclusion of a large

number of variables and therefore can provide more nuanced insights into the relationship between alcohol use and psychological constructs, such as impulsivity. However, findings for one endophenotype in particular – motor impulsivity – remain mixed. SSRT deficits were not always observed when comparing non-dependent alcohol-users to controls. For example, Sanchez-Roige et al., (2014) and Moreno et al. (2012) found comparable SSRT performances for binge-drinkers and non-binge-drinkers, and similarly here, SSRT was not a significant predictor of alcohol intoxication frequency. In contrast, however, differences in brain activity related to response inhibition have been observed in young adult drinkers, even in the absence of behavioural differences (Whelan et al., 2012). Thus, neural measures of inhibitory control have some potential to better characterise individual differences in alcohol misuse than behavioural metrics alone. Therefore, in Chapter 3, EEG in addition to behavioural measures were employed to examine the link between impulsivity and alcohol use.

3 Chapter 3: Inhibitory Control Event-Related Potential Predict Individual Differences in Alcohol Use[3]

3.1 Introduction

Chapter 2 demonstrated that impulsivity endophenotypes alone significantly predicted alcohol intoxication frequency in student drinkers, although this prediction was improved when other risk factors (e.g., demographics personality, smoking, reward sensitivity etc.) were incorporated. Furthermore, combining impulsivity endophenotypes with these risk factors significantly predicted individual differences in alcohol consumption frequency. Other studies have also demonstrated that combining various impulsivity endophenotypes, including neuroimaging data assaying inhibitory control, can effectively predict current and future alcohol misuse (e.g., Whelan et al., 2014).

The ability to suppress unwanted behaviours or to quickly cancel an already-initiated response relies on effective and rapid inhibitory control in the brain. The Stop-Signal task (SST) assays inhibitory control, and requires participants to respond as quickly as possible to frequent 'Go' cues, but to inhibit their ongoing motor response following intermittent and unexpected 'Stop' cues. The stop-signal reaction time (SSRT) indexes the time needed to successfully inhibit this prepotent response and is a reliable measure of deficits in inhibitory control. In neurologically healthy adults, SSRTs are approximately 200 ms (Wessel & Aron, 2015), and often longer in individuals with current addictions (e.g., Luijten et al., 2014).

Electroencephalography (EEG) measures may improve screening and assessment of alcohol misuse, as they offer high temporal resolution, are relatively convenient to use and are objective (see Mumtaz, Vuong, Malik, & Rashid 2017a for a review on this topic). Event-related potentials (ERPs), time-locked EEG, are modulated by performance during the SST.

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Two ERP components, the N2 and P3b (hereafter P3), are predominantly associated with response inhibition: the former is a fronto-central negative component peaking around 200-250 ms and the latter is a positive component peaking around 300-350 ms over central and parietal areas. Larger N2 amplitudes are often observed for failed vs. successful Stop trials (Kok et al., 2004), and larger P3 amplitudes are consistently observed for successful vs. failed Stop trials in healthy participants (Kok et al., 2004; Lansbergen et al., 2007). A reduction in P3 amplitude during response inhibition is considered a marker for alcoholism (see Campanella et al., 2018; Luijten et al., 2014; Mumtaz et el., 2017a). However, as with behavioural measures of inhibitory control, ERP findings in non-dependent alcohol users are inconsistent. For example, in a study with a relatively large sample size, no P3 or N2 amplitude differences were found between 48 young adult heavy drinkers and 49 lighter drinkers during successful response inhibition on a Go No-Go task (GNG; Franken et al., 2017). Conversely, in a sample of 40 student drinkers performing the same task, heavy drinkers had reduced NoGo P3 amplitudes on successful trials, compared to light drinkers, although N2 was relatively comparable for the groups (Oddy & Barry, 2009). A longitudinal study of student drinkers found no stop-related P3 amplitude differences between 23 heavy and 25 lighter drinkers, however at follow-up, students who engaged in binge drinking for at least two years showed larger P3 amplitudes during successful response inhibition (López-Caneda et al., 2012). There is also some evidence that alterations in earlier ERP components (e.g., P1) are linked to alcohol misuse, as has been found among individuals with alcohol use disorder (AUD; Maurage et al., 2007), yet, these early components have received surprisingly little attention. It is important to establish whether the link between ERPs and alcohol misuse

is specific to later N2 and P3 components, or if deficits are already present earlier in the cognitive processing stream.

Mixed findings, such as those related to ERP correlates of alcohol use, are common in cognitive neuroscience. One reason for this is that electrophysiological or neuroimaging studies have typically used small sample sizes, which increases the probability of false positive findings –Type I errors (Button et al., 2013). Secondly, neural data are high dimensional: in the case of EEG data, there are typically more than 64 channels, acquired at a sampling rate of over 256 Hz (i.e., >1,600 data points per 100 ms per subject). In order to decrease the likelihood of Type I errors, data from high density EEG arrays are usually reduced in dimension by selecting a specific time interval and a subset of channels in which to define the ERPs. As a result, EEG studies examining alcohol use have typically been restricted to single ERP components (i.e., N2, P3) over predefined scalp regions, raising the possibility of false negative (Type II) errors.

In order to identify neural correlates of alcohol use and misuse, a multivariable approach, based on a weighted combination of diverse electrophysiological variables, will likely be more useful for predicting outcomes than single ERPs. However, when generating models, a high ratio of variables to participants will result in 'overfitting'. That is, apparently accurate predictions actually reflect idiosyncrasies of the sample, and will thus fail to generalise to new samples (see Whelan & Garavan 2014 for a discussion of this issue in relation to neuroimaging). Machine learning methods, such as the Elastic Net (Zou & Hastie, 2005), are well suited for data with high dimensionality and inherent multicollinearity. In contrast to null-hypothesis statistical testing, in machine learning, accurate prediction on

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previously unobserved data indicates success (Yarkoni & Westfall, 2017). EEG-based machine learning methods to predict alcohol-related outcomes show promising results (Kuncheva & Rodrıguez, 2013; Mumtaz et al., 2017b). Mumtaz and colleagues (2017b) applied a machine learning approach to resting-state EEG data, and found that EEG features (spectral power and inter-hemispheric coherences) accurately classified 30 patients with AUD from 15 healthy controls (Accuracy=89.3%, sensitivity=88.5%, specificity=91%). However, machine learning has been rarely used to interrogate ERPs (but cf. Johannesen et al., 2016; Kiiski et al., 2018; Stock et al., 2015). Furthermore, the use of a task probing specific cognitive systems markedly improves performance over resting-state data (Greene, Gao, Scheinost, & Constable, 2018).

Here, machine learning was applied to predict alcohol misuse from inhibitory control ERPs, collected from 79 participants with a range of alcohol use. In order to quantify the relative utility of other potential predictors, models were also tested that combined ERPs with other data (including demographic, personality, and behavioural measures of impulsivity) to predict alcohol use. It was hypothesized that P3 ERPs would significantly predict alcohol use, based on previous research with heavy drinkers. Due to mixed findings in previous research, there were no a priori hypotheses about early ERPs or the N2. It was predicted that behavioural measures of impulsivity, in particular trait impulsivity, would also predict alcohol use.

3.2   Materials & Methods

3.2.1   Sample

Seventy-nine student drinkers (40 female; mean age=23.59 years) participated. Exclusion criteria included being under 18-years-old, history of any head trauma (including concussion) or stroke, regular drug or cannabis use (greater twice a month), history of any major mental health illness (DSM axis I with the exception of depression), or any learning difficulties or physical disability that would impact task performance (e.g., motor impairment).

3.2.2   Procedure

Participants were recruited via posters displayed on university campuses, and those who expressed an interest were phone-screened to determine eligibility. Eligible participants were emailed a link to questionnaires via an online survey platform and requested to complete this in the week prior to attending a 2-hour laboratory session. After reading the information sheet and providing informed consent, participants then completed measures under EEG. Participants were provided with €20 compensation, in addition to travel expenses (maximum value €10) or course credit. The study procedure was approved by the University College Dublin School of Psychology Ethics Committee and the Trinity College Dublin School of Psychology Ethics Committee.

3.2.3 Measures

Self-report measures

The *Alcohol Use Disorders Identification Test* (AUDIT) is a 10-item alcohol screening questionnaire assessing alcohol consumption, alcohol-related problems and drinking behaviour and quantifying risk from low-level to hazardous drinking. Individual responses are scored from 0-4, with a maximum of 40 for total AUDIT score. Other self-report measures included: the *Barratt Impulsiveness Scale 11th version* (BIS-11) to assess trait impulsivity–Motor, Attentional and Non-planning impulsivity; the *Drug Abuse Screening Test* (DAST-20) to assess illegal drug use; the Depression, Anxiety and Stress Scale (DASS) to assess stress, depression and anxiety symptoms; the *Neuroticism-Extraversion-Openness Five Factor Inventory* (NEO-FFI) to assess personality traits of Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness; the Perceived Stress Scale (PSS) to assess stress appraisal related to common life situations within the last month; and the *Multidimensional Scale of Perceived Social Support* (MSPSS) to assess perceived support from family, friends and a significant other . See Supplemental (self-report measures) file for further details for each of these measures.

Task-based measures

An adaptive Stop Signal Task (SST) assessed inhibitory control, recorded under EEG in a 9-minute run. The task consisted of 135 Go trials interspersed with 45 Stop trials; with one randomized Stop trial appearing within four Go trials. The task was presented in 3 blocks of 60 trials. A tracking algorithm adjusted task difficulty by varying the stop-signal delay

(SSD; the time interval between Go signal and Stop signal onsets), in order to produce 50% successful and 50% unsuccessful inhibition trials. The SSRT quantifies behavioural response inhibition (i.e., time taken to cancel a prepotent motor response after Stop stimulus presentation). According to the horse-race model (Logan and Cowan, 1984), the finish of the stop process can be estimated from a participants' distribution of reaction times on Go trials (see Figure 3.1). Full task details are contained in the Supplemental (task-based measures) file. Cognitive impulsivity, i.e., lapses in sustained attention, was assessed by examining trial-to-trial individual response variability (IRV) on the SST, and was calculated using the intra-individual coefficient of variation formula (dividing the standard deviation of Go RTs by mean Go RTs), which controls for differences in an individual's overall speed of responding.

Other task-based measures included the following. The Stroop Colour–Word Test, in which participants were presented with a colour name and were required to identify the colour. The word name was printed in either a congruent or incongruent colour (e.g., the word 'red' printed in blue ink). Reaction time on incongruent trials is typically slower than for congruent trials, known as the "Interference Effect", which was calculated by subtracting incongruent from congruent trials, with lower numbers indicating better performance. The Probabilistic Selection Task (PST) assessed individual differences in learning from positive feedback (reward sensitivity) versus negative feedback learning (punishment sensitivity). An adaptive delay discounting task (DDT) assessed choice impulsivity, with delay discounting rates (k) calculated using a hyperbolic discounting model. The DDT consisted of 149 trials in total in an 8-minute run and required participants to choose between a series of choices between sooner, immediate rewards (SIR; ranging from $11 to $80) or later, delayed rewards

(LDR; ranging from $20 to $85, in delays from 7 to 186 days). The task algorithm adapted to the participant's own k value. See the Supplemental (task-based measures) file for further details for each of these measures.
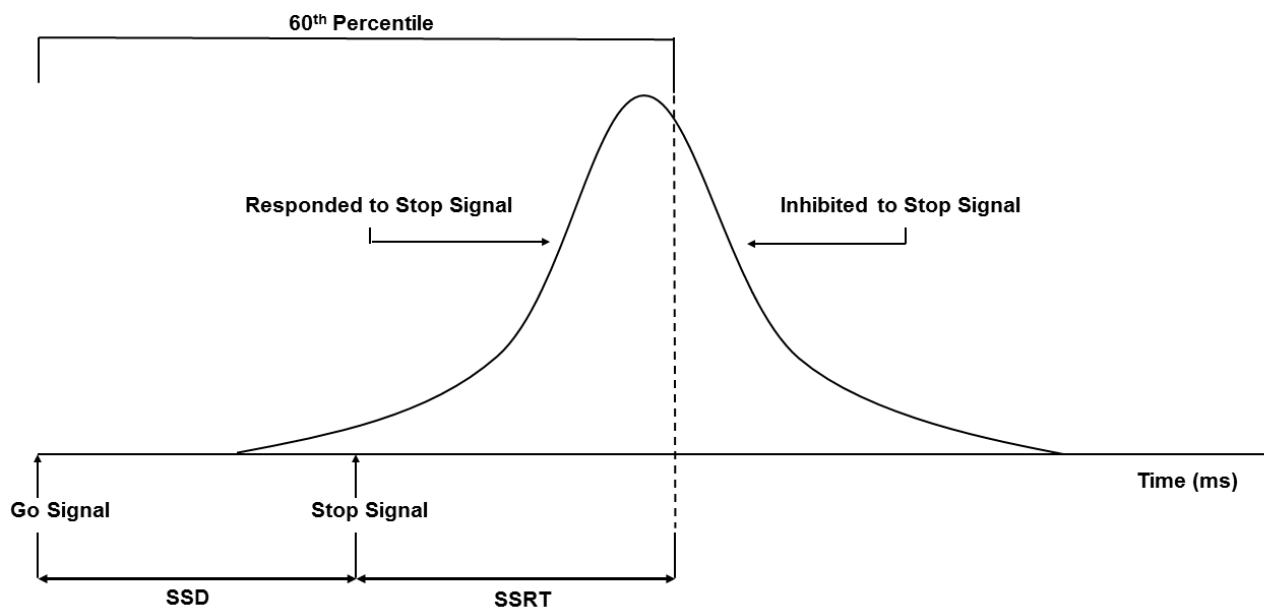
Figure 3.1. Illustration of the horse-race model of behavioural inhibition on the SST. The distribution reflects a particular subject's distribution of reaction times on "go" trials, superimposed onto a timeline for "stop" trials. This particular subject had a successful stop rate of 40%, such that the upper 40% of the distribution corresponds to slower "go" reaction times that would produce successful stop trials (SSTs) and the lower 60% of the distribution corresponds to faster "go" reaction times that would produce unsuccessful stop trials (USSTs).

3.2.4 EEG recording and pre-processing

EEG data during the SST were recorded using an ActiveTwo Biosemi™ system in a soundproofed, darkened room from 70 electrodes (64 scalp electrodes) organised according to the 10–5 system (Oostenveld and Praamstra, 2001). Activity related to eye movement was recorded bilaterally from approximately 2 cm below the eye and from the outer canthi. EEG data pre-processing was carried out using the EEGLAB toolbox (Delorme & Makeig, 2004; http://sccn.ucsd.edu/eeglab) in conjunction with the FASTER plug-in (Fully Automated Statistical Thresholding for EEG artefact Rejection; Nolan, Whelan, & Reilly, 2010, http://sourceforg e.net/projects/faster). The data were bandpass filtered between 0.1 and 95 Hz, notch filtered at 50 Hz and average referenced across all scalp electrodes. Data were subsequently epoched from 500 ms pre-stimulus to 2000 ms post-stimulus, which corresponds to the Go cue in Go trials and the Stop cue in Stop trials (Go trials and Stop trials are defined separately). Artefactual (i.e. non-neural) independent components were identified and removed from the EEG data automatically using FASTER, as were epochs containing large artefacts (e.g., muscle twitches). Channels with poor signal quality were interpolated. The EEG data were then visually inspected to ensure good quality and that any remaining noisy data were removed.

3.2.5 ERP calculation

Three trial types from the SST were identified and epoched in the EEG: trials in which participants successfully responded after a Go cue; trials in which participants had to inhibit their response after a Stop cue (Successful Stop); and trials in which participants failed

to inhibit their response after a Stop cue (Failed Stop). Based on the "horse-race" model of inhibition in the SST, slower reaction times in Go trials are related to successful inhibition, and faster reaction times are related to failed inhibition (Kok et al., 2004; Logan & Cowan, 1984). For this reason, "fast" and "slow" Go trials were defined based on the participant's median reaction time on Go trials. The epoch for fast Go, slow GO, successful stop and failed stops were each defined as -100ms to 600ms. The resulting fast Go and slow GO ERPs were subtracted from the Failed and Successful Stop ERP, respectively (Palmwood, Krompinger & Simons, 2017). All ERPs were baseline-corrected with the mean value of the interval between -100ms to 0 s with respect to the Go/Stop cue prior to the subtraction of "fast" and "slow" Go trials. This procedure was applied per channel, per participant.

3.2.6   Machine learning analysis

Machine learning approach with penalised linear regression was used to conduct outcome prediction in this study (similar to Jollans et al., 2017 and Kiiski et al., 2018). The outcome measure used was total AUDIT score (range 0-40; see Table 3.1). Four models were tested in the machine-learning analysis, which are described below.

Model 1: ERP-only. Successful and Failed Stop ERPs were downsampled to 256 Hz in the window from 0 to 600 ms after the Stop cue. Data from 26 channels were examined and are labelled here according to 5 regions of interest from Wessel & Aron (2015), namely: *fronto-polar* (Fpz, Fp1, Fp2, AF3, AF4); left *fronto-lateral* (AF7, F5, F7); *right central* (FC6, FT8, C6, T8); *fronto-central* (Fz, FCz, Cz, FC1, C1, FC2, C2); *left central* (FC5, FT7, C5, T7). Both Successful and Failed Stop trial types (after fast or slow Go trials were subtracted)

were included as input data, resulting in a matrix of 79 rows (participants) by 8008 columns (ERP data). *Model 2: all non-ERP variables*: self-report and behavioural measures of impulsivity, including, trait (BIS-11 −Attentional, Motor and Non-planning), motor (SSRT), cognitive (IRV), choice (DDT *k*) impulsivity, and Interference Effect (Stroop); demographics (relationship status, monthly income and years of education); drug use (DAST); broad personality traits (NEO-FFI −Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness); psychological variables, including stress, anxiety and depression (DASS), perceived stress (PSS), perceived social support from friends family and significant other (MSPSS); and learning reinforcement (PST—punishment sensitivity and reward sensitivity). *Model 3: non-ERP (impulsivity-only)*: trait (BIS-11 −Attentional, Motor and Non-planning), motor (SSRT), cognitive (IRV), choice (DDT *k*) impulsivity, and Interference Effect (Stroop). *Model 4: ERP plus all non-ERP* (Model 1 and 2 combined).

Data analysis

A 10-fold nested cross-validation was applied on the data. In each main fold, 90% of the data were used for training and 10% for testing. In each subfold (inner cross-validation), the data were z-scored and extreme values were replaced with a value of 3 (i.e. Winsorizing; i.e., with a value 3 standard deviations from the mean). Penalized regression utilised the Elastic Net (Zou and Hastie, 2005), which includes L1 regularization (as in LASSO - least absolute shrinkage and selection operator, which allows parameters to equal 0, promoting parsimonious solutions) and L2 regularization (ridge or Tikhonov regression). Lasso

regularization; whereas ridge regularization encourages parameters to be small, avoiding overfitting. In this model, the objective is to minimize the following equation:

$$\min \left[\frac{1}{2} \|Y - X\beta\|^2 + \lambda\alpha\|\beta\|_{l_1} + \frac{\lambda(1-\alpha)}{2} \|\beta\|_{l_2}^2 \right]$$

where Y is the continuous outcome variable (AUDIT total scores), X is the input data with the ERPs and covariates, β is the regression coefficients, λ is the penalisation for complexity and α is the weighting parameter between ridge and LASSO regression. The complexity and weighting parameters (λ and α, respectively) are not known a priori. Therefore, a range of values was explored: 15 linearly-spaced values of both parameters in the range of 0.01 to 1 and all their possible combinations (i.e., a search grid of 225 parameter-pair values). The prediction accuracy of each parameter combination was assessed using the mean squared error. The parameter combination that yielded the lowest error was selected per sub-fold. The mode of α and the median of λ across sub-folds were selected as parameters per main fold. These optimal parameters from the nested cross validation were used to fit a model using the test set of the main fold (outer cross-validation). The prediction of the model on the test set of each main fold was saved and pooled across main folds.

The analysis on the original set was performed 100 times where the training and test sets were randomly assigned. In order to quantify model performance further, I repeated the entire procedure using random-label permutation (i.e., each participant was randomly assigned to an AUDIT score from a different participant). The accuracy achieved using this null model was then compared to the accuracy of the model with real data by performing a t-test. Results reported for the original set are mean values across all 100 iterations of the

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analysis. The real data model was deemed to be successful if its Pearson's r was statistically significantly higher than those of the null model (p<0.05).

3.3   Results

3.3.1   Behavioural results

Seventy percent of participants had AUDIT total scores ≥8, indicating alcohol-risk (see Table 3.1). Participants with SSRT < 75ms were excluded from the analysis (nine were excluded from an original sample of 88 participants). Participants' anxiety symptoms, stress and depression (DASS) were in the normal range, and drug-use risk (DAST) was low (see Table 3.2). Sex differences were not observed, with the exception of females scoring significantly higher for Agreeableness (NEO-FFI; p = 0.02), and for perceived social support from family, friends and significant other (MSPSS; p = 0.008, p = 0.001, p = 0.003, respectively; see Table 3.2). See Appendix 3.1 (Table S3.1) for correlations among variables.

Table 3.1

AUDIT sample characteristics

AUDIT Total Score	Risk Level	Sample (N=79)	
		Frequency	Percent
0-7	Low-risk	23	29.1%
8 -15	Risky or hazardous	41	51.9%
16 - 19	High-risk or harmful level	10	12.7%
20 or more	High-risk / dependent	5	6.3%

Table 3.2

Self-report and Task-based Measures Sample Characteristics

	Females (n=40)		Males (n=39)		Total		p
	M	SD	M	SD	M	SD	
Outcome							
AUDIT Total	10.10	4.41	11.31	5.62	10.70	5.05	.29
Demographic							
Age	24.02	5.95	22.23	4.78	23.59	5.39	.47
Relationship Status	1.25	0.49	1.15	0.49	1.20	0.49	.38
Monthly Income	1.53	1.09	1.69	1.42	1.61	1.25	.55
Yrs. of Education	16.08	3.02	15.69	4.04	15.89	3.54	.65
DAST Drug-use Total	2.13	4.06	3.00	4.42	2.56	4.24	.36
Smoker / Non-smoker	15/25	-	25/14	-	29/50	-	.88
Personality							
NEO-FFI Extraversion	30.58	7.13	29.59	7.14	30.09	7.11	.54
NEO-FFI Openness	31.45	5.94	31.56	6.48	31.51	6.17	.93
NEO-FFI Agreeableness	33.00	5.98	29.87	5.79	31.46	6.06	.02 [a]
NEO-FFI Conscientiousness	30.45	9.69	27.56	7.41	29.03	8.71	.14
NEO-FFI Neuroticism	25.93	7.91	23.90	8.60	24.92	8.27	.27
Psychological							
DASS Stress	12.83	9.60	12.87	7.71	12.85	8.66	.98
DASS Anxiety	6.88	5.95	7.72	6.37	7.29	6.14	.54
DASS Depression	8.93	7.75	8.72	7.38	8.82	7.52	.90
MSPSS Significant other	6.23	0.98	5.36	1.76	5.80	1.48	.008 [a]
MSPSS Family	5.89	1.05	4.80	1.67	5.35	1.49	.001 [a]
MSPSS Friends	6.22	0.82	5.36	1.55	5.79	1.30	.003 [a]
PSS Total	21.78	6.89	19.95	7.06	20.87	6.99	.24
Impulsivity							
BIS-11 Attentional	16.73	4.04	17.44	3.57	17.08	3.81	.41
BIS-11 Motor	24.60	4.78	24.54	4.06	24.57	4.41	.95
BIS-11 Non-planning	24.50	5.57	25.15	4.49	24.82	5.05	.56
DDT (k) [b]	-1.77	1.28	-1.81	1.72	-1.79	1.50	.90
SST SSRT	181.30	42.34	171.01	34.86	0.22	0.04	.24
SST IRV	0.23	0.03	0.22	0.04	104.22	105.73	.44
Stroop (Interference)	100.80	107.43	107.72	105.25	17.08	3.81	.77
Learning							
PST Approach A (Reward)	71.35	24.84	78.04	24.25	74.65	24.63	.22
PST Avoid B (Punishment)	61.70	21.41	69.59	23.33	65.59	22.58	.12

[a] Significant differences between females and males, using Mann-Whitney t-tests. [b] A logarithmic base 10) transformation of the geometric mean of k. Relationship status: 1=single, 2=cohabiting, 3=civil partnership/marriage, 4=separated/divorced, 5=widowed; Monthly Income: 1=<€900, 2=€900-1350, 3=€350-1800, 4=€1800-2250, 5=€2250-2700, 6=€>2700.

3.3.2 Machine learning results

Model 1, ERP-only, significantly predicted AUDIT scores, (mean cross-validated Pearson's $r = 0.28$, $p = 0.03$; outperforming the null model on 92% of runs), see *Figure 3.2*. Table 3.3 displays results from Models 2 and 3. Model 2, all non-ERP variables, significantly predicted AUDIT scores (mean cross-validated Pearson's $r = 0.34$, $p = 0.004$; outperforming the null model on 96% of runs). Model 3, impulsivity-only, significantly predicted AUDIT scores (mean cross-validated Pearson's $r = 0.37$, $p = 0.002$; outperforming the null model on 97% of runs). Model 4, ERP plus all non-ERP, also predicted AUDIT scores (mean cross-validated Pearson's $r = 0.29$, $p = 0.02$; outperforming the null model on 94% of runs). See the Supplemental Table S3.2 for each model and corresponding null model results, and Table S3.3 contains a spreadsheet of all model weights.
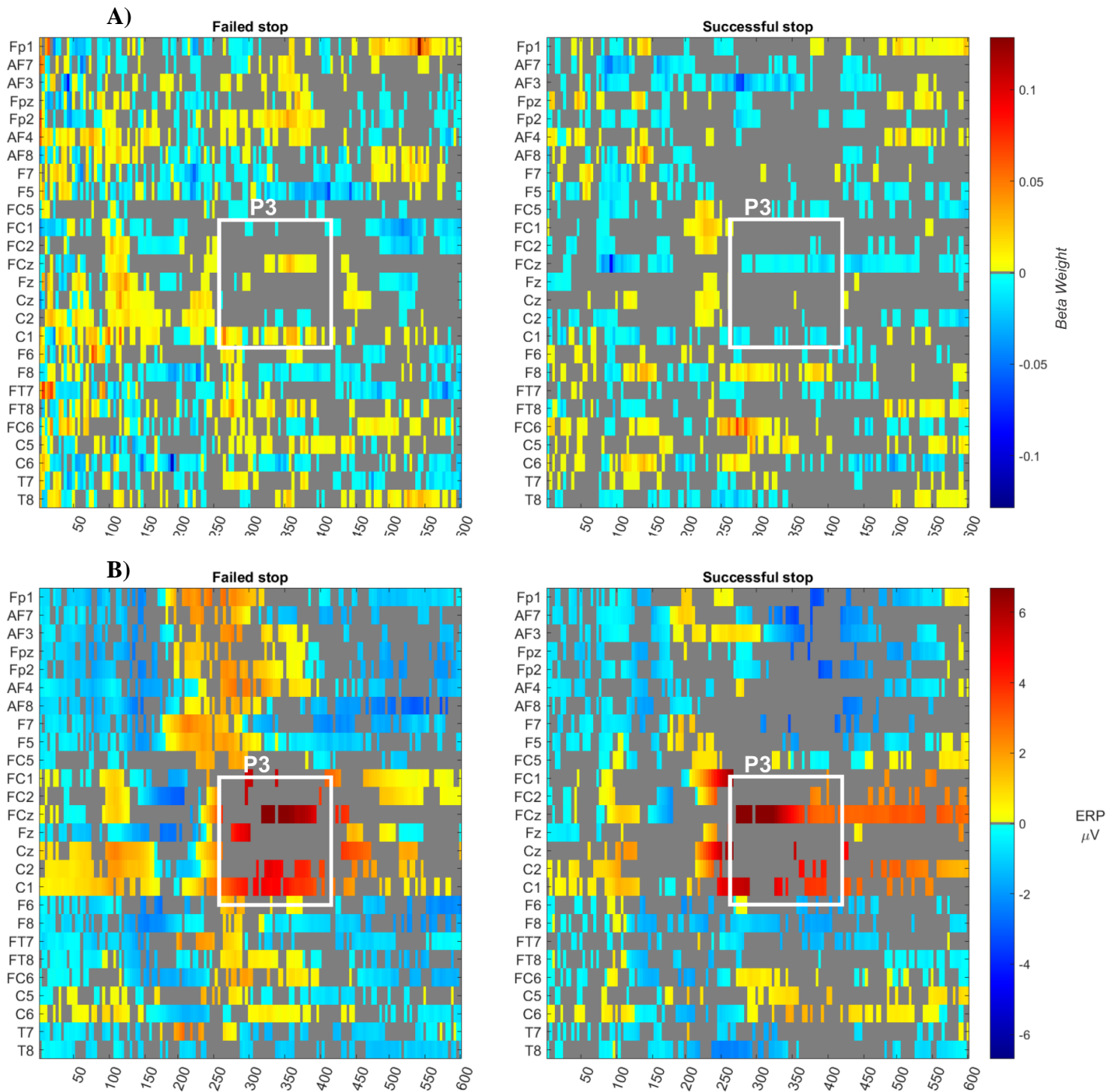
Figure 3.2. A) Map of beta values across main folds for the failed stop (left image) and successful stop (right image) conditions. ERP-based features that survived the 99th percentile

threshold from the null distribution. The colours indicate the direction of the relationship between ERP amplitude and AUDIT scores, based on the beta weight values (i.e. warm colours indicate a positive ERP-AUDIT relationship, and cool colours indicate negative ERP-AUDIT relationship); B) Maps of the grand average ERP of the failed stop (left image) and successful stop (right image) conditions. Areas corresponding to the N2 and P3 components are highlighted in a purple box.

Table 3.3

Non-EEG: All variables (CV $r = 0.34$, $p = 0.004$)			Non-EEG: Impulsivity only (CV $r = 0.37$ $p = 0.002$)		
Features	Mean Frequency	Beta Weight	Features	Mean Frequency	Beta Weight
Relationship Status*	10	-0.87	BIS-11 Non-planning	10	1.12
DASS Anxiety*	10	0.99	Stroop Interference	9.99	1.02
Stroop Interference*	10	1.20	BIS-11 Motor	9.93	0.71
BIS-11 Non-planning*	10	0.97	SST IRV	8.51	0.68
BIS-11 Motor*	9.98	0.45	DDT k	7.63	0.30
MSPSS Family	9.91	-1.14	BIS-11 Attentional	7.6	0.12
MSPSS Friend	9.9	-1.25	SST SSRT	7.41	0.10
Yrs. Of Education	9.88	0.68	-	-	-
SST IRV	9.86	0.61	-	-	-
NEO-FFI Neuroticism	9.85	-0.64	-	-	-
NEO-FFI Agreeableness	9.79	0.41	-	-	-
MSPSS Partner	9.78	-0.51	-	-	-
NEO-FFI Openness	9.7	-0.26	-	-	-
NEO-FFI Conscientiousness	9.69	-0.33	-	-	-
PSS Total	9.68	-0.30	-	-	-
DDT k	9.61	0.22	-	-	-
SST SSRT	9.54	0.13	-	-	-
DAST Drug Total	9.48	-0.04	-	-	-
BIS-11 Attentional	9.45	0.23	-	-	-
NEO-FFI Extraversion	9.41	-0.22	-	-	-
DASS Stress	9.37	-0.20	-	-	-
Monthly Income	9.32	0.14	-	-	-
Smoker / Non-smoker	9.28	-0.06	-	-	-
PST Approach A	9.02	-0.05	-	-	-
PST Avoid B	8.91	-0.87	-	-	-
DASS Depression	8.85	0.07	-	-	-

Machine-learning results for non-EEG models

Features ranked in order of highest mean frequency of being picked across main-folds and random set assignments. * Non-EEG features that were significant in 9/10 main-folds compared to null results, for the EEG + non-EEG model. Impulsiveness Scale 11th version; DDT: Delay Discounting Task; SST: Stop Signal Task; PST: Probabilistic Selection Task; DASS: Depression, Stress & Anxiety Scale.

3.4   Discussion

Here, individual differences in alcohol use (AUDIT scores) from ERP time-courses derived from an assay of inhibitory control were predicted, with moderate accuracy. The use of machine learning facilitated the inclusion of 8,008 ERP variables per participant, and results were quantified using out-of-sample validation. Optimal variables for predicting alcohol use were widespread spatially and occurred early in the ERP, rather than being solely confined to the N2-P3 complex over medial scalp regions. Indeed, the model of ERP variables that best predicted alcohol use was not sparse, even when thresholding the variables based on the 99th percentile of a null distribution. Combining ERP data with non-ERP data improved prediction of AUDIT scores – the most important predictors included early ERPs from the Failed Stop condition, relationship status, trait impulsivity (Motor and Non-planning impulsivity), Stroop Interference Effect, and anxiety. The most accurate predictions were generated by a model that included a wide range of behavioural measures of impulsivity.

With respect to the N2 ERP component, more negative N2 ERPs were associated with higher alcohol use. Crego et al. (2009) found larger N2 amplitudes for student binge drinkers during a visual working memory task compared to non-bingers, with similar results also previously reported in adults with AUD (Olbrich et al., 2000). However, in contrast, Pandey and colleagues (2012) found lower No-Go N2 amplitude in males with alcohol dependence who had been detoxified for 30 days, compared to controls without AUD diagnosis. Franken and colleagues (2017) found no differences for both NoGo N2 and P3 amplitudes when comparing young heavy drinkers to lighter drinkers during a GNG task. Comparable NoGo N2 amplitudes were also found for student heavy drinkers versus lighter

drinkers during a GNG task (Oddy & Barry, 2009). Reduced P3 amplitude during response inhibition is thought to represent a component of the alcoholic phenotype (see Campanella et al., 2018; Luijten et al., 2014; Mumtaz et el., 2017a for reviews). Here, reduced P3 amplitude was associated with higher alcohol use, particularly during successful stops. Some studies have also shown reduced P3 amplitudes on successful NoGo trials when comparing heavier drinkers to lighter drinkers (Oddy & Barry, 2009), whilst others have found no group differences (Franken et al., 2017). With respect to both N2 and P3 findings, there are some methodological differences between previous research and the present study. First, I used the SST, and not the GNG, to examine response inhibition. The former requires action cancelation, rather than the action restraint required in the GNG, and may therefore be a more sensitive measure of inhibitory control because it requires more effortful neural activity. Second, previous studies used a variety of cut-off scores from single consumption-based measures of alcohol use. For example, heavy drinkers were categorized by number of monthly alcohol units over a month ($\geq$ 6 units and $\geq$ 9 drinking days; Franken et al., 2017) and number of standard drinks over a month (e.g., $\geq$ 10 drinks.; Oddy & Barry, 2009). Cut-off scores may not always be appropriate for group dichotomisation ((Havard, 2016; Pearson, Kirouac, & Witkiewitz, 2016), and therefore the author tested the correlation with AUDIT scores. Third, previous ERP studies on alcohol use have typically focused on ERPs during successful stop trials (López-Caneda et al., 2012; Oddy & Barry, 2009). However, here increased P3 amplitude during failed stops was found to be associated with higher alcohol use, suggesting that the Stop Fail condition is perhaps more relevant to high risk drinking.

Although some evidence of N2 and P3 involvement was found, the best prediction of alcohol use was achieved by including early ERP activity (before the N2) across the scalp. This is a novel finding, although there is some, limited, precedence for this. For example, deficits have been reported in early pre-attentive sensory processing (P50: Freedman et al., 1987; Marco et al., 2005) and visuo-perceptual processing (P1: Maurage et al., 2007) in alcohol-dependent samples. The P50 reflects a predominantly preattentional (Freedman et al., 1987) inhibitory filter mechanism that could protect the integrity of higher-order functions (Lijffijt et al., 2009), suggesting that impaired P50 associated with increased alcohol use could relate to diminished inhibition. The P1 'attention effect' is thought to reflect a top-down inhibitory process, whereby P1 enhancement indicates inhibitory processes that blocks competing information of task-irrelevant stimuli (Slagter et al., 2016). Wessel and Aron (2015) observed significant P1 amplitude onset (i.e., statistically significant deviation between stop- and matched go-trial ERPs during an SST) for some participants that preceded the N2/P3 complex on Stop trial, however, in order to focus solely on the P3, they defined a minimum latency (120 ms) that excluded the P1. The fact that early components, predicted AUDIT scores lend support to a dual-process theory of alcohol misuse, whereby a lack of a cognitive control mechanism to inhibit drinking (i.e., deficits in later ERP components) is exacerbated by early attentional biases (i.e., deficits in early ERP components; see Campanella et al., 2018). Thus, neural deficits seen with alcohol misuse may not be exclusive to inhibitory control impairments *per se* – early processing impairments could underlie failures of later higher-level processing. As well as the findings for early attention-related components, the behavioural measure of sustained attention, IRV, was also a significant

predictor of alcohol use. Given that top-down, goal-driven attentional biases for alcohol have been observed in social drinkers (Brown, Duka, & Forster, 2018), it would be useful to further examine how goal-directed and involuntary aspects of attention are related to alcohol-outcomes.

Evidence for the utility of impulsivity-specific (e.g. BIS-11) versus broad trait personality measures (e.g., NEO-FFI) for prediction of alcohol is mixed. Adan and colleagues (2017) reviewed personality correlates of binge-drinking across studies and found that high impulsivity, as well as anxiety sensitivity, neuroticism, extraversion and low conscientiousness across studies were most strongly related to binge-drinking. This was examined in Model 2 (all non-ERP variables) and found that high anxiety symptoms, followed by high impulsivity (Stroop Interference Effect; BIS-11 Non-planning and Motor subscales; IRV), high Agreeableness and lower Neuroticism were most robustly linked to AUDIT scores. In Model 2, the most important variable was relationship status. Interestingly, dating in early adolescence (by age 14) is an important predictor of alcohol-use initiation (Squeglia et al., 2016), and of subsequent binge-drinking (Whelan et al., 2014). In young adulthood, romantic relationships are associated with heavier drinking (Fleming et al., 2018; Salvatore et al., 2014), and being in a stable relationship is associated with less drinking (Fleming et al., 2018). The stability of relationships also interacts with personality traits, such as lower neuroticism (Mund, Finn, Hagemeyer & Neyer, 2016). Therefore, dating in early adolescence may be considered a risky-behaviour (i.e., a risk-factor for alcohol misuse), being in a relationship in adulthood may be a protective factor. Given that young adult

romantic relationships and alcohol-use experiences are formative life choices, understanding how these experiences are related is an important task.

Model 3, the non-ERP impulsivity-only model, predicted alcohol use, as similarly demonstrated with drunkenness as the outcome variable in a different sample (Chapter 2). Trait impulsivity measures, including BIS-11 Non-planning and Attentional (but not Motor) subscales were among the strongest predictors of intoxication frequency (Chapter 2). Here, Non-planning and Motor (but not Attentional) subscales were the strongest predictors of alcohol use. Studies examining group differences have also found significantly increased scores for Non-planning and Motor subscales in alcohol users, compared to controls (Moreno et al., 2012; Sanchez-Roige et al., 2014). These findings provide further evidence that different impulsivity endophenotypes underlie different patterns of alcohol use. As well as AUDIT scores here, Non-planning is also related to increased number of weekly alcohol units (Caswell, Celio, Morgan, & Duka, 2015a) and binge drinking scores (Sanchez-Roige et al., 2014), indicating that this trait may be particularly salient for alcohol use in young adults, regardless of alcohol phenotyping.

SSRTs were the weakest variable in the model, similar to previous findings (Chapter 2), and no SSRT differences have been found in other drinking samples (Caswell, Celio, Morgan, & Duka, 2015., 2015; Sanchez-Roige   et al., 2014). There is, therefore, growing evidence that SSRT – the behavioural metric of response inhibition – is less sensitive to individual differences in alcohol use than ERPs or measures of trait impulsivity. In contrast to the SSRT, the Interference Effect on the Stroop was an important predictor of alcohol misuse. Despite the ostensible similarity in the underlying processes of inhibitory control, it is

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unlikely that these tasks measure the same effect (Bartholow et al., 2018). The Stroop has also been categorised as a measure of cognitive impulsivity in the form of inattention (i.e., longer Interference times indicate less resistance to distracting/conflicting stimuli; Sharma et al., 2014). Although various measurements of behaviour are rarely included in the same study, a meta-analysis by Sharma and colleagues (2014) examined impulsivity measures across studies and generated latent factors of impulsivity in order to obtain task-independent estimates of ability. They indicated that the Stroop was an important impulsivity-based factor that overlaps with executive functioning via inattentiveness, and is strongly linked to alcohol use, consistent with previous findings (O' Halloran et al., 2018a). Here, the importance of including measures that assay different aspects of impulsivity in determining factors that are most closely related to alcohol misuse is clearly demonstrated.

Despite the well-established links between impulsivity and alcohol misuse, neuroimaging predictors of alcohol use have only shown modest utility to date (Chapter 1). The advantages of machine learning approaches are that the most important variables can be identified from a large search space, and that correlated variables can be accommodated in the same model. Nevertheless, not all channels could be included – which would produce more than 20,000 data points for each of 79 participants – in my analysis. This was because simulated data (Jollans et al., 2015) indicated that detecting relevant variables given low-moderate effect sizes is not possible if the ratio of variables to cases is very large, across a variety of machine learning methods. Therefore, several regions based on prior work in this area were defined (Wessel & Aron, 2015), that included 26 channels. This generated over 8,000 variables per participant, many of which were highly correlated. Machine learning may

be particularly useful for finding new relationships among variables because analyses are not restricted to specific time intervals or electrodes. It is suggested that ERPs have potential to be a valuable clinical tool for assessing alcohol misuse. However, the generalisability of this model should be tested on other populations with inhibitory deficits, particularly alcohol-dependent samples. Future research may also explore the ability of ERP data to accurately classify those with AUD from controls, using machine learning methods that classify individuals into groups.

Conclusion

Individual differences in alcohol use were predicted by ERPs. Model performance and variable relevance was elucidated by comparing the original model with a model created from random-label permuted data. SSRT was not a predictor of alcohol use for either of the young adult samples in Chapters 2 and 3, with similar findings reported in relatively substance naïve adolescents (Whelan et al., 2012). On the other hand, brain data, including EEG measures in this Chapter and fMRI functional activation in (Whelan et al., 2012) are sensitive to the detection of alcohol use. Interestingly, unlike the behavioural SSRT, IRV was a significant predictor of alcohol use in adult student samples for both Chapters so far. However, the relationship between IRV and alcohol use in adolescents is relatively unknown and the related neural mappings underlying IRV have yet to be identified. Given that a previous task-based fMRI study identified disrupted attention-relevant functional networks in healthy adults, and these networks predicted ADHD symptoms in a separate sample of children (Rosenberg et al., 2016), it is possible that IRV may also be sensitive to early alcohol use in adolescents. Therefore, in Chapter, 4 a data-driven fMRI analysis was

employed to examine the link between IRV and functional connectivity patterns in adolescents, as well as their relationship with alcohol use.

4 Chapter 4: Neural Circuitry Underlying Cognitive Impulsivity: An Examination of Sustained Attention in Healthy Adolescents[4]

4.1   Introduction

Chapters 2 and 3 indicated that behavioural cognitive impulsivity, i.e., lapses in sustained attention measured using IRV on an SST, was an important predictor of alcohol-related outcomes. Chapter 2 also evidenced a relationship between disruption in attentional processes early in the ERP and higher levels of alcohol use. Yet, the relationship between IRV and alcohol use in adolescents has not been previously examined. IRV may provide a better metric of cognitive impairment than other neuropsychological test measures, such as standardized cognitive or psychomotor tasks (Balota et al., 2010; Cherbuin, Sachdev & Anstey, 2010; Haynes, Bauermeister & Bunce, 2017) or simple RT (Dixon et al., 2007), and higher IRV is commonly reported in ADHD (Bellgrove, Hawi, Kirley, Gill & Robertson, 2005; Castellanos et al., 2005; Castellanos, Sonuga-Barke, Milham & Tannock, 2006; Kofler et al., 2013; Kuntsi & Klein, 2011; Mullins, Bellgrove, Gill & Robertson, 2005; Vaurio, Simmonds & Mostofsky, 2009).

4.1.1   Brain Correlates of Sustained Attention.

Neuroimaging studies have identified brain regions involved in sustained attention. For example, task-based fMRI analysis in 42 adults showed that high IRV (i.e., poorer sustained attention) was associated with activation in the middle frontal gyrus (MFG), motor (precentral gyrus and pre-supplementary area; SMA), parietal, thalamic and insula regions (Bellgrove, Hester & Garavan, 2004). In healthy adults, low IRV (i.e., better sustained attention) was associated with stronger activation of anterior cingulate cortex (ACC) during a response inhibition task (Go/no-go task; Johnson et al., 2015), and during a gradual onset

continuous performance task (Esterman, Noonan, Rosenberg & DeGutis, 2012). In children (thirty 8-12-year-olds), low IRV (i.e., better sustained attention) on a Go-No/Go task was associated with stronger Go activation in anterior cerebellum (culmen) and stronger No-Go activation in motor, frontoparietal (medial frontal gyrus; inferior parietal lobe, IPL) and cerebellar networks, while high IRV associated with stronger Go and No-Go activation in MFG, caudate and thalamus (Simmonds et al., 2007). To date, however, the brain correlates of sustained attention in healthy adolescents, as indexed by IRV, have not been comprehensively characterised. Furthermore, there has been a surge of interest not only in characterizing task-evoked regional activity, but also in discovering how such regions fit within large-scale neural networks in supporting sustained attention (Fortenbaugh, DeGutis & Esterman, 2017).

Recent research has posited that sustained attentional processes may emerge from an array of large-scale functional connectivity networks (Castellanos, Kelly & Milham, 2009; Kessler, Angstadt & Sripada, 2016), rather than from single brain regions (Chun, Golomb & Turk-Browne, 2011; Rosenberg, Finn, Scheinost, Constable & Chun, 2017). Functional connectivity – synchronous fluctuations in neural activity across the brain – can be measured by correlating the blood oxygenation level-dependent (BOLD) signal time course between two brain regions. The *dorsal attention network* (DAN; comprising intraparietal sulcus (IPS), superior parietal lobule; primate frontal eye fields, and inferior pre-central sulcus) and *frontoparietal network* have been established for their involvement in sustained attention (Petersen & Posner, 2012; Szczepanski, Konen & Kastner, 2010). Stronger anticorrelations between task-positive networks and the default mode network (DMN; including medial

prefrontal cortex, posterior cingulate, anterior temporal and precuneus) is associated lower IRV (Kelly, Uddin, Biswal, Castellanos & Milham, 2008). However, the extent to which other networks outside classic vigilance networks (e.g., cerebellum) contribute to sustaining attention is less well understood (Fortenbaugh et al., 2017; Glickstein, 2007). One study in particular (Rosenberg et al., 2016) examined the relationship between task-based functional connectivity and sustained attention (a measure of sensitivity called d' on a gradual-onset continuous performance task) in 25 healthy adults. They identified a low sustained attention network whose connectivity was associated with poorer sustained attention (low d'), and a high sustained attention network whose connectivity was associated with better sustained attention (high d'). The authors also tested the generalisability of these networks in comparison to separate resting-state data. Stronger connectivity between cerebellum with motor and occipital networks, and occipital with motor networks predicted better sustained attention. In contrast, stronger connectivity between temporal and parietal regions, and within the temporal lobe and cerebellum predicted poorer sustained attention, and also largely predicted ADHD symptom severity when applied to an independent sample of 113 8-16-year-olds with and without a diagnosis of ADHD. However, the d' measure used to assess sustained attention in this case likely captures a different facet of sustained attention than IRV. Moreover, examining commonalities in the brain networks implicated in sustained attention across different behavioural measures and datasets is an important step in elucidating the neural underpinning of individual differences in response variability.

4.1.2 The Present Study

Firstly, this study sought to examine the relationship between fMRI activation and sustained attention, as measured by IRV on trials requiring a speeded response, in a large, normative sample of adolescents (N=758). Next, given that sustained attention may be better characterised by the dynamic interactions of large-scale brain networks than the degree of neural activation within single brain regions (Castellanos et al., 2005; Glickstein, 2007; Kelly et al., 2008; Kuntsi & Klein, 2011; Mullins et al., 2005), the relationship between functional connectivity patterns and IRV was examined in the normative sample. A task-based functional connectivity matrix was computed by correlating the BOLD signal time courses of every pair of regions in a 268-node brain atlas (Shen, Tokoglu, Papademetris & Constable, 2013). This connectivity matrix was then correlated with each individual's IRV score, in order to identify networks associated with high and low IRV. Rosenberg et al. (2016) applied the functional networks that indexed sustained attention in healthy adults, to an external sample of children with ADHD to validate their model. Therefore, significant clusters associated with fMRI activation, as well as the IRV-linked networks identified in the normative sample, were validated on a separate sample of adolescents with ADHD symptoms and were compared to a matched asymptomatic control group. Lastly, the IRV-linked networks identified in the normative sample in high alcohol use and non-alcohol using groups within the sample.

4.2   Materials & Method

4.2.1   Participants

Fourteen-year-olds were recruited at eight sites, and completed two fMRI sessions, psychiatric and neuropsychological assessments. Details of the full study protocol and data acquisition have been provided previously (Schumann et al., 2010; (http://www.imagen-europe.com/en/Publications_and_SOP.php). Here, participants were allocated to three groups. The first was designated as the *normative sample* (n=758; Table 4.1). The second, the *ADHD symptom* sample, (n=30; Table 4.2) were selected according to the total score of ADHD parent ratings on the Development and Well Being Assessment (DAWBA; description below), with a threshold of two standard deviations higher than the mean ADHD score of the Imagen sample. A third group, the *asymptomatic control* sample (n=30; Table 4.2), had scores of 0 on the DAWBA for ADHD symptoms, and were matched for age, sex, recruitment sites, handedness, pubertal development, performance IQ and verbal IQ to the ADHD symptom group.

4.2.2   Measures

The Alcohol Use Disorders Identification Test (AUDIT). The AUDIT (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001) is a 10-item alcohol screening questionnaire that assessed alcohol consumption, alcohol-related problems and drinking behaviour and quantifying risk from low-level to hazardous drinking. The AUDIT has demonstrated a high degree of internal consistency (Cronbach's a between 0.75 to 0.97; Reinert & Allen, 2007). Responses are scored from 0-4, with a maximum of 40 for total AUDIT scores.

Development and WellBeing Assessment (DAWBA) Interview. The DAWBA (Goodman, Ford, Richards, Gatward & Meltzer, 2000) is a structured set of questions designed to generate DSM-IV psychiatric diagnoses for children and adolescents aged 5–17 years. The ADHD subscale of the DAWBA consists of 31 questions, and includes specific ADHD subscales: hyperactive-impulsive, inattentive and combined. The DAWBA was administered to parents of the adolescents by questionnaire, under the supervision of a research assistant. Groups were constructed based on similar symptom cut-offs suggested by previous studies examining sub-clinical ADHD (Langley, Heron, Smith & Thapar, 2012; Salum et al., 2014). The three subscales were added together to form an ADHD total score and the cut-off score for ADHD symptoms was calculated as two standard deviations from the mean total score, while a score of zero was required in order to classify a participant as a member of the control group (i.e. asymptomatic with respect to ADHD).

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

Puberty Development Scale (PDS). The PDS scale (Petersen, Crockett, Richards, & Boxer, 1988) assessed the pubertal status of the adolescent sample, by means of 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) mid-pubertal, (4) advanced pubertal, (5) post-pubertal. Participants answered questions about their growth in stature and pubic hair, as well as menarche in females and voice changes in males.

Stop Signal Task. Participants performed an adaptive event-related Stop Signal Task (SST; Rubia, Noorloos, Smith, Gunning, & Sergeant, 2003; Rubia, Smith, Taylor, & Brammer, 2007), which took approximately 16 minutes to complete. The task consisted of 400 Go trials intermingled with 80 Stop trials; with between 3 and 7 Go trials between successive Stop trials. During Go trials participants were presented with arrows pointing either to the left or right, shown centrally on a screen for 1000 ms. During Go trials participants were required to make a single button-press response with their left or right index finger corresponding to the direction of the arrow. In the unpredictable Stop trials, the arrows pointing left or right were followed (on average 300 ms later) by arrows pointing upwards (i.e. the Stop signal, shown for for 100–300 ms), which required participants to inhibit their motor responses during these trials. A tracking algorithm (Rubia et al., 2003; 2007) adjusted task difficulty by varying the stop-signal delay (SSD; the time interval between Go signal and Stop signal onsets; 250–900 ms in 50-ms increments), in accordance with each participant's performance on previous trials (average percentage of inhibition over previous Stop trials, recalculated after each Stop trial). The aim of this was to produce 50%

successful and 50% unsuccessful inhibition trials. The inter-trial interval was jittered between 1.6 and 2.0 s (mean: 1.8 s) to enhance statistical efficiency (Dale, 1999). If the participant responded to the Go stimulus before Stop stimulus presentation (i.e. stop too early; STE), then the trial was repeated (up to a maximum of seven trials).

We calculated each participants' Stop Signal RT (SSRT), an index of inhibitory function, by subtracting the mean stop-signal delay (SSD) from the Go RT at the percentile corresponding to the proportion of unsuccessful stop trials. In other words, the SSRT refers to the time taken to cancel a prepotent motor response after Stop stimulus presentation. IRV was calculated by dividing each individual's standard deviation of mean Go RT scores by their mean Go RT scores.

4.2.3   MRI acquisition and analysis

Functional MRI data were collected at eight IMAGEN sites (London, Nottingham, Dublin, Mannheim, Dresden, Berlin, Hamburg, and Paris) with 3T MRI systems made by various manufacturers (Siemens: 4 sites, Philips: 2 sites, General Electric: 1 site, and Bruker: 1 site). Standardised hardware for visual stimulus presentation (Nordic Neurolab, Bergen, Norway) was used at all sites. The MR scanning protocols, cross-site standardisation and quality checks are further described in (Schumann et al., 2010). Functional runs included 444 whole-brain volumes acquired for each participant using echo-planar imaging (EPI) sequence. Each volume contained 40 axial slices aligned to the anterior commissure–posterior commissure (AC–PC) line (2.4-mm slice thickness, 1-mm slice gap). The echo time

(TE) was optimized (TE = 30 ms, repetition time 2200 ms; flip angle = 75°; acquisition matrix= 64 × 64)   to provide reliable imaging of subcortical areas.

4.2.3.1   *Preprocessing.*

Preprocessing of the fMRI imaging data from IMAGEN was performed centrally using an automated pipeline with SPM8 (Statistical Parametric Mapping, (http://www.fil.ion.ucl.ac.uk/spm/). fMRI BOLD images were co-registered with the T1W structural image (MPRAGE). Functional images were then realigned to correct for head motion and slice-time corrected using the first slice (top-down scanning) as reference for interpolation. T1W images were spatially normalized and non-linearly warped on Montreal Neurological Institute Coordinate System (MNI) space, using a custom EPI template. The custom template (53 × 63 × 46 voxels) was based on a subset of 240 participants' (30 from each of IMAGEN's eight sites) mean 480 EPI images that showed good spatial normalization, as measured by the overlap quality between individual EPI masks and the MNI mask (EPI images were spatially-realigned and their temporal-mean image was rigidly co-registered to their respective anatomical image). This normalization was applied to the EPI, and EPIs were then averaged to form an EPI template that was subsequently applied to all T1W data. Voxels were resampled at a resolution of 3 × 3 × 3 mm. The functional data was then smoothed with a 4-mm full width half maximum Gaussian isotropic kernel. The contrast   images   were   subsequently   analyzed   using   SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) and custom Matlab scripts (Mathworks).

4.2.3.2   fMRI Activation.

First-level activation maps were computed for go-trials, stop-success trials, and stop-fail trials versus baseline in individually specified general linear models (GLM). Design matrices included regressors for stop-success trials, stop-failure trials, Go too-late response trials, Go wrong response trials (i.e. wrong button press), movement parameters, and nuisance covariates (age, sex, pubertal status, handedness, performance IQ, verbal IQ, and data collection sites). On the second level, average fMRI activation for go-trials, stop-success trials, and stop-fail contrasts were each correlated with IRV for the normative sample using SPM12. Uncorrected p-values of .001 (recommended as the minimum lower limit; Eklund, Nichols & Knutsson, 2016; Woo, Krishnan, & Wager, 2014), and a cluster extent of 32 contiguous voxels were used to provide a corrected family-wise error rate of $p < .05$. Significant clusters from each statistical parametric maps for the three contrasts were anatomically labelled by examining the MNI coordinates to xjview (http://www.alivelearn.net/xjview). Mean beta values from the significant clusters derived from the normative samples were extracted for the ADHD symptom group and asymptomatic control group. Between-group two-sample t-tests were performed to compare regions of interest (ROI) between groups. Bonferroni correction was applied based on the total number of ROIs.

4.2.3.3   Task-based Functional Connectivity.

Whole-brain task-based functional connectivity was calculated using the following approach: I first removed the effect of Stop trials from the fMRI time series (using a similar

principle to that described in Fair et al., 2007). Specifically, I generated a general linear model (GLM) that included Stop-fail and stop-success trials and movement parameters. The Go condition (83% of trials) was not explicitly modelled. The residuals from this GLM, with stop-related activity and movement removed, were used in the task-based connectivity analysis. ROIs were derived from a 268-node functional brain atlas (referred to as the 'Shen atlas') that encompasses fine-grained, spatially homogeneous functional parcellations of the entire brain, including cortex, subcortical areas, and cerebellum, which serve as nodes for network analysis (Shen et al., 2013). Network labels, Brodmann areas (BA), and Montreal Neurological Institute (MNI) coordinates were automatically generated, and comprises ROIs with more coherent time courses than those defined by other atlases (e.g. automatic anatomic labelling atlas; Shen et al., 2013). For each participant, the ROI time-course was calculated by averaging the BOLD signal of all of its constituent voxels. This yielded 444 x 268 data points for each participant.

Since head motion occurs at low frequencies as intrinsic blood-oxygen level-dependent (BOLD) signal fluctuations, it can generate discrete neural artifacts that cannot be subjugated by increasing sample size or scan duration (Castellanos & Aoki, 2016). In order to further control for head motion artifacts, framewise displacement was included as a nuisance covariate in all connectivity analyses when computing partial correlations between functional connections and IRV (see below). Framewise displacement was defined as the sum of absolute scan to scan difference of the six translational and rotational realignment parameters (Power et al., 2014). Additional analyses were also conducted to exclude head motion as a cause of spurious results: these analyses are described in Supplemental Information. The

global signal (GS; average value across all gray-matter voxels) was included as a nuisance covariate once when computing the partial correlation between ROIs for each group (see below). The GS mitigates against between-subject effects of head motion (see Fox, Zhang, Snyder & Raichle, 2009; Yan et al., 2013). Although GS regression can bias group differences by enhancing anti-correlated connections, and some caution should be taken when interpreting results (Saad et al., 2012), much of the variance in the global signal can be explained by head motion, respiratory noise, and scanner hardware-related artifacts (Power, Plitt, Laumann & Martin, 2017).

A partial Pearson's correlation score was calculated among the 268 ROIs to determine their pairwise functional connectivity strength, with GS regressed as a nuisance covariate at this point. This yielded a connectivity matrix of size 268×268, with 35,778 unique connections between ROIs for each individual. Data file Supplemental_data_1.mat contains all pairwise correlations for all subjects. Matrices were not thresholded based on raw connection strength, allowing us to consider both low-variance connections (i.e., those that are consistently strongly positive or strongly negative across participants) and high-variance connections (i.e., those that are positive in some participants and negative in others); the latter, especially, may contain signal related to individual differences in IRV (see Garrison, Scheinost, Finn, Shen, & Constable, 2015; Scheinost et al., 2012).

4.2.3.4 *Functional connectivity correlated with behaviour.*

To assess the relevance of functional connections to behaviour the following analysis was performed: The 268 x 268 matrix of connections between ROIs was correlated with each

participant's IRV across the normative sample. Framewise displacement, age, sex, pubertal status, handedness, performance IQ, verbal IQ, and data collection site were nuisance covariate regressors. Type 1 error was estimated via random-label permutation by randomly shuffling IRV across participants and re-running the correlation analysis 1000 times in order to obtain an empirical null distribution. This analysis quantifies the probability of obtaining a particular r value between IRV and functional connectivity by chance. The observed r values between IRV and functional connectivity were considered significant if their associated p value exceeded a particular percentile of the random-label permutation. The resulting thresholded matrix consisted of connections between ROIs that were negatively correlated with IRV (i.e., indexing good sustained attention) and connections between ROIs that were positively correlated with IRV (i.e., indexing poor sustained attention). This thresholding was repeated using a series of significance thresholds ($p < 0.001$, and $p < 0.0001$) to identify networks associated with the task. Regional and network labels for the significant results were obtained from the previously available Shen atlas.

Alcohol. This method was repeated for the normative sample, however, rather than using their IRV scores, the 268 x 268 matrix of connections were correlated each participant's total AUDIT scores, and two thresholds ($p < 0.001$, $p < 0.05$) were used to identify networks associated with alcohol use.

Validation of IRV-linked networks. Having identified connections between ROIs that were significantly positively and negatively related to IRV using the $p < 0.001$ cut-off, (for comparison to similar research, see Rosenberg et al., 2065), the same connections for the ADHD symptom and asymptomatic control groups were extracted and computed. For each

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functional connection, the *r*-values were Fisher-normalized and then averaged across participants, within the ADHD symptom and asymptomatic control groups. This yielded two matrices for each group 1): connections positively correlated with IRV and 2) connections negatively correlated with IRV. Between-group two-sample *t*-tests were then conducted to examine group differences for each of these two connection types.

4.3 Results

Table 4.1 displays the summary characteristics of the normative sample and Table 4.2 displays the summary characteristics for the ADHD and control groups.

Table 4.1

Summary statistics for the normative sample

	Normative (n=758)[‡]
Age (years)	14.55 (0.45)
Sex	425 Females
Handedness	664 Right
Pubertal Development	3 (0.69)
Performance IQ	110 (14)
Verbal IQ	113 (13)
AUDIT Total	1.33 (4.24)
IRV	0.235 (.038)
'Go' trial RT St. Dev. (ms)	101 (24)
'Go' trial mean RT (ms)	429 (61)
SSRT	217(37)
Head Motion (Framewise displacement)	0.212 (.139)
Head Motion/IRV correlation	.22[†]

[‡] Mean (standard deviation), unless otherwise indicated [†] Spearman correlation, $p < .0001$.

Table 4.2

Summary statistics for ADHD symptom and asymptomatic control groups

	ADHD (n=30)	Control (n=30)	p
ADHD Total Score (DAWBA)	43 (9.83)	0	
Age	14(0.38)	14(0.41)	.16[†]
Sex	26 Males	23 Males	.32[††]
Handedness	27 Right	24 Right	.28[††]
Pubertal Development	3 (0.50)	3 (0.71)	.66[†††]
Performance IQ	101 (13.06)	103 (15.11)	.61[†]
Verbal IQ	109 (17.20)	105 (17.97)	.48[†]
AUDIT Total	2.03 (4.04)	1.10 (1.82)	.06[†††]
IRV	0.258 (0.04)	0.228 (0.36)	<.005[†]
'Go' trial St. Dev. (ms)	115 (26.20)	90 (22.26)	<.005[†]
'Go' trial mean RT (ms)	446 (72)	391 (58.56)	<.005[†]
SSRT	231(39)	228(41)	.76[†]
Head Motion (Framewise displacement)	0.291 (0.218)	0.195 (0.100)	.03[†]
Head Motion/IRV correlation	-.03[†]	.08[†]	

[†] Two-sample two-tailed *t* test [††] Chi-square test [†††]Non-parametric Mann-Whitney U test

[†]Spearman correlation, p>.05

4.3.1   Behavioural Results

The standard deviation of Go trial RT significantly correlated with the mean Go trial RT for the normative sample (r = 0.77, p < .001), the ADHD symptom group (r = 0.67, p < .001) and asymptomatic control group (r = 0.72, p < .001). The ADHD symptom group had significantly greater IRV (M = 0.258) than the matched asymptomatic control group (M = .228, t(58)= -2.951, p = .005), and significantly greater IRV than the normative sample (M = .235, t(786)= -3.216, p = .001), while there was no significant difference in IRV between the

normative sample and control group (t(786)= -1.026, p = .305). SSRT was not significantly correlated with IRV for the normative sample (r = .06, p = .09), the ADHD sample (r = .24, p = .19), or the control group (r = -.08, p = .66).

Alcohol. AUDIT total scores for the normative sample did not significantly correlate with IRV (r = .06, p = .07). AUDIT total scores did not significantly correlate with IRV for the ADHD symptom (r = .20, p = .26) or control (r = - .07, p = .70) groups, and no statistically significant group differences were found (t(58)= 3.4526, p = .06).

4.3.2 fMRI Activation Results

Normative Sample. Whole-brain task activity (for Go trials, Stop Success and Stop Fail trials) significantly correlated with IRV in several brain areas in the normative sample (see Table 4.3 and *Figure 4.1*). During Go trials, IRV was positively correlated with activation in bilateral postcentral gyrus, fusiform gyrus, superior temporal gyrus (STG), and right insula and precuneus. During Stop Fail trials, IRV was positively correlated with activation in left postcentral gyrus, and was negatively correlated with activation in insula bilaterally and right anterior cingulate cortex (ACC). During Stop Success trials, IRV was positively correlated with activation in precentral gyrus bilaterally, left postcentral gyrus, right SMA, left medial orbitofrontal cortex (OFC), precuneus bilaterally, and left superior temporal gyrus (STG). During Stop Success trials, IRV was negatively correlated with activation in right MFG and insula bilaterally.

ADHD Symptom & Control Groups. Compared to the control group, the ADHD symptom group had significantly greater activation in left postcentral gyrus during Stop Fail

trials (ADHD $m = .30$, control $m = -.20$, $p = .03$), during Stop Success trials (ADHD $m = .12$, control $m = -.27$, $p = .03$). No other significant differences emerged (using $p < 0.003$ the Bonferroni-corrected threshold for statistical significance).

Table 4.3

fMRI Activation correlated with IRV (Normative sample)

Brain Region (direction of effect)	Brodmann Area	Cluster Size	Z score	Montreal Neurological Institute (MNI) Coordinates		
				x	y	z
Go trial (Positive)						
Postcentral Gyrus R		280	4.564	60	-28	46
Postcentral Gyrus L		405	5.083	-45	-25	64
Insula R		54	4.908	39	-7	1
Fusiform Gyrus (Occipital) L	18	47	4.903	-21	-76	-14
Fusiform Gyrus (Occipital) R		41	4.884	21	-34	-20
Lingual Gyrus (Occipital) R		113	5.143	18	-85	-8
Precuneus R		39	4.713	27	-70	37
STG L	22	50	4.368	-54	-10	7
STG L	41	47	4.237	-45	-25	7
Paracentral Lobule		43	3.866	-3	-19	64
Stop Fail (Positive)						
Postcentral Gyrus L	3 4 6	102	4.447	-15	-28	76
Stop Fail (Negative)						
Insula L	13 47	105	5.062	-36	14	-2
Insula R	13 47	96	4.827	42	17	-5
ACC R	424	85	4.442	3	23	25
Stop Success (Positive)						
Precentral Gyrus R	4 6	98	5.418	27	-25	76
Precentral Gyrus R	4 6	84	5.200	54	-7	52
Postcentral Gyrus L	3 4 6	127	5.086	-24	-31	55
SMA L	6	57	5.026	0	-22	61
Medial Orbitofrontal L	10	45	4.698	-6	62	-5
Precuneus L	31	176	4.499	-12	-55	16
Precuneus R	23	46	4.465	18	-58	19
Postcentral Gyrus L	3 4 6	52	4.222	-48	-13	49
STG L	22 6	37	3.898	-60	-16	4
Stop Success (Negative)						
MFG R	8 9	39	4.699	48	11	43
Insula R	13 47	52	4.675	45	17	-5
Insula L	13 47	34	4.485	-36	14	-2

*All regions survived corrections for multiple comparisons (FWE $p < 0.05$) at the whole brain cluster level. Abbreviations: L=Left, R=Right, PCC=Posterior Cingulate Cortex, MOG=Middle Occipital

Gyrus, ACC=Anterior Cingulate Cortex, SMA=Supplementary Motor Area, OFC=Orbitofrontal cortex, STG Superior Temporal Gyrus, MFG=Middle Frontal Gyrus
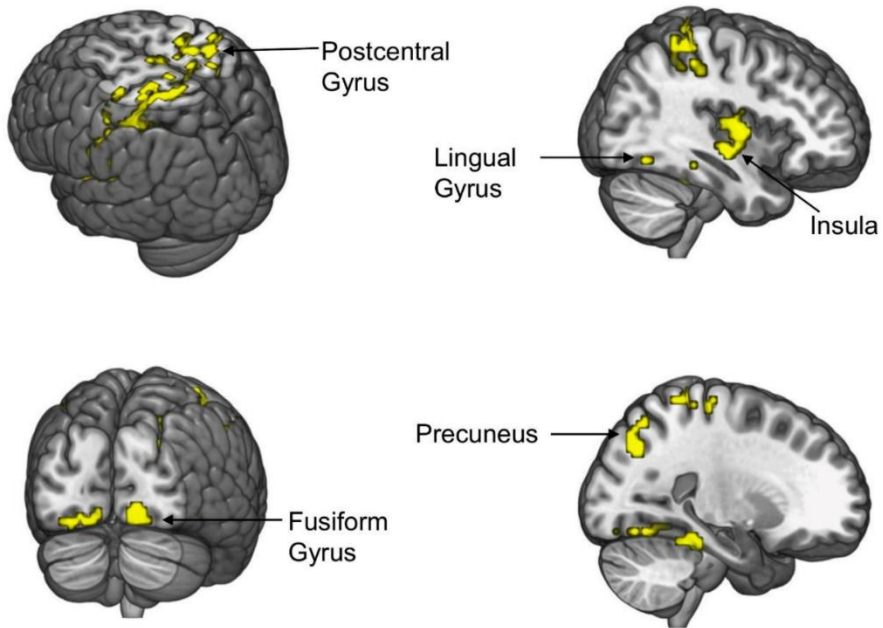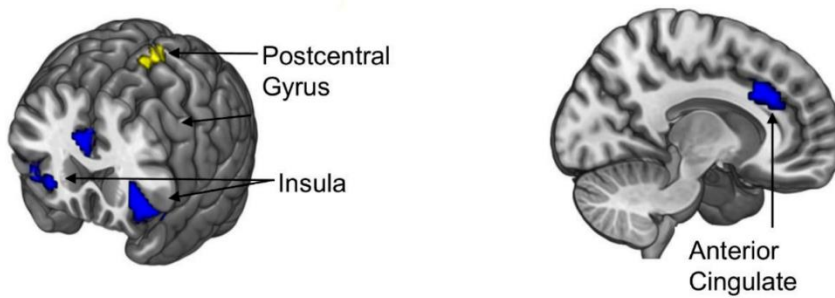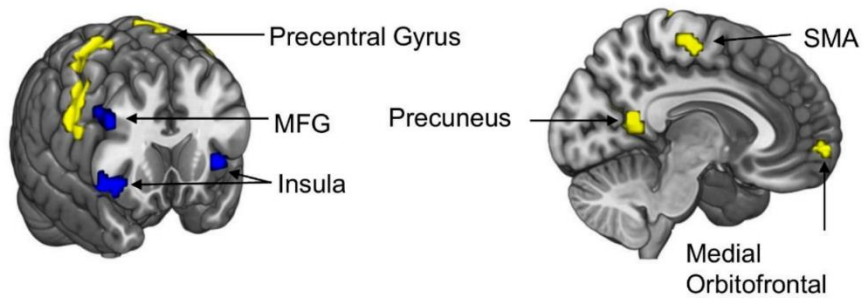
Figure 4.1. ROIs that positively correlated with IRV (yellow; poor sustained attention) and negatively

correlated with IRV (blue; good sustained attention) for the normative sample during (A) Go trials (B) Stop Fail and (C) Stop Success trials. Average fMRI activation images were created using MRIcroGL software (http://www.cabiatl.com/mricrogl/).

4.3.3 Functional connectivity results

IRV. At the significance threshold of $p < 0.001$ (absolute r-value $>.12$ derived from null models), 1368 connections between ROIs were associated with IRV. Networks linked with high and low IRV were identified (*Figure 4.2*). The networks linked with high IRV (i.e., poor sustained attention) were primarily characterised by positive correlations between ROIs (610 connections between ROIs, 80% of which were positively correlated), while the networks linked with low IRV (i.e., good sustained attention) were primarily characterised by negative correlations between ROIs (758 connections between ROIs, 86.7% of which were anticorrelated). In order to aid the interpretation of the findings (Böttger, Schäfer, Lohmann, Villringer, & Margulies, 2014), the top connections between ROIs correlated with IRV are reported in Table 4.4 and *Figure 4.2*.

Alcohol. No significant results were observed for functional connections with alcohol use at thresholds of $p < 0.001$ (absolute r-value $= 004$, $p = .93$, derived from null models), or at a liberal threshold ($p < 0.05$ uncorrected, absolute r-value $=.03$, $p = .79$, derived from null models).

4.3.3.1 *Functional anatomy of attention networks.*

Network anatomy was intricate. However, several trends emerged (see *Figure 4.2*). Connections positively correlated with IRV (i.e. poor sustained attention) were primarily located bilaterally within the motor network and between motor with parietal, prefrontal and

limbic networks. The top 10 nodes positively correlated with IRV comprised positively correlated connections between ROIs between and within bilateral precentral and postcentral gyri. Connections negatively correlated with IRV (i.e. good sustained attention) were primarily negative (i.e., anti-correlated), indexing functional segregation between cerebellum with motor, prefrontal and parietal regions, and between occipital and motor networks. The top 10 connections between ROIs negatively correlated with IRV consisted of anti-correlations between left cerebellum crus I/II and right precentral/postcentral gyri.

4.3.3.2   *ADHD Symptom & Control Groups.*

With respect to connections associated with high IRV (i.e., poor sustained attention), the ADHD symptom exhibited significantly stronger positive connectivity between ROIs (Fisher-normalized r value = .207) than the control group (Fisher-normalized r value = .156 $t(1218) = 2.92$, $p = .003$). There were no significant group differences in mean correlation strength for connections associated with low IRV (ADHD group, Fisher-normalized r value $m = -.132$; control group, Fisher-normalized r value $m = -.148$, $t(1514) = 1.34$, $p = .177$) See *Figure 4.3.*

Table 4.4

Top 30 Connections between ROIs Correlated with IRV

Brain Region 1	Brain Region 2	Hem 1	Hem 2	BA 1	BA 2	MNI 1			MNI 2				Normative FC & IRV	FC	Control	ADHD
						x	y	z	x	y	z	p	r	r	r	r
High Sustained Attention																
Postcentral Gyrus	Cerebellum Crus 1	R	L	2		42	-22	52	-25	-71	-30	.00	-0.219	-0.124	0.056	0.017
Precentral Gyrus	Cerebellum VI	R	L	6		49	-3	49	-7	-68	-18	.00	-0.216	-0.373	-0.311	-0.548
Precentral Gyrus	Cerebellum Crus 1	R	L	6		49	-3	49	-25	-71	-30	.00	-0.21	-0.269	-0.199	-0.203
Postcentral Gyrus	Cerebellum Crus 2	R	L	2		42	-22	52	-9	-82	-32	.00	-0.205	-0.064	0.053	-0.144
SMA	Cerebellum Crus 1	R	L	6		27	-11	65	-25	-71	-30	.00	-0.204	-0.09	0.089	0.064
Precentral Gyrus	Cerebellum VI	R	L	6	38	49	-3	49	-20	-55	-22	.00	-0.2	-0.361	-0.244	-0.437
Precentral Gyrus	Cerebellum VI	R	R	6		49	-3	49	7	-69	-20	.00	-0.198	-0.308	-0.217	-0.488
Postcentral Gyrus	Cerebellum Crus 1	R	L	2	37	42	-22	52	-35	-55	-31	.00	-0.197	-0.163	-0.09	-0.017
Postcentral Gyrus	Cerebellum Crus 1	R	L	2		21	-32	67	-25	-71	-30	.00	-0.193	0.052	0.292	0.241
Precentral Gyrus	Cerebellum Crus 1	R	L	6	37	49	-3	49	-35	-55	-31	.00	-0.193	-0.29	-0.274	-0.256
Postcentral Gyrus	Cerebellum Crus 1	R	L	2		42	-22	52	-25	-71	-30	.00	-0.191	0.000	0.202	-0.038
Precentral Gyrus	Cerebellum Crus 2	R	L	6		49	-3	49	-9	-82	-32	.00	-0.191	-0.217	-0.209	-0.275
SMA	Cerebellum Crus 2	R	L	6		27	-11	65	-9	-82	-32	.00	-0.189	-0.053	0.014	-0.08
DLPFC	MTG	R	R	46	37	47	35	19	59	-45	-15	.00	-0.188	-0.412	-0.617	-0.352
Postcentral Gyrus	Cerebellum VI	R	L	2		42	-22	52	-7	-68	-18	.00	-0.187	-0.269	-0.153	-0.386
Precentral Gyrus	Cerebellum V	R	L	6		49	-3	49	-6	-56	-25	.00	-0.185	-0.359	-0.267	-0.506

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Postcentral Gyrus	Cerebellum Crus 2	R	L	40		53	-27	41	-9	-82	-32	.00	-0.183	-0.147	-0.071	-0.12
Postcentral Gyrus	Cerebellum VI	R	R	2		42	-22	52	24	-73	-28	.00	-0.183	-0.018	0.153	-0.016
Postcentral Gyrus	Cerebellum Crus 1	R	L	40		53	-27	41	-25	-71	-30	.00	-0.181	-0.235	-0.09	0.000
Postcentral Gyrus	Cerebellum Crus 1	L	L	1		-36	-23	64	-25	-71	-30	.00	-0.179	-0.026	0.222	0.014
SMA	Cerebellum Crus 1	R	L	6	37	27	-11	65	-35	-55	-31	.00	-0.179	-0.119	-0.052	-0.04
SMA	Cerebellum VI	R	L	6		27	-11	65	-7	-68	-18	.00	-0.178	-0.287	-0.254	-0.398
Postcentral Gyrus	Cerebellum Crus 2	R	L	2		21	-32	67	-9	-82	-32	.00	-0.178	0.06	0.176	0.009
IPL	Cerebellum Crus 2	R	L	2		33	-39	48	-9	-82	-32	.00	-0.176	-0.02	0.003	-0.029
SMA	Cerebellum VI	R	R	6		27	-11	65	24	-73	-28	.00	-0.176	-0.011	0.111	0.097
MTG	DLPFC	R	L	37	46	59	-45	-15	-42	41	14	.00	-0.174	-0.372	-0.573	-0.314
IPL	Cerebellum Crus 1	R	L	2		33	-39	48	-25	-71	-30	.00	-0.174	-0.091	0.067	0.101
Postcentral Gyrus	Cerebellum Crus 2	L	L	1		-36	-23	64	-9	-82	-32	.00	-0.172	-0.052	0.167	-0.248
SFG	MTG	R	R	10	37	37	36	35	59	-45	-15	.00	-0.172	-0.437	-0.545	-0.308
Postcentral Gyrus	Cerebellum VI	R	L	40		53	-27	41	-7	-68	-18	.00	-0.171	-0.294	-0.165	-0.333
Low Sustained Attention																
Precentral Gyrus	Postcentral Gyrus	R	L	2	1	42	-22	52	-24	-32	61	.00	0.243	0.307	0.318	0.579
Postcentral Gyrus	Postcentral Gyrus	R	L	2	4	42	-22	52	-41	-16	45	.00	0.227	0.206	0.02	0.047
Postcentral Gyrus	IPL	R	L	2	40	42	-22	52	-36	-39	46	.00	0.226	0.17	0.06	0.425
Precentral Gyrus	Postcentral Gyrus	R	L	4	1	57	-9	29	-24	-32	61	.00	0.223	-0.152	-0.261	-0.033
Precentral Gyrus	Claustrum	R	L	4	7	57	-9	29	-28	-9	55	.00	0.221	0.053	-0.132	-0.048
Precentral Gyrus	Postcentral Gyrus	R	L	4	1	57	-9	29	-36	-23	64	.00	0.216	-0.178	-0.441	0.002
Precentral Gyrus	IPL	R	L	4	40	57	-9	29	-36	-39	46	.00	0.215	-0.067	-0.318	0.026
MFG	IPL	R	L	6	40	27	-11	65	-36	-39	46	.00	0.212	0.19	0.22	0.393

Postcentral Gyrus	Postcentral Gyrus	R	L	2	1	42	-22	52	-36	-23	64	.00	0.212	0.294	0.235	0.413
Precentral Gyrus	Precuneus	R	L	4	8	57	-9	29	-6	-34	64	.00	0.211	-0.073	-0.171	0.032
Postcentral Gyrus	SFG	R	L	2	7	42	-22	52	-16	-18	68	.00	0.21	0.338	0.52	0.591
Precentral Gyrus	Postcentral Gyrus	R	L	6	1	49	-3	49	-36	-23	64	.00	0.204	0.161	-0.004	0.379
Precentral Gyrus	Insula	R	L	4	6	57	-9	29	-45	-1	49	.00	0.204	-0.049	-0.276	-0.161
Postcentral Gyrus	Postcentral Gyrus	R	L	40	1	53	-27	41	-24	-32	61	.00	0.204	0.198	0.188	0.552
Precentral Gyrus	Postcentral Gyrus	R	L	6	1	49	-3	49	-24	-32	61	.00	0.201	0.108	0.012	0.407
MFG	Postcentral Gyrus	R	L	6	1	27	-11	65	-24	-32	61	.00	0.2	0.293	0.286	0.391
Postcentral Gyrus	SPL	R	L	2	1	42	-22	52	-51	-25	40	.00	0.198	0.084	-0.027	0.12
Precentral Gyrus	SMA	R	R	4	6	57	-9	29	6	-22	63	.00	0.198	-0.043	-0.117	0.013
MFG	Postcentral Gyrus	R	L	6	1	27	-11	65	-36	-23	64	.00	0.197	0.354	0.381	0.409
MFG	Postcentral Gyrus	R	L	6	4	27	-11	65	-41	-16	45	.00	0.196	0.281	0.228	0.151
Postcentral Gyrus	Precuneus	R	L	2	8	42	-22	52	-6	-34	64	.00	0.195	0.407	0.516	0.718
Precentral Gyrus	Postcentral Gyrus	R	R	4	2	57	-9	29	42	-22	52	.00	0.195	0.022	-0.346	-0.135
MFG	IPL	R	L	6	7	27	-11	65	-25	-55	59	.00	0.193	0.224	0.329	0.44
Precentral Gyrus	Postcentral Gyrus	R	L	4	4	57	-9	29	-41	-16	45	.00	0.192	-0.14	-0.453	-0.113
IPL	Postcentral Gyrus	R	L	2	1	33	-39	48	-24	-32	61	.00	0.189	0.309	0.389	0.466
Postcentral Gyrus	SFG	R	L	40	7	53	-27	41	-16	-18	68	.00	0.187	0.245	0.375	0.493
MFG	SPL	R	L	6	1	27	-11	65	-51	-25	40	.00	0.187	0.141	0.175	0.245
Precentral Gyrus	Insula	R	L	4	7	57	-9	29	-23	12	54	.00	0.184	0.27	0.155	-0.011
Postcentral Gyrus	Postcentral Gyrus	R	L	40	4	53	-27	41	-41	-16	45	.00	0.183	0.093	-0.174	-0.215
Postcentral Gyrus	Precuneus	R	L	40	8	53	-27	41	-6	-34	64	.00	0.182	0.347	0.428	0.722

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Abbreviations: L=Left, R=Right, SMA= Supplementary Motor Area, DLPFC=dorsolateral prefrontal cortex, MTG=Middle Temporal Gyrus, IPL=Inferior Parietal Lobule, SFG=Superior Frontal Gyrus, MFG=Middle Frontal Gyrus, SPL=Superior Parietal Lobule
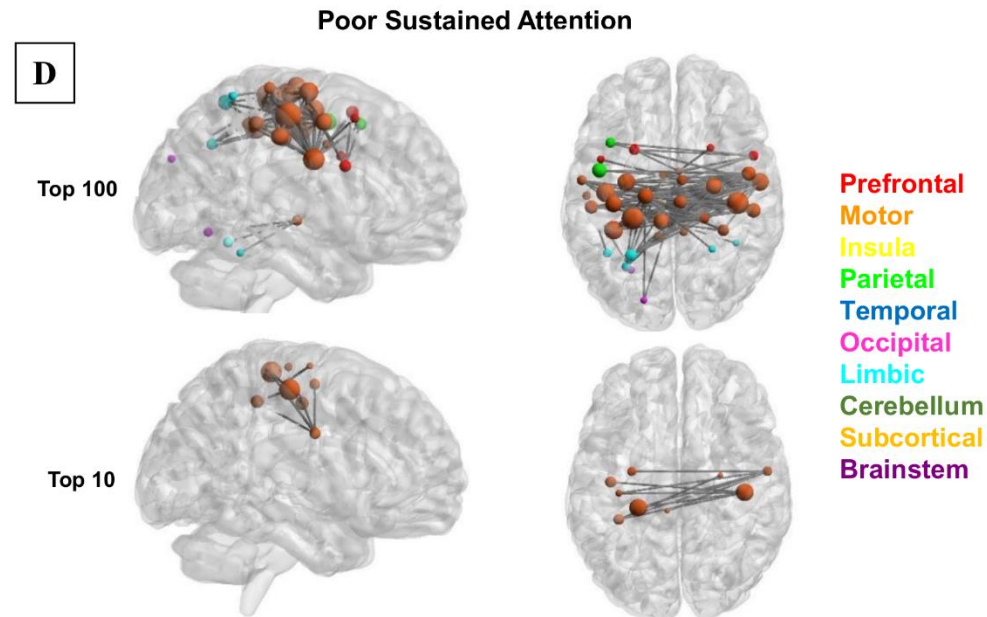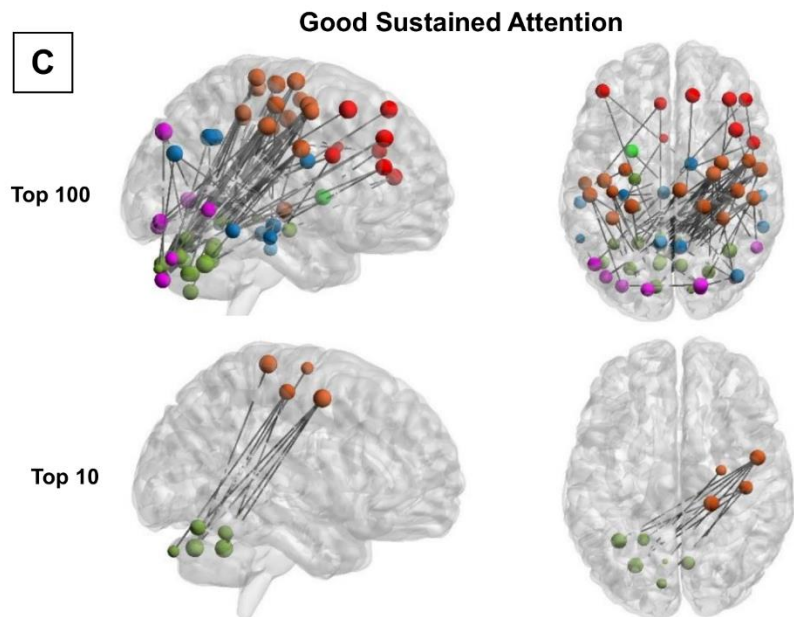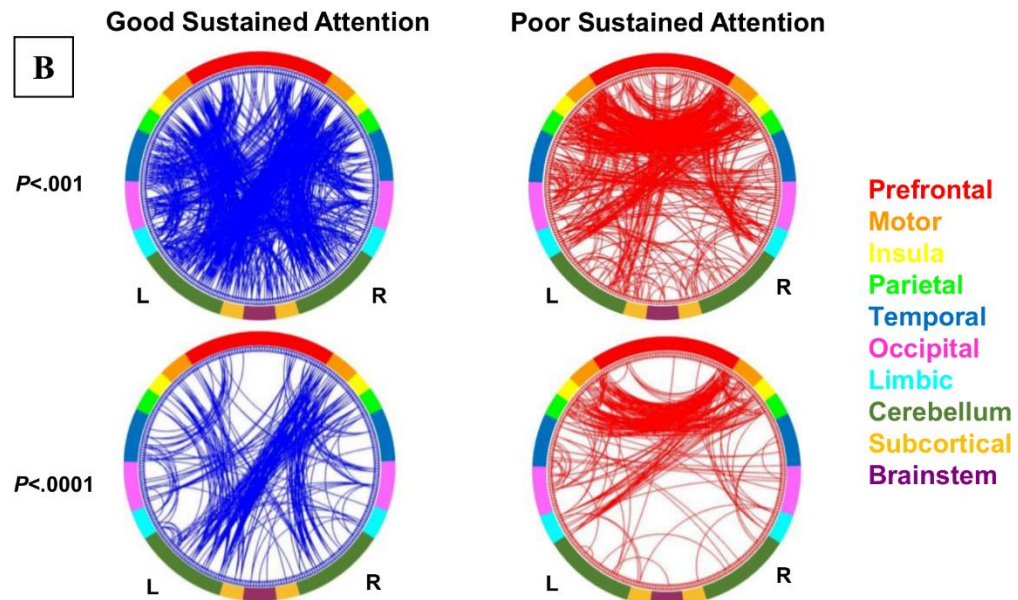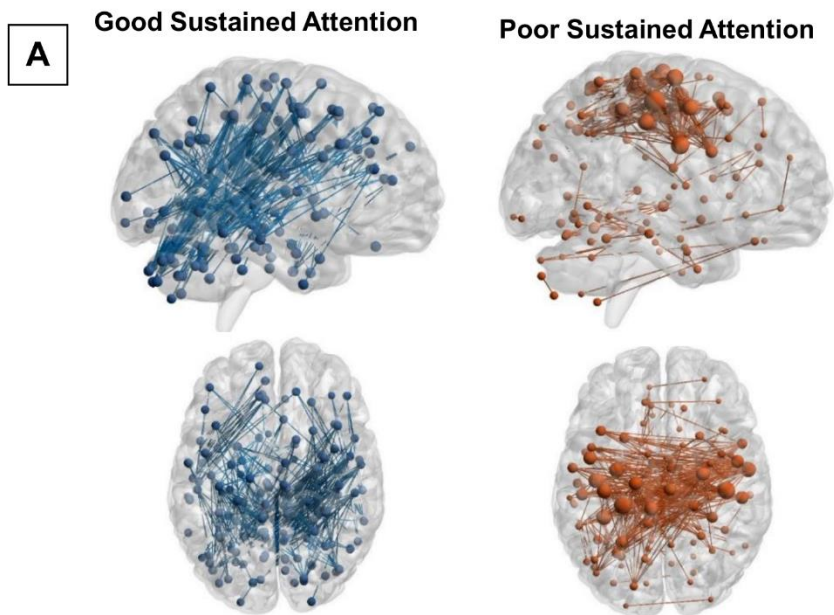
A

Good Sustained Attention   **Poor Sustained Attention**

B

Good Sustained Attention   **Poor Sustained Attention**

P<.001

P<.0001

L   R   L   R

Prefrontal
Motor
Insula
Parietal
Temporal
Occipital
Limbic
Cerebellum
Subcortical
Brainstem

C

Good Sustained Attention

Top 100

Top 10

D

Poor Sustained Attention

Top 100

Top 10

Prefrontal
Motor
Insula
Parietal
Temporal
Occipital
Limbic
Cerebellum
Subcortical
Brainstem

Figure 4.2. **(A)** BrainNet was used to visualise network connectivity (Xia, Wang & He, 2013), based on specific guidelines (see Shen et al., 2017), whereby nodes are grouped into localised regions. Good sustained attention denotes all connections between ROIs that negatively correlated with IRV (blue); poor sustained attention denotes all connections between ROIs that positively correlated with IRV (orange) for the normative sample. **(B)** Circle plots were generated using a custom-written Matlab function (based on http://www.mathworks.com/matlabcentral/fileexchange/48576-circulargraph) to visualize good sustained attention (blue) and poor sustained attention (red) for the normative sample. The plots are arranged in two half circles reflecting left and right hemisphere brain anatomy from anterior (top of the circle) to posterior (bottom of the circle). Nodes are colour-coded according to the cortical lobes (Shen et al., 2017). **(C)** The top 100 nodes and 10 nodes denoting good sustained attention (i.e. connections between ROIs that negatively correlated with IRV, where p<.001). (D) The top 100 nodes and 10 nodes denoting poor sustained attention (i.e. connections between ROIs that positively correlated with IRV where p<.001). Nodes were colour-coded according to network as identified in (Xia et al., 2013).

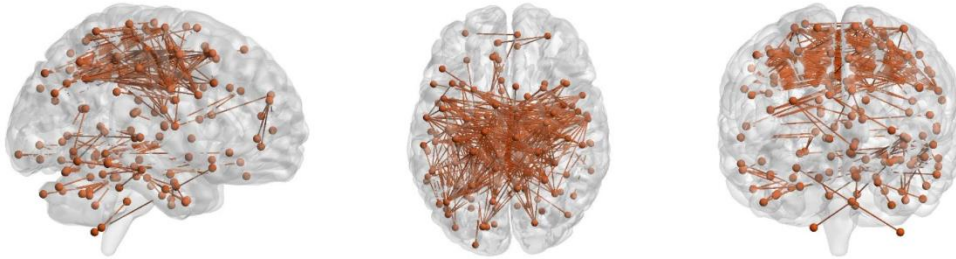**ADHD > Controls**
Poor Sustained Attention

Figure 4.3. With respect to ROI connections associated with high IRV (i.e., poor sustained attention), the ADHD symptom exhibited significantly stronger connectivity between ROIs, compared to controls.

4.4   Discussion

The current research is the first population-based functional imaging study to examine IRV with respect to both average fMRI activity and functional connectivity in a large cohort of adolescents. Sustained attentional processes are facilitated by an array of neural networks, particularly in connectivity between the cerebellum and motor networks, while atypically strong connectivity within motor networks characterises poor attentional capacity in both typically developing and ADHD symptomatic adolescents.

4.4.1   Alcohol: sustained attention and the brain

There were no significant findings for functional connectivity correlated with alcohol (even with a low, uncorrected, threshold, $p<.05$), nor was IRV associated with alcohol use for the normative sample, or for the ADHD symptom and control groups. The ADHD symptom group did have elevated AUDIT scores, relative to controls, however group differences did not reach significance. These results are likely due to relatively low levels of alcohol use at this age. On the other hand, the ADHD symptom adolescents had significantly higher IRV, relative to controls, as previously demonstrated (Albaugh et al., 2017; Rubia et al., 2003). Whelan and colleagues (2014), found no behavioural differences for motor impulsivity (SSRT) between 14-year-old alcohol misusers (<4 lifetime uses of alcohol) and non-drinkers, however, they did find group differences in neural networks underlying inhibitory control (note this study also used the IMAGEN sample). It is possible that inhibitory control is an early marker of vulnerability to alcohol misuse, whereas IRV may not be able to detect subtle differences underlying sustained attention deficits associated with low levels of alcohol use.

4.4.2 Brain correlates of sustained attention

With respect to good sustained attention (i.e., low IRV) in the normative sample, fMRI Stop-related activation was found in the MFG, insula and ACC. The functional connectivity results indicated predominantly negative left cerebellar connections with right parietal (postcentral gyrus) and frontal areas (SMA and DLPFC), a finding that bears similarity sustained attention connectivity in adults (Rosenberg et al., 2016). The task-active frontoparietal network (including SMA and DLPFC) is typically activated during attention-demanding tasks than during rest (Corbetta & Shulman, 2002; Konrad & Eickhoff, 2010; Langner & Eickhoff, 2013). Furthermore, the cerebellum is thought to have a critical role in sustained attention (Buckner, 2013; Brisenden et al., 2016; Habas et al., 2009; Stoodley, 2012). In healthy adults, recent work has shown that enhancing cerebellar functional connectivity via transcranial magnetic stimulation decreases IRV (Esterman et al., 2017). Adding to this work, the current results also implicate distinct subregions of the cerebellum, i.e., left lateralized Crus I/II, in characterising good sustained attention. No significant differences in these networks were found between the ADHD symptom and asymptomatic control groups.

With respect to poor sustained attention (i.e., high IRV) in the normative sample, fMRI activation was found in the precentral and postcentral gyri bilaterally on all trials, and in the left SMA during successful stop trials, a region responsible for successful stopping, monitoring and resolving task conflict (Verbruggen & Logan, 2008). Poor sustained attention was also associated with activation in the DMN (precuneus) during Go and Stop-Success

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trials, a region that is typically deactivated for efficient sustained attentional processes (Broyd et al., 2009; Kelly et al., 2008), therefore, this positive IRV-DMN is unsurprising. However, DMN deactivation typically increases with maturation into young adulthood (Anderson et al., 2011; Fair et al., 2007). The functional connectivity results for poor sustained attention showed robust positive interhemispheric connections within the motor network, as well as between motor with parietal and limbic networks. This bilateral motor activation likely reflected the task format (i.e., left- and right-hand responses). Consistent with these observations, the sample of adolescents with ADHD symptoms also had increased fMRI activation and stronger positive connectivity within the same motor network, compared to controls. The observed positive motor-motor coupling may reflect a snapshot of neural development in early adolescence. For example, age-related decreases in motor connectivity have been observed in a large sample of healthy children and young adults (Van Duijvenvoorde et al., 2016). Furthermore, adults with poor sustained attention show connections between temporal and parietal networks and within the cerebellum (Rosenberg et al., 2016). Nevertheless, the findings lend support for a more predominant functional segregation of neural networks in childhood and greater functional integration later on in adulthood (Konrad & Eickhoff, 2010).

Alternatively, there is increasing agreement among fMRI studies that decreased pre-SMA activation may lead to increased, compensatory prefrontal activity during response inhibition in ADHD individuals (Suskauer et al., 2008). In an fMRI study using the SST, 16 children with ADHD (8-12-years-old) had higher BOLD responses for Stop Success over Stop Fail trials in the fronto-striatal network, ACC and cerebellum (Massat et al., 2016).

Furthermore, these ADHD children had higher activations in the striatum (caudate, putamen), right insula and cingulate cortex for Stop Success trials, relative to 16 typically developing children. Similar to the current findings, higher activation in inhibitory control-related networks in children with ADHD indicates reduced efficiency with compensatory neural efforts in situations in which most individuals could depend on less demanding processes to reach normal performance levels (Massat et al., 2016). This need for compensatory brain activation is potentially linked to a less mature response inhibition neural system (Braet et al. 2009) in children with ADHD. However, in adulthood, diagnostic remission may actually arise from compensatory maturation of prefrontal, cerebellar, and thalamic circuitry (Proal, Reiss et al. 2011).

4.4.3   Strengths and limitations

The findings of Chapter 4 solidify the importance of data-driven functional connectivity analyses, rather than constraining ROIs a priori, in order to better characterise cognitive processes (Ernst, Torrisi, Balderston, Grillon & Hale, 2015; Turk-Browne, 2013). Tamnes and colleagues (2012) suggested that the relationship between IRV and age may be a sensitive marker of neural development. Furthermore, adolescents with ADHD (Shaw et al., 2007) and subclinical attention deficits (Ducharme et al., 2012; Shaw et al., 2011) display delays in cortical maturation, and this localized motor hyper-connectivity may subside as more global, specialized brain networks develop. Considering the major brain changes that occur during adolescence (Luciana, 2010), it is unclear if the observed functional trends reflect some sort of developmental delay or if they will persist as these adolescents develop. Secondly, the large normative sample was relatively substance naïve and their AUDIT scores

did not correlate with IRV. However, given that Chapters 2 and 3 found a positive association between IRV and alcohol use in students, the networks identified here provide a basis for examining later neural changes and their association with drinking trajectories. Thirdly, the ability to rigorously measure fluctuations in temporal resolution, combined with the corresponding physiological responses (head motion, respiration) remains a challenge (Kuntsi & Klein, 2011; Poldrack, 2015). Broadly speaking, nuisance regression is the dominant approach for removing signal confounds, although it increases the risk of reducing signals of interest (Caballero-Gaudes & Reynolds, 2017). Scrubbing procedures can alter the temporal structure of timeseries data (Yan et al., 2013), therefore it was not implemented in this case. Some previous work indicates functional connectivity patterns remain largely unchanged after scrubbing, and that including mean framewise displacement as a group-level covariate yields similar results to scrubbing (Yan et al., 2013; Di Martino et al., 2014; Fair et al., 2013). The issue of head motion was at least partially addressed here by considering motion parameters as covariates in the statistical analysis (Yan et al., 2013). Global signal regression was also used in the current analyses, given that several reports have indicated its merits in robustly handling in-scanner movement (Burgess et al., 2016; Ciric et al., 2017; Power, Laumann, Plitt, Martin & Petersen, 2017). Nevertheless, head motion (i.e., mean framewise displacement) significantly correlated with IRV in the large normative sample (n=758; $r =$ .22), but not in the smaller ADHD symptom and control samples (each n=30) similar to previous research (Rosenberg et al., 2016). This further highlights the importance of large sample sizes in order to control for spurious effects on functional connectivity data.

Conclusion

The current findings serve to advance our understanding of the brain networks associated with sustained attentional processes. Functional connectivity between a global array of networks, including the cerebellum, motor, and prefrontal cortices, serve as a robust indicator for sustained attention. The involvement of motor connectivity in both low and high attention networks highlights its significant role in adolescent attention and cognitive impulsivity. However, functional connectivity associated with IRV was not sensitive to alcohol use in 14-year-old adolescents, although one future direction could be to examine if these networks predict alcohol use trajectories into adulthood.

5 Overall Discussion

5.1 Review of general aims and summary of main findings

The aim of this thesis was three-fold: the first objective was to capture the relationship between impulsivity endophenotypes, and other important risk factors, including different alcohol-related outcomes. Using this framework, machine learning methods facilitated the inclusion of large datasets, whilst also safeguarding against overfitting (out-of-sample nested cross-validation) to help yield greater generalisability of results. Secondly, the ERP literature indicates that attentional and inhibitory control processes are impaired in individuals with AUD. Using a novel machine learning approach, the objective was to quantify the utility of ERPs, indexing inhibitory control on the SST, for predicting alcohol use. This approach capitalises on recent trends that use machine learning techniques to classify alcohol misusers based on their fMRI signatures. Thirdly, sustained attention, an important aspect of cognitive impulsivity, has been explored extensively in individuals with ADHD, however, a measure of sustained attention – IRV on the SST – had yet to be examined. Using task-based fMRI, an objective here was to tackle the interesting and timely question of how average brain activation and functional connectivity patterns were related to individual differences in sustained attention, and if this may elucidate some of the nascent aetiological cognitive mechanisms that contribute to risks related to substance misuse in adolescents and beyond.

5.2   Impulsivity phenotypes and different patterns alcohol use

The use of multiple alcohol measurements, as well as intermediate levels of alcohol use, may better capture the relationship between alcohol involvement and endophenotypic diversity. In Chapter 1 various challenges in quantifying alcohol consumption (e.g., definitions of heavy vs. light alcohol use) and alcohol-related consequences (e.g., single consumption-based measures of alcohol use) were highlighted. It was also suggested that the integration of different patterns of alcohol use, such as drunkenness, rather than solely focusing on alcohol quantity, would offer a more accomplished method to phenotype alcohol use. The findings in Chapter 2 lends support to this. Two orthogonal latent factors of alcohol use were generated (based on the frequency of alcohol use, binge drinking frequency, and perceived intoxication questions on the ESPAD; Hibell et al., 2009), and named 'intoxication frequency' and 'consumption frequency'. Chapter 3 also applied machine learning to impulsivity endophenotypes to predict alcohol use, using a separate sample. Here, individual differences in AUDIT scores were also significantly predicted by impulsivity endophenotypes, but unlike Chapter 2, increased AUDIT scores were characterised by increased trait impulsivity (Motor and Non-planning BIS-11 subscales), increased cognitive impulsivity (IRV) and an increased Interference Effect on the Stroop. However, in Chapter 4, functional connectivity associated with IRV was not significantly associated with alcohol use, albeit in a sample of adolescents with low alcohol exposure. Some of these distinctions and overlaps in individual variables may attributable to the alcohol-related outcomes measured, which will now be explored further.

5.2.1 Trait impulsivity

Some of the strongest predictors of alcohol use in Chapters 2 and 3 (including intoxication frequency and AUDIT scores) were trait impulsivity measures, in line with previous studies (Caswell et al., 2015b; Mackillop et al., 2016; Sanchez-Roige et al., 2014). Increased Non-planning (BIS-11) was an important predictor of alcohol misuse, regardless of alcohol measure and sample differences, predicting both increased intoxication frequency (*Chapter 2*) and increased AUDIT scores (*Chapter 3*), as supported in by various other studies (Carbia et al., 2018; Mackillop et al., 2016; Moreno et al., 2012; Sanchez-Roige et al., 2014). Furthermore, students with higher negative expectations of alcohol have also shown higher levels of Non-planning impulsivity (Balodis et al.,2009). However, distinctions between the studies did emerge on BIS-11 subscales, with higher Attentional (but not Motor) trait impulsivity predicting intoxication frequency (Chapter 2), whilst higher Motor (but not Attentional) was observed for AUDIT scores. (Chapter 3). These findings further highlight the importance of distinguishing subscales of the BIS-11 scale in relation to alcohol use (Stevens et al., 2018).

Zuckerman's Sensation Seeking Scale (SSS, Zuckerman, Eysenck, & Eysenck, 1978), posited another strand of impulsivity, derived from aspects of trait impulsivity, where high 'sensation seeking' indicates a need for stimulation and novel experiences, regardless of the risks, and it is also a subscale of the SURPS. However, whether impulsivity and sensation seeking are dissociable constructs, or whether they converge, has been unclear. For instance, although MacKillop and colleagues (2016) initially included sensation seeking in their latent structures of trait impulsivity, the inclusion of sensation seeking to their overall factor model

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did not improve the overall construct validity, whereas its removal did. In Chapter 2, trait Disinhibition (SSS-V) was the only trait predictor of consumption frequency, and has been previously linked to student binge drinking (+6 drinks threshold; Moreno et al., 2012). However, this thesis found that higher Experience Seeking indicated *lower* levels of intoxication frequency, and suggested that it is possible that this sub-trait is redolent of the pursuit of an unconventional lifestyle that actually requires a degree of planning and consideration (e.g., travelling, parachuting). This is discordant with previous definitions of impulsivity (i.e., rapid, unplanned actions, without consideration for the negative consequences Moeller et al., 2001), and has led to some (Castellanos-Ryan et al., 2011) suggesting that developing a joint construct of, impulsivity and sensation seeking, that is, "disinhibited personality", may be more conceptually useful. Because findings in Chapter 2 lent support to Mackillop and colleagues' (2016) findings, SSS-V was not included in subsequent analysis in Chapter 3, however, it would be interesting to see whether impulsivity or sensation seeking traits best classify alcohol-using groups.

5.2.2 Choice impulsivity

When it came to choice impulsivity, Chapter 1 highlighted that youth alcohol users were more likely to demonstrate suboptimal choices, and in turn select a smaller more immediate reward over a larger delayed reward, as previously demonstrated in 13-15-year-old adolescents on a DDT (Schneider, Peters, Peth, & Büchel, 2014), and in 16-18-year-old binge-drinkers on the IGT (Xiao et al., 2013). However, the empirical study in Chapter 2 did not fully support this, finding that choice impulsivity, as measured by the delay discounting

task (DDT), was a weak-to-moderate predictor for intoxication frequency, and it only became a significant predictor for consumption frequency when combined with other risk factors. In Chapter 3, the DDT was also a relatively weaker predictor of alcohol use, compared to other task-based impulsivity measures (e.g., Stroop and IRV). In contrast to the DDT, self-reported steeper discounting rates on the MCQ was a significant predictor for intoxication frequency in Chapter 2, but not consumption frequency. Although the MCQ measure was not included in the experimental design in Chapter 3, other studies have also found notable measurement-related differences for questionnaire- and task-based choice impulsivity in student samples. For example, choice impulsivity, indexed by the MCQ, was not found to be related to the number of weekly alcohol units in a student sample (Caswell et al., 2015b). Similarly, another study found no differences between binge-drinkers and non-binge-drinkers for choice impulsivity, indexed by the DDQ (Sanchez-Roige et al, 2014), which is consistent with a number of studies using the DDQ (Fernie et al, 2010; MacKillop et al, 2007). However, Sanchez-Roige and colleagues (2014) did find that binge-drinkers had greater choice impulsivity on a behavioural task (TCIP). Moreover, MacKillop and colleagues (2016) found that a latent factor of choice impulsivity (DDT and MCQ) was associated with alcohol use in lighter drinkers (AUDIT mean = 4). It is evident that different paradigms measuring discounting rates (choice impulsivity) produce varying results, but it might also indicate that there are perhaps important distinctions related to patterns of alcohol use. Designs for future research need to reflect such considerations in order to elucidate on these relationships. Moreover, despite strong associations between choice impulsivity on the DDT and disordered substance use (Amlung et al., 2017), there is little other examination of the DDT and how it

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relates to non-disordered alcohol use. These findings provide a potentially interesting and important avenue for alcohol-related research, given that steeper discounting is also increasingly being linked to new addictive disorders that are particularly pertinent in young people, such as Internet Gaming Disorder (Tian et al., 2018).

5.2.3   Motor impulsivity

Poor inhibitory control, indexed by longer SSRTs on Stop Signal Tasks (SST) have been observed for disordered alcohol-use (Mole et al., 2015) and for acute alcohol dosages (Caswell et al., 2013a). Studies reviewed in Chapter 1 pointed to comparable behavioural performances for motor impulsivity indexing inhibitory control between alcohol misusers and controls (Caswell *et al*., 2015b; MacKillop et al., 2016; Moreno et al., 2012; Sanchez-Roige et al., 2014). SSRT did not significantly predict any indices of alcohol use in Chapters 2 and 3. Furthermore, in Chapter 4, the SSRT was not significantly correlated with the sustained attention (IRV) in a large normative sample of adolescents, or in the smaller sample of individuals with elevated symptoms of ADHD, or the asymptomatic control group. Given the young age of the participants sampled for this thesis, it is possible that non-dependent alcohol users have not yet experienced the cumulative neurotoxic effects of repeated alcohol abuse, which is thought to weaken top-down cognitive control (López-Caneda et al., 2013; Robbins & Dalley, 2017; Stephens & Duka, 2008).

In contrast to the behavioural results however, there was some indication that differences in brain activation patterns underlying response inhibition could be detected, even in the absence of behavioural differences (Whelan et al., 2012). In the longitudinal studies

reviewed in Chapter 1, measures of baseline brain activity tended to show hypoactivation in frontoparietal, temporal and orbitofrontal brain regions in low-moderate alcohol misusers, which predicted subsequent heavier drinking (Wetherill et al., 2013b; Worhunsky et al., 2016). This suggested that neural measures of inhibitory control could have potential to better characterise alcohol misuse than behavioural metrics alone. This thesis sought to investigate this further using EEG techniques.

5.2.3.1   *ERP correlates of alcohol use.*

It was hypothesised that a multivariable approach, based on a weighted combination of diverse electrophysiological variables, would be more useful for predicting outcomes than single ERPs. In Chapter 3, this assumption was tested. Results showed that individual differences in AUDIT scores were predicted from ERP time-courses derived from an assay of inhibitory control (stop success and stop fail conditions), with moderate accuracy. Over 8,000 ERP variables per participant were included in the model, and out-of-sample validation was used to quantify generalisability of the results. It was expected that the optimal parameters for predicting alcohol use would predominantly fall within the N2-P3 complex. Interestingly however, the optimal ERP variables for predicting alcohol use were widespread spatially and tended to occur early in the inhibitory control time course, over medial scalp regions. Indeed, the model of ERP variables that best predicted alcohol use was not sparse, even when utilising stringent thresholding approaches.

Greater N2 amplitude (i.e., more negative N2) was associated with higher alcohol use, with similar findings in other student binge drinkers (Crego et al. (2009), and in adults with

AUD (Olbrich et al., 2000). However, findings for N2 abnormalities in alcohol misusers, compared to control, have been equivocal. For example, Pandey and colleagues (2012) found lower No-Go N2 amplitude in males with alcohol dependence, while no NoGo differences in N2 amplitude were found when comparing heavy drinkers to lighter drinkers (Franken et al., 2017), as between student heavy drinkers and lighter drinkers (Oddy & Barry, 2009). With regards to the P3, reduced P3 amplitude was associated with higher alcohol use, particularly during successful stops, a finding that is also a marker of AUD (Campanella et al., 2018; Luijten et al., 2014; Mumtaz et el., 2017). Reduced P3 amplitude during response inhibition is also thought to represent a component of the alcoholic phenotype (Campanella et al., 2018; Luijten et al., 2014; Mumtaz et el., 2017a). However, similarly to the N2, findings for the P3 are not consistent across studies. For example, Franken and colleagues (2017) found no group differences related to the P3.

Notably, the current study used the SST to index motor impulsivity, while the abovementioned studies used GNG tasks. This may account for, in part, some of the discrepancies between the findings, given that hemispheric activation differences have been observed for these tasks (D'Alberto, Funnell, Potter, & Garavan, 2017; Nikolaou, Critchley, & Duka, 2013; Rubia et al., 2001). Further still, evidence from Littman and Takács, (2017) distinguishes the SST from the GNG task by demonstrating that exposure to negative stimuli impaired performance on Go trials and improved inhibitory performance on Stop trials of the SST, while inhibitory performance on the GNG task was unaffected. Few other studies have examined ERPs and alcohol use using the SST, and comparisons drawn between current results and previous findings must be considered tentatively. Although out-of-sample

methods helped to substantiate the generalisability of the findings, replication studies examining the SST would be beneficial.

Unexpectedly, a novel finding emerged from Chapter 3, with the best prediction of alcohol use in the ERP model indicated by early activity (before the N2) across the scalp. Some studies have examined earlier components in alcohol-dependent samples, with deficits found in the P50, an early predominantly preattentional component (Freedman et al., 1987; Marco et al., 2005) and in the P1, a visuo-perceptual processing component (Maurage et al., 2007). It is possible the P50 observed here is linked to an inhibitory filter mechanism that could protect the integrity of higher-order functions (Lijffijt et al., 2009), suggesting that impaired P50 associated with increased alcohol use could relate to diminished inhibition. Furthermore, the significant finding for the P1 'attention effect' may reflect a top-down inhibitory process, whereby P1 enhancement indicates inhibitory processes that blocks competing information of task-irrelevant stimuli (Slagter et al., 2016). The finding supports a dual-process theory of alcohol misuse, whereby a lack of a cognitive control mechanism to inhibit drinking (i.e., deficits in later ERP components) is exacerbated by early attentional biases (i.e., deficits in early ERP components; see Campanella et al., 2018). It has also previously been suggested, that the ability to sustain attention could be considered as part of the first phase of response inhibition, given that important components of an individual's capacity to inhibit a response is related to their capacity to attend to stimuli (Aragues, Jurado, Quinto & Rubio, 2011). Indeed, the SST requires sustained attention to monitor for the Stop signal in order to initiate response inhibition, as well as engagement of attention for both correct go and stop responses (Li & Sinha, 2008). Thus, neural deficits seen with alcohol

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misuse may not be exclusive to inhibitory control impairments *per se* – early processing impairments could underlie failures of later higher-level processing. Indeed, sustained attention appears to be an important aspect of alcohol misuse in this study.

5.2.4   Cognitive impulsivity

An interesting finding emerged from Chapters 2 and 3: cognitive impulsivity via sustained attention, was an important predictor of some of the alcohol-related outcomes. In both Chapters 2 and 3, IRV significantly predicted individual differences in alcohol intoxication frequency for the impulsivity-only model and for impulsivity combined with other risk factors, but it was not significant for models predicting alcohol consumption frequency. However, the IRV using the SST has received little attention in relation to alcohol use and its neural components had yet to be clearly mapped.

In the final study, Chapter 4, task-based fMRI was used to tackle the interesting and timely question of how average brain activation and functional connectivity patterns are related to individual differences in sustained attention (i.e., IRV on the Go trials of the SST) in a large sample of healthy 14-year-old adolescents, which were subsequently validated in a separate sample of adolescents with ADHD symptoms and a matched asymptomatic control sample. Functional connectivity patterns underlying individual differences in alcohol use (AUDIT scores) were also explored for the large normative sample, however the findings were not significant. Furthermore, despite the IRV-alcohol relationships observed in Chapters 2 and 3 for student samples, IRV was not associated with AUDIT for any of the adolescent samples in Chapter 4. However, these adolescents were relatively substance naïve, and

Whelan and colleagues (2014) also found behavioural difference for motor impulsivity (SSRT) in the IMAGEN cohort. Nevertheless, sustained attentional processes were facilitated by an array of neural networks, and provide an empirical account of how the functional role of specific cerebellar subregions Crus I/II extends to cognition in adolescents. This work also highlights the involvement of motor cortex in the integrity of sustained attention, and suggests that atypically strong connectivity within motor networks characterises poor attentional capacity in both typically developing and ADHD symptomatic adolescents. Moreover, a previous task-based fMRI study identified similar disrupted attention-relevant functional networks in healthy adults, and these networks predicted ADHD symptoms in childhood (Rosenberg et al., 2016). At the time of writing this thesis, this was the largest population-based functional imaging study to examine both average fMRI activity and functional connectivity as it related to sustained attention in adolescents. Given that top-down, goal-driven attentional biases for alcohol have been observed in social drinkers (Brown, Duka, & Forster, 2018), it would be useful to further examine how goal-directed and involuntary aspects of attention are related to alcohol-outcomes.

5.3   The role of other risk factors

An accumulation of different risk factors is linked to higher binge-drinking rates (Gowin et al., 2017). Risk factors that were associated with adolescent alcohol-use-initiation, including gender, cannabis and nicotine (Squeglia et al., 2016; Whelan et al., 2014) and executive functioning (Peeters et al., 2015), also held for heavier college-age drinkers in Chapter 2. Furthermore, gender and lifetime cannabis use were significant for both

intoxication and consumption frequency. Gender has been shown to predict various aspects of alcohol consumption. For example, Henges and Marczinski (2012) found that gender was related to total number of drinks consumed, highest number of drinks consumed, number of heavy drinking days and number of drunk days in past 30 days (assessed using a Timeline Follow-back Interview) in 109 18–21-year-old student drinkers. In Chapter 2, being male was associated with higher consumption frequency scores. A previous study also found that being male was a contributing factor for heavier alcohol-use by age 18 (Squeglia et al., 2016). Indeed, numerous studies indicate that males consume more alcohol than females (WHO, 2014) and are at a higher risk of BD (Gmel, Rehm, & Kuntsche, 2003), and perhaps this result is unsurprising, and embedded in sociocultural norms. Interestingly however, Chapter 2 showed that females were more likely to become intoxicated. There is indication that the gender gap between male and female university students is narrowing with regard to excessive alcohol consumption (Davoren et al., 2016), and establishing which impulsivity predictors diverge or overlap according to gender will be an important future consideration for prevention and treatment.

Alcohol use and cigarette smoking commonly co-occur (Dawson, 2000). Among 217 university students, smokers reported higher expectation for increased nicotine use while under the influence of alcohol, and for increased alcohol effects as a result of concurrent alcohol and nicotine use (McKee et al., 2004). The combination of smoking and drinking may also be associated with higher levels of impulsivity. For example, a study (Moallem & Ray, 2012) examining heavy drinkers only (N =107), smokers only (N=67), and heavy drinking smokers (N=213) found that heavy drinking smokers displayed steeper delay

discounting (DDT) than smokers only and heavy drinkers only, indicating that those who both drink heavily and smoke cigarettes daily had increased choice impulsivity. Cannabis use predicted both intoxication frequency and consumption frequency, while smoking predicted intoxication frequency only in Chapter 2, which supports previous findings that early adolescent drunkenness is associated with cannabis and nicotine use (Kuntsche et al., 2013). However, debate is ongoing as to whether individuals use alcohol and cannabis as either complements or substitutes for one another. There is some indication that alcohol use positively predicts the likelihood of cannabis use among university students, indicating complementary use (O'Hara, Armeli & Tennen, 2016), with evidence that students primarily drink and use cannabis for social reasons (Beck et al., 2009; Christiansen et al., 2002; Lee et al., 2007). However, students were also more likely to use one substance (i.e., the more they drank on a given evening, the less likely they were to use cannabis) in order to cope with stress (O'Hara, Armeli & Tennen, 2016). Variables related to stress were not included in Chapter 2, and this was remedied in Chapter 3.

In Chapter 3, the some of the most important predictors of alcohol use included anxiety on the DASS, while stress and depression were weakly linked to alcohol use. Alcohol misuse is often associated with increased symptoms of depression, anxiety and stress in both the general population (Wiener et al., 2018) and among university students (Walters, Bulmer, Troiana, Obiaka & Bonhomme, 2018). Although general psychological distress has consistently been associated with alcohol use among college students (Obasi et al., 2016), differential effects of anxiety and depression on alcohol use have been observed among college students. For example, although depression (Linden & Lau-Barraco, 2013) and

anxiety (Magrys & Olmstead, 2015) independently predict increased alcohol use among college students, only anxiety is associated with more alcohol use when looking at both anxiety and depression simultaneously (Armeli et al., 2014). Some other studies have also indicated that there is a differential association of anxiety and depression with alcohol use that needs to be considered when studying affect-drinking relationships. For example, differentiating between drinking to cope with anxiety versus depression improves fit for models examining mood-drinking relationships (e.g., Grant, Stewart, & Mohr, 2009) and motivation to cope with depression versus anxiety is related to different patterns of alcohol use and problems (Grant, Stewart, O'Connor, Blackwell, & Conrod, 2007). Furthermore, college students reporting higher motivation to use alcohol to cope had reduced alcohol use on days they reported symptoms more closely related to depression (i.e., sadness) and increased alcohol use on days they reported symptoms more closely related to anxiety (i.e., fear; Hussong, Galloway, & Feagans, 2005). Neurobiological studies show that alcohol use appears to selectively reduce anxiety but not fear (Moberg & Curtin, 2009). Collectively, these findings indicate that affective states more closely related to anxiety may increase likelihood of more problematic alcohol use, yet few studies make the distinction between symptoms of depression and anxiety when examining such affect-drinking relationships. Depression and anxiety are typically overlapping two constructs that may have resulted in multicollinearity even after accounting for shared variance in the model. Therefore, examining depression and anxiety as distinct constructs in separate models (or using machine learning techniques) may yield distinct results. However, issues relating to causation are important to acknowledge, and it is not clear whether people with mental health issues seek

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out alcohol as a coping mechanism, or whether alcohol abuse contributes to the aetiology of mental health issues. This relationship is likely to be quite nuanced, dynamic and interactive, with individuals who experience mental health issues and substance abuse problems possessing common underlying traits that make them vulnerable to experiencing such difficulties (Hawkins, 2009). On the other hand, Prince et al. (2007), argue that factors that adversely impact physical health, such as alcohol abuse, will ultimately lead to an increased risk of mental illness, and in fact the relationship is likely to be bi-directional. Previous studies show that affect underlying trait impulsivity is strongly related to heavy student drinking (Carlson et al., 2010), and a growing body of literature indicates emotional and physiological states, such as anxiety and stress, may play an important role in exerting a significant influence on behavioural impulsivity (Herman, Critchley & Duka, 2018). Yet, it is not clear whether symptoms of psychological distress or impulsivity have better predictive utility when accounting for alcohol use/misuse.

Relationship status was the strongest predictor of alcohol use in Chapter 3; being in a relationship was associated with lower levels of alcohol use. This is important when considering adolescent and young adult developmental trajectories, as previous research has shown that early dating in adolescence is associated with early onset of alcohol-use (Squeglia et al., 2016) and binge drinking (Whelan et al., 2014). On the other hand, in young adults being in healthy romantic relationship is associated with lower levels of alcohol consumption (Fleming et al., 2018). Although research has shown that the presence of an intimate relationship is associated with less problematic alcohol use among university students (Braithwaite, Delevi, & Fincham, 2010; Simon & Barrett, 2010; Whitton, Weitbrecht,

Kuryluk, & Bruner, 2013), few studies have examined the effects of relationship quality on alcohol use among young adults. One study examined the associations between relationship satisfaction and hazardous drinking in 219 college students (aged 18–25) in current dating relationship (Khaddouma et al., 2016). The authors found that high relationship satisfaction was related to lower alcohol consumption and a greater willingness to decrease alcohol consumption among hazardous drinkers (Khaddoumaet al., 2016). However, lower relationship satisfaction among hazardous drinkers was not associated with a desire to decrease consumption. The findings support previous research demonstrating the beneficial impact of supportive, healthy romantic relationships on unhealthy behavior patterns (Lewis et al., 2006). However, the links between heavy alcohol consumption and marital quality are mixed. Increased binge-drinking among older adults bi-directionally linked to poorer marital quality for women, but, for men, only poor marital quality was unidirectionally linked to increased binge-drinking (Roberson et al., 2018). Although it is clear that there is a relationship between relationship quality and drinking, the direction of this association and the type of relational influences (emotional vs functional) is still unclear. It is possible that the same behaviours that influence risk-taking behaviour in early adolescence influence the behaviours that lead to the initiation of early romantic relationships and early alcohol-use onset and binge-drinking. Studies like the My World Survey in Ireland have shown that having one stable adult relationship can be an important protective factor and reduce the use of maladaptive coping mechanisms like alcohol use (Dooley & Fitzgerald, 2012).

At the time of composing this thesis, no known study had examined the PST in non-dependent drinkers. Intoxication frequency was associated with a decrease in learning from

punishment (negative feedback) on the PST, and this finding suggests that alcohol users may be less sensitive to negative outcomes. This lends support to addiction models that suggest that outcome desensitisation (to punishment, in this case) occurs following repeated substance use (Baker et al., 2013; Volkow et al., 2016). Recently, the PST also demonstrated the ability to predict smoking status in students (Rai et al., 2018). Given that impulsivity is characterised by a disregard for future consequences, this finding certainly warrants further exploration.

5.4   Implications for alcohol use among adolescents and young adults and emergence of alcohol-use disorders

In Chapter 2, patterns of alcohol use were found to be directly related to negative consequences, with students who experienced injury, negative sexual experiences, as well as problems with friends and academic performance, reporting significantly higher intoxication frequency, compared to groups without these experiences. Conversely, groups who had positive expectations of alcohol-use had lower intoxication frequency scores. In other words, increased alcohol intoxication frequency rather than increased consumption frequency was associated with individuals reporting adverse consequences of alcohol use (and less likely to attribute positive consequence of alcohol use). The finding underscores drunkenness as a crucial risk factor for adverse consequences of alcohol use (Kuntsche et al., 2013; Prince et al., 2018). This has important clinical implications, and future research and prevention/treatment programmes may benefit from incorporating cut-offs that reflect the number or severity of alcohol-related consequences, in conjunction with self-reported

intoxication frequency or consumption frequency. Such an approach may help to improve the clinical effectiveness of treatments as well as identifying findings that are clinically significant and have strong clinical utility. In terms of public health, policies which aim to reduce harmful patterns of alcohol consumption such as intoxication frequency, should be introduced rather than focusing exclusively on the quantity of consumption. For instance, in Ireland, where there are strict laws relating to times where alcohol can be sold, levels of pre-drinking are still the highest (based on a comparison of 25 international countries; Labhart, Ferris, Winstock, & Kuntsche, 2017), which also coincides with the 2nd highest level of binge-drinking globally (WHO, 2014). It is possible that these factors are interrelated and altering laws relating to the time at which alcohol can be sold may help to ameliorate pre-drinking and this harmful pattern of alcohol consumption.

A focus on endophenotypes may help to inform prevention strategies. Understanding the aetiology of addiction may involve demarcating people according to impulsivity endophenotypes, rather than using symptom clustering consistent with DSM/ICD-based diagnostic criteria or methods of differentiation (e.g., heavy versus light alcohol use). This is in keeping with newly proposed classifications for research on mental disorders, put forward by the National Institute of Mental Health (Insel et al., 2010).

5.4.1 Limitations

Despite the well-established links between impulsivity and alcohol misuse, neuroimaging predictors of alcohol use have only shown modest utility to date. The advantages of a machine learning approach, like the Elastic Net used here, is that key features can be

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identified from a large search space, and correlated variables can be accommodated. The sample size in Chapter 2 was relatively large (N=79) compared to other EEG studies. ERPs across the whole-scalp could not be examined because of the ratio of variables (over 20,000 in the case of 64-channel) to cases, detecting important variables would not have been possible, given low-moderate effect sizes, as has been previously shown (Jollans et al., 2015). However, several regions believed to be important for indexing ERPs that are typically of interest (e.g., N2-P3) were defined, based on prior work in this area (Wessel & Aron, 2015), although future studies with large sample sizes could replicate these methods and incorporate electrophysiological activity recorded across the entire scalp.

There are other impulsivity endophenotypes, as well as other measures, that were not investigated in this research but are worth outlining for future integration. For example, "reflection impulsivity" (i.e., a tendency to make decisions in situations of uncertainty; Kagan, 1965) can be measured on the Information Sampling Task and Matching Familiar Figures Task (Clark et al., 2006) and "waiting impulsivity" (i.e., anticipatory premature responding before the onset of a target stimulus; Robinson et al., 2009) can be measured on the Continuous Performance Task (CPT; Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956) and is associated with higher BD levels (Sanchez-Roige et al., 2014). The 5-Choice Serial Reaction Time Task (5-CSRTT, Carli, Robbins, Evenden, & Everitt, 1983) developed to study waiting impulsivity in rodents, was also recently adapted to be used in humans (Sanchez-Roige et al., 2014; Voon et al., 2014) and successfully distinguished drinking groups. Future studies should strive to expand the impulsivity battery. Moreover, Sharma et al. (2014) proposed the term "cognitive impulsivity" as the inability to sustain attention

assessed using impulsivity-specific measures, which was subsequently used in this thesis. However, cognitive impulsivity by definition also implicates aspects of decision-making that are associated with impulsive behaviors (i.e., choice impulsivity). Perhaps 'Impulsive Inattention' may be a more appropriate term to denote this dimension of impulsivity

. Furthermore, there are other constructs that were not included in this thesis. Compulsivity, which refers to maladaptive perseveration of behaviour, partially overlaps with aspects of impulsivity (response disinhibition, e.g., SSRT). Both constructs are implicated in addiction, in the devolution of voluntary impulsive substance use to compulsive repeated abuse (Robbins, Gillan, Smith, de Wit & Ersche, 2012). However, studies have yet to integrate these dimensions to inform alcohol-related research, as well as how their relative neural underpinnings inform different patterns of alcohol use (Chamberlain, Stochl, Redden, & Grant, 2018). A putative reward processing endophenotype is also considered to play a critical role in youth alcohol use and misuse (Luijten, Schellekens, Kühn, Machielse & Sescousse, 2017; Lyvers et al., 2012; Nees et al., 2012; van Hemel-Ruiter, de Jong, Ostafin & Wiers, 2015). Future studies could attempt to include these constructs in a model to investigate whether compulsivity/reward endophenotypes observed in SUD patients also exist on continuum, with similar traits observed in healthy populations.

Executive functioning is a broad term that includes working memory, attention, and decision-making, and often invokes activity in the dorsolateral PFC and anterior cingulate cortex (Bechara et al., 2001; Koob & Volkow, 2016; Volkow, Wang, Fowler, Tomasi & Telang 2011; Whelan, 2012). Several studies have indicated that poorer performance on executive functioning tasks (Squeglia et al., 2016), as well as reduced brain activation during

tasks measuring response inhibition, reward processing, and working memory are predictors of early adolescent alcohol-use (Norman et al., 2011; Wetherill et al., 2013a; Whelan et al., 2014) and influence alcohol-use initiation (Whelan et al., 2014). Future studies of impulsivity endophenotypes and how the relate to alcohol use, may benefit from examining the potential moderating role of executive functioning.

Although standardised alcohol measures were used (e.g., AUDIT), and memory biases were alleviated by using similar questions at multiple timepoints (e.g., ESPAD), all alcohol measures in these studies were questionnaire-based and self-reported. Chapter 2 used self-report measures of drunkenness, which can only account for an individual's perceptions of their level of intoxication, and may have indirectly acted as a proxy for measuring individual differences in absorption and metabolism rates. Some studies have directly accounted for this. For example, Gowin and colleagues (2017) designed a carefully controlled experimental paradigm, in which 159 young social drinkers self-administered alcohol intravenously. Their findings showed that drinkers at risk for AUD had higher rates of binging throughout the session and greater overall exposure to alcohol than low-risk drinkers, despite similar AUDIT scores between the both groups. Future studies should look to include variables which may help to indirectly account for and approximate alcohol absorption rates and metabolic rate, such as BMI, and sex.

Adopting a prospective, longitudinal approach will better characterise the relative contribution of risk factors in the transition from alcohol use onset, to misuse, dependence, and finally to individual differences in vulnerability to relapse (Thompson et al., 2014). Alcohol-use typically begins in adolescence, with early use predictive of dependence in

adulthood (Behrendt et al., 2009; Hawkins, Catalano & Miller, 1992; Hingson, Heeren & Winter, 2006). Despite broad exposure to early substance use, many individuals remain resilient to addiction or problematic use in later life (Ostaszewski & Zimmerman, 2006). In the adult literature, the progression form substance use to disordered use is interpreted as the shift from goal-directed, voluntary use to compulsive, uncontrolled use, despite the adverse consequences. However, once initiated early substance use can have a wide-ranging detrimental impact on cognition, brain structure and function, as well as psychological well-being. Abnormal brain function in areas underpinning impulse control, reward processing and executive function, have been implicated in problematic adolescent drinking behaviours (Verdejo-García et al. 2008; Galavan et al., 2006; Squeglia et al., 2016). The challenge has been to separate predisposing neurobiological risk factors out from alterations that occur as a result of early alcohol-consumption.

In order to better understand root causes leading to addiction, individuals need to be examined in early adolescence *before* alcohol misuse, and to then track any changes that occur across later development. Uncovering risk factors early will help understand the aetiology of early alcohol initiation, which is important as the odds of alcohol dependence decrease by 14% with each increasing year of age at onset of alcohol-use in adolescents (Grant & Dawson, 1997). However, the identification of neural predictors for alcohol initiation is under-represented in the addiction literature. Although beyond the scope of this research, a collaborative effort and a large amount of research is currently being conducted, tracking the neurobiological and behavioural changes that occurs across adolescent development.

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5.5 Future directions

5.5.1 The role of neuroimaging for identifying predictors of alcohol use

Neuroimaging studies have the potential to answer important clinical questions about the risk factors underpinning adolescent alcohol misuse, however, predictive models emerging from neuroimaging research are not routinely incorporated in clinical practice (Pencina & Peterson, 2016). The use of large data sets (Volkow et al., 2011) provides a partial solution to this problem. Comprehensive and rich datasets, such as IMAGEN, and ABCD (https://abcdstudy.org/) will help to advance the understanding of alcohol use initiation and the neurobiological pathways that lead to alcohol abuse.

The IMAGEN project is a European multi-centre study with a baseline cohort of 2,000 14-year-olds, with neuroimaging follow-up assessments at 19 and 23 years-old. As well as gathering demographic, genetic and neuroimaging data, the test battery also includes several self-report measures of substance misuse, including any harmful prenatal exposures to tobacco or alcohol. Behavioural and cognitive assessments include broad personality measures, such as the NEO-FFI (Costa & McCrea, 1992), and those specific to addiction such as the SURPS (Woicik, Stewart, Pihl & Conrod, 2009). This database has facilitated studies which focus on neuroimaging measures assaying impulsivity via the SST (Whelan et al., 2012) reward processing via the Monetary Incentive Delay task (MID; Peters et al., 2011), and emotional reactivity via the Faces Task (Tahmasebi et al., 2012). In Chapter 4, a data-driven analysis was used to identify the functional connections underlying sustained attention from an IMAGEN sample, however, data-driven methods are particularly useful

when combined within a statistical testing framework or for tasks such as prediction or classification (Calhoun & Adali, 2012; Rosenberg et al., 2016). Therefore, using the networks identified in Chapter 4, a follow-up study with same cohort at aged 18 would be beneficial.

The ABCD study is an American multisite longitudinal study, with the goal of following 10,000 individuals, including twin cohorts, for 10 years, beginning from the age of 9 years-old. ABCD is examining risk and resilience factors influencing substance use trajectories, as well as the impact of substance use on neurocognitive, health and psychosocial development and outcomes (Morris, Squeglia, Jacobus, & Silk, 2018; Lisdahl et al., 2018). The baseline ABCD sample is largely substance-naïve, however measures sensitive to low-level exposures are included (e.g., iSay Sip Inventory; Jackson, Barnett, Colby & Rogers, 2015) because children as young as 9 may initiate or try substances (e.g., sipping alcohol, first puffs of cannabis and nicotine; Lisdahl et al., 2018). The ABCD imaging protocol measures brain structure and function, including resting state and task-based fMRI. Neuroimaging assays six behavioural domains – reward processing, motivation, impulsivity, impulse control, working memory and emotion regulation. (SST, MID and an emotional version of the n-back task; see Casey et al., 2018). An important aspect of the ABCD study is the intentional recruitment of an American community sample that accounts for sociodemographic variation (Garavan et al., 2018). Large longitudinal databases like IMAGEN and ABCD will offer researchers a chance to further current knowledge, and answer questions that have been methodologically challenging to date.

Given the open-access nature of some datasets and increased availability of machine learning tools, addiction researchers have greater opportunity to engage in Big Data research.

Big Data can help set the foundation for developing alcohol risk indices or risk scores. As such developing a neuroimaging risk score which combines a multitude of data including structural information (volumetric and cortical thickness), and white matter tractography, as well as mapping pertinent neurocognitive systems may be used to generate neuroimaging risk scores which may contribute greater predictive utility of neuroimaging data.

Larger sample sizes also facilitate the examination of important moderators and mediators of risk. For example, the role of puberty (with males typically developing two years later than females) is relatively underexamined. For example, some research has examined interactions between genetic, neurobiological, and environmental factors in predicting resilience in children (Cicchetti & Rogosch, 2007), as well as identifying specific neurobiological correlates of resilience (e.g., stress hormone changes; Curtis & Cicchetti, 2007; Heitzeg et al., 2010). A recent MRI study of 1,870 adolescents (Burt et al., 2016) examining the structural brain correlates of adolescent resilience found that within the group of more resilient adolescents, grey matter volume in the middle frontal gyrus correlated with risk of problems with alcohol-use. Identifying why some individuals, despite clearly disadvantageous environmental circumstances, do *not* misuse alcohol is important, yet little is known about the neurobiological and brain correlates of resilient functioning and how that ties into adolescent alcohol initiation.

Increasing the utility of neuroimaging for prediction of future alcohol-use will also require a broader array of imaging sequences and analysis methods than have been employed to date. For example, the vast majority of studies have focused on gray matter, either structural or functional; however, it is well known that white matter changes substantially

during adolescence. Advances have been made with respect to *in vivo* estimations of neuronal morphology, including advanced diffusion MRI techniques that measure tissue microstructure features directly (e.g., NODDI; Zhang, Schneider, Wheeler-Kingshott & Alexander, 2012). Augmenting better metrics of white matter, in future functional activity will likely be described in terms of the *connectivity* among brain regions, rather than average activity per condition. Connectivity metrics have the potential to provide a more nuanced picture of vulnerability to alcohol misuse, perhaps by examining changing patterns of connectivity or by changing network strengths (Ernst, Torrisi, Balderston, Grillon & Hale, 2015). In sum, more sophisticated methods with better resolution will help researchers identify better predictors of substance misuse. The next step is to integrate this innovative technology with genetics, epigenetics, neuroimaging, and developmental and environmental factors in order to provide a picture of the layered interactions associated with adolescent substance use trajectories and alcohol misuse.

5.5.2   Online datasets

Chapter 4 utilised a large population-based sample, based on multiple European locations, which helps ensures sociodemographic variation (Garavan et al., 2018). Two out of three of the Chapters examined student samples, which was motivated by the large body of work indicating particularly high levels of alcohol misuse in this cohort (Balodis et al., 2009; Davoren et al., 2017; Lyvers et al., 2012; Moure-Rodriguez, et al., 2018). However, the need to acquire data in a laboratory setting, has led to psychology and cognitive neuroscience to over-rely on student samples (Henrich et al., 2010), reducing generalisability. Broad claims

about human psychology are often based on samples drawn from Western, Educated, Industrialised, Rich, and Democratic (WEIRD) societies (Henrich et al., 2010), whereas individuals with addiction are predominately from lower socioeconomic backgrounds and have lower education (Henkel & Zemlin, 2016).

Online recruitment methods can successfully target participants with addiction (Nosek, Banaji, & Greenwald, 2002), whereas in-laboratory participant recruitment can be both costly and difficult (Ramo & Prochaska, 2012; Thornton et al., 2016), Furthermore, online research provides a level of anonymity for people hindered by embarrassment and stigma (Chebli, Blaszczynski, & Gainsbury, 2016; Gainsbury, Hing, & Suhonen, 2014), physical disability and geographical remoteness (Proudfoot et al., 2011). Strickland and Stoops (2018) demonstrated the feasibility, acceptability and validity of collecting longitudinal alcohol use data using Mechanical Turk, finding expected associations between heavier drinking and higher AUDIT scores. Given the robustness of trait and behavioural impulsivity endophenotypes for predicting alcohol use in this thesis, availing of platforms, such as public social networking sites (e.g., Twitter, Facebook), and general crowdsourcing (e.g., Amazon's Mechanical Turk) will significantly change this field of research, although there are significant ethical ramifications that need to be considered first.

5.5.3 Intervention

Early adolescent alcohol use including binge drinking remains a critical public health issue (see Jang et al., 2017), despite public health initiatives to curtail adolescent alcohol misuse (Kieling et al., 2011). Moving away from generic prevention approaches and towards

the targeting of particular endophenotypes (e.g., specific impulsive personality traits) may be more effective. Personality-targeted approaches have been shown to have a moderate effect size in reducing various substance use outcomes (Conrod, 2016). The application of Big Data methods may further aid implementation of tailored treatment interventions (Gillan & Whelan, 2017). Mindfulness may play a positive role in reducing youth alcohol use, with trait mindfulness linked to lower levels of alcohol consumption (Brett, Leffingwell, & Leavens, 2017) and lower levels of self-reported trait impulsivity (Peters et al., 2011). A recent randomised controlled trial found that mindfulness training implemented in schools lead to decreased levels of self-reported impulsivity (BIS-11) and aggressive behaviours (Franco, Amutio, López-González, Oriol & Martínez-Taboada 2016), other research has shown that school-based yoga (which incorporates mindfulness) lead to decreased reports of substance use (Butzer, LoRusso, Shin & Khalsa, 2017). Future research should look to examine the role of mindfulness on alcohol use in school/college-based populations.

5.6   Concluding remarks

This thesis illuminates some of the nuances underpinning the relationship between impulsivity endophenotypes and alcohol use patterns. A multi-domain approach, combining EEG with trait and task-based behavioural data predicted alcohol use. This approach therefore adds to a comprehensive, and more holistic profile of alcohol users and misusers. Impulsive personality traits of disinhibition and poorer planning skills, and behavioural indicators of difficulties sustaining attention, appear to be the most important markers across different alcohol use patterns in young adults. In particular, compelling results were found for

predicting alcohol use from inhibitory control ERPs – a finding that may lead to the improvement of objective screening and assessment of alcohol misuse. In this thesis, a range of measures – behaviour, EEG and fMRI – were used to investigate impulsivity and alcohol use. Furthermore, analytic methods such as machine learning, factor analysis and data-driving neuroimaging approaches were employed. By combining these measures and methods, this thesis has shed new light on the complex relationship between impulsivity and addiction. These findings will ultimately pave the way for refining future methodologies and have important clinical utility and implications for health policy.

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7 Appendices

7.1 Supplemental 2.1

Methods

Task-based Measures

All computerized tasks were presented, and responses recorded by the Presentation® software package (Neurobehavioral Systems). Each task began with on-screen instructions that were also read out to participants by the experimenter. The experimenter checked that the participant understood the instructions and participants were given time to read over the instructions again themselves before commencing the task in their own time by pressing the '1' key on the keyboard. Task responses were made via an *Xbox 360* game controller.

 The adapting delay discounting task (DDT). Participants were presented with a series of dichotomous choices between immediate versus relatively larger but delayed hypothetical monetary rewards. The adapting DDT was designed to estimate an individual's rate of delay discounting progressively more accurately from trial to trial by adapting the hypothetical magnitude and timing of the delayed rewards it offered participants on each trial based upon their preceding responses (Ortiz *et al*., 2015). The rate at which the DDT modified the value of the delayed reward it offered participants was governed by an adaptive algorithm using a double-limit procedure that modified the model parameter k based on two sets of boundaries designed to adjust to the point at which the participant would choose the immediate and delayed outcome with equal probability. The model parameter k characterises an individual's rate of delay discounting such that higher values of k indicate a higher rate of delay

discounting. The delayed reward was presented at a randomly chosen delay of between 1 and 180 days (phrased in days, weeks or months as appropriate), and a randomly chosen immediate reward of between $10-50 (see *Figure S2.1*). When participants chose the immediate reward on a given DDT trial the obtained estimate of k was decreased and then used to calculate the value of the delayed choice being offered on the next DDT trial, and vice-versa if the delayed reward was chosen. The DDT's adaptive algorithm is designed to converge upon a participant's individual k value. Following 10 initial practice trials, a single block of 74 DDT test trials commenced with initial $k = 0.018$. Each trial began with a fixation cross positioned centre screen for 700ms. If participants did not respond within five seconds of the choice they were prompted with the message "Please respond" directly underneath. Failure to respond within two further seconds resulted in the trial completing without recording any response or thus updating the value of k.
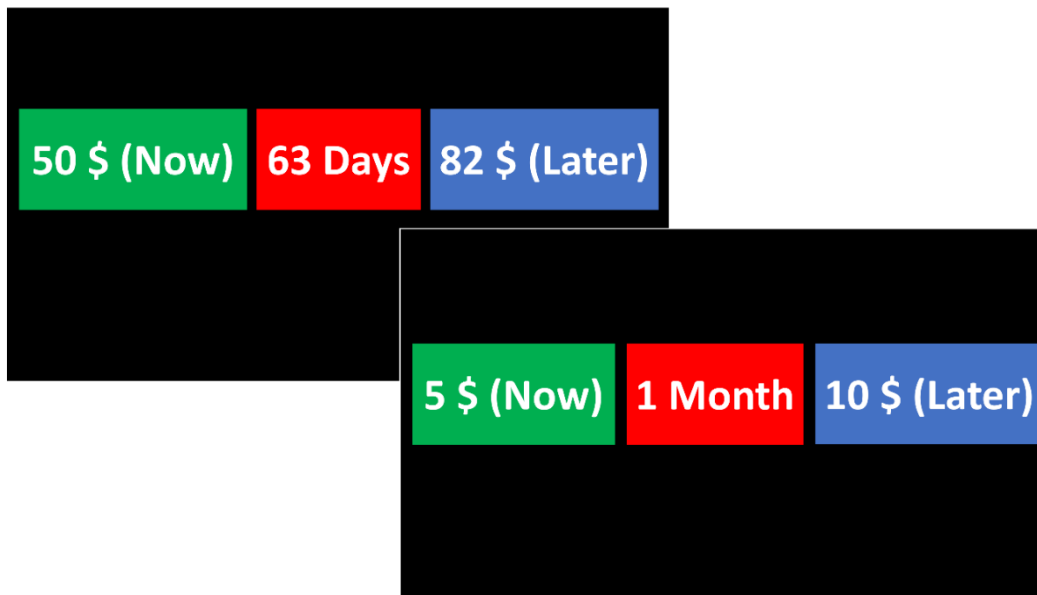
Figure S2.1. Visual representation of DDT

The Stop Signal Task (SST): consisted of two phases, a practice phase followed by the test phase of 119 trials in a 12-minute run. Each trial of the task began with the fixation sign (a "+" sign) which remained on screen for 750ms before being replaced by the primary stimulus, which remained on the screen for 1000ms (see *Figure S2.2*). Participants were instructed to distinguish between left and right pointing arrows ('Go' stimulus), and respond as quickly as possible to the orientation of the stimulus with a left or right- button press. There duration of trials was fixed and independent of reaction time (RT). On 25% of the trials, after the 'go' stimulus, an upward pointing arrow ('Stop Signal' stimulus) was presented at variable delays (Stop Signal Delay), during which participants were instructed to withhold responding. The initial SSD was presented at 250ms, but was adjusted according to a participant's performance, according to an adaptive algorithm using a double-limit procedure. The first set of limits ensures that the SSD is never shorter than 50ms and never longer than 450ms. These limits remain constant and act as a buffer within which the second set of limits is adapted. The second set of limits is used to define the length of the SSD. These limits are adjusted depending on task performance, making the average SSD shorter (i.e. the task easier) after an unsuccessful stop trial, and the average SSD longer (i.e. the task more difficult) after a successful stop trial. Participants were presented with a "Speed up!" prompt for 2s if they failed to respond to 2 out of 5 Go trials, or response to the last trial was too slow (i.e. if their last RT was longer than 1.5 times their average RT while the proportion of successful stops remained within 40-60%, or if their last RT exceeded their average RT and the proportion of successful stops was >60%). The rolling average RT monitoring began on

the 10th trial. The algorithm aimed to find the point at which participants had 50% successful inhibition responses and 50% unsuccessful inhibition responses.

The Stop Signal Reaction Time (SSRT), an index of inhibitory function, was calculated for each participant by subtracting the mean SSD from the Go RT at the percentile corresponding to the proportion of unsuccessful stop trials. The SSRT refers to the time taken to cancel a prepotent motor response after Stop stimulus presentation.
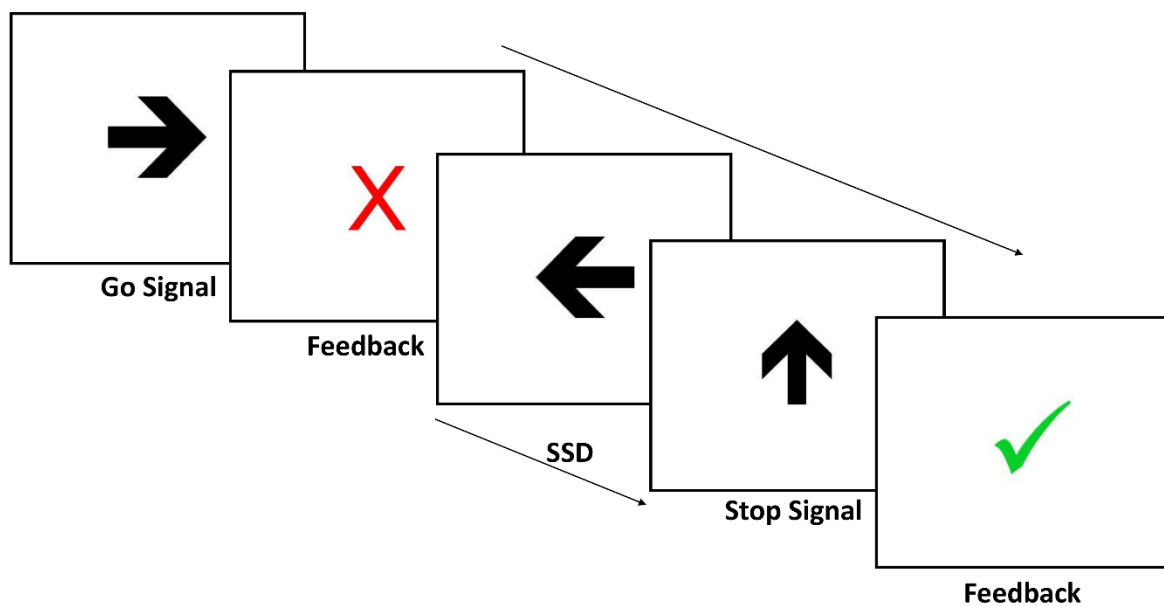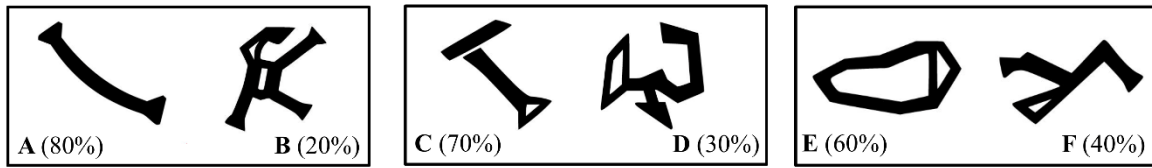

Figure S2.2. Visual representation of the SST

Probabilistic Selection Task (PST): Participants completed a version of the Probabilistic Selection Task (Frank, Seeberger & O'Reilly, 2004) to assess reward and punishment learning. The PST comprised of a training and test phase, each 120 trials in length. During the training phase, participants were randomly presented with three stimulus

pairs (AB, CD, EF), and required to select the 'correct' stimulus in each pair based on probabilistic feedback. The stimulus reward probabilities were predetermined (A: 80%; B: 20%; C: 70%; D: 30%; E: 60%; F: 40%). The position of each stimulus on screen was randomly varied across trials (e.g. AB, or BA). Stimulus pairs were presented on screen until a response was made. Feedback was presented for 750ms in the form of a green tick "✓" signalling correct responses or red 'X' for incorrect responses respectively (see *Figure S2.3*). There was no criterion to reach in the training phase.

In the Test phase, novel combinations of the six stimuli were presented, and participants were again required to select the correct stimulus in each pair. No feedback was provided in the Test phase of the PST. As in previous research, performance in the Test phase was measured by comparing how often participants selected the A stimulus versus how often they avoided the B stimulus in novel pairs. If participants have correctly learned the relative values of symbols during the learning phase, positive stimulus (A) choices over all other symbols indicated that the participant learned from positive feedback (reward sensitivity), while avoidance of the negative stimulus (B) over other symbols indicated negative feedback learning (punishment sensitivity). Stimuli were presented on screen until a response was made, and a fixation cross was presented for 500ms between trials.

Testing

A (80%)   B (20%)   C (70%)   D (30%)   E (60%)   F (40%)

Training

A (80%)   C (70%)   B (20%)   E (60%)   D (30%)   F (40%)
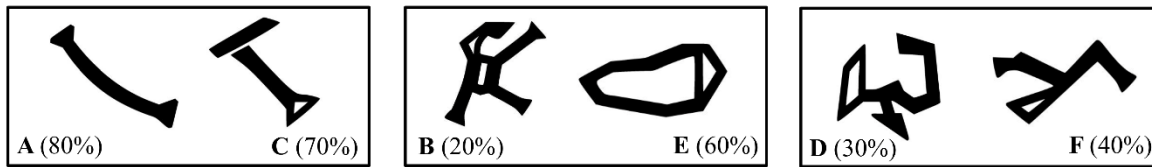
Seek Reward   **Avoid Punishment**

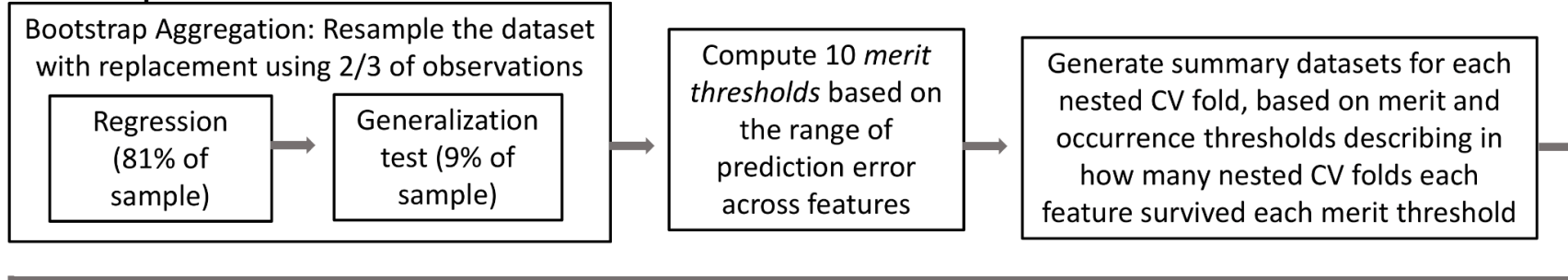*Figure S2.3.* Visual representation of the PST

Machine Learning

We conducted a logistic regression with elastic net regularization for feature selection (Zou & Hastie, 2005). All predictor variables were first feature scaled (z-score transformed). I then implemented ten-fold cross-validation with nested cross-validation for tuning and validating the model. A detailed description of the machine learning is contained in Kiiski et al. (2018; Appendix 1). Here I provide a short description.

The dataset was initially divided into 10 cross-validation (CV) folds. The entire analysis was performed 10 times, using 90% of the dataset (the training set) to create a regression model which was then tested on the remaining 10% of the data (the out-of-sample test, or holdout, set). Within each CV fold I used nested cross-validation to set the Elastic Net parameters. All analysis steps up to this point were conducted using 25-fold bootstrap aggregation (i.e., bagging). The combination of model parameters that resulted in the model with the lowest prediction error was identified for each nested CV partition. The optimal model parameters from each nested CV partition were used to identify the parameters to create the final prediction model in each main CV fold. This analysis was carried out 10 times, using different CV fold allocations each time (i.e., a different out-of-sample test set). The entire analysis was repeated 10 times in order to attenuate idiosyncrasies of any given model. Results are mean values across all iterations of the analysis. The performance of each model was further validated by creating a null model. The null models were generated by a random-label permutation (i.e., randomly assigning the outcome variable across subjects). Using this permuted outcome variable, the entire analysis was performed again. The accuracy achieved using the null model was then compared to the accuracy of the model with real data

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(i.e. actual model) by ranking the cross-validated r values from iterations of both actual and null models, giving an estimate of the level of optimism inherent in the model. The actual model was deemed to have performed better than the null model in 100% of iterations (i.e., 10/10 of the highest cross-validated r values were from actual models). Cross-validated r is the most appropriate measure to use with linear regression conducted using machine learning (see for example Jollans et al. 2016).
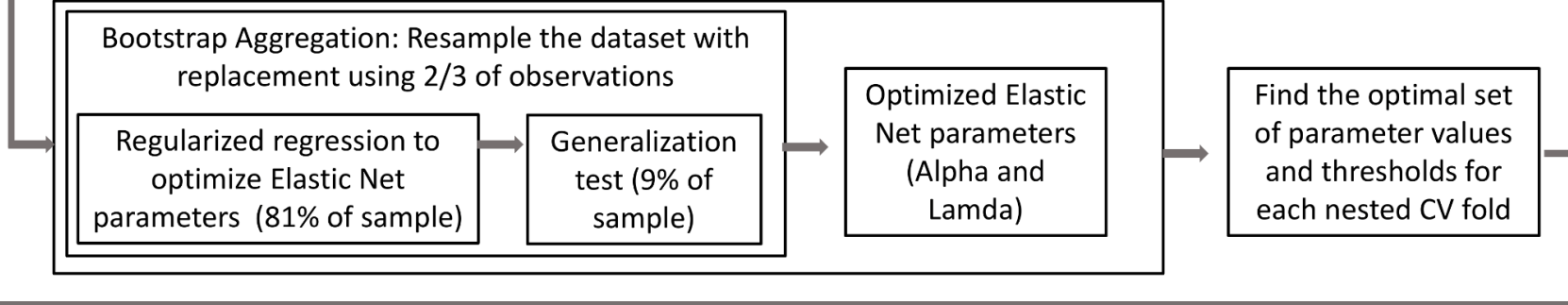
1. Feature thresholding using nested cross-validation (90% of sample in each loop)

Calculate prediction error for each feature

Bootstrap Aggregation: Resample the dataset with replacement using 2/3 of observations		Compute 10 *merit thresholds* based on the range of prediction error across features	Generate summary datasets for each nested CV fold, based on merit and occurrence thresholds describing in how many nested CV folds each feature survived each merit threshold
Regression (81% of sample)	Generalization test (9% of sample)		

2. Parameter optimization using nested cross-validation (90% of sample in each loop)

Calculate prediction error for all merit and occurrence thresholds

Bootstrap Aggregation: Resample the dataset with replacement using 2/3 of observations		Optimized Elastic Net parameters (Alpha and Lamda)	Find the optimal set of parameter values and thresholds for each nested CV fold
Regularized regression to optimize Elastic Net parameters (81% of sample)	Generalization test (9% of sample)		

3. Outer cross-validation (100% of sample in each loop)

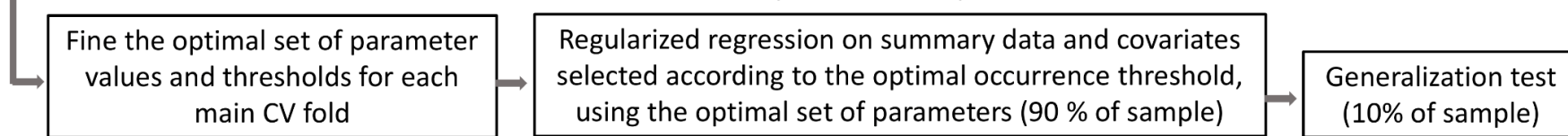| Fine the optimal set of parameter values and thresholds for each main CV fold	Regularized regression on summary data and covariates selected according to the optimal occurrence threshold, using the optimal set of parameters (90 % of sample)	Generalization test (10% of sample)

Figure S2.4. Schematic description of the RAFT algorithm.

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Table S2.1

Relationship among impulsivity variables

Measure	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Self-report														
1. BIS-11 Attention	1													
2. BIS-11 Motor	*0.48*	1												
3. BIS-11 Non-planning	**0.48**	**0.43**	1											
4. SSS adventure seeking	0.12	*0.26*	0.15	1										
5. SSS Boredom	**0.23**	**0.19**	**0.21**	*0.28*	1									
6. SSS Disinhibition	*0.39*	*0.38*	*0.38*	**0.21**	*0.41*	1								
7. SSS Experience seeking	0.08	0.15	0.12	*0.31*	**0.28**	**0.23**	1							
8. MCQ k	**0.22**	*0.29*	**0.28**	-0.2	0.11	**0.20**	0.03	1						
Task-based (index)														
9. DD k (choice)	0.07	0.14	0.16	-0.1	0.04	0.1	-0.1	*0.67*	1					
10. SST SSRT (motor)	-0.05	0.05	-0.05	-0.09	-0.09	-0.08	-0.08	0.16	**0.19**	1				
11. SST IRV (cognitive)	0.16	0.09	0.11	0.17	0.05	*0.15*	0.07	0.08	0.00	***-0.31***	1			
12. Stroop (interference)	0.01	0.05	**0.22**	-0.1	-0.1	0.1	-0.1	0.15	*0.31*	0.09	-0.1	1		
13. PST Approach A (reward)	-0.09	0.00	0.00	0.16	0.11	0.05	0.02	0.00	-0.10	-0.12	0.16	0	1	
14. PST Avoid B (punishment)	-0.07	0.05	0.01	0.01	0.05	0.05	0.10	0.12	0.11	0.00	0.11	0.10	***0.56***	1

Note: Bold correlations are weakly correlated, or are >0.03 Bayes factor (i.e. not considered null). Bolded and i*t*alicized correlations are significant at $p < 0.0037$, Bonferroni corrected for multiple comparisons.
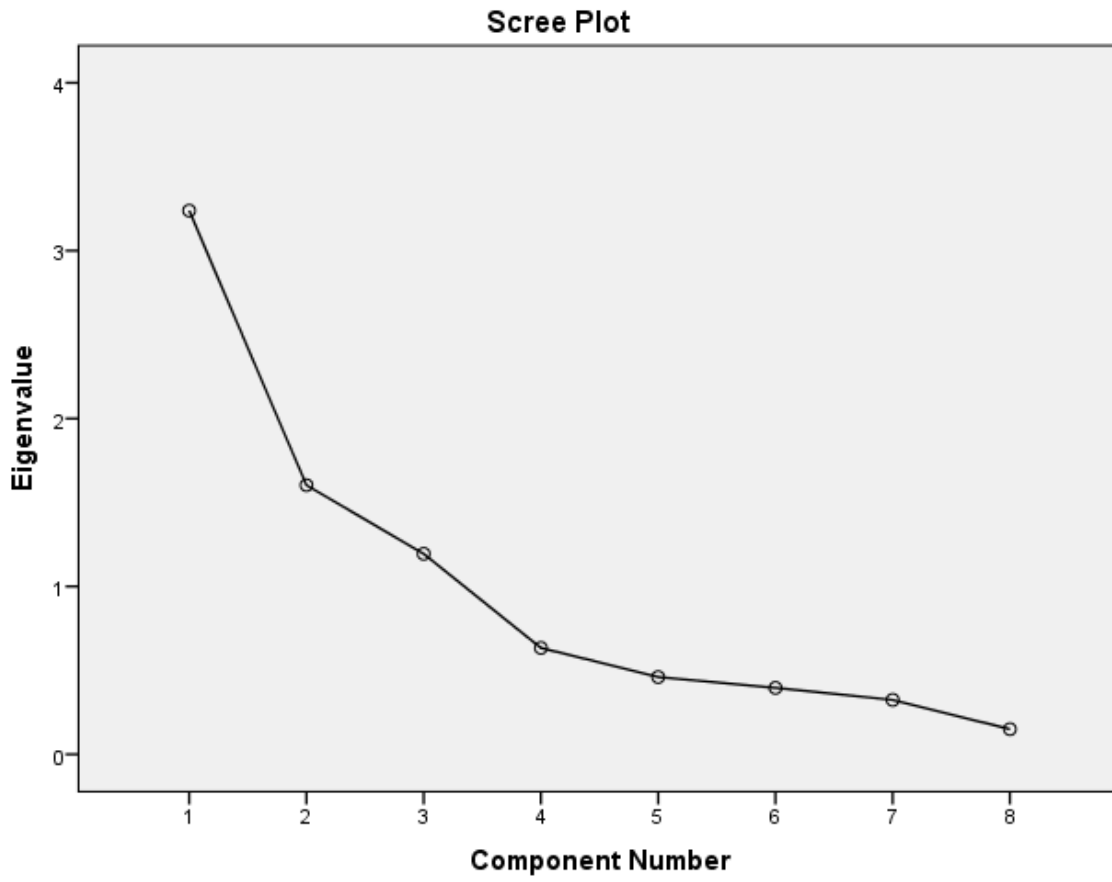
Figure S2.5. Scree plot of eigenvalues for principal components analysis of alcohol-use questions.
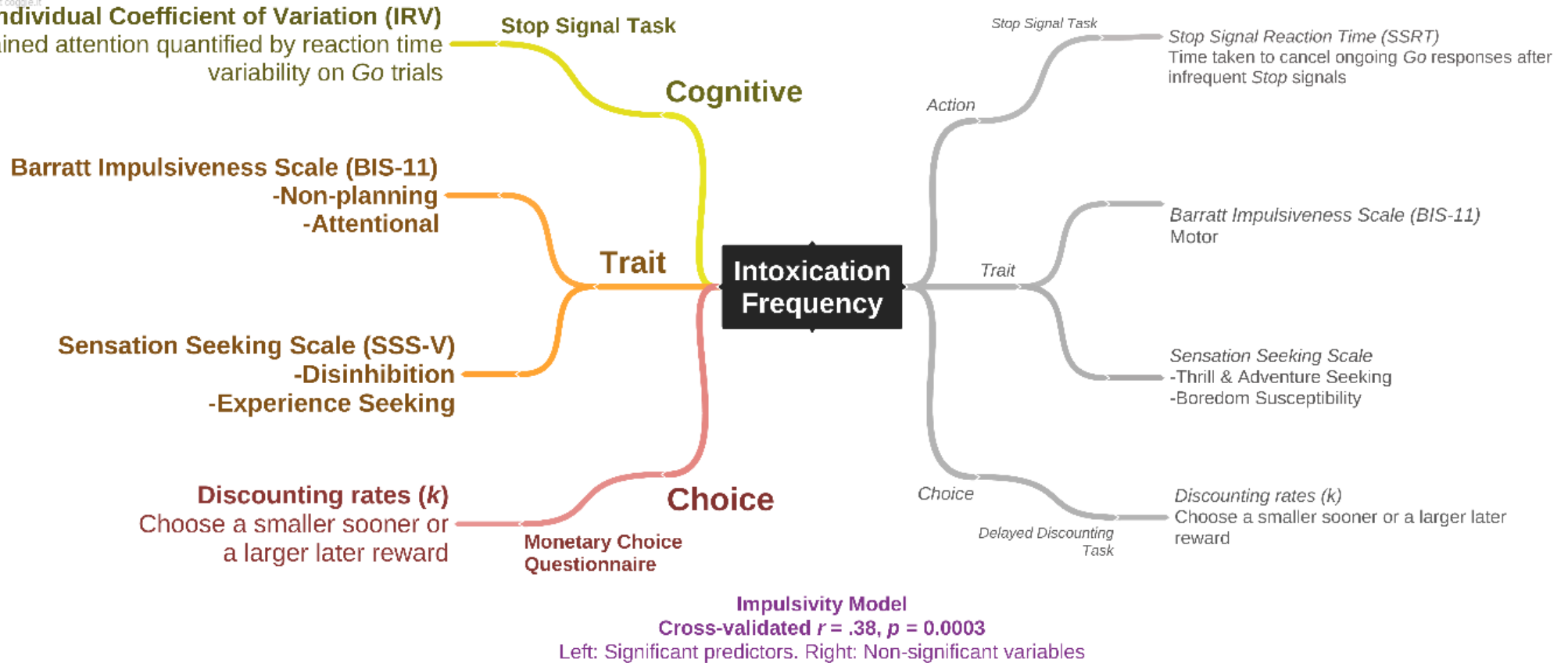
Figure S2.6. Machine learning results for predicting intoxication frequency. Significant predictors are in warm colours (left) and non-significant variables are in grey colour (right).

Machine Learning Results

Two of the SSS-V subscales contained questions regarding alcohol and drug use – for Disinhibition "Keeping the drinks full is the key to a good party; I feel best after taking a couple of drinks" and for Experience Seeking "I have tried marijuana or would like to; I would like to try some of the new drugs that produce hallucination". To ensure that results of these models were not driven by factors influencing the outcome variable (i.e. intoxication frequency), I ran a separate analysis, excluding these variables from the SSS-V subscales. I then ran a model with the same impulsivity variables for intoxication frequency. The results indicated that these questions did not alter the beta weight values for the predictor variables, and the model remained significant (median $r=0.31$, $p=0.002$). Therefore, I concluded that the inclusion of these questions in the final analysis was appropriate.

Table S2.2

Items included from the ESPAD

On how many occasions (if any) have you had any alcoholic beverage to drink?
   a. In your lifetime
   b. During the last 12 months
   c. During the last 30 days

Think back again over the LAST 30 DAYS. How many times (if any) have you had five or more drinks on one occasion?

On how many occasions (if any) have you been intoxicated from drinking alcoholic beverages, for example staggered when walking, not being able to speak properly, throwing up or not remembering what happened?
   a. In your lifetime
   b. During the last 12 months
   c. During the last 30 days

How likely is it that each of the following things would happen to you personally, if you drink alcohol?
   a. Feel relaxed
   b. Get into trouble with police
   c. Harm my health
   d. Feel happy
   e. Forget my problems
   f. Not be able to stop drinking
   g. Get a hangover
   h. Feel friendlier and more outgoing
   i. Do something I regret
   j. Have a lot of fun
   k. Feel sick

WHILE UNDER THE INFLUENCE OF ALCOHOL, how often during the LAST 12 MONTHS have you experienced the following?
   a. Physical fight
   b. Accident/ injury
   c. Serious problems with your parents
   d. Serious problems with your friends
   e. Performed poorly as school/ work
   f. Victimised by robbery/ theft
   g. Trouble with the police
   h. Hospitalized/ admitted to an emergency room
   i. Engaged in sexual intercourse without a condom

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j. Engaged in sexual intercourse you regretted the next day

On how many occasions (if any) during your lifetime have you smoked cigarettes?

On how many occasions (if any) have you used marijuana or hashish (cannabis)?

    a. In your lifetime

    b. During the last 12 months

    c. During the last 30 days

On how many occasions (if any) have you used any of the following drugs (amphetamines, tranquilizers or sedatives, ecstasy, cocaine, crack, other drugs)?

    a. In your lifetime

    b. During the last 12 months

    c. During the last 30 days

References

Frank, M.J., Seeberger, L.C. and O'Reilly, R.C., 2004. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science, 306(5703), pp.1940-1943.

Mazur, J.E., 1987. An adjusting procedure for studying delayed reinforcement. Commons, ML.; Mazur, JE.; Nevin, JA, pp.55-73.

Ortiz, N., Parsons, A., Whelan, R., Brennan, K., Agan, M.L., O'Connell, R., Bramham, J. and Garavan, H., 2015. Decreased frontal, striatal and cerebellar activation in adults with ADHD during an adaptive delay discounting task. Acta Neurobiol. Exp.(Wars), 75(3), pp.326-338.

7.2   Supplemental 3.1

Self-report measures

The *Alcohol Use Disorders Identification Test* (AUDIT; Babor, Higgins-Biddle, Saunders & Monteiro, 2001) is a 10-item alcohol screening questionnaire that assessed alcohol consumption, alcohol-related problems and drinking behaviour and quantifying risk from low-level to hazardous drinking. The AUDIT has demonstrated a high degree of internal consistency (Cronbach's a between 0.75 to 0.97; Reinert & Allen, 2007). Responses are scored from 0-4, with a maximum of 40 for total AUDIT scores.

The *Drug Abuse Screening Test* (DAST-20; Skinner, 1982) is a 20-item questionnaire that assessed illegal drug use in the past 12 months, and has shown moderate to high levels of internal consistency (α's between 0.74 to 0.94) (Yudko, Lozhkina & Fouts, 2007).

The *Depression, Anxiety and Stress Scale* (DASS; (Henry & Crawford, 2005) is a 21-item questionnaire that assessed cognitive and behavioural distress symptoms experienced within the past week. This measure utilised three subscales: Anxiety (7 items; "I felt I was close to panic"), Stress (7 items; "I found it difficult to relax") and Depression (7 items; e.g., "I felt that life was meaningless"). Participants rated items on a 4-point Likert-scale (1=did not apply to me at all, 4=applied to me very much or most of the time), and higher scores indicated higher levels of depression, anxiety, or stress (Henry & Crawford, 2005). Antony and colleagues (1998) assessed internal consistency of the DASS-21 using a total of 307 individuals with panic disorder (n= 67), obsessive compulsive disorder (n= 54), social phobia (n= 74), specific phobia (n= 17), or major depressive disorder (n= 46) and a group of nonclinical volunteers for comparison (n= 49). Internal consistency using Cronbach's alpha

for the DASS-21 Depression, Anxiety, and Stress subscales were .94, .87, and .91, respectively, in both clinical and nonclinical samples.

The *Neuroticism-Extraversion-Openness Five Factor Inventory* (NEO-FFI; Costa & McCrae, 1992) assessed personality traits, including individual differences on 5 subscales for Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness. Each subscale comprised 12 items on a 5-point Likert scale, (0=strongly disagree; 4=strongly agree). Internal consistency for each of the five domains has been shown to be adequate (α = .68 to .86; Costa & McCrae, 1992)

The Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983) assessed stress appraisal related to common life situations within the last month. The scale comprised 10 items on a 5-point scale (0=never; 4=very often), and has shown high internal reliability (α = .85; Lavoie & Douglas, 2012).

The *Multidimensional Scale of Perceived Social Support* (MSPSS; Zimet et al., 1988) is a 12-item scale that assessed perceived support from family, friends and a significant other, measured on a 7-point Likert scale (1 =very strongly disagree; 7=very strongly agree). Internal consistency has been shown to be strong (α's between 0.85 to 0.91) (Dahlem, Zimet, & Walker, 1991).

The *Barratt Impulsiveness Scale 11th version* (BIS-11; Patton and Stanford, 1995) assessed trait impulsivity with 30 items on a 5-point Likert scale (ranging from disagree strongly to agree strongly), yielding three second-order factors—Motor, Attentional and Non-planning impulsivity. The scale has shown strong internal consistency and reliability (Stanford et al., 2009).

Task-based measures

All computerized tasks were presented and responses recorded by the Presentation® software package (Neurobehavioural Systems). Each task began with on-screen instructions that were also read out to participants by the experimenter. The experimenter checked that the participant understood the instructions and participants were given time to read over the instructions again themselves before commencing the task in their own time by pressing the '1' key on the keyboard. Task responses were made via an Xbox 360 game controller. Participants were seated in front of a cathode ray tube computer monitor with a screen resolution of 1024 x 768 pixels at a refresh rate of 75 Hz. The distance from the position of the chair to the monitor (screen size 32 x 24 cm) was standardized (screen to back of chair = 108 cm). Participants were asked to maintain their focus on the stimuli on the screen during the experiment.

The *Stroop Colour–Word Test* (MacLeod, 1991) assessed cognitive conflict. Participants were presented with the name of a colour and were required to name the colour when the word name was printed in either a congruent (e.g., blue) or incongruent colour (e.g., the word red printed in blue ink). Following 12 initial practice trials, participants completed a single block of 96 test trials in total. Reaction time on incongruent trials is typically slower than for congruent trials, known as the "interference effect" (MacLeod, 1991), which was calculated by subtracting incongruent from congruent trials. Lower interference effect indicates better performance.

The *Probabilistic Selection Task* (PST; Frank, Seeberger & O'Reilly, 2004) assessed reward and punishment learning. The PST comprised of a training and test phase, each 120 trials in length. During the training phase, participants were randomly presented with three stimulus pairs (AB, CD, EF), and required to select the 'correct' stimulus in each pair based on probabilistic feedback. The stimulus reward probabilities were predetermined (A: 80%; B: 20%; C: 70%; D: 30%; E: 60%; F:

40%). The position of each stimulus on screen was randomly varied across trials (e.g. AB, or BA). Stimulus pairs were presented on screen until a response was made. Feedback was presented for 750ms in the form of a green tick "✓" signalling correct responses or red 'X' for incorrect responses respectively. There was no criterion to reach in the training phase. In the Test phase, novel combinations of the six stimuli were presented, and participants were again required to select the correct stimulus in each pair. No feedback was provided in the Test phase of the PST. As in previous research, performance in the Test phase was measured by comparing how often participants selected the A stimulus versus how often they avoided the B stimulus in novel pairs. If participants have correctly learned the relative values of symbols during the learning phase, positive stimulus (A) choices over all other symbols indicated that the participant learned from positive feedback (reward sensitivity), while avoidance of the negative stimulus (B) over other symbols indicated negative feedback learning (punishment sensitivity). Stimuli were presented on screen until a response was made, and a fixation cross was presented for 500ms between trials.

The *adaptive delay discounting task* (DDT) assessed choice impulsivity. Participants were presented with a series of dichotomous choices between immediate versus relatively larger but delayed hypothetical monetary rewards. The adapting DDT was designed to estimate an individual's rate of delay discounting progressively more accurately from trial to trial by adapting the hypothetical magnitude and timing of the delayed rewards it offered participants on each trial based upon their preceding responses (Ortiz et al., 2015). The rate at which the DDT modified the value of the delayed reward it offered participants was governed by an adaptive algorithm using a double-limit procedure that modified the model parameter k based on two sets of boundaries designed to adjust to the point at which the participant would choose the immediate and delayed outcome with

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equal probability. The model parameter k characterises an individual's rate of delay discounting such that higher values of k indicate a higher rate of delay discounting. The delayed reward was presented at a randomly chosen delay of between 1 and 180 days (phrased in days, weeks or months as appropriate), and a randomly chosen immediate reward of between $10-50. When participants chose the immediate reward on a given DDT trial the obtained estimate of k was decreased and then used to calculate the value of the delayed choice being offered on the next DDT trial, and vice-versa if the delayed reward was chosen. The DDT's adaptive algorithm was designed to converge upon a participant's individual k value. Following 10 initial practice trials, a single block of 149 DDT test trials commenced with initial $k = 0.018$. Each trial began with a fixation cross positioned centre screen for 700 ms. If participants did not respond within five seconds of the choice they were prompted with the message "Please respond" directly underneath. Failure to respond within two further seconds resulted in the trial completing without recording any response or thus updating the value of k.

An *adaptive Stop Signal Task* (SST) assessed inhibitory control. Participants performed an adaptive event-related Stop Signal Task (SST), which took approximately 9 min to complete. Following 10 initial practice trials, the task consisted of 135 Go trials interspersed with 45 Stop trials; with one randomized Stop trial appearing within four Go trials. The task was presented in 3 blocks of 60 trials. Each trial began with a central fixation cross for 1000 ms and the total duration of a trial was always 1000ms. On every trial, participants were presented with arrows pointing either to the left or right (stimuli size 122 x 108 mm), shown centrally on the screen for 750 ms. During Go trials, participants were required to make a single button-press response on the keyboard with their left or right index finger corresponding to the direction of the arrow as fast as possible. In Stop trials,

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the Go stimulus was followed by an arrow pointing upwards (i.e., the Stop signal, shown between 550-950 ms; stimuli size 113x126 mm), which required participants to inhibit their motor responses. A tracking algorithm adjusted task difficulty by varying the stop-signal delay (SSD; the time interval between Go signal and Stop signal onsets). The initial SSD was 250 ms, but was adjusted according to a participant's performance, to between 50 ms and 450 ms. These limits were adjusted depending on task performance, making the SSD shorter (i.e., the task easier) after an unsuccessful stop trial, and the SSD longer (i.e., the task more difficult) after a successful stop trial. A moving average of go reaction times (RTs) began on the 10th trial. Participants were presented with a "Speed up!" prompt for 2 s if they failed to respond to 2 out of 5 Go trials, or if their last RT was longer than 1.5 times their average RT. The aim was to produce 50% successful and 50% unsuccessful inhibition trials. If the participant responded to the Go stimulus before Stop stimulus presentation (i.e. responded during the SSD) then this was recorded as a stop too early (STE). STEs were considered to be an unsuccessful stop trial and as a result, the SSD was adjusted accordingly (i.e. shorted delays following STE trials).

The SSRT refers to the time taken to cancel a prepotent motor response after Stop stimulus presentation. Under the horse-race model, the Go and Stop responses are considered to be independent processes, with successful inhibition determined by the ability to complete the stop process before the go process (Band et al., 2003; Verbruggen & Logan, 2008). According to the horse-race model (Logan and Cowan, 1984), the finish of the stop process can be estimated from a subject's distribution of RTs on Go trials. The left side of the distribution of the RTs on Go trials represents faster responses that indicate failure to inhibit a response, whereas the right side represents slower responses that indicate successful inhibition. If a subject failed to inhibit on n% of Stop trials,

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the finishing time of the stop process will approximately be equal to the nth percentile of the go RT distribution. The mean SSD was then subtracted from the nth percentile of the go RT distribution, resulting in an estimate of SSRT. The average successful stop rate was 54.6% on the SST, indicating that the tracking procedure was successful in making performance-based dynamic adjustments. Participants with SSRT < 75 ms were excluded from the analysis.

Table S3.1 Spearman's Rho correlations among variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1.NEO extraversion	1.00																				
2.NEO openness	.02	1.00																			
3.NEO agreeableness	.35**	.22	1.00																		
4.NEO conscientiousness	-.22*	.00	.11	1.00																	
5.NEO neuroticism	.12	-.25*	-.03	-.18	1.00																
6.DASS stress	.05	-.02	-.21	-.23*	.43**	1.00															
7.DASS anxiety	.03	-.20	-.24*	-.14	.58**	.61**	1.00														
8.DASS depression	.14	-.19	-.13	-.44**	.59**	.50**	.70**	1.00													
9.MSPSS significant other	-.06	.07	.24*	.01	-.04	-.09	.00	-.14	1.00												
10.MSPSS family	.04	.06	.26*	.19	.02	-.16	-.24*	.53**	1.00												
11.MSPSS friends	.05	.18	.25*	.08	.01	-.04	-.07	-.11	.58**	.53**	1.00										
12.PSS total	.01	-.05	-.17	-.10	.59**	.48**	.49**	.47**	-.01	.05	-.04	1.00									
13.BIS-11 attentional	.13	.18	-.23*	-.61**	.42**	.41**	.40**	.42**	.02	-.14	-.16	.33**	1.00								
14.BIS-11 motor	.16	.45**	-.12	-.49**	.04	.28*	.19	.34**	.00	-.12	-.02	.17	.58**	1.00							
15.BIS-11 non-planning	-.03	.32**	.02	-.54**	.06	.00	.05	.24*	-.01	-.11	-.08	-.07	.45**	.43**	1.00						
16.DDT (*k*)	.05	.02	.08	.03	-.20	-.03	-.14	-.10	-.05	.04	-.02	-.05	-.06	-.03	.10	1.00					
17.SST SSRT	-.02	.00	-.13	.14	-.06	.05	.10	.04	.09	.04	.16	-.08	-.12	.01	-.23*	-.06	1.00				
18.SST IRV	-.05	.07	-.05	.23*	.11	.21	.19	-.04	.27*	.15	.27*	.23*	.04	-.07	-.12	.12	-.07	1.00			
19.Stroop (Interference)	-.16	-.04	-.33**	.12	.15	.08	.16	.09	-.02	-.04	-.11	.13	.12	.04	.02	-.13	.05	.14	1.00		
20.PST approach A	.00	.36**	.01	.05	-.04	-.02	.02	-.05	-.05	-.01	-.04	.17	.01	.10	-.07	-.02	-.04	-.03	.17	1.00	
21.PST avoid B	-.08	.17	-.11	.04	.06	-.05	.12	-.01	-.11	-.14	-.05	.13	-.04	-.07	-.03	.00	.05	-.03	-.04	.76**	1.00

*Correlation is significant at *p* < 0.05 level (2-tailed), ** *p* < 0.01 level (2-tailed)
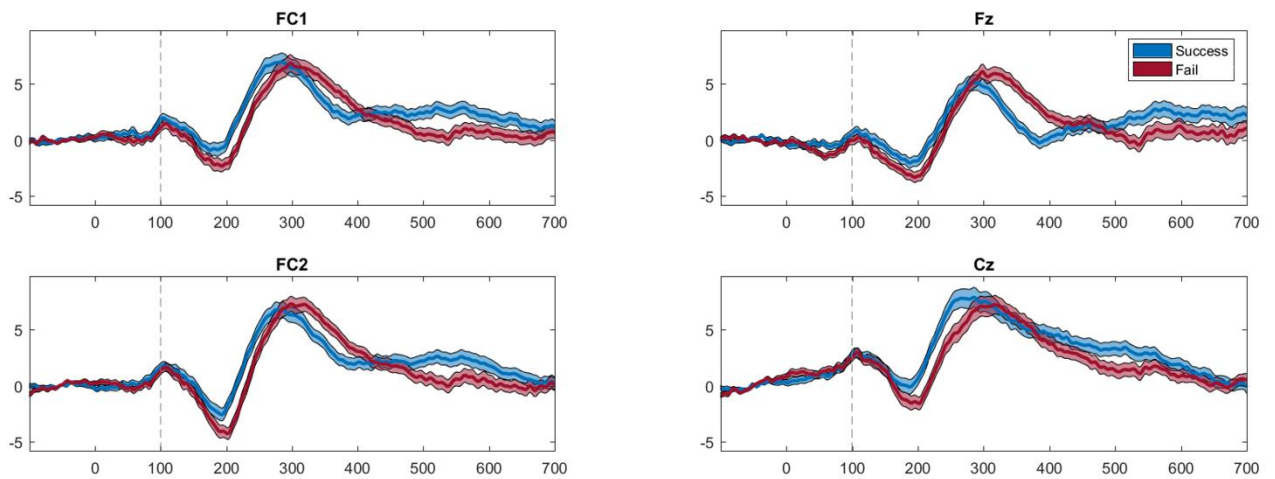
Figure S3.1. ERP grand-average across participants, based on all non-artifact independent components, time-locked to the stop-signal for four fronto-central channels.

Table S3.2 Results of machine learning models

| Model | Measure | Model type | | Two-sample *t*-test | *p*-value |
		Original	Null		
EEG only	MSE	-147.37	-152.95	t(198)=1.58 e+01	5.78 e-37
	Pearson's correlation	0.28	-0.01	t(198)=1.89 e+01	3.18 e-46
Non-EEG	MSE	-138.68	-146.05	t(198)= 1.83 e+01	1.06 e-44
All variables	Pearson's correlation	0.34	0.00	t(198)= 2.19 e+01	7.54 e-55
Non-EEG	MSE	-22.48	-27.63	t(198)= 2.66 e+01,	2.22 e-67
Impulsivity only	Pearson's correlation	0.37	-0.03	t(198)= 2.47 e+01	1.79 e-62
EEG + Non-EEG	MSE	-146.04	-151.93	t(198)= 1.60 e+01	8.26 e-38
	Pearson's correlation	0.28	-0.02	t(198)= 1.89 e+01	2.31 e-46

Averaged mean-squared error (MSE) and Pearson's correlation across set assignments for the original and null models. The t-test between the accuracy measures for the original and null models shows a strong difference.

Table S3.3. Machine-learning results for all models

EEG only (CV $r = 0.28$, $p = 0.03$)			Non-EEG: All variables (CV $r = 0.34$, $p = 0.004$)			Non-EEG: Impulsivity only (CV $r = 0.37$ $p = 0.002$)			EEG + Non-EEG (CV $r = 0.28$, $p = 0.02$)		
Features	Mean Frequency	Beta Weight	Features	Mean Frequency	Beta Weight	Features	Mean Frequency	Beta Weight	Features	Mean Frequency	Beta Weight
Fail AF7 [541 ms]	9.91	0.17	Relationship Status	10	-0.87	BIS-11 Non-planning	10	1.12	Fail AF7 [541 ms]	9.89	0.19
Fail T7 [190 ms]	9.79	-0.11	DASS Anxiety	10	0.99	Stroop Interference	9.99	1.02	Fail T7 [190 ms]	9.67	-0.12
Success Fz [92 ms]	9.37	-0.10	Stroop Interference	10	1.20	BIS-11 Motor	9.93	0.71	Success Fz [92 ms]	9.22	-0.11
Fail Fpz [41 ms]	9.29	-0.10	BIS-11 Non-planning	10	0.97	SST IRV	8.51	0.68	Fail F5 [221 ms]	9.11	-0.07
Fail F5 [220 ms]	9.21	-0.06	BIS-11 Motor	9.98	0.45	DDT k	7.63	0.30	BIS-11 Non-planning*	9.09	0.12
Fail T7 [147 ms]	9.21	-0.06	MSPSS Family	9.91	-1.14	BIS-11 Attentional	7.6	0.12	Fail Fpz [41 ms]	9.03	-0.11
Fail FT7 [225 ms]	9.16	-0.05	MSPSS Friend	9.9	1.25	SST SSRT	7.41	0.10	Fail C6 [135 ms]	9.01	-0.04
Fail FC5 [412 ms]	9.09	-0.07	Yrs. Of Education	9.88	0.68	-	-	-	BIS-11 Motor*	8.98	0.07
Fail F5 [61 ms]	9.07	-0.05	SST IRV	9.86	0.61	-	-	-	Fail FC5 [443 ms]	8.89	-0.08
Fail C6 [135 ms]	8.96	-0.03	NEO Neuroticism	9.85	-0.64	-	-	-	Fail F5 [61 ms]	8.87	-0.06
Fail FC5 [443 ms]	8.95	-0.06	NEO Agreeableness	9.79	0.41	-	-	-	Stroop Interference*	8.78	0.07
Fail Cz [123 ms]	8.93	0.04	MSPSS Partner	9.78	-0.51	-	-	-	Relationship Status*	8.69	-0.09
Success Fpz [279 ms]	8.92	-0.08	NEO Openness	9.7	-0.26	-	-	-	Fail FT7 [225 ms]	8.65	-0.04
Success C5 [271 ms]	8.89	0.09	NEO Conscientiousnes	9.69	-0.33	-	-	-	Success Fpz [84 ms]	8.62	-0.06
Fail FCz [529 ms]	8.85	-0.04	PSS Total	9.68	-0.30	-	-	-	DASS Anxiety*	8.6	0.08
Success Fpz [84 ms]	8.83	-0.05	DDT k	9.61	0.22	-	-	-	Fail T7 [147 ms]	8.53	-0.06

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Fail T7 [342 ms]	8.82	-0.04	SST SSRT	9.54	0.13	-	-	-	Success C5 [272 ms]	8.52	0.10
Fail FP1 [221 ms]	8.79	-0.03	DAST Drug Total	9.48	-0.04	-	-	-	Fail FC5 [412 ms]	8.52	-0.09
Fail F8 [76 ms]	8.78	0.08	BIS-11 Attentional	9.45	0.23	-	-	-	Fail FT8 [6 ms]	8.52	0.09
Success AF3 [88 ms]	8.77	-0.06	NEO Extraversion	9.41	-0.22	-	-	-	Fail FCz [529 ms]	8.5	-0.04
Fail F6 [264 ms]	8.77	0.06	DASS Stress	9.37	-0.20	-	-	-	Fail T8 [475 ms]	8.49	-0.06
Fail T8 [475 ms]	8.76	-0.05	Monthly Income	9.32	0.14	-	-	-	Fail FP1 [221 ms]	8.48	-0.04
Fail Cz [115 ms]	8.76	0.03	Smoker / Non-smoker	9.28	-0.06	-	-	-	Fail F6 [263 ms]	8.45	0.06
Fail F6 [115 ms]	8.74	0.07	PST Approach A	9.02	-0.05	-	-	-	Fail Cz [123 ms]	8.41	0.04
Success FP1 [4 ms]	8.73	-0.04	PST Avoid B	8.91	-0.87	-	-	-	Success FP1 [3.9 ms]	8.37	-0.04
Fail AF3 [60 ms]	8.73	-0.06	DASS Depression	8.85	0.07	-	-	-	Fail F8 [76 ms]	8.37	0.08

Top 30 features ranked in order of highest mean frequency of being picked across mainfolds and random set assignments, for each model respectively. For EEG results, each time sample ranges within ~4ms. * Non-EEG variables that were combined with EEG variables. Impulsiveness Scale 11th version; DDT: Delay Discounting Task; SST: Stop Signal Task; PST: Probabilistic Selection Task; DASS: Depression, Stress & Anxiety Scale.

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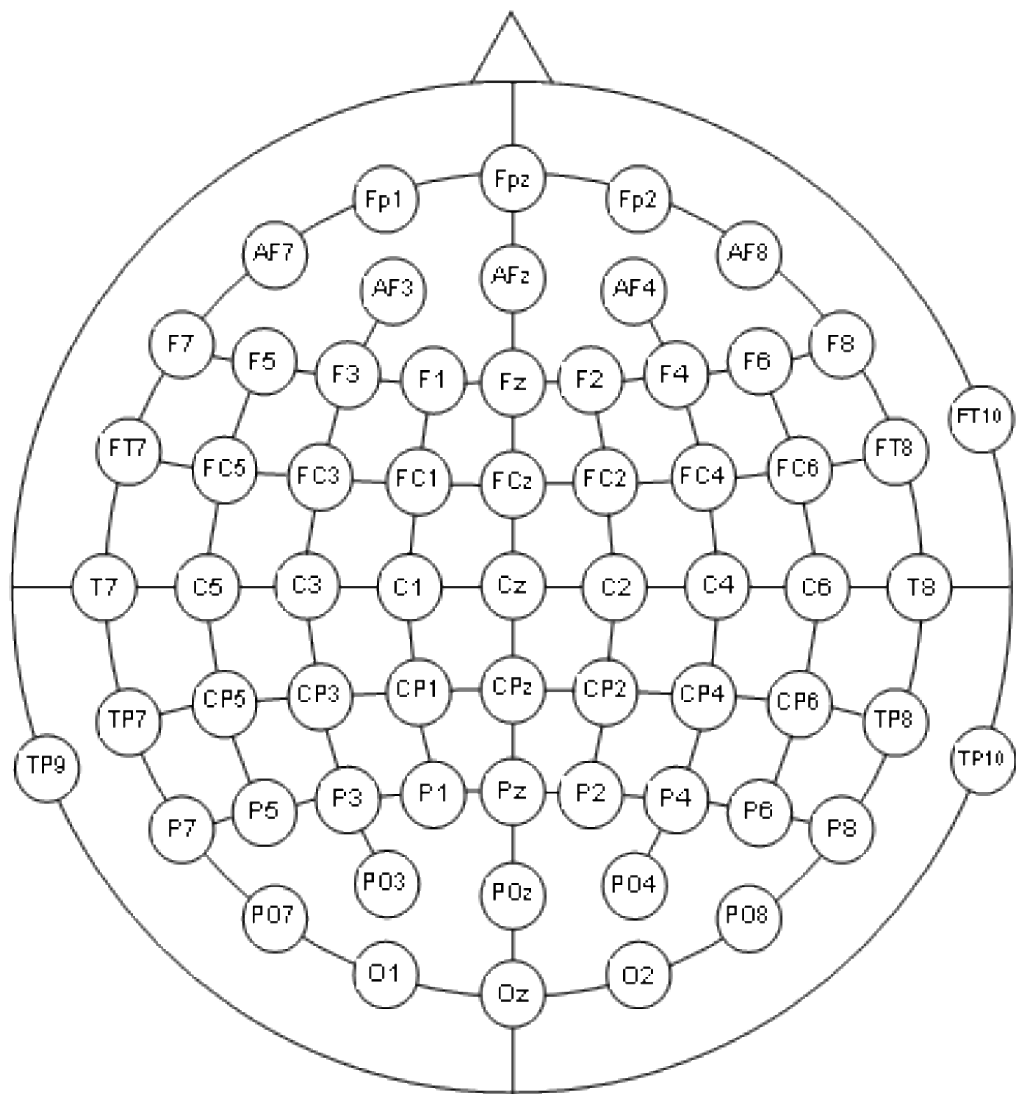
Figure S3.2. Map of 64-channel set-up across the scalp during EEG recording.

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7.3   Supplemental 4.1

Controlling for Motion Artifacts

Ideally, motion correction should eliminate any statistical relationship between functional connectivity and in-scanner motion artifacts, although a trade-off inevitably arises among the possible methods for motion regression (Caballero-Gaudes & Reynolds, 2017; Ciric et al., 2017) (note that the examination of motion confounds have generally been carried out using resting-state data). Therefore, I conducted additional analyses to demonstrate that the FC-IRV relationships hold, regardless of head motion. I used the summary statistic of mean framewise displacement (mFWD; Power 2014) to quantify the degree of head motion for each subject.

Motion Analysis 1. Progressive elimination of higher motion subjects from the normative sample. I separated the normative sample into groups according to the amount of motion: (mFWD <0.2 mm, n=457; <0.3 mm, n=621; <0.4 mm, n=692; <0.5 mm, n=726) and a group consisting only of subjects with higher motion (i.e., all participants with mFWD>0.2 mm, n=301). Separately for each group, timeseries data were extracted and a Pearson's correlation score was calculated among the 268 ROIs. This yielded a connectivity matrix (268 × 268) with 35,778 unique connections between ROIs for each group. I then correlated these connections with individual IRV scores within each group. Although each group contained different numbers of participants, for consistency a significance threshold of $p < 0.001$ was applied to each set of results. Due to the computational expense, I did not run the permutation analysis, but simply applied the significance threshold ($p<0.001$) to the FC-IRV matrices for

each motion group. *Figure S4.1* displays these results, with additional information in Table S4.1. Note the high motion subgroup was relatively underpowered to detect FC-IRV effects at p<.001 (*Figure S4.1*, Panel I) and therefore I include a figure with p<.005 threshold to this group's FC-IRV to better show the strongest FC-IRV connections (*Figure S4.1*, Panel J).

Motion Analysis 2. Examination of subgroup without mFWD-IRV correlation. Head motion and IRV were correlated in the normative sample (Spearman's Rho = .22). Therefore, in order to examine if the FC-IRV relationship resulted from the mFWD-IRV relationship, I examined a subset of subjects (n=360) excluding particularly high-motion/high-IRV subjects with no correlation between mFWD and IRV (Spearman's Rho = .09, p>.05; mFWD<.17; IRV<.3). Similar to Motion Analysis 1, I recalculated the ROI connectivity matrix and then correlated this matrix with IRV (*Figure S4.1*, Panel F). Note that the sample size is smaller and, by examining only a subset of values within a particular range, the correlations will be inherently weaker (i.e., due to range restriction; see additional information in Table S4.1). As a result, we also include a figure with p<.005 threshold to this group's FC-IRV (*Figure S4.1*, Panel G).

A. mFDW<0.2mm Group
(N=457)
p<.001
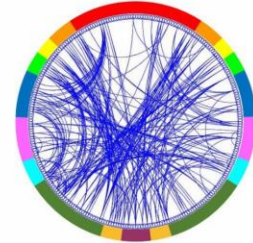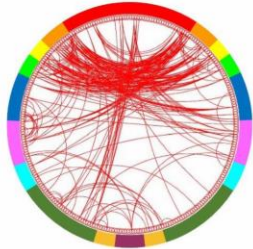
B. mFDW<0.3mm Group
(N=621)
p<.001
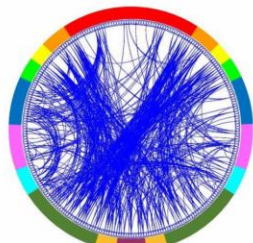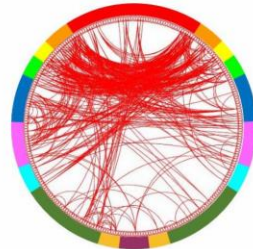
C. mFDW<0.4mm Group
(N=692)
p<.001
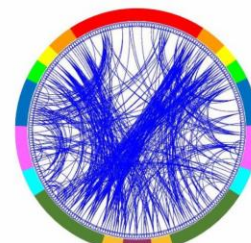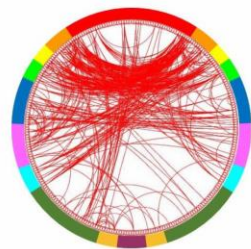
D. mFDW<0.5mm Group
(N=726)
p<.001
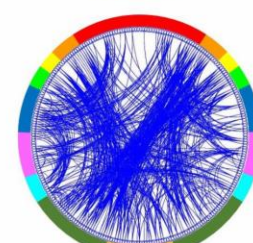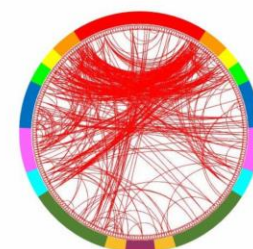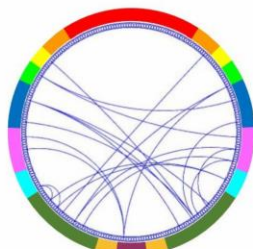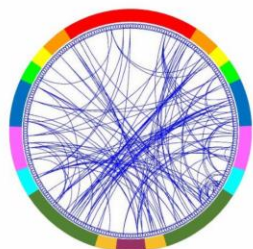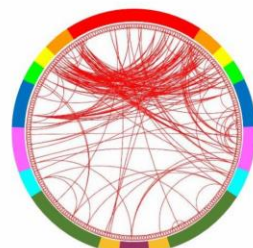
E. All mFDW Group
(N=758)
p<.001
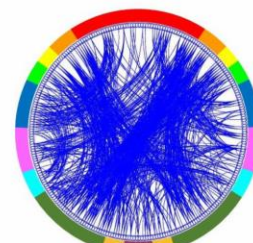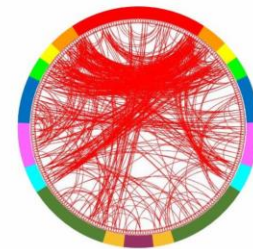
F. No Correlation Group
(mFDW-IRV r=0.09; N=360)
p<.001
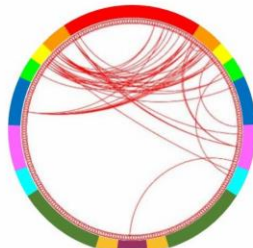
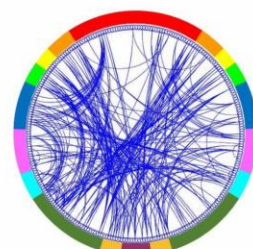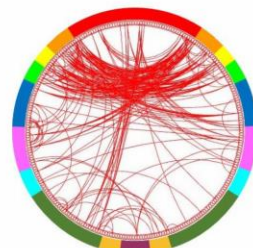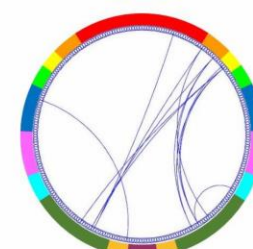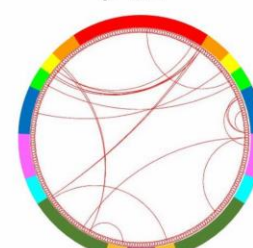G. No Correlation Group
(mFDW-IRV r=0.09; N=360)
p<.005

H. Low Motion Group
(mFDW<.2mm; N=457)
p<.001

I. High Motion Group
(mFDW>.2mm; N=301)
p<.001

J. High Motion Group
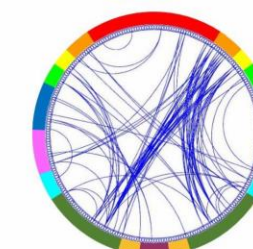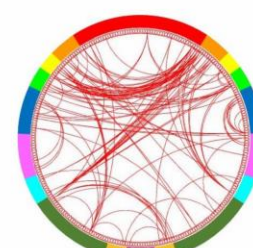(mFDW>.2mm; N=301)
P<.005

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Figure S4.1. Examination of distributions of FC-IRV correlations for various motion-determined subgroups. Good sustained attention (i.e. functional connections positively correlated with IRV) is denoted by the colour red (top images); poor sustained attention (i.e. functional connections negatively correlated with IRV) is denoted by the colour blue (bottom images).

Motion Analysis 3. Network overlap between motion groups: It is important to demonstrate that the most important connections within the normative sample are preserved, regardless of the motion characteristics of the subjects. the top 100 FC-IRV connections (absolute *r* values) from the normative sample were identified, and extracted and computed the same connections for a low motion group mFWD<.2), a higher motion group (mFWD>.2), and the mFWD-IRV uncorrelated group (see Table S4.1 below). These FC-IRV connections remained significant within each group, with similar absolute r values and broadly similar p values (note that sample sizes were different across groups).

Table S4.1

r values of the top 100 FC-IRV connections identified from the normative sample. That is, the mean r values for the Low Motion, High Motion and Uncorrelated Groups were calculated based on connections identified in the normative sample.

	Normative Group (N=758)	Low Motion Group (N=457)	High Motion Group (N=301)	Uncorrelated Group (N=360)
Mean FC-IRV absolute *r*	0.187	0.181	0.156	0.150
Standard error of mean absolute *r*	0.002	0.004	0.003	0.004
Mean p	<0.001	<0.001	0.022	<0.001

In summary, the most important FC-IRV connections are present in various subsamples of the data, regardless of head motion.

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7.4   Experimental Information

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Alcohol Study
Alcohol drinkers Welcome!

You receive €20 for participating + €10 max receipted travel!
This study involves a non-invasive EEG & questionnaires

How to participate: Text/Ring **0852851333**

*Email **laohallo@tcd.ie***

Participant ID: _____

Please Circle: Smoker / Non-smoker

	PLEASE CIRCLE	
Have you ever been in an accident during which you suffered blunt force trauma to the head?	YES	NO
Have you ever had a stroke?	YES	NO
Do you have Receptive Language difficulties?	YES	NO
Do you ingest/smoke cannabis regularly (twice a month)?	YES	NO
Do you currently or have you previously had an alcohol problem?	YES	NO
Do you currently or have you previously had a drug problem?	YES	NO
Do you have a learning disability? (e.g. dyslexia)	YES	NO
Have you ever been diagnosed with any general and/or specific intellectual disability?	YES	NO
Have you ever been diagnosed with a mental illness? (e.g. major depressive disorder or personality disorder)	YES	NO
Do you have a physical disability, which you feel might negatively affect your performance in this study? (e.g. motor impairment)	YES	NO

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Consent Form

I confirm that I have read the information sheet and understand:

	Please tick
What my participation involves	
That my privacy will be respected by anonymous data storage	
That I am free to withdraw from the study before and during data collection	
That once my data is collected, I cannot withdraw my data	
That I must be between 18-30 years of age to participate	

I consent to:

Completing the questionnaires outlined in the attached information sheet	
Taking part in a battery of computer-based tasks outlined in the attached information sheet	
Taking part in the EEG component of the study	
Having my physiological responses measured	
Having my anonymised data archived indefinitely and used for future research and publications	

I also confirm that any questions I had about the research have been answered	

For UCD students:

That my studies in TCD will not be affected by my participation/non-participation	

Name (PLEASE PRINT): _____

Signature: _____ Date: _____

Information Sheet

Study Title: Identifying risk and resilience factors for patterns of alcohol misuse in young adulthood

Thank you for expressing interest in participating in this research being conducted by Dr. Robert Whelan (Principal Investigator) and Laura O'Halloran (PhD candidate).

What is this research about? This study aims to identify risk and protective factors for particular patterns of problematic alcohol use, such as binge drinking, in young adulthood. This will allow us to examine factors that might either constitute a risk for developing alcohol dependence, or might protect people from becoming addicted to alcohol.

Am I eligible to participate in this research? You are eligible to participate in this study if you are between 18 and 30 years old. However, we may not use your data under the following circumstances:

- History of traumatic brain injury and/or stroke.
- Dependence on substances other than nicotine.
- Diagnosis of a mental health disorder
- Receptive language difficulties
- Learning disability
- General and/or specific intellectual disability
- Physical disability, which you feel might negatively affect performance in this study (e.g. motor impairment).

If the experimenter becomes aware of such circumstances during the assessment, your participation in the study will unfortunately no longer be possible.

What are the benefits of taking part in this research study? Your willingness to participate in the study would represent an important contribution to the study of alcohol consumption patterns in young adults. You would help the researchers gain a better understanding of the characteristics of individuals who binge drink and the psychological changes that occur when people binge drink. Furthermore, a benefit of participating in this research is gaining insight into your own drinking levels and gaining awareness of health and safety in terms of alcohol use.

What is involved if I agree? You will arrange a time with the researcher to participate in the

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study in a psychology lab room in Trinity College Institute of Neuroscience (see map provided). You will be asked to provide some background information, carry out some psychological questionnaires, and tell us about your experience with alcohol, nicotine and other drug use. Following this, you will complete computer-based tasks while having your brain activity recorded using electroencephalography (EEG). EEG is a safe method of measuring electrical activity in the brain, and poses no risk to you as a participant. Your physiological arousal will also be measured through use of two electrodes placed on your fingers to measure skin conductance, and a heart rate monitor. Participation in this study will take about 2 hours 30 mins, with a break in between.

What are the risks of taking part in this research study? If you decide to volunteer in the study, you will participate in a wide range of assessments. There is a possibility that you may experience feelings of fatigue, frustration, anxiety or distress. However, the risks you will encounter during the study will not exceed ordinary day-to-day risks. In addition, we will minimize any social or an emotional risk to you by ensuring your data is confidential and stored anonymously. Should something in the study upset you, please take note of the following supportive listening services:

Samaritans provide immediate support for anyone.
     Free phone: 116 123
     Website: www.samaritans.org
Niteline is a listening, support and information service run by and for the students of UCD, TCD,
     DCU, NUIM, NCAD, RCSI and their affiliate colleges. It is open during term from
     9:00pm – 2:30am.
     Free phone: 1800 793 793
     Online Listening: http://www.niteline.ie/onlinelistening.php
AWARE is a support services for people who are affected by stress and depression.
     Telephone 01-661 7211.
     Email: info@aware.ie
Alcoholics Anonymous is a support service for people with alcohol issues.
     Telephone 01-8420700
     Email: gso@alcoholicsanonymous.ie

How will my data be used? The data generated from this study will be used to learn more about the risk and resilience factors associated with alcohol consumption. The data collected will be used for presentations conferences and published in peer reviewed journals, however all data used will be anonymous.

Can I withdraw from the study? You have the right to withdraw from the study at any time during testing and also have the right to request a break. However, once your data has been collected you will no longer be able to withdraw your data from the study because the file connecting your name and the code assigned to you will be destroyed two weeks following data collection. Therefore, following this initial two-week period, your data will be unidentifiable.

 You may withdraw from the study before or during the assessment by informing the experimenter that you no longer wish to take part. Once your data is collected (i.e. anytime after the assessment is completed), you will not we will not be able to withdraw you data from the

study. Your data will remain identifiable for a two week period following your participation in order to contact you if mental health issues arise in your data and following this period, your data will be de-identified. If you exhibit severe levels of depression, anxiety or stress, indicate serious alcohol issues or indicate mental health issues following your data collection, you will be contacted by email in the first week after testing and advised to contact your G.P. You can also contact an alternative free option, St. Patrick's Support & Information Service, which is a telephone and email service staffed by experienced mental health nurses 9-5 Monday to Friday with an answering and call-back facility outside hours. You can contact the Support & Information service by calling 01 249 3333, or emailing your query to info@stpatsmail.com.

How will my privacy be protected? Your data will remain identifiable for a two week period following your participation in order to contact you if any mental health issues arise in your data. A unique, random code will be assigned your data. This code will be connected your name and dated in a locked electronic file, separate from the test data. This data will be stored on a password-protected computer. The file connecting your name and the code assigned to you will be destroyed two weeks following data collection. Therefore, following this two week period, your data will be unidentifiable.

However, if the researcher strongly believes that there is a serious risk of harm or danger to either the participant or another individual, or if a serious crime has been committed, it may be necessary for them to reveal some of what you tell them to third parties even without your permission.

How Can I find out what happens with this research? If you would like to find out what happens with this research, you can contact the researcher listed below.

If Any Issues arise for you during the Study: Just in case that did bring up anything you might want to talk about further we have some contact numbers for support services here. We give them out to everyone. Feel free to use them as you see fit. You are also advised to contact your G.P. if you feel that any serious issues arise. You can also contact an alternative free option, St. Patrick's Support & Information Service, which is a telephone and email service staffed by experienced mental health nurses 9-5 Monday to Friday with an answering and call-back facility outside hours. You can contact the Support & Information service by calling 01 249 3333, or emailing your query to info@stpatsmail.com.

Your data will be identifiable for two weeks following study participation, in order to contact you if mental health issues arise in your data (i.e. if you score in the severe range for depression, anxiety and/or stress).

Payment: You will receive €10 for your participation, as well as up to €10 maximum for travel expenss (with a receipt) for coming into Trinity College on the day of participation will be reimbursed to you by the experimenter.

Contact Details:
If you have any further questions about the study, you can contact:

Dr. Robert Whelan: Robert.whelan@gmail.com
Trinity School of Psychology
Scoil na Síceolaíochta

VISITOR MAP

1 Book of Kells
2 Trinity Tours
3 Zoological Museum
4 Science Gallery
5 The Douglas Hyde Gallery
6 Arts Café
7 Buttery Restaurant
8 Hamilton Restaurant

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Debrief

- Your participation may help researchers gain a better understanding of the characteristics of individuals who binge drink. As well as gaining insight into your own drinking levels and gaining awareness of health and safety in terms of alcohol use.
- Your data will remain identifiable for a two week period following your participation in order to contact you if any mental health issues arise in your data.

List of Support Services for Participants

If you have been affected by any of the issues raised in this study, here is a list of Ireland's many dedicated help-lines. We give them out to everyone. Feel free to use them as you see fit:

Niteline
http://www.niteline.ie
Niteline is a free-phone, confidential, non-judgmental helpline run by and for students, and are there to help with any issues. Phone Niteline between 9pm and 2:30am every night of term on 1800 793 793, or alternatively you can instant message Niteline at http://www.niteline.ie/onlinelistening.php

Aware
http://www.aware.ie
Aware provides face-to-face, phone and email support for individuals who are experiencing depression, anxiety and related mood disorders, as well as for friends and families who are concerned for a loved one. The Aware Lo-Call Helpline is open 7 days from 10am -10pm on 1890 303 302. Aware's e-mail support service is open from 9 -5 Monday to Friday on wecanhelp@aware.ie

Samaritans
http://www.samaritans.org/
Samaritans is a phone service that is available 24 hours a day to provide confidential emotional support for people who are experiencing feelings of distress, despair or suicidal thoughts. You can free phone the Samaritans on: 116 123

Alcoholics Anonymous is a support service for people with alcohol issues.
Telephone 01-8420700
Email: gso@alcoholicsanonymous.ie

St. Patrick's Support & Information Service
A telephone and email service staffed by experienced mental health nurses 9-5 Monday to Friday with an answering and call-back facility outside hours. You can contact the Support & Information service by calling 01 249 3333, or emailing your query to info@stpatsmail.com

If you feel you suffer from a mental health problem, please speak to your GP. Trinity College students can make an appointment with a doctor in Trinity by emailing the Student Health Service on healthp@tcd.ie. Please note a consultation will cost €20.