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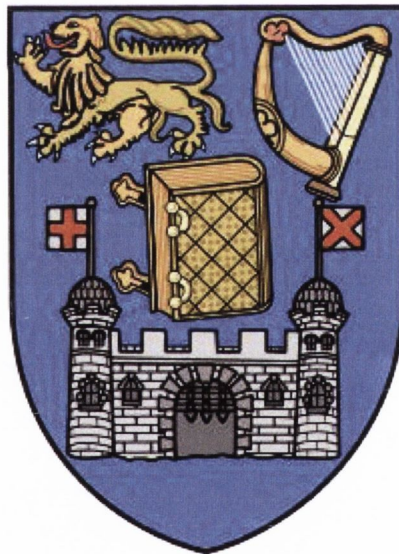
Social Cognition in Borderline Personality Disorder - An MRI Investigation

A thesis submitted to the University of Dublin for the degree of

Doctor of Philosophy

by

Arun Ambrose D'Souza



Trinity College, March 2013

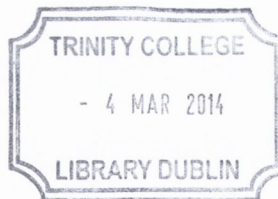
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Summary

There is increasing evidence for subtle changes in brain morphology and function in patients with borderline personality disorder (BPD). The four study arms in this thesis seek to investigate the differences in personality, brain structure, and functional connectivity, behavioural and neural responses to Theory-of-Mind (*ToM*) stimuli.

The *Psychometric Assessment* used questionnaires and a structured clinical interview to compare a sample of diagnosed BPD patients and a sample of healthy control participants matched for age and gender. Differences were found all of the personality traits that are characteristic for BPD. In particular, patients scored higher on scales measuring depression, anxiety, negative affect, neuroticism, and gelotophobia, the latter being a novel finding.

The aim of *Study 1* was to investigate neurocognitive correlates of *ToM* reasoning in healthy participants and their relationship with a measure of Neuroticism: Nineteen participants performed a cognitive task while undergoing functional MRI. The task was to watch and respond to visual jokes that were presented in the form of cartoon pictures. Three different types of cartoons were presented as the independent variable: 1) cartoons containing a residual semantic incongruity that remained unresolved (INC), 2) cartoons in which a residual incongruity was resolved by a 'punch line' in a meaningful way (PUN), 3) cartoons in which in order to get the punch line participants had to apply a Theory-of-Mind (TOM). Statistical analysis of functional MRI scans revealed differences in the temporo-parietal junction (TPJ) and supratemporal sulcus (STS) for mental processing of TOM cartoons vs. *non*-TOM cartoons. Further, activity the left inferior frontal lobe was linearly related to neuroticism scores during *ToM* reasoning.

Study 2 looked for functional brain changes between nineteen healthy individuals and seventeen patients with BPD in the above cognitive paradigm. Differences were found in STS, temporal lobes and the precuneus for TOM versus *non*-TOM trials. The same 'social brain'-areas, however, showed increased neural activity in patients during trials in the (unresolvable) INC condition. Response times and accuracy indicated that BPD patients are impaired in processing Theory-of-mind tasks.

The analysis of functional coupling in *Study 3* revealed increased connectivity of the default mode network (DMN) with other parts of the brain (such as the inferior frontal lobe) in BPD patients compared to healthy controls suggesting that patients are dysfunctional in down-regulating the DMN during resting state. Decreased functional connectivity was found for patients compared to controls between the ACC and three brain areas involved in *ToM* processes; the left superior temporal, right mid cingulate cortex, and right supramarginal/inferior

parietal lobes. Increased functional connectivity was found in patients compared to controls between the precuneus as DMN seed and the left inferior frontal lobe, left precentral/middle frontal, and left middle occipital/superior parietal lobes.

Study 4 compared structural MR images of twenty-one BPD patients and twenty-one healthy controls using voxel-based morphometry (VBM). Reduced grey matter volumes for BPD patients were found in the hippocampus, orbito-frontal cortex, dorsolateral prefrontal cortex, and the caudate nucleus. No volume reductions were found in the amygdalae. The study reaffirms the existence of hippocampal volumetric, prefrontal and caudate abnormalities in BPD and lends support to the stress-related explanation of these reductions, whilst also bringing new data to the topic in terms of the abnormalities found in the sub regions.

Conclusion: Reduced functional coupling between the emotional and the *ToM* network showed a dysfunctional or even lack of modulation of the *ToM* network from regions involved in emotion processing in line with emotion regulation dysfunctions in BPD.

Abbreviations

AAL – Anatomic Labelling Toolbox

ACC – anterior cingulate cortex

AC–PC – Anterior Commissure-Posterior Commissure line

ASD – Autism Spectrum Disorder

AS – Asperger Syndrome

BA – Brodman Area

BDI – Beck's Depression Inventory

BIS – Barratt Impulsiveness Scale

BPD – Borderline Personality Disorder

BOLD – Blood-Oxygen-Level-Dependent

DBT – Dialectic Behavioural Therapy

DLPFC – dorsolateral prefrontal cortex

DMN – default mode network

EPI – Echo Planar Imaging

EPQ – Eysenck Personality Questionnaire

fMRI – functional Magnetic Resonance Imaging

FWHM – Full-Width Half-Maximum

GM – grey matter

HDRS – Hamilton Depression Rating Scale

Abbreviations

HMRF – Hidden Markov Field

HRF – Haemodynamic Response Function

INC – residual incongruity (experimental condition)

LM – logical mechanism

MNI – Montreal Institute of Neurology

MPFC – medial prefrontal cortex

MP-RAGE – Magnetization-Prepared Rapid Acquisition Gradient-Echo

MSAT – Modified Social attribution task

OFC – orbito-frontal cortex

PANAS – Positive Affect Negative Affect Scale

PUN – ‘punch line’ (meaningful resolution, experimental condition)

PTSD – Post-traumatic Stress Disorder

RT – response time

SPM – Statistical Parametric Mapping (software)

SSS – Sensation Seeking Scale

STAI – State-Trait Anxiety Inventory

STCI – State-Trait Cheerfulness Inventory

STS – Supratemporal Sulcus

T_1 – spin-lattice-relaxation time

T_2 – spin-spin relaxation time

TE – spin-echo time

ToM – Theory-of-Mind (mental process)

TOM – Theory-of-Mind (experimental condition)

TPJ – temporo-parietal junction

TR – repetition time

VBM – voxel-based morphometry

VMPFC – ventromedial prefrontal cortex

WM – white matter

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Dedicated to my godchild Lea Anouk D'Souza

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Table of Contents

Declaration	ii
Summary	iii
Abbreviations	v
Acknowledgements	viii
Table of Contents.....	x
List of Tables.....	xv
List of Figures	xvi
1 General Introduction	19
1.1 Borderline Personality Disorder.....	19
1.1.1 Description and Epidemiology of BPD	19
1.1.2 Diagnosis and Psychopathology	22
1.1.3 Etiology of BPD	25
1.1.4 Genetics and Development	33
1.1.5 Neuroimaging in BPD	35
1.1.6 Treatment of BPD	39
1.2 Social Neuroscience and the Anatomy of Social Cognition.....	45
1.2.1 Theory of Mind	47
1.2.2 Mental states of others	52
1.2.3 Perspective taking	53
1.2.4 Empathy	55
1.2.5 Self and Emotion in the Brain	57
1.3 Social Cognition and BPD	59
1.3.1 ToM related symptoms	59

1.3.2	Behavioural studies in BPD	64
1.3.3	Neuroimaging studies of social cognition in BPD	69
1.3.4	Emotional arousal, BPD, and PTSD	70
1.4	Humour	71
1.4.1	Humour and Social Cognition	73
1.4.2	MRI studies using visual cartoons.....	74
1.5	Objectives	76
2	Overall Methods	78
2.1	Design	78
2.2	Participants.....	78
2.3	Psychometric assessment.....	80
2.3.1	Hamilton Depression Rating Scale (HDRS)	80
2.3.2	Beck's Depression Inventory (BDI)	81
2.3.3	Eysenck Personality Questionnaire (EPQ).....	81
2.3.4	Barratt Impulsiveness Scale (BIS)	83
2.3.5	Sensation seeking scale (SSS).....	83
2.3.6	Positive Affect Negative Affect Scale (PANAS).....	84
2.3.7	State-Trait Cheerfulness Inventory (STCI)	84
2.3.8	Gelotophobia-gelotophilia-katagelasticism (PhoPhiKat)	84
2.3.9	State-Trait Anxiety Inventory (STAI)	85
2.4	Stimuli	85
2.4.1	Incongruent Condition (INC)	86
2.4.2	Meaningful Resolution Condition (PUN).....	87
2.4.3	Theory-of-Mind Condition (TOM)	88
2.4.4	Rest Condition (NULL).....	90
2.5	fMRI task	90
2.6	MRI Data acquisition	92
2.7	MRI data analysis	93
2.8	Statistical power	93

2.9	Anatomic labelling	95
3	Psychometric Assessment	96
3.1	Introduction	96
3.2	Methods	98
3.3	Results	100
3.3.1	Hamilton Rating Scale for Depression (HDRS) and Beck's Depression Inventory (BDI)	100
3.3.2	Eysenck Personality Questionnaire (EPQ).....	101
3.3.3	Barratt Impulsiveness Scale (BIS)	102
3.3.4	Sensation seeking scale (SSS).....	103
3.3.5	Positive Affect Negative Affect Scale (PANAS).....	104
3.3.6	State-Trait Cheerfulness Inventory (STCI)	108
3.3.7	Gelotophobia-gelotophilia-katagelasticism (PhoPhiKat).....	109
3.3.8	State-Trait Anxiety Inventory (STAI)	110
3.4	Discussion	111
4	Neural Correlates of Humour Perception (<i>Study 1</i>).....	115
4.1	Introduction	115
4.2	Methods	121
4.2.1	Participants.....	121
4.2.2	fMRI task	122
4.2.3	Data Acquisition.....	123
4.2.4	fMRI pre-processing	124
4.2.5	SPM8 Statistical Analysis	125
4.2.6	Multiple Regression: Neuroticism	127
4.3	Results	127
4.3.1	Behavioural results	127
4.3.2	Imaging results	128
4.4	Discussion	137
5	Functional activity changes in BPD (<i>Study 2</i>).....	146

5.1	Introduction	146
5.2	Methods	149
5.2.1	Participants.....	149
5.2.2	Data Acquisition.....	150
5.2.3	fMRI task	151
5.2.4	fMRI Analysis.....	152
5.3	Results	153
5.3.1	Behavioural results	153
5.3.2	Imaging results	158
5.4	Discussion	164
6	Functional connectivity changes in BPD (Study 3).....	169
6.1	Introduction	169
6.2	Methods	173
6.2.1	Participants.....	173
6.2.2	Psychometric assessment	173
6.2.3	fMRI task	173
6.2.4	MRI Data Acquisition	174
6.2.5	Data analysis	175
6.3	Results	177
6.3.1	Default mode network.....	177
6.3.2	Affective network	179
6.4	Discussion	180
7	Structural brain matter changes in BPD (Study 4)	186
7.1	Introduction	186
7.2	Methods	190
7.2.1	Participants.....	190
7.2.2	Structural MRI acquisition sequence.....	191
7.2.3	VBM8 Pre-processing.....	192
7.2.4	DARTEL Toolbox.....	193

7.2.5 Extraction of grey matter volumes from VBM contrasts 194

7.3 Results 194

7.3.1 Socio-demographic and psychometric data 194

7.3.2 Morphometric data..... 196

7.4 Discussion 201

8 General Discussion 209

References 219

Appendix 261

List of Tables

Table 3-1: Demographic information	99
Table 3-2: Comparison of Eysenck Personality Questionnaire Ratings.....	101
Table 3-3: Comparison of Barrett Impulsiveness Scale Ratings.	102
Table 3-4: Comparison of Positive Affect Negative Affect– <i>General Dimensions</i> ratings.	104
Table 3-5: Comparison of Positive Affect Negative Affect– <i>Negative Emotion</i> ratings	105
Table 3-6: Comparison of Positive Affect Negative Affect – <i>Positive Emotion</i> Ratings.	106
Table 3-7: Comparison of Positive Affect Negative Affect– <i>Other Affective States</i> ratings.	107
Table 3-8: Comparison of State-Trait Anxiety Inventory ratings.	110
Table 4-1: Demographic and psychometric information of participants (<i>N</i> =19).	122
Table 4-2: Number of responses (NR) and response times (RT); (<i>N</i> =19).....	128
Table 4-3: Table of brain activities under each contrast.	129
Table 4-4: Table of activity differences for [TOM>INC] masked (incl.) by [PUN>INC].	134
Table 4-5: Table of brain activities from multiple Regressions (Neuroticism)..	136
Table 5-1: Demographic information.	150
Table 5-2: Table of activity differences (Pat>HC) under each contrast.	159
Table 5-3: Table of activity differences (Pat<HC) under each contrast.	159
Table 5-4: Table of activity differences for [INC>PUN]+[INC>TOM].	160
Table 5-5: Table of activity differences for [TOM>PUN]+[TOM>INC].	163
Table 6-1: Default mode network: Pat > HC, seed region: Precuneus.	178

Table 6-2: Connectivity changes PAT<HC for [TOM-NULL]; seed region: ACC 180

Table 7-1: Demographic information. 195

Table 7-2: Changes in grey matter corrected for brain regions of interest. 196

Table 7-3: Changes in white matter corrected for the whole brain. 200

List of Figures

Figure 1-1: The biopsychosocial model of borderline personality disorder 27

Figure 1-2: fMRI analysis in a task with Theory-of-mind items..... 52

Figure 1-3: Observation of biological motion elicits activity in STS..... 53

Figure 2-1: Eysenck chart. 83

Figure 2-2: Example of INC cartoon..... 87

Figure 2-3: Example of PUN cartoon. 88

Figure 2-4: Example of TOM cartoon..... 89

Figure 2-5: Time course of the fMRI task. 92

Figure 3-1: Ratings of Depression. 100

Figure 3-2: Interview and self-rating. 101

Figure 3-3: Personality ratings (EPQ). 102

Figure 3-4: Impulsiveness ratings. 103

Figure 3-5: Sensation seeking ratings..... 104

Figure 3-6: PANAS *General Dimensions*..... 105

Figure 3-7: PANAS Negative emotion..... 106

Figure 3-8: PANAS Positive emotion..... 107

Figure 3-9: PANAS Other affective states. 108

Figure 3-10: Cheerfulness ratings. 109

Figure 3-11: Laughter-related ratings.....	110
Figure 3-12: Anxiety ratings.	111
Figure 4-1: Flow diagram of the fMRI pre-processing steps.....	125
Figure 4-2: Statistical map of brain activity under for the contrast [TOM>PUN].	132
Figure 4-3: Statistical map of brain activity under contrast [TOM>PUN].....	133
Figure 4-4: Statistical map of brain activity for [TOM>INC] masked by [PUN>INC]......	135
Figure 4-5: Statistical map of brain activity for [TOM>INC] (Regressor: Neuroticism).	136
Figure 4-6: Statistical map of brain activity for the [TOM>PUN] (Regressor: Neuroticism).	137
Figure 5-1: Mean number of positive responses.....	154
Figure 5-2: Mean percentage of positive responses.....	155
Figure 5-3: Mean response times.....	156
Figure 5-4: Mean response times for positive responses.	157
Figure 5-5: Mean response times for negative responses.	158
Figure 5-6: Statistical map of brain activity for [INC>PUN]+[INC>PUN].	162
Figure 5-7: Statistical map of brain activity for [TOM>PUN]+[TOM>INC], Pat<HC.	164
Figure 6-1: Resting state network, (Pat+HC), seed region: Precuneus.	178
Figure 6-2: Resting state network: Pat > HC.....	179
Figure 6-3: Connectivity changes PAT<HC for [TOM-NULL].	180
Figure 7-1: Grey matter reductions in BPD patients (ROI: DLPFC) at [38 42 21].	197
Figure 7-2: Grey matter reductions in BPD patients (ROI: L OFC) at [38 45 -5].	198

List of Figures

Figure 7-3: Grey matter reductions in BPD patients (ROI:R Caudate) at [21 6 24].
..... 199

Figure 7-4: Grey matter reductions in BPD patients (ROI: R Hippocampus) at [21 -33 7]...... 199

Figure 7-5: Statistical map of white matter differences in BPD patients vs. healthy controls. 200

1 General Introduction

The last years of research have shown that not only emotion processing, but rather social cognition as a whole is of major relevance in a range of developmental and psychiatric disorders such as Schizophrenia, Autism Spectrum Disorder (ASD)/Asperger Syndrome and Borderline Personality Disorder (BPD). The present dissertation seeks to investigate the neural substrates of social cognition as evoked by a task that required processing of visual cartoons with functional magnetic resonance imaging (fMRI). The activity of the neural circuit in healthy subjects was then contrasted with the brain activity in BPD patients who had performed the same task in the scanner. The functional connectivity of emotion- and resting state networks was compared between the two samples. Further, the structural differences of brain tissue between the two groups are investigated in a voxel-based morphometry (VBM) study.

1.1 Borderline Personality Disorder

1.1.1 Description and Epidemiology of BPD

Borderline personality disorder (BPD) is a severe psychiatric disorder with high mortality. Data suggest that BPD affects from 1.2% to almost 6% of the general population, approximately 10% of those who seek outpatient services, and as many as 20% of those who undergo inpatient treatment (Grant et al., 2008). Earlier studies reported that BPD affects 1–2% (Skodol, Gunderson, Pfohl, et al., 2002; Torgersen, Kringlen, & Cramer, 2001) of the general population and the prevalence rises as high as 15–20% in psychiatric settings (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004).

Up to 10% of those who meet criteria for BPD eventually commit suicide, this rate is 50 times that observed in the broader population (American Psychiatric Association Practice, 2001). Thus, BPD is associated with tremendous emotional and financial burdens to

individuals, families, and society. In light of these costs, identifying precursors to the disorder must be a priority.

While in the population-based studies men and women are affected in equal proportion (Grant et al., 2008), the clinical population mainly consists of young women (Zanarini, Frankenburg, Hennen, Reich, & Silk, 2006). Skodol and Bender (2003) stated that BPD is diagnosed three times more often in females than in males but that the reasons for this distribution remain unclear. The ratio of 3:1 may be an artefact of selecting samples (Skodol & Bender, 2003).

The significance of the disorder can indirectly be inferred from studies on the making use of available therapies. Bender et al. (2001) showed that compared to depressive patients people suffering from BPD make significantly more use of both in-patient as well as out-patient psychiatric services. Some authors have estimated that, for example in the case of Germany, 15% of the total budget spent on treating psychiatric disorders is accounted for by BPD (Sanderson, Swenson, & Bohus, 2002).

Affective instability, impulsiveness, aggressive and auto-aggressive behaviour together with instability of interpersonal relationships and self-image are the core features of borderline personality disorder (APA, 1994). BPD manifests itself during late adolescence and early adulthood, causes significant social impairment and yields a lifetime suicide mortality of almost 10% (Skodol, Gunderson, Pfohl, et al., 2002). With regard to an etiological conceptualisation, a combination of inherited genetic predispositions and environmental factors are considered to be of fundamental importance (Skodol, Siever, et al., 2002).

With regard to scientific studies in biological psychiatry the *DSM-IV* offers a more precise description of diagnostic criteria for BPD compared to the international ICD-10. According to *DSM-IV* (American Psychiatric Association. & American Psychiatric Association. Task

Force on DSM-IV., 2000), BPD is manifested by a pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts.

The dominating and best discriminating features of BPD psychopathology can be described by four facets of psychopathological symptoms: affective disturbance, impulsivity, disturbed cognition, and intense unstable relationships (Lieb et al., 2004; Zanarini, Gunderson, Frankenburg, & Chauncey, 1990). For a more in-depth description see (Sabine C. Herpertz et al., 2007).

Affective disturbance in BPD is characterised by dysphoric affect, usually experienced as aversive tension, including qualitatively rather diffuse feelings of rage, fear, sorrow, shame, guilt and inner emptiness. Patients exhibit intense mood reactivity in the interpersonal realm, with frequently and rapidly changing affective states within one day. Impulsivity is reflected in different modes of more or less severe self-harm, self-injurious and suicidal behaviour, in particular, but also as disordered eating, substance abuse, reckless driving, wasting money, etc. Aggressive behaviour against others may also occur, with BPD being one of the most frequent personality disorders in forensic settings (Coid & Cordess, 1992). Manifestations of disturbed cognition are mostly non-psychotic and appear as overvalued ideas of being bad, as dissociative experiences of depersonalisation, derealisation and pseudo-hallucinations (i.e. patients recognise the delusional nature) (Zanarini, Gunderson, & Frankenburg, 1990). However, delusions and hallucinations may also occur, typically of transitory, circumscribed nature, often related to former traumatic experiences and usually occurring in the context of affective derangement (therefore called quasi-psychotic symptoms). Relationships are dominated by a profound fear of abandonment and by unpredictable changes between idealisation and longing for closeness at one time and arguments and sudden breakups at another (see 1.3.1).

1.1.2 Diagnosis and Psychopathology

The ICD-10 refers to the diagnostic category of *Emotionally Unstable Personality Disorder* with an 'Impulsive' and a 'Borderline' subtype. The 'Borderline' subtype is similar to the BPD DSM-IV definition, which consists of nine criteria, with the definite diagnosis requiring that five of these be met in addition to the general criteria of Personality Disorder:

1. Frantic efforts to avoid real or imagined abandonment. Note: Do not include suicidal or self-mutilating behaviour covered in (5).
2. A pattern of unstable and intense interpersonal relationships characterised by alternating between extremes of idealisation and devaluation. This is called "splitting."
3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). Note: Do not include suicidal or self-mutilating behaviour covered in (5).
5. Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour.
6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

Some authors (e.g. (Lieb et al., 2004) have categorised the above list of symptoms into four areas:

The first area is *affective disturbance* (DSM criteria 6, 7, 8). Patients with borderline personality disorder have a range of intense dysphoric affects, sometimes experienced as aversive tension, including rage, sorrow, shame, panic, terror, and chronic feelings of emptiness and loneliness. These individuals can be distinguished from other groups by the overall degree of their multifaceted emotional pain (Ludascher et al., 2010; Zanarini et al., 1998). Another aspect of their affective disturbance is their tremendous mood reactivity (Koenigsberg et al., 2002); patients often move from one interpersonally reactive mood state to another, with great rapidity and fluidity, experiencing several dysphoric states and periods of euthymia during the course of one day.

Second is *disturbed cognition* (criteria 3, 9). Patients show three levels of cognitive symptomatology (Zanarini, Gunderson, & Frankenburg, 1990):

- troubling but non-psychotic problems, such as overvalued ideas of being bad, experiences of dissociation in terms of depersonalisation and derealisation, and non-delusional suspiciousness and ideas of reference
- quasi-psychotic or psychotic-like symptoms — i.e., transitory, circumscribed, and somewhat reality-based delusions and hallucinations
- genuine or true delusions and hallucinations. The last category mostly happens in the context of psychotic depression (Zanarini, Gunderson, & Frankenburg, 1990). Serious identity disturbance is thought to be in the cognitive realm because it is based on a series of false beliefs—e.g., one is good one minute and bad the next (see also 1.3.1).

The third area is *impulsivity* (criteria 4, 8). Patients engage in two types: deliberately physically self-destructive and more general forms of impulsivity. Self-mutilation, suicidal communication, and suicide attempts are the constituent elements of the first type of impulsivity, and

common forms of the second are substance abuse, disordered eating, spending sprees, verbal outbursts, and reckless driving.

The fourth area is *intense unstable relationships* (criteria 2, 9), which are characterised by two separate but interlocking types of problem. The first is a profound fear of abandonment, which tends to manifest itself in desperate efforts to avoid being left alone, e.g. calling people on the phone repeatedly or physically clinging to them. The second is a tumultuous quality to close relationships, which are marked by frequent arguments, repeated break-ups, and reliance on a series of maladaptive strategies that can both anger and frighten others, e. g. highly emotional or unpredictable responses.

(But see also Arnoud Arntz and Haaf (2012) whose interview-based evaluations by BPD-patients could not be discriminated from non-patients in cognitive complexity. Their results indicate that dichotomous thinking, and not so much splitting, negativity, or less complexity, is central in the interpretation of others by BPD-patients.)

The aspects of inner pain and suffering, that play an important role in the experience of BPD patients, are not accounted for in the two major classification systems (Zittel Conklin & Westen, 2005). The tendency of BPD patients to react irrationally when confronted with emotional situations likewise is poorly appreciated according to Zanarini et al. (1998). This symptom together with the way of dichotomising the world into “completely good” and “completely bad” (commonly referred to as black-and-white thinking) is an indicator of the relevance of cognitive patterns for the disorder of BPD.

BPD is associated with negatively biased cognitive content that appears to differentiate people with BPD from people with other Axis II disorders. Specifically, evidence suggests that BPD is characterised by beliefs that the world and other people are hostile, untrustworthy, and dangerous; that others will reject and abandon; and that protective action is necessary to prevent negative interpersonal events. People with BPD

also tend to believe that the self is vulnerable, helpless, unlucky, and needs constant support from others; that it is best to respond to emotion by detaching from one's experience (Baer, Peters, Eisenlohr-Moul, Geiger, & Sauer, 2012).

The diagnosis of BPD is often complicated by the frequency of comorbidities. The emotional instability is often secondary to another mental disorder. According to a review by Skodol, Gunderson, Pfohl, et al. (2002) a proportion of 40-60% of patients with affective disorders also fulfilled the criteria for BPD. The spectrum of psychiatric comorbidities ranges from eating disorders, ADHD, and addictions to Obsessive-Compulsive Disorder (OCD) and Anxiety. On the other hand it is said by many clinicians that after carrying out the "The Structured Clinical Interview for DSM-IV Axis II (SCID-II)" a considerable proportion of patients fulfil the criteria for more than one personality disorder.

Among Axis I comorbidity, the highest prevalence rates are found for major depression, dysthymia, bipolar disorder, substance abuse disorders, posttraumatic stress disorder, social phobia, and eating disorders, while in terms of Axis II disorders, avoidant, dependent, and paranoid personality disorders are most frequently diagnosed (Sabine C. Herpertz et al., 2007).

1.1.3 Etiology of BPD

The course of BPD is less stable than expected for personality disorders (Leichsenring, Leibing, Kruse, New, & Leweke, 2011). The causes are not yet clear, but genetic factors and adverse life events seem to interact to lead to the disorder.

Linehan's biosocial theory of BPD (Fonagy & Bateman, 2008; 1993a) is among the most thoroughly delineated etiological models of borderline pathology (for other models, see Kernberg (1967); Fonagy, Target, & Gergely (2000); Judd & McGlashan (2003); and Fonagy & Bateman (2008)). According to Linehan, BPD is primarily a disorder of emotion dysregulation and emerges from transactions between individuals with

biological vulnerabilities and specific environmental influences. The dysfunction proposed by Linehan is one of broad dysregulation across all aspects of emotional responding. As a consequence, individuals with BPD have

- a) heightened emotional sensitivity,
- b) inability to regulate intense emotional responses, and
- c) slow return to emotional baseline.

Furthermore, from Linehan's perspective, the construct of emotion (and thus of emotion dysregulation) is very broad and includes emotion-linked cognitive process, biochemistry and physiology, facial and muscle reactions, action urges, and emotion-linked actions. Emotion dysregulation subsequently leads to dysfunctional response patterns during emotionally challenging events. Linehan suggested a number of possible biological substrates of emotional dysregulation (e.g., limbic dysfunction). However, the literature on the biology of psychological disorders was extremely limited when Linehan (1993b) first articulated her theory.

Neurobiological research suggests that abnormalities in the frontolimbic networks are associated with many of the symptoms. It is now widely accepted that biological components play a significant role in developing BPD. According to a biopsychosocial causal model an interaction between biological (e.g. temperamental) and psychosocial factors (e.g. adverse childhood events) provides the best explanation of how the condition develops (Gabbard, 2005).

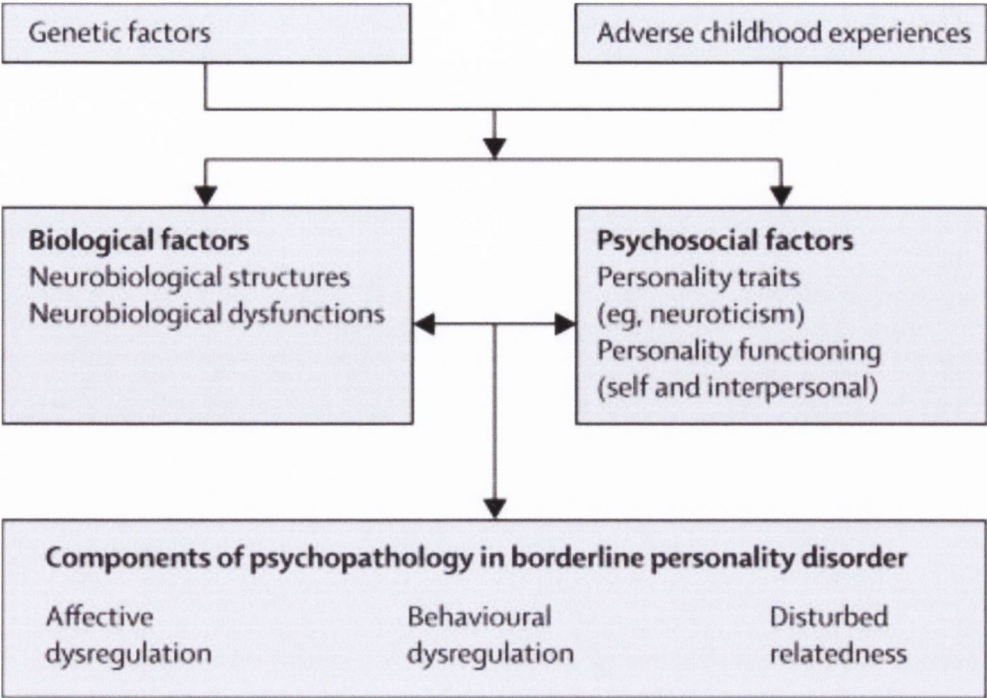


Figure 1-1: The biopsychosocial model of borderline personality disorder (from Leichsenring et al. (2011))

Figure 1-1 reflects Linehan’s (1993a) theory that the relation between psychopathology/emotion dysregulation and persistent cognitive, emotional, social, and behavioural outcomes is mediated by a history of increasingly more extreme and more disorganising emotional responses. When these reactions occur repeatedly over months and years, emotion dysregulation becomes trait-like and outcomes such as social isolation, hopelessness, sadness, shame, anger, and repetitive impulsive behaviours become canalised. These traits and behaviours, which likely first emerged in instances of extreme dysregulation, become increasingly frequent and reinforcing via their discovery as an emotion regulation and/or avoidance strategies. Early vulnerability interacts with learning history to shape and maintain dysregulated emotional, behavioural, interpersonal, and cognitive aspects of the *self* and thereby create the *borderline* personality.

A number of research articles have discussed potential causes and factors which may lead to BPD, though none has of yet produced any conclusive evidence in support of a single-cause theory. In fact, considering the heterogeneity of the disorder, it is more likely that a

combination of factors is involved in its manifestation; each to different degrees within individuals (Asnaani, Chelminski, Young, & Zimmerman, 2007; Wingenfeld, Spitzer, Rullkotter, & Lowe, 2010). The main postulated theories cite the experience of early life trauma (e.g., childhood abuse or maternal separation), genetics, neurobiological alterations, or a combination of the above as being responsible, at least in part, along with external factors such as environmental and psychosocial stressors, for the onset of BPD (Steele & Siever, 2010a).

Cloninger et al. (1993) proposed a psychobiological theory, including four dimensions of temperament and three dimensions of character. Initially, the model included only three temperament dimensions, i.e. Novelty Seeking (NS), Harm Avoidance (HA) and Reward Dependence (RD). The temperament dimensions were assumed to be independently heritable and to manifest early in development. Variation in each of the dimensions was supposed to be associated with monoaminergic activity (Cloninger, 1986): NS with low basal dopaminergic activity, HA with high serotonergic activity and RD with low basal noradrenergic activity (Stallings et al., 1996). The three temperament dimensions are defined in terms of individual differences in behavioural learning mechanisms, explaining responses to novelty, danger or punishment and cues for reward (NS), avoiding aversive stimuli (HA), and reactions to rewards (RD) (Cloninger, 1987). Cloninger developed the Tri-Dimensional Personality Questionnaire (TPQ; Cloninger 1987) cited in Ando et al. (2004)) to measure the three temperament dimensions. However, research with the TPQ has demonstrated that the former RD subscale 'Persistence', proved to be relatively independent of the former three temperament factors and was therefore proposed as an additional fourth temperament dimension. In order to more adequately represent individual differences, the four-dimensional model was extended to a seven-dimensional scheme, including three additional dimensions of character, i.e. Self-directedness (SD), Cooperativeness (CO) and Self-transcendence (ST). Self-directedness refers to the self-determination of the subject and it is conceptually related to Rotter's locus of control

construct. Cooperativeness accounts for traits characterising the interpersonal circumplex (cited in McCrae and Costa (1989)) and the Self-transcendence dimension refers to the experiencing of spiritual ideas. Cloninger (1993) assumed that character is less heritable than temperament and matures with age. A 15-step model of personality development (C Robert Cloninger, Adolfsson, & Svrakic, 1996), the so-called 'canonical sequence', has been described, linking personality development to stages in development distinguished by Piaget, Freud and Erikson (Gillespie, Cloninger, Heath, & Martin, 2003).

Risk Factors

Patients with borderline personality disorder (BPD) frequently report early, multiple, and chronic adverse or even traumatic experiences, such as repeated sexual or physical abuse or emotional or physical neglect (Golier et al., 2003; McLean & Gallop, 2003). It has been suggested that early life stress might be an important risk factor in the development of BPD (Driessen et al., 2002; McLean & Gallop, 2003) although this may not be the case in all BPD patients (Golier et al., 2003). However, early life stress/traumatisation is not a risk factor that applies exclusively to BPD, as traumatisation is also thought to confer higher risk for many other psychiatric, psychosomatic, and physical complaints (Goodwin & Stein, 2004; Heim et al., 2006) For example, it has been shown that women with a history of childhood sexual or physical abuse, compared with women without such adverse early life experiences, are more likely to exhibit symptoms of anxiety and depression and are more likely to meet criteria for the diagnosis of several DSM IV axis I and II mental disorders, such as major depressive disorder (MDD) or posttraumatic stress disorder (PTSD).

Bandelow et al. 2005) identified the following environmental factors to be associated with BPD:

- separation from one or both parents
- childhood sexual abuse

- alcoholism of one or both parents
- violence in family
- birth risk factors
- unfavourable parental attitude
- family history of neurotic spectrum disorders (first degree relatives)

Family environment and childhood trauma

Linehan (1993a) proposed that the development of BPD occurs in part due to an invalidating family environment. There are some prospective data to support the notion that emotional under-involvement by parents impairs a child's ability to socialise effectively. J. G. Johnson et al. (2002) found that children raised in such environments are at increased risk for engaging in suicidal behaviours and making suicide attempts, even after controlling for parental psychopathology. Despite the retrospective nature of nearly all studies relating abuse and self-injurious behaviours (Crowell, Beauchaine, & Linehan, 2009), results are remarkably consistent with those from a prospective study, suggesting that adolescents and young adults with an abuse history are about three times more likely to engage in suicidal behaviours than controls (Dube et al. (2001), cited in a recent meta-analysis by Norman et al. (2012)). Older findings from the literature on non-suicidal self-injury suggest that childhood trauma is a significant risk factor for the initiation of "self-destructive behaviour" (Green, 1978) but that a lack of secure attachment may maintain the behaviour. These findings are clearly relevant to the development of BPD.

A high correlation between childhood trauma and later development of BPD has been shown in numerous studies and it is generally accepted that such stressors are significant to the onset of the disorder, though the mechanisms involved are still under debate (R. A. Cohen et al., 2006). Abuse (physical and/or sexual) and neglect are common childhood experiences of adults with BPD, so, more than with other personality disorders. In one study, of the 358 BPD patients

participating, 91% reported experiences of childhood abuse and 92% reported experiences of childhood neglect; much higher rates than those found amongst the patients with other personality disorders (Zanarini et al., 1997). In a later study, Zanarini et al. (2002) found a significant correlation between the severity of the reported child abuse and/or neglect of 290 BPD patients and the overall severity of the disorder.

Over the years, an increasing number of attempts have been made to produce a more genetic explanation of BPD, though the research is still far overshadowed by studies examining the relationship of early life adversity and BPD. A commonly discussed topic is the heritability of BPD, which has produced a number of twin studies, sibling environment/adoption studies, and self-report measures, though the findings from this approach have been less than consistent. Self-report measures, involving BPD patients, usually support an argument for at least a partial heritability, however, it is important to be mindful of the subjective nature of these measures and note that their findings do not always correspond with the relevant behavioural data (Jacob et al., 2010).

BPD and emotional dysregulation

Emotional dysregulation is hypothesised to be a core feature of BPD (Lieb et al., 2004). It is shown to be of prognostic relevance for the development of a BPD and criterion 6 (affective instability) of DSM-IV is strongly related to it (Tragesser & Robinson, 2009). Emotional dysregulation is usually characterised by strong emotional reactivity. According to the prominent model of Linehan (1993a), emotions are said to be easily triggered in BPD patients, to rise quickly to an abnormally high level and to last longer than in healthy individuals. While emotional dysregulation is related to negative emotions in general, anger and rage are seen as prominent emotions in BPD (criterion 8 in DSM-IV).

Some studies show higher reactivity of negative emotions in BPD. Herpertz et al. (1998) showed higher self-rated scores over a broad range of emotions in response to an emotional short story in BPD patients compared with patients with avoidant personality disorder. Levine et al. (1997) found a more intense experience of negative emotions in BPD subjects than in non-BPD controls. Koenigsberg et al. (2002) reported increased self-reported affective lability for anger, anxiety, and oscillation between depression and anxiety in BPD subjects compared with other personality disordered patients, while self-rated affective intensity was not associated with BPD in this study. Arntz et al. (2005) found stronger increases in fear as a reaction to an emotional film in BPD patients as compared with healthy and Cluster C personality disordered controls. Different fMRI-studies have shown significantly increased amygdala activation in response to facial expressions of different emotions (Donegan et al., 2003) and to emotionally aversive pictures taken from the International Affective Picture System (IAPS) (S. C. Herpertz et al., 2001). In a field study with frequent measurement points, Stiglmayr et al. (2005) reported stronger self-rated aversive tension in BPD subjects and a stronger fluctuation of tension over time as compared with healthy controls. In a similar design, Stein (1996) found greater negative affect and more fluctuations in negative affect over time in BPD as compared with healthy controls and patients with anorexia nervosa.

Other studies report basically higher negative emotionality in BPD over all types of negative emotions, independently of the presence of actual emotional stimuli. BPD groups typically indicate high levels of trait anger (Linehan, Tutek, Heard, & Armstrong, 1994) and anxiety sensitivity (Gratz, Tull, & Gunderson, 2008). Rusch et al. (2007) found elevated state and trait shame and other negative emotions in BPD subjects as compared with healthy participants and to women with social phobia. In an experimental study on the evaluation of non-interpersonal emotional situations by Sieswerda et al. (2005), patients with BPD appeared to be characterised best by a generally negative evaluative style.

This is probably why patients diagnosed with BPD are known to score high on scales measuring Neuroticism (Distel et al., 2009; Grootens & Verkes, 2005). See *Introduction* (3.1) to *Psychometric Assessment*. Individuals who score high on Neuroticism are more likely than the average to experience such feelings as anxiety, anger, envy, guilt, and depressed mood (Yousfi, Matthews, Amelang, & Schmidt-Rathjens, 2004).

1.1.4 Genetics and Development

The study of candidate genes in BPD research has identified a number of genes of particular interest. Genes currently under investigation include the 7-repeat polymorphism of the dopamine D4 receptor (DRD4), which has been linked to disorganised attachment, while the combined effect of the 7-repeat polymorphism and the 10/10 dopamine transporter (DAT) genotype have been linked to abnormalities in inhibitory control, both noted features of BPD (Congdon & Canli, 2008; Friedel, 2004).

Previous BPD research had consisted mainly of studies exploring the psychological aspects of the disorder from characteristic behaviours to psychosocial triggers and risk factors, with early-life stress proving to be strongly associated with the occurrences of the disorder. In recent years, however, appreciation has increased dramatically for the neurobiological abnormalities which have been associated with dimensions of personality dysfunction, with findings from a number of studies confirming the biological underpinnings of the disorder (M. Foti et al., 2011; Goodman, New, & Siever, 2004). As incidents of early life trauma are so highly correlated with the occurrence of BPD, the disorder is quite often classed as being on a spectrum of trauma-related psychiatric disorders, of which post-traumatic stress disorder (PTSD) is the core (C. Schmahl & Bremner, 2006b).

Different cerebral systems have been related to emotional unstable personalities. Since the 1970's research has focussed on the

serotonergic system. It is known that impulsive as well as aggressive behaviour is related to a reduced serotonergic activity. The function of serotonin in this case is the modulation of inhibitory cortical structures (orbito-frontal cortex (OFC), medial frontal cortex (MFC), and cingulate cortex). It is believed that this reduction in serotonergic activity is related to a disinhibition of aggressiveness as serotonin metabolites were found in the cerebrospinal fluid (CSF) of auto-aggressive and suicidal patients alike (Skodol, Siever, et al., 2002).

It should be noted that the serotonergic neurotransmitter system has been implicated in a number of diagnostic conditions, including depressive disorders and obsessive compulsive disorder. Therefore, reduced serotonergic functioning does not appear to be specific to BPD.

In a PET study (by Oquendo et al., 2005) with clinically depressed (Major Depression, MDD) and patients who suffered from both MDD and BPD an alternated pattern of regional glucose (18-F-Desoxyglucose) uptake could be shown. An increased glucose uptake in temporo-parietal regions and a decreased uptake in ACC was recorded in patients with only BPD ($N=11$). In the second step of the experiment were given fenfluramine (an anti-obesity drug that exhausts the serotonergic system by causing the release of serotonin). This did not change the effect of BPD on temporo-parietal uptake whereas the effect in ACC was reversed (Oquendo et al., 2005).

Increased explorative and impulsive-aggressive behaviour (and, for some patients, productive-psychotic episodes) have also been related to increased dopaminergic activity although only very few studies exist that analysed dopamine metabolites in the CSF (see de Bruijn et al., 2006; Grootens & Verkes, 2005).

Affective instability and the tendency to develop anxiety symptoms have been related to the noradrenergic system. Skodol, Siever, et al. (2002) suggested a synergistic effect of the increased noradrenergic response

combined with the serotonin deficit that contributes to the development of BPD symptoms.

Recently, an altered activity of the oxytocin system has been discussed to play a prominent role in BPD, which is thought to be closely related to traumatic experiences in childhood and is characterised by (para)-suicidal behaviours as well as aggressive outbursts (Bertsch, Schmidinger, Neumann, & Herpertz). Oxytocin is known to reduce anxiety and stress in social interactions as well as to modulate approach behaviour. Evidence suggests that the amygdala might be the primary neuronal basis for these effects (Gregor Domes et al., 2007).

Using an EEG approach to investigate biological markers of brain development, Houston, Ceballos, Hesselbrock, and Bauer (2005) studied 123 female BPD patients between 14 and 19 years of age and found a decrease in the amplitude of event-related P300-potentials. The authors concluded a defect in brain maturation.

1.1.5 Neuroimaging in BPD

Neuroimaging research exploring neurobiological abnormalities in PTSD has provided the building blocks for similar research in BPD, with the methodologies used in PTSD neuroimaging studies such as volumetry of different brain regions frequently transferred to studies in BPD; these methodologies themselves often originating in other better researched areas including Schizophrenia and Alzheimer's disease (C. Schmahl & Bremner, 2006a).

From a neurobiological perspective, the failure of frontolimbic functions has been linked to the core elements of the psychopathology of BPD, like impulsivity, emotional instability and impulsive aggression (Rusch et al., 2003). It has been postulated that emotional dysregulation is the key feature of BPD and predisposes individuals to the emotional disinhibition and impulsive aggression responsible for many of the volatile behaviours seen in patients (P. A. Johnson, Hurley, Benkelfat, Herpertz, & Taber, 2003). In this context, it has been suggested that

emotional dysregulation in patients with BPD is caused by prefrontal deficits or hyperactivity of the limbic system or a combination of both (S. C. Herpertz et al., 2001). Prefrontal deficits lead to a failure to control negative emotions (top-down modulation) and heightened activity in the limbic system leads to disordered emotional behaviour (bottom-up modulation).

The conceptualisation of frontolimbic dysfunction in BPD resulted in a number of imaging studies using different imaging methods (Lis, Greenfield, Henry, Guile, & Dougherty, 2007).

Structural Imaging

Initial structural MRI studies revealed volume reductions in the frontal lobe (Lyyo, Han, & Cho, 1998a), the left orbito-frontal cortex (OFC, Hazlett et al., 2005b) and right parietal cortex (E. Irle, C. Lange, & U. Sachsse, 2005). Reductions in grey matter volume have also been found in frontal, temporal and parietal cortices in men with BPD (Vollm et al., 2009b). Conversely, in another structural MRI study using voxel-based morphometry (VBM, Rusch et al., 2003) no group differences between patients with BPD and healthy control subjects could be found in the frontal lobe.

With regard to limbic structures conflicting results have been reported (Lis et al., 2007). In structural MRI studies (Driessen et al., 2000a; C. G. Schmahl, Elzinga, et al., 2003), reduced volumes (16%) of the hippocampus in both hemispheres have been found in BPD patients compared to healthy controls (Gabbard, 2005). Overall, the hippocampus was the region most consistently found to display alterations in BPD patients. The hippocampus plays an important role in memory consolidation, declarative memory, and is highly sensitive to the effects of stress, with stress-related increases in glucocorticoid levels being associated with smaller hippocampal volumes in animal studies (Brambilla et al., 2004b). It has been suggested that volumetric reductions of the hippocampus, the most frequently produced result in

human studies, may lead to the neurocognitive deficits, dissociative symptoms, perceptual distortions, and identity instability seen in BPD patients (Brambilla et al., 2004b).

Although the reductions in regions of the brain known to play important roles in emotional regulation, processing, and other functions usually impaired in individuals with BPD are largely accepted, it is worth noting again that reductions in the hippocampus, amygdala, and ACC are not specific to BPD. Reductions in these areas have also been shown in trauma-exposed individuals, both with and without psychiatric disorders (most commonly PTSD and MDD) (L. R. Cohen & Hien, 2006; MacQueen & Frodl, 2011) and in the same neural structures of nonhuman primates that have experienced early life stress (H. Cohen, Matar, Richter-Levin, & Zohar, 2006). However in the human studies, the magnitude of these reductions is generally greater in those with the psychiatric disorders than in those without. As these structural abnormalities are not specific to BPD, Wingenfeld et al. (2010) suggested that these findings in BPD patients support the theory that early life stress does indeed have a damaging effect in certain brain regions. However, the exact cause of the volume reductions observed and whether the high incidence of BPD patient comorbidity with PTSD and MDD is due predominantly to trauma-related aspects of the disorder remain to be seen. It is further important to acknowledge at this point that the depth of the interaction between traumatisation and other factors such as familial/genetic factors, environment, and pharmacological intervention on long-term neurobiological changes as yet is not well understood (Bremne & Vermetten, 2001; Kaufman & Charney, 2001).

With regard to the amygdala, in adult patients with BPD compared with healthy controls, three studies found increased amygdala volumes (Driessen et al., 2000a; C. G. Schmahl, Elzinga, et al., 2003; Ludger Tebartz van Elst et al., 2003) while two found decreased amygdala volumes (Brambilla et al., 2004b; Rusch et al., 2003). One VBM study

found higher relative grey matter concentration in the amygdala compared to a group of healthy control subjects (Minzenberg, Fan, New, Tang, & Siever, 2008b). Another study revealed that only patients with both BPD and a comorbid diagnosis of major depression demonstrated a larger amygdala volume in both hemispheres compared with those without major depression (Zetsche, Frodl, Preuss, Schmitt, Seifert, Leinsinger, Born, Reiser, Möller, et al., 2006).

Two studies reported structural changes in adolescents with BPD (Chanen et al., 2008b; Whittle et al., 2009b) where volumetric changes in cortical and subcortical structures have been reported in adolescents with BPD using manual tracing of multiple regions of interests (ROIs). Compared with healthy controls, adolescent patients with BPD demonstrated grey matter reduction in the right orbito-frontal cortex. Hippocampal or amygdala volumetric differences could not be detected. In a subsample of 15 female adolescents with BPD of this former sample (Chanen et al., 2008b), a decrease in volume of the left anterior cingulate cortex (ACC; Whittle et al., 2009b) as well as a shorter adhesio interthalamica (Takahashi et al., 2009) could be revealed in comparison with healthy controls. Recently, R. Brunner et al. (2010) confirmed their findings of reduced grey matter in adolescents with BPD for the orbito-frontal cortex but not for the amygdala.

Functional Imaging

Recently, O'Neill and Frodl (2012) reviewed the literature on brain structure and function in BPD. The most common finding amongst functional MRI studies is that of exaggerated activity in the amygdala of patients with BPD compared to controls during procedures that involve the processing of emotionally aversive stimuli (Donegan et al., 2003; S. C. Herpertz et al., 2001; Minzenberg, Fan, New, Tang, & Siever, 2007). Of particular interest is an emotional linguistic study by Silbersweig et al. (2007) which examined the brain function of BPD patients compared to controls under conditions associated with the interaction between behavioural inhibition and negative emotion. In the study, a significant

reduction in activity was seen in the ventromedial prefrontal cortex (including the medial OFC and subgenual ACC) in the BPD patients compared to controls.

A strong correlation was found between decreasing ventromedial prefrontal activity and decreasing constraint (impulsivity), whilst a strong correlation was also found for increased amygdala ventral striatal activity and increased negative emotions in the patients (Silbersweig et al., 2007); impulsivity and the experience of exaggerated negative emotions being diagnostic features of the disorder.

1.1.6 Treatment of BPD

The American Psychological Association (APA) Guidelines for the treatment of BPD recommend a symptom targeted approach (APA 2001). Based on a comprehensive review of evidence-based and 'best practice' treatment strategies in BPD, psychotherapy was designated as the primary treatment, with pharmacotherapy recommended as an adjunctive, symptom-targeted component of treatment. Specific algorithms were developed which were related to three main symptom clusters of BPD:

- cognitive-perceptual symptoms
- affective disturbance, and
- impulsive-behavioural dyscontrol.

Low-dose neuroleptics were recommended as first-line treatment for cognitive-perceptual symptoms. For affective disturbance, selective serotonin reuptake inhibitors (SSRIs) or related antidepressants were recommended, with switch to a second SSRI or other antidepressant in the case of nonresponse. SSRIs were also reported as the first-line treatment for impulsive-behavioural dyscontrol followed by a change to or adding a low-dose neuroleptic if treatment response is not sufficient.

Pharmacotherapy

Following the Cochrane criteria, evidence for the pharmacological treatment of BPD was reviewed in 2006 (Binks et al.); only ten small randomised controlled trials (RCTs) were identified. The authors concluded that evidence for the pharmacological treatment of BPD was poor.

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Personality Disorders (2007) classified and evaluated four categories of pharmacological approaches to the treatment of BPD which showed at least some evidence of symptom improvement:

- Antidepressants: Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and irreversible monoamine oxidase inhibitors (MAOIs)
- Neuroleptics: aripiprazole, clozapine, olanzapine, risperidone, ziprasidone
- Mood stabilisers: carbamazepine, divalproex sodium, topiramate, lamotrigine
- Other pharmacological approaches: omega-3 fatty acids, clonidine, naltrexone (opiate antagonist), benzodiazepines (strongly discouraged for BPD).

Studies in BPD are based on rather small samples of mostly outpatients and not on inpatients that have more current co-occurring disorders. Thus, the level of evidence is generally limited for inpatients (for a comprehensive review see Herpertz et al. (2007)). Moreover, studies are hampered by high drop-out rates because of difficulty in keeping patients with borderline personality disorder on medication for sustained periods. In several psychosocial and pharmacological treatment (reviewed in Lieb et al. (2004)) trials only female patients were investigated making generalisation of effects to male patients difficult.

The benefit of a combination of pharmacotherapy and psychotherapy in BPD is unclear to date. Fluoxetine combined with Dialectical Behaviour Therapy (DBT, see Psychotherapy) provided no additional benefit compared with DBT plus placebo (Simpson et al., 2004). In a study by Soler et al. (2005) study, olanzapine added to DBT provided an additional benefit compared with DBT alone, although no differences were reported in another study in favour of the combined treatment (Linehan, McDavid, Brown, Sayrs, & Gallop, 2008). The combination of interpersonal therapy and fluoxetine was superior to fluoxetine plus clinical management (Bellino, Zizza, Rinaldi, & Bogetto, 2006).

Psychotherapy

The three main forms of psychological treatment of BPD are

- Dialectical Behaviour Therapy (DBT)
- Schema-focused therapy (SFT)
- Mentalization-Based Treatment (MBT) and

DBT and schema-focused therapy are based on psychodynamic principles; MBT and is based on cognitive-behavioural (CBT) principles (for a review and comparison of recommended psychotherapies see Clarkin and Levy (2006) and S. C. Herpertz et al. (2007)).

DBT was developed by Linehan (1993b). It is one of the psychosocial interventions developed specifically for the treatment of BPD and has been proven effective in several well-controlled clinical outcome studies (Bohus et al., 2004; McMain et al., 2009; Verheul et al., 2003). All previous studies have shown that DBT treatment consistently achieves clinical improvement, predominantly indicated by a decrease in self-harming and (para-)suicidal behaviour, less time spent in hospital, lower depression and hopelessness and higher overall social functioning (Verheul et al., 2003).

The standard DBT procedure (Linehan, 1993b) includes four modes of intervention: group therapy, individual psychotherapy, phone calls, and

consultation team meeting. The group component consists of approximately 2 hours a week of skills coaching, aiming at increasing behavioural capabilities, an approach that has already been used alone (Soler et al., 2009). These skills are divided into four modules: *Interpersonal Effectiveness*, *Emotion Regulation*, *Distress Tolerance* and *Mindfulness*. Lindenboim, Comtois, and Linehan (2007) examined the type and frequency of skills practiced by patients with DBT. Their study found that mindfulness skills, along with Distress tolerance skills, were the most commonly practiced by the patients in standard DBT treatment (Lindenboim et al., 2007).

SFT is based on a cognitive–integrative conceptualization of personality disorders using a broader and more eclectic approach than the usual cognitive therapy approaches, integrating various theoretical formulations (Young J, Klosko J, & M, 2003). The therapy targets the establishment of a working relationship through emphasising the patient's emotions and bonding issues. By specific interventions such as limited re-parenting combined with experiential techniques on adverse childhood interpersonal experiences the patient learns to contain and endure the negative effects of abandonment and despair. In the therapeutic model, the schema mode change is emphasized, where the patient learns to deal with his or her various modes (abandoned child, angry child, punitive parent and detached protector) through experiential techniques and the therapy relationship. By working with a modification of schema modes and maladaptive coping styles the patients are treated for periods of one to four years (Young J et al., 2003). Schema-focused therapy (SFT) retains a cognitive theoretical framework, and suggests that personality disorders result from early maladaptive schemas that interfere with the individual's ability to meet his or her core needs. Matusiewicz et al. (2010) reviewed the empirical support from 1999 to 2009 for cognitive therapies (of which SFT is one) and concluded that that CBT in general is an effective treatment modality for reducing symptoms and enhancing functional outcomes among patients with personality disorders.

However, they also expressed the need for further development and evaluation in order to provide specific and more unambiguous treatment recommendations.

MBT derives from the attachment and cognitive theory and hypothesises that early attachment difficulties have led to impairments in the capacity of BPD patients to mentalize, in other words, to be aware of and understand their own and others' mental states. The therapy focuses on increasing mentalizing capacities to achieve stability of affect and impulses (A. Bateman & Fonagy, 2010). MBT has been found to be superior to Treatment as Usual (TAU) in two trials conducted by the developers of MBT (A. Bateman & Fonagy, 2009) where suicidality, para-suicidality, interpersonal problems and depression were significantly reduced with very large effects (Stoffers et al., 2010). A recent random controlled trial (RCT), conducted by an independent team, found no evidence for superiority of MBT above a less intensive control treatment, supportive group therapy offered once every two weeks (Jorgensen et al., 2012).

Mentalization is the process by which we implicitly and explicitly interpret the actions of ourselves and others as meaningful on the basis of intentional mental states (e.g., desires, needs, feelings, beliefs, and reasons). The capacity develops during childhood within the context of an attachment relationship. It is suggested that the borderline patient shows a reduced capacity to mentalize and that this has resulted from disruption of the attachment relationship because of adverse interaction between biological and environmental factors (A. W. Bateman & P. Fonagy, 2004).

Patients with BPD have vulnerability in regulating emotional responses and generating effective strategies for controlling their thoughts and feelings, which challenges their capacity for thinking about their own actions in terms of subtle understandings of their thoughts and feelings (see 1.1.1). They slip into what A. W. Bateman and P. Fonagy (2004) described as a kind of mindless state, both in relation to others and to

themselves. However, things are more complicated, because these incapacities, palpable at certain times, are not always evident. But, at moments of emotional distress, particularly distress triggered by actual or threatened loss, the capacity for mentalization is most likely to apparently evaporate.

The initial task in MBT is to stabilize emotional expression, because without improved control of affect there can be no serious consideration of internal representations (A. W. Bateman & P. Fonagy, 2004). MBT assumes that it is uncontrolled that affect leads to impulsivity, and only once this affect is under control it is possible to focus on internal representations and to strengthen the patient's sense of self (A. Bateman & Fonagy, 2010).

In a recent evaluation of their treatment model the authors themselves (2010) themselves recommended that in MBT the therapist's mentalizing therapeutic stance should include:

- humility deriving from a sense of “not knowing”
- patience in taking time to identify differences in perspectives
- legitimising and accepting different perspectives
- actively questioning the patient about her experience – asking for detailed descriptions of experience (“what questions”) rather than explanations (“why questions”)
- careful eschewing of the need to understand what makes no sense (i.e., saying explicitly that something is unclear).

Patients with borderline personality disorder usually start their treatment meeting criteria for multiple axis I disorders, which vary over time in their severity and urgency. Effective treatment, therefore, integrates the full range of evidence-based behavioural treatments for axis I disorders. However, maintenance of a consistent focus on multiple serious maladaptive behaviour patterns without frequent changes in priorities can be difficult. With the more severe patients, in particular, the clinician must engage the patient in setting clear and explicit goals for therapy,

prioritise their importance, and adhere to these treatment targets. Both DBT and MBT treatments are multimodal; every modality of treatment targets a specific aspect of the patient's overall difficulty. In DBT, the individual psychotherapist serves as the primary therapist managing, with the patient, the application of other treatment modalities. These treatments also balance the focus on change and the patient's responsibilities to actively engage in problem solving, with a corresponding focus on empathy, validation, and active therapeutic support. Finally, both treatments provide support for the therapists treating the patient.

Patient personality can play an important role during the therapeutic process, leading to better clinical outcomes. Recent research has shown that BPD patients with higher levels of trait Agreeableness undergoing DBT exhibited better clinical outcomes than other patients either low in Agreeableness or not being treated with DBT. This association was mediated through the strength of a working alliance between patient and therapist; that is, more Agreeable patients developed stronger working alliances with their therapists which in turn led to better clinical outcomes (Hirsh, Quilty, Bagby, & McMain, 2012).

1.2 Social Neuroscience and the Anatomy of Social Cognition

Social interaction involves bi-directional processes: individuals are emitters and recipients of social signals. The function of adequately perceiving and processing social signals (consciously or unconsciously) has been referred to as social cognition (C. D. Frith & Frith, 2007). The outcome of this process depends upon the interpretation of social signals. Thus, social cognitive skills are necessary for successful social interactions and they allow humans to establish and maintain, short- and long-term relationships with significant others.

Social cognition refers to cognitive-emotional processes about ones' self and others and includes various aspects such as theory of mind

(*ToM*), action observation and understanding, emotion processing, attribution style and agency judgments. It therefore relies on the successful integration of social, emotional, cognitive and self-referent information. The social cognition construct, originating in the late early 1970s, provides a broad theoretical framework that focuses on how people process information within social contexts (Penn, Sanna, & Roberts, 2008). The ability e.g. to recognise affect in faces of others is an important component of social cognition. Deficits in this domain contribute uniquely to social skill deficits and mediate the correlation between neurocognition and social skills (Meyer & Kurtz, 2009).

Studying the neural correlates of social cognition is of particular importance, because deficits in these domains may explain the major dysfunctions in disorders that prevent effective (re-) integration into work and social life (Brekke, Hoe, Long, & Green, 2007). It has also become clearer that social cognition deficits, similar to emotion dysfunctions, may represent trait markers and endophenotypes of the diseases. A further major advantage of studying social cognition over the isolated study of emotional processing is that it includes the investigation of the interactions between cognition and emotion. Both processes are in continuous interaction and cannot be sufficiently separated in natural settings. Hence the experimental separation of emotion and cognition may be rather artificial.

Different abilities within the broad category of social cognition may require relatively different weighting of subcomponents of the same fronto-temporal social cognition network (Pinkham, Hopfinger, Ruparel, & Penn, 2008). The medial prefrontal cortex (MPFC), the prefrontal cortex, the amygdala and the inferior parietal lobe are especially implicated in such functions (Brunet-Gouet & Decety, 2006). Most likely, disturbances in social cognition in BPD may represent an abnormal interaction between the frontal lobe and its functionally connected cortical, especially temporal, and subcortical areas. In the integration of emotion and cognition within the domain of social cognition the orbito-

frontal region may play a substantial role, as it is supposed to code for more stable values and relationships (Derntl & Habel, 2011). However, the nature and extent of dysfunctional interactions of cognitive and emotional deficits in BPD remain to be elucidated.

Humans often are thought to be the most social of all animals and their social lives is the most fascinating. Surely our social nature has contributed to our success as a species. Yet, it is only since the last decade that scientists of the human mind and brain have begun to explore the biological basis of our social abilities and their evolution (Adolphs, 1999; K. N. Ochsner & Lieberman, 2001). Social psychologists have been investigating social behaviour for upwards of a century, but this work, which has contributed valuable insights on how people influence each other, occurred largely in isolation from the rest of neurobiology. Instead, the impetus for the recent marriage of social psychology with neurobiology came from comparative studies providing us with the term 'social brain' (Brothers, 1990).

This social brain, for humans at least, has a 'theory of mind', which enables us to predict what others are going to do on the basis of their desires and beliefs.

It also has a 'mirror system', which enables us to understand others' goals and intentions and to empathise with their emotions by a mechanism of motor resonance. (This system is not discussed further, for a recent review see Gallese and Sinigaglia (2011)).

1.2.1 Theory of Mind

Fodor (1978) as well as Premack and Woodruff (1978) used the term "Theory-of-Mind" (*ToM*) to describe a special mental faculty, namely to (try to) put oneself in someone else's position in order to understand his perception, thoughts, and goals. *ToM* is a complex cognitive function that requires integration of information from many sources. Two theories attempt to explain the psychological processes underlying *ToM*. The *Theory Theory* (TT) postulates that a set of causal laws

relating external states, internal states, and behaviours are used to construct theories about the mental states of others (Gallese & Sinigaglia, 2010). The *Simulation Theory* (ST) suggests that the mental states of others are simulated using the same mental mechanisms involved in experiencing each state oneself (Gallese & Sinigaglia, 2010); Furthermore, it has been proposed that the simulation of mental states (Gallese, Rochat, Cossu, & Sinigaglia, 2009) may be supported by mirror neurons, which were first identified in non-human primates (di Pellegrino et al., 1992; Rizzolatti et al., 1996). The theory and simulation theories of *ToM* need not be mutually exclusive: it is plausible that the more cognitively demanding TT may be adopted when ST is inappropriate.

ToM arguably is the basis of social and further of “moral” behaviour in humans and perhaps also of other species. Without any interest in others, without any concept of their beliefs and their desires and without a differentiated understanding of their perspective no form of ‘sympathy’, let alone ‘respect’, could evolve.

An impairment of *ToM* does lead to severe deficits in the ability to interact socially. The absence of *ToM* can unleash tremendous resources for special talents (*idiots savants*) which can be taken as an indicator of how many resources are normally attached to *ToM*-associated social skills.

As with many cognitive functions, it is likely that *ToM* may also have a localized neurobiological basis. In this dissertation, the term *ToM* is used to describe the processes by which most healthy human adults

- 1) attribute unobservable mental states to others (and under certain circumstances, to the self, (Happe, 2003b)), and
- 2) integrate these attributed states into a single coherent model (Meltzoff, 1999) that can be used to explain and predict the target’s behaviour and experiences.

Both of these characteristics are reflected in hemodynamic response of one brain region – the right temporo-parietal junction (RTPJ).

TPJ is more strictly defined as the cortex at the intersection of the posterior end of the superior temporal sulcus (STS), the inferior parietal lobule, and the lateral occipital cortex (Maurizio Corbetta, Patel, & Shulman, 2008).

It may be mentioned that the first neuroimaging studies had identified other brain regions that were active when participants engaged in *ToM* tasks. In an fMRI study Harris, Todorov, and Fiske (2005) studied the brain activity of 12 participants who performed the classic attribution task (McArthur, 1972). The authors concluded that the left medial prefrontal cortex (MPFC) played a significant role in *ToM*. However, this finding has not been consistent ever since.

Saxe and Wexler (2005) found that enhanced BOLD response in only the RTPJ is selective to the attribution of mental states, and is not recruited by processing other socially relevant facts about a person. Activity in the RTPJ was modulated by the congruence or incongruence of multiple relevant facts about the target's mind. Further, RTPJ activity was enhanced when the protagonist of a story professed a belief or desire that was inconsistent with the subject's expectations, based on the protagonist's background (R. Saxe & Wexler, 2005). Finally, none of the other brain regions commonly implicated in Theory of Mind reasoning – the left temporo-parietal junction (LTPJ), posterior cingulate (PC) and medial prefrontal cortex (MPFC) – showed an equally selective profile of response (R. Saxe & Wexler, 2005). These results are consistent with neuropsychological deficits in patients with selective damages of the brain. Damages to the RTPJ are associated with a selective impairment of *ToM* whereas damages to the MPFC are not (R. Saxe & Wexler, 2005).

However, this does not necessarily imply that the RTPJ is selective for *ToM*. The rather domain-specific view of brain functioning has been

challenged by others who point out that the RTPJ also serves other rather low-level computations involved in attention and multi-sensory integration (M. Corbetta & Shulman, 2002; Decety & Lamm, 2007; Mitchell, 2008). A within-subject comparison of reorienting and *ToM* paradigms revealed that both activated very similar TPJ regions (Mitchell, 2008) implying that TPJ is also involved in non-social mental processes. Interestingly, the Saxe lab (2009) replicated the study immediately replicated Mitchell's study but their results suggest that there are neighbouring but distinct regions within the RTPJ implicated in Theory-of-Mind and orienting attention.

Also, a loss of prefrontal inputs (from DLPFC) may have decreased top-down control over TPJ, resulting in inappropriate reorienting to distracting stimuli (Snow & Mattingley, 2006a, 2006b). A meta-analysis by (Decety & Lamm, 2007) showed the close correspondence between activations during attentional reorienting and social cognition in RTPJ. Taken together, the evidence suggests a more general role in switching between networks, which may explain recent evidence of its involvement in functions such as social cognition, as concluded by Maurizio Corbetta et al. (2008).

The standard paradigm to test for *ToM* processes is to read stories in which one character has a belief. The story is followed by a sentence that reveals that the belief is false (BELIEF condition):

The morning of high school dance Sarah placed her high heel shoes under her dress and then went shopping. That afternoon, her sister borrowed the shoes and later put them under Sarah's bed.

Sarah gets ready assuming her shoes are under the dress.

This condition is then contrasted with when the participant listens to a story of a photograph that was taken. The following sentence reveals that the photograph contains outdated information. Although the content is false, it is not necessary to apply a *ToM* (PHOTO condition):

The traffic camera snapped an image of the black car as it sped through the stoplight. Soon after, the car was painted red and the license plates were changed.

According to the traffic camera, the car is black.

In fMRI settings this paradigm is usually displayed to participants on a screen (Scholz et al., 2009).

Scholz et al. 2009) asked whether brain regions that reliably respond to belief information across subjects also respond reliably across *ToM* items. They performed whole brain subject- and item-wise analysis on a data set from participants who listened to different items of the above two conditions with varying degrees of mentalizing required to understand the false or outdated belief.

Figure 1-2 depicts the brain regions significantly more active for the BELIEF versus PHOTO stories across subjects, and across items, in the whole brain. All of the brain regions thought to comprise the *ToM* network (left and right temporo-parietal junction [TPJ], precuneus [PC], medial PFC) were reliably active in both subject- and item-wise analysis indicating that the *ToM* network also has a reliable response across items (Scholz et al., 2009).

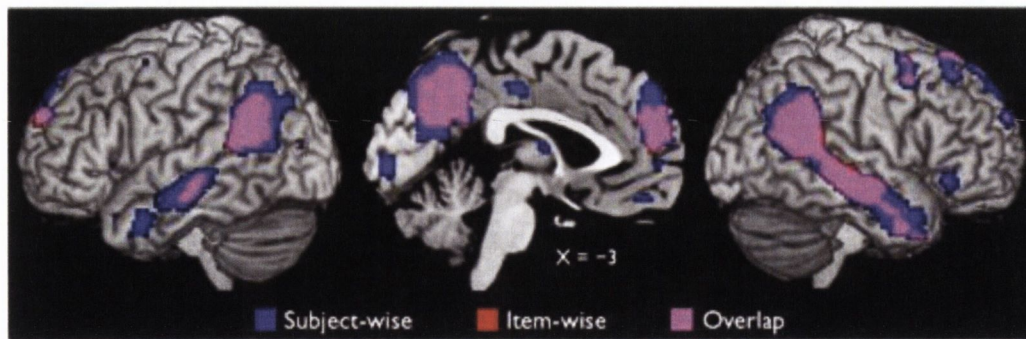


Figure 1-2: fMRI analysis in a task with Theory-of-mind items.

Whole brain subject-wise (blue activations; $N=62$ participants) and item-wise (red activations; $N=40$ items; 20 BELIEF and 20 PHOTO items) revealed overlap (magenta activations) in commonly observed *ToM* brain regions: RTPJ, LTPJ, PC, RSTS, LSTS, RTP, and MPFC. (From Scholz et al. (2009))

The most recent focus of imaging studies (functional as well as structural) in social neuroscience is arguably the involvement of RTPJ in moral behaviour. Morishima et al. (2012) showed that grey matter volume in the RTPJ predicts individuals' altruism and individual-specific conditions under which this brain region is recruited during altruistic decision making, revealing a link between brain structure and functional activity in altruistic choice.

On a broader level of social cognition, neuroimaging work has suggested that multiple regions of cortex in the human brain are dedicated to components of the process of perceiving and reasoning about other people, including recognising and identifying human faces (Grill-Spector, Knouf, & Kanwisher, 2004), perceiving other human bodies (Downing, Jiang, Shuman, & Kanwisher, 2001; R. Saxe, Jamal, & Powell, 2006), identifying human-like biological motion (K. A. Pelphrey, Singerman, Allison, & McCarthy, 2003), perceiving intentional actions (Castelli, Happe, Frith, & Frith, 2000; R. Saxe, Xiao, Kovacs, Perrett, & Kanwisher, 2004) and orienting towards and recognising basic emotional expressions (Whalen et al., 2001).

1.2.2 Mental states of others

Whenever we face another person (or 'agent'), we interpret the cause of the movement. Even infants perceive moving agents as having goals

and expect them to achieve these goals in a rational way, e.g. by moving along the shortest path (Csibra, Gergely, Biro, Koos, & Brockbank, 1999). When two agents act contingently, then we perceive that one caused the behaviour of the other. For this scenario, it is not necessary that the agent looks like a human. It is remarkably easy to imbue even a shapeless object with intentions as long as it appears to move in response to something you do or say (S. C. Johnson, 2003). Heider & Simmel (1944) showed that geometric shapes moving in a silent animation evoked attributions of intentions in ordinary viewers. This effect is highly robust and has been investigated in neuroimaging studies in terms of intuitive attribution of mental states (Castelli et al., 2000). Activation of the posterior superior temporal sulcus (PSTS) was seen, as well as of other regions relevant to theory of mind (Figure 1-3). This suggests that perception of biological motion and the attribution of intention and other mental states share a common neural basis.

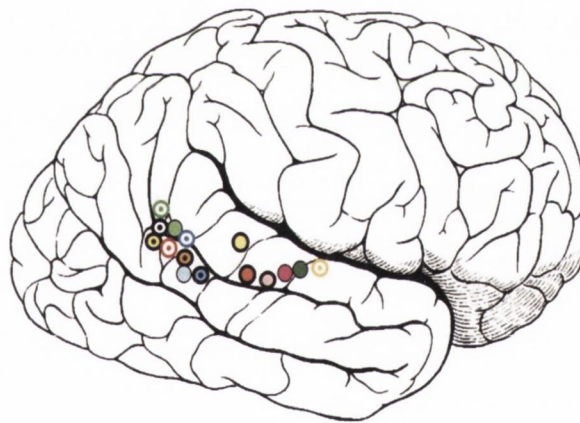


Figure 1-3: Observation of biological motion elicits activity in STS.
The schematic figure shows regions where observation of many different kinds of biological motion elicits activity along STS (from U. Frith & Frith, 2010).

1.2.3 Perspective taking

If we notice that another person cannot see what we can see, then we have a certain advantage. We might hide something from its line of sight or else make sure we bring something into its line of sight. This kind of perspective taking does not need to be social. For example, we need to be able recognise that a place or an object is the same when

we see it again from a different point of view. Tasks in which people have to infer what an object would look like from a different position (Meltzoff, 1999) elicit activity in TPJ. This region is also activated by tasks in which it is necessary to take account of a person's out-of-date (and hence false) belief as opposed to taking account of an out-of-date photograph (R. Saxe & Kanwisher, 2003). These are both tasks that create a strong contrast of perspectives: one spatial and the other mental.

Imagining how another person feels and how one would feel in a particular situation requires distinct forms of perspective-taking that likely carry different emotional consequences (Batson, Early, & Salvarani, 1997). Research in social psychology (see Batson et al. (2003)) has documented this distinction by showing that the former may evoke empathic concern (defined as an other-oriented response congruent with the perceived distress of the person in need), whereas the latter induces both empathic concern and personal distress (i.e., a self-oriented aversive emotional response). In an fMRI study by Jackson et al. (2006), participants were shown pictures of people with their hands or feet in painful or non-painful situations with the instruction to imagine themselves or to imagine another individual experiencing these situations. Both the self-perspective and the other-perspective were associated with activation in the neural network involved in pain processing, including the parietal operculum, the anterior medial cingulate cortex (aMCC), and the anterior insula. These results reveal the similarities in neural networks representing first-person and third-person information, which is consistent with the shared representations account of social interaction (Decety & Grezes, 2006; Decety & Sommerville, 2003). In addition, the self-perspective yielded higher pain ratings and involved the pain matrix (Derbyshire, 2000; Brent A Vogt, 2005) more extensively in the secondary somatosensory cortex, the posterior part of the anterior cingulate cortex (ACC), and the middle insula. These results highlight important differences between the self- and other-perspectives. For instance, although the anterior insula is

activated both when participants imagine their own and when they imagine another's pain, non-overlapping clusters can be identified within the middle insula. Likewise, both self- and other-perspectives are associated with a common subarea in the anterior medial cingulate cortex (aMCC), but the self-perspective selectively activated another part of this region (Brent A Vogt, 2005).

Finally, being aware of one's own emotions and feelings enables us to reflect on them. Among various emotion regulation strategies, when observing a target in pain, reappraisal by denial of relevance (i.e., taking a detached observer position) by implicitly or explicitly generating an image of the observing self which is unaffected by the target is known to reduce the subjective experience of anxiety, sympathetic arousal, and pain reactivity (Kalisch et al., 2005). Such a strategy is likely to play an important role in preventing empathic over-arousal (think about a psychotherapist and his/her client). Functional MRI studies have identified a limited number of regions in the anterolateral prefrontal and medial prefrontal (MPFC)/orbito-frontal (OFC) cortices that mediate such function (Kalisch et al., 2005; Lamm, Nusbaum, Meltzoff, & Decety, 2007).

1.2.4 Empathy

Imagining how another person feels and how one would feel in a particular situation requires distinct forms of perspective-taking that likely carry different emotional consequences. Research in social psychology has documented this distinction by showing that the former may evoke empathic concern (defined as an other-oriented response congruent with the perceived distress of the person in need), whereas the latter induces both empathic concern and personal distress (i.e., a self-oriented aversive emotional response) (Decety & Lamm, 2006).

While Theory-of-Mind (*ToM*) refers to the knowledge of thoughts, beliefs and intentions of others, empathy describes the ability to have insight into emotional states and feelings of others (U. Frith & Frith, 2010;

Uekermann et al., 2008). The basic level of empathy is characterised by emotion recognition, e.g. to understand the other person's feelings (Singer et al., 2006). The second level of empathy implies emotional state reasoning, which allows the empathiser to understand the other person's feelings and to predict the consequences of those feelings (U. Frith & Frith, 2010). This requires more cognitive effort than the basic level of empathy (Uekermann et al., 2010). The third process underlying empathy, is having the intention to respond compassionately to another person's sorrows (Decety, 2009). Empathy is influenced by observations, memory, knowledge and reasoning (Ruby & Decety, 2004). PFC regions are also involved in empathy (Uekermann et al., 2008). Moreover, empathy is associated with activation of the anterior cingulate cortex, limbic areas, somatosensory and insular cortices (Gallese & Sinigaglia, 2011; Vollm et al., 2006).

Although MPFC is not selectively involved in reasoning about mental state contents, sub-regions of MPFC do appear to support distinct components of human social cognition. One such component is emotional empathy; recent evidence points to a neural substrate of emotional empathy in ventral MPFC. Although the definition of empathy differs somewhat from study to study (see a detailed review in Decety (2009)), it can be broadly defined as the experiencing of an affective or sensory state similar to that shown by a perceived individual, where one is aware as to whether the source of the state is oneself or another. This operational definition allows empathy to be distinguished from related concepts such as sympathy and theory-of-mind (both of which involve an understanding but no sharing of another's state), as well as emotional contagion (where there is no awareness as to whether the source of the experienced state is the self or another).

Studies of neuropsychological patients suggest a double dissociation between 'cognitive empathy' (that is, Theory-of-Mind) and 'emotional empathy' (Blair, 2005), i.e., the cognitive and neural processes that produce a congruent emotion in the observer in response to others'

directly perceived emotional displays or to descriptions of others' emotion-laden experiences. Blair (2005) argued that autism (ASD) is characterised primarily by deficits of 'cognitive empathy', leaving emotional empathy relatively intact. Psychopathy and antisocial behaviour, by contrast, are related to diminished emotional empathy but not to impaired Theory-of-Mind. A similar dissociation is observed following pure autonomic failure (Heims, Critchley, Dolan, Mathias, & Cipolotti, 2004).

Accumulating evidence suggests that the distinct neural substrate of emotional empathy is a region in ventral MPFC. Two studies using fMRI explicitly compared cognitive and emotional empathy. Vollm et al. (2006) compared reasoning about a protagonist's thoughts versus feelings in nonverbal cartoons; Hynes, Baird, and Grafton (2006) investigated a similar contrast using verbal stories. Both report selective activation in the ventral MPFC.

1.2.5 Self and Emotion in the Brain

Important aspects of internally directed processing, such as introspection, self-referential thoughts, or projecting oneself into a situation (e.g., envisioning or planning one's future or remembering one's past as in episodic memory) are thought to involve the so-called *default mode network* (DMN, Raichle et al., 2001). This network of cortical regions is strongly deactivated during a wide range of demanding cognitive tasks relative to a passive resting or viewing state (Binder et al., 1999; Mazoyer et al., 2001). It has been proposed that these regions mediate a number of *default* processes to which the brain returns in the absence of a task (Raichle et al., 2001).

Over the past decade, there has been a growing interest in research on the neural mechanisms that mediate empathy, particularly following the seminal paper by Preston and de Waal (2002) in which they reviewed an impressive array of evidence in support of the perception–action model and its fundamental role in social interaction. This model posits

that perception of emotion activates the neural mechanisms that are responsible for the generation of emotions. Such a system prompts the observer to resonate with the emotional state of another individual, with the observer activating the motor representations and associated autonomic and somatic responses that stem from the observed target (i.e., a sort of inverse mapping). For instance, a handful of functional magnetic resonance imaging (fMRI) studies have shown that the observation of pain in others is mediated by several brain areas that are implicated in processing the affective and motivational aspects of pain (Philip L Jackson et al., 2006). In one study, participants received painful stimuli in some trials and, in other trials, observed a signal that their partner, who was present in the same room, would receive the same stimuli (Singer et al., 2006). The anterior medial cingulate cortex (Brent A Vogt, 2005) the anterior insula, and the cerebellum were activated during both conditions. Similar results were reported by (Morrison, Lloyd, di Pellegrino, & Roberts, 2004) who applied a moderately painful pinprick stimulus to the fingertips of their participants, and—in a second condition—showed them a video clip showing another person undergoing similar stimulation. Both conditions resulted in common hemodynamic activity in pain-related areas of the right cingulate cortex. In contrast, the primary somatosensory cortex showed significant activations in response to tactile stimuli only, but not to visual stimuli. The different response patterns in the two areas are consistent with the role of the ACC in coding the motivational-affective dimension of pain, which is associated with the preparation of behavioural responses to aversive events (B. A. Vogt, 2005).

In another study, participants were shown photographs depicting right hands and feet in painful or neutral everyday life situations, and were asked to imagine the level of pain that these situations would produce (P. L. Jackson, Meltzoff, & Decety, 2005). Significant activation in regions involved in the network processing the affective aspect of pain, notably the ACC and the anterior insula, was detected. Moreover, the level of activity within the ACC was strongly correlated with participants'

mean ratings of pain attributed to the different situations. These results lend support to the idea that common neural circuits are involved in representing one's own and others' affective pain-related states. Furthermore, Singer and colleagues (2006) demonstrated that the hemodynamic response in this circuit is modulated by learned social preferences, especially in male participants.

1.3 Social Cognition and BPD

1.3.1 *ToM related symptoms*

Distortions or deficits of *ToM* are manifested in BPD in various ways. First, people with BPD can have a strong fear of abandonment even though another person does not intend to leave them. Second, people with BPD may alternately strongly idealise another person and then, a few minutes later, strongly devalue them even though the other person may have done nothing to evoke these strong feelings. Third, people with BPD may also suffer deficits in reasoning about their own motivations or intentions. This deficit appears to manifest itself in an identity disturbance that the DSM-IV-TR describes as "...markedly and persistently unstable self-image or sense of self" A comparison of the nine DSM-IV criteria for BPD (1.1.2) with the definition of *ToM* (see 1.2.1) indicates how related BPD may be to impairment in *ToM*.

Imagined abandonment

"Frantic efforts to avoid real or imagined abandonment" (criterion 1, DSM-IV) suggests a patient's unilateral interpretation of the thoughts and goals of others. It is the anticipation that the abrupt ending of interpersonal relationships at any time is possible and likely to happen. In addition, the BPD patient may be (falsely) generalising that her own instable pattern of interpersonal relationships holds true for another person or partner. Gabbard (2005) described in a case study how patients get disturbed even when they misinterpret signs by the therapist as an announcement of wanting to terminate the relationship.

Idealisation and Devaluation

The tendency of BPD patients to “idealise and devalue” (criterion 2, DSM-IV) shows the difficulty they have with perceiving another person will (different) thoughts, desires, and feelings. Idealising and devaluating could be seen as a simplification of a *ToM* in that only one aspect of the other person is given consideration and is subsequently evaluated. It is widely reported that patients switch rapidly between idealisation and devaluation not only in their everyday lives but also with their therapists. Oftentimes patients are occupied with their way of perceiving others to the extent that the other’s contrary perspective cannot be understood or related to.

(But: See a recent study by Arntz & Haaf (2012) whose interview-based evaluations by BPD-patients could not be discriminated from non-patients in cognitive complexity. Their results indicate that dichotomous thinking, and not so much splitting, negativity, or less complexity, is central in the interpretation of others by BPD-patients).

Identity disturbance

The reason for a disturbed identity (or image of the *self*) most likely is an unreliable appraisal of one’s own thoughts, desires, and feelings. Similarly to idealisation and devaluation, patients often switch between extreme self-confidence, during which therapy can be experienced as an unnecessary intervention, and extreme helplessness. Bateman & Fonagy (2004) have thus defined two oscillating basic modes (“equivalency mode” and “*as-if*-mode”) in which to conduct therapy with BPD patients. The equivalency mode assumes that the patient’s inner reality is experienced as equal and non-separable from the outer world whereas the *as-if*-mode assumes that inner and outer reality are experienced differently and independently. The authors claim that by steadily and reliably switching modes a continuing *ToM* becomes possible and feasible for BPD patients.

Stress-related paranoid ideation

The tendency to develop “stress-related paranoid ideation” (criterion 9, DSM-IV) points towards intense feelings of insecurity much as is the case with *ToM* deficits in schizophrenia (Meyer & Kurtz, 2009). However, in schizophrenic patients it was recently discovered that cognitive flexibility has an impact on *ToM* performances but that these difficulties were not associated with clinical symptoms (Champagne-Lavau, Charest, Anselmo, Rodriguez, & Blouin, 2012).

Attachment theory and BPD

The reciprocity between a mother (or caregiver), which includes behaviours such as touching, holding, and soothing on the parent’s side, and smiling, clinging, and crying on the infant’s side creates an enduring bond between mother/caregiver and infant. John Bowlby in 1969 referred to this enduring bond as ‘attachment’, and saw it as the foundation for the infant to develop internal working models of self and other which can then function as templates for future relationships (cited in Bretherton (1992)). With regard to the fact that BPD patients fear to be abandoned (criterion 1, DSM-IV) and their difficulty of maintaining stable interpersonal relationships (criterion 2, DSM-IV) early social experience and attachment has been studied in BPD.

There is suggestive evidence that those suffering from BPD have a history of insecure disorganised attachment. Two longitudinal studies following children from infancy to early adulthood have found associations between insecure attachment in early childhood and BPD symptoms on follow-up (Lyons-Ruth, Yellin, Melnick, & Atwood, 2005; Sroufe, 2005).

Further, preliminary evidence that the capacity for change in attachment organisation decreases over development underlies the danger that persistent trauma will lead to long-term disorganisation of attachment, with attendant poor development of social cognition and substantially raised risks of psychopathology (RISK, 2006).

Interpersonal relationships and BPD

Disturbed interpersonal relatedness has been identified as a key aspect of BPD pathology differentiating it from other personality disorders (S. C. Herpertz et al., 2007; Skodol, Gunderson, Pfohl, et al., 2002). Social experience triggers key problem behaviours. Environmental triggers of suicide attempts are more likely to be interpersonal stressors in BPD than in other disorders associated with depression (Fertuck et al., 2009). Observational studies consistently suggest that patients with BPD exhibit abnormalities in interpersonal emotional perception, experience and expression. Specifically, they showed that those patients with BPD exhibit emotional hyper-responsiveness deficits in emotion recognition (Skodol, Gunderson, McGlashan, et al., 2002) and the 'capacity for empathy' (Bland, Williams, Scharer, & Manning, 2004).

However, it is not clear how best to understand the connection between BPD and various social cognitive deficits as this connection appears to be context dependent. For example, in relation to their deficit in facial emotion processing, while patients with BPD show a normal ability to recognise isolated facial or prosodic emotions, they appear to have impaired recognition of emotions with integrated facial/prosodic stimuli, as well as impaired discrimination of non-emotional facial features (see Minzenberg, Poole, and Vinogradov (2006). However, the deficit clearly relates to functioning: impaired recognition of integrated emotional stimuli has been shown to be associated with interpersonal antagonism, particularly suspiciousness and assaultiveness (Minzenberg et al., 2006). When mentalization is less precariously established, its loss will be more apparent in the emergence of unusual alternative strategies rather than in the loss of the capacity itself. For example, mentalization underpins normal self-regulation via self-talk and other processes that involve thinking about internal states according to philosopher Dennett (2001).

Sharp et al. (2011) have sought to link parental mentalization to the development of affect regulation and secure attachment in BPD.

Ultimately, failure of mentalization (Westen, 1991) in BPD patients is marked by an inclination to misread minds, both their own and those of others, resulting in distorted 'mentalizing' (Sharp et al., 2011). They consequently perform dramatically badly in social contexts, not only upsetting people whom they wish to recruit but also frequently exhibiting deficits in social problem-solving. This tendency may be considered a general marker of psychopathology, but certain features of temporary social cognitive deficit appear not to characterise other clinical groups (e.g. producing less specific solutions during means-ends problem-solving, and reporting higher levels of problem orientation and more impulsive/careless style towards solving social problems (Bray, Barrowclough, & Lobban, 2007)).

It has consistently been demonstrated that patients with BPD present others' mental states with less complexity and differentiation than patients with other disorders such as MDD (Westen, 1991). When emotionally aroused, and when their relationship to another person moves into the sphere of attachment, the intensification of that relationship means that their ability to think about the mental state of the other person can rapidly disappear. When this happens, pre-mentalistic modes of organising subjectivity emerge, which have the power to disorganise these relationships and destroy the coherence of self-experience that the narrative provided by normal mentalization (A. W. Bateman, Ryle, Fonagy, & Kerr, 2007).

Bateman and Fonagy (2004) believe that the clinical experimental data show that patients with BPD have vulnerabilities in the higher-order integration of social information, and ways of coping with this vulnerability which may be related to some of the more serious symptoms of the disorder. Although interpersonal problems can refer to a whole constellation of difficulties, including dramatic shifts from 'idealisation of others' to 'disillusionment with others', frantic efforts to avoid perceived abandonment, and inappropriate interpersonal aggression (Barrow et al., 2007; Nestor, 2002) an emerging literature

suggests that all of these may share common mechanisms to deal with the unstable perception of the other, where the stability of that social perspective is normally guaranteed by a relatively clear perception of intentionality behind behaviour.

In conclusion, the mentalization account of BPD is based on clinical evidence (A. Bateman & P. Fonagy, 2004; A. Bateman & Fonagy, 2009, 2010) and points to a specific difficulty that patients with BPD appear to have in accurately differentiating and representing the mental states of people who are significant to them, as well as in having a clear grasp of having their own subjective experience (Fonagy & Bateman, 2008).

1.3.2 Behavioural studies in BPD

Using self-report measures on ability of cognitive empathy, Guttman & Laporte (2000) found perspective taking, as assessed with the Interpersonal Reactivity Index (IRI, Davis, 1983), to be impaired in BPD patients compared to patients with anorexia nervosa and non-clinical controls. Harari et al. (2010) and New et al. (2012) replicated this finding on the IRI perspective taking scale in BPD patients compared to non-clinical controls. Fonagy et al. (1996) used a clinical interview (cited in Fonagy and Bateman (2008)) and found further evidence that BPD patients had deficits in understanding the mental states of others compared to a clinical non-BPD control group.

Despite long term impairment in social functioning in many patients (Zanarini, Frankenburg, Reich, & Fitzmaurice, 2010) BPD has high rates of remission. In contrast, to other psychiatric disorders involving impairments in social functioning such as schizophrenia or ASD, less attention has been directed to deficits in mentalizing. This seems surprising because deficits in mentalizing play an essential role in therapeutic approaches to BPD. In the mentalization-based therapy (MBT: A. W. Bateman et al., 2007) for instance, the ability to mentalize is considered unstable during emotional arousal and the therapy aims towards an improvement of the patients' abilities to understand their

own and other mental states (A. Bateman & Fonagy, 2008). Only a few recent studies addressed the ability of BPD patients to attribute mental states to other people (A. Arntz, Bernstein, Oorschot, & Schobre, 2009; Fertuck et al., 2009; Ghiassi, Dimaggio, & Brune, 2010; Harari et al., 2010). Surprisingly, the majority of these indicate equal or superior mentalizing ability in BPD.

According to the body of behavioural literature it seems that emotional empathising is impaired in BPD whereas cognitive empathising, i.e. empathy with little or no involvement of emotions is not. In the following *cognitive empathy* shall be referred to as the ability to understand the mental states of others, i.e., their thoughts, desires, beliefs, intentions, and knowledge, “Cognitive empathy” and “mentalizing” are used interchangeably. *Emotional empathy* is referred to as the ability to share the emotional state of another person, emotional reaction in an observer to the affective state of another individual.

At present, there is no clear evidence that one specific form of psychotherapy is superior to another (Zanarini, 2009). For a recent summary of RCT studies that compare different forms of psychotherapy please see Leichsenring et al. (2011).

The available forms of psychotherapy do not yet lead to remission of borderline personality disorder for most patients (i.e. no longer fulfilling the DSM criteria for BPD).

Borderline empathy

Clinical observations (Krohn, 1974) and early empirical studies focusing on accuracy in inferring others' emotional states (Frank & Hoffman, 1986; Ladisich & Feil, 1988) gave rise to the descriptive term “borderline empathy”, which refers to enhanced cognitive empathy in BPD. Frank and Hoffman (1986) analysed the ability of BPD patients to infer the emotional states of others compared to non-BPD patients. Participants had to choose one of two alternative affective descriptions after watching a 10-min video sequence containing depictions of

different emotional situations, each portrayed by the same female actor. The borderline group showed significantly fewer errors and was more sensitive to nonverbal communication than the control group, thus indicating increased cognitive empathy in BPD. Ladisich and Feil (1988) measured how well a particular member of an interacting group predicted the self-rated feelings of the other group members. BPD patients achieved higher scores compared to non-BPD patients but did not differ from the psychiatrist's ratings, which served as further argument for increased cognitive empathy in BPD. (Flury, Ickes, & Schweinle, 2008) used a comparable study design including participants with high and low BPD traits. In the first step, the authors replicated the results of Ladisich and Feil (1988), with individuals with high BPD traits showing enhanced accuracy in attributing mental states (thoughts and feelings) to others. In a second step, however, reanalysis of the data revealed that these effects were a consequence of the participants with high BPD traits having more unusual, harder-to-predict personalities, and thoughts and feelings that were difficult to infer compared to their counterparts with low BPD traits. This led to lower accuracy scores in the participants with low BPD traits (Flury et al., 2008). The authors concluded that the difference in accuracy between individuals with low and high BPD traits was not related to a difference in performance but to the difficulty in reading high BPD trait participants. Thus, this study presented a first hint that emission of social signals might be abnormal in BPD.

Two studies homogenously point towards a superior ability of BPD patients to identify mental states. With help of the 'Reading the mind in the eyes test' Fertuck et al. (2009) showed an enhanced sensitivity in BPD when attributing a mental state based on information derived from pictures portraying the eye region of the face. Arntz et al. (2009) applied the Happe Test which requires subjects to infer other subjects' thoughts, feelings, and intentions in complex social situations described in several stories that involve double bluff, mistakes, persuasion, and white lies. BPD patients performed superior to non-patients when

performance was controlled for IQ. In contrast, deficits in *ToM* could be observed in both of these tests in patients with anorexia nervosa as could be shown in a study by Russell et al. (2009). However, Harari et al. (2010) suggest that *ToM* abilities are impaired in BPD patients at least in a subdomain of *ToM* abilities. Reduced performance became obvious in cognitive *ToM*, i.e. the ability to make inferences regarding other people's beliefs, but not in affective *ToM*, i.e. the ability to make inferences regarding other peoples' emotions (often referred to *emotional empathy*). These results contradict the results of Arntz et al. (2009) in that the latter found superior performance for BPD patients in the Happe Test that can be regarded as a cognitive *ToM* task which requires "thinking about thinking" and deductive reasoning skills (Russell et al., 2009).

Beyond that, these deficits could not be found in a study by Ghiassi et al. (2010) who applied the MSAT, a test of cognitive mentalizing skills. They found a comparable performance in BPD and healthy control subjects during the task in which scenes of cartoon picture stories about social interactions had to be sorted. Additionally, BPD patients and non-patients assessed the beliefs, intentions, false beliefs, as well as deception and reciprocity of the characters involved in these stories in a comparable manner (Ghiassi et al., 2010).

Although Ghiassi et al. (2010) did not find that BPD patients had deficits in understanding others' minds using a cartoon task, self-reported negative maternal behaviour was a negative predictor for cognitive empathy later in adulthood, indicating the negative influence of early stressors.

Franzen et al. (2011) used the trust game to analyse processes of mentalizing in a simulated social interaction situation. BPD patients adjusted their investment to the fairness of their partner. In contrast, healthy controls disregarded the trustees' fairness in the presence of emotional facial expressions. Both groups performed equally in an emotion recognition task and assessed the trustees' fairness

comparably (Franzen et al., 2011). When the unfair trustee provided emotional cues, BPD patients assessed their own behaviour as more fair, while the lack of cues led patients to assess their own behaviour as unfair. The authors (Franzen et al., 2011) thus concluded that BPD are superior in the attribution of mental states to interaction partners when emotional cues are present. While the emotional expressions of a partner dominated the exchange behaviour in healthy controls, BPD patients used the objective fairness of their social counterparts to guide their own behaviour despite the existence of emotional cues. In other words, the patients noticed the unfair behaviour of the partner with lower repayment ratio in spite of emotional cues and adjusted their behaviour accordingly (Franzen et al., 2011).

Unoka et al. (2009) was able to show that BPD patients fail to develop trust in the course of a 5-round trust game during which they did not receive feedback about their interaction partner's behaviour: While healthy controls increased their investments over the course of the game, BPD patients did not change their behaviour (Unoka et al., 2009). These data suggest alterations in interaction behaviour might be the result of deficits in social functioning.

Whereas earlier work on accuracy has found no deficits in cognitive empathy, more recent work using more ecologically valid and complex stimuli has shown that BPD patients have subtle deficits in the ability to infer the emotions, thoughts, and intentions of others (Dziobek et al., 2011; Preissler, Dziobek, Ritter, Heekeren, & Roepke, 2010)). High arousal might additionally interfere with BPD patients' ability for cognitive empathy (Sharp et al., 2011).

In search of the causes underlying interpersonal dysfunction in BPD various studies have investigated the contribution of single processes assumed to be involved in this impairment. Most of these studies have focussed upon alterations in emotion recognition (see G. Domes, Schulze, & Herpertz, 2009 for a review). However, results across studies are inconsistent. They point to subtle impairments in basic

emotion recognition (Bland & Rossen, 2005), a negativity bias (Dyck et al., 2009; Guitart-Masip et al., 2009), but also to a heightened sensitivity for the detection of negative emotions (Lynch et al., 2006), or no alterations in emotion recognition at all (G. Domes et al., 2008; Minzenberg et al., 2006) e.g. emotion processing become obvious in BPD when subjects have to assess the emotional state of a face quickly (Dyck et al., 2009).

Whether this points toward that impairment in automatic processing is based on neurobiological alterations, or whether this is the result of a learning history that taught the subjects to evaluate a social interaction partner more carefully without relying on the first automatic judgment, has to be the topic of MRI studies.

1.3.3 Neuroimaging studies of social cognition in BPD

At present there are two studies in patients with BPD addressing the issue of altered social cognition processing during fMRI. They were both published at the time of writing this thesis and had inconclusive results. Dziobek et al. (2011) applied a version of the MET (Multifaceted Empathy Test, a measure to assess cognitive and emotional empathy) to BPD patients during MRI: Brain responses during cognitive empathy were significantly reduced in patients compared to controls in the left superior temporal sulcus and gyrus (STS/STG) and during emotional empathy, patients with BPD exhibited greater brain activity than controls in the right middle insular cortex. According to the authors their findings support a “conceptualisation of BPD as involving deficits in both inferring others' mental states and being emotionally attuned to another person” (Dziobek et al., 2011).

Mier et al. (2012) applied a paradigm with three social cognition tasks, differing in their complexity: basal processing of faces with a neutral expression, recognition of emotions, and attribution of emotional intentions (affective *ToM*). BPD patients showed no deficits in social cognition on the behavioural level. However, while the control

participants showed increasing activation in areas of the social brain with increasing complexity in the social-cognitive task, BPD patients had *hypoactivation* in these areas and *hyperactivation* in the amygdala which were not modulated by task complexity. From this activation pattern the authors concluded an enhanced emotional approach in the processing of social stimuli in BPD that allows good performance in standardised social-cognitive tasks, but might be the basis of social-cognitive deficits in real-life social interactions (Mier et al., 2012).

Eliciting Theory-of-Mind processes with fMRI tasks is difficult, because presentation of stimuli does not allow having a real person interacting with the participant. One option to get closer to an ecologically valid way (as opposed to questionnaires) of evoking *ToM* processes may be to use humour (see 1.4).

1.3.4 Emotional arousal, BPD, and PTSD

Using standardised emotional slides which are supposed to evoke emotional responses, early fMRI investigations in healthy subjects found activation of the amygdala region, (Irwin et al., 1996 and Morris et al., 1998), anterior cingulate cortex as well as ventromedial prefrontal cortex areas (Mayberg et al., 1999; Teasdale et al., 1999). PET studies revealed neural correlates of different emotional states, such as grief, shame, guilt, and anger, using scripts specific for each emotion (Dougherty et al., 1999, George et al., 1995 and Shin et al., 2000). For example, during the imagination of situations associated with anger, alterations of prefrontal blood flow with increased activity in ACC were found (Dougherty et al., 1999 and Kimbrell et al., 1999). Using standardised negative emotional material from the International Affective Picture System (IAPS) Herpertz et al. (1998) found increased activity in the amygdala of six patients with BPD without comorbid psychiatric disorders compared to controls. In a larger sample of 12 BPD patients with comorbid anxiety and depressive disorders, these findings could be replicated (S. C. Herpertz et al., 2001).

Another method of emotional challenge consists of presenting standardised pictures of faces which express a specific emotion such as anger, fear, or sadness (Ekman, 1993). Donegan et al. (2003) used this paradigm to investigate BPD patients with and without PTSD and controls. They found different effects for the two BPD groups: For BPD patients with PTSD left-lateralised amygdala hyper-reactivity was found, whereas those BPD patients without PTSD showed bilateral amygdala hyper-reactivity. In the cingulate cortex, these investigators found deactivation in response to fearful faces for patients with BPD and comorbid PTSD but not for those BPD patients without PTSD. In frontal polar prefrontal cortex (BA 10), they found an opposite pattern of deactivation for BPD patients without PTSD but not for those with PTSD. These findings are consistent with findings of left-lateralised amygdala hyper-reactivity (Rauch et al., 2000) as well as decreased cingulate activation in PTSD.

Recapitulation:

- Cognitive Empathy (=Mentalizing) – Attribution of goals, thoughts, desires
- Emotional Empathy – shared feelings
- Affective *ToM* – Attribution of feelings (not necessarily shared)

1.4 Humour

Humour is considered “fundamentally a social phenomenon” and its occurrence in the absence of other persons usually “is pseudo-social in nature” (Martin, 2007). It is proposed to have its origins in primate social play (Gervais & Wilson, 2005). Humour and laughter have a broader emotional scope, such as positive affect, reward processes and improved mood (CHARLES & SCHAEFER, 2002) and reduced negative affective responses to stressful events (Keltner & Bonanno, 1997) Its impact on disease course in several clinical groups implicates a palliative role in immunology (Rosner, 2002). Humour can be seen as an important tool in social interaction, supporting relationships but also

communicating indirectly opinions that cannot be expressed overtly. In order to understand and appreciate humorous stimuli, several cognitive abilities are required, such as an abstract understanding of ideas and the capacity to integrate information into a new concept.

Humour as a universal human phenomenon encompasses numerous functions, such as an effective coping mechanism in the struggle with difficult situations throughout life but also as a useful communication tool in social situations. The latter is particularly successful if the communicating subjects are able to laugh about the same style of humour, as well as humorous contents (W. Ruch, Hehl, F.-J., 2007). Laughter is one of the observable behaviours that accompany the humour process which consists of the cognitive processing of a stimulus and, usually, appreciation. Experiencing humour is understood here as a more cognitively sophisticated ability, involving the processing of incongruity with meaningful resolution.

According to psychological and also cognitive-linguistic humour theories an incongruity, i.e., a conflict between two initially opposed scripts or schemas, has to be detected and then playfully resolved by recognising a relation between the two scripts (Attardo, 1991). In order to resolve an incongruity, cognitive rules, also called logical mechanism (LM) have to be recognised (e.g., that a joke is based on role exchange or analogy, etc.).

The comprehension–elaboration theory of humour claims that humour processing can be segregated into two phases, comprehension and elaboration. Comprehension includes both the experience of surprise resulting from encountering unexpected or incongruous information *and* the re-establishment of coherence which results when the unexpected information is reinterpreted using concepts and schemas from a different knowledge domain. The elaboration phase involves cognitive elaboration of the implications of the reinterpreted situation and subsequent inducement of the feeling of amusement.

1.4.1 Humour and Social Cognition

The concept of humour, could be simply defined by the presence of amusing effects, such as laughter or well-being sensations, plays a relevant role in our lives. The main function of humour is to release emotions, sentiments or feelings that positively impact on human health. In a social context, humour's cathartic properties make most people react to a humorous stimulus regardless of their beliefs, social status or cultural differences. Moreover, humour provides valuable information related to linguistic, psychological, neurological and sociological phenomena (Reyes, Rosso, & Buscaldi, 2012). Due to its complexity and central role in human life, Ruch (2001) has recommended the study of humour not just for the study of social cognition but for the study of consciousness.

Since BPD individuals have problems predominantly with the perception of the emotions fear and anger (Koenigsberg et al., 2002; Levine et al., 1997) and given the above mentioned *ToM* related criteria it seems likely that BPD is associated with impairment of social cognition. Using humour appreciation seems to be an ecologically valid way to investigate this as has already been the case with ASD.

Impaired humour appreciation is well described in ASD, the mental disorder of which social impairment is the hallmark and that includes issues with social referencing, difficulty initiating and responding to social cues, difficulty initiating and maintaining eye contact, failing to engage in joint attention, or displaying inappropriate emotional reactions (for an overview see Happe (2003a)). As a result of their difficulties with social interactions, children with ASD are often rejected by peers, have difficulty achieving success in school, and may develop other mental health problems (Simon Baron-Cohen, 1988). *ToM* impairment in ASD is so salient that one of the leading theoretical models of ASD, the *Mindblindness* theory, is based on impairment in *ToM* in this population (S. Baron-Cohen, 1995; Simon Baron-Cohen, Leslie, & Frith, 1985; Uta Frith, Morton, & Leslie, 1991). Not surprisingly, social (cognitive)

impairment in ASD has been related to brain dysfunction of the right hemisphere (Mason, Williams, Kana, Minshew, & Just, 2008), in particular the RTPJ (Lombardo, Chakrabarti, Bullmore, & Baron-Cohen, 2011).

Early studies on humour skills in relation to individuals with AS (Asperger Syndrome, a 'high-functioning' subtype of the autism spectrum) suggested that they do not understand humour (Asperger (1944) cited in Lyons and Fitzgerald (2004)). Baron-Cohen (1997) demonstrated that individuals with autism persistently fail to "get the joke" and that they do not refer to the speaker's intention to joke. St James and Tager-Flusberg (1994) showed that children with autism can produce and appreciate humour to a limited extent in naturalistic settings: no differences were found in earlier forms of humour (e.g., humour based on rhyme, slapstick funny sounds) but in nonverbal incongruity and riddles (children with autism produced no riddles at all). Another study showed children with autism laugh as much as children with Down's syndrome in response to tickling and slapstick humour, but exhibit less laughter in response to socially inappropriate acts (Reddy et al. 2002). In a more experimental setting, two studies showed that comprehension of humorous material is poorer in individuals with AS or autism than controls (Ozonoff & Miller, 1996). The participants had to choose one out of five possible funny joke endings. Individuals with AS had poorer comprehension of cartoons and jokes. Instead of choosing the correct funny ending, they most frequently chose humorous, but not coherent endings (Ozonoff & Miller, 1996).

1.4.2 MRI studies using visual cartoons

Gallagher et al. (2000) were the first to use a combined visual joke and verbal short story *ToM* imaging paradigm on a group of six healthy controls to investigate brain regions activated by the two different *ToM* modalities. In the visual joke *ToM* condition, significant activations were observed in the medial prefrontal and right middle frontal and fusiform gyri, right temporo parietal junction, and the precuneus, compared to

those visual jokes that did not require mentalizing abilities. Marjoram et al. (2006) employed the same visual joke paradigm as Gallagher et al. (2000) and hypothesised that significant group differences would be found in the superior temporal sulcus (STS), temporal poles, and prefrontal cortex (PFC, both medial and dorsolateral) in the high-risk relatives, particularly those who were experiencing psychotic symptoms at the time compared to the controls. These three areas had previously been identified as key regions involved in a mentalizing 'circuit' (Gallagher & Frith, 2003).

Two previous studies (A. C. Samson, Hempelmann, Huber, & Zysset, 2009; A. C. Samson, Zysset, & Huber, 2008) revealed that different LMs have different cognitive requirements which, in turn, were shown to influence neural activation patterns. Visual puns (PUN, which are based on one visual element simultaneously evoking two meanings, see example in Figure 2-4) were shown to evoke more activation in the visual cortex whereas *ToM* cartoons (TOM, that require additional mentalizing skills in order to be understood: it has to be recognised that one character portrayed in the cartoon has a false belief, see example in 2.4.3) require more involvement of so-called "mentalizing areas" [e.g., medial prefrontal cortex, temporo-parietal junction (TPJ)]. Goel & Dolan (2001, 2007) were the only authors to have found affective brain areas, namely the ventromedial prefrontal cortex (VMPFC) and the subcortical nucleus accumbens along with the aforementioned network (TPJ and STS).

See introduction to Chapter 4 for detailed information.

1.5 Objectives

The objectives of this thesis project are:

To investigate humour processing in relation to *ToM* and the resolvability of incongruity as stimulus characteristics and in relation to neuroticism in healthy individuals (as this personality characteristic is known to be associated with BPD).

The anatomical hypothesis is that attending visually to cartoon pictures that include a *ToM* component will recruit the 'mentalizing' areas or '*ToM* network' of the brain compared to looking at a picture that is lacking this component.

Although no regions of interest (ROI) are defined, regions that consistently have been activated by standard Theory-of-mind tasks in the literature (mostly false-belief stories, see 1.2) are expected to respond to *ToM* jokes: right and left temporo-parietal junction (RTPJ/LTPJ), superior temporal sulcus (STS), precuneus (PC) and medial prefrontal cortex (MPFC) (Dodell-Feder, Koster-Hale, Bedny, & Saxe, 2011; Kliemann, Young, Scholz, & Saxe, 2008; Lombardo et al., 2011; Mitchell, 2008; R. Saxe & Wexler, 2005; Scholz et al., 2009; Young, Camprodon, Hauser, Pascual-Leone, & Saxe, 2010).

Thus, a neural network including the areas of the ventro-medial prefrontal cortex (VMPFC), inferior-frontal gyrus (IFG), and temporo-parietal junction (TPJ) is expected to be active during mental processing of *ToM* jokes vs. jokes that are lacking the *ToM* component.

Study 2 investigates differences in neural response to stimuli characteristics between 17 patients with BPD and 19 healthy individuals with the anatomical hypothesis that there is less activity in areas such as TPJ/STS in BPD patients for condition TOM vs. *non-TOM*. This activity difference should remain after accounting for age, levels of depression, and neuroticism. Greater overall activity should be seen in

BPD patients vs. healthy individuals in incongruity vs. non-incongruity conditions.

Similarly, the behavioural hypothesis is that BPD patients should show more difficulties understanding visual cartoons with a *ToM* component that without that component as reflected by their response times.

Study 3 investigates the functional connectivity of brain areas in BPD patients vs. healthy controls. Given that emotional dysregulation is a core feature of BPD the hypothesis is that in patients there is higher functional coupling of the affective and the *ToM* cortical network, i.e., there is synchronised activity in both networks that is modulated by the same stimuli.

The anatomical hypothesis for *Study 4* is that there is less grey matter (GM) in the hippocampal areas, basal ganglia (striatum/caudate/putamen/pallidum), DLPFC, and the OFC in patients compared to healthy individuals. The study also tests for changes in white matter (WM). Volumetric differences are measured using the VBM method.

A *Psychometric Assessment* is conducted in the beginning as an exploratory to assess the profile of the samples of BPD patients and healthy controls that will be used in the following studies and in order to use measures of impulsivity and neuroticism as covariates in *Study 1* and *Study 4*, respectively. It is further aimed to confirm higher impulsivity, neuroticism, negative emotion and depression scores in BPD compared to controls. Due to the rather small sample sizes for behavioural measurements this is not a primary aim of the thesis. No specific *a priori* hypotheses is made.

2 Overall Methods

2.1 Design

Data acquisition for all studies consisted of two separate sessions that were covered in one day per participant and took place at the Trinity College Institute of Neuroscience, Dublin between April 2009 and June 2011. In the first session all participants were asked to undergo a comprehensive psychological assessment that included filling in questionnaires and a structured interview conducted by a licensed psychiatrist. The average time spent on the first session was 90 minutes. Subsequently, participants underwent MR imaging for 50 minutes during the first and last 15 minutes of which anatomical images were acquired. Most session days were conducted on a Tuesday afternoon. Participants spent roughly three hours at the institute. Prior to the study, participants were informed about all its aspects and signed a written consent form (see Appendix A).

All participants were screened for their suitability of undergoing MRI (i.e. no internal metal parts, non-claustrophobic) and gave their informed consent according to the guidelines of the St. James's and Ethics Committee of the Adelaide and Meath Hospital incorporating the National's Children's Hospital (AMNCH) in Dublin, by which the study had been approved.

2.2 Participants

As BPD is much less frequently found in men (75% of those with the disorder are women (John M. Oldham, 2004)), it was decided to have the participant groups consist solely of women to avoid potential gender based differences. The BPD patient group were receiving continuous treatment from the South-West mental health services in Dublin. The BPD participants were all attending outpatient clinics for years. Thus, patients were well known to the service and mainly were treated in

outpatient and home care, when necessary with crisis admission. Only when the continuous care consultant indicated these inclusion criteria we further interviewed them for suitability to the study. Diagnosis according to DSM-IV was thus confirmed by a second psychiatrist. SCID-II was used to diagnose BPD and SCID-I was used to exclude comorbid axis-I disorders other than MDD. A cohort of 21 healthy female volunteers with ages between 20 and 47, and a mean age of 30.1 years ($SD=8.0$), was recruited from the local community. An effort was made to match both samples with respect to gender and age in so far as similar age ranges were chosen and the distributions regarding age and education levels did not significantly differ from each other.

Healthy volunteers did not undergo conventional SCID-I/II interviews, however, they completed the same battery of psychometric assessment on the day of testing and immediately before MRI scans were obtained. This battery importantly included scales of Depression (BDI and HRSD) on the basis of which one healthy volunteer had to be excluded from the control subjects' sample.

The volunteers and patients were carefully screened for medical conditions to ensure that none had a personal history of neurological disorder, severe medical illness, head injury or substance dependency. Healthy participants were excluded if they had a personal history of any psychiatric disorder (axis I or axis II (APA, 1994)) and the BPD participants were excluded if they had any additional psychiatric disorder other than comorbid major depression (MDD) at present or in the past. Demographic variables and inclusion and exclusion criteria were assessed using a standardised questionnaire and through structured interview based on SCID-I by registered psychiatrists.

One patient had not completed the first session and another patient had not completed the second session. Three patients had to be excluded from functional MRI analysis due to excessive movement at some point during the scanning session. The cut-off point chosen for this purpose

was a head movement of >3.5mm in any direction which relates to the size of one voxel used in the functional analysis (see 2.6).

Exclusion criteria for all patients and controls were severe medical illnesses, drug or alcohol dependency, other psychiatric axis one diagnosis other than depression. Additionally, healthy controls were not allowed to have any psychiatric disorder.

The details on the samples sizes used for each study please are given in each chapter.

The samples used in *Study 2* and *Study 3* were made up of seventeen BPD-patients (Pat) and the nineteen participants (HC) from *Study 1* whom they were compared to.

Study 4 included all participants, except the two healthy controls that had been excluded on the basis of psychological assessment: 20 Pat were compared to 21 HC.

2.3 Psychometric assessment

A number of psychometric questionnaires and a clinical interview were administered to all participants. These questionnaires have been proven useful in previous clinical studies (American Psychiatric Association Practice, 2001; A. Arntz & ten Haaf, 2012; Baer et al., 2012; Suvak et al., 2012). A questionnaire to assess the appreciation of humour (W. Ruch, 1992) was added since a humour task (see 2.5) was used analyse brain function later on in the thesis.

In the following each of the questionnaires that were used to assess participants psychologically is described briefly. The complete questionnaires can be found in the *Appendix*.

2.3.1 Hamilton Depression Rating Scale (HDRS)

The HDRS (M. Hamilton, 1967) is a structured interview that is used to determine the level of depression before during, and after treatment. It

is based on the clinician's interview with the patient and probes symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels and weight loss. The interview and scoring takes about 15 minutes. The examiner enters a number for each item (scale 1-3). Since the HC sample had volunteered as "healthy participants" in the first place the main purpose of conducting the HDRS interview was to make sure they were not clinically depressed at the time of scanning. Correspondingly the scoring of item number (see *Appendix*) was adjusted to "0" in the case that participants 'denied being depressed at all'.

2.3.2 Beck's Depression Inventory (BDI)

The BDI (A. T. Beck & Steer, 1984) is a series of questions developed to measure the intensity, severity, and depth of depression in patients with psychiatric diagnoses. It is composed of 21 items, each designed to assess a specific symptom common among people with depression.

2.3.3 Eysenck Personality Questionnaire (EPQ)

The EPQ measures a person's personality traits based on Eysenck's (S. B. Eysenck & Eysenck, 1964) theory of personality. The short scale version of this questionnaire has 48 yes/no questions). Eysenck initially conceptualised personality as three, biologically-based independent dimensions of temperament measured on a continuum:

Extraversion/Introversion: Extraversion is characterised by being outgoing, talkative, high on positive affect (feeling good), and in need of external stimulation. Extraverts, according to Eysenck's theory, are chronically under-aroused and bored and are therefore in need of external stimulation to bring them up to an optimal level of performance. About 16% of the population tends to fall in this range. Introverts, on the other hand, (also about 16% of the population) are chronically over-aroused and jittery and are therefore in need of peace and quiet to bring them up to an optimal level of performance. Most people (about 68% of

the population) fall in the midrange of the extraversion/introversion continuum, an area referred to as *ambiversion*.

Neuroticism/Stability: Neuroticism or emotionality is characterised by high levels of negative affect such as depression and anxiety. Individuals who score high on neuroticism are more likely than the average to experience such feelings as anxiety, anger, envy, guilt, and depressed mood. At the opposite end of the spectrum, individuals who score low in neuroticism are more emotionally stable and less reactive to stress.

Psychoticism/Socialisation: Psychoticism is associated not only with the liability to have a psychotic episode (or break with reality), but also with aggression. Psychotic behaviour is rooted in the characteristics of tough-mindedness, non-conformity, inconsideration, recklessness, hostility, anger and impulsiveness.

The fourth scale of the EPQ is the 'Lie' Scale that assessed the examinees likelihood to lie.

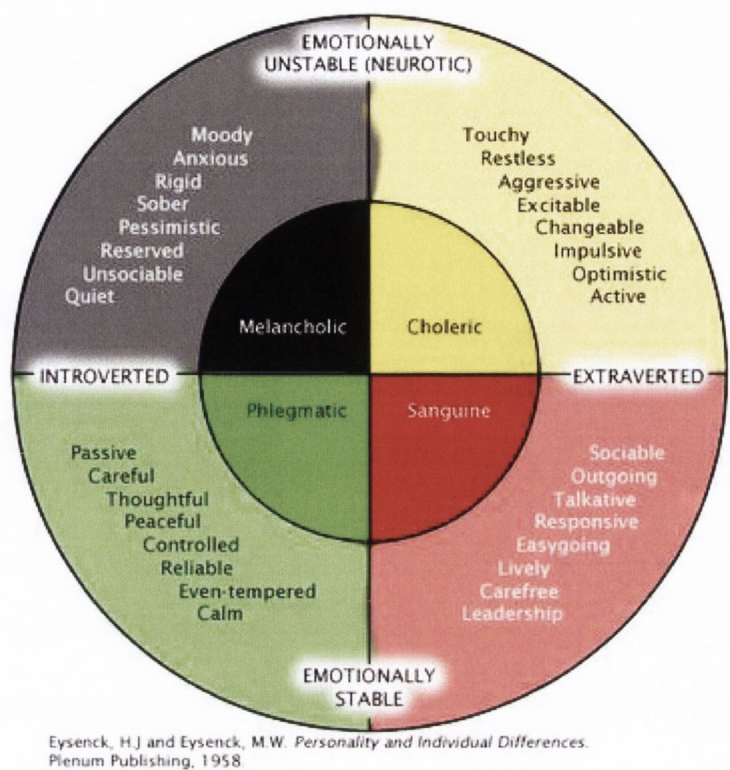


Figure 2-1: Eysenck chart.

2.3.4 Barratt Impulsiveness Scale (BIS)

The Barratt Impulsiveness Scale (Patton, Stanford, & Barratt, 1995) is a 30-item self-report instrument designed to assess the personality/behavioural construct of impulsiveness. The BIS-11 includes 30 items which may be scored to yield six first-order (attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability impulsiveness) and three second-order factors (attentional, motor, and non-planning impulsiveness).

2.3.5 Sensation seeking scale (SSS)

The SSS (Zuckerman & Link, 1968) consists of 40 items, each having two options from which the participant must choose one. It has four primary scales (Disinhibition, Boredom Susceptibility, Thrill and Adventure Seeking, Experience Seeking) and one total score.

2.3.6 Positive Affect Negative Affect Scale (PANAS)

The PANAS is a 20-item self-report measure of positive and negative affect developed by Watson, Clark, and Tellegen (1988). Negative Affect (NA) and Positive Affect (PA) reflect dispositional dimensions, with high-NA epitomised by subjective distress and unpleasurable engagement, and low NA by the absence of these feelings. By contrast, PA represents the extent to which an individual experiences pleasurable engagement with the environment. Thus, emotions such as enthusiasm and alertness are indicative of high PA, whilst lethargy and sadness characterise low PA (D. Watson et al., 1988). The PANAS is claimed to provide independent measures of PA and NA.

2.3.7 State-Trait Cheerfulness Inventory (STCI)

The STCI (W. Ruch, Kohler, & vanThriel, 1996) is a self-report instrument measuring the three concepts of cheerfulness, seriousness, and bad mood as both states (STCI-S) and traits (STCI-T). They are 20 and 10 items per scale in the STCI-T and STCI-S, respectively, and both parts utilize a 4-point Likert scale (“*strongly disagree*” to “*strongly agree*”).

The concepts are considered to assess the temperamental basis of humour and the scales have been validated in a variety of studies. The trait part is reliable and state part is sensitive to change.

2.3.8 Gelotophobia-gelotophilia-katagelasticism (PhoPhiKat)

The PhoPhiKat (W. Ruch, Beermann, & Proyer, 2009) is a 45-item questionnaire. It yields three scores that measure the extent of gelotophobia, gelotophilia, and of katagelasticism in the personality of the examinee.

Gelotophilia describes the joy of being laughed at. Gelotophiles are persons that actively seek and establish situations in which others may laugh at them.

Katagelasticism refers to the psychological condition in which a person excessively enjoys laughing at others. Katagelasticists actively seek and establish situations in which they can laugh at others (at the expense of these people).

Gelotophobia is used to describe people who have a “*fear of being laughed at*”. Gelotophobia correlates highly with introversion and neuroticism.

2.3.9 State-Trait Anxiety Inventory (STAI)

The STAI (Spielberger, 1983) investigates how respondents felt at a particular time in the recent past and how they anticipate they will feel either in a specific situation that is likely to be encountered in the future or in a variety of hypothetical situations. It is found to be a sensitive indicator of changes in transitory anxiety. The STAI assesses the level induced by stressful experimental procedures and by unavoidable real-life stressors such as imminent surgery, dental treatment, job interviews, or important school tests.

The *S-Anxiety* scale consists of twenty statements that evaluate how respondents feel “right now, at this moment.” The *T-Anxiety* scale consists of twenty statements that assess how respondents feel “generally.” Responses are given on a 4-point Likert-scale from “almost never” (1) to “almost all the time” (4).

2.4 Stimuli

According to psychological theories of humour a residual incongruity, i.e., a conflict between two initially opposed scripts or schemas has to be detected and then playfully resolved by recognising a relation between the two scripts. Examples of the three experimental conditions INC, PUN, and TOM are given below. The cartoon used in the experiments had successfully been used by Samson et al (2008) and had been classified on the basis of ratings according to the 3 WD

humour test (W. Ruch, 1992). The three groups of cartoons were also shown to be processed differently by subjects with varying degrees of empathising skills: for example, people with lower empathising skills tend to give fewer emotional/motivational and mentalistic explanations, particularly in TOM cartoons when asked to explain why they think a cartoon is funny (A. C. Samson et al., 2009).

The complete set of cartoons that were used as stimuli in this dissertation can be seen in the *Appendix*.

2.4.1 Incongruent Condition (INC)

The INC condition in this experiment was made up of trials which are cartoons in which the above mentioned incongruity could not be resolved meaningfully. For example, in Figure 2-2 a human teacher explains a map to a non-human robot (residual incongruity). It remains unclear why she does this (non-resolution). Cartoons of this type nevertheless may be perceived as funny. However the cognitive logical mechanism of stepwise resolution does not apply.

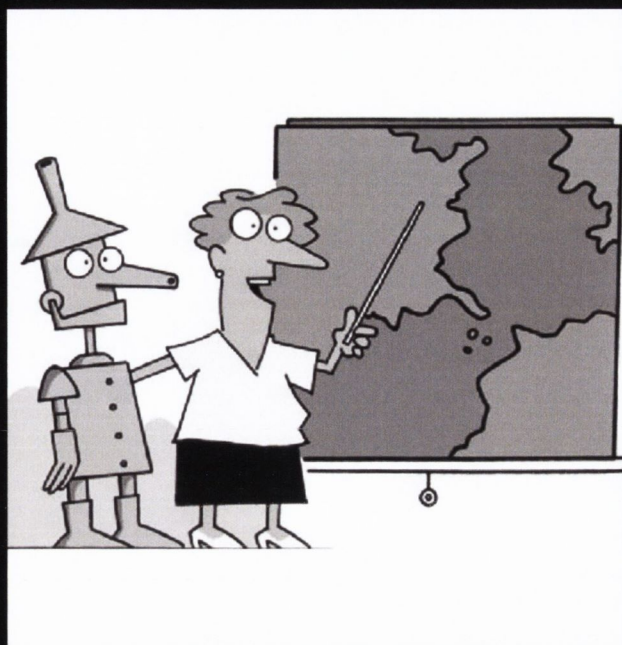


Figure 2-2: Example of INC cartoon.
The incongruity in this picture cannot be resolved meaningfully.

2.4.2 Meaningful Resolution Condition (PUN)

The PUN condition consisted of cartoons in which a residual incongruity can potentially be resolved meaningfully. This resolution represents the “punch line” of the joke. An example of a PUN picture is given in Figure 2-3: at first glance a little fish seems to be about to be eaten by a bigger fish. Only at second glance does the bigger fish appear to be made up of a swarm of little fish (resolution).

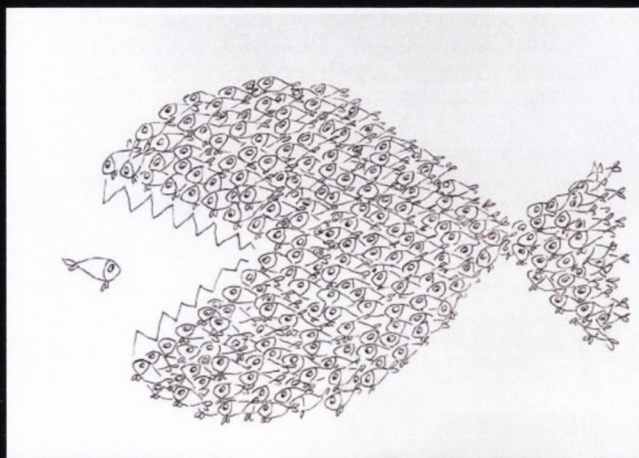


Figure 2-3: Example of PUN cartoon.

The meaningful resolution is that the little fish will not be eaten by a bigger fish.

2.4.3 Theory-of-Mind Condition (TOM)

Residual incongruities in cartoons of the TOM condition could be resolved logically and in a meaningful way much like in PUN cartoons. The main characteristic, however, of TOM cartoons was that in order to meaningfully resolve the initial incongruity one was required to mentally take the perspective of one of the characters in the cartoon. Only if a pre-structured expectance can be attributed to a person effortlessly is one able to “get the joke” instantly in the given amount of time.

Figure 2-4 shows two people the woman is about to be hit by a rock and nothing seems to prevent that from happening. Instead, the man is ready to take a picture of her. It is important to notice that the man, who would not be affected by the rock crashing down, is clearly able to see it already in motion. One may conclude that the woman is the man’s annoying wife whom he tries to trick into being buried by a stone.



Figure 2-4: Example of TOM cartoon.

The resolution includes a Theory-of-Mind component: The woman has a false belief; she does not see the stone. The man has a different intention than taking a photograph.

The characteristic of every TOM stimulus can be summarised in three crucial steps of which the last one represents the Theory-of-Mind component:

- The observer (of the cartoon) realises that something is about to happen and acknowledges that Agent 1 (here: the man taking the picture) realises this as well.
- Agent 2 (here: the woman) does not know or has a 'false belief', respectively.
- The observer identifies Agent 2's belief as false (here: the observer sees that Agent 2 cannot see the rock, hence she will expect to be photographed).

Since it is known that humour with sexual content is perceived differently and personality characteristics influence how this type of humour is perceived, sexual cartoons were explicitly excluded already in the pre-examinations: ". . .[it was]. ..searched . . . for single-frame,

nonverbal cartoons that intended to be primarily funny (not political) without sexual content, because the preference or dislike for sexual cartoons is known to correlate highly with certain personality characteristics.” (A. C. Samson et al., 2008, p. 128).

2.4.4 Rest Condition (NULL)

In order to be able to measure the brain activity during resting state (the so called default mode network, see *Study 3*) a fourth condition was added to the original

2.5 fMRI task

The stimulus material consisted of three types of cartoons described above (INC, PUN, and TOM). All pictures were low in aggressive, violent, and sexual content. During the experiment, a total of 90 cartoon pictures were presented. In order to investigate brain activity during resting state (see Chapter 6) 30 rest trials (NULL) were interleaved.

Before entering the MRI facilities participants were given a written instruction (see Appendix). While lying in the scanner they would be holding a button box in their right hand and required to make one of two responses (left/right button press) after each of the stimuli that were presented to them. All participants processed a total of 120 trials.

- 30 INC pictures
- 30 PUN pictures
- 30 TOM pictures
- 30 NULL-events

Each stimulus was onset for 6000ms. Below each picture (cartoon) the word “understood” was printed on the left side and the words “not understood” were printed on the right side. Participants were asked to press the corresponding button (left/right) with their index or middle finger, respectively, depending on whether they understood the joke or did not recognise any sort of punch line. It was explained to them that

not all the cartoons would contain jokes and that not all jokes would necessarily be funny. It was further stressed to participants that, owing to the subjective nature of humour appreciation, none of their responses could ever be “incorrect” and that they ought to press a button on every trial as soon as they had made up their minds. Figure 2-5 shows the time course of a trial in the fMRI task.

Stimuli were presented every 10s on average and with variable stimulus onset delays (0, 400, 800, 1200, or 1600 ms). The cartoons were projected with an LCD-Projector onto a translucent screen behind the subject's head. The screen was viewed with mirror lenses attached to the head coil. The following stimuli were projected visually in one of 5 counterbalanced pseudo-random orders using the stimulus delivery software Presentation (Neurobehavioral Systems, Inc.):

By pressing a button the participants had to indicate whether they understand the joke in the cartoon or not, while recognition time is measured. This procedure allowed for the distinction between cartoons that were understood but not considered funny and cartoons that were not understood and therefore not funny. Cartoons that were not understood were excluded from further analysis. Comprehensibility responses were given via a button press with either the index (understood) or middle (not understood) finger of the right hand.

The functional neuroimaging part started after 15 minutes of the scanning session (during which the structural image was acquired) and took about 18 minutes.

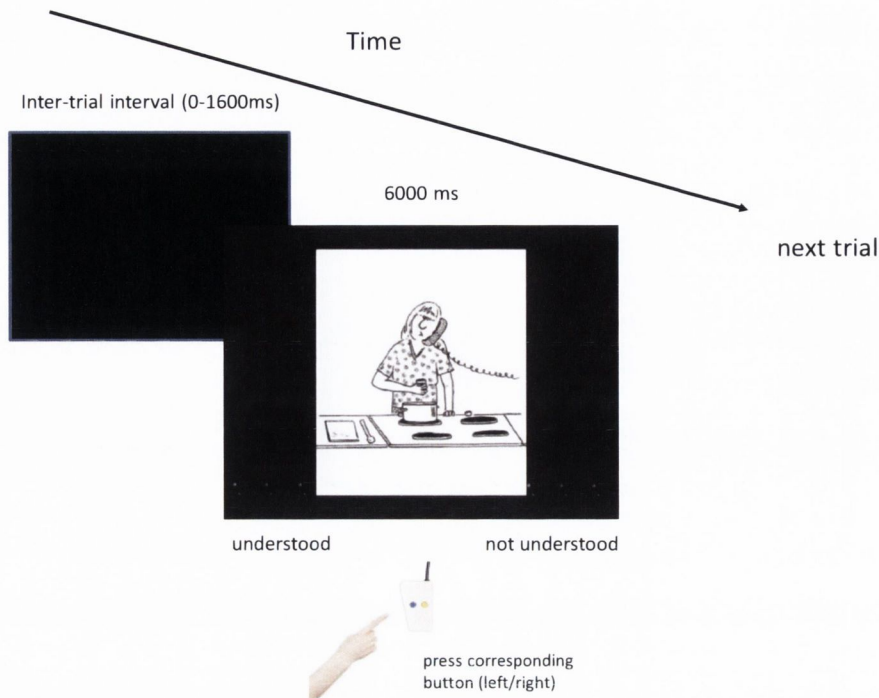


Figure 2-5: Time course of the fMRI task.

2.6 MRI Data acquisition

MRI images were obtained with a 3.0 Tesla MRI scanner dedicated to research (Phillips Achieva). For the cognitive paradigm, 26 axial slices (3.5 mm× 3.5 mm× 3.5 mm resolution, 0.75 mm spacing), parallel to the AC-PC plane and covering the whole brain were acquired using a single shot, gradient recalled EPI sequence (TR 2000 ms, TE 30 ms, 90° flip angle). One functional run with 620 time points was acquired, with each time point sampling over the 26 slices. Prior to the functional run, 180 anatomical slices T₁-weighted 3D-MPRAGE sequence (repetition time, 11.0 ms; echo time, 4.4 ms; total acquisition time, 7 min 30 sec; number of acquisitions, 1; field of view, 250 mm× 256 mm × 160 mm; matrix: 256 mm × 256 mm; resolution: 0.9 mm × 0.9 mm × 0.9 mm) with the same spatial orientation as the functional data were acquired.

2.7 MRI data analysis

For data analysis SPM8 (Statistic Parametric Mapping, Wellcome Trust Centre for Neuroimaging, UCL, UK) was used. The contrasts chosen and statistics employed are described in the respective chapters.

Results were superimposed on axial (z), coronal (y), and sagittal sections (x) of the single-subject structural MNI MRI template (used in all figures and displayed in neurological convention).

For all comparisons, functional (*Studies 1-3*) and structural (*Study 4*) differences (increases/decreases) were assessed at whole-brain level using cluster level statistical analyses (cluster level, $p < 0.05$, FWE corrected with a primary threshold of $p < 0.001$). Regions of interest (Poldrack, Halchenko, & Hanson, 2009) were defined using the Wake Forest University PickAtlas Toolbox, Version version 3.0.3 (Maldjian et al., 2003). For all reported contrasts clusters of difference were reported with a spatial extent threshold of 15 contiguous voxels for group interactions was chosen. As no functional neuroimaging studies of BPD were available at the time data collection for this thesis started it was decided to use the same spatial extent threshold as Lisiecka et al. (2011) who carried out a similar analysis on a data set from patients with MDD. A functional MRI study that was published later (Mier et al., 2012) and used a BPD sample chose to set the spatial extent threshold for reported clusters at 10 voxels.

To further protect against *Type I* error, a small-volume correction (SVC) was applied at peak- level (cut-off value: 0.05, FWE voxel-corrected). Coordinates of peak significant voxels were assigned to anatomical regions by means of Automated Anatomical Labelling (AAL, see 2.9).

2.8 Statistical power

The analysis of statistical power based for the different MRI modalities is not straightforward since for computational analysis methods such as voxel-based morphometry, the effect size largely varies between brain

location and will be influenced by the number of voxels analysed (Ewers et al., 2005). However, a number of voxel-based analysis studies are now available that allow for a rough estimate of the sample size required in order to detect AD (Alzheimer's disease) typical pattern of atrophy. For region-of-interest (ROI) analyses (Poldrack et al., 2009), meta-analytical studies were available to provide a robust estimate of the expected effect size.

For region-of-interest analyses of key structures affected in BPD such as the hippocampus, The Derimonian-Laird pooled effect size revealed bilateral statistical significance: -0.38 (95% CI= -0.65 to -0.11) for the left hippocampus and -0.32 (95% CI= -0.56 to -0.08) for the right hippocampus in a meta-analysis over 12 studies (Videbech & Ravnkilde, 2004). The sample size required to detect such an effect with a power of 0.85 and an alpha significance level of 0.05 is $N = 20$. This is also the sample size that other recent neuroimaging studies have used with BPD patient samples (Kluetsch et al., 2012; Mier et al., 2012).

Using voxel-based morphometry (VBM, see Chapter 7) 15 patients with depression showed reduced grey matter concentration (GMC) in the left inferior temporal cortex (BA 20), the right orbito-frontal (BA 11) and the dorsolateral prefrontal cortex (BA 46) compared to 14 healthy controls. Reduced grey matter volume (GMV) was found in the left hippocampal gyrus, the cingulate gyrus (BA 24/32) and the thalamus (Vasic, Walter, Hose, & Wolf, 2008). In voxel-based morphometry study, Frodl et al. (2008) detected significant alterations of GMV in the hippocampus and prefrontal regions between 14 patients homozygous for the L-allele of the serotonin transporter polymorphism and 22 patients homozygous for the s-allele of this polymorphism. The sample size should therefore be 20 patients.

In general, the blood-oxygen-level-dependent (BOLD) signal change, being the basis of the fMRI experiment, is highly variable and generally out of the experimenter's control. Simulation studies combined with

parameters derived from experimental sessions have shown that for an alpha threshold of 0.002 about 20 subjects are required to achieve 80% power at the single-voxel level for typical activations (Desmond & Glover, 2002).

2.9 Anatomic labelling

In order to guarantee objective and consistent labelling of brain regions the Automated Anatomic Labelling Toolbox (AAL, Tzourio-Mazoyer et al., 2002) was used to identify in which activity differences were observed. Hence, all the tables use the specific terminology specified by the AAL toolbox. Depending on the context (functional, structural) research discipline (neurology, psychology, linguistics) and resolution of brain images in which the brain is described different terminologies have been used to label brain regions. This holds especially true for regions of the network involved in social cognition that were discovered in recent years. The temporo-parietal junction (TPJ) for example is a junction between two lobes (morphological units) functionally related to a social context, much like the orbito-frontal cortex (OFC) is a functional unit that between several BA units that has been related to reward in the brain.

To date there is no standard social (cognitive) neuroscience terminology for regions such as TPJ and OFC the AAL labels are reported in all results tables and all coordinates are reported in terms of MNI space. These labels are then functionally re-interpreted in the discussion.

3 Psychometric Assessment

3.1 Introduction

Personality traits can be considered a class of potential etiological factors that may serve as a predisposition or vulnerability to BPD pathology. For example, the presence of a particular personality trait or combination of traits may make it more likely that an individual will develop BPD features. The personality traits that have been most consistently associated with BPD are impulsivity and affective instability, particularly negative affect (see 1.1.1). Impulsivity is reflected in the oftentimes erratic behaviour of BPD patients; the tendency to react quickly, intensely, and inappropriately to real or perceived frustrations and setbacks; and susceptibility to substance use, eating, or impulse-control problems (John M. Oldham, 2004). At least two studies have demonstrated that BPD diagnoses or symptom counts are positively correlated with inventory scores reflecting impulsivity or disinhibition (Ball et al., 1997; Svrakic, Whitehead, Przybeck, & Cloninger, 1993).

Measures of Neuroticism consist of items referring to negative affect, including anxiety, irritability, anger, worry, frustration, self-consciousness, sensitivity to criticism, reactivity, hostility, and vulnerability (Costa & McCrae, 1992; H. J. Eysenck & Eysenck, 1975). Hence, neuroticism is widely defined as the tendency to experience negative affect, especially when threatened, frustrated, or facing loss.

Neuroticism is also the single most important factor associated with many forms of psychopathology and behavioural health, in particular the common mental disorders including anxiety, depressive, and substance use disorders (see for reviews Kotov, Gamez, Schmidt, and Watson (2010); Lahey (2009); Ormel et al. (2013)). The prospective associations between neuroticism and psychopathology have prompted many authors to consider neuroticism a robust independent predictor of

psychopathology (Lahey, 2009). In a recent attempt to integrate the behavioural, neuroimaging and neuropsychological findings Ormel et al. (2013) reviewed evidence and concluded it suggests that neuroticism reflects reduced control over and increased self-referential evaluation of negatively valenced stimuli.

Impulsivity, a core feature of BPD, is considered to be an underlying dimension of this disorder (Lieb et al., 2004; Paris, 2007) and a central aspect in the understanding of the nature of BPD psychopathology (Paris, 2005a, 2007). It had previously been correlated with BPD morbidity and mortality (J. M. Oldham, 2004; Oldham, 2006) and clinically it is characterised by severe behavioural disturbance expressed by a pattern of impulsive aggressive behaviours like repetitive self-destructive behaviour, substance abuse, risky sexual behaviour, angry outbursts, among others (APA, 1994).

The broad concept of impulsivity understood as a stable trait of personality has been characterised as a multidimensional construct (Flory et al., 2006). Several previous studies found that BPD patients present high levels of trait impulsiveness and aggressiveness when measured by standard self-report instruments that have shown to capture these concepts of impulsivity. Impulsiveness as a broad personality trait can be measured by the Barratt impulsiveness scale (BIS, Patton et al., 1995), a widely used instrument in the study of impulsivity. Different studies suggested that when assessed by this instrument, BPD patients report high levels across all aspects of impulsivity (Kunert, Druecke, Sass, & Herpertz, 2003; Paris, 2005b).

Finally, there is a high association between BPD and clinical depression (MDD). MDD is the most frequent comorbidity to BPD as outlined in 1.1.1. Although genotype- and endophenotype-comparisons revealed that the two disorders are distinct from each other (Goodman, New, Triebwasser, Collins, & Siever, 2010) a recent study was able to show that patients with BPD and MDD are not distinguishable by their neuropsychological performance (Beblo et al., 2011).

It is useful to replicate and clarify previous results in order to accomplish a complete understanding of the role of impulsivity and neuroticism in BPD. It is not clear whether *ToM* dysfunction plays a role in BPD, and/or if this dysfunction is related to these traits.

A *Psychometric Assessment* was conducted as an exploratory to assess the profile of the samples of BPD patients and healthy controls that were used in the further studies and in order to use measures of impulsivity and neuroticism as covariates in *Study 1* and *Study 4*, respectively. It was further aimed to confirm higher impulsivity, neuroticism, negative emotion and depression scores in BPD compared to controls. Due to the rather small sample sizes for behavioural measurements this was not a primary aim of the thesis. No specific a priori hypotheses were made.

3.2 Methods

A structured interview (HDRS (M. Hamilton, 1967), see 2.3.1) and the below self-report measures were administered to 20 BPD patients and 21 healthy controls as described and outlined in the Overall Methods section (Chapter 2):

- Beck's Depression Inventory (A. T. Beck, Rial, & Rickels, 1974)
- Eysenck Personality Questionnaire (S. B. Eysenck, 1962)
- Barratt Impulsiveness Scale (BIS) (Zuckerman & Link, 1968)
- Sensation seeking scale (SSS) (Patton et al., 1995; Zuckerman & Link, 1968)
- Positive Affect Negative Affect Scale (D. Watson et al., 1988)
- State-Trait Anxiety Inventory (Spielberger, 1983)
- State-Trait Cheerfulness Inventory (W. Ruch et al., 1996)
- Gelotophobia-gelotophilia-katagelasticism Questionnaire (W. Ruch, 1992)

T-test comparisons were made after checking the variables for normal distributions and homogeneity of variance (df were adjusted were

necessary). Results are presented for the groups (Pat and HC) for which neuroimaging data are available (see also 2.2 for demographic information and exclusion criteria). Among the patient group not every participant completed each questionnaire. Group sizes (N) are reported for each comparison.

All participants underwent psychological assessment prior to an MRI scanning session. Participants were sat in a quiet room and the above order in which the measures were taken was kept constant for all participants. All scores, means, and independent *t*-tests were computed using PASW Statistics 18 (Predictive Analytics SoftWare, SPSS Inc.). Demographic information is provided in Table 3-1. Twelve out of seventeen patients were taking anti-depressants of various types at the time of investigation.

Table 3-1: Demographic information

	BPD patients	Controls	Statistics
Age	31.4 ± 9.5	29.3 ± 7.5	ns
Height	165.2 ± 6.2	168.0 ± 5.3	ns
Weight	71.6 ± 14.7	60.7 ± 8.3	t=2.79; df=22.8; p<0.01
Cigarette consumption	11.7± 11.1	1.5 ± 3.6	t=3.68; df=17.6; p<.005
Alcohol units per week	4.1 ± 7.7	3.4 ± 3.7	ns
Education	2.5 ± 0.72	2.88± 0.33	t=-1.71; df=9.8; p<.05

The level of education was measured in three categories where 1=no completed secondary level education, 2= secondary education, 3=third level education and a t-test with adjusted number of degrees of freedom was used to assess the difference between groups. Given the amount of questionnaires that participants were asked to complete, it was decided not to obtain individual IQ measures, which, however, would have been optimal.

3.3 Results

3.3.1 Hamilton Rating Scale for Depression (HDRS) and Beck's Depression Inventory (BDI)

The severity of major depression symptoms as obtained by the HDRS total score was significantly higher in patients ($M_1=24.31$, $SD_1=10.29$) than in healthy controls ($M_2=0.37$, $SD_2=0.76$, $t(33) = 10.16$, $p<0.001$, Figure 3-1). A comparison of BDI total scores confirmed a significantly higher level of depression in patients ($M_1=41.62$, $SD_1=10.14$) than in healthy controls ($M_2=4.26$, $SD_2=3.60$, $t(33)=15.01$, $p<0.001$).

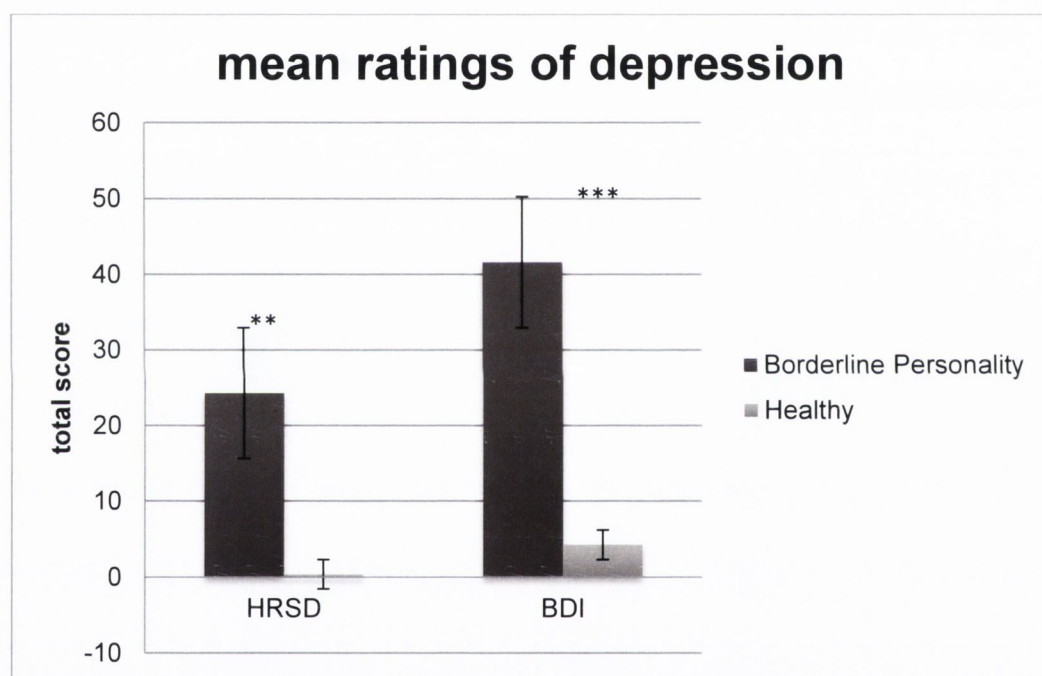


Figure 3-1: Ratings of Depression.

Mean HDRS and BDI total scores for BPD patients ($N_1=16$) vs. healthy controls ($N_2=19$).

Measures of depression obtained by administering a structured interview (HDRS) were highly correlated with those obtained by questionnaires (BDI). Pearson's $r=0.84$, $p=0.01$ (Figure 3-2).

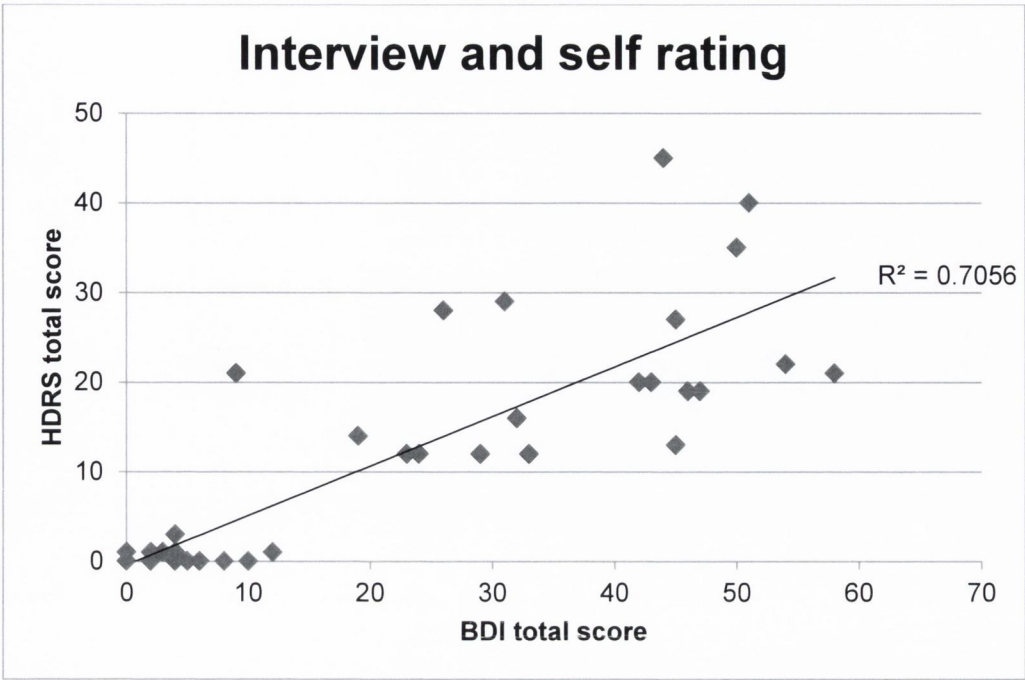


Figure 3-2: Interview and self-rating.
Correlation of HDRS- and BDI- total scores for all subjects who had undergone both examinations (N=41).

3.3.2 Eysenck Personality Questionnaire (EPQ)

BPD patients perceived themselves as more neurotic and less extraverted than did the healthy control group (Table 3-2). No significant differences were found regarding the EPQ-subscales ‘Psychoticism’ and ‘Lie’.

Table 3-2: Comparison of Eysenck Personality Questionnaire Ratings.
Borderline Personality Disorder (N₁=17) vs. Healthy Controls (N₂=19).

EPQ-subscale	M ₁	SD ₁	M ₂	SD ₂	t(34)	p (2-tailed)
Psychoticism	2.82	1.59	2.68	1.97	0.23	ns
Lie	3.76	2.2.17	4.15	2.29	-0.527	ns
Neuroticism	10.52	1.37	3.63	2.73	9.714*)	< 0.001
Extraversion	4.47	3.89	9.42	3.18	-4.195	< 0.001

*) The variances for Neuroticism differed significantly between the two groups (Levene’s $F=8.25$; $p<0.01$, 2-tailed). However, when using an adjusted t-test to account for that ($df=31.5$) the difference in Neuroticism scores remains highly significant ($p<0.001$, 2-tailed).

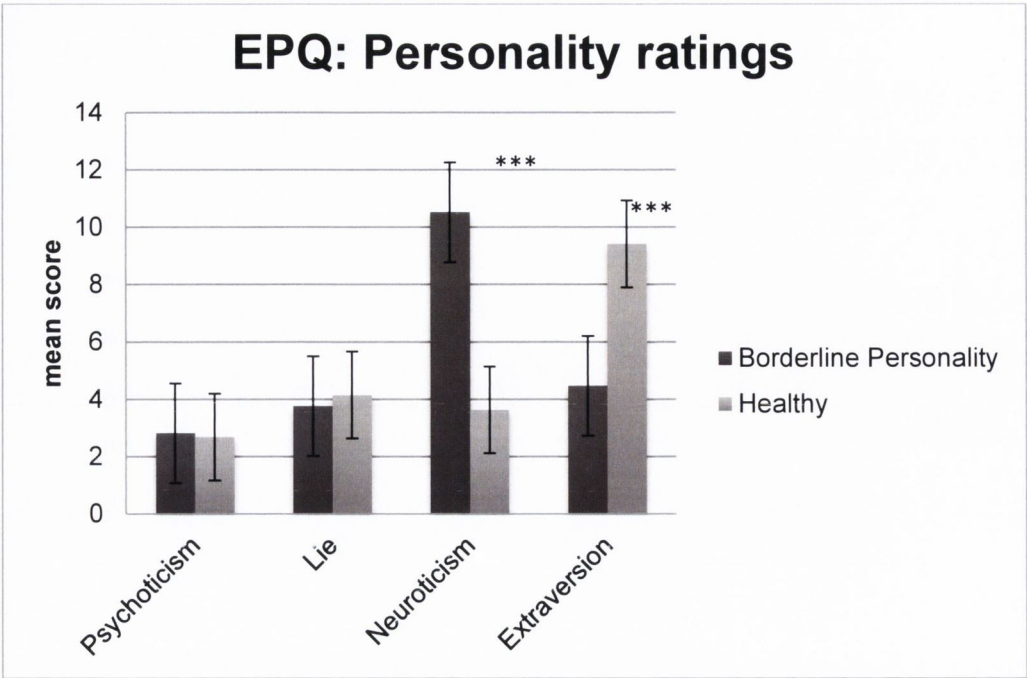


Figure 3-3: Personality ratings (EPQ).
Mean ratings for the EPQ subscales Psychoticism, Lie, Neuroticism, and Extraversion for BPD patients ($N_1=17$) vs. healthy controls ($N_2=19$).

3.3.3 Barratt Impulsiveness Scale (BIS)

According to the BIS total score, BPD patients rated themselves to be more impulsive ($M_1=79.56$, $SD_1=7.21$) than the healthy control group did ($M_2=64.0$, $SD_2=10.82$, $t(33)=5.54$, $p<0.05$). Significant differences can be traced back to each of the subscales of the BIS questionnaire.

Table 3-3: Comparison of Barrett Impulsiveness Scale Ratings.
BPD patients ($N_1=16$) vs. Healthy Controls ($N_2=19$).

2 nd order BIS scale	M ₁	SD ₁	M ₂	SD ₂	t(33)	p (2-tailed)
Attentional I.	20.47	2.63	15.32	3.26	5.52	<0.001
Motor I.	28.0	6.08	23.86	5.56	2.22	<0.001
Nonplanning I.	31.63	5.37	23.91	4.42	5.05	<0.05

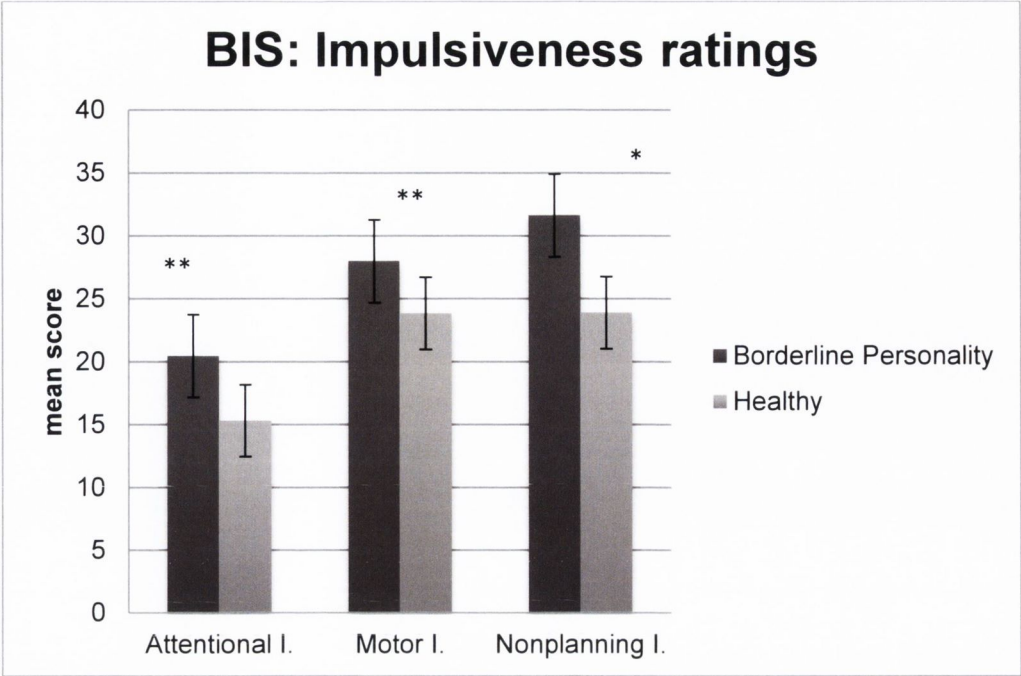


Figure 3-4: Impulsiveness ratings.
Mean BIS-subscale ratings for BPD patients ($N_1=16$) vs. healthy controls ($N_2=19$).

3.3.4 Sensation seeking scale (SSS)

Sensation seeking as obtained by the SSS was significantly different for the ‘Thrill’ and ‘Adventure Seeking’ (SSS_THR) subscale in that patients ($M_1=2.88$, $SD_1=3.29$) were more thrill seeking than were healthy controls ($M_2=2.38$, $SD_2=1.72$, $t(33)=-2.14$, $p<0.05$). No significant difference was found for the other subscales Disinhibition (SSS_DIS; $t(33)=-0.54$), ‘Boredom Susceptibility’ (SSS_BOR; $t(36)=0.93$), ‘Experience Seeking’ (SSS_EXP; $t(33)=-1.11$), and the total score (SSS_TOT; $t(33)=-1.27$).

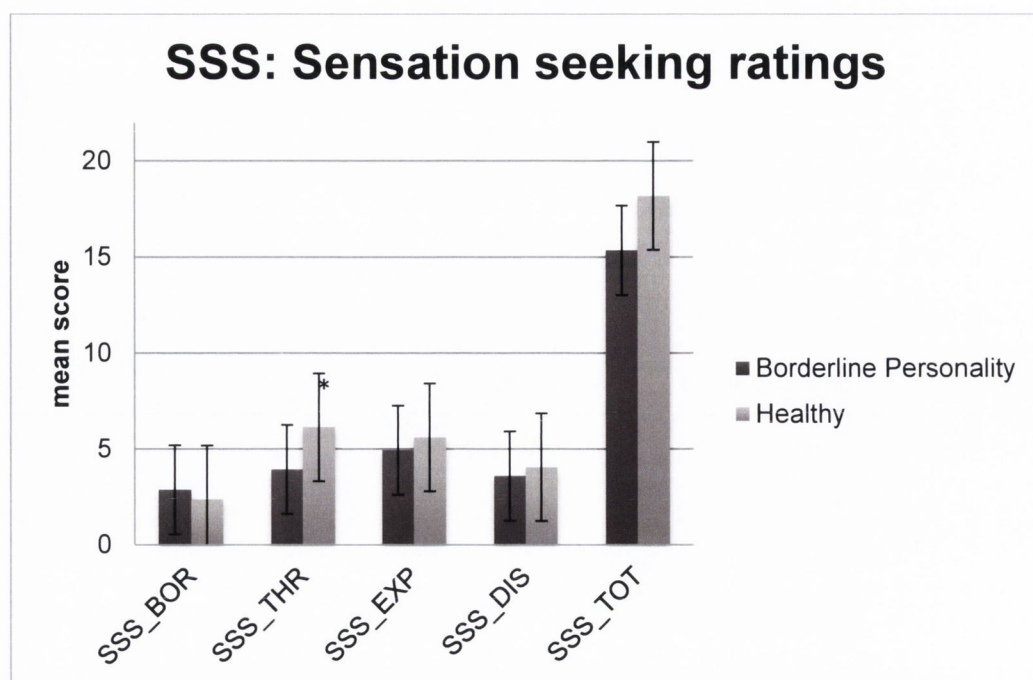


Figure 3-5: Sensation seeking ratings.

Mean SSS sub-scores and total score for BPD patients ($N_1=17$) vs. healthy controls ($N_2=19$).

3.3.5 Positive Affect Negative Affect Scale (PANAS)

The means of the two general Dimensions *Positive Affect* and *Negative Affect* as measured by the PANAS were both significantly different in patients and healthy controls. Indeed, the two groups showed highly significant ($p<0.01$) differences in for the means of nearly all the independent descriptors, the few exceptions being 'Sadness' and 'Surprise'.

General Dimensions

Table 3-4: Comparison of Positive Affect Negative Affect–General Dimensions ratings.

Borderline Personality Disorder ($N_1=16$) vs. Healthy Controls ($N_2=19$).

	M_1	SD_1	M_2	SD_2	df	t(df)	p
Negative Affect	31.67	8.15	16.50	6.09	32	6.74	< 0.001
Positive Affect	20.59	6.10	31.81	3.99	31	-5.02	< 0.001

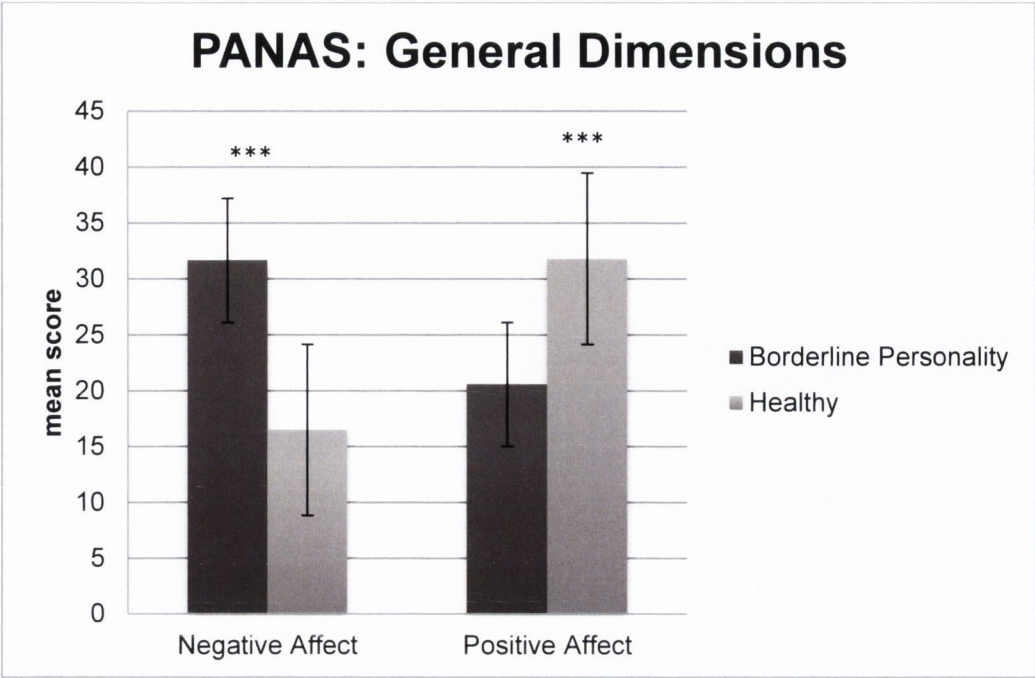


Figure 3-6: PANAS General Dimensions.
Mean scores for PANAS-Negative Affect and Positive Affect for BPD patients ($N_1=15$) vs. healthy controls ($N_2=19$).

Negative Emotion

Patients reported stronger feelings of ‘fear’, ‘hostility, and ‘guilt’ compared to healthy controls (Figure 3-7).

Table 3-5: Comparison of Positive Affect Negative Affect–Negative Emotion ratings
Borderline Personality Disorder ($N_1=16$) vs. Healthy Controls ($N_2=19$).

	M ₁	SD ₁	M ₂	SD ₂	df	t(df)	p
Fear	17.39	7.23	8.59	3.00	32	5.19	< 0.001
Hostility	16.81	3.99	9.81	4.14	31	5.22	< 0.001
Guilt	21.94	5.94	8.85	3.57	32	8.86	< 0.001
Sadness	12.22	3.69	12.54	3.23	32	-0.30	ns

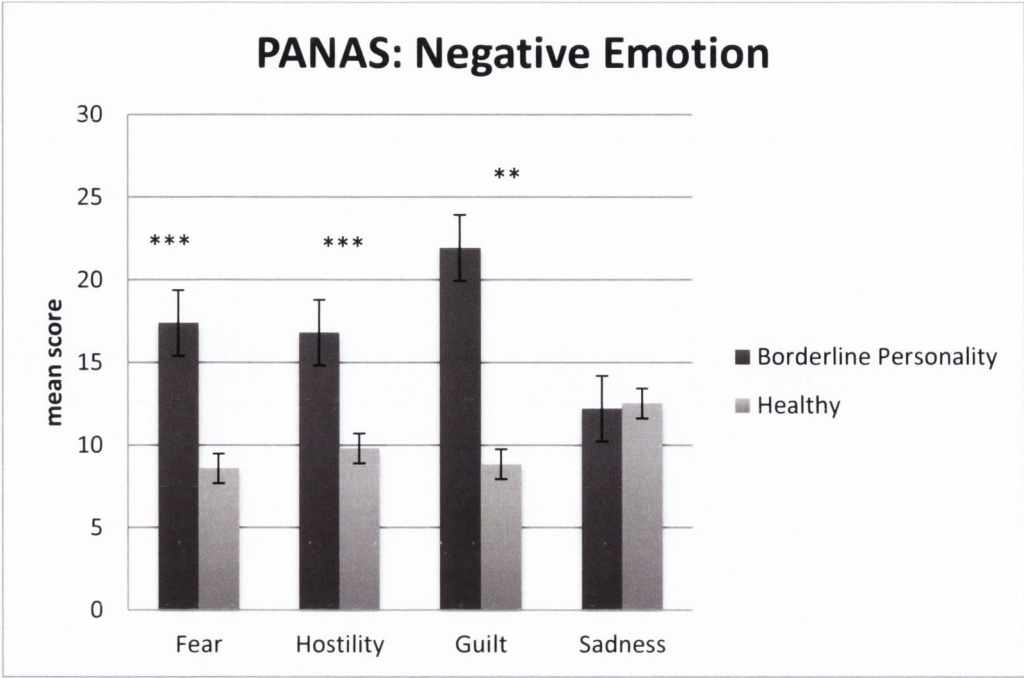


Figure 3-7: PANAS Negative emotion.
Mean PANAS-sub-scores for *Fear*, *Hostility*, *Guilt*, and *Sadness* for BPD patients ($N_1=16$) vs. Healthy Controls ($N_2=19$).

Positive Emotion

Patients reported fewer feelings of *joviality*, *self-assurance*, and *attentiveness* than healthy controls did (Figure 3-8).

Table 3-6: Comparison of Positive Affect Negative Affect –Positive Emotion Ratings.
Borderline Personality Disorder ($N_1=16$) vs. Healthy Controls ($N_2=19$).

	M ₁	SD ₁	M ₂	SD ₂	df	t(df)	p
Joviality	14.5	4.67	27.13	6.22	32	-7.13	<0.001
Self-Assurance	12.12	4.15	15.91	4.05	31	-2.90	<0.01
Attentiveness	9.67	3.01	12.86	2.88	32	-3.53	<0.001

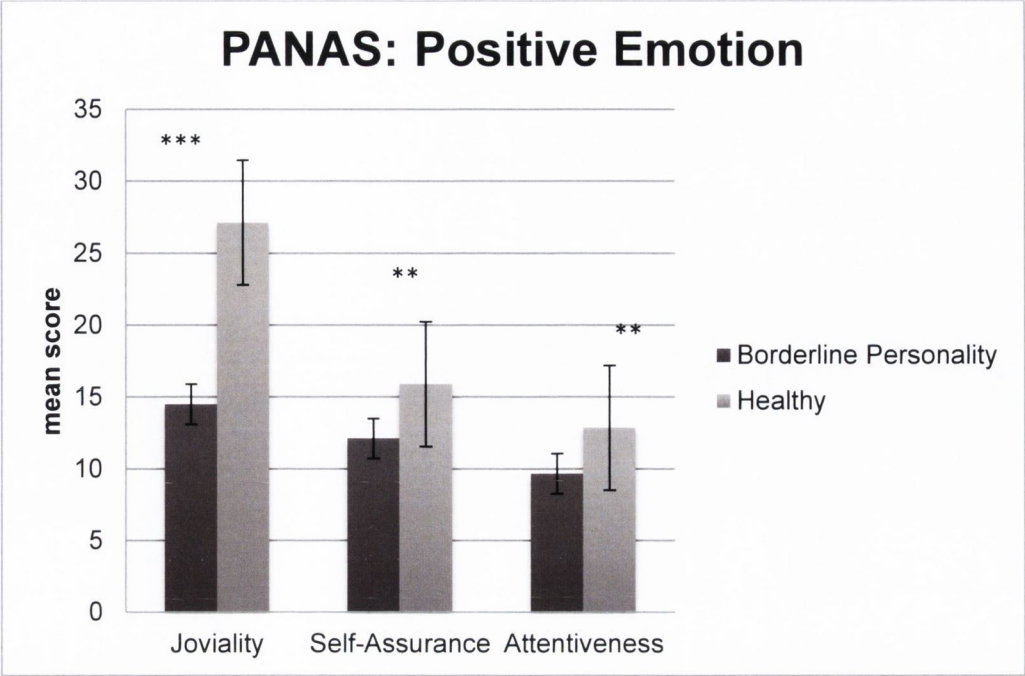


Figure 3-8: PANAS Positive emotion.
Mean sub-scores for *Joviality*, *Self-Assurance*, and *Attentiveness* for BPD patients ($N_1=16$) vs. healthy controls ($N_2=19$).

Other Affective States

Patients reported fewer feelings of shyness and fatigue but more feelings of serenity than healthy controls. Feelings of surprise were not significantly different (Figure 3-9).

Table 3-7: Comparison of Positive Affect Negative Affect–Other Affective States ratings.
Borderline Personality Disorder ($N_1=16$) vs. Healthy Controls ($N_2=19$).

	M ₁	SD ₁	M ₂	SD ₂	df	t(df)	p
Shyness	8.93	2.91	6.95	2.06	30	2.43	<0.05
Fatigue	13.53	3.54	9.68	3.75	31	3.26	<0.005
Serenity	6.00	1.97	10.45	2.60	32	6.00	<0.001
Surprise	6.06	3.17	6.00	2.39	32	0.06	>0.05

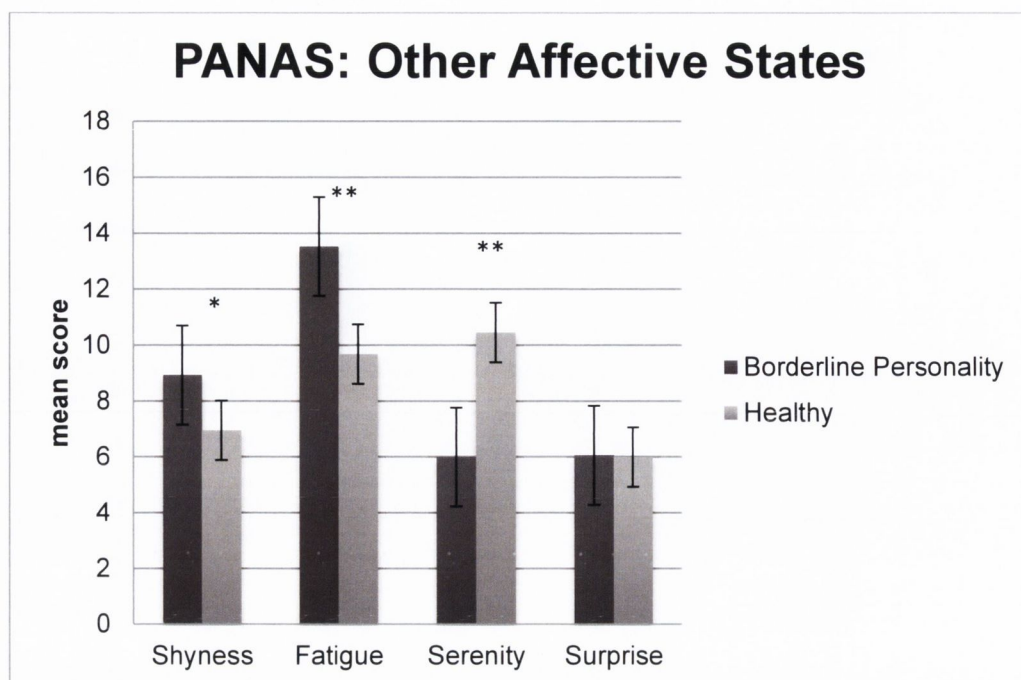


Figure 3-9: PANAS Other affective states.

Mean sub-scores for *Shyness*, *Fatigue*, *Serenity*, and *Surprise* for BPD patients ($N_1=16$) vs. healthy controls ($N_2=19$).

3.3.6 State-Trait Cheerfulness Inventory (STCI)

Trait-cheerfulness (CH) as measured by the STCI was significantly lower in patients ($M_1=24.11$, $SD_1=6.56$) than in healthy controls ($M_2=33.18$, $SD_2=4.12$, $t(33)=-5.33$, $p<0.001$). Trait-bad mood (BM) was significantly higher in patients ($M_1=29.78$, $SD_1=6.17$) than in healthy controls ($M_2=16.27$, $SD_2=5.88$, $t(33)=7.07$, $p<0.001$). The score for trait-seriousness (SE) was not significantly different in the two participant groups ($t(33)=1.11$, $p>0.05$). See Figure 3-10.

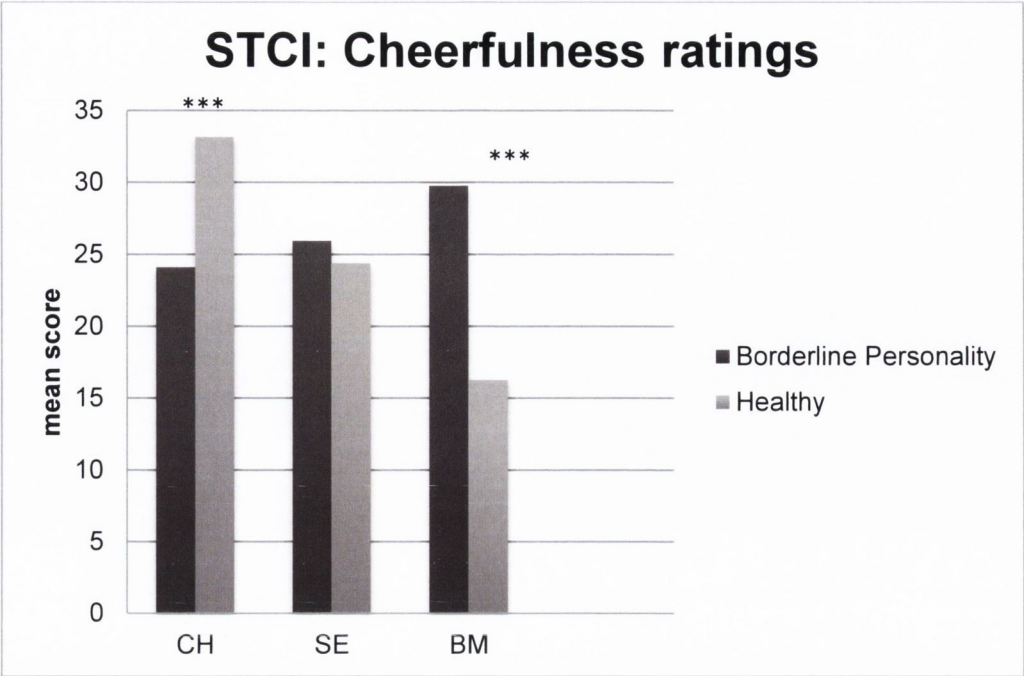


Figure 3-10: Cheerfulness ratings.
Mean sub-scores for *trait-cheerfulness* (CH), *trait-seriousness* (SE), and *trait-bad mood* (BM) for BPD patients ($N_1=16$) vs. healthy controls ($N_2=19$).

3.3.7 Gelotophobia-gelotophilia-katagelasticism (PhoPhiKat)

Self-ratings related to laughter as measured by the PhoPhiKat were significantly different for gelotophobia (PHO) in that patients indicated a greater fear of being laughed at ($M_1=41.94$, $SD_1=6.27$) than healthy controls did ($M_2=24.64$, $SD_2=8.76$, $t(33)=7.03$, $p<0.001$). Ratings for the subscales gelotophilia (PHI, $t(33)=-0.62$) and katagelasticism (KAT, $t(33)=1.29$) were not significantly different among groups.

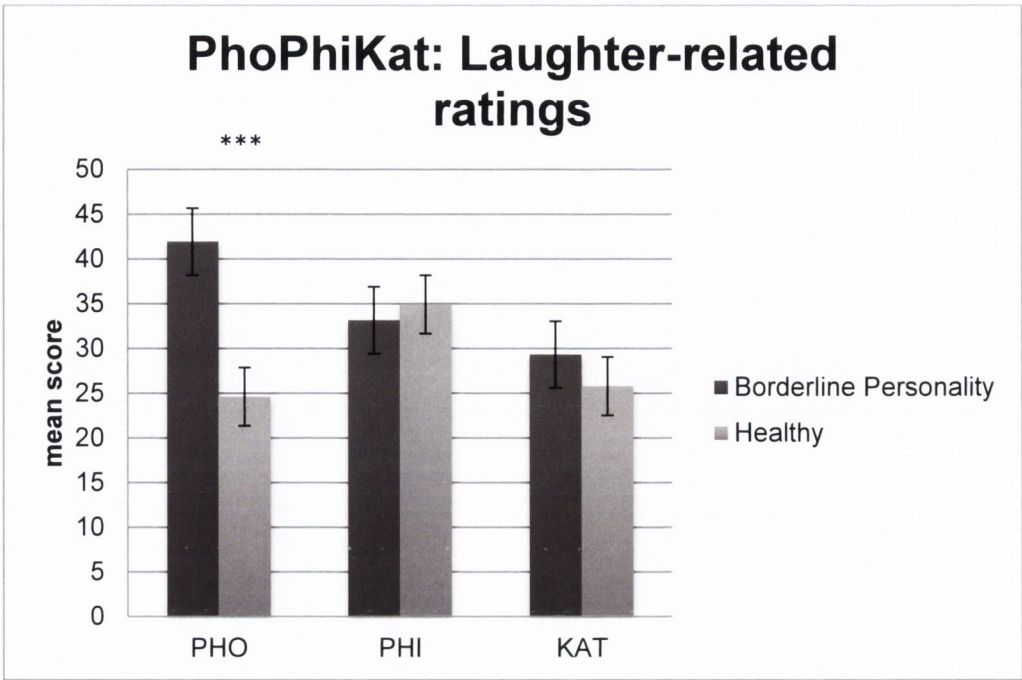


Figure 3-11: Laughter-related ratings. Mean sub-scores for *gelotophobia* (PHO), *gelotophilia* (PHI), and *katagelasticism* (KAT) for BPD patients ($N_1=16$) vs. healthy controls ($N_2=19$).

3.3.8 State-Trait Anxiety Inventory (STAI)

Both, *State-Anxiety* and *Trait-Anxiety*, as measured by the STAI, were significantly higher in patients than in healthy controls (Table 3-8).

Table 3-8: Comparison of State-Trait Anxiety Inventory ratings.

	M ₁	SD ₁	M ₂	SD ₂	t(36)	p
State-A.	53.89	9.91	32.53	10.64	6.40	<0.001
Trait-A.	61.47	7.29	36.15	10.82	8.45	<0.001

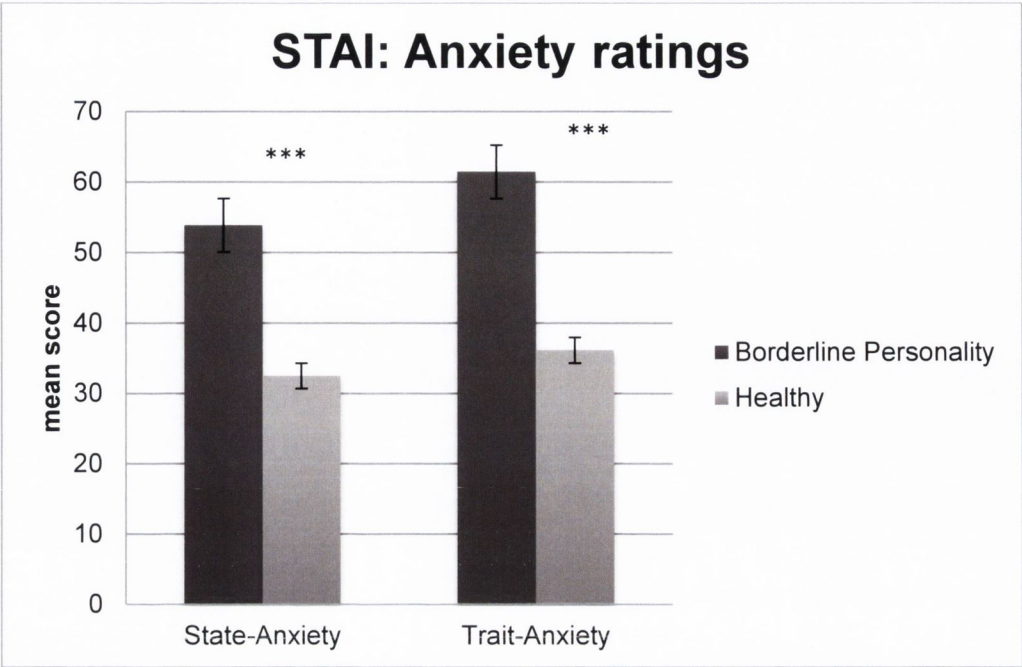


Figure 3-12: Anxiety ratings.
Mean scores for State-Anxiety and Trait-Anxiety for BPD patients ($N_1=16$) vs. Healthy Controls ($N_2=19$).

3.4 Discussion

The perhaps most striking finding in this assessment was patients' higher self-reported ratings on depression (HDRS and BDI) and anxiety (STAI) scales which is in line with the observation that MDD and clinical anxiety are the most common comorbidities of BPD (see 1.1.2 and S. C. Herpertz et al. (2007). Personality disorders as listed in DSM-IV in general tend to be associated with elevated neuroticism (Samuel & Widiger, 2008).

Rumination and worrying are considered possible mediating variables that may explain the relation between neuroticism and symptoms of depression and anxiety (Roelofs, Huibers, Peeters, Arntz, & van Os, 2008). Rumination itself, the maladaptive version of healthy self-reflection, has been identified as a good predictor for depression (Kühn, Vanderhasselt, De Raedt, & Gallinat, 2012) and might be a behavioural account for many of the BPD features especially since depression has likewise been related to volume reductions and neuropathological abnormalities in frontal brain regions in the anterior cingulate and the

prefrontal cortex hippocampus, amygdala and the striatum (Harrison, 2002; Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009).

According to some authors, impulsiveness and further impulsive aggression are heritable traits of temperament that may contribute to the development of BPD (Lieb et al., 2004; Skodol, Siever, et al., 2002). Cloninger (1987) suggested that impulsive aggression is observed clinically as a combination of high novelty seeking (NS) and low harm avoidance (HA), however subsequent findings have led to a revision of this prediction with more later publications suggesting that BPD is associated with high NS and high HA (Barnow et al., 2007) indicating that these temperament dimensions may be altered in BPD patients. Consistent with previous findings (Barnow et al., 2007), BPD patients exhibited significantly higher temperament dimensions of novelty seeking and harm avoidance, compared to healthy subjects. Temperament is hypothesised to involve heritable neurobiological dispositions to early emotions, and identify patterns of automatic behaviour reactions in response to specific environmental stimuli, like novelty and danger (C. R. Cloninger et al., 1993). According to the results reported in the literature, the combination of these extreme traits could be an indicator of a biological predisposition towards a behavioural disturbance and be related to the highly conflictive patterns of behaviour characteristic of borderline pathology.

The patient sample in the present study reported higher thrill seeking which is related to novelty seeking (Huang et al., 2011). Even though HA was not assessed directly lower ratings on self-assurance (PANAS) and higher scores on fear (PANAS), anxiety (STAI), shyness (PANAS) and, most notably, gelotophobia (fear of being laughed at, PhoPhiKat) would imply that the patients in this study would score high on HA.

Patients from this thesis obtained significantly higher scores than healthy controls across all BIS-11 subscales, which is consistent with previous studies (Kunert et al., 2003 and Paris et al., 2004) reporting

high levels of impulsiveness in BPD patients, concretely higher motor, attentional and non-planning impulsiveness. According to these results, impulsivity in BPD could involve a lack of behavioural control and a tendency to act without anticipating the consequences (Patton et al., 1995), which is consistent with the dysfunctional pattern of impulsive behaviours expressed by BPD patients generally involving a negative consequence for the individual, like episodes of substance abuse, binge eating or self-harming behaviours. The personality traits impulsivity itself is related to behavioural aggression, another key feature of BPD which was not assessed in this study but may be considered an even stronger measure of a BPD endophenotype. McCloskey et al. 2009) evaluated behavioural measures of aggression and impulsivity as potential endophenotypes for BPD. Subjects with BPD ($N=127$), OPD, a non-cluster B personality disorder, ($N=122$), or healthy controls ($N=112$) completed self-report and behavioural measures of aggression, motor impulsivity and cognitive impulsivity. Results showed that BPD subjects demonstrated more aggression and motor impulsivity than healthy controls (but not OPD) subjects on behavioural tasks (McCloskey et al., 2009).

In summary, the sample of patients appeared to have reported a personality profile typical for the disorder BPD. Almost the entire sample had comorbid depression. Neuropsychological testing (other than in the subsequent scanning session) was not carried out since the patient sample had already been diagnosed clinically. However, the strong correlation of interview and self-report measures of depression indicates that the patients, and healthy controls alike, provided valid data on all of the self-report measures. Even though cross-correlations were not performed on the samples, whose sizes were selected for the purpose of MRI studies the main personality traits, impulsivity, negative affect, and neuroticism were confirmed to be largely higher in BPD.

Cheerfulness, bad mood, and gelotophobia had not been previously investigated in BPD. If the findings from this study could be replicated in

a larger sample, this information could contribute to a more holistic concept of borderline personality.

Limitations of the study, other than the sample size, were that the intelligence was not controlled for, even though the samples did not significantly differ in level of education. The study did also not control for type or duration of medication other than meeting the exclusion criteria for MRI scanning (see 2.2) which by itself represents a limitation. Substance use problems are considered to be one example of impulsivity in the criteria set for BPD, ensuring some degree of overlap between BPD and SUD diagnoses.

Another limitation is that this study used mainly self-reports except for the HDRS, and did not include other levels and variables of emotional responding, such as psychophysiological parameters, although a combination of different variable levels would be optimal (Suvak et al., 2012). It is conceivable that the reported high negative affectivity in BPD is an expression of a general trait-like response style rather than due to a more substantive cause. However, although it is important to consider this, there is finally no definite way or method to ascertain. Finally, the study only investigated women; thus, the results cannot be generalised to men. In addition, we excluded patients with current substance use disorder.

In conclusion, the patient sample characterised with a larger battery of psychopathological and personality ratings in the present study is a typical BPD sample with regards to high impulsivity, neuroticism, negative emotions including depression. Thus, despite some limitations it is worthwhile investigations with MRI methods that are described in the following chapters.

4 Neural Correlates of Humour Perception (Study 1)

4.1 Introduction

Humour is unique to mankind and plays an important role in social settings. However, the neurological mechanisms underlying humour comprehension are still not fully understood. In recent years, new technologies have made it possible to develop progressively more refined understandings of these mechanisms.

While intuitive and theoretical concepts typically distinguish content classes of humour, Ruch and colleagues (W. Ruch, 1992; W. Ruch, Hehl, F.-J., 2007) used factorial analysis to show that structural aspects of humorous stimuli are at as important as their content. In their studies, two factors that differ regarding structural characteristics consistently emerged: humour appreciation of incongruity-resolution and of nonsense jokes and cartoons. Jokes and cartoons within each of these two groups may have different content but are similar with respect to their structural properties and in the way they are processed (W. Ruch, 2001). Incongruity-resolution and nonsense stimuli, i.e., for example, cartoons that are not meaningfully resolvable, put different loads on of different cognitive capacities which even influence the preference of one over the other depending on personality characteristics (W. Ruch, 2001; W. Ruch, Hehl, F.-J., 2007). On the basis of this theory, Samson (2008) hypothesised that the differentiation between stimuli that require incongruity-resolution and nonsense processing—which differ mainly regarding the resolvability of the incongruity—has an influence on the neural substrate of humour processing. These influences were reflected in the anterior medial prefrontal cortex, bilateral superior frontal gyri and temporo-parietal junctions (TPJ) which showed more activation during processing of incongruity-resolution than of nonsense cartoons indicating that processing of incongruity-resolution cartoons requires more integration of multi-sensory information and coherence building,

as well as more mental manipulation and organisation of information (A. C. Samson et al., 2009).

In the past decade, a number of other studies have made use of functional magnetic resonance imaging along with other tools to isolate and identify the different neural regions involved in humour processing. Most of the fMRI-based studies of humour in normal subjects (Azim, Mobbs, Jo, Menon, & Reiss, 2005; Bartolo, Benuzzi, Nocetti, Baraldi, & Nichelli, 2006; Bekinschtein, Davis, Rodd, & Owen, 2011; Goel & Dolan, 2001; Mobbs, Greicius, Abdel-Azim, Menon, & Reiss, 2003; A. C. Samson et al., 2008; Wild et al., 2006) as well as studies of patients suffering from brain damage (Reiss et al., 2008) have adopted funny and unfunny conditions for comparison. These studies have identified a number of regions associated with surface-level semantic processing, incongruity detection and resolution and the affective response to humour. For example, (Goel & Dolan, 2001) had participants listen to semantic and phonological stimuli, comparing standard jokes with stimuli in which the punch lines were replaced with unfunny sentences. They found that the jokes activated brain regions in the left inferior frontal gyrus (IFG), bilateral posterior middle temporal gyrus (MTG), and left posterior inferior temporal gyrus (ITG). The subjects' post-scan funniness ratings of jokes revealed higher activation in the ventromedial prefrontal cortex (VMPFC) and bilateral cerebellum for jokes receiving higher ratings.

Study 1 is similar to previous fMRI studies on humour perception in that it compares brain activity in funny vs. unfunny conditions; the funny condition contains a resolvable incongruity. In addition to the operations required to detect the incongruity, it should also call forth those required to successfully resolve the incongruity and, thereby, to comprehend the humour. Chan et al. (2012) found activation of the bilateral IFG during humour comprehension; other research has found greater activation in the left IFG (Bekinschtein et al., 2011; A. C. Samson et al., 2008) and right IFG (Moran, Wig, Adams, Janata, & Kelley, 2004) related to the

resolution process. Finally, the left inferior parietal lobe has been associated with semantic integration and coherence (Chou, Chen, Wu, & Booth, 2009).

Bartolo et al. (2006) also compared funny to unfunny cartoon stimuli and found that activation in the right IFG, left superior temporal gyrus (STG), left MTG, and left cerebellum was higher for funny cartoons. Comparing subjects' post-scan funniness ratings of jokes, they found also activation in the left amygdala.

Visual compared to language-dependent jokes also activated temporo-parietal areas (Moran et al., 2004). K. K. Watson, Matthews, and Allman (2007) found a common network for different types of jokes (visual and language-dependent) comprising the ACC and temporo-parietal areas. Wild et al. (2006) proposed that temporo-parietal involvement represents the integration of contextual aspects in later stages of humour processing, thus providing the “integration hub” of humour. Together with anterior cingulate cortex (ACC) also activated in humour processing tasks, the TPJ is a likely candidate for being an important hub more generally for theory of mind (*ToM*) or mentalizing (Gallagher et al., 2000; K. K. Watson et al., 2007).

This present study seeks to further contribute to the search for neural correlates of humour processing and, beyond that, test for brain activity during the processing of *ToM*-jokes, i.e. jokes where, in order to resolve an incongruity, a Theory-of-Mind has to be applied (e.g. by identifying a false belief). This was done by conducting Samson's (2010) Theory-of-Mind humour perception task (see section 2.5 of this thesis). The paradigm had successfully been used in earlier studies without the *ToM* condition (A. C. Samson et al., 2009; A. C. Samson et al., 2008) and is now being applied in comparative studies with psychiatric samples (individuals with Asperger syndrome, A. C. Samson & Hegenloh, 2010; social anxiety, A.C. Samson, Lackner, Weiss, & Papousek, 2012). The paradigm was later applied to a sample of BPD participants in *Study 2* of this thesis (Chapter 5) which was the rationale to test the behavioural

and brain responses to this *ToM* -humour task with healthy participants in an fMRI setting first.

Functional magnetic resonance (fMRI) studies have begun to characterise the neural correlates of “mentalizing” using *ToM* tasks, indicating that a network of cortical areas that includes the medial prefrontal cortex, the temporal-parietal junction, and the precuneus plays a key role in mentalizing and forming impressions of other people (Amodio & Frith, 2006; C. D. Frith & Frith, 2006; Gallagher & Frith, 2003; Rilling, Sanfey, Aronson, Nystrom, & Cohen, 2004); Sripada et al. (2009) showed that patients with clinically significant social anxiety exhibited less activation of parts of this network during mentalizing compared with the results of matched healthy controls.

Several brain areas have been implicated in *ToM* processing (see also 1.2), including the medial prefrontal cortex, posterior cingulate cortex, and the posterior superior temporal sulcus (PSTS) at the temporo-parietal junction (TPJ, Gallagher & Frith, 2003; R. Saxe & Kanwisher, 2003).

In the case of Autism Spectrum Disorder (ASD, the disorder most prominently characterised by *ToM* impairment, see also 1.4.1), fMRI studies have found that patients fail to activate these functionally specialised regions during *ToM* tasks (Lombardo et al., 2011; Kevin A. Pelphrey, Morris, & McCarthy, 2004). Although the MPFC and TPJ have been implicated primarily in processing *ToM*, the relative role of each region is a topic of debate. Adults with ASD have atypical MPFC activation patterns for judging the emotional states of others. In addition, adults with ASD do not differentially activate the PSTS for others’ gaze shifts (R. R. Saxe & Pelphrey, 2009), and, compared to typically developing peers, they have decreased activation in frontal areas when judging others’ emotion states based on images of their eyes (A. F. Hamilton, 2009).

Whereas Theory-of-Mind usually refers to inferences about the mental states of another person (see 1.2.1), some researchers include the understanding of one's own mental states as a part of the concept. Brain-based studies show that certain brain regions respond both when individuals are asked to infer the mental state of another individual and when they are asked to reflect upon their own mental state. These findings suggest that there may be a common biological basis related to a more elementary process of mentalizing about internal states; that is, about those of another person as well as about those of oneself (Gentili et al., 2009; Oberman & Ramachandran, 2007; R. Saxe et al., 2006). The brain structure that has been implied in self-referential thought is the precuneus (located in the medial parietal lobes). It has been linked to the processes involved in self-consciousness, such as reflective self-awareness, that involve rating one's own personality traits compared to those judged of other people (Lou et al., 2004).

The aim of this study was to identify neural correlates of humour as evoked by visual jokes and to reveal dissociation especially in the neural correlates between pure cognitive and social cognitive processes.

A further aim was to test whether there are brain regions in which activity is linearly correlated to an individual's Neuroticism score, as this personality feature is associated with BPD (see 1.1.2 and 3.3.2). Neuroticism further is the single most important factor associated with many forms of psychopathology and behavioural health, in particular the common mental disorders including anxiety, depressive, and substance use disorders (Kotov et al., 2010). The prospective associations between Neuroticism and psychopathology have prompted many in the field to consider Neuroticism a robust independent predictor of psychopathology (Fanous, Neale, Aggen, & Kendler, 2007; Kendler, Gardner, & Prescott, 2006; Khan, Jacobson, Gardner, Prescott, & Kendler, 2005; Ormel et al., 2013).

Other research has linked Neuroticism to biases at more conscious levels of cognitive processing.

For example, high-Neuroticism individuals have been shown to exhibit a greater tendency toward pessimism, lower self-efficacy and self-esteem, and negative self-appraisal. There is also some evidence demonstrating that worry and rumination are linked to Neuroticism (de Bruin, Rassin, & Muris, 2005). In addition, neurotics exhibit more meta-worry (worry about worry) and excessive monitoring of mood (Yousfi et al., 2004).

Most fMRI studies tend to include cognitive tasks involving emotional conflict or processing of emotional (face) stimuli, which are relevant to Neuroticism and psychopathology. In general, these studies have shown that Neuroticism is associated with increased activity in the amygdala and ACC (S. W. Chan, Harmer, Goodwin, & Norbury, 2008; S. W. Chan, Norbury, Goodwin, & Harmer, 2009; Haas, Omura, Constable, & Canli, 2007; Hooker, Verosky, Miyakawa, Knight, & D'Esposito, 2008) but associations have also been found with the medial PFC, insula, and hippocampus (Feinstein et al., 2006, Haas et al., 2008 and Hooker et al., 2008). Haas et al. (2007), for instance, found a positive association between Neuroticism and activation of the amygdala and sub-genual ACC during emotional conflict by comparing emotionally incongruent trials relative to emotionally congruent trials in a word-face Stroop task. Bruck, Wildgruber, Kreifelts, Kruger, and Wachter (2011) used an emotional prosody task (emotional information is presented in the tone of voice expressed in speech) and reported strong positive correlations between measures of Neuroticism and hemodynamic responses of the right amygdala, the left postcentral gyrus as well as medial frontal structures including the right ACC. Kehoe, Toomey, Balsters, and Bokde (2012) observed an increased fMRI response to emotional arousal in the right medial prefrontal cortex (MPFC) in individuals with high levels of Neuroticism. However, no previous study has correlated an increase of Neuroticism during a

visual task or a paradigm that was aimed at cognitive (rather than emotional) processing, respectively.

Hypothesis

There was expected to be a difference in brain activity, as measured by the BOLD signal in processing meaningful vs. non-meaningful or non-resolvable visual jokes.

The anatomical hypothesis was that looking at cartoon pictures that included a *ToM* component, would recruit the ‘mentalizing’ areas or ‘*ToM* network’ of the brain compared to looking at a picture that was lacking this component.

Although no regions of interest (ROI) were defined, regions that consistently had been activated by standard Theory-of-mind tasks (mostly false-belief stories, see 1.2) were expected to respond to *ToM* jokes: right and left temporo-parietal junction (RTPJ/LTPJ), superior temporal sulcus (STS), precuneus (PC) and medial prefrontal cortex (MPFC) (Dodell-Feder et al., 2011; Kliemann et al., 2008; Lombardo et al., 2011; Mitchell, 2008; R. Saxe & Wexler, 2005; Scholz et al., 2009; Young et al., 2010).

Thus, a neural network including the areas of the ventro-medial prefrontal cortex (VMPFC), inferior-frontal gyrus (IFG), and temporo-parietal junction (TPJ) was expected to be active during mental processing of *ToM* jokes vs. jokes that are lacking the *ToM* component.

A region or a network of regions will be linearly correlated to individual levels on Neuroticism.

4.2 Methods

4.2.1 Participants

Nineteen healthy female participants (age 21-47) volunteered in this study (for recruitment information, see 2.2). All participants underwent

psychometric assessment (see 2.3) and MR imaging as outlined in Chapter 2.

Rating scales of depression scales were completed for all participants included in the study for diagnostic and correlational purposes. The rating scales used for this study were the Eysenck Personality Questionnaire (S. B. Eysenck, 1962).

Other ratings used are described in the overall methods (chapter 2 of the thesis).

Ethical approval for the study was obtained from the Adelaide and Meath Hospital and St. James' Hospital, Dublin, Ireland ethics committee. All participants were given detailed oral and written information and had to sign an informed consent form prior to participating in the study.

The main demographics of the study sample are given in Table 4-1.

Table 4-1: Demographic and psychometric information of participants (N=19).

	M	SD
Age	29.26	7.54
HDRS total score	0.36	0.76
BDI total score	4.26	3.60
EPQ-Neuroticism	3.63	3.18

4.2.2 fMRI task

The stimulus material consisted of two types of cartoons, puns (PUN) and jokes requiring mentalizing (TOM) as well as a control condition that consisted of unfunny pictures containing an incongruity that could not be resolved meaningfully (INC). All pictures were low in aggressive, violent, and sexual content and were used in previous studies (A. C. Samson et al., 2009; A. C. Samson et al., 2008). In order to investigate brain activity during resting state (see *Study 3*) rest trials (NULL) were interleaved during which participants observed a blank screen. All participants processed a total of 120 trials (30 INC + 30 PUN + 30 TOM

+ 30 NULL). Stimuli were presented every 10s on average and with variable stimulus onset delays (0, 400, 800, 1200 or 1600 ms). Each stimulus was onset for 6000ms during which participants were instructed to make a response. Below each picture (cartoon) the word “understood” was printed on the left side and the words “not understood” were printed on the right side. Participants were asked to press the corresponding button (left/right) with their index or middle finger, respectively, depending on whether they understood the joke. The functional neuroimaging part started after 15 minutes of the scanning session (during which the structural image was acquired) and took about 18 minutes.

A complete description of the stimuli is found in the Overall methods Chapter 2 (2.4).

4.2.3 Data Acquisition

Magnetic resonance images were obtained with a Philips Achieva MRI scanner (Philips Medical System, Netherland BV, Veenphuis 4–6, 5684 PC Best, The Netherlands) operating at 3 Tesla. For the cognitive paradigm run, 26 axial slices (3.5 mm× 3.5 mm× 3.5 mm resolution, 0.75 mm spacing), parallel to the AC-PC plane and covering the whole brain were acquired using a single shot, gradient recalled EPI sequence (TR 2000 ms, TE 30 ms, 90° flip angle). One functional run with 620 time points was acquired, with each time point sampling over the 26 slices. Prior to the functional run, 180 anatomical slices T₁-weighted 3D-MPRAGE sequence (repetition time, 11.0 ms; echo time, 4.4 ms; total acquisition time, 7 min 30 sec; number of acquisitions, 1; field of view, 250 mm× 256 mm × 160 mm; matrix: 256 mm × 256 mm; resolution: 0.9 mm × 0.9 mm × 0.9 mm) with the same spatial orientation as the functional data were acquired.

For pre-processing information see Chapter 2, (2.6).

4.2.4 fMRI pre-processing

The fMRI data was processed with SPM8 (Statistic Parametric Mapping, Wellcome Trust Centre for Neuroimaging, UCL, UK). This software package contains tools for pre-processing, motion-correction registration, statistical evaluation and presentation of fMRI data. An overview of the pre-processing steps is shown in Figure 4-1.

To correct for the temporal offset between the slices acquired in one scan, a cubic-spline-interpolation was applied. A temporal high pass filter with a cut-off frequency of $1/120\text{Hz}$ was used for baseline correction of the signal and a spatial Gaussian filter with 5.65 mm FWHM was applied.

To align the functional data slices onto a 3D stereotactic coordinate reference system, a rigid linear registration with six degrees of freedom (three rotational, three translational) was performed. The rotational and translational parameters were acquired on the basis of the MPRAGE slices to achieve an optimal match between these slices and the individual 3D reference data set. The 3D reference data set with 26 slices and 1mm slice thickness was standardised to MNI stereotactic space (Montreal Neurological Institute). The obtained rotational and translational parameters were normalised, i.e., transformed by linear scaling to a standard size. The resulting parameters were then used to transform the functional slices using tri-linear interpolation, so that the resulting functional slices were aligned with the stereotactic coordinate system. Subsequently, a non-linear normalisation was performed (Thirion, 1998). This step improved the spatial alignment of the individual neuroanatomy onto the template of the (SPM-) reference brain.

The statistical evaluation was based on a least-squares estimation using the general linear model for serially auto-correlated observations (Aguirre, Zarahn, & D'Esposito, 1997; Zarahn, Aguirre, & D'Esposito, 1997). The design matrix was generated with a box-car function with

stimulus onset time as onset, convolved with a hemodynamic response function (HRF, gamma density function). The model equation, including the observation data, the design matrix and the error term, was convolved with a Gaussian kernel of dispersion of 4s FWHM to account for the temporal autocorrelation (Friston et al., 1995).

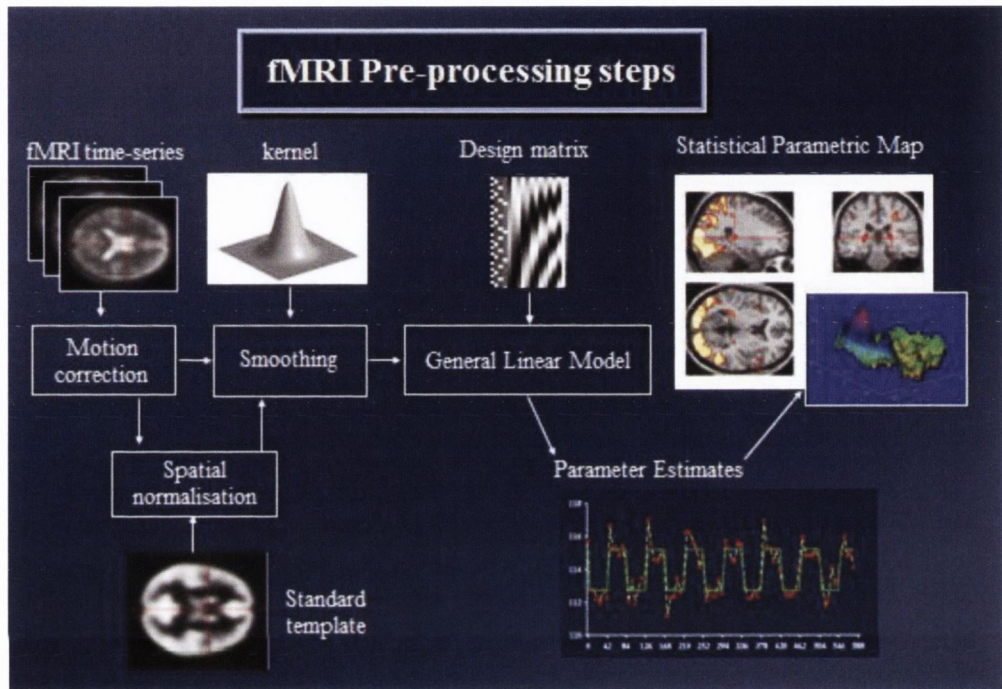


Figure 4-1: Flow diagram of the fMRI pre-processing steps.
(Adapted from the Institute of Neurology www.ion.ucl.ac.uk)

4.2.5 SPM8 Statistical Analysis

Data from each participant were entered into a general linear model using an event-related analysis procedure. Stimuli in the three experimental and rest conditions were treated as individual events for analysis and modelled for the brain activity during processing the meaning (or nonsense in the case of INC cartoons) using a canonical hemodynamic response function (HRF). There were four event types: INC, PUN, TOM, and NULL. Beta-values were estimated for the following different contrasts for each voxel at the subject level (1^{st} level):

- [INC>PUN]
- [INC>TOM]
- [PUN>INC]

- [PUN>TOM]
- [TOM>INC]
- [TOM>PUN]

Since the paradigm had not been tested in a sample of non-patents before, no *a priori* hypothesis, in the sense of a region of interest (ROI) analysis, was performed. Instead, parameter estimates from contrasts of the canonical HRF in single subject models were entered into random-effects analysis using one-sample *t*-tests across all participants to determine whether there was significant activation during a contrast.

As the individual functional datasets were all aligned to the same stereotactic reference space, the resulting single-participant contrast-images were then entered into a second-level random effects analysis for the relevant contrasts.

The group analysis consisted of one-sample *t*-tests across the contrast images of all subjects that indicated whether observed differences were significantly distinct from zero (Friston et al., 1998). Images were thresholded at $p < 0.001$ (uncorrected). Moreover, a region was considered significant only if it contained a cluster of 15 or more continuous voxels. Family-wise error of $FWE < 0.05$ was used to account for multiple comparisons at cluster and at voxel level across the whole brain.

Z (Gaussianised *T/F*) statistic images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$. Brain regions which were more active during meaningful resolution (of incongruity, see 2.4) than during non-resolution were revealed by inclusive masking of the contrasts [TOM>INC] and [PUN>INC]. An “inclusive mask” (activated [TOM>INC] regions masked by activated regions of [PUN>INC] in the Contrast Masking options of SPM8) determined the regions of activation common to *both* contrasts (“inclusive mask analysis”). *Z* (Gaussianised *T/F*) statistic images were

thresholded at $p=0.05$ (cluster corrected). In this study, all first order analyses were restricted to regions of positive activation.

Individual participants' scores from BDI-depression-, and EPQ-Extraversion scales (see Chapter 2) and the participants' age were entered as covariates into the 2nd-level random effects analysis at first. Since the voxel clusters remained the same (in size and location) as without the covariates it was decided to report only the latter results.

4.2.6 Multiple Regression: Neuroticism

To identify the brain activity that is related to a linear increase in Neuroticism a multiple regression factorial design was specified at the between-subjects level (2nd level) with the three experimental conditions (INC, PUN, TOM) as factors and with the participants' individual EPQ-Neuroticism score (see also 2.3.3) as a covariate. Statistical maps of difference in brain activity were calculated for each contrast. The same statistical thresholds were applied as mentioned above.

4.3 Results

4.3.1 Behavioural results

Ninety experimental trials (30 INC + 30 PUN + 30 TOM) were presented during the cognitive paradigm part (see 2.5) of the scanning session. All the trials that participants had responded to, regardless of whether they had *understood* or *not understood* the cartoon, were taken into account for the functional MRI analysis. Participants mean number of positive responses (i.e. '*understood*') was 42.4 ($SD=13.5$) which relates to a rate of 47% and was not significantly different from the number of negative responses ($M=46.6$, $SD=13.4$).

Table 4-2 shows the main characteristics of participants' responses for the three conditions.

Table 4-2: Number of responses (NR) and response times (RT); (N=19).

	INC	TOM	PUN
NR (positive responses)	4.95	20.16	17.32
RT (positive responses)	3.12 s	3.14 s	2.96 s
NR (negative responses)	24.89	9.55	12.21 s
RT (negative responses)	3.01 s	9.47s	3.51 s

4.3.2 Imaging results

Significant clusters of activity-difference were found for each of the contrasts of experimental conditions except for the contrast [PUN>TOM]. Note that all tables use the taxonomy of brain regions specified by the labelling software (AAL, 2.9). Further, only clusters that exceeded 15 voxels in size are reported. All reported coordinates of difference clusters refer to MNI space.

Table 4-3 shows the difference in BOLD signal under each of the experimental contrasts. The results are differences of one-sample *t*-tests (*t*-contrasts) and are reported at a threshold of *p*<0.05 (*FWE* corrected).

For [INC>PUN] a significant cluster was found in the right lingual. Bilateral occipital regions did not survive whole-brain corrections at voxel level.

For [INC>TOM], left middle occipital cortex and left hippocampus had significant differences corrected (*FWE*) both at cluster and at peak voxel level.

For [PUN>INC] left middle temporal and left inferior parietal lobes (together: left TPJ) were significantly more active. In addition, significant clusters were found in the right inferior frontal and right inferior parietal lobes.

For [PUN>TOM] there were no significant clusters of functional difference.

For [TOM>INC] significant activity differences were found in a large (>3500 voxels) right-lateralised cluster comprising middle temporal lobes in both hemispheres and the cerebellum. Another large cluster of difference was an area in the left frontal cortex. A third cluster was located in the left caudate.

For [TOM>PUN] activity differences were significant bilaterally in the middle temporal and middle occipital lobes and the precuneus. Bilateral clusters in the parahippocampus and the cerebellum did not survive whole-brain corrections at peak-voxel level.

Table 4-3: Table of brain activities under each contrast.
Within-group contrasts were performed for each of the three experimental conditions incongruity (INC), ‘puch line’ resolution (PUN), and Theory-of-Mind (TOM).
All differences are thresholded at $p<0.001$. Bold type indicates regions for which the difference in activity was significant at voxel level ($FWE<0.05$, for multiple correction). Regions printed in bold type were significant at both cluster level and voxel level.

Contrast	K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates [mm]		
						x	y	z
[INC>PUN]	296	<0.001	R Lingual	<0.001	10.85	17	-88	-8
			R Inf. Occipital	0.520	5.11	38	-84	-12
			R Fusiform	0.910	4.35	24	-57	-8
	62	0.009	R Sup. Occipital	0.086	6.36	20	-91	20
			R Sup. Occipital	0.448	5.24	24	-88	27
	50	0.022	L Mid. Occipital	0.257	5.68	-19	-95	17
			L Sup. Occipital	0.255	5.55	-12	-98	10
[INC>TOM]	57	0.015	L Mid. Occipital	0.001	8.73	-19	-98	10
	111	<0.001	L Hippocampus	0.001	8.60	-22	-42	13
	193	<0.001	R Sup. Occipital	0.023	7.05	20	-95	17
[PUN>INC]	1263	<0.001	L Mid. Temporal	<0.001	11.51	-50	-67	-1
			L Inf. Parietal	<0.001	11.36	-40	-39	41
			L Inf. Parietal	<0.001	10.43	-47	-32	45
	234	<0.001	R Inf. Temporal	<0.001	10.86	52	-56	-5
			R Mid. Temporal	0.033	6.85	48	-53	10
	421	<0.001	L Inf. Frontal	<0.001	10.34	-40	32	13
			L Inf. Front. Oper	0.074	6.44	-47	7	24
			L Inf. Frontal Tri.	0.125	6.18	-47	42	3
	455	<0.001	R Inf. Parietal	0.001	9.09	48	-32	48
			R Inf. Parietal	0.028	6.94	34	-49	52
			R Precuneus	0.113	6.23	13	-56	55

Neural Correlates of Humour Perception (Study 1)

	327	<0.001	L Mid. Frontal	0.058	6.57	-26	0	62
			L Precentral	0.101	6.28	-36	0	55
			L Precentral	0.118	6.21	-26	-7	48
	100	0.001	R Cerebellum	0.088	6.35	20	-77	-50
			R Cerebellum	0.427	5.28	20	-70	-33
	58	0.012	R Cerebellum	0.178	5.94	27	-49	-40
			R Cerebellum	0.524	5.11	17	-53	-50
	43	0.038	R Inf. Front. Oper.	0.303	5.56	52	7	27
			Inf. Fron. Oper.	0.957	4.19	52	7	10
[PUN>TOM]			no suprathreshold clusters			-	-	-
	-	-		-	-			
[TOM>INC]	3766	<0.001	R Mid. Temporal	<0.001	14.13	48	-67	17
			L Mid. Temporal	<0.001	13.69	-54	-56	13
			R Mid Occipital	<0.001	12.12	45	-74	31
	323	<0.001	R Cerebellum	0.001	9.15	10	-53	-50
			R Cerebellum	0.034	6.84	13	-84	-47
			R Cerebellum	0.054	6.6	34	-45	-50
	1392	<0.001	L Inf. Frontal	0.002	8.5	-50	28	17
			L Precentral	0.002	8.4	-40	0	52
			R Sup. Frontal	0.005	7.82	24	0	59
	176	<0.001	L Caudate	0.003	8.22	-5	0	10
			L Thalamus	0.092	6.33	-12	-7	6
			R Caudate	0.774	4.64	10	11	3
	90	0.002	L Cerebellum	0.039	6.77	-19	-77	-50
			L Cerebellum Crus.	0.070	6.47	-19	-74	-29
	103	<0.001	L Cerebellum left	0.091	6.33	-19	-49	-50
			L Cerebellum left	0.198	5.84	-8	-55	-50
			L Cerebellum Crus.	0.291	5.56	-40	-49	-40
	88	0.002	R Inf. Frontal Tri.	0.108	6.25	48	21	20
	70	0.006	R Lingual	0.440	5.23	10	-53	3
			Vermis	0.452	5.21	3	-60	6
[TOM>PUN]	694	<0.001	R Mid. Temporal	<0.001	9.59	41	-60	20
			R Mid. Occipital	0.008	7.58	38	-67	31
			R Mid. Occipital	0.486	5.16	34	-81	31
	398	<0.001	L Mid. Temporal	0.001	9.04	-54	-56	17
			L Mid. Occipital	0.240	5.71	-33	-84	27
			L Mid. Occipital	0.398	5.33	-47	-81	10
	436	<0.001	R Precuneus	0.004	8.04	6	-56	48
			L Precuneus	0.010	7.49	-8	-53	48
			L Precuneus	0.016	7.24	-5	-50	59
	115	<0.001	R Precuneus	0.012	7.38	17	-53	17
			R Precuneus	0.026	6.97	13	-49	10
	140	<0.001	R Mid. Temporal	0.037	6.79	52	-4	-19
			R Mid. Temporal	0.674	4.83	48	-25	-12
		<0.001	R Parahippocampal	0.080	6.40	24	-35	-15
	121		R Fusiform	0.094	6.32	41	-42	-19
			R Cerebellum	0.947	4.22	38	-46	-29
	61	0.011	L	0.114	6.22	-26	-39	-15

			Parahippocampal					
			L Cerebellum	0.978	4.05	-19	-49	-19
	88	0.002	L Mid. Temporal	0.145	6.07	-57	-11	-15
			L Mid. Temporal	0.267	5.64	-54	0	-22
			L Mid. Temporal Pole	0.339	5.46	-50	14	-33
	41	0.048	R Cerebellum	0.618	4.93	-5	-49	-50
			R Cerebellum	0.996	3.81	10	-53	-47
	129	<0.001	R Precentral	0.674	4.83	34	0	45
			R Mid. Frontal	0.766	4.67	27	14	48
			R Sup. Frontal	0.879	4.43	31	28	52

Figure 4-2 and Figure 4-3 show the differences in brain activity for the main contrast of interest [TOM>PUN]. Regions throughout the temporal lobes and especially around the TPJ were more active under the TOM condition than they were under the PUN condition.

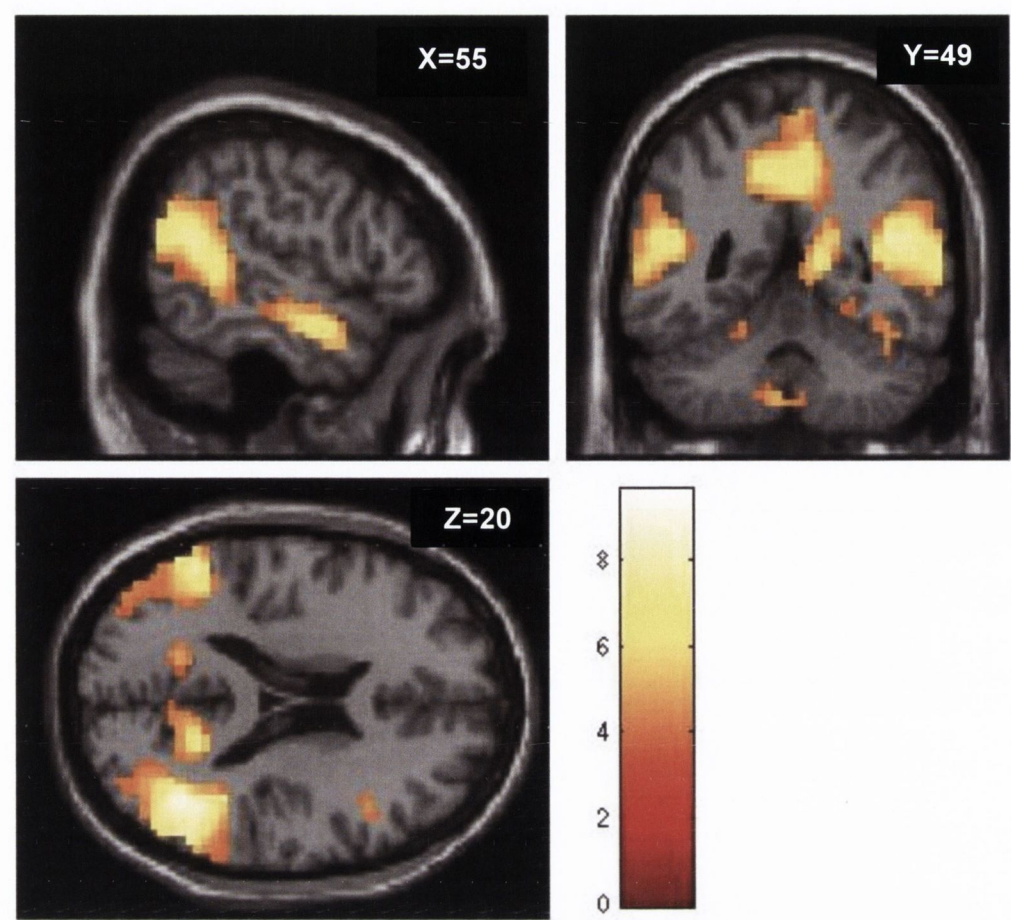


Figure 4-2: Statistical map of brain activity under for the contrast [TOM>PUN]. Regions throughout the temporal lobes and especially around the TPJ were more active while participants engaged in Theory-of-Mind processing. L/R Temporo-parietal junction (TPJ) and L Temporal lobe at [55 49 20]. Coloured bar shows *t*-value distribution.

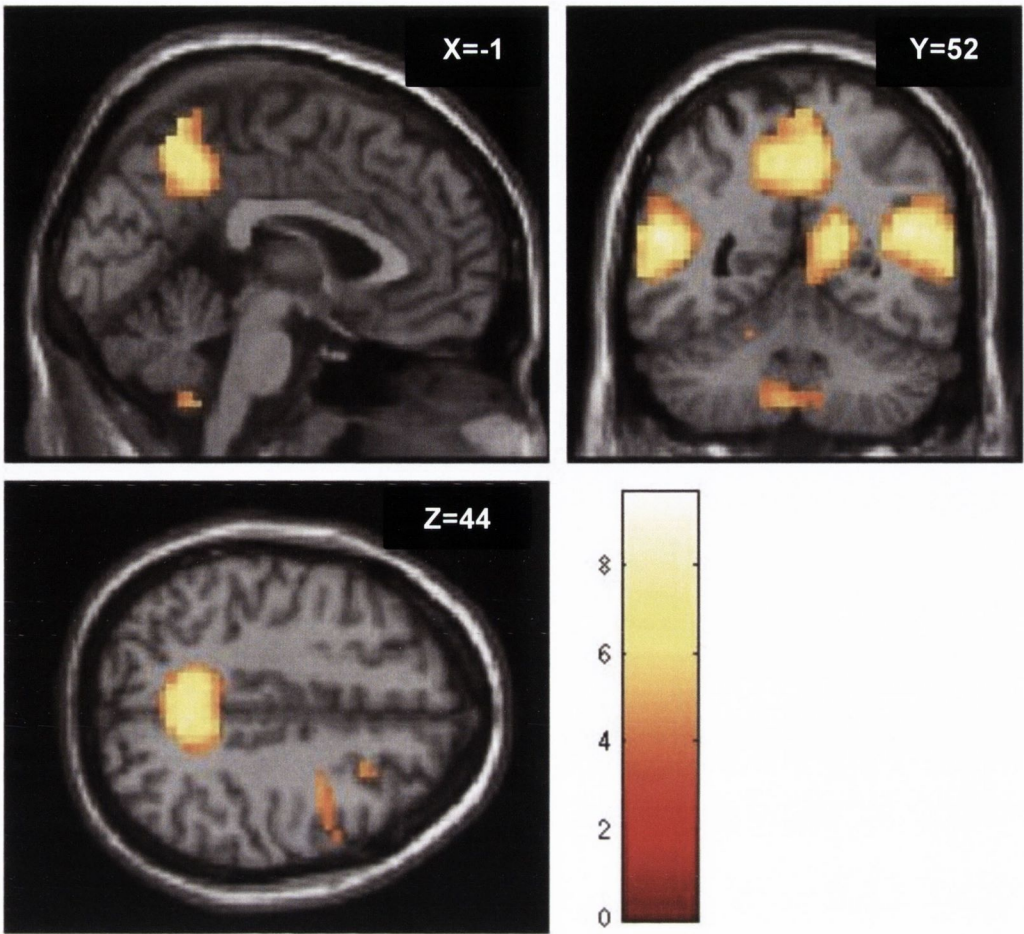


Figure 4-3: Statistical map of brain activity under contrast [TOM>PUN]. Precuneus (L/R) and Mid. Temporal (L/R) at [-1 52 44]. Coloured bar shows t -value distribution.

The contrast of [TOM>INC] masked (incl.) by [PUN>INC] (see Table 4-4 and Figure 4-4) represents areas of the brain that are active during the mental processing of “meaningful resolution” versus “non-resolvability”. This contrast has often been referred to as “funny vs. unfunny” in other studies. The main clusters of activity were in the middle temporal lobes (bilaterally) and the left inferior frontal lobe (IFG/S).

Table 4-4: Table of activity differences for [TOM>INC] masked (incl.) by [PUN>INC].

All differences are thresholded at $p < 0.001$. Bold type indicates regions for which the difference in activity was significant on a voxel level ($FWE < 0.05$, for multiple corrections). Regions printed in bold type were significant at both cluster level and voxel level.

K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates [mm]		
					x	y	z
3766	<0.001	R Mid. Temporal	<0.001	14.13	48	-67	17
		L Mid. Temporal	<0.001	13.69	-54	-55	13
		R Mid. Occipital	<0.001	12.12	45	-74	31
323	<0.001	R Cerebellum	0.001	9.15	10	-53	-50
		R Cerebellum	0.034	6.84	13	-84	-47
		R Cerebellum	0.054	6.60	34	-46	-50
1392	<0.001	L Inf. Frontal	0.002	8.50	-50	28	17
		L Precentral	0.002	8.40	-40	0	52
		R Sup. Frontal	0.005	7.82	24	0	59
176	<0.001	L Caudate	0.003	8.22	-5	0	10
		L Thalamus	0.092	6.33	-12	-7	5
		R Caudate	0.774	4.64	10	11	3
90	0.002	L Cerebellum	0.039	6.77	-19	-77	-50
		L Cerebellum	0.070	6.47	-19	-74	-29
103	0.001	L Cerebellum	0.091	6.33	-19	-49	-50
		L Cerebellum	0.198	5.84	-8	-55	-50
		L Cerebellum	0.291	5.56	-40	-49	-40
88	0.002	R Inf. Frontal	0.108	6.25	48	21	20
70	0.006	R Lingual	0.440	5.23	10	-53	3
		Vermis	0.452	5.21	3	-50	5

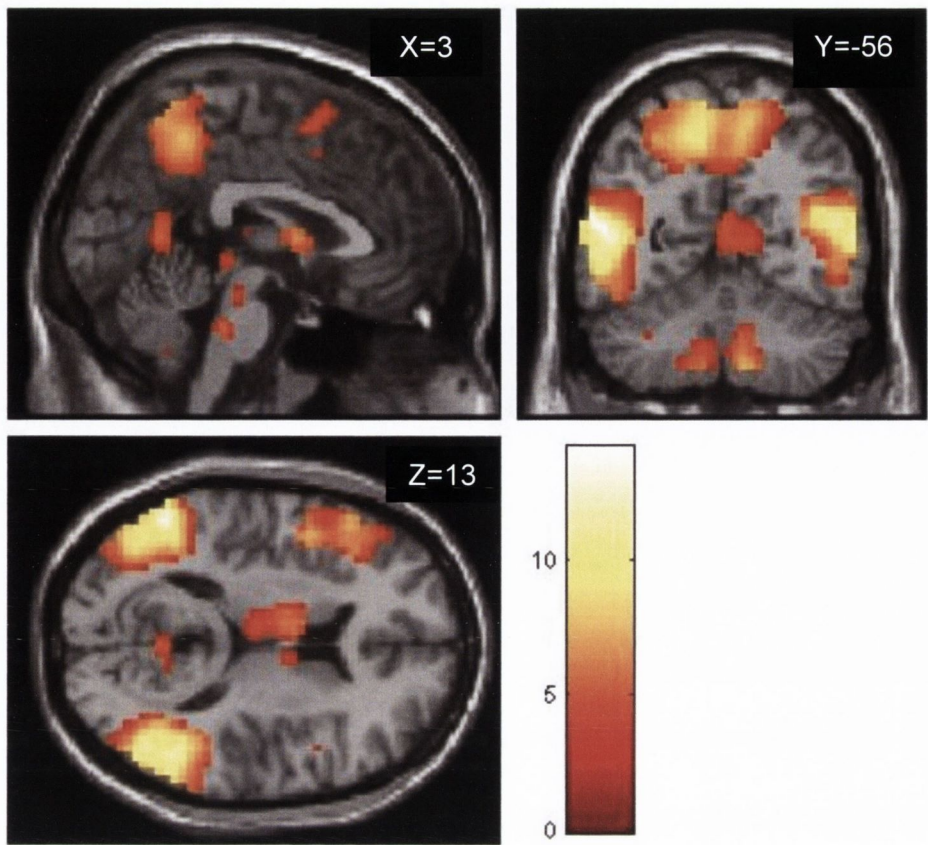


Figure 4-4: Statistical map of brain activity for [TOM>INC] masked by [PUN>INC], i.e. activity during processing of resolvable vs non-resolvable visual cartoons. MNI coordinates [3 -56 13]. Coloured bar shows distribution of *t*-values.

Table 4-5 shows the results from the multiple regression analysis. Differences found in these contrasts are linearly related to an increase of participants' scorings on the EPQ-Neuroticism scale. Only two contrasts yielded significant (each two clusters) of difference:

For [TOM>INC] (Figure 4-5), this activity was in the left inferior frontal lobe and in the precuneus. For [TOM>PUN] (Figure 4-6.), one cluster in the thalamus (bilaterally) and one comprising left anterior cingulate cortex (ACC) and left superior frontal lobe were more active the higher participants scored on EPQ-Neuroticism.

Table 4-5: Table of brain activities from multiple Regressions (Neuroticism).
All activities are thresholded at $p<0.001$. K is the number of voxels in the cluster. Significance ($FWE<0.05$ for multiple corrections) is indicated at both cluster and voxel level.

Contrast	K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates [mm]		
						x	y	z
[TOM>INC]	41	0.041	L Inf. Frontal Tri.	0.498	5.27	-36	14	31
	63	0.007	R Precuneus	0.527	5.22	10	49	13
			L Precuneus	0.781	4.75	13	-53	24
			L Calcarine	0.792	4.73	24	-60	13
[TOM>PUN]	47	0.021	L Thalamus	0.744	5.01	-5	-4	10
			R Thalamus	0.744	4.70	6	-4	6
			L Thalamus	0.867	4.15	-8	-14	13
	51	0.015	L Sup. Front. Medial	0.744	4.97	-12	35	31
			L Sup. Frontal	0.191	4.43	-15	42	27
			L Ant Cingulum	0.839	4.26	-5	39	24

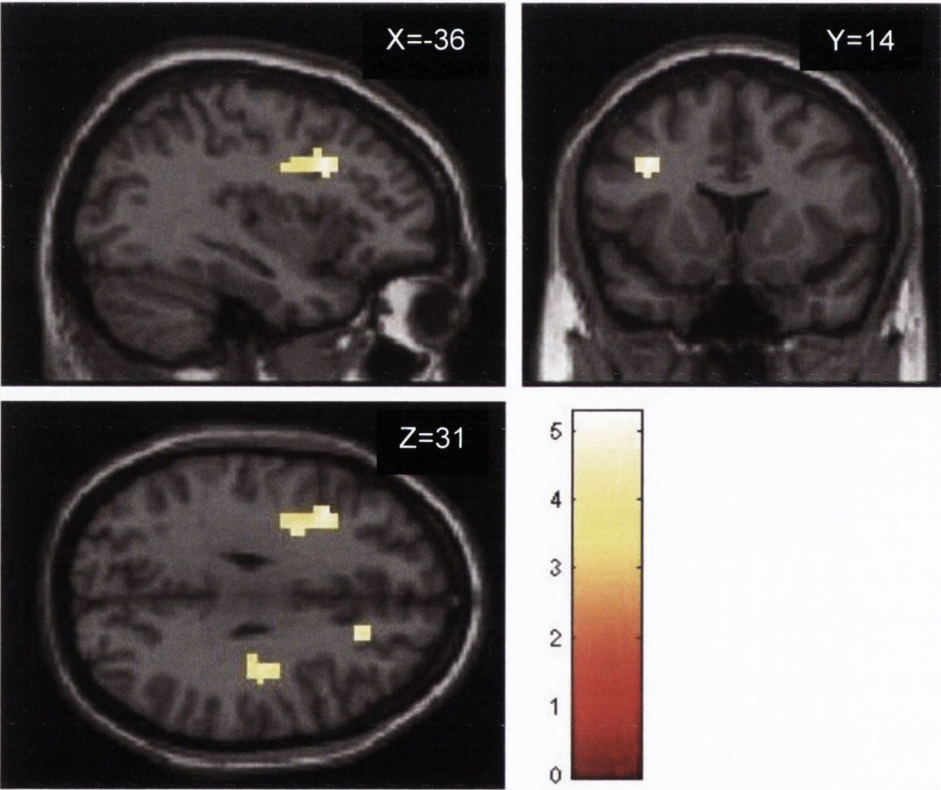


Figure 4-5: Statistical map of brain activity for [TOM>INC] (Regressor: Neuroticism).
ToM vs. incongruent condition, L Inferior Frontal at [-36 14 31]. Coloured bar shows t -value distribution.

Thalamus was more active (bilaterally) the higher participants scored on EPQ-Neuroticism (Figure 4-6).

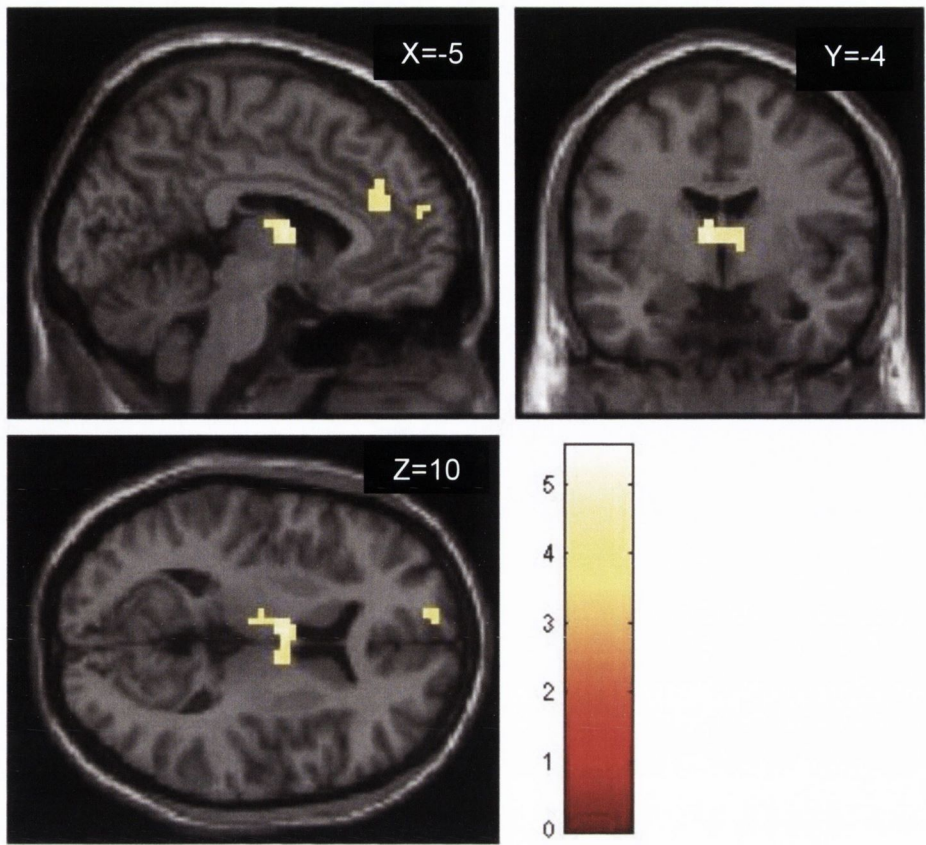


Figure 4-6: Statistical map of brain activity for the [TOM>PUN] (Regressor: Neuroticism). *ToM* vs. incongruent condition, Thalamus (L/R) and ACC (L, sagittal) at [-5 - 4 10]. Coloured bar shows *t*-value distribution.

4.4 Discussion

In this study, healthy participants were exposed to three different conditions in which they had to process visual jokes while MRI scans were acquired. Since only those trials that participants had responded to were used for the fMRI analysis it is most likely that participants were indeed mentally processing stimuli rather than just visually.

While there was no noticeable difference in response times for negative responses (i.e. trials to which participants responded “not understood”) participants took longest to respond to TOM trials. Even if the joke was not understood after all, TOM stimuli seem to have put the highest cognitive load on participants.

The type of LM that requires establishing a residual incongruity and then playfully resolving it was elicited by TOM- and by PUN-trials.

Taken together, the brain activity evoked during these trials was contrasted with the activity evoked during INC trials (in which the incongruity could not be resolved meaningfully) and corrected for whole-brain-comparisons. For [PUN>INC], the contrast that resembled the study of Samson et al. (2009), left middle temporal and left inferior parietal lobes (IPL) were significantly more active. The left IPL may be associated with the capacity to understand causal relationships between the setup and punch lines (A. C. Samson et al., 2009). These suggestions are also consistent with a study by Lee et al. (M. J. Lee & Shin, 2011) who found stronger semantic association to be correlated with greater activation in the left IPL (equivalent to BA 40, the inferior part of which belongs to the supramarginal gyrus).

Also, similar to the findings of Samson (2009), *Study 1* did not reveal any activity in areas associated with the experience of pleasure such as ventral striatum and OFC/nucleus accumbens (Goel & Dolan, 2001, 2007). This may be the case because both studies compared (meaningfully) resolvable cartoons with non-resolvable cartoons which after all still may have been enjoyable for no (rational) reason.

These results confirm that the left inferior frontal gyrus (IFG) (Bekinschtein et al., 2011; Mobbs et al., 2003; Moran et al., 2004; A. C. Samson et al., 2008; K. K. Watson et al., 2007) and right IFG (Bartolo et al., 2006; A. C. Samson et al., 2009) are involved in processing semantic aspects of incongruity–resolution. Two of the earlier studies also found activity in the left superior frontal gyrus (SFG) (Bekinschtein et al., 2011; A. C. Samson et al., 2009) leading Chan et al. (2012) to suggest that the IFG and SFG are responsible for incongruity detection, semantic decoding, semantic selection and semantic integration. *Study 1* did not find significant SFG activity for funny vs. non-funny cartoons after FWE corrections. The two mentioned studies used mixed-gender samples that may account for their findings. Also, Bekinschtein et al. (2011) used verbal jokes (read or listened to) as did most other fMRI studies.

The most significant result, which is in line with all aforementioned fMRI studies, is bilateral activation of the temporo-parietal junction for funny vs. non-funny cartoons, confirming its role as part of a humour processing network. This area has been considered the “integration hub” of humour processing, serving the comprehension of a joke and resolution of incongruity, which is a core aspect of cognitive humour processing (Kohn, Kellermann, Gur, Schneider, & Habel, 2011; A. C. Samson et al., 2009; Wild et al., 2006).

The main contrast of interest in *Study 1* revealed bilateral activity in large clusters in the temporal lobes, particularly TPJ, and in the precuneus for TOM vs. PUN trials, i.e. stimuli that differed from each other only in the presence or absence of the requirement to mentalize. These results are particularly striking in light of the fact that TPJ is one of the primary candidate regions involved specifically in representing mental state information (Lombardo et al., 2011). While PUN cartoons also recruited these areas (albeit to a lesser extent than TOM cartoons), the INC cartoons did not. This is in line with the findings of A. C. Samson et al. (2008) who assumed that the TPJ plays an important role in incongruity resolution, but *ToM* abilities might additionally enhance funniness. Especially, the right TPJ typically exhibits a marked domain-specific functional tuning for representing mental state information (Aichhorn et al., 2009; Perner, Aichhorn, Kronbichler, Staffen, & Ladurner, 2006; see also Chapter 1, R. Saxe et al., 2006) and is functionally and spatially dissociable from nearby dorsal clusters which respond to attentional reorienting (Decety & Lamm, 2007; Scholz et al., 2009) or ventral clusters in posterior superior temporal sulcus (PSTS) that are more responsible for aspects such as processing animacy, biological motion, and eye gaze (Castelli et al., 2000; Nummenmaa, Passamonti, Rowe, Engell, & Calder, 2010; K. A. Pelphrey et al., 2003; Scholz et al., 2009). While PUN cartoons also recruited these areas (albeit to a lesser extent than TOM cartoons), the INC cartoons did not. This is in line with the findings of A. C. Samson et al. (2008) who

assumed that the TPJ plays an important role in incongruity resolution, but *ToM* abilities might additionally enhance funniness.

The other large cluster of activity difference for the contrast [TOM>PUN] was found bilaterally in the precuneus. It is important to note that the cluster was not found for the contrast [PUN>INC] in which case it would have allowed us to relate brain activity in this area to either the funniness or the mere resolvability of PUN stimuli. Instead, given the size and the significance of the cluster for [TOM>PUN] and the fact that the activity is bilateral there is reason to believe that the precuneus is genuinely related to *ToM* processing.

The precuneus may have a mediating role between emotion and social cognition, as it is anatomically tightly connected to both networks (Leichnetz, 2001; Petrides & Pandya, 1984) as well as to areas related to reward and emotion processing, such as the thalamus, putamen and caudate nucleus (Leichnetz, 2001). Furthermore, the precuneus has connections via the basis pontis to several cerebellar sub-regions and seems anatomically very well suited to play an important role in a putative “humour-network” integrating emotional and social processing (Kohn et al., 2011).

Most previous fMRI studies of humour used a funny condition and an unfunny condition as stimuli. However, comparisons of these two conditions have not been able to distinguish the neural substrates involved in the comprehension and appreciation of *ToM* processing (not that they had intended to do so). Accordingly, the present study included *ToM* stimuli.

The second aim of *Study 1* was to test for brain areas in which activity was correlated to participants' individual Neuroticism scores which had not been performed with *ToM* tasks to date. Correlations of neural activity with participant's Neuroticism scores were found in the left IFG and bilateral and bilateral precuneus for [TOM>INC] and in bilateral thalamus and superior frontal regions for [TOM>PUN]. These findings

cannot definitely be interpreted in terms of brain areas that represent the personality trait neuroticism as clusters were not significant at the peak-voxel level ($FWE < 0.05$). However, it is interesting to note that these two were the contrasts that revealed differences. No differences were found for contrasts in which *non*-TOM stimuli (INC, PUN) had elicited larger brain activity than TOM cartoons. These findings may suggest that neuroticism has an impact only if participants apply a theory of mind.

Again, it is interesting to note that these clusters were distinct from the cluster for the contrast [TOM>INC] which were located in the precuneus, inferior frontal triangularis (equivalent to Boca's area, or BA 45, involved in semantic processing of language). While both trial types, TOM and PUN, require semantic processing, it was the Theory-of-Mind component to which high-Neuroticism individuals responded with higher neural activity in *affective* brain areas.

Hyper-reactivity in affective brain areas could be interpreted as reflecting increased arousal by emotional conflict and negative affect in high-Neuroticism individuals (S. W. Chan et al., 2008; Haas et al., 2007; Hooker et al., 2008). An alternative explanation could be that high Neuroticism individuals have greater vigilance for (emotional) conflict and increased attention to negative stimuli (Haas et al., 2007). In the study by Chan et al. (2009), high-Neuroticism individuals showed a linear trend for increased responses to increased fear intensities in the fusiform gyrus and middle temporal gyrus, which points to more intensive visual processing of threat-relevant face stimuli. Increased amygdala activity in high Neuroticism individuals might be due the role of this structure in directing attention to the salient parts of the environment (e.g. eyes) through its connections with these high-level visual areas (Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). Perlman et al. (2009) has shown that Neuroticism scores is positively associated with the time spent looking at the emotionally salient eye region of faces, in particular of fearful faces (Perlman et al., 2009).

Interestingly, both areas, ACC and thalamus have recently been linked to affective neural networks in connectivity studies (Cho et al., 2013). ACC has been known for a while to be involved in emotion regulation (Kevin N. Ochsner et al., 2004). Emotion regulation depends upon interactions between prefrontal and cingulate regions implicated in cognitive control and systems like the OFC, amygdala and insula that have been implicated in emotional responding. The ACC is also known to be involved in emotion processing, empathy, and cognition, with previous studies observing divergent neural dynamics in the ACC of BPD patients compared to healthy controls (Dziobek et al., 2011). A large body reviewing fMRI studies that have linked ACC to both, emotion regulation and cognitive control can be found e.g. in K. N. Ochsner, Silvers, and Buhle (2012).

Bjørnebekk et al. (2013) who recently reviewed the connectivity studies on ACC, stated its connections to both the “emotional” limbic system and the “cognitive” prefrontal cortex. Thus, the ACC likely has an important role in integration of neuronal circuitry for affect regulation and can be identified as a distinctive region in understanding psychopathology (Bjørnebekk et al., 2013).

Study 3 of this thesis (Chapter 6) investigated functional connectivity within the “emotion network” by analysing responses to theory of mind stimuli, using ACC as the seed region.

According a recent voxel based meta-analysis by Liu et al (2011), the thalamus, demonstrates a likelihood of increased blood oxygen level dependent (BOLD) signal activations during reward processing similar to other regions such as the amygdala (fear), the anterior insula (aversion) and OFC (reward).

One of the most striking aspects of fMRI studies over the past decade on emotional regulation is its demonstration that some forms of emotion regulation can depend upon cognitive processes not typically thought of as having emotion-related functions (K. N. Ochsner et al., 2012). Since

comparisons of emotion regulation (e.g. re-appraisal) to non-affective forms of control have not yet been made it is difficult, if not impossible to predict cognitive vs. emotional processes from brain activations.

Lastly, in the real world there are no such things as “purely cognitive” stimuli as little as there are “neutral faces”. Every kind of stimulus will necessarily have an affective quality, dependent on its characteristics, the context in which it arises, and the expectations of the observer. Any stimulus that is processed cognitively will be processed in an affective way as well. In the attempt to directly compare cognitive and affective processing and to investigate how affective processing interferes with cognitive processing, Prehn et al. (2008) used an analogical reasoning task (Van der Meer, 1989) participants with comparably higher neuroticism scores showed increased pupillary responses during conditions with emotional interference (i.e., during a conceptual task when they had to ignore incongruent information on the correspondence provided by the task-irrelevant emotional relations). The authors concluded from behavioural and physiological results that increased mental resource consumption due to emotional interference in participants with comparably higher neuroticism scores might reflect a possible mechanism making these individuals more vulnerable to mood or anxiety disorders (Prehn et al., 2008).

The results of the current study are likely reflective of real differences in brain function related to personality, as a whole-brain correlation approach which has been validated as a reliable, independent measure to detect brain-behaviour relationships (Lieberman et al., 2009; Poldrack and Mumford, 2009) was employed. Second, we employed a robust multiple comparison procedure which protects against the possibility of false positives.

Finally, by including only women in the current study, we greatly reduced the heterogeneity of our sample given that there have been considerable behavioural differences found between genders in emotional reactivity (Lang & Bradley, 2010) and in levels of neuroticism

(Lynn & Martin, 1997). A definite strength of this study compared to previous humour investigations is that an all-female sample was used since gender-differences in humour processing have been shown in a recent fMRI study (Kohn et al., 2011).

While one of the strengths of this paradigm was to ensure participants processed the stimuli cognitively there was no way to consider the reasons why some cartoons were funny and others not. Occasionally during the instruction session, when being asked directly participants explained that they experienced some cartoons as funny merely because of the way cartoon characters were caricaturised. Other limitations are the following.

As funniness ratings were not analysed for this study the quantity and quality of responses serve as an approximation of how the stimuli were perceived by our participants. A clear pattern funniness can be inferred from the percentage of positive responses that was highest for TOM trials (*“understood”*) and lowest for INC trials (which indeed contained an incongruity but no punch line). Mentalizing should arguably not increase with higher subjective funniness, since a joke perceived as funnier does not necessarily invoke stronger mentalizing processes. Nevertheless, the results seem to support the assumption of Samson et al. (A. C. Samson et al., 2008) that involvement of *ToM* abilities enhances the perceived funniness of a joke. To test this assumption, however, one would need to obtain and correlate funniness ratings and scores of mentalizing scales. It would further be interesting to know whether scores on emotional empathy scales would correlate with perceived funniness.

The study identified a novel relation between neuroticism and *ToM* processing. These results provide further evidence for the important role that this trait plays in individual responses to *ToM* stimuli, and they also suggest similarities between cognitive processing in individuals with high levels of neuroticism such as patients with BPD (Distel et al., 2009; Grootens & Verkes, 2005) which may help to elucidate the role

that this trait plays in the development of BPD and other affective disorders. Furthering the understanding of individual differences in neural reactivity to *ToM* stimuli may be important in furthering our understanding of the role that personality plays in humour processing, and may help to elucidate how personality influences cognitive empathy.

5 Functional activity changes in BPD (Study 2)

5.1 Introduction

Borderline Personality Disorder (BPD) is a commonly seen axis II psychiatric disorder prevalent through 1-2% of the population, with young women making up approximately 75% of the diagnosed group (John M. Oldham, 2004). Key features of the disorder include impulsivity, emotion dysregulation, severe relationship dysfunction (typified by depth and lability of mood), and chaos, instability, and disorganization within and across interpersonal relationships, sense of self, and behaviour (Steele & Siever, 2010a). In extreme cases these disturbances of sense of self may lead to periods of dissociation (one of the diagnostic criterion used by clinicians in identifying BPD cases) (DSM-IV-TR, 2000).

Empirical research on BPD has thus far mostly focused on affective instability. Although affective instability has been well established as a core symptom of BPD, it is not specific to the disorder and does not solely explain it, as it is a common characteristic in other psychiatric conditions e.g., depressive- and bipolar-spectrum conditions, and posttraumatic stress disorder (PTSD), see Koenigsberg (2010). There are a number of prominent symptoms of BPD—including repetitive suicidal behaviour, self-injury, aggressive outbursts, and increased emotional reactivity—that typically manifest themselves in an interpersonal context. This supports the idea of a superordinate deficit in the perception, processing and emission of social signals (Gunderson et al., 2008; Stiglmayr et al., 2005).

On the other hand, as mentioned in Chapter 1, the majority of recent behavioural studies (A. Arntz et al., 2009; Fertuck et al., 2009; Franzen et al., 2011; Ghiassi et al., 2010; Harari et al., 2010) indicate equal or superior mentalizing ability in BPD.

Perhaps the best example is from a recent study (Franzen et al., 2011) in which authors investigated the effects of emotional cues and the fairness of a social partner on the ability to infer other peoples' intentions in a virtual social exchange. 30 BPD patients and 30 non-patients were asked to play a multi-round trust game with four virtual trustees. The trustees varied in regard to fairness and presence of emotional facial cues which were both linked to repayment ratio. BPD patients adjusted their investment to the fairness of their partner. In contrast, healthy controls disregarded the trustees' fairness in the presence of emotional facial expressions. Both groups performed equally in an emotion recognition task and assessed the trustees' fairness comparably. When the unfair trustee provided emotional cues, BPD patients assessed their own behaviour as more fair, while the lack of cues led patients to assess their own behaviour as unfair. BPD patients are superior in the attribution of mental states to interaction partners when emotional cues are present. While the emotional expressions of a partner dominated the exchange behaviour in non-patients, BPD patients used the objective fairness of their social counterparts to guide their own behaviour despite the existence of emotional cues (Franzen et al., 2011).

With regard to neuroimaging studies results have been controversial with one supporting deficits in emotional empathy in BPD: Dziobek et al. (2011) used the "ecologically valid" MET (Multifaceted Empathy Test, see Chapter 1) to assess emotional empathy. In the emotional empathy items of the MET, participants were required to rate the amount of mirroring of an emotion that took place in response to a picture (e.g., if the mental state of the person was anxious, subjects were asked to rate how anxious they felt) and additionally rated the degree of empathic concern they felt for the person in the picture. Results from the MET revealed that BPD patients had significantly reduced tendencies to feel empathy for other people in emotionally distressing situations compared to non-clinical controls (Dziobek et al., 2011).

Applying the fMRI version of the MET, the authors (Dziobek et al., 2011) found that during emotional empathy the right mid-insula was more activated in individuals with BPD than in non-clinical controls. The mid-insula has been shown to react strongly to bodily states of arousal (Brendel, Stern, & Silbersweig, 2005). Further, Dziobek et al. (2011) found a positive association between the activation in the right middle insula and skin conductance during emotional empathy in individuals with BPD, which supports the notion of increased arousal when being emotionally involved with others. Higher levels of personal distress and arousal are commonly observed in individuals with BPD (Guttman & Laporte, 2000). Thus, the data of Dziobek et al. (2011) suggest that arousal might interfere with emotional empathy in BPD.

Studies of cognitive empathy in BPD, or the ability to mentalize have not produced consistent results (Roepke, Vater, Preissler, Heekeren, & Dziobek, 2012).

Shedding light on the proximate, neural substrates of mentalizing-related processes in BPD would help to identify and perhaps refine psychological treatment programmes.

As mentioned, scientific knowledge about social cognition in BPD is surprisingly sparse. Given that individuals with BPD tend to form inaccurate impressions about others (see *ToM*-related symptoms, 1.3.1), “Theory-of-Mind” tasks may serve as a potent probe of mentalizing abilities, because they require individuals to make inferences about beliefs, intentions, and behaviours of others.

The objective of the present study was to analyse whether neural response to stimuli characteristics is altered in BPD patients compared with healthy controls and to study the brain responses. To address this issue we tested BPD patients and matched controls using the visual humour task (A. C. Samson et al., 2008) task described in 2.5.

Hypotheses

The anatomical hypothesis was that there is less activity in areas of the social brain in BPD patients for condition TOM vs. *non*-TOM when compared to healthy controls.

This activity difference should remain after accounting for age, levels of depression, and neuroticism.

More overall activity should be seen in BPD patients vs. healthy individuals in incongruent vs. non-incongruity conditions.

Similarly, the behavioural hypothesis was that BPD patients should show more difficulties understanding visual cartoons with a *ToM* component than without that component as reflected by their response times.

5.2 Methods

5.2.1 Participants

The participants of this study were made up of the 19 participants from *Study 1* (4.2.1) who served as controls. In addition, 17 female BPD patients were recruited whom the healthy controls were compared to (see 2.1, for recruiting information). All participants underwent a psychometric testing and a MR imaging session as described in Chapter 2. One participant from the patient group did not complete all the questionnaires but completed the scanning session. Personality information from the most important variables is provided in Table 5-1. Twelve out of seventeen patients were taking anti-depressants of various types at the time of investigation.

Table 5-1: Demographic information.

	BPD patients	Controls	Statistics
Age	31.4 ± 9.5	29.3 ± 7.5	ns
Height	165.2 ± 6.2	168.0 ± 5.3	ns
Weight	71.6 ± 14.7	60.7 ± 8.3	t=2.79; df=22.8; p<0.01
Cigarette consumption	11.7± 11.1	1.5 ± 3.6	t=3.68; df=17.6; p<.005
Alcohol units per week	4.1 ± 7.7	3.4 ± 3.7	ns
Education	2.5 ± 0.72	2.88± 0.33	t=-1.71; df=9.8; p<.05
HDRS	24.31 ± 10.3	0.37 ± 0.76	t=6.84; df=37; p<.001
BDI-II	41.63 ± 10.13	4.26 ± 3.60	t=14.01; df=18.19; p<.001
BIS total	79.56 ± 7.21	62.63 ± 7.1	t=6.98; df=33; p<.001
EPQ-Neuroticism	10.52 ± 1.37	3.63 ± 2.73	t=9.71; df=27.2; p<.001
EPQ-Extraversion	4.47 ± 3.9	9.42 ± 3.16	t=-4.2; df=33; p<.001

5.2.2 Data Acquisition

Magnetic resonance images were obtained with a Philips Achieva MRI scanner (Philips Medical System, Netherland BV, Veenphuis 4–6, 5684 PC Best, The Netherlands) operating at 3 Tesla. For the cognitive paradigm run, 26 axial slices (3.5 mm× 3.5 mm× 3.5 mm resolution, 0.75 mm spacing), parallel to the AC-PC plane and covering the whole brain were acquired using a single shot, gradient recalled EPI sequence (TR 2000 ms, TE 30 ms, 90° flip angle). One functional run with 620 time points was acquired, with each time point sampling over the 26 slices. Prior to the functional run, 180 anatomical slices T₁-weighted 3D-MPRAGE sequence (repetition time, 11.0 ms; echo time, 4.4 ms; total acquisition time, 7 min 30 sec; number of acquisitions, 1; field of view, 250 mm× 256 mm × 160 mm; matrix: 256 mm × 256 mm; resolution: 0.9

mm × 0.9 mm × 0.9 mm) with the same spatial orientation as the functional data were acquired.

For fMRI data pre-processing information see Overall Methods, (2.6).

5.2.3 fMRI task

The stimulus material consisted of two types of cartoons, puns (PUN) and jokes requiring mentalizing (TOM) as well as a control condition that consisted of unfunny pictures containing an incongruity that could not be resolved meaningfully (INC). All pictures were low in aggressive, violent, and sexual content and were used in previous studies (A. C. Samson et al., 2009; A. C. Samson et al., 2008). In order to investigate brain activity during resting state (see *Study 3*) rest trials (NULL) were interleaved during which participants observed a blank screen. All participants processed a total of 120 trials (30 INC + 30 PUN + 30 TOM + 30 NULL). Stimuli were presented every 10s on average and with variable stimulus onset delays (0, 400, 800, 1200 or 1600ms). Each stimulus was onset for 6000ms during which participants were instructed to make a response. Below each picture (cartoon) the word “understood” was printed on the left side and the words “not understood” were printed on the right side. Participants were asked to press the corresponding button (left/right) with their index or middle finger, respectively, depending on whether they understood the joke. The functional neuroimaging part started after 15 minutes of the scanning session (during which the structural image was acquired) and took about 18 minutes.

A complete description of the stimuli is found in the Overall methods, Chapter 2 (2.4).

5.2.4 fMRI Analysis

SPM8 Pre-processing

The pre-processing and *1st-level* analysis of functional MRI data was carried out as described in Chapter 3.

Full factorial analysis: Pat vs. HC

In order to be able to group certain contrasts by means of inclusive masking a full factorial analysis was carried out with SPM8. Two factors were entered. Factor 1 had two levels (group “Pat” and group “HC”); Factor 2 contained the six levels which were the following contrasts of interest resulting from the *1st level* analysis:

- [INC>PUN]
- [INC>TOM]
- [PUN>INC]
- [PUN>TOM]
- [TOM>INC]
- [TOM>PUN]

The SPM8 Full-factorial design allowed tracking the effects of multiple conditions by grouping contrasts together. To determine the overall impact of the incongruity condition (INC) as contrasted with the two non-incongruity conditions (PUN, TOM) two contrasts were grouped together: [INC>PUN]+[INC>TOM].

Similarly, to determine the overall impact of the Theory-o-Mind condition (TOM) as contrasted with the two non-*ToM* conditions (INC, PUN) the following two contrasts were grouped together: [TOM>INC]+[PUN>INC].

Individual participants’ scores from HDRS-depression, BDI-depression-, and EPQ-Neuroticism scales (see Chapter 2) and the participants’ age were entered as covariates into the 2nd-level random effects analysis at first. Since the voxel clusters remained the same (in size and location) as without the covariates it was decided to report only the latter results.

5.3 Results

5.3.1 Behavioural results

Number of responses

No significant differences ($p > 0.05$) were found for the overall number of responses made ($t(34)=1.15$), subtotal of positive responses (“understood”; $t(34)=0.36$), and the subtotal of negative responses (“not understood”; $t(34)=0.94$).

The subtotal of responses among patients and healthy controls was not different in either condition: INC ($t(34)=-0.67$), PUN ($t(34)=-0.85$), TOM ($t(34)=-1.55$). However, when distinguishing between positive and negative responses within each condition patients were more likely to respond “understood” ($M_1=10.4$, $SD_1=5.8$) than healthy controls ($M_2=5.2$, $SD_2=5.7$) in the INC condition ($t(34)=2.72$, $p < 0.05$) and less likely to do so in the TOM condition ($M_1=15.6$, $SD_1=5.0$, $M_2=20.1$, $SD_2=5.0$, $t(34)=-2.58$, $p < 0.05$). No difference in the subtotal of positive responses was found for the PUN condition ($t(34)=-1.35$). Figure 5-1 shows the distribution of positive responses across the three experimental conditions.

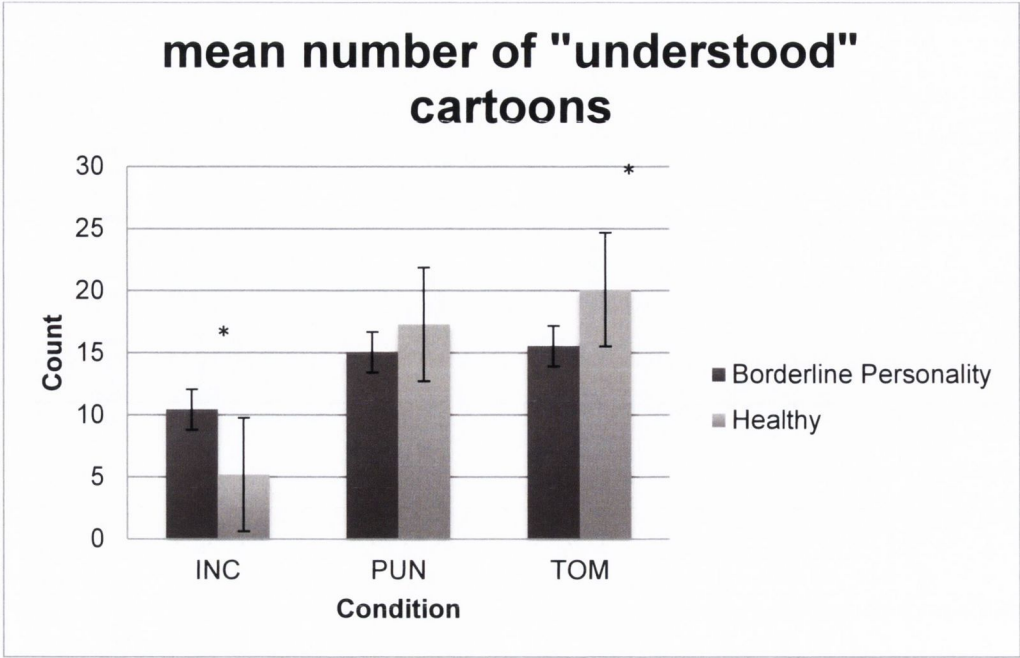


Figure 5-1: Mean number of positive responses.
for BPD patients ($N_1=16$) vs. healthy controls ($N_2=19$).

Quality of responses

When comparing the quality of responses in terms of the proportion of positive responses within each condition patients indicated to have “understood” more INC cartoons ($M_1=37.3\%$, $SD_1=20.0\%$) than healthy controls ($M_2=17.4\%$, $SD_2=19.0\%$), $t(33) = 3.1$, $p<0.005$) but less TOM cartoons ($M_1=53.7\%$, $SD_1=17.9\%$, $M_2=67.7\%$, $SD_2=16.3\%$, $t(33)=-2.50$, $p<0.05$). No significant difference was found for the proportion of positive responses within the PUN condition ($t(33) = -1.43$) or across all the three conditions combined ($t(33)=-0.14$). Figure 5-2 shows the proportion of positive responses across the three experimental conditions.

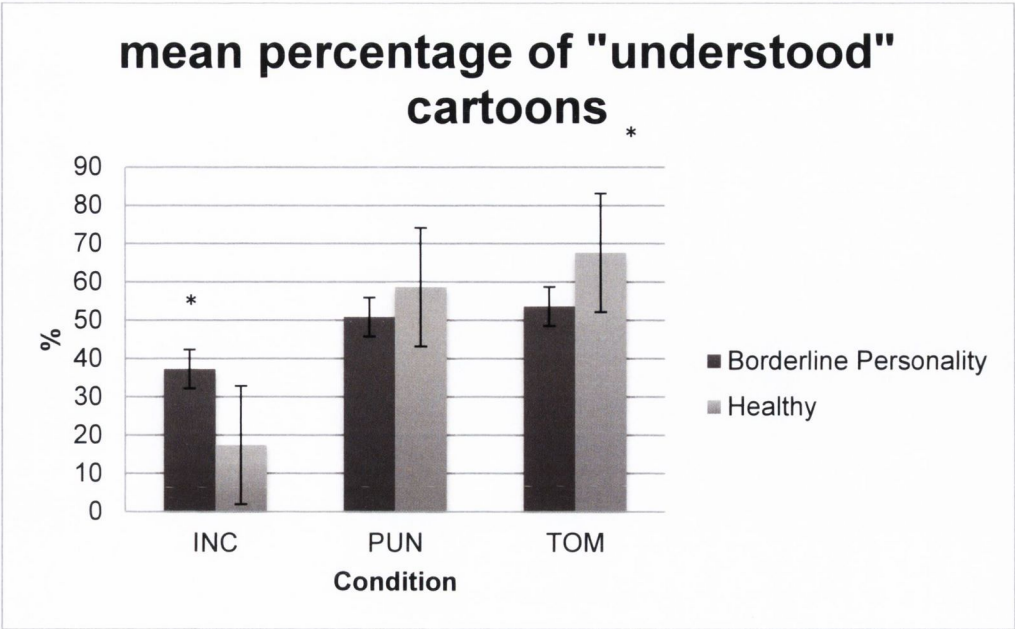


Figure 5-2: Mean percentage of positive responses. for BPD patients ($N_1=17$) vs. healthy controls ($N_2=19$).

Differences in mean response times were non-significant between patients and healthy controls across all conditions combined ($t(33)=1.85$), within the PUN condition ($t(33)=1.31$) and within the TOM condition ($t(33)=1.46$). Within the INC condition patients were significantly slower ($M_1=3.38s$, $SD_1=0.49s$) to press the response button than were healthy controls ($M_2=2.94s$, $SD_2=0.65s$, $t(33)=1.46$, $p<0.05$).

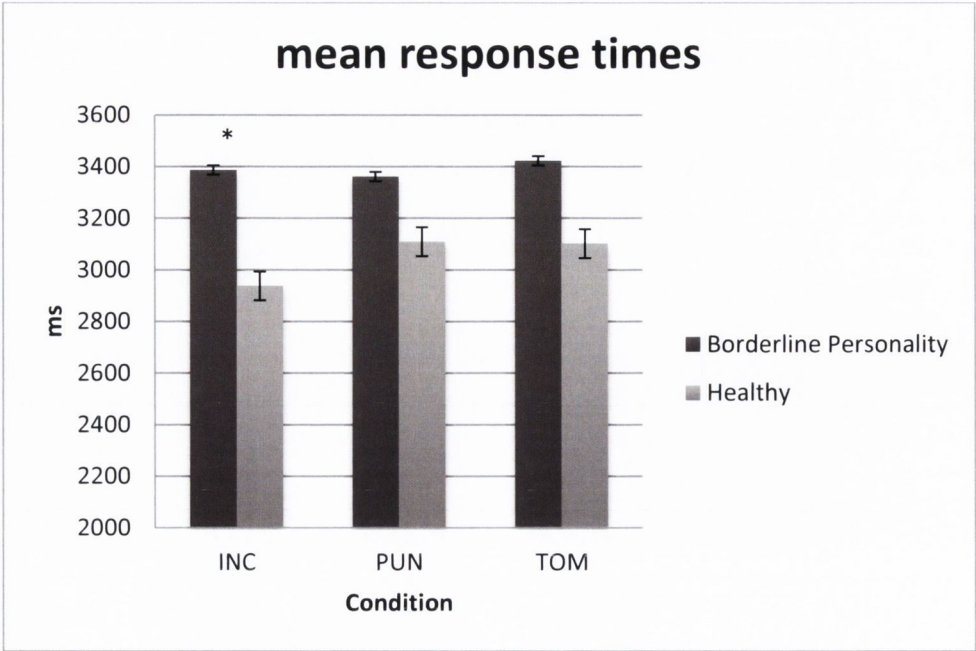


Figure 5-3: Mean response times.
for BPD patients ($N_1=17$) vs. healthy controls ($N_2=19$).

When discriminating between positive (*understood*) and negative (*not understood*) responses the pattern of differences became more sophisticated.

Patients took longer for positive responses across all conditions ($M_1=3.42s$, $SD_1=0.52s$) than did healthy controls ($M_2=3.01s$, $SD_2=0.54s$, $t(35)=2.33$, $p<0.05$). Within conditions this difference remained significant for PUN ($M_1=3.37s$, $SD_2=0.66s$, $t(35)=2.31$, $p<0.05$) and TOM ($M_1=3.53s$, $SD_1=0.52s$, $t(35)=2.37$, $p<0.05$) but not for INC ($t(31)^1=1.36$).

¹ Some participants had not once pressed “understood” when presented a type INC cartoon.

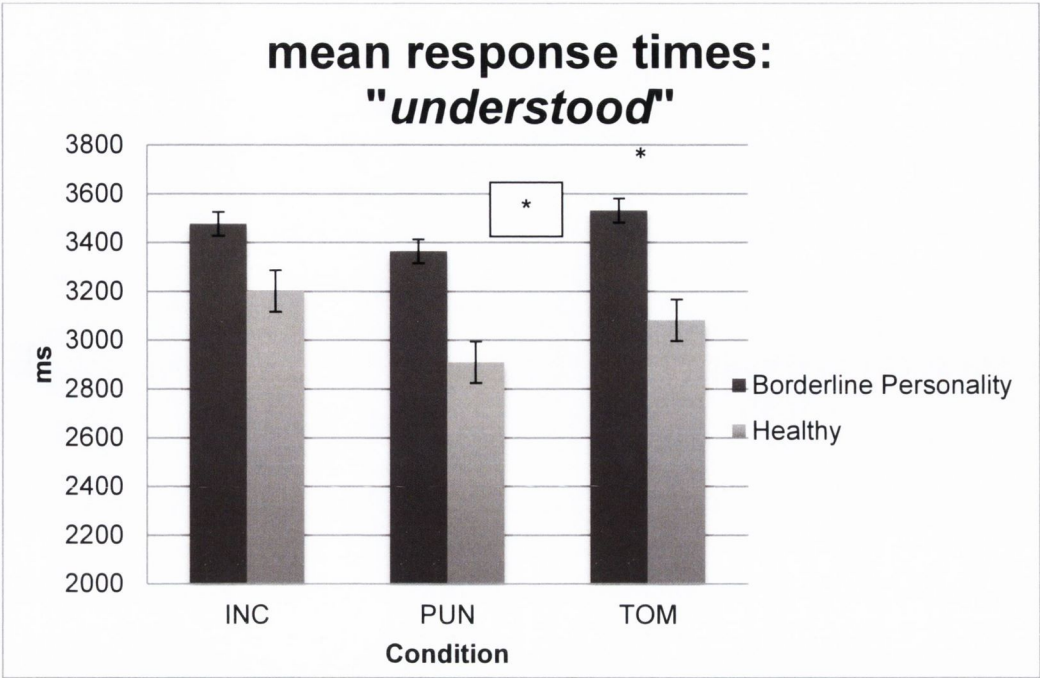


Figure 5-4: Mean response times for positive responses.
given by BPD patients ($N_1=17$) and healthy controls ($N_2=19$).

For negative responses (*not understood*) INC was the only condition in which patients were significantly slower to give a negative response ($M_1=3.42s$, $SD_1=0.55s$) than were healthy controls ($M_2=2.95s$, $SD_2=0.66s$, $t(34)=2.35$, $p<0.05$). No significant differences in response time were found for the other conditions PUN ($t(34)=0.07$) and TOM ($t(34)=0.22$). Figure 5-5 shows the distribution of response times for negative responses across the three experimental conditions.

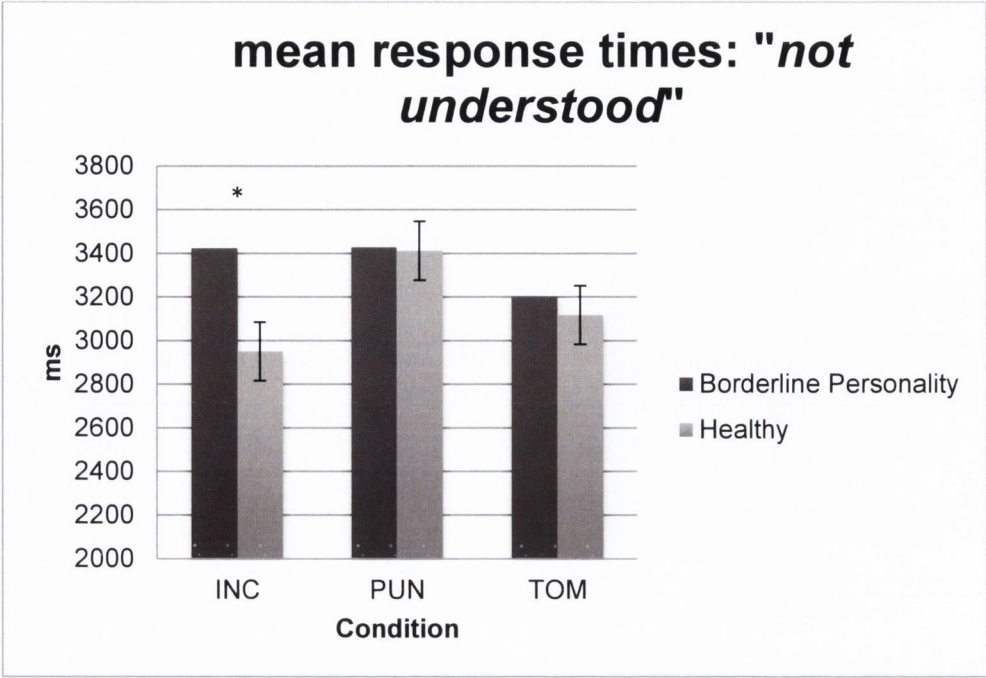


Figure 5-5: Mean response times for negative responses. given by BPD patients ($N_1=17$) and healthy controls ($N_2=20$).

5.3.2 Imaging results

Patients>Healthy Controls

Patients showed more brain activity in both of the contrasts in which the INC condition was compared to a *non*-INC condition (PUN, TOM). For the contrast [INC>PUN] this activity was located in the left inferior parietal lobe and for the contrast [INC>TOM] it was the left supramarginal that was significantly more active in patients than in healthy controls even after correction for multiple comparison (FWE) (Table 5-2).

Table 5-2: Table of activity differences (Pat>HC) under each contrast.
Between-group contrasts were performed for each of the three experimental conditions –incongruity (INC), ‘puch line’ resolution (PUN), and Theory-of-Mind (TOM).
All differences are thresholded at $p<0.001$.Significance at cluster level and at voxel level ($FWE<0.05$ for multiple corrections) is indicated.

Contrast	K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates [mm]		
						x	y	z
[INC>PUN]	73	0.26	L Inf. Parietal	0.227	4.12	-43	-35	41
			L Inf. Parietal	0.512	3.80	-57	-32	41
			L Supramarginal	0.622	3.70	-54	-35	27
[INC>TOM]	133	0.002	L Supramarginal	0.082	4.44	-57	-32	27
[PUN>INC]			no suprathreshold clusters					
[PUN>TOM]			no suprathreshold clusters					
[TOM>INC]			no suprathreshold clusters					
[TOM>PUN]			no suprathreshold clusters					

In neither of the contrasts TOM>non-TOM did patients show more activity than healthy controls, consistent with hypothesis.

Patients<Healthy Controls

Table 5-3: Table of activity differences (Pat<HC) under each contrast.
Between-group contrasts were performed for each of the three experimental conditions –incongruity (INC), ‘puch line’ resolution (PUN), and Theory-of-Mind (TOM).
All differences are thresholded at $p<0.001$.Significance at cluster level and at voxel level ($FWE<0.05$ for multiple corrections) is indicated.

Contrast	K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates [mm]		
						x	y	z
[INC>PUN]			no suprathreshold clusters					
[INC>TOM]			no suprathreshold clusters					
[PUN>INC]	72	0.027	L Inf. Parietal	0.233	4.11	-43	-35	41

[PUN>TOM]			no suprathreshold clusters					
[TOM>INC]	133	0.002	L Supramarginal	0.082	4.44	-57	-32	27
[TOM>PUN]			no suprathreshold clusters					

Healthy controls showed more activity for contrast [TOM>INC] in the left supramarginal gyrus. Similarly, patients showed more activity for contrast [INC>TOM]. Moreover, healthy controls also depicted significantly more brain activity for the contrast PUN>INC in the left inferior parietal cortex.

Grouped contrasts

To determine the overall impact of the incongruity condition (INC) as contrasted with the two non-incongruity conditions (PUN, TOM) two contrasts were grouped together. Table 5-4 shows the differences in brain activity for the contrasts [INC>PUN] and [INC>TOM].

Table 5-4: Table of activity differences for [INC>PUN]+[INC>TOM].
Between-group contrasts were grouped together in a full factorial analysis in order to determine the impact of the incongruity condition (INC) vs. the two non-incongruity conditions ('puch line' resolution (PUN), and Theory-of-Mind (TOM)).
All activities are thresholded at $p<0.001$. Regions printed in bold type were significant at both cluster level and voxel level ($FWE<0.05$ for multiple corrections).

Contrast	K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates [mm]		
						x	y	z
[Pat>HC]	396	<0.001	L Inf. Parietal	<0.001	5.76	-47	-35	45
			L Supramarginal	<0.001	5.71	-57	-32	27
			L Supramarginal	0.001	5.58	-57	-32	38
	137	0.008	L Mid. Temporal	0.002	5.42	-61	-53	3
			L Mid. Temporal	0.016	4.87	-47	-53	17
			L Mid. Temporal	0.507	3.80	-54	-57	-5
	91	0.025	L Sup. Temporal Pole	0.003	5.30	-47	4	-22
			L Sup.	0.049	4.59	-54	11	-15

			Temporal Pole					
			L Sup.			-35	21	-22
			Temporal Pole	0.234	4.11			
	122	0.009	R Mid.			48	14	-26
			Temporal Pole	0.020	4.83			
			R Sup.			52	11	-19
			Temporal Pole	0.043	4.52			
			R Sup.			45	-14	-8
			Temporal	0.050	4.58			
	86	0.025	Sup. Frontal	0.061	4.52	-15	4	52
			R Supp. Motor Area	0.534	3.58	10	0	52
			Supp. Motor Area	0.824	3.49	-1	11	59
	72	0.039	R Mid.			52	-39	-1
			Temporal	0.064	4.51			
			R Mid.			59	-46	6
			Temporal	0.095	4.40			
			R Sup.			45	-39	13
			Temporal	0.510	3.80			
[Pat<HC]	16	0.494	R Mid.	0.803	3.52	3	-11	24
			Cingulum					
			R Caudate	0.835	3.48	13	-4	27

Clusters in which patients showed higher BOLD activity for INC conditions than controls were clearly located in brain regions that resemble the left TPJ (left inferior parietal and supramarginal), the left temporal lobe, and bilateral temporal poles (and survived correction for multiple correction on cluster as well as voxel level (*FWE*, $p<0.05$)).

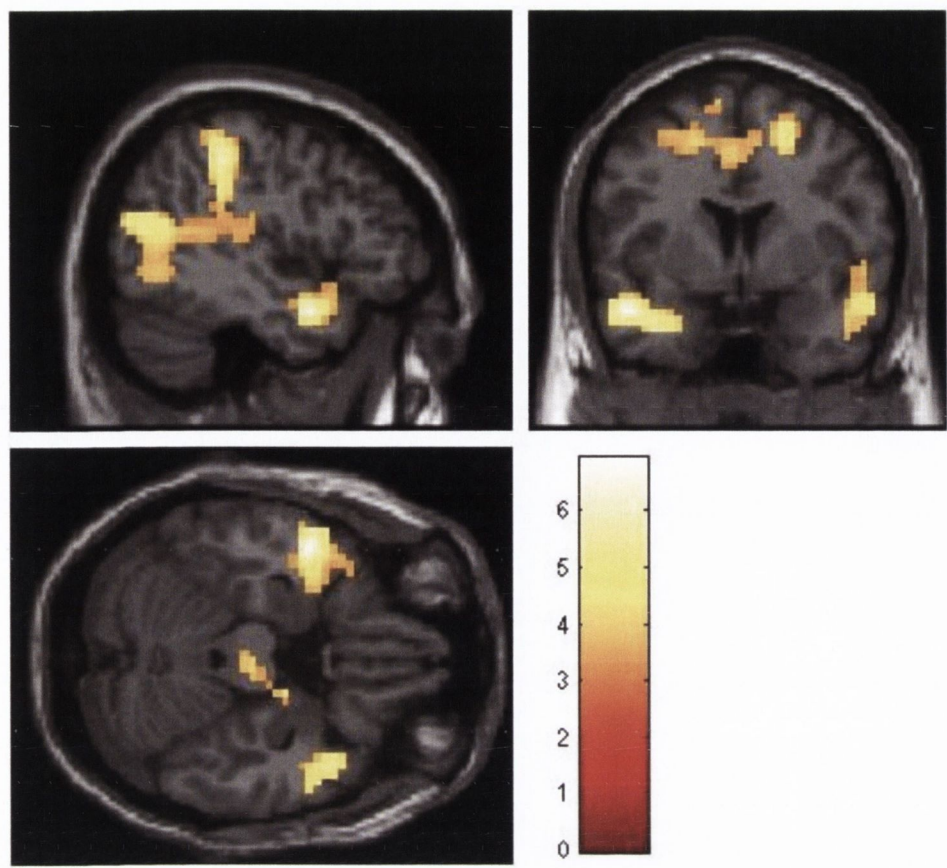


Figure 5-6: Statistical map of brain activity for [INC>PUN]+[INC>PUN]. Brain areas that were more active in BPD during processing of the incongruity condition at [-47 4 -22]. Left temporo-parietal junction and bilateral temporal poles. Coloured bar shows t-value distribution.

Healthy controls did not show significantly greater activity during INC condition than did patients.

Areas that were more active in TOM conditions versus *non*-TOM conditions were calculated by computing the grouped contrast [TOM>PUN]+[TOM>INC] (Table 5-5).

Table 5-5: Table of activity differences for [TOM>PUN]+[TOM>INC].
Between-group contrasts were grouped together in a full factorial analysis in order to determine the impact of the Theory-of-Mind (TOM) vs. the two non-TOM conditions ('puch line' resolution (PUN), and incongruity condition (INC)). All activities are thresholded at $p<0.001$. Bold type indicates regions for which the difference in activity was significant on a voxel level ($FWE<0.05$, for multiple correction).

Contrast	K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates [mm]		
						x	y	z
[Pat>HC]			no suprathreshold clusters					
[Pat<HC]	153	0.001	L Mid. Temporal	0.004	5.25	59	-42	3
			R Sup. Temporal	0.111	4.35	41	-42	13
			R Angular	0.355	3.95	48	-49	27
	65	0.038	L Sup. Frontal	0.036	4.67	-5	4	10
			L Caudate	0.947	3.29	-12	25	3
	89	0.013	R Sup. Temporal	0.038	4.65	55	0	-15
			R Sup. Temporal	0.177	4.20	45	-14	-8
			R Mid. Temporal	0.304	4.02	52	-18	-12
	135	0.002	L Precuneus	0.111	4.35	-8	-46	41
			R Precuneus	0.228	4.12	5	-53	52
			L Precuneus	0.231	4.11	-12	-55	48
	84	0.016	L Supramarginal	0.190	4.18	-47	-32	31

Healthy individuals showed more activity under *ToM* conditions in the right middle temporal, right STS, and left superior frontal while patients showed no differences in activity for TOM versus *non-TOM* conditions.

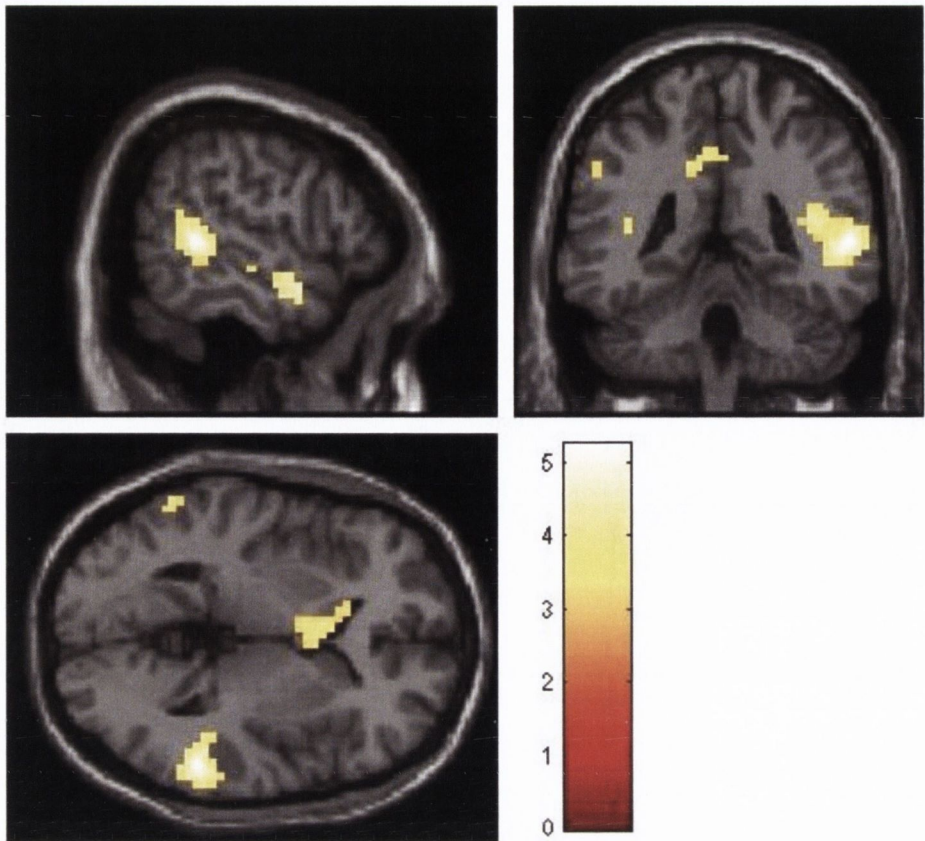


Figure 5-7: Statistical map of brain activity for [TOM>PUN]+[TOM>INC], Pat<HC.
Brain areas that were less active in BPD during Theory-of-Mind-processing
Mid. Temporal (R) and STS (R). Coloured bar shows *t*-value distribution.

5.4 Discussion

The present study investigated whether BPD patients are impaired in the processing of *ToM* stimuli. This was studied on the behavioural and the functional neural level. The analysis of behavioural data indicates that patients were impaired in the processing of *ToM* cartoons in that they responded “understood” less often and took significantly longer to respond compared to healthy controls. This has not been studied before and represents an interesting finding as the number of positive responses from patients was not different from that of healthy controls in the PUN condition (that differed from the TOM condition only in its lacking of a *ToM* component). Dziobek et al. (2011) came to a similar conclusion of “altered social cognition in BPD” after applying the MET to patients (in which to assess cognitive empathy, subjects were required to infer the mental states of individuals shown in photographs by

selecting one of two mental state descriptors). While their paradigm probably had more ecological validity – especially when carried out outside the scanner- in that participants were given more time and were challenged to make a qualitative response, the paradigm in *Study 2* used an ‘active’ control condition (PUN) that ruled out the possibility of patients generally tending to make less positive responses. Indeed, patients indicated to have “understood” significantly more INC-cartoons which, as the baseline, did not require any resolution at all. However, this does not mean that it is impossible to attempt applying a logical mechanism or “search for meaning”. When considering the trials that were responded to by pressing “not understood”, patients had significantly longer response times for INC trials but not for *non*-INC trials. This may suggest, that while patients were just as quick to respond “*I did not understand the joke*” or “*there is no joke contained*”, respectively, as were healthy controls, patients were trying to make sense of INC cartoons. This is reflected in the longer response times and in the total amount of INC cartoons that patients finally decided to have “*understood*”.

Finally, it cannot be ruled out that the ability to discriminate unfunny from funny materials does indeed differ between the two groups in *Study 2*, unlike the case of social anxiety patients whom Samson et al (2010) concluded not to differ from controls with regard to this ability on the basis of equal number of positive responses for INC cartoons.

The impact of *ToM* as a stimulus characteristic on neural activity was assessed by the combined contrasts [TOM>INC]+[TOM>PUN]. As expected, the right STS, left midtemporal and left TPJ (inferior part of the parietal lobe and superior part of the temporal lobe), some of the main functional regions to be related to cognitive empathy (R. Saxe & Wexler, 2005; R. Saxe et al., 2004; Singer, 2009), were less active in patients when processing TOM cartoons. This is in line with the behavioural findings from this study and also with the fMRI results in the study of Dziobeks’ and colleagues (2011). Likewise is the fact that TPJ

and the left superior frontal were the only regions in which differences were observed. It is likely that this difference represents a mental under-activity of *ToM* processing in BPD. However, since the control condition in this combined contrast included INC cartoons, it is not definitely clear whether this difference was due to patients' under-activity during the TOM condition or, alternatively, an over-activity during INC.

The present study shows novel results with regards to significantly increased neural activity in BPD compared to healthy controls during processing of the incongruity condition compared to PUN and TOM and also more positive responses within the INC condition. This may be of interest with regard to the causes of BPD. While BPD has been symptomatically classified as a disorder a few decades ago the causes remained unclear. One major (environmental) risk factor is consistency in upbringing and in the childhood environment (see also Chapter 1). Zannarini et al. (1997) have described how inconsistent parenting is related to BPD symptoms in that children at risk of developing BPD find it extremely difficult to deal with inconsistency, for example, if one parent makes a statement but is contradicted by the other parent. It has further been suggested that especially the mother needs to be consistent in parenting style (Bezirgianian, Cohen, & Brook, 1993) in order to prevent children from developing BPD. One of the predictions that can be drawn from such studies is that BPD patients would activate neural networks more when presented with incongruity than healthy controls, because of their inconsistent social background that might prime patients to look for incongruity. In other words, incongruity as a stimulus characteristic would be higher in salience to BPD patients than to individuals without this background.

More activation of the left inferior parietal lobe during incongruity as shown in the present study is in line with a study by Chan and colleagues' (2012) who found that the left inferior frontal gyrus and left inferior parietal lobe (IPL) were related to humour detection and

resolution (also observed by Bekinschtein et al. (2011) and confirmed in *Study 1* of this thesis). This pattern of neural activation again might indicate that patients indeed were resolving (un-resolvable) INC cartoons. Additionally, also other areas of the left TPJ and to a lesser extend the right TPJ were also more active during incongruity compared to other conditions in BPD patients compared to controls. This might suggest increased utilization of TOM regions even during processing of incongruity. One way to further experimentally test this hypothesis would be to treat the type of responses (understood/not understood) as an independent variable in a further analysis of the data set.

The methods of data analysis of this study could be improved by defining a regressor with negative responses across the three conditions, even though to have “not understood” a picture remains a ‘correct’ response after all.

One possibility to reveal clearer changes in neural response to ToM stimuli in BPD may be to use different degrees of cognitive challenge in the paradigm. After all the only other study that used a humour paradigm to investigate *ToM* in BPD (Dziobek et al., 2011) failed to show an impairment of patients’ *ToM* processing behaviourally in the easier fMRI version of the MET task even though the authors’ conclusion from the physiological data (fMRI and SCR) were that BPD is likely to feature an impairment in both cognitive as well as emotional empathy.

Finally, a limitation that applies to any study that uses humour stimuli to probe for social cognitive phenomena concerns the very nature of humour appreciation. The degree to which someone is able to experience amusement evoked by a joke or funny event depends on multiple factors. On the one hand, different people perceive humorous stimuli differently, and this depends on a variety of personality characteristics: experience seeking (W. Ruch, Hehl, F.-J., 2007), sense of humour, emotional responsiveness or temperamental mood states such as cheerfulness, seriousness and bad mood (W. Ruch et al.,

1996), cognitive skills such as cognitive flexibility or the ability to ascribe mental states to other people (A. C. Samson & Hegenloh, 2010) seem to influence humour processing.

This is what the behavioural and imaging results of *Study 1* indicate. It is further worth noting that the TOM stimuli required a form of mentalizing that is predominantly cognitive in nature. It may well be that BPD patients are less impaired in cognitive mentalizing but more in affective mentalizing. After all it was a task that required purely cognitive perspective-taking in the recent experiment of Franzen et al. (2011) that even led the authors to conclude that BPD patients were superior in cognitive mentalizing compared to healthy controls. However, they did report that patients' response times were longer compared to healthy controls' in their experiment as well (Franzen et al., 2011).

For conclusion, the current data lend support to the idea that TPJ is a specific neural system involved in *ToM* and its relationship in BPD. TPJ is known to show a degree of functional specialisation for coding mental state information (Mitchell, 2008; R. Saxe & Wexler, 2005) and this specialisation increases over a protracted period of development (R. R. Saxe & Pelphrey, 2009). In adults with ASD it has been have shown that the RTPJ lacks functional specialisation for representing mental state information (see General Introduction).

6 Functional connectivity changes in BPD (Study 3)

6.1 Introduction

The majority of past BPD research has explored the psychological aspects of the disorder from characteristic behaviours to psychosocial triggers and risk factors, with high levels of childhood trauma found to be strongly correlated with occurrences of BPD (R. A. Cohen et al., 2006). Current theories propose that the experience of early life trauma (e.g. childhood abuse or maternal separation), genetics, neurobiological alterations, or a combination of the above may play crucial roles in the development of the disorder (Goodman et al., 2004; Steele & Siever, 2010a).

In recent years, the spotlight has increasingly been focused on neurobiological abnormalities associated with dimensions of personality dysfunction, with a number of studies providing strong evidence for the existence of functional neurobiological disturbances in BPD (M. E. Foti et al., 2010; Goodman et al., 2004).

Due to its levels of location accuracy and non-invasiveness, functional magnetic resonance imaging (fMRI) has largely replaced positron emission tomography (PET) and other brain imaging methods in the study of brain activation patterns. By using magnetic fields and radio frequencies to measure changes in blood oxygenation, fMRI can be used as an indirect measure of neural activity, blood flow, or volume (O'Neill & Frodl, 2012). Using the symptomology of the disorder as a guideline, the majority of previous fMRI studies in BPD have looked at activation abnormalities in regions understood to be involved in the regulation of stress responses, emotion, and affect, amongst others. The most common finding amongst these studies is that of hypermetabolism in the amygdala of BPD patients compared to controls during tasks that involved the processing of emotionally aversive stimuli

(Donegan et al., 2003; Sabine C. Herpertz et al., 2001; Minzenberg et al., 2007; O'Neill & Frodl, 2012).

Less common in the BPD literature is work considering “functional connectivity” amongst neural networks. As we use the term here, functional connectivity describes the relationship between different brain regions and within particular networks by assessing the correlation of their neuronal activity (Nierhaus, 2012). This can be done utilizing several different methods, including assessing resting state (on-going brain activity) fMRI data, and assessing task based (evoked brain activity) fMRI data, both of which we shall use in the present study.

Regions within one particular neural network, the default mode network (DMN), have been found to display their greatest levels of activity when at rest, and decreased activity during task based stimulation (Sheline, Price, Yan, & Mintun, 2010). During these periods of “active rest”, the DMN is thought to be involved in internal processes such as self-referential processing, inner speech, emotional control, episodic memory, and theory of mind processes (Spreng, Mar, & Kim, 2009; Wolf et al., 2011). Research has shown the constituent regions of the DMN to include the medial temporal lobe, the medial prefrontal cortex, the posterior cingulate cortex, the precuneus, and the medial, lateral, and inferior parietal cortex (Broyd et al., 2009; Spreng et al., 2009; Wolf et al., 2011). Surprisingly, though interest in the DMN is on the rise generally, and, given the similarities between the DMN functional roles and the dysfunction observed in BPD making it likely that there exists some relationship between the two, there remains a dearth of research investigating abnormalities in DMN functioning in BPD. Of the research that exists, one study explored alterations in the functional connectivity of the DMN in patients with BPD during pain processing. Abnormalities in pain processing (self-harming as a means of regulating affect, decreasing dissociative symptoms, etc.) are another well documented characteristic of BPD (Ludascher et al., 2007). This particular study observed less integration of the left retrosplenial cortex and left superior frontal gyrus into the DMN in the BPD group than in the controls during

pain appraisal (Kluetsch et al., 2012). The researchers suggest that for BPD patients not only may this result in difficulties interpreting painful stimuli as self-relevant, but that there is also an observable positive correlation between this signal strength in the posterior DMN and clinical measures of symptom severity and trait dissociation during pain appraisal (Kluetsch et al., 2012). An earlier study explored prefrontal and limbic resting state networks in BPD patients without any external stimulus. To our knowledge, it is the only study thus far to explicitly examine DMN connectivity in BPD, yielding results that showed an increase in functional connectivity in the left fronto-polar cortex (FPC) and the left insula, and decreased connectivity in the left cuneus in the BPD group (Wolf et al., 2011). The researchers opine that, with regard to the increased connectivity observed in the FPC, these findings may have implications in terms of processing of internal thoughts, self-referential information, and interpersonal interactions, and may in the future be found to be a potential biological marker for the disorder (Wolf et al., 2011). Regarding the increased activation in the insula, the researchers suggest that abnormal activation may be related to both dissociative symptoms and decreased pain sensitivity observed in BPD patients (Wolf et al., 2011).

As part of the present research's focus, we shall also attempt to address the gap in the DMN BPD research by mapping the functional connectivity corresponding to a selected seed region of interest (ROI; precuneus) within the DMN in a sample of BPD patients compared to healthy controls. The precuneus was chosen as a region of interest as previous research has suggested it to play a crucial role in the DMN, with involvement in reflective, self-related processing, empathy, awareness and conscious information processing, and episodic memory, amongst other things (Fransson & Marrelec, 2008; Vollm et al., 2006; Zhang & Li, 2012). Additionally, abnormal functional connectivity of the precuneus during default mode has been documented in a range of psychiatric disorders with features also

common to BPD (Broyd et al., 2009; Sheline et al., 2010; Whitfield-Gabrieli et al., 2009), providing a basis for similar research in BPD.

For the task based portion of this study, again a selected seed region of interest from which to map functional connectivity was used, in this case the seed region being the anterior cingulate cortex (ACC). The ACC is known to be involved in emotion processing, empathy, and cognition (Bush, Luu, & Posner, 2000; A. C. Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013; Vollm et al., 2006, see also 1.2.5), with previous studies observing divergent neural dynamics in the ACC of BPD patients compared to healthy controls (Dziobek et al., 2011). However, despite this knowledge there also remains a lack of research examining functional connectivity of the ACC in BPD samples. In the present study we will investigate functional connectivity between the “emotion network” and the theory of mind processing regions of BPD patients by analysing responses to Theory-of-Mind (*ToM*) stimuli, using ACC as the seed region. The overall aims of the study were twofold; to examine functional connectivity within the DMN, and to examine the functional connectivity between the emotion network and the *ToM* regions, as the research investigating both is as yet still lacking. For the DMN investigation, the brain activity of the BPD patients during resting state was observed for any abnormalities (where precuneus was the ROI).

Hypotheses

There is an increased functional connectivity in the DMN during resting state in BPD patients compared to healthy controls.

There is decreased functional connectivity between the emotion network and the *ToM* network in BPD patients compared to healthy controls.

6.2 Methods

6.2.1 Participants

The same samples as in *Study 2* (Chapter 5, 17 Pat vs. 19 HC) were used in *Study 3*. For demographic and recruiting information see *Overall Methods* (Chapter 2).

6.2.2 Psychometric assessment

Rating scales of depression scales were completed for all participants included in the study for diagnostic and correlational purposes. The rating scales used for this study were the Hamilton Rating Scale for Depression (M Hamilton, 1960) and the Beck Depression Inventory (BDI-II) (Aaron T. Beck, Steer, & Carbin, 1988). Other ratings used are described in the overall methods (Chapter 2 of the thesis).

Ethical approval for the study was obtained from the Adelaide and Meath Hospital and St. James' Hospital, Dublin, Ireland ethics committee. All participants were given detailed oral and written information and had to sign an informed consent form prior to participating in the study.

6.2.3 fMRI task

The stimulus material consisted of two types of cartoons, puns (PUN) and jokes requiring mentalizing (TOM) as well as a control condition that consisted of unfunny pictures containing an incongruity that could not be resolved meaningfully (INC). All pictures were low in aggressive, violent, and sexual content and were used in previous studies (A. C. Samson et al., 2009; A. C. Samson et al., 2008). In order to investigate brain activity during resting state rest trials (NULL) were interleaved during which participants observed a blank screen. All participants processed a total of 120 trials (30 INC + 30 PUN + 30 TOM + 30 NULL). Stimuli were presented every 10s on average and with variable stimulus onset delays (0, 400, 800, 1200 or 1600ms). Each stimulus was onset

for 6000ms during which participants were instructed to make a response. Below each picture (cartoon) the word “understood” was printed on the left side and the words “not understood” were printed on the right side. Participants were asked to press the corresponding button (left/right) with their index or middle finger, respectively, depending on whether they understood the joke. The functional neuroimaging part started after 15 minutes of the scanning session (during which the structural image was acquired) and took about 18 minutes. For a full description of task and stimuli see Chapter 2).

Being not relevant to the research question of the present study, the PUN and INC trials were excluded from the analysis and only TOM and NULL trials were further considered for contrasts.

6.2.4 MRI Data Acquisition

Magnetic resonance images were obtained with a Philips Achieva MRI scanner (Philips Medical System, Netherland BV, Veenphuis 4–6, 5684 PC Best, The Netherlands) operating at 3 Tesla. For the cognitive paradigm run, 26 axial slices (3.5 mm× 3.5 mm× 3.5 mm resolution, 0.75 mm spacing), parallel to the AC-PC plane and covering the whole brain were acquired using a single shot, gradient recalled EPI sequence (TR 2000 ms, TE 30 ms, 90° flip angle). One functional run with 620 time points was acquired, with each time point sampling over the 26 slices. Prior to the functional run, 180 anatomical slices T₁-weighted 3D-MPRAGE sequence (repetition time, 11.0 ms; echo time, 4.4 ms; total acquisition time, 7 min 30 sec; number of acquisitions, 1; field of view, 250 mm× 256 mm × 160 mm; matrix: 256 mm × 256 mm; resolution: 0.9 mm × 0.9 mm × 0.9 mm) with the same spatial orientation as the functional data were acquired.

6.2.5 Data analysis

SPM8 Pre-processing

A standard analysis (see 5.2.4) was conducted on fMRI data of all subjects in order to obtain the regions with the strongest activation for the contrast [TOM>NULL] in the tasks. The CONN Toolbox was then be used to extract the mean voxel time series ROI for a 10 mm radius regions around the maximum of activation within the precuneus (for the default mode network) and ACC (for the emotion network) for each subject separately.

CONN toolbox

The CONN resting state software (<http://www.nitrc.org/projects/conn/>) performs seeded voxel correlations by estimating maps showing temporal correlations between the BOLD signal from given seed and that at every brain voxel. The toolbox implements a *CompCor* strategy for physiological noise source reduction, first-level General Linear Model for correlation and regression connectivity estimation, and second-level random-effect analyses.

Using CONN resting state software the data were temporally band-pass filtered ($0.009 < f < 0.08$). Several sources of spurious variance along with their temporal derivatives then were removed from the data by linear regression, such as signal from regions centred in the white matter, cerebrospinal fluid, movement and effects of rest. This regression procedure removes fluctuations unlikely to be involved in specific regional correlations.

First level analysis: A method previously introduced by Bokde et al. (2006). For whole brain mapping of ROI coupling, the time series representing right and left ROI was separately regressed on all fMRI time series in each individual's dataset (without prior convolution by a model of the hemodynamic response function). This results in maps of

the regression coefficients for the effect of (right and left) ROI activity on all other brain regions for each participant in the study.

Second level analysis: In order to identify locations of significant group, side and group-by-side effects on ROI coupling a 2x2 mixed effects ANCOVA was performed using the ROI coupling as the dependent variables as well as age and individual BDI-depression scores (see Chapter 2) as covariates. This model was specified to include a main effect of group (with 2 levels, BPD patients, and healthy volunteers) and a main effect of side (with 2 levels, left, and right). Statistical significance was based on a threshold of $p < 0.05$ (*FWE*, voxel level corrected). The anatomic localisation of significant clusters was identified using the AAL toolbox (Tzourio-Mazoyer et al., 2002, see 2.9).

Further, structural equation modelling (SEM) was applied to the data in order to test the functional connectivity within the default mode and affect/emotion regulation network.

Functional coupling analysis

To compute functional connectivity maps corresponding to a selected seed region of interest (ROI), the regional time course was correlated against all other voxels within the brain. Based on data from a previous resting state study by Sheline et al. (2010), the connectivity within the affective network, was explored. Correlation maps were produced by extracting the BOLD time course from a seed region, then computing the correlation coefficient between that time course and the time course from all other brain voxels. The anterior cingulate cortex (ACC; +/- $x=10$, $y=-35$, $z=2$) was extracted as the seed regions of interest in the affective network that was modulated between TOM trials and NULL events; and the precuneus (+/- $x=7$, $y=-60$, $z=21$) as the seed ROI in the resting state network during NULL events. The principal techniques used were computation of whole brain, voxel-wise intrinsic functional connectivity maps.

Statistical analysis

We analysed resting-state functional MRI data to determine significant differences in functional connectivity between BPD and control participants using a family wise error (FWE) whole brain corrected threshold of $p < 0.01$. The threshold was reduced to $p < 0.025$ from $p < 0.05$ because the connectivity was analysed within the 2 different networks. Moreover, mean connectivity data were extracted from areas that showed significant differences between patients and healthy controls.

6.3 Results

6.3.1 Default mode network

After visual inspection of the resting state network the differences between patients and controls were calculated. The resting-state network for all participants ($N=36$, Figure 6-1) with right precuneus used as the seeding region showed a standard DMN pattern, as described in detail by previous resting-state network studies (Buckner, Andrews-Hanna, & Schacter, 2008).

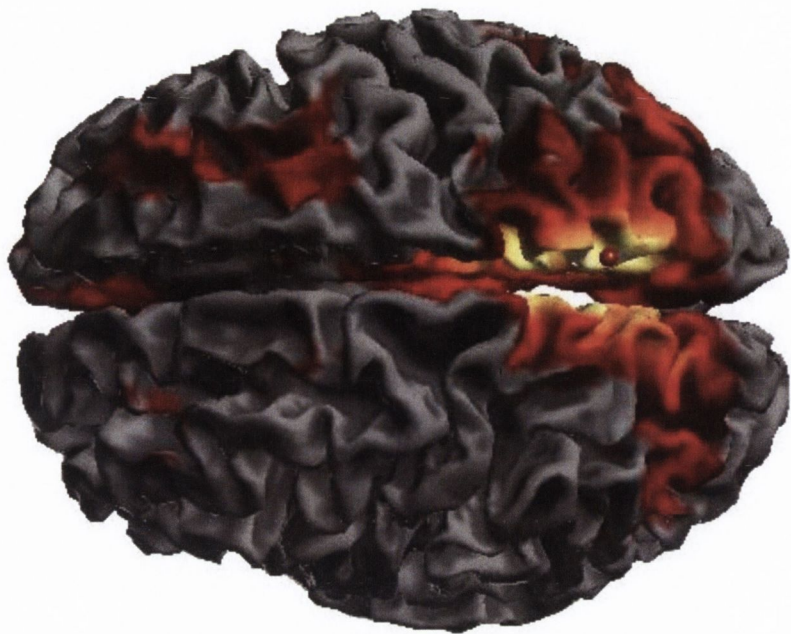


Figure 6-1: Resting state network, (Pat+HC), seed region: Precuneus. Functional connectivity superimposed on a 3D standardised template, dorsal view.

Increased functional connectivity was found in patients compared to controls between the precuneus (seed region) and three brain areas which were located left inferior frontal lobe, left precentral/middle frontal, and left middle occipital/superior parietal (Table 6-1, Figure 6-2).

Table 6-1: Default mode network: Pat > HC, seed region: Precuneus.

K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates [mm]		
					x	y	z
259	0.067	L Inf. Frontal Operculum	0.025	5.98	-42	14	16
		L Inf. Frontal Triangularis	0.350	4.72	-48	18	20
		L Inf. Frontal Triangularis	0.535	4.36	-38	22	16
401	0.014	L Precentral	0.137	5.17	-42	10	48
		L Mid. Frontal	0.335	4.72	-48	6	52
		L Precentral	0.915	3.95	-42	2	44
384	0.016	L Mid. Occipital	0.674	4.31	-24	-64	40
		L Sup. Parietal	0.888	4.01	-22	-74	54
		L Precuneus	0.913	3.95	-8	-74	54

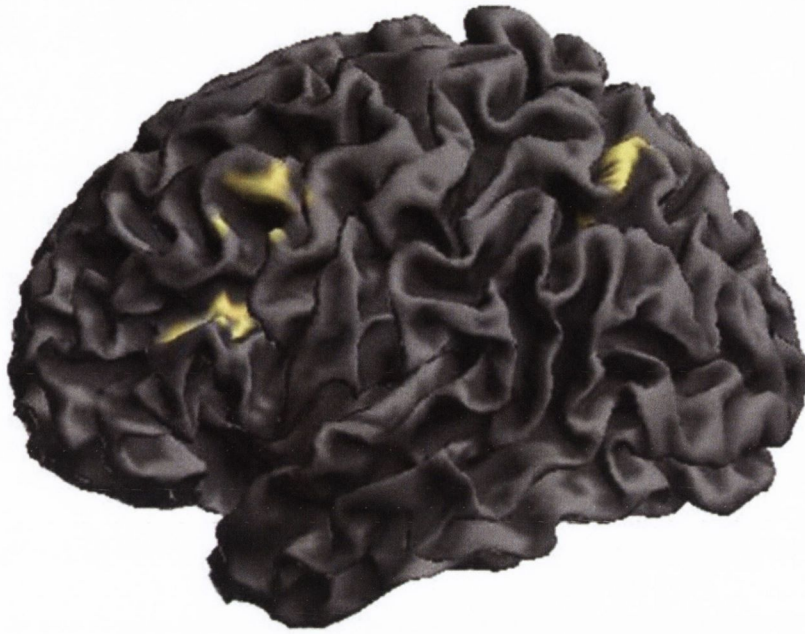


Figure 6-2: Resting state network: Pat > HC.
Increased functional connectivity between precuneus (seed) and left IFG (visible), L precentral, L midfrontal, L midoccipital, L sup. Parietal, superimposed on a 3D standardised template, lateral view.

6.3.2 Affective network

During trials where brain activity was modulated between TOM and NULL conditions decreased functional connectivity was found for patients compared to controls between the ACC (seed) and three brain areas left superior temporal, right mid-cingulum, and right supramarginal/inferior parietal (corresponding to the cognitive neuroscience term “temporo-parietal junction”, RTPJ).

Table 6-2: Connectivity changes PAT<HC for [TOM-NULL]; seed region: ACC

K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates [mm]		
					x	y	z
603	0.001	L Sup. Temporal	0.016	6.09	-60	-4	-2
		L Sup. Temporal	0.192	5.05	-60	4	-5
		L Sup. Temporal	0.486	4.57	-42	-35	22
1507	<0.001	R Mid. Cingulum	0.070	5.49	14	-26	40
		R Mid. Cingulum	0.203	5.03	10	-20	35
		R Mid. Cingulum	0.241	4.95	10	-40	50
844	<0.001	R Supramarginal	0.072	5.48	66	-32	36
		R Supramarginal	0.134	5.21	58	-32	40
		R Inf. Parietal	0.326	4.79	52	-35	45



Figure 6-3: Connectivity changes PAT<HC for [TOM-NULL]. Decreased functional connectivity between ACC (seed) and RTPJ and right MCC, superimposed on a 3D standardised template, caudal view.

6.4 Discussion

The objectives for the present BPD functional connectivity study were firstly, to test for abnormalities in brain activity during resting state (specifically monitoring the precuneus), and secondly to test for differences in connectivity between the ACC (the core region of affective network) and all other parts of the brain during mental processing of Theory-of-Mind stimuli vs. resting state.

The main finding of the present study was decreased functional connectivity of ACC with MCC, left STS, and right TPJ during processing of *ToM* stimuli (or mentalizing) in BPD patients. ACC has an important role in integration of neuronal circuitry for affect regulation and can be identified as a distinctive region in understanding psychopathology (Stevens, Hurley, & Taber, 2011). It was for this reason that we selected ACC as the seed region for the affective network. While the MCC was shown to be involved in both self-and other-perspective (B. A. Vogt, 2005), bilateral STS and TPJ belong to the core neural network of mentalizing (Dodell-Feder et al., 2011; R. Saxe & Wexler, 2005). Especially the right TPJ includes areas that are recruited exclusively by mentalizing (Scholz et al., 2009) and seems to be the only brain region for which this is true (R. R. Saxe & Pelphrey, 2009). Our data suggest dysconnectivity between the emotion (regulation) network and the *ToM* network in BPD compared to healthy controls supporting the theory of BPD as an emotional regulation disorder (Linehan, 1993a). An important testable prediction from this finding might be that BPD individuals have altered *ToM* processing compared to healthy controls when placed under emotional stress.

As extensive comorbidity has been documented for BPD with both Axis I disorders and other Axis II disorders of the DSM-IV (usually mood disorders, anxiety disorders, or substance disorders), comorbidities are a potential limitation in this study, although MDD was the only comorbidity that was clinically diagnosed in our BPD sample.

In order to identify the above mentioned dysconnectivity as a biological marker for BPD future studies should also carry out functional connectivity analyses in the most commonly documented comorbidities of BPD which are major depressive disorder (MDD), attention deficit hyperactivity disorder (ADHD), and post-traumatic stress disorder (PTSD) which is of particular interest given that both disorders are highly related to experiences of trauma (Pagura et al., 2010; Philipsen

et al., 2010; D. J. Stein et al., 2010; Zetsche, Frodl, Preuss, Schmitt, Seifert, Leinsinger, Born, Reiser, Moller, et al., 2006).

The second network investigated in the recent study was the default mode network. The approach of measuring BOLD signal independent of any task makes the method independent of any differences of performance between sessions and/or subjects. Therefore, resting-state fMRI can be easily employed in patients with potentially limited ability for participation in task paradigms. However, the rapid employment of these techniques by the imaging community over the past decade is due, in part, to both the ease of data acquisition and the similarity of results to previous finding using task-induced approaches. (Nierhaus, 2012).

The comparison of functional connectivity during rest revealed higher activity in BPD patients in areas that are not commonly found in the DMN. A first conclusion that may be drawn from this finding is that the DMN is altered in BPD. While there was no decrease in connectivity from the precuneus to any brain area, patients activated left IFG (comprising BA 44 and 45 which together are known as Broca's area), left mid-frontal, left precentral, and left mid-occipital/superior parietal in addition to the standard DMN regions and thus exhibited significantly higher activity in these regions compared to healthy controls. To further conclude that any processes of speech processing were at work during resting state would probably be too premature at this stage. This hypothesis however could be tested by investigating true "task-negative" resting state connectivity by contrasting it to the connectivity during a cognitive task that involves processing of language.

In the scope of the thesis project, it is worth noting that, in healthy subjects, left IFG was an area in which activity linearly correlated with neuroticism (see Chapter 3), a personality measure with typically high levels in BPD. These high levels could be related to an over-activity in the left IFG in the absence of external stimuli.

Recent neuroimaging studies also show involvement of BA44 together with, precentral/pre supplementary motor area (pre-SMA), mid-frontal, and mid-occipital in selective response suppression in go/no-go tasks and has therefore been interpreted as core neural substrates of error processing (van Gaal & Lamme, 2012)(Cohen et al, 2009;). Our data suggest that error processing could be active in BPD even in absence of external stimuli and hence of external errors. This does not necessarily mean that subjects are aware of this process as van Gaal, de Lange, and Cohen (2012) were able to show that the “inhibition network”, and in particular the left inferior frontal gyrus, is active during unconscious error processing.

Particularly in resting state connectivity studies caution must be made with regard to gender differences, which did not apply to our all-female sample. Healthy men and women differed in connectivity patterns across precuneus sub-regions (Zhang & Li, 2012).

In the past, other distinct neural networks have been identified in healthy subjects during resting-state conditions, including lateral fronto-parietal and medial-frontal networks (Damoiseaux et al., 2006; Smith et al., 2009). These resting-state networks (RSNs) have been suggested to reflect a dynamic functional organisation of the brain (Fox et al., 2005), a notion supported by the finding of a close correspondence between RSNs and activation patterns underlying a wide range of cognitive processes, such as attention, memory, behavioural inhibition and executive control (Smith et al., 2009). Thus, the investigation of multiple RSNs may provide a rich source of information with regard to the functional architecture of altered brain states in patients with mental disorders, as previously shown in patients with schizophrenia (Calhoun, Maciejewski, Pearlson, & Kiehl, 2008), affective disorders (Calhoun et al., 2008), and also BPD (Wolf et al., 2011). Investigating other RSNs in BPD and its comorbidities may hold future research potential. The only study that has attempted this is recent work by Wolf et al. (2011) – who

likewise found increased connectivity in BPD between precuneus and left inferior frontal lobe using a similar method.

In terms of the practical limitations of the methodology, we must look to past studies. The majority of past PET functional studies examined patients only during resting state, with results producing very little consistency (O'Neill & Frodl, 2012). One reason for the lack of consistency amongst these PET studies could be that at resting state the patients' emotional state is not known thus the range of neural activity could be vast, especially with a patient sample typified by emotional fluctuations. Whereas in the past studies, mostly involving specific tasks or images, the patients' emotional states could be more accurately predicted and the resulting images compared with more reliability (O'Neill & Frodl, 2012). This would suggest that when investigating neurobiological functioning in BPD patients, studies which employ specific emotion related stimuli provide a more reliable measure than resting state studies (O'Neill & Frodl, 2012). This may hold true for DMN functional connectivity studies in BPD as well, and is worth noting for future studies.

Given the similarity in symptomology observed between the two disorders, research methodologies in BPD have often followed those of PTSD. It has been suggested that DMN connectivity may have potential as a predictor of post-traumatic stress disorder symptom severity in acutely traumatised subjects (Lanius et al., 2010). Considering this and the more recent findings of Kluetsch et al. (2012) (who related signal strength in the posterior DMN to symptom severity), it may be of interest to future researchers to further explore this avenue.

Apart from that it will be necessary to study the sub-regions of the precuneus and their role in DMN function; specifically within BPD, as Zang and Li recently (2012) (Zhang & Li, 2012) provided evidence for different roles in 8 sub-regions of the precuneus. Thus, examining the precuneus as a whole may lead to distorted data as a number of studies have observed positive connectivity with the default network for

ventral but not dorsal precuneus (Buckner et al., 2008; Zhang & Li, 2012).

Finally, co-occurrent Axis I-disorders and medication use in this sample of patients with BPD have to be considered as potential limitations. However, the question of whether patients with BPD with psychiatric comorbidities should be excluded to homogenise clinical sample characteristics remains controversial (Lis et al., 2007).

The sample size in the present study was modest, though comparable to that of most functional imaging studies of psychiatric populations. Nevertheless a failure to detect possible differences at a behavioural level might be explained by a lack of statistical power. Also, because the samples consisted of only female patients with relatively typical clinical presentation, conclusive inferences for male BPD patients who make up a smaller proportion of all BPD patients and often exhibit atypical clinical features cannot be made.

A strength of the study is that the samples did not include any patients with a comorbid generalised anxiety disorder or with co-morbid panic disorder. Both, the BPD and the healthy sample were clinically assessed and one healthy participant was excluded for scoring outside the normal range on depression/impulsiveness scales.

For conclusion, a promising finding is the reduced functional coupling between ACC as seed region for the emotional network and the theory of mind (mentalizing) network indicating dysregulation between these two networks in line with emotion regulation dysfunctions in BPD. Moreover, higher resting state functional connectivity is also of interest since it may be linked to higher arousal in BPD which needs to be investigated further in future studies.

7 Structural brain matter changes in BPD (Study 4)

The content of Study 4 has already been accepted for publication by the Journal "Psychiatry Research: Neuroimaging" (O'Neill et al., 2013). The research article includes an manual-tracing volumetric analyses of the hippocampus by Ms Aisling O'Neill on the basis of structural MRI data that were collected by the candidate in the scope of his thesis research.

Only the results that were produced by the candidate are reported in Section 7.3 of this chapter. However, they are discussed together with the other results presented in the article of which the candidate is holds joint first-authorship and that can be found in the Appendix.

7.1 Introduction

Borderline Personality Disorder (BPD) is a commonly seen axis II psychiatric disorder typified by features such as severe relationship dysfunction, instability of mood, impulsivity, and in extreme cases, periods of dissociation (Steele & Siever, 2010b). The majority of past BPD research has explored the psychological aspects of the disorder from characteristic behaviours to psychosocial triggers and risk factors, with high levels of trauma found to be strongly correlated with occurrences of BPD. Studies investigating the neurobiology of the disorder are less common, though ever increasing. Structural MR imaging, the most frequently used neuroimaging technique in BPD research, is often focused on regions of the brain known to be involved in the regulation of stress responses, emotion, and affect. These areas include the hippocampus, the orbito-frontal cortex, the amygdala, and the anterior cingulate cortex. Recently we reviewed the literature relating to neuroimaging in BPD O'Neill and Frodl (2012). With structural MR imaging studies the two commonly used analytical techniques are manual tracing and voxel based morphometry (VBM). Manual tracing involves drawing regions of interest (be it the whole brain or its subparts) on images obtained from brain scans and

measuring the volume enclosed. It allows for the precise identification and delineation of regions of interest (Eva Irle, Claudia Lange, & Ulrich Sachsse, 2005), though it can be time consuming and is of more use for larger areas. In VBM each brain is mapped to a template then statistical tests are run across all voxels in the image to identify differences between testing groups. Though its results can be hard to validate, studies comparing the results of VBM to those of manual tracing or visual measurements have found relatively good correspondence (Whitwell, 2009), though its validity when dealing with atypical brains (such as those containing severe pathologies) has been questioned, due to its core features of normalization and segmentation to a template (Mechelli, Price, Friston, & Ashburner, 2005). Thus, information obtained from manual tracing and VBM will vary, but should add to each other when interpreted correctly.

In general, the brain region which most consistently showed alterations across all studies of BPD patients is the hippocampus, with a number of studies finding significant hippocampal volume reductions bilaterally in individuals with BPD compared to healthy controls (Brambilla et al., 2004b; C. G. Schmahl, Vermetten, Elzinga, & Douglas Bremner, 2003; van Elst et al., 2003). Interestingly, Brambilla et al. found with further examination that those BPD patients who had a history of childhood abuse, when compared to healthy controls, still displayed significant reductions in hippocampal volumes, whilst BPD patients without such a history did not display significant reductions (Brambilla et al., 2004a). A study by Driessen et al. reported similar findings, with 16% reductions in the hippocampal volumes of the BPD patients being studied, compared to healthy controls, and a negative correlation being observed between hippocampal volume and duration of reported early trauma (Driessen et al., 2000b). More recently however, a meta-analysis by Ruocco et al. rejected this association. Taking 11 studies into account, the meta-analysis found no significant relationship between reports of childhood abuse and any volumetric abnormalities identified in either hippocampus (Ruocco AC, 2012).

Another brain region in BPD patients which is frequently found to display significant reductions is the anterior cingulate cortex (ACC), with a number of studies replicating this finding over the years (Hazlett et al., 2005a; Minzenberg, Fan, New, Tang, & Siever, 2008a; L. Tebartz van Elst et al., 2003). A 2009 investigation of ACC volumes in adolescents with first presentation BPD and minimal exposure to treatment found a decrease in left ACC volume of the patient group compared to healthy controls (Whittle et al., 2009a).

Studies examining volumetric changes in other areas have been less consistent. Some structural MRI studies have suggested volumetric reductions in the frontal lobe (Lyo, Han, & Cho, 1998b), the left OFC (Hazlett et al., 2005a) and right parietal cortex (Eva Irlé et al., 2005). Using VBM, reductions in grey matter volume have also been found in frontal, temporal and parietal cortices in men with BPD (Vollm et al., 2009a). Conversely, in another VBM study no group differences between patients with BPD and healthy control subjects could be found in the frontal lobe (Rusch et al., 2003), though this BPD group was comprised solely of females.

With regard to the amygdala in adult patients with BPD compared to healthy controls, three manual tracing studies found increased amygdala volumes (Driessen et al., 2000b; C. G. Schmahl, Vermetten, et al., 2003; van Elst et al., 2003), while two other studies (one using VBM and one using manual tracing) found decreased amygdala volumes (Brambilla et al., 2004a; Rusch et al., 2003). Interestingly, a recent VBM study found a higher relative grey matter concentration in the amygdala of a sample of BPD patients compared to a group of healthy controls (Minzenberg et al., 2008a), whilst another manual tracing study found that only patients with both BPD and a comorbid diagnosis of major depression demonstrated a larger amygdala volume in both hemispheres compared with those without major depression (Zetsche, Frodl, Preuss, Schmitt, Seifert, Leinsinger, Born, Reiser, Moller, et al., 2006). In this last instance no difference was found in

amygdala volumes between the whole BPD group and the healthy controls (Zetsche, Frodl, Preuss, Schmitt, Seifert, Leinsinger, Born, Reiser, Moller, et al., 2006).

As the research stands, it is evident that more concrete findings are needed in order to gain a firmer understanding of the neurobiological underpinnings of the disorder. In particular, findings regarding frontal lobe regions have thus far been too inconsistent to allow any speculation on the biological mechanisms in these regions potentially contributing to the disorder. Another area lacking attention in BPD studies is the search to locate the actual source or sources of the abnormalities seen within the hippocampal structure. The hippocampus, as with most brain structures, is composed of a number of anatomically and functionally different sub-regions which play complex roles supporting the overall functions of the structure. It is thus unlikely that all sub-regions within the hippocampus are affected equally, if at all, by the abnormal biological processes of BPD, or any other disorder. For this reason, to only investigate the hippocampal volume as a whole could result in the attenuation of the effects of reductions in the affected sub-regions by those that remain unaffected (Peterson, 2010). The exact importance of these omissions for BPD is as yet unknown; however it is possible that the identification of biomarkers of this kind could be of enormous benefit to the development of pharmacological treatment of the disorder and in the formation of biological criteria for diagnosis. To our knowledge, no other study has investigated differences in sub-regional hippocampal volumes between patients with BPD and healthy controls. Furthermore, little work has been done to investigate the relationships between the characteristic symptoms of BPD and overall hippocampal volumes in BPD.

In this study we attempted to address these gaps in the research in two ways. Firstly, we explored the differences in volume for the whole hippocampus and hippocampal sub-regions between a sample of females with BPD and a sample of healthy female controls (HC) using

structural MR imaging and manual tracing. Additionally, using the VBM technique, we again investigated the hippocampus, and also the grey and white matter of the orbito-frontal cortex, basal ganglia, and anterior cingulate cortex for any potential abnormalities that may occur between the same sample groups. We expected the study to reveal significant reductions in the whole hippocampal volumes of the BPD patients compared to controls, and in particular to identify reductions in the hippocampal head, which has been shown to be stress sensitive. We also analysed the morphometric data from the manual tracing portion of the study for any correlations with the socio-demographic and psychometric data obtained from both the BPD group and the HC group.

Hypotheses

The aim of the study was to investigate whether structural abnormalities are related to the diagnosis of BPD. Five anatomical regions of interest (ROIs) were hypothesised to reveal differences in grey and/or white matter: amygdala, hippocampus, orbito-frontal cortex (OFC), basal ganglia, and the dorsolateral prefrontal cortex (DLPFC).

7.2 Methods

7.2.1 Participants

The group of patients formally diagnosed with borderline personality disorder (BPD) according to DSM-IV consisted of 20 female patients with an age range from 19 to 49, and a mean age of 32.6 (standard deviation: 10.1). As BPD is much less frequently found in men (75% of those with the disorder are women, J. M. Oldham (2004)) it was decided to have the participant groups consist solely of women to avoid potential gender based differences. The BPD patient group were receiving continuous treatment from the South-West mental health services in Dublin. The BPD participants were all attending our outpatient clinics for years. Thus, patients were well known to the

service and mainly were treated in outpatient and home care, when necessary with crisis admission. Only when the continuous care consultant indicated these inclusion criteria we further interviewed them for suitability to the study. Diagnosis according to DSM-IV was thus confirmed by a second psychiatrist. A cohort of 21 healthy female volunteers with ages between 20 and 47, and a mean age of 30.1 (standard deviation: 8.0), was recruited from the local community. The volunteers and patients were carefully screened for medical conditions to ensure that none had a personal history of neurological disorder, severe medical illness, head injury or substance dependency. Healthy participants were excluded if they had a personal history of any psychiatric disorder (Axis I or Axis II) and the BPD participants were excluded if they had any additional psychiatric disorder other than comorbid major depression (MDD) at present or in the past. Demographic variables and inclusion and exclusion criteria were assessed using a standardised questionnaire and through structured interview based on SCID-I by registered psychiatrists.

Self and observer rated scales were administered for all participants included in the study. The rating scales used are listed in Chapter 2.

7.2.2 Structural MRI acquisition sequence

Structural MR-images were obtained by a 3.0T MRI scanner (Philips Achieva, Best, The Netherlands) at the Trinity College Institute of Neuroscience, University of Dublin. Participants were scanned with a T1-weighted sequence (repetition time: 8.4 ms; echo time: 3.9 ms; total acquisition time: 15 min; number of acquisitions: 1; flip angle: 8 degrees; field of view: 230 mm x 230 mm x 162 mm yielding 180 contiguous axial slices with a defined voxel size of 0.9 mm x 0.9 mm x 0.9 mm). After manually reorienting and centring the images on the anterior commissure, data were pre-processed using the VBM approach previously shown by Good et al. (2001) implemented in the VBM8 toolbox (<http://dbm.neuro.uni-jena.de>), an extension of the SPM8

software package (see 4.2.4) running under MATLAB 2009a (The MathWorks, Natick, MA).

7.2.3 VBM8 Pre-processing

The present study employed the VBM8 toolbox, which utilises and extends the unified segmentation approach implemented in SPM8 (Ashburner & Friston, 2005). Unified segmentation provides a generative model of VBM pre-processing that integrates tissue classification, image registration and MRI inhomogeneous bias correction. Thus, the model avoids the circularity problem of the optimised VBM procedure, as the initial image registration does not require an initial tissue segmentation or vice versa (Good et al., 2001). The VBM8 toolbox extends the unified segmentation model as it increases the quality of segmentation by applying a Hidden Markov Field (HMRF) model on the segmented tissue maps (Cuadra, Cammoun, Butz, Cuisenaire, & Thiran, 2005). The HMRF algorithm provides spatial constraints based on neighbouring voxel intensities within a 3mm x 3mm x 3mm voxel cube. It removes isolated voxels which are unlikely to be a member of a certain tissue class and also closes holes in a cluster of connected voxels of a certain class, resulting in a higher signal-to-noise ratio of the final tissue probability maps. The VBM8 toolbox also offers the option of creating the estimated tissue probability maps without making use of the respective ICBM (International Consortium for Brain Mapping) tissue priors from SPM. In line with previous VBM research (Frodl, Reinhold, Koutsouleris, Reiser, & Meisenzahl, 2010), the present study used this option as it showed to improve the delineation of the subcortical structures and sulci in the final tissue maps. The final tissue maps of grey matter (GM) and white matter (Shihabuddin et al., 1998) and were modulated with the deformations fields obtained by normalization to standard space in order to analyse volume differences between study populations.

7.2.4 DARTEL Toolbox

DARTEL is a suite of tools that allows a highly accurate inter-subject registration of brain images. Therefore, grey and white matter images were imported into DARTEL and non-linear deformations for their optimal alignment were estimated by alternating between the making of a template and registering the tissue class images with the template. Subsequently, the Jacobian-scaled (“modulated”) warped tissue class images were created. Finally, the GM/WM partitions were smoothed with an 8 mm FWHM Gaussian kernel and used for statistical analysis. An analysis of covariance (ANCOVA) was designed in order to investigate focal GM/WM matter volume (GMV and WMV) differences between subject groups. For all comparisons, volume differences (increases/decreases) were assessed at whole-brain level using cluster level statistical analyses (cluster level, $p < 0.05$, *FWE* corrected with a primary threshold of $p < 0.001$).

Regions of interest (Tzourio-Mazoyer et al., 2002) were defined in order to test cross-sectional GMV and WMV differences in the hippocampus, the mid-frontal lobes, and the insulae. ROIs were identified using the Wake Forest University PickAtlas Toolbox, version 3.0.3. The PickAtlas software toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003) provides a method for generating ROI masks based on the Talairach Daemon database (Lancaster et al., 2000). The atlases include Brodmann area, Lobar, Hemisphere, Anatomic Label (gyral anatomy) and Tissue type. For the a priori set ROIs, a threshold of $p < 0.001$ (uncorrected) with a spatial extent threshold of 15 contiguous voxels for group interactions was chosen. To further protect against Type I error, a small-volume correction (SVC) was applied at peak-level (cut-off value: 0.05, FWE_{voxel} -corrected). Coordinates of peak significant voxels were assigned to anatomical regions by means of Automated Anatomical Labelling (AAL, Tzourio-Mazoyer et al., 2002).

7.2.5 Extraction of grey matter volumes from VBM contrasts

In order to compare results derived from manual tracing and VBM8 the software package MarsBar region of interest toolbox (Brett M, 2002) was used to extract the cluster of grey matter voxels in the hippocampus of all participants. MarsBaR (MARSeille Boîte À Région d'Intérêt) is a toolbox for SPM8 which provides routines for region of interest analysis. Features include region of interest definition, combination of regions of interest with simple algebra, extraction of data for regions with and without SPM pre-processing (scaling, filtering), and statistical analyses of ROI data using the SPM statistics machinery (reference).

We used the clusters of voxels from the VBM grey matter contrast between patients and healthy controls to define ROIs in the hippocampus, caudate, and middle frontal cortex. Volume equivalents were then extracted from these ROIs and correlated with the volumes in the corresponding ROIs from the manual-tracing method. Non-parametric correlations were computed between extracted volumes and psychometric measures.

7.3 Results

7.3.1 Socio-demographic and psychometric data

The results of the independent samples t-test analyses showed that the BPD and HC groups did not differ with respect to height, alcohol consumption per week, psychoticism, perseverance, boredom susceptibility, experience seeking, disinhibition, and total sensation seeking. However, significant differences were observed between the groups with regard to weight; cigarette consumption, level of education; HDRS total score; BDI-II; neuroticism; extraversion; thrill seeking; BIS (impulsivity) total; attentional impulsivity (second order factor); motor impulsivity (second order factor); non-planning impulsivity (second order

factor); and all the first order impulsivity factors excluding perseverance and including attention, motor, self-control, cognitive complexity, and cognitive instability (see Table 7-1). All BPD were either currently being treated with psychotropic medications or had been treated previously with psychotropic medications, or both. Three of the patients reported suffering from major depression along with their primary diagnosis of BPD.

Table 7-1: Demographic information.
List of measures for which there was a significant difference between the BPD and HC groups' scores

	BPD patients	Controls	Statistics
Age	32.6 ± 10.1	30.1 ± 8.0	t=0.87, df= 39, p=0.39
Height	164.1 ± 6.1	167.1 ± 5.7	t=1.6, df= 39, p=0.12
Weight	70.0 ± 14.6	59.7 ± 8.0	t=-2.8; df=39; p=0.008
HDRS	23.05± 10.0	0.4 ± 0.75	t=9.95; df=18.2; p<.001
BDI-II	40.21 ± 10.90	4.15 ± 3.54	t=14.05; df=21.6; p<.001
BIS total	80.05 ± 6.99	62.40± 10.0	t=7.88; df=37; p<.001
2 nd order Attentional	20.47 ± 2.63	14.80 ± 2.55	t=6.84; df=37; p<.001
2 nd order Motor	28 ± 6.08	22.9 ± 3.95	t=3.12; df=37; p<.005
2 nd order Non-planning	31.63 ± 5.37	23.65 ± 3.63	t=5.47; df=37; p<.001
1 st order Attention	12.26 ± 2.45	9.65 ± 1.76	t=3.83; df=37; p<.001
1 st order Motor	19 ± 5.02	15.50 ± 3.28	t=2.59; df=37; p<.05
1 st order Self Control	18.11 ± 3.49	12.40 ± 2.96	t=5.51; df=37; p<.001
1 st order Cognitive Complexity	13.53 ± 2.59	11.25 ± 2.0	t=3.08; df=37; p<.005
1 st order Cognitive Instability	8.21 ±1.47	5.15 ± 1.63	t=6.14; df=37; p<.001

7.3.2 Morphometric data

Grey Matter

Significantly smaller grey matter (GM) volumes were detected in the right DLPFC, right caudate and right hippocampus of the BPD patients compared to the healthy controls (Table 7-2, Figure 7-1). There was no difference between the OFC of the patients and the controls. No GM volume enlargement was detected in BPD patients in any areas.

Table 7-2: Changes in grey matter corrected for brain regions of interest. All differences are thresholded at $p<0.001$. Bold type indicates regions for which the difference in activity was significant on a voxel level ($FWE<0.05$, for multiple correction). Regions printed in bold type were significant at both cluster level and voxel level ($FWE<0.05$ for multiple corrections).

K	FWE _{cluster}	ROI	FWE _{voxel}	t	Coordinates [mm]		
					x	y	z
183	0.017	Mid. Frontal right	0.058	4.17	38	42	21
39	0.029	Mid. Orbital Frontal left	0.035	3.72	-38	45	-5
40	0.031	Caudate right	0.047	3.64	18	-9	24
41	0.030	Caudate right	0.057	3.55	21	6	24
95	0.013	Hippocampus right	0.003	4.72	21	-33	7

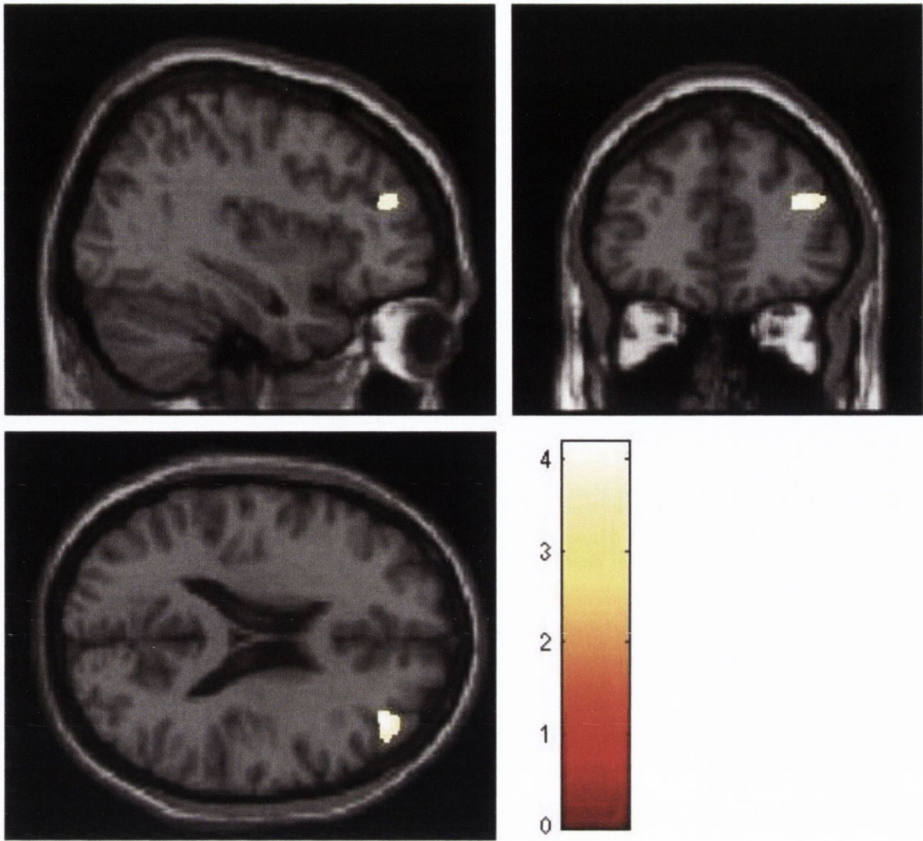


Figure 7-1: Grey matter reductions in BPD patients (ROI: DLPFC) at [38 42 21].
Coloured bar shows *t*-value distribution.

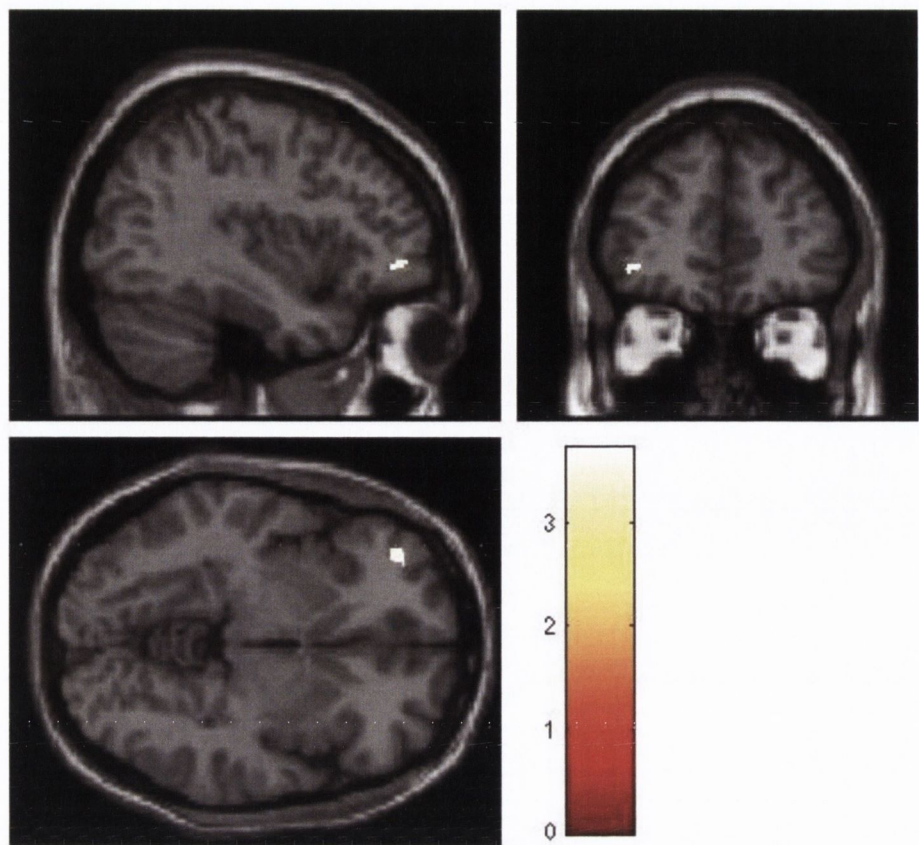


Figure 7-2: Grey matter reductions in BPD patients (ROI: L OFC) at [38 45 -5]. Coloured bar shows *t*-value distribution.

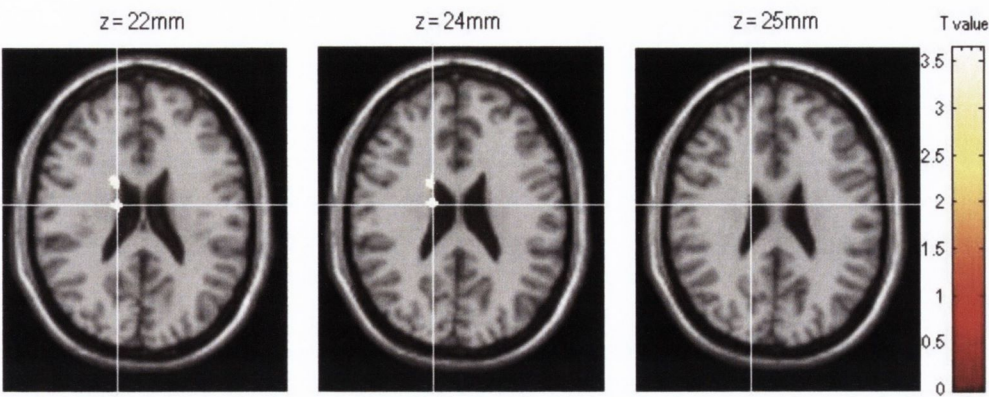


Figure 7-3: Grey matter reductions in BPD patients (ROI:R Caudate) at [21 6 24].
Two clusters are displayed in axial view. Coloured bar shows *t*-value distribution.

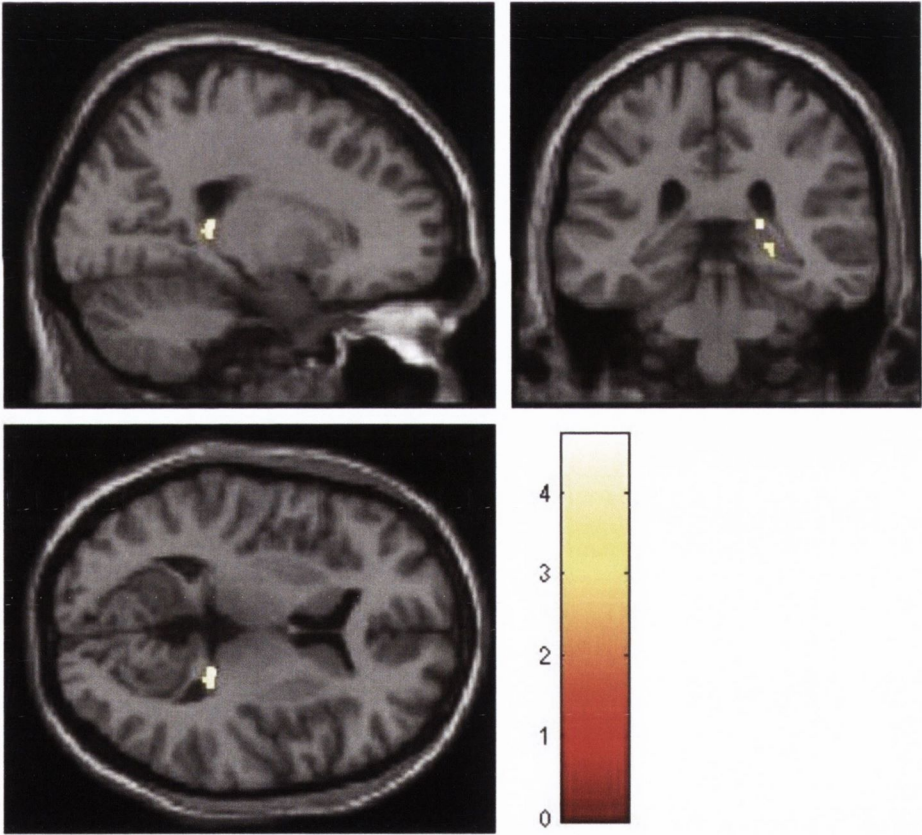


Figure 7-4: Grey matter reductions in BPD patients (ROI: R Hippocampus) at [21 -33 7].
Coloured bar shows *t*-value distribution.

White Matter

In the analysis of white matter (WM) the left insula was found to be smaller in patients with BPD compared to healthy controls (FWE cluster level corrected across the whole brain, Table 7-3). WM volumes in other regions like the insula (bilateral), middle frontal cortex, superior and inferior temporal cortex and middle occipital cortex were smaller thresholded with $p<0.001$ in BPD compared to healthy controls, but did not survive correction for multiple comparisons.

Table 7-3: Changes in white matter corrected for the whole brain.
All differences are thresholded at $p<0.001$. Bold type indicates regions for which the difference in activity was significant on a voxel level ($FWE<0.05$, for multiple correction).

Contrast	K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates [mm]		
						x	y	z
[Pat>HC]			no suprathreshold clusters					
[Pat<HC]	396	0.162	Sup. Temporal right	0.998	4.15	54	-39	19
	886	0.004	Insula left	0.999	4.08	-39	-9	22
			Insula left	1	4.04	-35	0	19

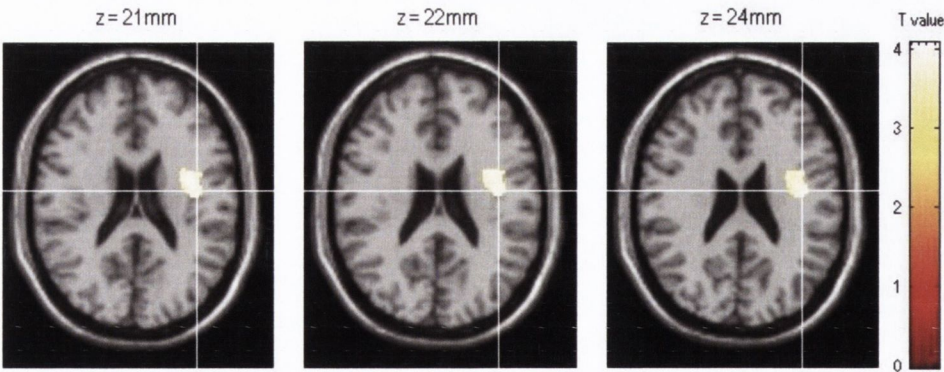


Figure 7-5: Statistical map of white matter differences in BPD patients vs. healthy controls.
Axial view of left insula at $[x=-29, y=-9]$. Coloured bar shows t -value distribution.

7.4 Discussion

The aim of this study was to investigate volumetric abnormalities of the whole hippocampi (left and right) and the hippocampal sub-regions (head, body, and tail) as well as grey and white matter differences in the caudate nucleus, amygdala, dorsolateral prefrontal cortex and orbitofrontal cortex in patients with borderline personality disorder compared to healthy controls. To achieve this we used two different structural MR imaging techniques; manual tracing and voxel based morphometry. As subsidiary analyses we examined the data for correlations between the manual tracing volumes and ratings for impulsivity as well as depression severity gathered from both the patient and healthy control groups.

The initial ANCOVAs for the manually traced data revealed there to be a significant effect due to the participant group on hippocampal volumes. As we expected, further examination found significant reductions in both the left (17%) and right (13%) hippocampal volumes of the BPD participants compared to those of the healthy participants; with greater significance being seen in the left hippocampi. Interestingly, the left hippocampal volume across the whole sample, and within each of the groups, was found to be significantly smaller than the right, with a greater difference between left and right hippocampal volumes being seen in the BPD group compared to the HC group. Further examination of the sub-regions revealed significantly smaller volumes for the BPD participants compared to the healthy participants in the left hippocampal head (reduced by 22%), body (reduced by 15%), tail (reduced by 16%), and the right hippocampal tail (reduced by 21%). The right hippocampal head and body showed no significant group differences.

Voxel based morphometry also showed a difference in the right hippocampus corrected for multiple testing and in the left hippocampus on an uncorrected $p < 0.001$ threshold between patients and controls. The manual tracing finding of reductions in the right hippocampal tail was reinforced by a significant correlation found between these

volumetric differences and those identified in the corresponding region of interest using VBM.

As we have seen with evaluation of the previous research, reductions in whole hippocampal volumes in BPD patients compared to healthy controls is not an uncommon finding. The magnitude of the reductions we have found is also within the range produced by others such as Tebartz van Elst et al., who found a 20% to 21% bilateral hippocampal reduction, Driessen et al., who found a 16% bilateral reduction, or Weniger et al., who found an 11% reduction in the hippocampi of patients with BPD but without PTSD (Driessen et al., 2000b; van Elst et al., 2003; Weniger, Lange, Sachsse, & Irle, 2009). Ruocco et al.'s previously mentioned meta-analysis also identified an average 11% decrease in the size of the hippocampus of patients with BPD compared to healthy controls (A. C. Ruocco, Amirthavasagam, S., Zakzanis, K.K., 2012). That there was a greater reduction in left hippocampal volume is an interesting finding, in keeping with that of an earlier study by Brambilla et al., who reported greater decreases in left hippocampal volume, though significant bilateral reductions were also observed (Brambilla et al., 2004a). As the majority of the earlier hippocampal studies have not reported any bilateral differences in volume in BPD patients, this would appear to be a plausible explanation (Dell'Osso, Berlin, Serati, & Altamura, 2010). However, it is possible still that a greater left than right hippocampal reduction could be a biological feature specific to the disorder, as meta analyses in PTSD have shown greater reductions in right hippocampal volumes, and MDD results have shown both bilateral and unilateral reductions (Malykhin, Carter, Seres, & Coupland, 2010; C. Schmahl & Bremner, 2006b; Woon, Sood, & Hedges, 2010).

The left hippocampus of the healthy group was found to have strong negative correlations with non-planning and self-control impulsivity, whilst the right hippocampus had a moderate negative correlation with non-planning impulsivity. The BPD group however reflected none of

these correlations. These findings were consistent with a study by Zetsche et al. (2007) who found no correlation between whole hippocampal volume and impulsivity in BPD patients and the above mentioned meta-analysis (A. C. Ruocco, Amirthavasagam, S., Zakzanis, K.K., 2012). However, a later contradictory BPD study by Schmahl et al. did find a significant correlation between hippocampal volume and impulsivity (C. Schmahl et al., 2009a). The meaning of the results for our analysis of the socio-demographic and psychometric data is unclear, as the findings were not definitely in keeping with any previous research. This is unfortunate, as confirmed correlations between hippocampal volumes and BPD traits could be of great benefit to researchers and clinicians alike, potentially providing biomarkers for differentiation from overlapping disorders and differentiation and diagnosis of different subtypes within the disorder.

As discussed earlier, the debate concerning the cause of the hippocampal reductions observed in BPD and other disorders is ongoing, though it is widely believed either to involve a dysregulation of stress-associated neural systems, including the HPA-axis, to be genetically determined, or both. A study found that in healthy participants, there was a strong correlation between the volume of the anterior hippocampus and greater psychological stress at the time of the scan (Szeszko et al., 2006). In the present study patients who had comorbidities other than a diagnosis of MDD were excluded, and though we did not include a diagnosis of MDD as a variable in the major analyses, we did not find any correlations between scores on the HDRS or the BDI-II and any of the hippocampal volumes for the BPD group, suggesting that in this population severity of depressive symptoms was not a significant predictive factor for hippocampal volume.

As a whole, one of the major roles played by the hippocampus is in memory consolidation. Consequently, it has been suggested that volumetric reductions in the hippocampus may result in a range of neurocognitive deficits and other symptoms often seen in BPD

(Brambilla et al., 2004a). Interpretation of the findings of abnormalities in the hippocampal sub-regions is more difficult as there is less research from which to draw comparisons. A PTSD study investigating such abnormalities in a sample of Gulf War veterans with the disorder found the veterans to have significantly smaller left, right, and mean hippocampal head volumes compared to healthy civilians (Vythilingam et al., 2005). The performance of the veterans on neuropsychological tests for verbal and visual immediate and delayed memory retrieval was significantly worse than that of the healthy civilians, and a significant positive correlation was seen between immediate verbal and visual memory scores and whole hippocampal head volume (Vythilingam et al., 2005). Anterior hippocampal volumes have also been positively correlated with prefrontal cortical activation and the region has been shown to be activated during normal encoding of associative memories (Sperling et al., 2003). Thus smaller volumes could underlie functional dysregulation in the region, which in turn could then be responsible for a number of neurocognitive deficits commonly seen in BPD. The overall results of a number of neuropsychological studies in BPD however may shed a different light on the present findings. A meta-analysis involving 10 studies showed significant impairments in both verbal and non-verbal memory amongst a BPD cohort when compared to healthy controls (A. C. Ruocco, 2005). Interestingly, a greater deficit was identified in the domain of non-verbal memory than in verbal memory; a finding which the researchers attributed to a potential fronto-temporal dysfunction more strongly lateralised to the right hemisphere (A. C. Ruocco, 2005). In light of the present finding of a significant volumetric reduction in the right hippocampal tail, it is possible that there lies an association between this and deficits in non-verbal memory seen in BPD patients. However, further studies examining the relationship between verbal and non-verbal memory and hippocampal sub-regional volume are necessary to assess this. As discussed earlier; the hippocampal sub-regions are anatomically and functionally distinct. As such they also have different vulnerabilities, which may be explained by their different structural organization (Malykhin et al., 2010). The

hippocampal body includes the greatest proportion of the dentate gyrus (DG), whilst the head and tail contain the greatest proportion of the cornu ammonis (CA) subfields (Malykhin et al., 2010). The DG is thought to play an important role in hippocampal neurogenesis and as a result is highly adaptive, however stress has been found to suppress this neurogenesis and cause atrophy of the CA subfields in animal studies (McEwen & Magarinos, 2001). Our observations of greater reductions in the left hippocampal head and tail than in the left hippocampal body are consistent with these findings, and imply that chronic stress and over exposure to glucocorticoids, to which CA neurons are particularly sensitive (Malykhin et al., 2010), may play an integral role in the neurobiological underpinnings of BPD. However, in the present study we investigated the sub-regions not the subfields. DG and CA are both within the hippocampal head and hippocampal body and thus it is different to relate the present findings to these subfields. A special protocol with high resolution hippocampal imaging might be a future step in this direction.

Functionally, the DG and CA regions have themselves been associated with a number of specific cognitive operations including recognition (DG), and spatial navigation (associated with both the DG and the CA3 region in animal studies) (Brickman, Stern, & Small, 2011; I. Lee, Hunsaker, & Kesner, 2005), disruptions of which may be related to symptoms of dissociation and perceptual distortions often noted in BPD.

A future direction for this research may be to use magnetic resonance spectroscopy to explore changes in the concentrations of neurometabolites in the hippocampus. Neurometabolites such as N-acetylaspartate (tNAA) and creatine (Cr) are thought to be involved in a number of neuronal features such as neuronal integrity and energy dependent functions, and evidence supporting the existence of concentration abnormalities in the amygdala and dorsolateral prefrontal cortex of BPD patients has previously been found (Hoerst et al., 2010; van Elst et al., 2007; van Elst et al., 2001). Such abnormalities if

identified could be potential precursors to cell death, decreased neurogenesis, and even volumetric reduction seen in the region. However the conclusions drawn from this data have been made tentatively, as further studies looking specifically at hippocampal sub-region volumes in BPD are needed to obtain a comparable data set. We can however emphasise the importance of the analysis of the individual hippocampal sub-region volumes as it is clear from the insignificance of the reductions in the right hippocampal head and body that masking of significant effects by the unaffected sub-regions could occur in the analysis of the hippocampal whole volumes.

The remaining findings of the VBM analysis were not entirely consistent with previous research. Our study found decreases in the GM of the right DLPFC, the right caudate, the right hippocampus and in the WM of the left insular cortex. Indeed the decrease in the DLPFC cortex is consistent with a 2010 study by Brunner et al. (Romuald Brunner et al., 2010), however very few other studies have supported this finding (Brambilla et al., 2004a; Rusch et al., 2003). The possible implications of these findings in relation to fMRI research and negative emotion processing in BPD however are worth noting. One study in particular identified activation in a sample of BPD patients not seen in healthy controls when recalling unresolved negative life events (Beblo et al., 2006). The regions found to display these abnormal activations reflected strongly those with decreases in GM/WM identified here; specifically regions such as the prefrontal brain areas and parts of the insula (Beblo et al., 2006). The DLPFC and the insula are thought to play important roles in affect regulation and anxiety. Thus disturbances in local energy metabolism, which are likely related to GM/WM loss in these areas, may also result in irregularities in the neuronal network for affect regulation in BPD. Interestingly, though we found no difference in the GM of the OFC of the BPD group here, one of the more common findings amongst the structural studies (both manual tracing and VBM) is of reductions in OFC volume (Romuald Brunner et al., 2010; Chanen et al., 2008a; van Elst et al., 2003).

The mechanisms influencing the relationship between traumatization and BPD still require further clarification, though it is clear that volumetric abnormalities in the hippocampus are features of the psychopathology of both. The lack of data relating to experiences of trauma within our sample groups meant that we could not explore in greater detail the separate roles of traumatization and BPD in the occurrence of hippocampal abnormalities and as a consequence could only make cautious conclusions based on our findings. This also limits the generalizability of our findings. Although this is inconsistent with the findings of studies such as that of Schmahl et al. which found no hippocampal differences between healthy controls and patients with BPD and without PTSD (C. Schmahl et al., 2009a), it would lend support to the stress-associated theories of reduction. Interestingly, studies in PTSD have found that up to 40% of the variation in hippocampal volume observed within the disorder can be attributed to genetics (Woon et al., 2010), whilst studies of victims of trauma without PTSD have also shown hippocampal reductions (Bremne & Vermetten, 2001), both of which lead Woon et al. to suggest that it may in fact be the combined influence of a small premorbid hippocampus and the triggering effect of external factors such as exposure to trauma which culminate in the (Bremner & Vermetten, 2001) onset of the disorder (Woon et al., 2010). Considering the range of shared characteristics belonging to the two disorders it is very possible that a similar mechanism could be involved in BPD. Our methodologies may also limit the conclusions drawn from this data as manual tracing does not guarantee abnormality detection due to restrictions in terms of resolution, signal to noise ratio, and image size, amongst other factors, though this is a limit of all volumetric studies (C. Schmahl et al., 2009a). Also in terms of methodology, the use of different protocols regarding hippocampal boundary definition in different studies means that comparisons between studies should be made with caution. With regard to the hippocampal sub-region analysis, the lack of similar BPD data made comparisons even more problematic. Other potential causes of heterogeneity amongst our findings and those of other studies include

the large disparity seen between sample sizes; gender differences, of which very little is understood; and the comorbidities and medication of the participant samples. However, it has to be mentioned that volumetric differences were not attenuated in patients being treated with psychotropic medications in a recent meta-analysis (A. C. Ruocco, Amirthavasagam, S., Zakzanis, K.K., 2012). The findings on correlations between brain structure and symptom rating scales need to be taken with caution. Using correction methods for multiple correlations such as the *Bonferroni* method would result in none significant findings. Thus these results need replication in a larger sample. It has to be stated also that it might have been worthwhile to obtain data about duration of cumulative depressive episodes or of the number of depressive episodes in order to see whether cumulative depression over time might also show negative effects on brain structure in BPD as it was demonstrated for major depressive disorder (Sheline, Sanghavi, Mintun, & Gado, 1999). However, it is not possible to decide retrospectively whether patients with borderline disorder really had clear additional depressive episodes that were not covered by the emotional-unstable disorder already and thus these retrospective data have to be kept with caution in anyway.

Our study reaffirms the existence of hippocampal volumetric abnormalities in BPD and adds strength to the theory that such abnormalities are at least partially a result of dysfunctional stress-related neural activity. Overall, the findings of the present study emphasise the need for further studies examining hippocampal sub-regions and their abnormalities in BPD, and additionally their association with BPD symptoms such as neurocognitive deficits. Furthermore, studies examining the accuracy of the manual tracing versus the voxel based morphometry techniques in BPD research and similar disorders are definitely warranted. Additional studies in these areas would surely advance our understanding of the mechanisms and markers of the disorder, and perhaps those of other trauma related disorders.

8 General Discussion

Many typical symptoms of borderline personality disorder (BPD) occur within interpersonal contexts, as outlined in the *General Introduction*, suggesting that BPD is characterised by aberrant social cognition. The results from this thesis contribute to previous findings that BPD patients have biases in mental state attribution. A strength of the paradigm used in the experiments is that the theory-of-mind condition (TOM) focussed on inferring mental states (i.e., cognitive empathy) where previous research (that mostly focussed on the attribution of emotions of others) has been less consistent (Preissler et al., 2010).

Thus, the present research aimed to investigate differences between TOM processing with particular focus on functional connectivity between emotional and TOM regions. Moreover, it should confirm structural changes in BPD compared to healthy controls using voxel based morphometry.

A general question was whether specific brain areas are associated with *ToM* processing in visual cartoons. The contrast of interest to answer this question is [TOM>PUN] in *Study 1*, where healthy subjects were investigated in order to explore the typical TOM network during our task. In this contrast activity during trials with resolvable *ToM* cartoons was compared with activity in trials in which the incongruity could be (meaningfully) resolved but did not require a theory-of-mind. The results were large and highly significant clusters of voxels in the middle temporal lobes (the inferior part of TPJ) and the precuneus bilaterally. TPJ has consistently been confirmed to be involved in representing *ToM* (Aichhorn et al., 2009; Perner et al., 2006; see also Chapter 1, R. Saxe et al., 2006). The precuneus (located in the medial parietal lobes) has been linked to the processes involved in self-consciousness, such as reflective self-awareness, that involve rating one's own personality traits compared to those judged of other people (Lou et al., 2004). This finding may be interpreted in the sense that

participants may have thoughts about how they would have felt/reacted if they were one of the cartoon characters indicating the at least partial application of *Theory theory* (TT) that postulates that a set of causal laws relating external states, internal states, and behaviours are used to construct theories about the mental states of others (Gallese & Sinigaglia, 2010).

While the *Psychometric Assessment* confirmed a prototypical clinical profile of the BPD sample with regard to symptoms such as impulsivity, depression scores, and sensations seeking, future investigations may consider using different psychometric measures to capture affective instability in addition. Wright, Pincus, and Lenzenweger (2010) suggested that neuroticism and affective instability--which are considered core aspects of personality pathology--are related but distinct constructs with unique correlates and different predictive abilities. Also, recently personality measures that are more specific to BPD symptoms have become available. During the time that the thesis research was undertaken, Huang et al. (2011) tested the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ, Aluja, Kuhlman, & Zuckerman, 2010) and found that its scales predict many of the BPD symptoms better than the big-five model, even in healthy individuals.

Study 2 shows novel results with regards to significantly increased neural activity in BPD compared to healthy controls during processing of the incongruity condition compared to PUN and TOM and also more positive responses within the INC condition. More activation of the left inferior parietal lobe during incongruity as shown in the present study is in line with a study by Chan and colleagues' (2012) who found that the left inferior frontal gyrus and left inferior parietal lobe (IPL) were related to humour detection and resolution. This pattern of neural activation again might indicate that patients indeed were resolving (un-resolvable) INC cartoons. Additionally, also other areas like the left TPJ and to a lesser extend the right TPJ were also more active during incongruity compared to other conditions in BPD patients compared to controls.

This might suggest increased utilization of TOM regions even during processing of incongruity. Furthermore, the present results might be in line with the observation that incongruity is a typical scheme in the interactions with parents during their childhood.

Structural changes associated with the BPD patient group in *Study 3* were found in the hippocampus, orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC) and basal ganglia (caudate). These findings bear possible implications in relation to fMRI research and negative emotion processing in BPD. The DLPFC and the insula are thought to play important roles in affect regulation and anxiety. Thus disturbances in local energy metabolism, which are likely related to grey and white matter loss in these areas, may also result in irregularities in the neuronal network for affect regulation in BPD. Although no difference in the GM of the OFC was found in the BPD group, one of the more common findings amongst the previous structural studies is of reductions in OFC volume (Romuald Brunner et al., 2010; Chanen et al., 2008a; van Elst et al., 2003).

Reduction in hippocampal volume as assessed by MR-based volumetry has also been a major neurobiological finding of the last decade in abuse related PTSD (Bremner et al., 2003, see *Chapter 1*). There is an on-going debate as to whether this volume reduction is due to an elevated activity of stress-associated neurobiological systems, such as the HPA axis or is genetically determined (C. Schmahl et al., 2009b). In contrast to the finding of reduced hippocampal volume, all published studies investigating amygdala volumes in patients with PTSD did not find any significant amygdala volume difference compared to controls (for a review see C. Schmahl & Bremner, 2006a). The only VBM study that tested for grey matter changes in the amygdala (Zetsche, Frodl, Preuss, Schmitt, Seifert, Leinsinger, Born, Reiser, Möller, et al., 2006) reported not significant clusters although the authors operated MR scanning at only 1.5T. The results of *Study 3* were able to confirm these results. However, it must be noted that the absence of amygdala

reductions in this case holds true with nearly all the patients having been clinically depressed whereas all the participants in the healthy control group had Hamilton scores below 4. Strength of *Study 3* is that age and depression levels were controlled for.

The main novel findings of the presented study thus were decreased hippocampal volumes and decreased functional connectivity of the seed emotional region ACC with the MCC, left STS, and right TPJ during processing of *ToM* stimuli in BPD patients. While the MCC has been shown to be involved in both self-and other-perspective (Brent A Vogt, 2005), the bilateral STS and TPJ belong to the core neural network of mentalizing (Dodell-Feder et al., 2011; R. Saxe & Wexler, 2005). As outlined in the *General Introduction*, these latter two areas make up the network known by the cognitive neuroscience term “temporo-parietal junction” (TPJ), known collectively to play a crucial role in self-other distinction processes, *Theory-of-Mind*, and the ability to make moral decisions (R. Saxe & Kanwisher, 2003). The right TPJ in particular includes areas that might be recruited exclusively by mentalizing (R. R. Saxe & Pelphrey, 2009; Scholz et al., 2009). In this context, the data indicate a dysconnectivity between the emotion network and the *ToM* network in BPD compared to healthy controls and thus a dysfunctional or even lack of modulation of the *ToM* network from regions involved in emotion processing.

In conjunction with the previous findings of Dziobek et al. (2011), this would in turn provide a biological basis for the theory that many difficulties faced by patients with BPD arise from an inability to utilise their *ToM* capacities in an efficient and balanced way. A recent study by A. C. Ruocco et al. (2013) also noted decreased activity in the ACC of a sample of BPD patients compared to healthy controls. Considering the ACC’s role in affect regulation, and the roles of the MCC and TPJ in *ToM* processes, a dysfunctional connection between their respective networks could potentially reflect the dysregulation of emotions during social cognitions in BPD. Interestingly, the ACC has repeatedly been

found to display increased activity in functional studies of Major Depressive Disorder, MDD (Fan, Wu, Yao, & Dong, 2013; Savitz & Drevets, 2009). This finding holds potential for the identification of biomarkers which may further distinguish BPD from mood disorders (without comorbid personality disorders) (A. C. Ruocco et al., 2013).

The comparison of functional connectivity during rest revealed higher activity in BPD patients in areas that are not generally included in the default-mode network (DMN). The initial conclusion that may be drawn from this finding is that in BPD the DMN is altered, perhaps including different regions in its baseline functioning than in controls.

While there was no decrease in connectivity from the precuneus (which is involved in reflective, self-related processing, empathy, awareness and conscious information processing, and episodic memory) to any brain area, patients displayed higher connectivity to left IFG, left mid-frontal, left precentral, and left mid-occipital/superior parietal regions compared to healthy controls. This increased connectivity between precuneus and the left frontal regions may have implications in terms of extensive processing of internal thoughts and self-referential information in BPD.

The DMN processes related to others such as theory-of-mind processes involved during rest (Spreng et al., 2009; Wolf et al., 2011) do not seem to be responsible for this increased connectivity, since *Study 4* was able to show a decreased connectivity between ACC and typical *ToM* regions. However, conclusions about whether there are more alterations in self-referential or processes related to others or whether these changes are related to inner speech would be premature at this stage.

This hypothesis, however, could be tested in future studies by investigating true “task-negative” resting state connectivity, and contrasting it to the connectivity during a cognitive task that involves processing of language or *ToM*.

Whereas in past studies, which generally involved specific tasks or images, the patients' emotional states could be more accurately predicted and thus the resulting images compared with more reliability (O'Neill & Frodl, 2012). This would suggest that when investigating neurobiological functioning in BPD patients, studies which employ specific emotion related stimuli provide a more reliable measure than resting state studies (O'Neill & Frodl, 2012). This may hold true for DMN functional connectivity studies in BPD as well, and is important to be aware of whilst interpreting any results both in the present study and in future studies.

Given the similarity in symptomology observed between the two disorders, research methodologies in BPD have often followed those of post-traumatic stress disorder (PTSD). It has been suggested that DMN connectivity may have potential as a predictor of post-traumatic stress disorder symptom severity in acutely traumatised subjects (Lanius et al., 2010). In an attempt to explore the potential of the above mentioned dysconnectivity as a biological marker for BPD, it is recommended that future studies also carry out functional connectivity analyses in the most commonly documented comorbidities of BPD which are MDD, attention deficit hyperactivity disorder (ADHD), and PTSD. PTSD is of particular interest given that both disorders are highly related to experiences of trauma (Philipsen et al., 2010; D. J. Stein et al., 2010), and many common neurobiological abnormalities have been identified between the two (O'Neill et al., 2013). Though MDD was the only comorbidity that was clinically diagnosed in our BPD sample, which increased the homogeneity of the sample, this in itself may limit the generalizability of the findings given the high occurrence of other/additional comorbidities found in the wider population of individuals with BPD.

Another avenue for future connectivity studies may lie in further investigation of the sub-regions of the precuneus and their role in DMN function; specifically within BPD. Recently Zhang and Li (2012) provided evidence for different roles in 8 sub-regions of the precuneus.

Thus, examining the precuneus as a whole may lead to distorted data as other studies have observed positive connectivity with the default network for ventral but not dorsal precuneus (Zhang & Li, 2012).

Deficits in social cognition anything but exclusive to BPD as they have been described in a number of psychiatric disorders (e.g., euthymic Bipolar Disorder., Autism Spectrum Disorder., Narcissistic Personality Disorder; see *General Introduction*). It will be an important task for future research to characterise the specific aspects of dysfunctional social cognition abilities unique to BPD by, for example, using comparative study designs including other disorders with social dysfunction. Social cognitive impairments displayed by the BPD sample in this thesis, are modulated by personal distress and arousal. To provide evidence for the specificity of the findings, further studies need to assess social cognition under different emotional conditions. In particular stimuli inducing perception of rejection or abandonment (see 1.3.1) are able to elicit arousal and strong negative emotions such as anger and rage in BPD (Berenson, Downey, Rafaeli, Coifman, & Paquin, 2011; Renneberg et al., 2012). Therefore, future studies should use these stimuli to assess social cognition under varying arousal and emotional conditions and in different social contexts.

Behavioural research on cognitive empathy has focused on either bias or accuracy. In the future, study designs should combine both approaches to gain an integrated understanding of mental state attribution in BPD. Further, emerging evidence in non-clinical groups has shown that cognitive empathy depends on motivation (Ickes, 2011), that is either externally induced and thus context-dependent (e.g., attractiveness of the encounter, which may or may not have mattered for visual cartoons) or related to personality characteristics or personality pathology.

For conclusion, a promising finding is the reduced functional coupling between ACC as seed region for the emotional network and the theory of mind (mentalizing) network indicating dysregulation between these

two networks in line with emotion regulation dysfunctions in BPD. Moreover, higher resting state functional connectivity is also of interest since it may be linked to higher arousal in BPD which needs to be investigated further in future studies.

The research projects have some limitations that need to be considered. Since one aim of the presented research was to investigate cognitive empathy in a humour context, rather artificial drawings (cartoons) were used as stimulus material, eventually raising the issue of ecological validity that has been pointed out by G. Domes et al. (2009, for emotional empathy) and by (Dziobek et al., 2011). Domes et al. (2008) examined the ratings of pictures of faces displaying two basic emotions at the same time. BPD patients showed a bias towards the perception of anger in comparison to non-clinical controls. Interestingly, when facial emotion recognition tasks approximate more complex and naturalistic situations (e.g., by setting time limits for recognising emotions in faces (Dyck et al., 2009) or by providing additional prosodic information (Minzenberg et al., 2006)), patients with BPD showed increased error rates compared to non-clinical controls. These findings might indicate that BPD patients show impairments in cognitive empathy mainly on tasks that are complex or more ecologically valid.

In order to truly relate *ToM* mentalizing to physiological processes the validity of “TOM” stimuli from visual cartoons needs to be assured. Following in the tradition of developmental investigations of *ToM* (Wimmer & Perner, 1983), neuroimaging studies have often used “false belief” stories to test belief reasoning (Dodell-Feder et al., 2011). In these stories, a protagonist performs an action based on a belief that is false (e.g., Maxi believes his chocolate is in the green drawer, but his mother moved it to the blue drawer). Participants reading these stories are thus required to represent the outdated belief of the protagonist in order to understand their actions (e.g., looking in the green drawer even though the chocolate is actually in the blue drawer). These stories are contrasted with “false photograph” stories, which also require the

representation of false or outdated content (e.g., an old photograph that no longer accurately depicts the landscape of a burgeoning city). False belief and false photograph stories are therefore matched in their general difficulty, logical complexity, and inhibitory demands, but differ in the need to think about someone's thoughts. Accordingly, a set of "false photograph"-type cartoons would be required as a control condition to accurately identify brain regions of the *ToM* network.

The studies presented in this thesis have further methodological limitations. The first is the small sample size, which is, however, comparable to samples reported previously in BPD studies (Kunert et al., 2003; Lamm, Batson, & Decety, 2007). A second limitation is that it was not possible to address possible gender differences since only female subjects were used and although BPD is more prevalent in women (APA, 2000), future studies should explore possible gender differences.

Inclusion of medication use in this sample of patients with BPD have to also be considered as potential limitations, since 12 of the 17 patients included were on antidepressants and four additional on antipsychotics. It is known that anti-depressants can affect brain function (Frodl et al., 2011; A. C. Samson et al., 2011). However, using medication status (none, antidepressant, antidepressant + antipsychotic) as additional covariate in *Study 4* did not change the connectivity results and thus, does not indicate a considerable medication effect. The question of whether treated patients and patients with BPD with psychiatric comorbidities should be excluded to homogenise clinical sample characteristics remains controversial and such exclusion might focus on a particular group of BPD patients (Lis et al., 2007).

The studies included in this thesis have several potential implications for the treatment of BPD. Given that data point toward deficits in social cognition that are likely amplified by emotion dysregulation and arousal, psychotherapeutic interventions designed to improve emotion regulation might also affect social cognition (e.g., MBT, DBT, see 1.1.6). This

potentially causal relationship needs to be explored in future empirical research with BPD patients.

Pharmacological intervention might be explored as an additional approach to improve social cognition capacities (e.g., Simeon et al., 2011). In summary, patients with BPD display a specific pattern of disturbance in cognitive and emotional empathy and expression of social signals. Given the importance of social cognition (on the part of both the sender and the recipient (Roepke et al., 2012) for maintaining stable interpersonal relationships and establishing therapeutic alliance, these deficits should be further explored in future studies.

The End

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Appendix



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ST JAMES'S
HOSPITAL
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Dublin 8
Tel.: 01-410-3000

Title of research study:

Neural correlates of humour and of cognitive-emotional autobiographic memory processing in patients with major depression, borderline personality disorder and healthy comparison subjects

This study and this consent form have been explained to me. My doctor has answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study.
I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this agreement

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

- I have read and understood the attached Participant Information Leaflet Yes ☐ No ☐
- I have had the opportunity to ask questions and to discuss the study ... Yes ☐ No ☐
- I have received satisfactory answers to all my questions Yes ☐ No ☐
- I have received enough information about this study Yes ☐ No ☐
- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care Yes ☐ No ☐
- I agree to take part in this study without prejudice to my legal or ethical rights Yes ☐ No ☐
- I filled out the MRI screening form..... Yes ☐ No ☐

PARTICIPANT'S NAME:

PARTICIPANT'S SIGNATURE:

Date:
Date on which the participant was first furnished with this form:

Appendix A: Participant consent form and MRI information.



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Where the participant is incapable of comprehending the nature, significance and scope of the consent required, the form must be signed by a person competent to give consent to his or her participation in the research study (other than a person who applied to undertake or conduct the study). If the subject is a minor (under 18 years old) the signature of parent or guardian must be obtained:-

NAME OF CONSENTOR, PARENT or GUARDIAN:
SIGNATURE:
RELATION TO PARTICIPANT:

Where the participant is capable of comprehending the nature, significance and scope of the consent required, but is physically unable to sign written consent, signatures of two witnesses present when consent was given by the participant to a registered medical practitioner treating him or her for the illness.

NAME OF FIRST WITNESS: SIGNATURE:
NAME OF SECOND WITNESS: SIGNATURE:

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's signature:
Date:

(Keep the original of this form in the participant's medical record, give one copy to the participant, keep one copy in the investigator's records, and send one copy to the sponsor (if there is a sponsor).

Appendix B: Participant consent form and MRI information.



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INFORMATION SHEET

Title of the Project:

Neural correlates of humour and of cognitive-emotional autobiographic memory processing in patients with major depression, borderline personality disorder and healthy comparison subjects

You are invited to take part in a research study. It is important for you to understand why this research is being carried out and which investigations it will involve, before you decide whether you would like to take part. This information sheet has been written for you and it is essential that you read it carefully and discuss it with your doctor, one of the researchers or anybody you wish. Please ask whatever you want to ask. Further information about the study can be provided. Take time to decide whether or not you wish to take part.

PURPOSE OF THE STUDY:

You were selected as a possible participant in this study either because you have depression or an emotional-instability or as a control participant.

The aim of the study is to identify neural processes underlying humour and emotion and to find alterations in psychiatric diseases with affective symptoms using neuroimaging (magnetic resonance imaging, MRI). We are asking you to take part in an MRI investigation and in a clinical interview on the history and acute symptomatology of your disease (for patients).

We will also ask you for a blood sample in order to examine genes that might be involved in emotion processing and humour.

The blood samples and brain scans that we obtain from you will be used for this study and closely related studies seeking to find the changes that major depression produces.

You will be required to visit once or twice to the Adelaide and Meath Hospital Incorporating The National Children's Hospital (AMNCH Hospital) in Tallaght or St. James's Hospital for the medical screening. You will visit once the MRI centre in the Trinity College Institute of Neuroscience (TCIN) on the main campus of Trinity College located in the Lloyd building for the brain scan.



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WHY HAVE I BEEN CHOSEN?

You have been chosen, because you have either major depression, emotional-instability or are a healthy person.

DO I HAVE TO TAKE PART?

It is your decision whether you take part or not. If you decide to get involved with the study, this Information Sheet will be handed out and you will be asked to sign the Consent Form. You may withdraw from the study at any time you wish and without giving a reason. This will not affect the care you receive from your doctor or any other person with whom you are involved.

WHAT WILL HAPPEN IF I AGREE TO TAKE PART IN THIS STUDY?

If you decide to participate, you will go to the Adelaide and Meath Hospital Incorporating The National Children's Hospital, Sheaf House in Tallaght, St. James's Hospital, or St. Marthas Day Hospital in order to take part in the clinical interview and psychiatric examination. This will take about 90 minutes for patients and 30 minutes for healthy controls. During this appointment a doctor or nurse will take the blood samples.

During the second visit, a magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) scan will be done at the MRI research centre in St. James's hospital. The MRI machine uses a magnetic field to take pictures of the brain. Before you enter the room where the machine is located, you will have to remove all the metallic things you may be wearing such as bracelets, earrings, watch, or keys. You will be asked to lie on a long narrow couch for about 90 minutes while the MRI machine gathers information. The narrow couch is within a tube, so that you may feel a bit confined. If you feel claustrophobic while lying on the couch, you can discontinue the scan at any time. Each scan may take between 5 and 15 minutes and during this time you will hear tapping noises. As the noise can sometimes be loud, we will give you earplugs so that the noise is reduced. While lying on the couch, we will place pads around your head so that it remains still. The padding is to help you keep your head still. You will be able to speak and move your head if it becomes uncomfortable.

While you are lying on the couch, you will be able to speak with the operator of the scanner at any time. In addition, you will have a button in your hand that you can use to stop the measurement.

You will be asked to look at pictures on a screen while lying on the couch. While viewing these pictures you have to provide answers by pressing a button in your hand. What you need to do will be explained to you before you go to the scanner and you will have the opportunity to see a short example of the test.



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There are no drugs involved in the study.

The blood samples you give will be examined by our staff at our genetic research laboratory in St. James's Hospital, Trinity Health Centre and in the Trinity College Institute of Neuroscience Dublin and by our collaborating colleagues at Ludwig-Maximilian-University (Munich, Germany). The staff at the MRI centre of St. James Hospital and the staff of our research group will know the identity of your blood sample by a code number and the key to this code and any personal information will be kept confidentially by Professor Thomas Frodl, head of the research group, Trinity College Dublin. At a later stage these results may form part of a collaborative study with researchers in Ireland and abroad.

WHAT WILL BE THE POSSIBLE BENEFITS OF TAKING PART?

This study will be of no direct benefit to you, but will be used to help identify biological parameters that would diagnose the presence and the risk of major depression. It is expected that important diagnostic and treatment changes will emerge in the future, as a result of these discoveries. No individual genetic or non-genetic (protein expression) result will be available from the study, to you or to anyone else, and this study does not involve screening for genetic diseases. If you wish, we will keep you informed of the progress of the study in general.

WHAT ARE THE POSSIBLE DISADVANTAGES OF TAKING PART?

The risk for the blood sample is a standard clinical procedure and very safe. There may be minor pain with the procedure but it will be localized and of short duration. Occasionally there is an infection, and if so, it will be treated.

This MRI machine uses a strong magnet to make images of the brain. You will be asked to lie on a long narrow couch for about 90 minutes while the machine gathers data. During this time you will be exposed to a magnetic field which, however, you will not feel. You will, however, hear repetitive tapping noises that arise from the scanner around your body. We will provide earplugs and headphones that you will be required to wear so that it is not too loud. The space within the large magnet in which you lie is narrow, although we have taken many steps to relieve the "claustrophobic" feeling.

There are no known significant risks with this procedure since the main magnetic field at the strengths used are felt to be without harm. There are conservative guidelines for radiofrequency magnetic fields and main magnetic field exposure and our examinations fall within those guidelines. We feel these are safe levels and less hazardous than a comparable x-ray computed tomography examination.



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MRI can be also obtained in pregnant women and for foetal diagnosis, however, this will be avoided in the present study. MRI has an excellent safety record. Issues for the developing foetus include heat absorption and noise. Therefore, current guidelines recommend that MR should be avoided in the first trimester of pregnancy, unless there are compelling maternal reasons for imaging studies. For safety reasons, you will be asked to tell the staff, if you are expecting a baby. The staff will ask you about your actual contraception methods.

People who cannot be scanned using MRI include persons who have a cardiac pacemaker or a certain type of metallic clip in their body (i.e., an aneurysm clip in the brain); persons who have worked with metal or had a piece of metal removed from the eye(s); or persons who have shrapnel, bullets, or buckshot in their body.

There is a risk of heating from the imaging coils, and/or the cables from monitoring devices that record physiologic processes such as heart beats per minute. Please report any heating sensation immediately. You may have the scan stopped at any time if this occurs.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and shouldn't be painful. However, you may have the scan stopped at any time if this occurs.

Dizziness and nausea may occur if the head is moved rapidly while you are lying in the scanner.

Please take note that some subjects have experienced claustrophobia; you may discontinue the scan at anytime.

You will be told if any new information is learned which may affect your condition or influence your willingness to continue participation in this study.

While participating in this study, you should not take part in any other research project without approval from all of the investigators. This is to protect you from possible injury arising from such things as extra blood drawing, effects of research drugs, or similar hazards. The alternative to participation is not to participate.

WILL MY TAKING PART BE CONFIDENTIAL?

Yes.

All information, which is collected about you, during the course of the research, will be kept strictly confidential. Your name will not be attached to any information about you that leaves the hospital.



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WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results will be published in scientific journals and presented at conferences, again without any breach of confidentiality.

LEGAL ISSUES:

The doctors involved in this study are covered by standard medical malpractice insurance. Nothing in this document restricts or curtails your rights.

PERMISSION:

This study has been approved by the St. James's and AMNCH Committee.

FURTHER INFORMATION:

If you would like to obtain further information about the nature of the study you can do so by contacting:

Prof. Thomas Frodl PhD MRCPI MRCPsych

Professor of Integrated Neuroimaging
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St James' Hospital and AMNCH Hospital
Trinity Health Centre
Dublin 24
Tel: 00353 1896 8484

Thank you for your help with this project.

THE HAMILTON RATING SCALE FOR DEPRESSION

(to be administered by a health care professional)

Patient's Name

Date of Assessment

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

1. DEPRESSED MOOD (Sadness, hopeless, helpless, worthless)

0= Absent

1= These feeling states indicated only on questioning

2= These feeling states spontaneously reported verbally

3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep

4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication
2. FEELINGS OF GUILT

0= Absent

1= Self reproach, feels he has let people down

2= Ideas of guilt or rumination over past errors or sinful deeds

3= Present illness is a punishment. Delusions of guilt

4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
3. SUICIDE

0= Absent

1= Feels life is not worth living

2= Wishes he were dead or any thoughts of possible death to self

3= Suicidal ideas or gesture

4= Attempts at suicide (any serious attempt rates 4)
4. INSOMNIA EARLY

0= No difficulty falling asleep

1= Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour

2= Complains of nightly difficulty falling asleep
5. INSOMNIA MIDDLE

0= No difficulty

1= Patient complains of being restless and disturbed during the night

2= Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

Adapted from Hedlung and Vieweg. The Hamilton rating scale for depression. *Journal of Operational Psychiatry*, 1979;10(2):149-165.

Appendix C: Hamilton rating scale for depression

6. INSOMNIA LATE

0= No difficulty

1= Waking in early hours of the morning but goes back to sleep

2= Unable to fall asleep again if he gets out of bed

7. WORK AND ACTIVITIES

0= No difficulty

1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies

2= Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)

3= Decrease in actual time spent in activities or decrease in productivity

4= Stopped working because of present illness

8. RETARDATION: PSYCHOMOTOR (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

0= Normal speech and thought

1= Slight retardation at interview

2= Obvious retardation at interview

3= Interview difficult

4= Complete stupor

9. AGITATION

0= None

1= Fidgetiness

2= Playing with hands, hair, etc.

3= Moving about, can't sit still

4= Hand wringing, nail biting, hair-pulling, biting of lips

10. ANXIETY (PSYCHOLOGICAL)

0= No difficulty

1= Subjective tension and irritability

2= Worrying about minor matters

3= Apprehensive attitude apparent in face or speech

4= Fears expressed without questioning

11. ANXIETY SOMATIC: Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

0= Absent

1= Mild

2= Moderate

3= Severe

4= Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

- _____ 0= None
1= Loss of appetite but eating without encouragement from others. Food intake about normal
2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

- _____ 0= None
1= Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2= Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

- _____ 0= Absent
1= Mild
2= Severe

15. HYPOCHONDRIASIS

- _____ 0= Not present
1= Self-absorption (bodily)
2= Preoccupation with health
3= Frequent complaints, requests for help, etc.
4= Hypochondriacal delusions

16. LOSS OF WEIGHT

- _____ A. When rating by history:
0= No weight loss
1= Probably weight loss associated with present illness
2= Definite (according to patient) weight loss
3= Not assessed

17. INSIGHT

- _____ 0= Acknowledges being depressed and ill
1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2= Denies being ill at all

18. DIURNAL VARIATION

- _____ A. Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none
0= No variation
1= Worse in A.M.
2= Worse in P.M.
_____ B. When present, mark the severity of the variation. Mark "None" if NO variation
0= None
1= Mild
2= Severe

19. DEPERSONALIZATION AND DEREALIZATION (Such as: Feelings of unreality; Nihilistic ideas)

0= Absent

1= Mild

2= Moderate

3= Severe

4= Incapacitating

20. PARANOID SYMPTOMS

0= None

1= Suspicious

2= Ideas of reference

3= Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

0= Absent

1= Mild

2= Severe

Total Score

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DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.				
	O Rarely/Never	O Occasionally	O Often	O Almost Always/Always
1	I plan tasks carefully.		O	O O O O
2	I do things without thinking.		O	O O O O
3	I make-up my mind quickly.		O	O O O O
4	I am happy-go-lucky.		O	O O O O
5	I don't "pay attention."		O	O O O O
6	I have "racing" thoughts.		O	O O O O
7	I plan trips well ahead of time.		O	O O O O
8	I am self controlled.		O	O O O O
9	I concentrate easily.		O	O O O O
10	I save regularly.		O	O O O O
11	I "squirm" at plays or lectures.		O	O O O O
12	I am a careful thinker.		O	O O O O
13	I plan for job security.		O	O O O O
14	I say things without thinking.		O	O O O O
15	I like to think about complex problems.		O	O O O O
16	I change jobs.		O	O O O O
17	I act "on impulse."		O	O O O O
18	I get easily bored when solving thought problems.		O	O O O O
19	I act on the spur of the moment.		O	O O O O
20	I am a steady thinker.		O	O O O O
21	I change residences.		O	O O O O
22	I buy things on impulse.		O	O O O O
23	I can only think about one thing at a time.		O	O O O O
24	I change hobbies.		O	O O O O
25	I spend or charge more than I earn.		O	O O O O
26	I often have extraneous thoughts when thinking.		O	O O O O
27	I am more interested in the present than the future.		O	O O O O
28	I am restless at the theater or lectures.		O	O O O O
29	I like puzzles.		O	O O O O
30	I am future oriented.		O	O O O O

Appendix D: Barratt Impulsiveness Scale (BIS-11)

A brief summary of the factor structure of the BIS-11 and scoring protocol.

The Barratt Impulsiveness Scale, Version 11 (BIS-11; Patton et al., 1995) is a 30 item self-report questionnaire designed to assess general impulsiveness taking into account the multi-factorial nature of the construct. The structure of the instrument allows for the assessment of six first-order factors (attention, motor, self-control, cognitive complexity, perseverance, cognitive instability) and three second-order factors (attentional impulsiveness [attention and cognitive instability], motor impulsiveness [motor and perseverance], nonplanning impulsiveness [self-control and cognitive complexity]). A total score is obtained by summing the first or second-order factors. The items are scored on a four point scale (Rarely/Never [1], Occasionally [2], Often [3], Almost Always/Always [4]).

BIS-11 English Version

1st Order Factor Item Content

Attention (5 items): 5, 9*, 11, 20*, 28

Motor (7 items): 2, 3, 4, 17, 19, 22, 25

Self-Control (6 items): 1*, 7*, 8*, 12*, 13*, 14

Cognitive Complexity (5 items): 10*, 15*, 18, 27, 29*

Perseverance (4 items): 16, 21, 23, 30*

Cognitive Instability (3 items): 6, 24, 26

2nd Order Factor Item Content

Attentional Impulsiveness (8 items): 6, 5, 9*, 11, 20*, 24, 26, 28

Motor Impulsiveness (11 items): 2, 3, 4, 16, 17, 19, 21, 22, 23, 25, 30*

Nonplanning Impulsiveness (11 items): 1*, 7*, 8*, 10*, 12*, 13*, 14, 15*, 18, 27, 29*

*Reversed item scored 4, 3, 2, 1

Appendix E: BIS-11 Scoring information

PANAS-X Protocol Illustrating "Past Few Weeks" Time

This scale consists of a number of words and phrases that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you have felt this way during the past few weeks. Use the following scale to record your answers:

1 2 3 4 5
very slightly a little moderately quite a bit extremely
or not at all

	cheerful		sad		active		angry at self
	disgusted		calm		guilty		enthusiastic
	attentive		afraid		joyful		downhearted
	bashful		tired		nervous		sheepish
	sluggish		amazed		lonely		distressed
	daring		shaky		sleepy		blameworthy
	surprised		happy		excited		determined
	strong		timid		hostile		frightened
	scornful		alone		proud		astonished
	relaxed		alert		jittery		interested
	irritable		upset		lively		loathing
	delighted		angry		ashamed		confident
	inspired		bold		at ease		energetic
	fearless		blue		scared		concentrating
	disgusted with self		shy		drowsy		dissatisfied

STCI - T <30>

Name/Code: _____ Age: |__| |__| Gender: ☐ male ☐ female

Instructions:

The following statements refer to your moods and mentality **in general**. Please try as much as possible to describe your **habitual** behavior patterns and attitudes by marking an X through one of the four alternatives. Please use the following scale:

- (1) strongly disagree
- (2) moderately disagree
- (3) moderately agree
- (4) strongly agree

For example:

I am an active person. (1) (2) (3) (4)

If you strongly agree with this statement, that is, if you are **in general** an active person, **mark an X through (4)**. If you strongly disagree, that is, if you are **habitually not** active **at all**, **mark an X through (1)**. If you have difficulty answering a question, pick the response that **most** applies.

Please answer *every* question, do not omit any.

1	Everyday life often gives me the occasion to laugh.	(1) (2) (3) (4)
2	I prefer people who communicate with deliberation and objectivity.	(1) (2) (3) (4)
3	I am a rather sad person.	(1) (2) (3) (4)
4	One of my principles is: "first work, then play."	(1) (2) (3) (4)
5	I am often sullen.	(1) (2) (3) (4)
6	I can easily unwind and enjoy the moment.	(1) (2) (3) (4)
7	I am a serious person.	(1) (2) (3) (4)
8	Many adversities of everyday life actually do have a positive side.	(1) (2) (3) (4)
9	I often smile.	(1) (2) (3) (4)
10	In everything I do, I always consider every possible effect and compare all pros and cons carefully.	(1) (2) (3) (4)
11	When friends try to cheer me up by joking or fooling around, I sometimes become more morose and grumpy.	(1) (2) (3) (4)
12	I am often in a joyous mood.	(1) (2) (3) (4)
13	There are many days on which I think, "I got up on the wrong side of the bed."	(1) (2) (3) (4)
14	In most situations, I initially see the serious aspect.	(1) (2) (3) (4)
15	I like to laugh and do it often.	(1) (2) (3) (4)

© Ruch, Köhler, Deckers, & Carrell, August 1996After checking *every* statement, turn the page.

Appendix G: State-Trait Cheerfulness Inventory (STCI).

	(1) strongly disagree	(2) moderately disagree	(3) moderately agree	(4) strongly agree
16	Even if there is no reason, I often feel ill-humored.	(1)	(2)	(3) (4)
17	When I communicate with other people, I always try to have an objective and sober exchange of ideas.	(1)	(2)	(3) (4)
18	I feel completely contented being with cheerful people.	(1)	(2)	(3) (4)
19	I am often in a bad mood.	(1)	(2)	(3) (4)
20	When I watch TV, I prefer informative reports to "shallow" programs.	(1)	(2)	(3) (4)
21	I often feel despondent.	(1)	(2)	(3) (4)
22	I try to spend my free time doing things as useful as possible.	(1)	(2)	(3) (4)
23	I often feel so gloomy that nothing can make me laugh.	(1)	(2)	(3) (4)
24	My everyday life is filled mainly with important things and matters.	(1)	(2)	(3) (4)
25	Laughing has a contagious effect on me.	(1)	(2)	(3) (4)
26	Some annoying circumstances are capable of spoiling my mood for quite a while.	(1)	(2)	(3) (4)
27	I am a cheerful person.	(1)	(2)	(3) (4)
28	Sometimes I am distressed for a very long time.	(1)	(2)	(3) (4)
29	It is easy for me to spread good cheer.	(1)	(2)	(3) (4)
30	When I am in contact with others, I often find that I have thought many things through more thoroughly than they.	(1)	(2)	(3) (4)

Please check to see that you have answered *every* statement.



Appendix H: Set of INC cartoons



Appendix H: Set of INC cartoons



Appendix I: Set of PUN cartoons



Appendix I: Set of PUN cartoons



Appendix J: Set of TOM cartoons

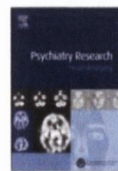


Appendix J: Set of TOM cartoons



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Magnetic resonance imaging in patients with borderline personality disorder: A study of volumetric abnormalities



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ABSTRACT

Volumetric abnormalities of the hippocampus and frontal cortex are of major interest in the study of borderline personality disorder (BPD). To our knowledge, no study has examined volumetric abnormalities in the hippocampal subregions (head, body, and tail). Our aims were to investigate hippocampal volumetric abnormalities as well as abnormalities in the gray and white matter of the frontal cortex, basal ganglia, and anterior cingulate cortex in BPD in a sample of BPD patients compared to healthy controls. Using manual volumetry as well as optimized voxel based morphometry (VBM) we assessed the volumetric differences in a sample of females with BPD ($n=20$), compared to healthy female controls ($n=21$) (HC). The analyses revealed reductions in the left hippocampal head, body, and tail, and the right hippocampal tail. Hippocampal changes were confirmed also using VBM and additional volumetric reductions were found in the caudate and dorsolateral prefrontal cortex of the BPD group. Our study reaffirms the existence of hippocampal volumetric, prefrontal and caudate abnormalities in BPD and lends support to the stress-related explanation of these reductions, whilst also bringing new data to the topic in terms of the abnormalities found in the subregions.

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1. Introduction

Borderline personality disorder (BPD) is a commonly seen axis II psychiatric disorder typified by features such as severe relationship dysfunction, instability of mood, impulsivity, and in extreme cases, periods of dissociation (Steele and Siever, 2010). The majority of past BPD research has explored the psychological aspects of the disorder from characteristic behaviors to psychosocial triggers and risk factors, with high levels of trauma found to be strongly correlated with occurrences of BPD. Studies investigating the neurobiology of the disorder are less common, though ever increasing. Structural magnetic resonance imaging (MRI), the most frequently used neuroimaging technique in BPD research, is often focused on regions of the brain known to be involved in the regulation of stress responses, emotion, and affect. These areas include the hippocampus, the orbitofrontal cortex, the amygdala, and the anterior cingulate cortex. Recently we reviewed the

literature relating to neuroimaging in BPD (O'Neill and Frodl, 2012). With structural MR imaging studies the two commonly used analytical techniques are manual tracing and voxel based morphometry (VBM). Manual tracing involves drawing regions of interest (be it the whole brain or its subparts) on images obtained from brain scans and measuring the volume enclosed. It allows for the precise identification and delineation of regions of interest (Irlé et al., 2005), though it can be time consuming and is of more use for larger areas. In VBM each brain is mapped to a template then statistical tests are run across all voxels in the image to identify differences between testing groups. Though its results can be hard to validate, studies comparing the results of VBM to those of manual tracing or visual measurements have found relatively good correspondence (Whitwell, 2009), though its validity when dealing with atypical brains (such as those containing severe pathologies) has been questioned, due to its core features of normalization and segmentation to a template (Mechelli et al., 2005). Thus, information obtained from manual tracing and VBM will vary, but should add to each other when interpreted correctly.

In general, the brain region which most consistently showed alterations across all studies of BPD patients is the hippocampus, with a number of studies finding significant hippocampal volume reductions bilaterally in individuals with BPD compared to healthy controls (Brambilla et al., 2004; Schmahl et al., 2003; van Elst

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et al., 2003). Interestingly, Brambilla et al. (2004) found with further examination that those BPD patients who had a history of childhood abuse, when compared to healthy controls, still displayed significant reductions in hippocampal volumes, whilst BPD patients without such a history did not display significant reductions. A study by Driessen et al. (2000) reported similar findings, with 16% reductions in the hippocampal volumes of the BPD patients being studied, compared to healthy controls, and a negative correlation being observed between hippocampal volume and duration of reported early trauma. More recently, however, a meta-analysis by Ruocco et al. (2012) rejected this association. Taking 11 studies into account, the meta-analysis found no significant relationship between reports of childhood abuse and any volumetric abnormalities identified in either hippocampus.

Another brain region in BPD patients which is frequently found to display significant reductions is the anterior cingulate cortex (ACC), with a number of studies replicating this finding over the years (Hazlett et al., 2005; Minzenberg et al., 2008; Tebartz van Elst et al., 2003). A 2009 investigation of ACC volumes in adolescents with first presentation of BPD and minimal exposure to treatment found a decrease in left ACC volume of the patient group compared to healthy controls (Whittle et al., 2009).

Studies examining volumetric changes in other areas have been less consistent. Some structural MRI studies have suggested volumetric reductions in the frontal lobe (Lyo et al., 1998), the left orbitofrontal cortex (OFC) (Hazlett et al., 2005) and right parietal cortex (Irlle et al., 2005). Using VBM, reductions in gray matter volume have also been found in frontal, temporal and parietal cortices in men with BPD (Vollm et al., 2009). Conversely, in another VBM study no group differences between patients with BPD and healthy control subjects could be found in the frontal lobe (Rusch et al., 2003), though this BPD group was comprised solely of females.

With regard to the amygdala in adult patients with BPD compared to healthy controls, three manual tracing studies found increased amygdala volumes (Driessen et al., 2000; Schmahl et al., 2003; van Elst et al., 2003), while two other studies (one using VBM and one using manual tracing) found decreased amygdala volumes (Brambilla et al., 2004; Rusch et al., 2003). Interestingly, a recent VBM study found a higher relative gray matter concentration in the amygdala of a sample of BPD patients compared to a group of healthy controls (Minzenberg et al., 2008), whilst another manual tracing study found that only patients with both BPD and a comorbid diagnosis of major depression demonstrated a larger amygdala volume in both hemispheres compared with those without major depression (Zetzsche et al., 2006). In this last instance no difference was found in amygdala volumes between the whole BPD group and the healthy controls (Zetzsche et al., 2006).

As the research stands, it is evident that more concrete findings are needed in order to gain a firmer understanding of the neurobiological underpinnings of the disorder. In particular, findings regarding frontal lobe regions have thus far been too inconsistent to allow any speculation on the biological mechanisms in these regions potentially contributing to the disorder. Another area lacking attention in BPD studies is the search to locate the actual source or sources of the abnormalities seen within the hippocampal structure. The hippocampus, as with most brain structures, is composed of a number of anatomically and functionally different subregions which play complex roles supporting the overall functions of the structure. It is thus unlikely that all subregions within the hippocampus are affected equally, if at all, by the abnormal biological processes of BPD, or any other disorder. For this reason, to only investigate the hippocampal volume as a whole could result in the attenuation of the effects of reductions in the affected subregions by those that remain unaffected (Peterson, 2010). The exact importance of these omissions for BPD is as yet

unknown; however it is possible that the identification of biomarkers of this kind could be of enormous benefit to the development of pharmacological treatment of the disorder and in the formation of biological criteria for diagnosis. To our knowledge, no other study has investigated differences in subregional hippocampal volumes between patients with BPD and healthy controls. Furthermore, little work has been done to investigate the relationships between the characteristic symptoms of BPD and overall hippocampal volumes in BPD.

In this study we attempted to address these gaps in the research in two ways. Firstly, we explored the differences in volume for the whole hippocampus and hippocampal subregions between a sample of females with BPD and a sample of healthy female controls (HC) using structural MR imaging and manual tracing. Additionally, using the VBM technique, we again investigated the hippocampus, and also the gray and white matter of the orbitofrontal cortex, basal ganglia, and anterior cingulate cortex for any potential abnormalities that may occur between the same sample groups. We expected the study to reveal significant reductions in the whole hippocampal volumes of the BPD patients compared to controls, and in particular to identify reductions in the hippocampal head, which has been shown to be stress sensitive. We also analyzed the morphometric data from the manual tracing portion of the study for any correlations with the socio-demographic and psychometric data obtained from both the BPD group and the HC group.

2. Methods

2.1. Participants

The group of patients formally diagnosed with borderline personality disorder (BPD) according to DSM-IV consisted of 20 female patients with an age range from 19 to 49, and a mean age of 32.6 (standard deviation: 10.1). As BPD is much less frequently found in men (75% of those with the disorder are women) (Oldham, 2004), it was decided to have the participant groups consist solely of women to avoid potential gender based differences. The BPD patient groups were receiving continuous treatment from the South-West mental health services in Dublin. The BPD participants were all attending our outpatient clinics for years. Thus, patients were well known to the service and mainly were treated in outpatient and home care, when necessary with crisis admission. Only when the continuous care consultant indicated these inclusion criteria we further interviewed them for suitability to the study. Diagnosis according to DSM-IV was thus confirmed by a second psychiatrist. A cohort of 21 healthy female volunteers with ages between 20 and 47, and a mean age of 30.1 (standard deviation: 8.0), was recruited from the local community. The volunteers and patients were carefully screened for medical conditions to ensure that none had a personal history of neurological disorder, severe medical illness, head injury or substance dependency. Healthy participants were excluded if they had a personal history of any psychiatric disorder (Axis I or Axis II) and the BPD participants were excluded if they had any additional psychiatric disorder other than comorbid major depression (MDD) at present or in the past. Demographic variables and inclusion and exclusion criteria were assessed using a standardized questionnaire and through structured interview based on SCID-I by registered psychiatrists.

2.2. Psychometric assessment

Self- and observer rated scales were administered for all participants included in the study. The rating scales used are listed below.

- The 21-item version of the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1969).
- The Beck Depression Inventory (BDI-II) (Beck et al., 1961).
- The Barratt Impulsiveness Scale (BIS) (Patton et al., 1995).
- The revised short scale Eysenck Personality Questionnaire (EPQ-R short scale) (Eysenck and Eysenck, 1975).
- The Sensation-Seeking Scale (SSS) (Zuckerman et al., 1978).

Written informed consent was obtained from all participants after having been given detailed description of the study, which was designed and performed in accordance to the ethical standards laid out by the Declaration of Helsinki and was approved by the local ethics committees.

2.3. MRI data acquisition

Magnetic resonance images were obtained with a Philips Achieva MRI scanner (Philips Medical System, Netherlands B.V., Veenphuis 4-6, 5684 PC Best, Netherlands) operating at 3 T. An axial T1IR three dimensional magnetization prepared rapid gradient echo (MPRAGE) was used to scan all participants (TR was user defined to 8.4 ms; TE was set to “shortest”; with a total scan duration of 5:43 min; field of view (FOV) of FH (foot to head): 162 mm, AP (anterior to posterior): 230 mm, RL (right to left): 230 mm; and a matrix of 256×256). Slice thickness was 1 mm and voxel size was 0.9×0.9×0.9 mm³.

2.3.1. Definition of hippocampal formation

All data sets were realigned and resampled three dimensionally in the anterior commissure to posterior commissure (AC–PC) line, according to the coordinate of Talairach, with the software program BRAINS2 (Brain Research: Analysis of Images, Networks and Systems) (Andreasen et al., 1992; Magnotta et al., 2002). For a detailed definition of the borders of the hippocampal formation and of hippocampal subregional analysis please see our previous work (Carballedo et al., 2012). In brief, the most posterior slice of the hippocampal head was the first slice where the uncus apex was clearly present. The coronal plane provided a clear view of this, and the sagittal plane was used to help delineate the superior and anterior boundaries when the uncus recess was no longer present in the coronal plane. The superior boundary separated the hippocampal head from the amygdala. The hippocampal body folds into an S-shaped structure, with the upper portion including the subiculum, ambient cistern, dentate gyrus and fimbria. The white matter of the parahippocampal gyrus was used to separate the subiculum from the entorhinal cortex, with a line connecting the inferior part of the hippocampal body to the quadrigeminal cistern. The most anterior hippocampal body slice was the slice just before the appearance of the uncus. The most anterior slice of the hippocampus tail was the first where the fornix was clearly seen in full profile.

The evaluating and tracing staff (A.O’N.) was blind to participant status. The hippocampus was outlined manually using a mouse-driven cursor using the software program, BRAINS2. The intraclass correlation for inter-rater reliability of both total hippocampus and sub-regions was high (left hippocampus: 0.92, right hippocampus: 0.88, left head: 0.98, right head: 0.88, left body: 0.87, right body: 0.90, left tail: 0.78, right tail: 0.79).

2.3.2. Statistics for hippocampal volumes and demographic data

The Kolmogorov–Smirnov test was used to establish the normal distribution of the data. In the case of the data being normally distributed we used Student’s *t*-test to test for group differences. Levene’s test was used to test for homogeneity of variance. On the basis that the data were normally distributed and their variances were homogenous, a battery of parametric analyses were performed on the morphometric data obtained, for which all statistical analyses were considered to be significant if $p < 0.05$. The hippocampal volumes were subjected to an omnibus analysis of variance (ANOVA) to assess the main and interaction effects of the within-subjects factors of hemisphere (left, right) and of hippocampal subregions (head, body, and tail) and the between-subjects factors of group (BPD, controls) on hippocampal subregions (left and right head, body, and tail). Total brain volume and age were included as covariates in these analyses. For significant interactions post-hoc analyses were carried out to determine the sources of the effects. Non-parametric correlations were run to assess the relationships between the morphometric data and the socio-demographic/psychometric data. We performed the statistical analyses using the SPSS version 16 software package.

2.4. Whole brain voxel based morphometry

2.4.1. VBM8 pre-processing

After manually reorienting and centering the images on the anterior commissure, data were pre-processed using the VBM approach previously shown by Good et al. (2001) implemented in the VBM8 toolbox (<http://dbm.neuro.uni-jena.de>), an extension of the SPM8 software package running under MATLAB 2009a (The MathWorks, Natick, MA). The present study employed the VBM8 toolbox, which utilizes and extends the unified segmentation approach implemented in SPM8 (Ashburner and Friston, 2005). Unified segmentation provides a generative model of VBM preprocessing that integrates tissue classification, image registration and MRI inhomogeneous bias correction. Thus, the model avoids the circularity problem of the optimized VBM procedure, as the initial image registration does not require an initial tissue segmentation or vice versa (Good et al., 2001). The VBM8 toolbox extends the unified segmentation model as it increases the quality of segmentation by applying a Hidden Markov Field (HMMF) model on the segmented tissue maps (Cuadra et al., 2005). The HMMF algorithm provides spatial constraints based on neighboring voxel intensities within a 3 mm×3 mm×3 mm voxel cube. It removes isolated voxels which are unlikely to be a member of a certain tissue class and also closes holes in a cluster of connected voxels of a certain class, resulting in a higher signal-to-noise ratio of the final tissue probability maps. The VBM8 toolbox also offers the option of creating the estimated tissue probability maps without making use of the respective ICBM (International Consortium for Brain Mapping)

tissue priors from SPM. In line with previous VBM research (Frodl et al., 2010), the present study used this option as it showed to improve the delineation of the subcortical structures and sulci in the final tissue maps. The final tissue maps of gray matter (GM) and white matter (Shihabuddin et al., 1998) were modulated with the deformations fields obtained by normalizing to standard space in order to analyze volume differences between study populations. We used the option light cleanup to remove non-brain tissue but still to include the brain stem. Gray and white matter images were imported into DARTEL and non-linear deformations for their optimal alignment were estimated by alternating between the making of a template and registering the tissue class images with the template. Finally, the GM/WM partitions were smoothed with an 8 mm FWHM Gaussian kernel and used for statistical analysis. An analysis of covariance (ANCOVA) was designed in order to investigate focal GM/WM matter volume (GMV and WMV) differences between subject groups using age as a covariate. For all comparisons, volume differences (increases/decreases) were assessed at the whole-brain level using cluster level statistical analyses (cluster level, $p < 0.05$, FWE corrected with a primary threshold of $p < 0.001$). Regions of interest (Tzourio-Mazoyer et al., 2002) were defined in order to test cross-sectional GMV and WMV differences in the hippocampus, the mid-frontal lobes, and the insulae. ROIs were identified using the Wake Forest University PickAtlas Toolbox, Version 3.0.3 (Maldjian et al., 2003). For the priori set ROIs hippocampus, amygdala, orbitofrontal cortex, dorsolateral prefrontal cortex and caudate nucleus, a threshold of $p < 0.001$ (uncorrected) with a spatial extent threshold of 15 contiguous voxels for group interactions was chosen. To further protect against Type I error, a small-volume correction (SVC) was applied at peak-level (cut-off value: 0.05, FWE voxel-corrected). Coordinates of peak significant voxels were assigned to anatomical regions by means of Automated Anatomical Labeling (AAL) (Tzourio-Mazoyer et al., 2002).

2.4.2. Extraction of gray matter volumes from VBM contrasts

In order to compare results derived from manual tracing and VBM the software package MarsBar region of interest toolbox (Brett et al., 2002) was used to extract the cluster of gray matter voxels in the hippocampus of all participants. MARSeille Boite À Région d’Intérêt (MarsBaR) is a toolbox for SPM which provides routines for region of interest analysis. Features include region of interest definition, combination of regions of interest with simple algebra, extraction of data for regions with and without SPM preprocessing (scaling, filtering), and statistical analyses of ROI data using the SPM statistics machinery (reference).

We used the clusters of voxels from the VBM gray matter contrast between patients and healthy controls to define ROIs in the hippocampus, caudate, and middle frontal cortex. Volume equivalents were then extracted from these ROIs and correlated with the volumes in the corresponding ROIs from the manual-tracing method. Non-parametric correlations were computed between extracted volumes and psychometric measures.

3. Results

3.1. Socio-demographic and psychometric data

The results of the independent samples *t*-test analyses showed that the BPD and HC groups did not differ with respect to height, alcohol consumption per week, psychoticism, perseverance, boredom susceptibility, experience seeking, disinhibition, and total sensation seeking. However, significant differences were observed between the groups with regard to weight; cigarette consumption, level of education; HDRS total score; BDI-II; neuroticism; extraversion; thrill seeking; BIS (impulsivity) total; attentional impulsivity (second order factor); motor impulsivity (second order factor); non-planning impulsivity (second order factor); and all the first order impulsivity factors excluding perseverance and including attention, motor, self-control, cognitive complexity, and cognitive instability (Table 1). All BPD were either currently being treated with psychotropic medications or had been treated previously with psychotropic medications, or both. Three of the patients reported suffering from major depression along with their primary diagnosis of BPD.

3.2. Morphometric data

3.2.1. Manual tracing: hippocampal volume (head, body, and tail)

An initial test to compare the total brain volumes of the BPD group and the HC group revealed no significant difference ($t = -1.95$, $d.f. = 39$, $p > 0.05$).

Table 1

List of measures for which there was a significant difference between the BPD and HC groups' scores.

	BPD	Controls	Statistics
Age	32.6±10.1	30.1±8.0	$t = -0.87$, d.f. = 39, $p = 0.39$
Education (years in school)	13.3±2.0	15.3±2.7	$t = 2.1$, d.f. = 39, $p = 0.04$
Height	164.1±6.1	167.1±5.7	$t = 1.6$, d.f. = 39, $p = 0.12$
Weight	70.0±14.6	59.7±8.0	$t = -2.8$, d.f. = 39, $p = 0.008$
HDRS	23.05±10.0	0.4±0.75	$t = 9.95$, d.f. = 18.2; $p < 0.001$
BDI-II	40.21±10.90	4.15±3.54	$t = 14.05$, d.f. = 21.6; $p < 0.001$
BIS total	80.05±6.99	62.40±10.0	$t = 7.88$, d.f. = 37; $p < 0.001$
2nd order attentional	20.47±2.63	14.80±2.55	$t = 6.84$, d.f. = 37; $p < 0.001$
2nd order motor	28±6.08	22.9±3.95	$t = 3.12$, d.f. = 37; $p < 0.005$
2nd order non-planning	31.63±5.37	23.65±3.63	$t = 5.47$, d.f. = 37; $p < 0.001$
1st order attention	12.26±2.45	9.65±1.76	$t = 3.83$, d.f. = 37; $p < 0.001$
1st order motor	19±5.02	15.50±3.28	$t = 2.59$, d.f. = 37; $p < 0.05$
1st order self control	18.11±3.49	12.40±2.96	$t = 5.51$, d.f. = 37; $p < 0.001$
1st order cognitive complexity	13.53±2.59	11.25±2.0	$t = 3.08$, d.f. = 37; $p < 0.005$
1st order cognitive instability	8.21±1.47	5.15±1.63	$t = 6.14$, d.f. = 37; $p < 0.001$
Total brain volume	1294.6±126.5	1366.3±108.6	$t = 1.95$, d.f. = 39, $p = 0.06$

Data expressed as mean±S.D. HDRS=Hamilton Depression Rating Scale; BDI-II=Beck Depression Index; BIS=Barratt Impulsiveness Scale.

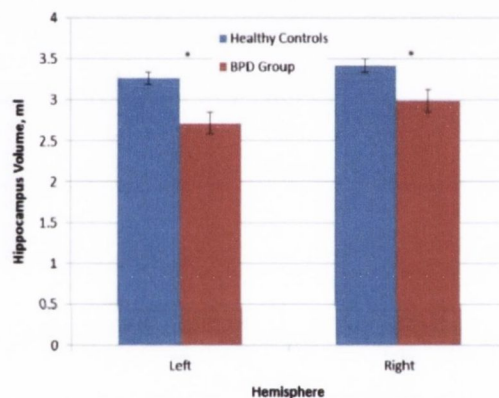


Fig. 1. Significantly smaller left and right hippocampal volumes in the BPD group compared to the HC group. Mean left and right hippocampal volumes for the HC ($n = 21$) and BPD ($n = 20$) groups. Error bars represent the standard deviation. * Indicates a statistically significant difference between BPD and HC mean volumes, $p < 0.05$. Participant type (BPD vs. HC) effect for the left hippocampus was statistically significant ($F = 12.1$; d.f. = 1, 40; $p < 0.05$), as is the effect of participant type for the right hippocampus ($F = 6.4$; d.f. = 1, 40; $p < 0.05$).

The between subjects effect of participant type on hippocampal volumes was found to be significant ($F = 9.0$; d.f. = 1, 37; $p < 0.005$). Post-hoc univariate ANCOVAs showed this effect to be present in both the left and right hippocampi, and examination of the means informed us that the effect resulted in smaller volumes in the BPD group compared to the HC group for both the left and right hippocampi (Fig. 1). Moreover, these smaller volumes in BPD compared to HC were present in all three left hippocampal subregions (i.e. head, body, and tail), whereas in the right hippocampus the between subjects effect of participant type was only significant for the hippocampal tail (Fig. 2).

The ANCOVA found no significance for the within subjects interactive effect of hemisphere and participant type on the hippocampal subregion volumes ($F = 2.8$; d.f. = 1, 37; $p > 0.05$) and there was no significant effect of hemisphere alone on the hippocampal subregion volumes ($F = 0.7$; d.f. = 1, 37; $p > 0.05$). The within subjects interactive effect of factors hippocampal subregion and participant type was found to be insignificant ($F = 0.7$; d.f. = 1, 37; $p > 0.05$). No significant interactive effect was observed for hemisphere and hippocampal subregion ($F = 0.04$; d.f. = 1, 37; $p > 0.05$). No significant interactive effect was observed between

the three factors of hemisphere, hippocampal subregion, and participant type ($F = 0.018$; d.f. = 1, 37; $p > 0.05$).

3.2.2. Voxel-based morphometry: gray matter

Significantly smaller gray matter (GM) volumes were detected in the right DLPFC, right caudate and right hippocampus of the BPD patients compared to the healthy controls (Table 2, Fig. 3). There was no difference between the OFC of the patients and the controls. No GM volume enlargement was detected in BPD patients in any areas. For overview of smaller gray matter volumes corrected for $p < 0.001$ see Table 3.

3.2.3. Voxel based morphometry: white matter

In the analysis of white matter (WM) the left insula was found to be smaller in patients with BPD compared to healthy controls (FWE cluster level corrected across the whole brain, Table 4). WM volumes in other regions like the insula (bilateral), middle frontal cortex, superior and inferior temporal cortex and middle occipital cortex were smaller thresholded with $p < 0.001$ in BPD compared to healthy controls, but did not survive correction for multiple comparisons.

3.2.4. Correlations between the morphometric data and the socio-demographic and psychometric findings

Using Spearman's rho (two-tailed) to test for correlations in the left and right hippocampal volumes in the healthy controls, non-planning impulsivity showed a significant negative correlation with left whole hippocampus ($r = -0.55$; $p < 0.05$) and right hippocampus ($r = -0.45$; $p < 0.05$). In the BPD group no significant associations were detected between hippocampal volumes and attentional impulsivity. Hippocampal volumes were not associated with scores from BDI or HDRS.

The analysis of the size of volumetric differences as extracted from ROIs in the VBM approach revealed the following results: In the BPD group non-planning impulsivity was negatively correlated with right caudate ($r = -0.88$, $p < 0.01$). Among healthy participants attentional impulsivity was negatively correlated with volume differences in right hippocampal tail ($r = -0.54$, $p < 0.055$). None of the three ROI's were associated with BDI or HDRS in both groups. For the Spearman correlations we did not correct for multiple correlations; thus these results need replication.

3.2.5. Correlations between the manual tracing findings and VBM analysis

The volumes derived from manual tracing the right hippocampal tail were significantly correlated with the volumetric differences as

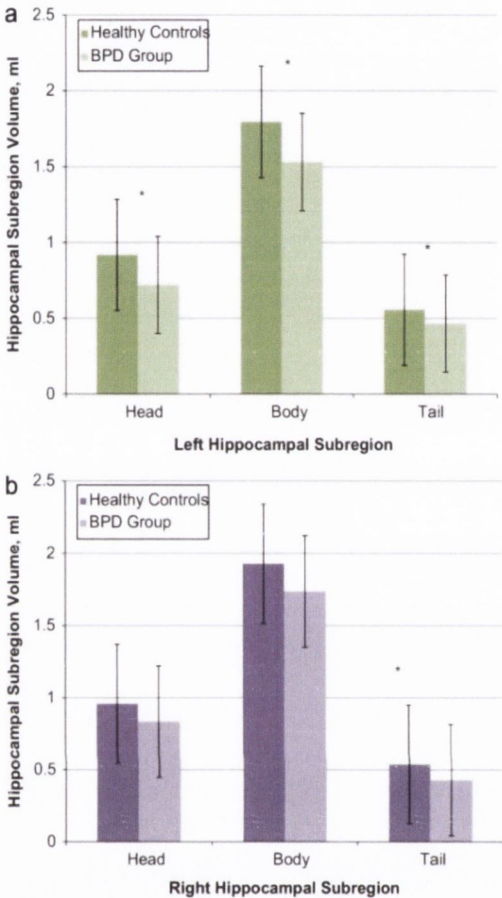


Fig. 2. (a) Significantly smaller left hippocampal head, body, and tail volumes in the BPD group compared to the HC group. Mean left hippocampal head, body, and tail volumes for the HC ($n=23$) and BPD ($n=20$) groups. Error bars represent the SEM. * Indicates a statistically significant difference between BPD and HC mean volumes, $p<0.05$. Effect of the type of participant for the left hippocampal head ($F=8.3$; $d.f.=1, 40$; $p<0.05$), left hippocampal body ($F=4.1$; $d.f.=1, 40$; $p<0.05$), and the left hippocampal tail ($F=5.7$; $d.f.=1, 40$; $p<0.05$) corrected for total brain volume. (b) Significantly smaller right hippocampal head, body, and tail volumes in the BPD group compared to the HC group. Mean right hippocampal head, body, and tail volumes for the HC ($n=23$) and BPD ($n=20$) groups. Error bars represent the SEM. * Indicates a statistically significant difference between BPD and HC mean volumes, $p<0.05$. Effect of the type of participant for the right hippocampal head ($F=2.9$; $d.f.=1, 40$; $p>0.05$), right hippocampal body ($F=1.0$; $d.f.=1, 40$; $p>0.05$), and the right hippocampal tail ($F=13.0$; $d.f.=1, 40$; $p<0.05$) corrected for total brain volume.

assessed by means of VBM gray matter contrasts in the corresponding region of interest (Pearson's $r=0.50$, $p=0.01$, two-tailed).

4. Discussion

The aim of this study was to investigate volumetric abnormalities of the whole hippocampi (left and right) and the hippocampal subregions (head, body, and tail) as well as gray and white matter differences in the caudate nucleus, amygdala, dorsolateral prefrontal cortex and orbitofrontal cortex in patients with borderline personality disorder compared to healthy controls. To achieve this

Table 2
Changes in gray matter in BPD patients compared to healthy controls corrected for brain regions of interest. Participants' age was entered as a covariate. All differences are thresholded at $p<0.05$ cluster-level. Bold type indicates regions for which the difference in gray matter was significant at voxel-level (FWE<0.05, for multiple correction). Regions printed in bold type were significant at both cluster-level and voxel-level (FWE<0.05 for multiple corrections).

K	FWE _{cluster}	ROI	FWE _{voxel}	T	Coordinates [mm]		
					x	y	z
196	0.014	Mid-frontal right (DLPFC right)	0.070	4.13	39	44	21
31	0.020	Caudate right	0.059	3.57	21	6	24
24	0.043	Caudate right	0.049	3.65	17	-9	24
135	0.007	Hippocampus right	0.002	4.93	21	-33	7

we used two different structural MR imaging techniques; manual tracing and voxel based morphometry. As subsidiary analyses we examined the data for correlations between the manual tracing volumes and ratings for impulsivity as well as depression severity gathered from both the patient and healthy control groups.

The initial ANCOVAs for the manually traced data revealed there to be a significant effect due to the participant group on hippocampal volumes. As we expected, further examination found significant reductions in both the left (17%) and right (13%) hippocampal volumes of the BPD participants compared to those of the healthy participants; with greater significance being seen in the left hippocampi. Interestingly, the left hippocampal volume across the whole sample, and within each of the groups, was found to be significantly smaller than the right, with a greater difference between left and right hippocampal volumes being seen in the BPD group compared to the HC group. Further examination of the subregions revealed significantly smaller volumes for the BPD participants compared to the healthy participants in the left hippocampal head (reduced by 22%), body (reduced by 15%), tail (reduced by 16%), and the right hippocampal tail (reduced by 21%). The right hippocampal head and body showed no significant group differences. Voxel based morphometry also showed a difference in the right hippocampus corrected for multiple testing and in the left hippocampus on an uncorrected $p<0.001$ threshold between patients and controls. The manual tracing finding of reductions in the right hippocampal tail was reinforced by a significant correlation found between these volumetric differences and those identified in the corresponding region of interest using VBM.

As we have seen with evaluation of the previous research, reductions in whole hippocampal volumes in BPD patients compared to healthy controls is not an uncommon finding. The magnitude of the reductions we have found is also within the range produced by others such as Tebartz van Elst et al., who found a 20–21% bilateral hippocampal reduction, Driessen et al., who found a 16% bilateral reduction, or Weniger et al., who found an 11% reduction in the hippocampi of patients with BPD but without PTSD (Driessen et al., 2000; van Elst et al., 2003; Weniger et al., 2009). Ruocco et al.'s previously mentioned meta-analysis also identified an average 11% decrease in the size of the hippocampus of patients with BPD compared to healthy controls (Ruocco and Zakzanis KK, 2012). That there was a greater reduction in left hippocampal volume is an interesting finding, in keeping with that of an earlier study by Brambilla et al. (2004), who reported greater decreases in left hippocampal volume, though significant bilateral reductions were also observed. As the majority of the earlier hippocampal studies have not reported any bilateral differences in volume in BPD patients, this would appear to be a plausible explanation

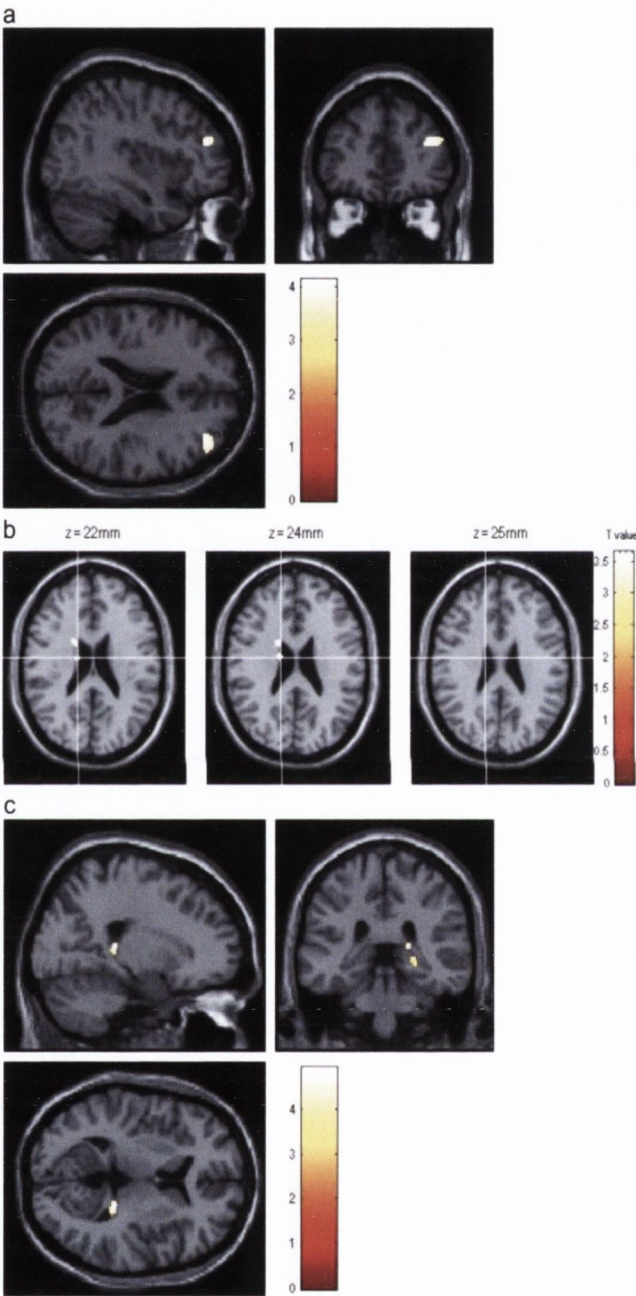


Fig. 3. Reduction of gray matter in patients with BPD compared to healthy controls in (a) right middle frontal cortex at [38 42 21], and (b) right caudate at [17 -9 24] and (c) right hippocampal tail at [21 -33 8]. *P*-threshold was *p*<0.05 cluster level corrected for the region of interest.

(Dell'Osso et al., 2010; Schmahl and Bremner, 2006). However, it is possible still that a greater left than right hippocampal reduction could be a biological feature specific to the disorder, as meta-analyses in PTSD have shown greater reductions in right hippocampal volumes, and MDD results have shown both

bilateral and unilateral reductions (Malykhin et al., 2010; Woon et al., 2010).

The left hippocampus of the healthy group was found to have strong negative correlations with non-planning and self-control impulsivity, whilst the right hippocampus had a moderate

negative correlation with non-planning impulsivity. The BPD group however reflected none of these correlations. These findings were consistent with a study by Zetsche et al. (2007) who found no correlation between whole hippocampal volume and impulsivity in BPD patients and the above mentioned meta-analysis (Ruocco and Zakzanis, 2012). However, a later contradictory BPD study by Schmahl et al. (2009) did find a significant correlation between hippocampal volume and impulsivity. The meaning of the results for our analysis of the socio-demographic and psychometric data is unclear, as the findings were not definitely in keeping with any previous research. This is unfortunate, as confirmed correlations between hippocampal volumes and BPD

traits could be of great benefit to researchers and clinicians alike, potentially providing biomarkers for differentiation from overlapping disorders and differentiation and diagnosis of different subtypes within the disorder.

As discussed earlier, the debate concerning the cause of the hippocampal reductions observed in BPD and other disorders is ongoing, though it is widely believed either to involve a dysregulation of stress-associated neural systems, including the HPA-axis, to be genetically determined, or both. A study found that in healthy participants, there was a strong correlation between the volume of the anterior hippocampus and greater psychological stress at the time of the scan (Szeszko et al., 2006). In the present study patients who had comorbidities other than a diagnosis of MDD were excluded, and though we did not include a diagnosis of MDD as a variable in the major analyses, we did not find any correlations between scores on the HDRS or the BDI-II and any of the hippocampal volumes for the BPD group, suggesting that in this population severity of depressive symptoms was not a significant predictive factor for hippocampal volume.

As a whole, one of the major roles played by the hippocampus is in memory consolidation. Consequently, it has been suggested that volumetric reductions in the hippocampus may result in a range of neurocognitive deficits and other symptoms often seen in BPD (Brambilla et al., 2004). Interpretation of the findings of abnormalities in the hippocampal subregions is more difficult as there is less research from which to draw comparisons. A PTSD study investigating such abnormalities in a sample of Gulf War veterans with the disorder found the veterans to have significantly smaller left, right, and mean hippocampal head volumes compared to healthy civilians (Vythilingam et al., 2005). The performance of the veterans on neuropsychological tests for verbal and visual immediate and delayed memory retrieval was significantly worse than that of the healthy civilians, and a significant positive correlation was seen between immediate verbal and visual memory scores and whole hippocampal head volume (Vythilingam et al., 2005). Anterior hippocampal volumes have also been

Table 3
Changes in gray matter in BPD patients compared to healthy controls corrected for the whole brain. Participants' age was entered as a covariate. All differences are thresholded at $p<0.001$; $k>15$.

Contrast	K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates [mm]		
						x	y	z
Pat>HC	1	24	Sup. parietal left	1	3.61	-38	51	67
Pat<HC	379	0.176	Thalamus right	0.145	5.68	24	-30	70
	248	0.515	Precuneus right	0.986	4.37	15	-42	48
	196	0.728	Mid. frontal right	0.999	4.13	39	44	21
	73	0.999	Hippocampus left	1	4.12	-26	-31	7
	74	0.999	Mid. temporal right	1	4.08	59	-40	7
	40	1	Sup. frontal left	1	4.02	-18	44	30
	130	0.949	Precuneus left	1	3.87	-57	-3	56
	34	1	Precuneus right	1	3.71	54	5	22
	62	1	Calcarine left	1	3.69	-11	-96	-2
	48	1	Caudate right	1	3.65	17	-9	24
	73	0.999	Inf. occipital right	1	3.59	51	-93	-21
	52	1	Caudate right	1	3.57	21	6	24
	31	1	Precuneus left	1	3.54	-6	-84	86
	15	1	Sup. parietal left	1	3.49	-6	-84	52
	19	1	Cerebellum	1	3.46	-5	-100	-27

Table 4
Changes in white matter in BPD patients compared to healthy controls corrected for the whole brain. Participants' age was entered as a covariate. All differences are thresholded at $p<0.001$.

Contrast	K	FWE _{cluster}	Region	FWE _{voxel}	t	Coordinates [mm]		
						x	y	z
Pat>HC	102	0.986	Mid. temporal right	0.793	4.64	47	-67	-2
	34	1	Cerebellum	0.907	3.96	-41	-27	-41
	75	0.998	Sup. temporal pole right	0.938	3.86	68	15	-2
Pat<HC	520	0.056	Lingual left	1	4.75	-36	-91	-17
	461	0.091	Sup. temporal right	1	4.59	50	-39	19
	485	0.074	Mid. occipital left	1	4.52	-41	-88	36
	120	0.964	Mid. frontal right	1	4.11	39	39	30
	30	1	Mid. occipital left	1	4.04	-21	-94	4
	747	0.010	Insula left	1	3.97	-41	-9	25
	200	0.708	Cerebellum	1	3.93	-35	-69	-21
	74	0.999	Angular left	1	3.93	-44	-72	39
	186	0.765	Insula right	1	3.90	33	3	19
	21	1	Cerebellum	1	3.82	39	-63	-23
	49	1	Mid. cingulum right	1	3.80	15	-31	42
	69	0.999	Hippocampus right	1	3.78	33	-22	-9
	22	1	Inf. occipital right	1	3.72	39	-84	-8
	61	1	Sup. frontal left	1	3.70	-18	69	12
	57	1	Mid. orbital frontal left	1	3.62	-44	54	-11
	24	1	Lingual left	1	3.60	-18	-123	-35
	51	1	Mid. frontal left	1	3.58	-24	32	25
	55	1	Calcarine left	1	3.58	-8	-90	7
	37	1	Med. sup. frontal left	1	3.56	-14	57	9
	19	1	Med. sup. frontal right	1	3.54	15	74	6
	50	1	Mid. frontal right	1	3.53	32	26	19
	37	1	Mid. occipital left	1	3.50	-18	-85	-6
	19	1	Sup. temporal right	1	3.42	66	-22	4

positively correlated with prefrontal cortical activation and the region has been shown to be activated during normal encoding of associative memories (Sperling et al., 2003). Thus smaller volumes could underlie functional dysregulation in the region, which in turn could then be responsible for a number of neurocognitive deficits commonly seen in BPD. The overall results of a number of neuropsychological studies in BPD however may shed a different light on the present findings. A meta-analysis involving 10 studies showed significant impairments in both verbal and non-verbal memory amongst a BPD cohort when compared to healthy controls (Ruocco, 2005). Interestingly, a greater deficit was identified in the domain of non-verbal memory than in verbal memory; a finding which the researchers attributed to a potential fronto-temporal dysfunction more strongly lateralised to the right hemisphere (Ruocco, 2005). In light of the present finding of a significant volumetric reduction in the right hippocampal tail, it is possible that there lies an association between this and deficits in non-verbal memory seen in BPD patients. However, further studies examining the relationship between verbal and non-verbal memory and hippocampal subregional volume are necessary to assess this. As discussed earlier, the hippocampal subregions are anatomically and functionally distinct. As such they also have different vulnerabilities, which may be explained by their different structural organization (Malykhin et al., 2010). The hippocampal body includes the greatest proportion of the dentate gyrus (DG), whilst the head and tail contain the greatest proportion of the cornu ammonis (CA) subfields (Malykhin et al., 2010). The DG is thought to play an important role in hippocampal neurogenesis and as a result is highly adaptive; however, stress has been found to suppress this neurogenesis and cause atrophy of the CA subfields in animal studies (McEwen and Magarinos, 2001). Our observations of greater reductions in the left hippocampal head and tail than in the left hippocampal body are consistent with these findings, and imply that chronic stress and over exposure to glucocorticoids, to which CA neurons are particularly sensitive (Malykhin et al., 2010), may play an integral role in the neurobiological underpinnings of BPD. However, in the present study we investigated the subregions not the subfields. DG and CA are both within the hippocampal head and hippocampal body and thus it is difficult to relate the present findings to these subfields. A special protocol with high resolution hippocampal imaging might be a future step in this direction.

Functionally, the DG and CA regions have themselves been associated with a number of specific cognitive operations including recognition (DG), and spatial navigation (associated with both the DG and the CA3 region in animal studies) (Brickman et al., 2011; Lee et al., 2005), disruptions of which may be related to symptoms of dissociation and perceptual distortions often noted in BPD.

A future direction for this research may be to use magnetic resonance spectroscopy to explore changes in the concentrations of neurometabolites in the hippocampus. Neurometabolites such as N-acetylaspartate (tNAA) and creatine (Cr) are thought to be involved in a number of neuronal features such as neuronal integrity and energy dependent functions, and evidence supporting the existence of concentration abnormalities in the amygdala and dorsolateral prefrontal cortex of BPD patients has previously been found (Hoerst et al., 2010; van Elst et al., 2001, 2007). Such abnormalities if identified could be potential precursors to cell death, decreased neurogenesis, and even volumetric reduction seen in the region. However the conclusions drawn from this data have been made tentatively, as further studies looking specifically at hippocampal subregion volumes in BPD are needed to obtain a comparable data set. We can however emphasize the importance of the analysis of the individual hippocampal subregion volumes as it is clear from the insignificance of the reductions in the right

hippocampal head and body that masking of significant effects by the unaffected subregions could occur in the analysis of the hippocampal whole volumes.

The remaining findings of the VBM analysis were not entirely consistent with previous research. Our study found decreases in the GM of the right DLPFC, the right caudate, the right hippocampus and in the WM of the left insular cortex. Indeed the decrease in the DLPFC cortex is consistent with a 2010 study by Brunner et al. (2010); however very few other studies have supported this finding (Brambilla et al., 2004; Rüscher et al., 2003). The possible implications of these findings in relation to fMRI research and negative emotion processing in BPD however are worth noting. One study in particular identified activation in a sample of BPD patients not seen in healthy controls when recalling unresolved negative life events (Beblo et al., 2006). The regions found to display these abnormal activations reflected strongly those with decreases in GM/WM identified here; specifically regions such as the prefrontal brain areas and parts of the insula (Beblo et al., 2006). The DLPFC and the insula are thought to play important roles in affect regulation and anxiety. Thus disturbances in local energy metabolism, which are likely related to GM/WM loss in these areas, may also result in irregularities in the neuronal network for affect regulation in BPD. Interestingly, though we found no difference in the GM of the OFC of the BPD group here, one of the more common findings amongst the structural studies (both manual tracing and VBM) is of reductions in OFC volume (Brunner et al., 2010; Chanen et al., 2008; van Elst et al., 2003).

4.1. Limitations

The mechanisms influencing the relationship between traumatization and BPD still require further clarification, though it is clear that volumetric abnormalities in the hippocampus are features of the psychopathology of both. The lack of data relating to experiences of trauma within our sample groups meant that we could not explore in greater detail the separate roles of traumatization and BPD in the occurrence of hippocampal abnormalities and as a consequence could only make cautious conclusions based on our findings. This also limits the generalizability of our findings. Although this is inconsistent with the findings of studies such as that of Schmahl et al. (2009) which found no hippocampal differences between healthy controls and patients with BPD and without PTSD, it would lend support to the stress-associated theories of reduction. Interestingly, studies in PTSD have found that up to 40% of the variation in hippocampal volume observed within the disorder can be attributed to genetics (Woon et al., 2010), whilst studies of victims of trauma without PTSD have also shown hippocampal reductions (Bremne and Vermetten, 2001), both of which lead Woon et al. (2010) to suggest that it may in fact be the combined influence of a small premorbid hippocampus and the triggering effect of external factors such as exposure to trauma which culminate at the (Bremner and Vermetten, 2001) onset of the disorder. Considering the range of shared characteristics belonging to the two disorders it is very much possible that a similar mechanism could be involved in BPD. Our methodologies may also limit the conclusions drawn from this data as manual tracing does not guarantee abnormality detection due to restrictions in terms of resolution, signal to noise ratio, and image size, amongst other factors, though this is a limit of all volumetric studies (Schmahl et al., 2009). Also in terms of methodology, the use of different protocols regarding hippocampal boundary definition in different studies means that comparisons between studies should be made with caution. With regard to the hippocampal subregion analysis, the lack of similar BPD data made comparisons even more problematic. Other potential causes of heterogeneity amongst our findings and those of other studies include the large

disparity seen between sample sizes; gender differences, of which very little is understood; and the comorbidities and medication of the participant samples. However, it has to be mentioned that volumetric differences were not attenuated in patients being treated with psychotropic medications in a recent meta-analysis (Ruocco and Zakzanis KK, 2012). The findings on correlations between brain structure and symptom rating scales need to be taken with caution. Using correction methods for multiple correlations like bonferroni would result in no significant findings. Thus these results need replication in a larger sample. It has to be stated also that it might have been worthwhile to obtain data about duration of cumulative depressive episodes or of the number of depressive episodes in order to see whether cumulative depression over time might also show negative effects on brain structure in BDP as it was demonstrated for major depressive disorder (Sheline et al., 1999). However, it is not possible to decide retrospectively whether patients with borderline disorder really had clear additional depressive episodes that were not covered by the emotional-instable disorder already and thus these retrospective data have to be kept with caution anyway.

4.2. Conclusion

Our study reaffirms the existence of hippocampal volumetric abnormalities in BPD and adds strength to the theory that such abnormalities are at least partially a result of dysfunctional stress-related neural activity. Overall, the findings of the present study emphasize the need for further studies examining hippocampal subregions and their abnormalities in BPD, and additionally their association with BPD symptoms such as neurocognitive deficits. Furthermore, studies examining the accuracy of the manual tracing versus the voxel based morphometry techniques in BPD research and similar disorders are definitely warranted. Additional studies in these areas would surely advance our understanding of the mechanisms and markers of the disorder, and perhaps those of other trauma related disorders.

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