Exploring Functional Connectivity in Borderline Personality Disorder, Post Traumatic Stress Disorder and Dissociation

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Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Table of Contents

List of Tables

Empirical Paper

List of Figures

Literature Review

Empirical Paper

Appendix

Overview

The overall focus of this thesis relates to resting state functional connectivity (RSFC) of the default mode network (DMN) in borderline personality disorder (BPD), post traumatic stress disorder (PTSD) and dissociative disorders.

Part one of the thesis systematically reviewed 19 studies investigating RSFC of the DMN in PTSD, BPD and dissociative disorders to establish the value of DMN in understanding the three psychopathology. Current research suggests that RSFC of the DMN is distinct when comparing participants with PTSD, participants with PTSD co-morbid with MDD, and healthy controls. In addition, studies also showed that RSFC of the DMN was associated with PTSD severity and trauma experiences. In terms of BPD, findings seem to indicate the presence of aberrant RSFC of the DMN when compared to healthy controls and bipolar disorder. However, in order to interpret these results, it is essential to consider the potential influence of co-morbid MDD. As there was only one research investigating dissociative disorder, it is premature to conclude if RSFC of the DMN is atypical in this disorder. Overall, the reviewed studies seems to indicate that the value of the DMN in understanding psychopathology is strongest in PTSD but lacking in BPD and dissociative disorder. Part one concludes by addressing current limitations and implications for future research.

Part two presents an empirical study investigating RSFC of the DMN in participants with BPD and healthy controls. In order to further elucidate the associations with indices of core symptomatology, self-reports measures pertaining to dissociation, trauma, emotional dysregulation, general clinical symptomatology and personality psychopathology were also administered. The findings suggest that BPD participants display higher RSFC between core brain regions. However, as only

one of the obtained finding remained significant after correcting for multiple comparisons, the results should be interpreted cautiously. Additionally, higher RSFC in BPD participants were also associated with higher self-reported trauma experiences, dissociation and general clinical symptomatology. Similarly, these results did not survive correction for multiple comparisons and hence should be further investigated in future studies. This section concluded by discussing implications of these findings and limitations of the current study.

Part three provided a critical appraisal of the entire research process. Firstly, it considers the implications of the current study, namely the influence on therapeutic approaches, our understanding of BPD, PTSD and dissociation, reflections on the wider issues in neuroimaging studies and in BPD research. This is then followed by a discussion of the challenges and opportunities in research investigating multiple constructs. Lastly, whilst acknowledging the limitations of neuroimaging, the critical appraisal also put forth suggestions aimed at maximizing clinical utility of neuroimaging findings.

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Part One: Systematic Literature Review

Default Mode Network Connectivity in Post Traumatic Stress Disorder, Borderline Personality Disorder and Dissociative Disorders

Abstract

Aims

This systematic literature review highlights research investigating neural connectivity of the default mode network (DMN) in the absence of external tasks and demands across post-traumatic stress disorder (PTSD), borderline personality disorder (BPD) and dissociative disorders.

Method

Relevant databases were searched for studies spanning the past three decades up to 28th December 2014. In order to explore grey literature, PsycEXTRA was also searched. The reference list of relevant articles were also used to identify additional studies. In total, 19 studies were selected for review.

Results

Across the disorders, findings suggest the presence of aberrant neural connectivity for specific DMN regions, including the posterior cingulate cortex, anterior cingulate cortex, prefrontal cortex, insula and cuneus.

Conclusions

The current literature suggests differences in DMN connectivity across PTSD, BPD and dissociative disorders, and when compared to healthy controls. However, it is important for future research to address existing limitations, such as the influence of co-morbidities. To enhance clinical relevance, DMN connectivity and associations with core clinical symptomatology should be further explored.

Introduction

Since the 1970s, there has been an increase in research utilizing neuro-imaging techniques to investigate various aspects of the brain, including anatomy, normal functioning, as well as pathology underlying both physical and mental health disorders. However, in clinical psychology, emphasis and interest in understanding the neuroscience and genetics of mental health disorders only gained prominence in the last two decades. Consequently, clinical psychology is now able to understand mental health disorders not only by considering environmental and social factors, characteristics of the individual including developmental history, appraisal styles and coping strategies, but also in terms of genetics and neural activity. This guiding framework is commonly referred to as the biopsychosocial model (Gilbert, 1995).

Despite the increased use of neuro-imaging in mental health research, there is still limited synthesis of findings in relation to symptomatology and clinical implications. Thus, this review aims to focus on neural connectivity occurring in the absence of external demands within a demarcated brain region, termed the default mode network (DMN). Specifically, the primary aim of this review is to synthesize DMN findings in borderline personality disorder (BPD). However, it is well-established that individuals with BPD commonly present with co-morbidities (Lenzenweger, Lane, Loranger, & Kessler, 2007), including post-traumatic stress disorder (PTSD) (Hooley & Wilson-Murphy, 2012; Korzekwa, Dell, & Pain, 2009; Laporte, Paris, Guttman, & Russell, 2011; Sack, Sachsse, Overkamp, & Dulz, 2013; Schmahl, Vermetten, Elzinga, & Bremner, 2004; Steele & Siever, 2010; Van Dijke, 2012; Venta, Kenkel-Mikelonis, & Sharp, 2012; Vermetten & Spiegel, 2014; Wolke, Schreier, Zanarini, & Winsper, 2012), depression, substance abuse and eating disorders (Gunderson & Links, 2008). Thus, the secondary aim of this review is to

highlight DMN research in psychopathologies commonly associated with BPD. Therefore, a search was conducted to ascertain the prevalence of common co-morbidities in BPD and existence of relevant DMN research.

Consequently, dissociative disorders, post-traumatic stress disorder (PTSD) and major depressive disorder (MDD) were shortlisted. In order to maintain sufficient specificity of findings, it was decided that the 34 MDD studies will be excluded. In addition, apart from prevalent co-morbidities, a search of DMN research in relation to emotional dysregulation reflected a range of disorders and emotions, including bipolarity, anxiety, depression and anger. Therefore, it was decided that this review will exclude studies focusing on MDD and emotional dysregulation, but will nonetheless discuss their implications where relevant.

Aims

Presently, it is still unclear whether DMN connectivity is convergent or divergent across the three disorders and how connectivity is in turn associated with core symptomology. Therefore, this review aims to address the following:

1. Are there differences in DMN connectivity across BPD, dissociative disorders and PTSD, and as compared to healthy controls?
2. How is DMN connectivity associated with core symptomatology?
3. What is the general value of using DMN connectivity to understand psychopathology?

Blood Oxygen Level Dependent Functional Magnetic Resonance Imaging

In recent decades, our understanding of the brain has been largely facilitated by two main technologies. Firstly, electroencephalography (EEG) and magnetoencephalography allows us to directly measure electrical activity arising from neural activity (Lopes da Silva, 2013). Alternatively, physiological or metabolic

changes due to neural activity can be tracked using functional magnetic resonance imaging (fMRI, Logothetis, 2008); the focus of this review. Neural activity facilitates communication between regions of the brain (Van den Heuvel & Hulshoff Pol, 2010), with increased neural activity resulting in incremental consumption of oxygen (Coid, Min, Tyrer, Roberts, & Ullrich, 2006). Thus, the use of blood oxygen level dependent fMRI (BOLD fMRI) allows researchers to extrapolate a proxy measure of neural activity, data which is usually represented by the unit Hertz, Hz (Gusnard & Raichle, 2001).

Three Main Types of Brain Connectivity

Neuro-imaging techniques allows us to study three types of brain connectivity. The first is that of structural connectivity. As communication between brain regions are facilitated by electrical impulses conducted via axons (Toga, 2015), structural connectivity is constrained by the location of axons. In contrast, functional connectivity which is the focus of this review, refers to the interactions between and within established networks/regions in the brain. Therefore, as compared to structural connectivity, these connections are not constrained by anatomy. Functional connectivity is best understood as plausible statistical correlations between brain regions that are active over a specified temporal duration (Toga, 2015). It is important to note that the fundamental distinction between correlation and causation is crucial here. In this case, whilst we can infer that there is increased likelihood of functional connectivity between brain regions displaying temporally synchronous neural activity, we have yet to eliminate any mediating or moderating influence. The question of causality raised by functional connectivity is addressed by effective connectivity, in which both the directionality and causal influences of neural activity is established (Smith, 2012).

Perspectives on Brain Functioning

Before elaborating on the use of fMRI to enhance our understanding of mental health disorders, it is worth highlighting two perspectives on brain functioning. The first can be traced to the early work of Sherrington (1906), who argued that the brain is mainly "reflexive, driven by the momentary demands of the environment" (Raichle, 2009). The contrasting perspective posits that the brain is active even in the absence of external tasks in order to obtain and maintain information required to predict, interpret and respond to environmental demands (Raichle, 2009), an idea first introduced by Brown (1914), but had only attracted research interest in the past two decades.

Some researchers have differentiated these two perspectives as the old and new paradigm respectively (Callard & Margulies, 2011; Raichle, 2010a). The old paradigm underpins traditional task-based fMRI research in which evoked neural activity to external stimuli and tasks is used to study brain functions and behaviour. These elicited neural activity typically occur at frequencies above 1Hz (Callard & Margulies, 2011). Contrastingly, in the new paradigm, fMRI is used to measure the brain's intrinsic neural activity occurring in the absence of external demands. Thus, the best way to distinguish these two perspectives pertains to the source of neural activity. That is, external tasks/demands results in *evoked* neural activity, whilst absence of external tasks/demands produces *intrinsic* neural activity (Raichle & Snyder, 2007). This latter category of temporally synchronous intrinsic neural activity is the focus in this review and is commonly referred to as resting state functional connectivity (RSFC), which occurs within the range of .01 to .1 Hz (Callard & Margulies, 2011; Cordes et al., 2001).

Resting State Networks

The use of fMRI to investigate intrinsic neural activity in the absence of external demands is commonly termed resting state fMRI, rs-fMRI (Beckmann, Deluca, Devlin, & Smith, 2005; Biswal, Zerrin, Haughton, & Hyde, 1995; De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006; Fox et al., 2005; Fransson, 2005; Greicius, Krasnow, Reiss, & Menon, 2003). It is also important to point out that the term 'resting state' is used interchangeably to describe both the behavioural state where participants are awake in the absence of external demands as well as the state of the brain in the absence of task engagement (Raichle et al., 2001).

In 1995, Biswal, Zerrin, Haughton, & Hyde (1995) obtained the pioneer set of RSFC findings within a clearly defined cluster of brain regions consisting of the left and right hemisphere of the primary motor network (Biswal et al., 1995; Biswal, Kylen, & Hyde, 1997). Since then, numerous resting state networks have been found, including the dorsal attention network (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006), the fronto-parietal control network (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008) and visual cortical areas (Beckmann et al., 2005; Cordes et al., 2000).

The Default Mode Network (DMN)

What We Know About the DMN

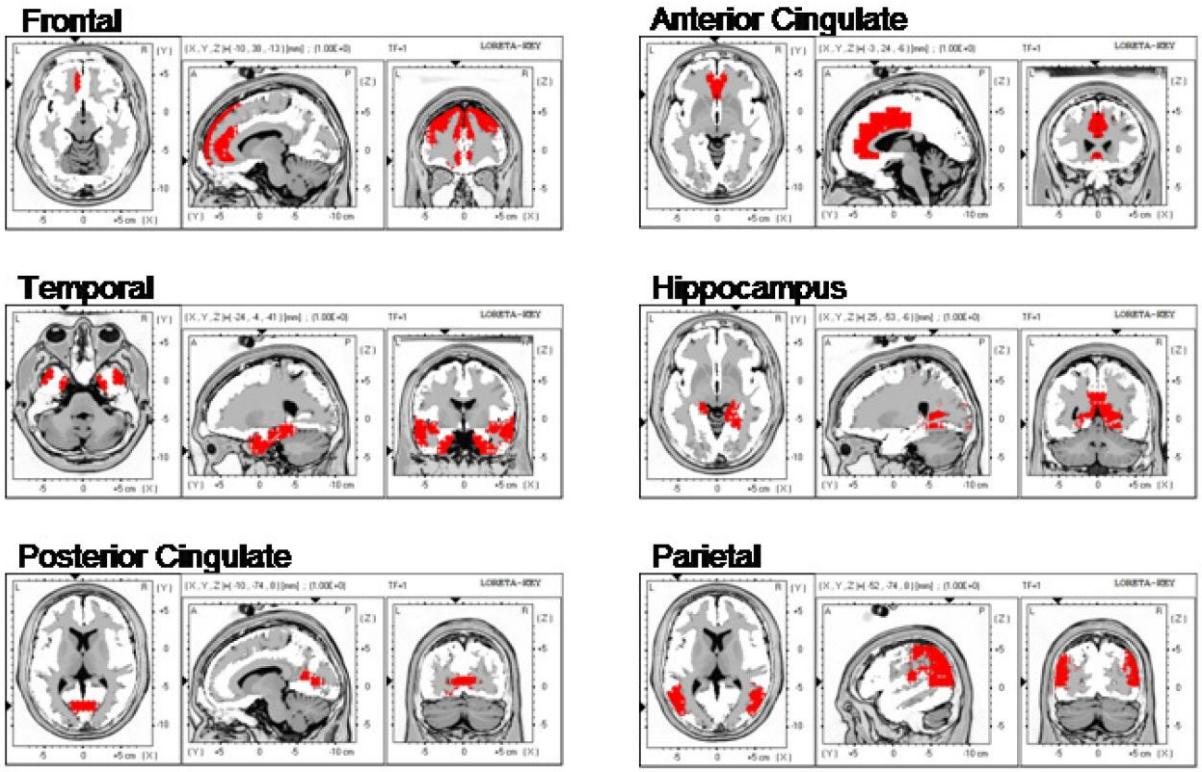
This section provides an overview of research contributing to the field of DMN, starting with the key study that found increased intrinsic neural activity in the absence of external task engagement, wherein the state of the brain is referred to as the "default mode" (Raichle et al., 2001). This is then followed by outlining findings that provided evidence of a clearly demarcated network of brain regions during

default mode, with these brain regions collectively termed the "default mode network" (Raichle et al., 2001).

In a meta-analyses of positron emission tomography studies, Shulman et al. (1997) found that selected brain regions displayed higher connectivity during resting state and that these same regions displayed lower connectivity when participants were engaged in external tasks, findings that were subsequently replicated (Binder et al., 1999; Mazoyer et al., 2001; Whitfield-Gabrieli & Judith, 2012). Using fMRI, Greicius et al. (2003) provided further evidence of increased organized functional connectivity when the participant is at resting state and decreased connectivity during task engagement, thereby supporting the presence of the DMN. Anatomically, the DMN comprises of the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), precuneus, medial temporal lobe (MTL) and inferior parietal cortex (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010a; Buckner, Andrews-Hanna, & Schacter, 2008; Greicius et al., 2003; Gusnard & Raichle, 2001; Shulman et al., 1997), as depicted in Figure 1.

Lastly, across research, three consistent patterns of DMN connectivity emerged: 1. decreased connectivity during external task engagement (Greicius et al., 2003; Gusnard & Raichle, 2001) 2. increased connectivity during the absence of external tasks (Beckmann et al., 2005; Greicius et al., 2003; Raichle et al., 2001) 3. distinct connectivity patterns of the DMN when participants engage in social cognition tasks, an area that will be further elaborated (Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008; Eickhoff et al., 2009). For readers who are interested, Appendix A1 provides an overview of the two main analytic methods used in RSFC research.

Figure 1. Six Key Regions of the DMN depicted using the Key Institute LORETA voxels (Lancaster et al., 2000).



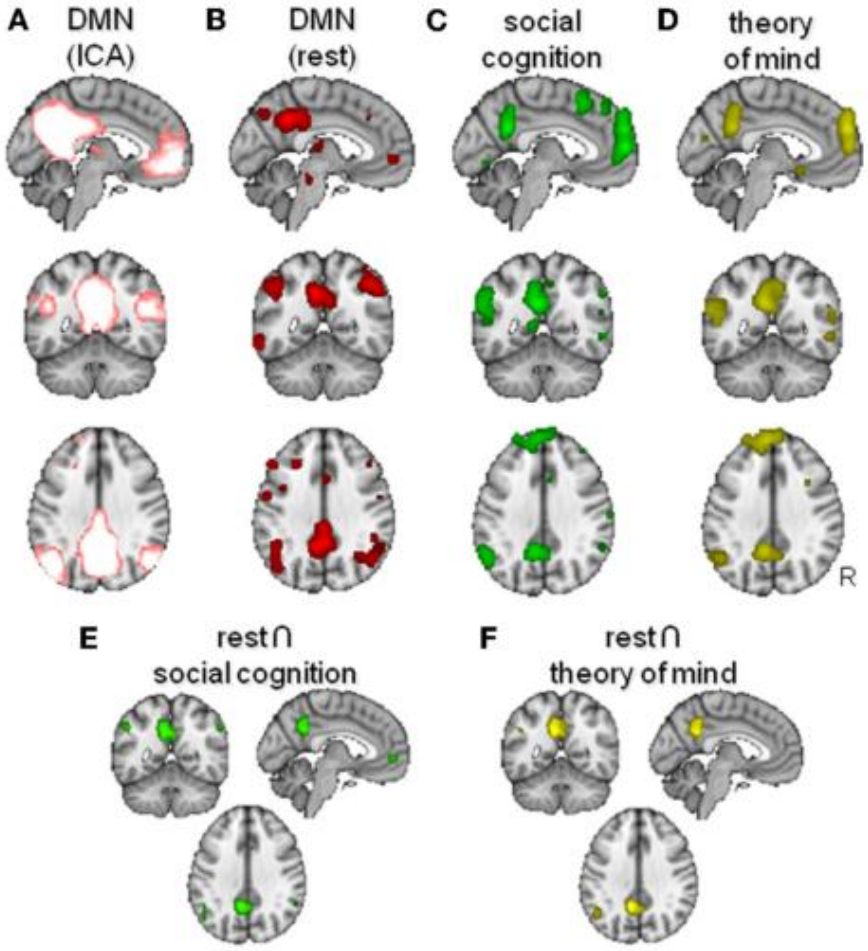
Functions of the DMN

Thus far, this review has focused on the technical and anatomical aspects of the DMN, which raises the question of the functions of the DMN. One hypothesized function is that the DMN obtains and maintains information required to predict, interpret and respond to environmental demands (Gusnard & Raichle, 2007; Raichle et al., 2001; Shulman et al., 1997). This "sentinel hypothesis" posits that the DMN explores and monitors the external environment as well as creates mental simulations of plausible scenarios (Buckner, 2012). This in turn enables our brain to react when required, thereby increasing both efficiency and flexibility of our responses (Gilbert, Dumontheil, Simons, Frith, & Burgess, 2007; Shulman et al., 1997). Consequently, some researchers have argued that the DMN confers an evolutionary advantage, analogous to a surveillance system that ensures rapid responses (Buckner & Vincent, 2007; Raichle et al., 2001).

Apart from the "sentinel hypothesis", the DMN is also hypothesized to have a myriad of functions, including self-generated internal mental activities such as social cognition, which encompass theory of mind (TOM) and mentalization (Li, Mai, & Liu, 2014), retrospective and prospective thinking (Andreasen et al., 1995; Andrews-Hanna et al., 2010a; Craig, 2009; Spreng & Grady, 2010), mind-wandering and spontaneous thoughts, (Andrews-Hanna, Reidler, Huang, & Buckner, 2010b; Binder, et al., 1999; Buckner et al., 2008; Gusnard, Akbudak, Shulman, & Raichle, 2001; Mason et al., 2007) and self-referential processing (Beer, 2007; Frith & Frith, 2010; Greicius et al., 2003; Northoff & Bermpohl, 2004; Raichle et al., 2001; Raichle, 2010a; Raichle, 2010b).

Evidence supporting the role of the DMN in internal mentation stems mainly from self-reports of participants (Andrews-Hanna et al., 2010b; Delamillieure et al., 2010; Flavell, Green, & Flavell, 2000; Gorgolewski et al., 2014; Killingsworth & Gilbert, 2010; Klinger & Cox, 1987) as well as corroborating fMRI data reflecting increased connectivity in DMN regions associated with internal mentation, such as the mPFC and PCC (Qin & Northoff, 2011; Whitfield-Gabrieli et al., 2011). Furthermore, in a meta-analysis by Mars et al. (2012), the overlap between the DMN and brain regions associated with social cognition and TOM was investigated by comparing 1648 DMN rs-fMRI studies, 186 social cognition task-based fMRI studies and 99 TOM tasked-based fMRI studies. Focusing on core DMN regions comprising the mPFC, medial posterior cortex and lateral temporoparietal areas (termed the "social brain network"), the researchers found overlapping patterns of connectivity during resting state and social cognition tasks (Mars et al., 2012), as seen in Figure 2. Overall, these findings provide support for the purported functions of the DMN.

Figure 2. Overlap between the DMN and Areas activated by Social Cognition Paradigms (Mars et al., 2012)



(A) Regions of the DMN as obtained using the model-free analysis method of ICA (Independent Component Analysis). Activation likelihood maps of neural activity during resting state (B) social cognition tasks (C) TOM tasks (D). Conjunction maps depicting overlap between resting state and social cognition (E) and that of resting state and theory of mind (F)

It is worth noting that these functions of the DMN are linked to specific brain regions. For example, the precuneus and PCC are hypothesized to monitor both internal and external environments (Raichle et al., 2001) whilst the mPFC underpins social cognition and mental simulations relevant to oneself (Amodio & Frith, 2006; Buckner et al., 2008; Dutta, Mckie, & Deakin, 2014; 2004; Hagmann et al., 2008; Saxe, Carey, & Kanwisher, 2004).

Lastly, apart from the above mentioned functions, the DMN also interacts with other networks such as the central executive network (CEN), comprising of the dorsolateral PFC (dlPFC) and anterior inferior parietal lobule, and is involved in cognitive processes such as attention and working memory (Menon, 2011). The DMN also interacts with the salience network comprising of the frontoinsular cortex and dorsal ACC. The salience network monitors both internal and external inputs before signals are sent to activate or de-activate either the DMN or CEN (Menon, 2011). As a result of these interactions, aberrant RSFC between these networks has been associated with clinical psychopathology such as schizophrenia and mania (Bressler & Menon, 2010).

In summary, this section presented research findings supporting the existence of not only the concept of the DMN, but, more crucially, the existence of the DMN (for arguments against the DMN, please refer to Appendix A2). This stems from two main lines of evidence. Firstly, corroborating research findings of increased DMN connectivity in the absence of external task engagement (Beckman et al., 2005; Greicius et al., 2003; Raichle et al., 2001) as well as corresponding decreased DMN connectivity in the presence of external task engagement (Greicius et al., 2003; Gusnard & Raichle, 2001). Secondly, in line with the proposed functions, increased DMN connectivity has been linked to internal mentation processes such as social cognition (Li et al., 2014), self-referential processing (Beer, 2007; Frith & Frith, 2010; Greicius et al., 2003; Northoff & Bermpohl, 2004; Raichle et al., 2001; Raichle, 2010a; Raichle, 2010b), retrospective and prospective thinking (Andrews-Hanna et al., 2010a; Craig, 2009; Spreng & Grady, 2010). For further supporting evidence for the DMN, please refer to Appendix A3. Moreover, these functions of the DMN resonates with our personal experiences of how our mind is never idle,

even in the absence of external demands. When we are not externally engaged, we find ourselves either monitoring our environment, having spontaneous thoughts underpinning creativity or performing internal mentation relevant to ourselves and social relationships. This then concludes the technical aspects of the DMN, with the subsequent sections focusing on DMN research across PTSD, BPD and dissociative disorders.

Method

Overall Systematic Literature Search

Relevant articles were obtained by searching the following databases from first publication to 28th December 2014: Cochrane library, PsycINFO, Annual reviews search, CINAHL Plus, Highwire, Jstor, Medline Ovid, Nature, PILOTS, PyscARTICLES, PyscCRITIQUES, PubMed, Science Direct, Scopus, Web of science, Wiley and PsycEXTRA. In addition, reference list of relevant articles were used to identify additional studies. After removal of duplicates, 32 articles were obtained. Two initial exclusion criteria were used to screen the titles and abstracts: 1. studies that were not relevant to the identified psychopathology 2. Studies that did not investigate DMN connectivity. This resulted in 19 articles that was included in this review.

For DMN and related fMRI concepts, search terms were standardized across the three psychopathologies: default mode Network/DMN, default state network, default network, task-negative network/TNN, resting state fMRI, resting state functional connectivity, resting state network and resting-state functional MRI. Specific information pertaining to search terms for each of the three psychopathology is stipulated in the relevant sections.

Quality Critical Appraisal Tool

The QualSyst is used to evaluate either quantitative studies using 14 criteria or qualitative studies using ten criteria (Kmet, Lee, & Cook, 2004); of which the former is applicable in this review. Broadly, the criteria relates to 1. *sufficient description of* objective, subject and comparison group, intervention, random allocation, blinding procedures, controlling for confounds, method, outcomes, estimates of variance and results; 2. *Appropriateness of* study design, sample size, methods of analyses and conclusions (Appendix A4).

As all the reviewed studies are non-experimental, three of the criteria relating to random allocation as well as blinding of both investigators and subjects do not apply and were therefore omitted. Each study was independently scored by two raters on the 11 relevant items, either not meeting criteria (score of 0), partially meeting criteria (score of 1), completely meeting criteria (score of 2) or not applicable, yielding a maximum score of 22.

Outcomes from Quality Critical Appraisal

The studies in this review had total scores in the range of 19 to 22 (Appendix A5). Overall, the studies were of high quality, with all included papers possessing appropriate study design and analytical methods as well as providing sufficient description of the research question, method and results. However, the omission of information pertaining to co-morbidities lowered the scores in five studies (Bluhm et al., 2009; Das, Calhoun, & Malhi, 2014; O'Neill et al., 2014; Qin et al., 2012; Schlumpf et al., 2014). In addition, the study by Qin et al. (2012) and Bluhm et al. (2009) put forth conclusions only partially supported by the results and the study by Schlumpf et al. (2014) did not provide explanations for the excluded co-morbidities. Lastly, small sample size of less than 15 participants per group was a limitation in six

studies (Das et al., 2014; Doll et al., 2013; Krause-Utz et al., 2014; Lanius et al., 2010; Philip et al., 2013a; Philip et al., 2013b).

Post Traumatic Stress Disorder (PTSD)

Apart from criteria relevant to stressor, duration and functional impairments, DSM-5 stipulates that a diagnosis of PTSD warrants symptoms related to re-experiencing, avoidance, negative changes in thoughts and mood, increased arousal and reactivity as well as specification of the presence of dissociative symptoms (American Psychiatric Association, 2013[APA]; Appendix A6).

Systematic Literature Search

Standardized search terms for DMN and related fMRI concepts were combined with the following search terms: PTSD, post-traumatic stress disorder, trauma and early trauma. This yielded a total of 18 articles. After excluding studies that did not investigate RSFC of the DMN in PTSD, 12 articles were found to be relevant. Appendix A7 provides a summary of key findings.

DMN Research in PTSD: Community Samples

The first study investigating RSFC of the DMN in relation to PTSD made use of seed-based analysis. Bluhm et al. (2009) found reduced RSFC between the PCC, precuneus and mPFC in 17 females diagnosed with PTSD due to childhood abuse as compared to 15 female healthy controls. However, an inconsistency in this study limited the interpretation of the findings. Specifically, in the method section, the researchers stated that clinical participants were excluded if they had any past or current mental health disorders apart from PTSD; however in the result section, MDD and panic disorder were listed as the most prevalent co-morbidity (Bluhm et al., 2009). In conclusion, even though this was the first research investigating RSFC

of the DMN in PTSD, the lack of clarity precludes attributing these RSFC findings to PTSD rather than co-morbidities.

In another study, Qin et al. (2012) were interested to determine if RSFC is altered post-accident. In total, 62 participants completed a rs-fMRI scan within two days after the accident. At the end of six months, 22 participants were diagnosed with PTSD. From the total sample, 19 age and gender matched trauma exposed controls were selected. Even though all participants were scanned, RSFC findings were only obtained for 17 out of the 19 PTSD participants (five females and 12 males) and 15 out of the 19 controls (three females and 12 males). The researchers did not explain omission of the four scans. Participants with PTSD were found to display lower RSFC in the right lingual and right middle temporal gyrus (Qin et al., 2012). Interestingly, negative correlation between the scores on the clinician administered PTSD scale (CAPS) and RSFC of the mPFC was explained by co-morbidities including depression even though all participants were assessed using the Mini-International Neuropsychiatric Interview in order to exclude participants with any current or past mental health disorders. Therefore, as detailed in the quality critical appraisal, this study omitted pertinent information about the sample and put forth conclusions only partially supported by the results. More importantly, these results by Qin et al. (2012) directly contradicts findings by Lanius et al. (2010) presented in the section 'RSFC of the DMN and PTSD Severity'. Lastly, scanning within two days after an accident elicits an intriguing but unanswered question about the basis of obtained DMN findings: are the purported differences due to acute symptoms or vulnerability factors associated with PTSD development?

DMN Research in PTSD: Samples Including Military Veterans

The first of the five reviewed studies involving military veterans is an all–male study where 15 military veterans with PTSD and 15 military veterans without PTSD were compared with 15 civilians (Sripada et al., 2012). Using seed-based analysis, the researchers found that veterans with PTSD had reduced RSFC in the rostral ACC and ventral medial PFC (vmPFC). This is consistent with findings from the first community-based study by Bluhm et al. (2009). In a different study, Kennis, Rademaker, Van Rooij, Kahn, & Geuze (2014) also conducted an all-male study using the same three categories of participants: 37 military veterans with PTSD, 27 military veterans without PTSD and 26 civilians. With the use of seed-based analysis, they found that veterans with and without PTSD displayed lower RSFC between the caudal ACC and the precentral gyrus, and between the perigenual ACC, superior medial gyrus and middle temporal gyrus (Kennis et al., 2014). However, in order to make sense of these findings, it is important to note that 20 of the veterans with PTSD had existing co-morbidities, ten of whom with MDD and six with both MDD and anxiety. In view of numerous publications supporting the presence of atypical RSFC in MDD (Buchanan, Wang, & Gollan, 2014; Dichter, Gibbs, & Smoski, 2015; Dutta et al., 2014; Sambataro, Wolf, Pennuto, Vasic, & Wolf, 2014; Zhu, et al., 2012), these findings should be interpreted cautiously. Directly related to this conundrum, a separate study by Kennis, Rademaker, Van Rooij, Kahn, & Geuze (2013) discussed at the end of this section sought to address this issue.

The third all-male study included 20 military veterans with PTSD and 22 trauma exposed veterans with no PTSD diagnosis (Brown et al., 2013). Apart from MDD, all other mental health disorders were excluded. Of the 20 military veterans with PTSD, nine had co-morbid MDD. Using seed-based analysis, the researchers

were interested in the RSFC between the amygdala and the DMN. They found that veterans with PTSD had higher RSFC between the amygdala and the pregenual ACC, dmPFC and dorsal ACC, as compared to the trauma exposed veterans (Brown et al., 2013). Whilst interpreting these findings, it is vital to consider two methodological and clinical issues. Firstly, as discussed, there is a need to address the influence of MDD when interpreting RSFC findings (Buchanan et al., 2014; Dichter et al., 2015; Dutta et al., 2014; Sambataro et al., 2014; Zhu, et al., 2012). Secondly, apart from stating that the CAPS was used, there was no further information regarding what constitutes "trauma exposed" in the matched control. Thus, there are unclarified questions regarding the nature of exposed trauma, the cut off scores for symptom severity and the duration of symptom presentation. Apart from this study, Rabinak et al. (2011) investigated RSFC between the amygdala and the insula using a sample of 17 veterans with PTSD and 17 combat exposed veterans without PTSD. Using seed-based analysis, the researchers found higher RSFC between the amygdala and insula for veterans with PTSD, which was tentatively linked to hypervigilance and hyper arousal in PTSD (Etkin, 2009; Rabinak et al., 2011). Similar to the rest of the above-mentioned studies, slightly more than half of the veterans with PTSD in this study had either current or pre-existing co-morbidity, mainly MDD or alcohol abuse (Rabinak et al., 2011).

When reviewing the RSFC research in veterans with PTSD (Brown et al., 2013; Kennis et al., 2014; Rabinak et al., 2011) and an accepted manuscript in the BPD section (O'Neill et al., 2014), specificity of DMN findings is questionable in view of the high prevalence of co-morbid MDD. This was addressed in an all-male military veteran study by Kennis et al. (2013) which investigated RSFC between the ACC and insula in 27 veterans with PTSD and MDD, compared with 23 veterans

with PTSD but not MDD. Based on results obtained from seed-based analysis, veterans with both PTSD and MDD displayed increased RSFC between the ACC and insula as well as decreased RSFC between the ACC and thalamus. These findings by Kennis et al. (2013) is interesting when compared to Sripada et al. (2012) and a previously mentioned paper by Kennis et al. (2014). Namely, veterans with only PTSD displayed reduced RSFC in the ACC (Kennis et al., 2014; Sripada et al., 2012) compared to increased RSFC in the ACC for veterans with both PTSD and MDD (Kennis et al., 2013). Based on this, Kennis et al. (2013) hypothesized that the ACC could be a potential biological marker for MDD in PTSD.

In the past five years, the rapid increase of DMN research in MDD warrants a brief discussion in order to address the potential influence of co-morbid MDD on RSFC findings. In MDD, increased RSFC has been found in the mPFC (Davey, Harrison, Yücel, & Allen, 2012; Dutta et al., 2014; Kerestes, Davey, Stephanou, Whittle, & Harrison, 2014; Zhu et al., 2012), ACC (Davey et al., 2012; Dutta et al., 2014; Kerestes et al., 2014; Zhu et al., 2012) , PCC (Dutta et al., 2014), and between the ACC and PCC (Berman, et al., 2011; Dutta et al., 2014; Greicius et al., 2007). Overall, replicated findings of increased RSFC of the ACC in MDD is the most significant as this directly contrasts with decreased RSFC of the ACC in PTSD. Further corroborating evidence of reduced RSFC of the ACC in PTSD is drawn from a study by Krause-Utz et al. (2014) discussed in the BPD section where participants with BPD and trauma were also found to display reduced RSFC of the ACC.

In summary, despite different regions of interest (ROIs), two main sets of findings arose from the five studies investigating DMN connectivity in veterans with PTSD. Firstly, both Sripada et al. (2012) and Kennis et al. (2014) found reduced RSFC in the ACC whilst Kennis et al. (2013) found increased RSFC of the ACC in

veterans with both PTSD and MDD. Secondly, both Brown et al. (2013) and Rabinak et al. (2011) found increased RSFC between the amygdala and specific regions of the DMN. Taken together, these findings suggests the presence of aberrant RSFC within the DMN as well as between the DMN and selected brain regions. Whilst this is the case, it is important to acknowledge the presence of confounds and methodological issues that might limit generalizability and interpretability of these findings.

RSFC of the DMN and PTSD Severity

Thus far, the seven reviewed PTSD articles focused on investigating differences in RSFC of the DMN between individuals with PTSD and healthy controls. This section will consider studies that investigated the relationship between RSFC of the DMN and severity of PTSD. In a study by Lanius et al. (2010), the strength of RSFC between PCC, precuneus and amygdala predicted severity of PTSD as measured by the CAPS 12 weeks post-accident in 11 participants, a sample comprising of six females and five males. Exclusion criteria included mental health disorders and the use of psychotropic medications within a stipulated timeframe.

In another rs-fMRI study, 40 male and 81 female survivors of an earthquake were assessed using the PTSD checklist and completed the non-clinician version of the PTSD checklist, within 15 months of an earthquake (Gong et al., 2013). Participants were excluded if they had a history of mental health disorders, drug abuse or alcohol abuse. Of the 121 participants, 65 were diagnosed with PTSD at the time of the assessment. However, Gong et al. (2013) chose to investigate the RSFC of the whole brain rather than simply focusing on the DMN. They concluded that a network of brain regions including the left superior parietal lobule, right angular gyrus, right superior and middle occipital gyri, right cerebellum and the right uncus predicted PTSD severity.

Even though these two studies were interested in the relationship between RSFC of the DMN and PTSD severity, the use of different ROIs unfortunately limits direct comparison. Nonetheless, results from these two studies alongside other reviewed studies seems to suggest that specific regions of the DMN might be associated with PTSD symptomatology. If this is the case, it will be crucial to conduct further research as well as consider clinical implications.

Impact of Abuse and Maltreatment on RSFC of the DMN

Thus far, all the studies reviewed here focused on DMN findings in PTSD. However, an interesting question regarding the directionality of aberrant RSFC was investigated in three studies. Instead of PTSD, the links between abuse, maltreatment and RSFC of the DMN were explored by including participants who had experienced abuse and maltreatment but not diagnosed with PTSD.

In an all-female study, eight participants without mental health disorders but had experienced early life stress (ELS) were compared with four participants without experiences of ELS (Philip et al., 2013b). ELS was defined to include physical, sexual and emotional abuse experienced in childhood. Individuals with ELS were found to display reduced RSFC between the PCC, mPFC and inferior temporal cortex (Philip et al., 2013b) which led the researchers to postulate that aberrant RSFC was associated with ELS rather than co-morbidities and medication. In the second study, Philip et al. (2013a) investigated RSFC of the DMN in 14 individuals who had experienced ELS (seven males and seven females) as compared to 13 controls (four males and nine females). Overall, reduced RSFC within the DMN was found in participants who had experienced ELS, specifically, reduced RSFC between the inferior parietal lobule and right precuneus, PCC, left fusiform gyrus, cerebellum and caudate (Philip et al., 2013a).

Moving away from ELS, one study investigated the impact of emotional maltreatment on RSFC of selected regions (Van Der Werff et al., 2013). In this study, emotional maltreatment was assessed using the Netherlands Mental Health Survey and Incidence Study trauma interview (De Graaf, Bijl, Smit, Vollebergh, & Spijker, 2002; Robins et al., 1988), comprising of questions related to emotional neglect and abuse, physical abuse and sexual abuse before the age of 16. From the initial total of 301 participants, 22 male and 22 female participants who had only experienced emotional maltreatment were selected. The researchers then identified 44 controls matched for gender (20 males and 24 females), age and handedness. Participants who had experienced emotional maltreatment were found to display lower RSFC between the amygdala and the following regions: precuneus, insula and putamen. In addition, reduced RSFC was also found between the ACC and precuneus, mPFC and the frontal pole (Van Der Werff et al., 2013). Overall, across the three studies investigating RSFC in healthy controls with childhood experiences of abuse and maltreatment but not PTSD (Philip et al., 2013a; Philip et al., 2013b; Van Der Werff et al., 2013), all found reduced RSFC within core regions of the DMN. This is similar to the first study mentioned in this section by Bluhm et al. (2009) where reduced RSFC was found in individuals diagnosed with PTSD as a result of childhood abuse.

In summary, this section sought to review DMN findings in PTSD by focusing on community-based participants, military veterans and participants who had experienced childhood abuse but not diagnosed with PTSD. In addition, three studies investigated the utility of RSFC to predict PTSD symptoms. Even though the presence of methodological issues and lack of common ROIs limits synthesis of these findings, current findings provide preliminary evidence of the involvement of

the DMN in PTSD, reinforcing the position that there is functional value of using the DMN to explore PTSD. However, in order to enhance our understanding, future research should address current limitations and emphasize relationship between neural abnormalities and clinical symptomatology.

Borderline Personality Disorder (BPD)

BPD is characterized by a pervasive pattern of unstable interpersonal relationships, self-image, affect, and marked impulsivity that begins by early adulthood (APA, 2013) Appendix A8 lists the diagnostic criteria for BPD. In the UK, the weighted prevalence of BPD is approximately 4.4% (Coid et al., 2006).

Systematic Literature Search

Standardized search terms for DMN and related fMRI concepts were combined with the following: borderline personality disorder, BPD, borderline PD and emotionally unstable personality disorder. This yielded a total of 12 articles. After excluding studies that did not address DMN findings in BPD, six articles remained.

DMN Research in BPD

Here, the focus is to discuss and synthesize key RSFC findings in BPD (summarized in Appendix A9) and to consider outstanding gaps in our understanding. The first study investigating RSFC in BPD compared 17 participants with BPD with 17 female healthy controls using ICA (Wolf et al., 2011). All the clinical participants were medicated females without co-morbid schizophrenia, bipolar disorder, PTSD, drug and alcohol abuse six months prior to their participation and active suicidal ideation. From a clinical perspective, the exclusion criteria might suggest that these BPD participants had less severe BPD symptomology. However, comparison of scores on the short form Borderline Symptom Checklist with another reviewed study by Doll et al. (2013) suggest that

there were no significant differences in BPD symptomatology. The average scores obtained were 57.6 for Wolf et al. (2011) and 51 for Doll et al. (2013). In this study, the researchers found that participants with BPD displayed increased RSFC in the left frontopolar cortex (FPC) and the left insula as well as decreased RSFC in the left cuneus (Wolf et al., 2011). Increased RSFC of the FPC was also associated with increased impulsivity. In addition, increased dissociative tendencies was related to increased RSFC of the insula and decreased RSFC of the cuneus. Furthermore, BPD participants were found to display lower RSFC in the lateral frontoparietal networks (part of the CEN) and medial-frontal networks. Taken together, Wolf et al's (2011) study provided preliminary evidence for differences in RSFC of the DMN between BPD participants and healthy controls. Additionally, these aberrant RSFC was in turn associated with indices of impulsivity and dissociation. However, when interpreting these results, it is important to consider the replicability and generalizability of the findings. Specifically, the applicability of these findings to males with BPD and the influence of co-morbidities such as PTSD warrants further investigation. Despite these limitations, the study by Wolf et al. (2011) raises the interesting question regarding the utility of RSCF of the DMN to investigate the presence of neurobiological abnormalities in BPD.

In another study, 20 un-medicated females with BPD and a history of trauma (nine of whom had co-morbid PTSD) were compared with 17 female healthy controls using seed-based analysis (Krause-Utz et al., 2014). Specifically, the researchers were interested in RSFC of the bilateral amygdalae, salience network (dorsal and ventral ACC) and the ventral ACC of the DMN. In terms of findings that have a bearing on this review, they found that individuals with BPD displayed reduced RSFC between key regions of the salience network and the DMN, which

was hypothesized to be associated with increased vigilance to non-relevant stimuli and inflexibility of attention observed in BPD (Kluetsch et al., 2012; Krause-Utz et al., 2014; Li & Bohus, 2013). Interestingly, increased RSFC of the insula related to increased dissociation obtained by Wolf et al. (2011) was not replicated. Instead, Krause-Utz et al. (2014) found that RSFC of the amygdala and PFC was positively correlated with dissociation, and argued that since these results were obtained for both BPD only and BPD co-morbid with PTSD participants, this supports the specificity of aberrant RSFC in BPD. In order to further discern the influence of PTSD on RSFC, Krause-Utz et al. (2014) performed separate statistical analyses on BPD participants with and without PTSD. Even though there were significant difference between BPD participants and healthy controls, no significant differences were found between BPD only and BPD-PTSD sub-group (Krause-Utz et al., 2014). As all the BPD patients in this study had existing trauma history, the researchers also factored in the possible influence of trauma when trying to account for increased RSFC between the amygdala, putamen and insula. In order to reconcile these findings with those presented in the preceding PTSD section, it is useful to compare findings with that of Van Der Werff et al. (2013), who included similar ROIs and participants who had experienced early trauma but not diagnosed with PTSD. As compared to Krause-Utz et al. (2014), Van Der Werff et al. (2013) obtained decreased RSFC between the amygdala, putamen and insula. Based on these contrasting findings, Krause-Utz et al. (2014) argued that RSFC obtained in BPD can be distinguished from that observed only in the presence of trauma experiences. Overall, these findings seem to suggest distinct RSFC across BPD, PTSD and trauma experiences.

In a different study, Doll et al. (2013) investigated the RSFC between the salience network, CEN and the DMN as well as intra RSFC of these three networks using ICA. Briefly, the CEN is involved in cognitive processes such as attention and working memory whilst the salience network monitors both internal and external inputs before signals are sent to activate or de-activate either the DMN or CEN (Menon, 2011). There were only two male participants in this study, one in the BPD group and one in the control group. BPD participants were only excluded if they have co-morbid psychosis or bipolar disorder. In the 14 individuals with BPD, Doll et al. (2013) found that similar to Wolf et al. 2011, higher RSFC was found in the PFC and insula. In addition, BPD participants displayed lower RSFC between the CEN and the other two networks, but higher RSFC of the salience network in relation to interactions with CEN and DMN as compared to the 16 healthy controls. The researchers hypothesized that lower inter-CEN RSFC is plausibly related to lower cognitive control and higher emotional processing in BPD. In terms of what we know about BPD, this hypothesis possess good ecological validity. That said, findings of aberrant inter-RSFC between the three networks have also been observed in other disorders such as schizophrenia (Palaniyappan & Liddle, 2012) and depression (Hamilton et al., 2011). Therefore, in order to enhance our understanding, it is imperative not to merely focus on obtained findings, but to consider underlying mechanisms and conduct replication studies.

Based on findings from an accepted manuscript, RSFC between the precuneus and selected brain regions was investigated using seed-based analysis in 19 healthy females and 17 females with BPD (O'Neill et al., 2014). Stated exclusion criteria for both groups included neurological disorder, severe medical illness, head injury, and alcohol or substance dependency whilst MDD was the only co-morbidity

allowed for participants with BPD. Increased RSFC between the precuneus and left inferior frontal gyrus, left precentral/middle frontal, and left middle occipital/superior parietal lobes were found in individuals with BPD, leading O'Neill et al. (2014) to conclude that their findings were consistent with Wolf et al. (2011). However as previously discussed in the PTSD section, in order to make sense of findings by O'Neill et al., (2014), the influence of MDD on the DMN should be considered.

In clinical settings, it is not unusual to hear of misdiagnoses between BPD and bipolar disorder as well as the high prevalence of co-morbidities (Garno, Goldberg, Ramirez, & Ritzler, 2005; Paris, Gunderson, & Weinberg, 2007). However, to date, only one all-female rs-fMRI study investigated RSFC in BPD and bipolar disorder using ICA. 14 participants with BPD, 16 participants with euthymic bipolar disorder and 13 healthy controls completed rs-fMRI as well as self-report measures of emotional dysregulation and impulsivity (Das et al., 2014). Participants with bipolar disorder were not only found to display higher RSFC between the DMN and precuneus as compared to participants with BPD and healthy controls, higher RSFC was also associated with increased emotional awareness. Consequently, the researchers hypothesized that RSFC between the DMN and precuneus network might provide preliminary discriminatory neuro-imaging evidence between bipolar disorder and BPD. Interestingly, even though atypical RSFC in brain regions involved in self-referential processing were observed for both disorders, there were crucial differentiations. In BPD, aberrant RSFC was found within the precuneus, an area relevant for thinking about oneself in context as informed by autobiographical memory. Contrastingly, in bipolar disorder, atypical RSFC was associated with the vmPFC, an area linked to processing of information relating to oneself. Moreover, for participants with BPD, apart from impairments in self-referential processing,

additional aberrant RSFC was also found in brain regions regulating emotions, which was in turn linked to decreased clarity and awareness of emotions. For the BPD group, RSFC was also linked to increased impulsivity. Despite the small sample size and lack of information regarding co-morbid disorders, this study by Das et al. (2014) seems to suggest that as compared to participants with bipolar disorder, observed RSFC in BPD is related to greater impairments in the domain of emotional regulation and impulsivity.

Moving away from DMN findings centred on self-referential processing, the last study in this section investigated pain sensitivity and RSFC of the DMN, where pain was induced using heat (Kluetsch et al., 2012). Exclusion criteria for BPD participants included co-morbidities of current MDD, alcohol/substance abuse or dependence in the last six months, bipolar disorder, schizophrenia, and pain disorder. As compared to the 22 female healthy controls, 25 females with BPD were observed to display lower RSFC between the left retrosplenial cortex, right inferior temporal, left superior frontal gyrus and that of the DMN in the absence of pain stimuli (Kluetsch et al., 2012). When pain was induced, individuals with BPD were observed to display lower RSFC between the PCC and PFC. In addition, increased dissociative tendencies obtained from self-report measures were associated with reduced RSFC of the DMN. In summary, these neuro-imaging findings parallels clinical symptomatology of lower modulation of pain and emotions as well as increased dissociative tendencies in BPD (Kluetsch et al., 2012).

In order to synthesize DMN findings within BPD, it is important to firstly consider participant-related variables that have an impact on DMN findings. This includes gender (Filippi et al., 2013; Tian, Wang, Yan, & He, 2011), co-morbidities and use of medication (Schleim & Roiser, 2009). For example, all but one of the

reviewed studies included only female participants, citing rationale of higher prevalence of BPD in females and attempts to control the influence of gender on obtained fMRI findings. Across the six studies, there was also variability of included/excluded co-morbidities which in turn has an impact on the generalizability of findings as well as our confidence that these findings are related to BPD rather than attributable to these co-morbidities. A related observation is that only two of the studies included screening of other PDs (Doll et al., 2013; Kluetsch et al., 2012). However, even then, the study by Doll et al. (2013) did not specify the co-morbid PD, except that the participant has "multiple personality disorders". Kluetsch et al. (2012) on the other hand provided a breakdown of co-morbid PDs: five Avoidant PD, one Histrionic PD, one Narcissistic PD and one Dependent PD, but no further analyses were conducted. Across the six BPD studies, small sample size further limits the generalizability of the findings. Furthermore, none of the studies reported considerations of power and sample size calculation. Despite these limitations, it is imperative to bear in mind that DMN research in BPD is still a very new field, with publications dating back only to the past four years. Lastly, it should be emphasized that overall, these studies were still of good quality.

The use of rs-fMRI allows researchers to investigate RSFC of any brain regions, with the expectation that selection is informed by relevant theory and research. When reviewing the six studies, it is apparent that most of the selected DMN regions are core regions commonly associated with social cognition. That said, within the DMN, researchers are still required to select between cortices, lobes and gyrus which consequently resulted in numerous permutations of both over-lapping and distinct ROIs across studies. Bearing this in mind, across the six BPD studies, replicated findings of increased intra RSFC was found in both the PFC and insula

(Doll et al., 2013; Wolf et al., 2011) whilst decreased inter RSFC was observed between the DMN, CEN and salience network (Doll et al., 2013; Krause-Utz et al., 2014; Wolf et al., 2011). In addition, four RSFC patterns in BPD participants were attained: decreased intra RSFC in the cuneus (Wolf et al., 2011), lower RSFC between the precuneus and DMN in BPD participants as compared to individuals with bipolar disorder (Das et al., 2014), increased inter RSFC between precuneus, frontal cortex and parietal cortex (O'Neill et al., 2014) as well as decreased inter RSFC between the left retrosplenial cortex, frontal cortex and temporal lobe (Kluetsch et al., 2012). Crucially, corroborating evidence from task-based fMRI studies should also be considered. For example, focusing on the same regions identified in Wolf et al. (2011), task-based fMRI research found increased left FPC activation in BPD patients performing emotion-inducing tasks (Ruocco, Medaglia, Ayaz, & Chute, 2010) and increased activation was also positively correlated with measures of impulsivity in BPD (Goethals et al., 2005; Juengling et al., 2003; New et al., 2007). Using task-based fMRI studies, the insula which is involved in dissociation, pain processing and emotional regulation has also been found to display increased activation in BPD (Apkarian, Bushnell, Treede, & Zubieta, 2005; Krause-Utz et al., 2012; Lanius et al., 2005; Ludäscher et al., 2010; Napadow et al., 2010; Niedtfeld et al., 2010; Ploghaus et al., 1999; Schulze et al., 2011). Thus, convergent findings within specific DMN regions have been found in both task based fMRI and rs-fMRI, which might indicate preliminary support for the utility of the DMN in understanding BPD. Overall, DMN research in BPD is still a new area and, based on the studies reviewed here, there is certainly a need for additional research which takes into consideration current limitations and unanswered questions in order to enhance our understanding of underlying neurobiological circuitry in BPD.

Dissociative Disorders

Dissociative disorders in the DSM 5 include dissociative identity disorder (DID), dissociative amnesia, depersonalization disorder, other specified and unspecified dissociative disorder (Appendix A10; APA, 2013). Thus, dissociation can be understood to exist on a continuum (Bernstein & Putnam, 1986) encompassing day-dreaming, reduced awareness, memory lapse, derealisation and depersonalization which in turn influence consciousness, memory, identity and perception (APA, 2013). It is also useful to note that in the DSM-5 diagnostic criteria for BPD, dissociative symptoms are characterized by "transient stress-related paranoid ideation or severe dissociative symptoms" (APA, 2013). Research has shown that dissociative symptoms are prevalent in BPD (Conklin & Westen, 2005; Ross, 2007; Sar et al., 2003). Conversely, BPD is also a common co-morbidity in dissociative disorders (Ellason, Ross, & Fuchs, 1995; Ross, 2007). Finally, based on the research literature, we are also aware of the associations between pathological dissociation, abuse and PTSD (Spitzer, Barnow, Freyberger, & Grabe, 2006) and that abuse and PTSD is also associated with dissociation in BPD (Simeon, Nelson, Elias, Greenberg, & Hollander, 2003; Van Den Bosch, Verheul, Langeland, & Van Den Brink, 2003).

Systematic Literature Search

Standardized search terms for DMN as listed in the aforementioned sections and related fMRI concepts were combined with the following search terms: dissociation, dissociative symptoms, dissociative disorder(s) and dissociative experiences. This yielded a total of two articles. Only one article was found to be relevant after excluding one study that did not investigate RSFC of the DMN.

DMN Research in Dissociative Disorders

The only study that investigated RSFC of the DMN in dissociative disorders included 15 females with DID and 15 female healthy controls and made use of ICA (Schlumpf et al., 2014). Appendix A11 highlights key findings from this study. Participants were excluded if they had co-morbid psychosis, drug abuse and addiction, anti-social personality disorder and histrionic personality disorder. Overall, for DID patients, higher RSFC was found in the temporal pole of the middle temporal gyrus, precuneus, angular gyrus and dmPFC (Schlumpf et al., 2014). When comparing the only overlapping region investigated here and the six BPD studies, increased intra RSFC of the PFC was obtained across both BPD and dissociative disorders. A potential explanation for this finding might be attributable to the high prevalence of co-morbidity between these two disorders. However, it is also worth holding in mind that the PFC constitutes a considerable portion of the brain and performs a myriad of functions, including executive functioning, social cognition and attention (Mars et al., 2012). In order to enhance our understanding, it is therefore imperative to have greater spatial localization of RSFC findings.

From a clinical perspective, this study omitted crucial methodological information. Firstly, no rationale was provided for the decision to exclude participants with histrionic and anti-social PDs. Secondly, there was no information regarding the number of clinical participants who presented with co-morbid BPD, considering the high prevalence rates (Ross, 2007). As this is the first and only study investigating RSFC of the DMN in dissociative disorders, it is important that future studies address current limitations. What is interesting, however, is that a quick search of the current literature highlights the paucity of both non neuro-imaging and

neuro-imaging studies in dissociative disorders. In conclusion, there is currently limited evidence regarding the use of DMN in understanding dissociative disorders.

Discussion

Conclusions

This review aimed to evaluate the general value of the DMN in understanding clinical psychopathology and how RSFC of the DMN is associated with core symptomatology. Specifically, this review sought to delineate RSFC of the DMN across three highly co-morbid disorders of BPD, PTSD and dissociative disorders, and as compared to healthy controls.

Across the three identified disorders, there are consistent findings of aberrant inter and intra RSFC of the DMN when compared with healthy controls. The strength of evidence is stronger for PTSD and BPD. In particular, for PTSD, studies recruited from both community and military populations distinguished between PTSD and trauma experiences and attempted to predict PTSD symptomatology using RSFC of the DMN. On account of these factors, the current value of the DMN can be said to be the most useful for PTSD. Correspondingly, there is limited utility of the DMN in understanding dissociative disorders, mainly due to the lack of research in this domain. In terms of BPD, whilst RSFC of the DMN has been found to be associated with core dysregulation, it is difficult to establish specificity of these findings since none of the studies considered the influence of both PTSD and dissociative disorders on RSFC of the DMN.

Firstly, based on the reviewed PTSD studies which included military veterans, there is preliminary evidence of aberrant RSFC of the ACC, that is, reduced RSFC is associated with PTSD (Kennis et al., 2014; Sripada et al., 2012) whilst increased RSFC is associated with co-morbid MDD (Kennis et al., 2013). Whilst the

ACC has been tentatively put forth as a potential biological marker, it is imperative that future studies consider the influence of co-morbidities and higher stringency of the spatial localization of the ACC as a ROI. The finding of increased RSFC between the amygdala and DMN was also obtained in more than one study (Brown et al., 2013; Rabinak et al., 2011). In the two studies investigating RSFC of the DMN in community-based PTSD participants, inconsistencies regarding the presence of co-morbid MDD precluded reliable interpretations of the findings (Bluhm et al., 2009; Qin et al., 2012). However, the value of using RSFC of the DMN to understand psychopathology is promising given that two of the reviewed studies found that that RSFC patterns predicted subsequent PTSD severity (Gong et al., 2013; Lanius et al., 2010). That said, it is crucial that these findings are cautiously interpreted as the study by (Gong et al., 2013) relied on RSFC analysis of whole brain rather than selecting ROIs based on theoretical understanding of PTSD symptomatology. Lastly, three reviewed PTSD studies sought to elucidate the directionality of RSFC findings by focusing on the impact of abuse but not PTSD on RSFC (Philip et al., 2013a; Philip et al., 2013b; Van Der Werff et al., 2013). Interestingly, all three studies found lower RSFC for core DMN regions which then raises the question of whether RSFC of the DMN can constitute a biological marker for not only PTSD symptomatology but also vulnerability. However, based on the current review, research in this area is still at its infancy and therefore warrants further research that not only investigates neurobiological underpinnings but, also a wider consideration of the influence of environmental and individual factors in PTSD development. Despite the limited synthesis of findings due to the presence of co-morbidities, lack of statistical analyses to investigate effects of confounds, small sample and diversity of ROIs, the

12 reviewed PTSD studies established preliminary evidence of aberrant RSFC of the DMN in PTSD.

From reviewing the five BPD studies, there appears to be initial support for aberrant RSFC of the DMN in BPD. This was first demonstrated by Wolf et al. (2011) where atypical RSFC in FPC, insula and cuneus was associated with indices of dissociation and impulsivity. Some of these findings were further replicated and extended in three other studies. Firstly, by including BPD participants with and without co-morbid PTSD, Krause et al. (2014) sought to investigate RSFC of the DMN, salience network and amygdala. They found that reduced RSFC between the DMN and salience network was linked to inflexibility of attention in BPD but did not replicate Wolf et al. (2011)'s finding that the RSFC of the insula was related to dissociation. The second study by Doll et al. (2013) found that similar to Wolf et al. (2011), there was increased RSFC of the PFC and insula. In addition, aberrant RSFC between and within the DMN, CEN and salience network was also obtained and hypothesized to be associated with cognitive and emotional dysregulation in BPD. Lastly, O'Neill et al. (2014) obtained higher RSFC between the precuneus and inferior frontal gyrus, left precentral/middle frontal, and left middle occipital/superior parietal lobes. In the next reviewed BPD study, Das et al. (2014) obtained preliminary evidence of distinct RSFC of the DMN in BPD and bipolar disorder. Specifically, they found that higher RSFC between the DMN and precuneus in bipolar disorder was associated with heightened emotional awareness. Contrastingly, for participants with BPD, aberrant RSFC was related to reduced emotional awareness but increased impulsivity. In the final reviewed BPD study by Kluetsch et al. (2012), reduced RSFC between the left retrosplenial cortex, right inferior temporal, left superior frontal gyrus and that of the DMN was associated with

increased dissociative tendencies and lower pain modulation in BPD. Overall, despite the small number of BPD studies and the limitations posed by co-morbidities, small sample, exclusion of male participants and myriad of ROIs, findings suggest preliminary evidence of aberrant RSFC of the DMN and other brain regions. Furthermore, the studies by Das et al. (2014) and Krause-Utz et al. (2014) provide initial support that these underlying neurobiological abnormalities might be specific to BPD. However, further research that address the influence of confounds is necessary in order to discern the specificity of these findings and associations with core BPD symptomatology.

The only study that investigated RSFC of the DMN in dissociative disorders found increased RSFC in the temporal pole of the middle temporal gyrus, precuneus, angular gyrus and dmPFC (Schlumpf et al., 2014). However, the lack of information pertaining to co-morbid PDs limits further delineation of findings and more crucially, since this is the first study in this area, it is pertinent that further research is conducted in order to enhance our understanding of underlying neurobiological abnormalities in dissociative disorders.

Overall, the field of the DMN is still a relatively new one that has only recently captured research interest in clinical psychology. We can expect that as the field matures and future studies address current limitations, this would facilitate the development of a coherent clinical research framework that might identify neurobiological abnormalities underlying psychopathology.

Limitations of Current Review

With BPD as the primary focus in this review, it was vital that common co-morbidities were identified in order to accurately explicate the underlying neurobiological abnormalities. Whilst this was the aim, the complexity of BPD

meant that not only were there a range of co-morbidities to consider, there were also core transdiagnostic dysregulation. Unfortunately, both abundance (for example in MDD) and absence (for example in eating disorder) of RSFC studies across co-morbidities and lack of specificity in the concept of emotional dysregulation imply that our understanding of BPD is limited to the psychopathology discussed here. As with any new research area, there are two major limitations in this review, the small number of studies and the "file drawer effect" (Fanelli, 2012; Rosenthal, 1979). In particular, the "file drawer effect" arises when non-significant findings are not published, causing a small number of significant findings to dominate the field, creating the sense that the literature is fragmented, and un-synthesized due to the lack of replication studies.

The second major limitation pertains to the plausible uncontrolled variability due to the use of different models of scanners across the reviewed research (Appendix A12). In fMRI, changes in frequencies associated with study variables is commonly termed signal. Conversely, non-signal related changes in frequencies is labelled noise. It has been established that one source of noise is attributable to scanner instability (Greve et al., 2013). Since different scanners were used, we need to consider the potential influence of noise on observed signal when reviewing the literature. In addition, differences in the strength of magnetic field, indicated by the magnitude of unit Tesla (T), was also observed across the scanners (Appendix A12). Thus, apart from the above-mentioned variability of regions of interest, analysis methodology, co-morbidities, we need to also consider the implications of inter-scanner variability and noise when synthesising the findings.

Future Research and Clinical Implications

Based on findings from this review, future research should simultaneously investigate RSFC of the DMN across BPD, PTSD and dissociation, by incorporating the use of relevant clinical measures. In addition, it is important that selected ROIs are informed by theoretical and clinical understanding of BPD in order to maximize clinical utility of research. In order to increase generalizability of findings, future research should also include male participants with BPD. In summary, the aforementioned limitations has a bearing on how clinical psychology can benefit from current RSFC research. Greater specificity of the associations between neurobiological underpinnings and psychopathology will better allow clinical psychologists to utilize findings.

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Part Two: Empirical Paper

Exploring the Relationship between Default Mode Network Connectivity, Childhood Trauma, Dissociation and Emotional Dysregulation in Borderline Personality Disorder

Abstract

Aims

Research has found preliminary evidence of aberrant functional connectivity in borderline personality disorder (BPD) in the absence of external demands, commonly referred to as resting state functional connectivity (RSFC). This study aims to investigate RSFC and its associations with core symptomology of trauma, dissociation and emotional dysregulation in BPD as compared to healthy controls. Additionally, associations between RSFC, general clinical symptomatology and personality psychopathology will also be explored.

Method

44 participants with BPD and 30 healthy controls completed fMRI scans in the absence of external demands and self-reports assessing experiences of trauma, dissociation, emotional dysregulation and personality psychopathology. To assess RSFC, eight regions of interest were chosen, namely the left and right posterior cingulate cortex (PCC), left and right temporal parietal junction (TPJ), left and right anterior medial prefrontal cortex (amPFC), dorsal medial prefrontal cortex (dmPFC) and ventromedial prefrontal cortex (vmPFC).

Results

After controlling for the influence of gender, income and IQ, BPD participants displayed higher RSFC between five brain regions of interest and the rest of the brain. However, only the finding between dmPFC and left middle temporal gyrus remained significant after correction for multiple comparisons. None of the associations between RSFC and self-report measures were significant after correction for multiple comparisons.

Conclusions

The findings obtained here tentatively suggest that as compared to healthy controls, BPD participants displayed higher RSFC between core brain regions which are in turn associated with trauma, dissociation and general clinical symptomatology. However, future studies are warranted to further investigate underlying neurobiological abnormalities in BPD.

Introduction

Borderline Personality Disorder

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (APA, 2013) defines borderline personality disorder (BPD) as "*a pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity that begins by early adulthood and is present in a variety of contexts*" (Appendix A8). BPD is frequently and typically associated with self-injurious behaviour (Black, Blum, Pfohl, & Hale, 2004; Broyd et al., 2009) and co-morbidities including mood disorders, post-traumatic stress disorder (PTSD), eating disorders, substance and alcohol abuse (Leichsenring, Leibing, Kruse, New, & Leweke, 2011; Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004; Mosquera, Gonzalez, & Leeds, 2014) as well as other personality disorders (McGlashan et al., 2000; Zanarini et al., 1998). In view of the heterogeneity and complexity of BPD, it is more likely that multiple factors contribute to the development of BPD. Thus, in order to better understand and treat BPD, it is imperative that research investigating the underlying mechanisms of BPD symptomatology and common co-morbidities is guided by a coherent theoretical framework. In order to achieve this aim, the four main foci in this paper are: 1. aetiological framework of mentalization in relation to core BPD symptomatology 2. the links between mentalization, BPD, childhood trauma, dissociative symptoms and emotional dysregulation 3. neuroimaging findings in BPD and 4. current gaps in the literature and the present study.

Mentalization Framework

One such framework to shed light on the development of BPD is the mentalization-based developmental psychopathology framework which highlights the links between early experiences, attachment and BPD symptoms, in particular

that of emotional dysregulation and interpersonal difficulties (Fonagy & Luyten, 2009; Goodman, New, & Siever, 2004). Mentalization is conceptualized as a specific form of social cognition; of which the latter encompasses a range of mental processes involved in how we perceive, process, remember, retrieve and utilize social information (Fonagy, Gergely, Jurist, & Target, 2002). Mentalization is defined as the acquired and learnt ability to implicitly or explicitly interpret social information based on subjective states and mental processes of self and other, including needs, emotions, beliefs and goals (Allen, Fonagy, & Bateman, 2008; Bateman & Fonagy, 2006). Using a myriad of paradigms, there is evidence that individuals with BPD have difficulties mentalizing, which is further compromised in the presence of emotional arousal (Fonagy, Luyten, & Strathearn, 2011).

Returning to the framework, mentalization is directly influenced by attachment and early experiences. Significantly, disruptions to secure attachment and traumatic experiences impair the ability to mentalize both oneself and others (Agrawal, Gunderson, Holmes, & Lyons-ruth, 2004; Lyons-ruth, Fivaz-depeursinge, Fitzgerald, Guedeney, & Paul, 2008; Schore, 2000). In addition, PTSD as a result of early experiences of abuse and neglect is a prevalent co-morbidity in BPD (Golier et al., 2003; McLean & Gallop, 2003). Research has also shown that individuals with BPD tend to possess preoccupied and disorganized attachment style rather than good enough secure attachment; with the latter conducive for the development of mentalization (Fonagy et al., 1996; Patrick, Hobson, Castle, & Howard, 1994; West, Keller, Links, & Patrick, 1993).

Understanding the Mentalization Framework Using Neuroimaging

With technological advances, clinical psychology can now understand psychopathology above and beyond the use of self-reports and behavioural

observations. This is achieved by investigating genetic biomarkers, electrical impulses of neurons, structural abnormalities of the brain or metabolic changes due to neuronal activity using functional magnetic resonance imaging (fMRI), with this paper focusing solely on fMRI findings. The use of fMRI enables us to investigate temporally synchronous interactions between and within brain regions, commonly termed functional connectivity (Toga, 2015).

In healthy individuals, there is established evidence for neural circuitry underpinning social cognition (Buckner & Vincent, 2007; Callard & Margulies, 2011; Fingelkurts & Fingelkurts, 2011). Brain regions implicated in mentalization include the anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), medial temporal lobe (MTL), temporal parietal junction (TPJ) and superior temporal sulcus (STS) (Dimaggio, Lysaker, Carcione, Nicolo, & Semerari, 2008; Dziobek et al., 2011; Frith & Frith, 2003).

Mentalization and Trauma

PTSD

In the DSM-5, a diagnosis of PTSD requires the presence of symptoms relating to intrusion, avoidance, alterations in mood, cognitions, arousal and reactivity. There are also two specifications, that of delayed expression and presence of dissociation (DSM-5; Appendix A6). Furthermore, early experiences of abuse and neglect is prevalent in BPD (Alvarez et al., 2011; Yen et al., 2002; Zanarini et al., 2002), and PTSD is also highly co-morbid with BPD (Eichelman, 2010; Zanarini et al., 2011; Zlotnick et al., 2003). Lastly, studies have also found positive correlation between the severity of abuse and/or neglect and BPD symptomatology (Zanarini et al., 2002).

Mentalization, PTSD and BPD

Both research findings and clinical presentations converge on the profound impact of early traumatic experiences. However, instead of focusing on disparate symptoms and disorders, we can enhance our understanding using an overarching mentalization framework. Mainly, early traumatic experiences increases the likelihood of developing insecure attachment which impairs the ability to mentalize, thereby limiting self and emotional regulation, resulting in interpersonal difficulties and behavioural dysregulation (Fonagy, Gergely, Jurist, & Target, 2002). Thus, the mentalization framework posits crucial developmental pathways between early trauma, quality of attachment, adult PTSD and BPD (Lazarus, Cheavens, Festa, & Zachary, 2014; Preissler, Dziobek, Ritter, Heekeren, & Roepke, 2010; Roepke, Vater, Preissler, Heekeren, & Dziobek, 2012).

Task-based fMRI Studies in PTSD

As compared to healthy controls, individuals with PTSD display aberrant connectivity of the hippocampus, amygdala, anterior insula, mPFC and ACC (Brown et al., 2013; Shin et al., 2005; Squire, Stark, & Clark, 2004). In terms of brain-behaviour links, aberrant neuroimaging findings of the amygdala and ACC are in turn associated with indices of emotional dysregulation (Brown et al., 2013; Phan, Wager, Taylor, & Liberzon, 2002), impaired cognitive control (Chouinard & Paus, 2006; Paus, 2001) and deficits in fear conditioning and extinction in PTSD (Chen et al., 2012; Dunsmoor, Prince, Murty, Kragel, & LaBar, 2011) whilst hippocampal findings are linked to impairments of memory processes and fear extinction in PTSD (Apfel et al., 2011; Brewin, Kleiner, Vasterling, & Field, 2007). In addition, task-based fMRI studies have also found that reduced connectivity of the mPFC leads to under-modulation of brain regions involved in emotional arousal and attention,

thereby resulting in hyper arousal and intrusive symptoms (Brown et al., 2013; Shin et al., 2005). Moreover, atypical connectivity of the insula and amygdala results in emotional dysregulation, increased dissociation and hypervigilance (Ludäscher et al., 2010; Niedtfeld et al., 2010; Paulus & Stein, 2006). Lastly, atypical connectivity of brain regions underpinning mentalization has also been associated with dissociation and fragmentation of trauma-related memories in PTSD (Daniels et al., 2010; Lanius et al., 2010). In summary, the links between mentalization, BPD and PTSD are reinforced by neuroimaging studies depicting aberrant neural connectivity in selected brain regions.

Mentalization and Dissociation

Dissociation

Dissociation characterized by dissociative identity disorder (DID), dissociative amnesia and depersonalisation disorder disrupts continuity in consciousness, memory, identity and perception (Appendix A10; APA, 2013). In BPD, dissociative symptoms are conceptualized as "transient stress-related paranoid ideation or severe dissociative symptoms" (APA, 2013), and have been found to be highly prevalent (Korzekwa, Dell, Links, Thabane, & Fougere, 2009; Vermetten & Spiegel, 2014). In addition, the common occurrence of dissociative symptoms in PTSD (Korzekwa, Dell, Links, Thabane, & Fougere, 2009; Lanius et al., 2010; Van Der Kolk, Mcfarlane, & Weisaeth, 1996) is reflected in the specification requirement of the DSM-5 (APA, 2013).

Understanding Dissociation within the Mentalization Framework

As outlined, the focus is not the presenting symptom or disorder, but to better understand psychopathology using an overarching framework in order to address transdiagnostic features that represent overlapping co-morbidities of BPD, PTSD and dissociation. The mentalization framework posits that early adverse experiences are

the basis of disorganised and pre-occupied attachment which in turn influences the developmental ability to mentalize resulting in dysregulation in key domains (Liotti, 1992; Putnam, 1997). Further extending this framework, dissociative symptoms are then conceptualized as a (defensive) emotional regulation strategy to manage overwhelming experiences and internal states (Armstrong 1994; Putnam, 1997), but due to frequent dissociation, this exacerbates dysregulation. This is convergent with research findings indicating high prevalence of repeated trauma and PTSD in individuals with DID (Putnam, Guroff, Silberman, Barban, & Post, 1986; Ross, 1991). Furthermore, frequent dissociation has been found to impede identity formation (Putnam, 1997), memory consolidation (Freyd, 1996; Spiegel & Cardena, 1991) and emotional regulation (Brand & Lanius, 2014). In this sense, dissociation is conceived as hyper modulation. This conceptual understanding of dissociation is therefore contrasted with hyper arousal in which there is hypo modulation (Boon & Draijer, 1993; Weiss, Tull, Lavender, & Gratz, 2013).

fMRI Studies Across Dissociation, PTSD and BPD

Using task-based fMRI, researchers obtained distinct neurobiological circuitry associated with dissociation and hyper arousal (Hopper, Frewen, Van der Kolk, & Lanius, 2007; Lanius, Bluhm, Lanius, & Pain, 2006). Specifically, hyper arousal was associated with reduced connectivity of the ACC, mPFC, thalamus and inferior frontal gyrus (Lanius et al., 2001; Shin et al., 2005) whilst dissociation was associated with increased connectivity (Lanius et al., 2002). In line with the notion that dissociation and hyper arousal are contrasting emotional dysregulation strategies, similar connectivity patterns obtained during hyper arousal in PTSD were also found in BPD during heightened emotional reactivity (Krause-Utz, Winter, Niedtfeld, & Schmahl, 2014; Vermetten & Spiegel, 2014) whilst connectivity

patterns associated with dissociation parallel connectivity during pain processing in BPD (Scoboria, Ford, Lin, & Frisman, 2008) and in the absence of external demands (McLaughlin et al., 2010). Emotional dysregulation is a diagnostic criterion and common clinical feature in dissociative disorders, PTSD and BPD. In PTSD, several studies have found that emotional dysregulation predicted dissociative symptoms in participants with PTSD (Briere, 2006; Lewis, K.L., & Grenyer, 2009). Emotional dysregulation in BPD is in turn related to increased dissociation and self-referential processing (Kluetsch et al., 2012; Kraus et al., 2009; Schmahl et al., 2006). In conclusion, obtained neurobiological findings across PTSD and BPD are aligned with the fundamental conceptualization of dissociation as a form of emotional dysregulation.

fMRI Studies in BPD

In terms of fMRI research, BPD is the most investigated PD in the DSM-5. Despite growing research interest and publications, there are still considerable gaps in our understanding of the neurobiological basis of BPD (Ducasse, Courtet, & Olié, 2014; Foti et al., 2011; Krause-Utz et al., 2014). Therefore, this section will highlight key functional connectivity abnormalities in BPD during task-based fMRI where emotions, pain and cognitions are induced in a bid to investigate behavioural dysregulation and interpersonal difficulties. This is then followed by a review of fMRI studies where BPD and healthy control participants were compared in the absence of external task engagement.

Task-based fMRI Studies Investigating Emotional Dysregulation

In the past two decades, neuroimaging research investigating emotional dysregulation in BPD highlighted the interactions between emotional modulation, pain and dissociation (Schmahl et al., 2014). Emotional dysregulation in BPD is

characterized by hyper-sensitivity, hyper-reactivity and hypo-modulation of emotions. fMRI studies have found that increased connectivity of the amygdala results in heightened and prolonged emotional experiences (Hazlett et al., 2012; Kamphausen et., 2013; Koenigsberg et al., 2009) whilst reduced PFC and PFC-amygdala connectivity is linked to heightened impulsivity and reduced modulation of emotions (Cullen et al., 2011; Minzenberg, Fan, New, Tang, & Siever, 2007; Scherpiet, Bruhl, Opialla, Roth, Jancke, & Herwig, 2013). In summary, task-based neuroimaging studies suggest that hyperactivity of emotional modulation limbic regions such as the amygdala and hypoactivity of regulatory frontal regions might underpin emotional dysregulation in BPD.

Task-based fMRI Studies Investigating Pain Processing

Pain processing and self-injurious behaviours are closely related to emotional and behavioural dysregulation, especially in terms of reduced pain perception and reactivity (Welch, Linehan, Sylvers, Chittams, & Rizvi, 2008). In a study by Kraus et al. (2010), a script detailing self-harming behaviour and fMRI was used to study underlying connectivity associated with pain processing. The researchers found that there was reduced connectivity of the orbitofrontal cortex (OFC), which was hypothesized to be related with increased impulsivity and inhibition difficulties (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Kraus et al., 2010; Rubia, Smith, Brammer, & Taylor, 2003). Another line of evidence pertains to decreased ACC and ACC-amygdala connectivity in BPD participants (Kraus et al., 2010). Significantly, the ACC is established to be involved in cognitive control (Ochsner, Bunge, Gross, & Gabrieli, 2002) and nociception (Klossika et al., 2006). Additionally, reduced emotional modulation, cognitive control and pain sensitivity with regards to self-harming in BPD was also replicated in two other fMRI studies (Carpenter & Trull,

2103; Niedtfeld, Kirsch, Schulze, Herpertz, Bohus, & Schmahl, 2012). Together, these studies suggest the presence of atypical neurobiological circuitry associated with pain processing in BPD.

Task-based fMRI Studies Investigating Behavioural Dysregulation

Apart from self-injurious behaviours, individuals with BPD typically manifest behavioural dysregulation including substance abuse, binge eating and risky sexual behaviours (Dougherty, Bjork, Huckabee, Moeller, & Swann 1999; Trull, Sher, Minks-Brown, Durbin, & Burr, 2000). It is important to bear in mind that similar to other processes discussed thus far, behavioural dysregulation is a multi-faceted concept comprising of a myriad of cognitive processes including response inhibition and reward processing (Bornovalova, Lejuez, Daughters, Zachary, & Lynch, 2005; Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001), which is hugely modulated by emotions (Sebastian, Jacob, Lieb, & Tuscher, 2013; Stahl et al., 2013). As discussed, the PFC and ACC, established to be key regions underpinning behavioural and cognitive regulation have also been found to be less active in individuals with BPD (Wingenfeld et al., 2009; Wolf et al., 2012). Adding to the complexity of behavioural dysregulation, individuals with BPD tend to have more difficulties managing emotions in situations demanding cognitive control, response inhibition and reward processing, which further aggravates behavioural dysregulation (Enzi et al., 2013; Fertuck, Lenzenweger, Clarkin, Hoermann, & Stanley, 2006; Silbersweig et al., 2007).

Task-based fMRI Studies Investigating Cognitive Dysregulation

As seen, cognitive dysregulation in BPD permeates across domains of pain processing as well as behavioural dysregulation. Across task-based fMRI studies, increased connectivity of frontal lobes and corresponding reduced connectivity of

limbic brain regions have been found to be associated with indices of dissociation (Ludäscher et al., 2010; Wolf et al., 2012), which in turn disrupt cognitive processes of perception, attention and memory (APA, 2013). In order to explain these patterns of neural connectivity, it is hypothesized that dissociation is an emotional strategy aimed to avoid overwhelming emotions and cognitive aspects of oneself (Lanius et al., 2010; Menon & Uddin, 2010; Sierra & Berrios, 1998). Moreover, functional abnormalities in frontal regions is also associated with disruptions to attentional processes, memory and impulse control (Hofstadter et al., 2014; Silbersweig et al., 2007).

Task-based fMRI Studies Investigating Interpersonal Difficulties

Interpersonal difficulties in BPD are manifested in the strong perception that others will abandon them, maladaptive strategies used to manage raptures in relationships, and emotional arousal (Gunderson, 2007; King-Casas et al., 2008; Lis & Bohus, 2013). This corroborates with fMRI findings that in BPD, interpersonal cues are associated with heightened emotional reactivity of the limbic regions (Frick et al., 2012; Minzenberg et al., 2007). In addition, as compared to healthy controls, individuals with BPD display reduced connectivity in core regions underpinning social cognition, such as the superior temporal sulcus and insula (Dziobek et al., 2011; Mier et al., 2013). Unsurprisingly, individuals with BPD also tend to perceive social exclusion even when they are socially included, which is in turn related to increased emotional negativity corresponding to increased ACC and reduced insula connectivity (Domsall et al., 2014; Ruocco et al., 2010). In the trust-game paradigm, as compared to healthy controls, individuals with BPD displayed lower trust, which led to ruptures in cooperation (King-Casas et al., 2008). This was further reinforced by fMRI findings in which individuals with BPD only displayed increased anterior

insula connectivity in association with the amount of monetary units they gave out but not with amount received. This contrasted with healthy controls who showed increased anterior insula connectivity even when they received money. The anterior insula is activated when there is perceived violations of social conventions; thus, based on these findings, it is hypothesized that since individuals with BPD do not trust others, they therefore did not experience any norm violations (King-Casas et al., 2008). Overall, task-based fMRI studies highlighted in the preceding sections suggest evidence of neurobiological basis of core BPD symptomatology.

Resting State Functional Connectivity of the Default Mode Network in BPD

Rather than investigating isolated symptoms, this paper aims to explore the neurobiology of BPD, informed by an overarching framework; in this case, the aforementioned mentalization-based developmental psychopathology framework (Fonagy & Luyten, 2009; Goodman, New, & Siever, 2004; Steele & Siever, 2010). The existence of a network of brain regions underpinning mentalization is not only based on findings from task-based fMRI, but also from increased connectivity when an individual is awake but not engaged in external tasks, which is commonly termed the 'resting state'. Correspondingly, research also found that these brain regions, including the precuneus, posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC) as well as parietal cortex were less active in the presence of external demands (Binder et al., 1999; Fox et al., 2005; Greicius, Krasnow, Reiss, & Menon, 2003; Gusnard & Raichle, 2001). This network was subsequently denoted the 'default mode network' (DMN; Raichle et al., 2001). Thus, the DMN can be likened to "baseline" brain function (Wolf et al., 2011) reflecting the intrinsic neural architecture of the brain. It is purported that instead of our brain simply going blank in the absence of task engagement, we have the capacity to reflect on ourselves and

social situations (D'Argembeau et al., 2005; Gusnard & Raichle 2001; Johnson et al., 2002; Moran, Macrae, Heatherton, Wyland & Kelley, 2006; Northoff et al., 2006). Thus, it is hypothesized that the core function of the DMN pertains to internal mentalizing independent from external stimuli and environment (Buckner, Andrews-Hanna, & Schacter, 2008; Spreng, Mar & Kim, 2009).

In order to make sense of the mentalization processes that occur when our mind is free to wander, resting state fMRI (rs-fMRI) is used to explore connectivity between core DMN regions and other brain regions. Connectivity due to intrinsic neuronal activity is referred to as resting state functional connectivity (RSFC), established to occur at frequencies between the range of .01 to .1 Hz as compared to the above 1 Hz task-based evoked neural activity (Callard & Margulies, 2011; Cordes et al., 2001).

Despite an increase in fMRI research investigating BPD symptomatology in the past decade, little is known about the RSFC of individuals with BPD in comparison to healthy controls, with only five published studies to date (Doll et al., 2013; Kluetsch et al., 2012; Krause-Utz et al., 2014; O' Neil et al., 2014; Wolf et al., 2011). The pioneer study investigating RSFC of the DMN compared 17 females with BPD and 17 healthy female controls (Wolf et al., 2011). The researchers found increased RSFC in the left frontopolar cortex (FPC) and the left insula, but decreased connectivity in the left cuneus, inferior parietal lobule and the right middle temporal cortex. In addition, they also found positive correlations between RSFC of the FPC and measures of impulsivity, as well as between connectivity of the insula and dissociation (Wolf et al., 2011). The finding of increased RSFC of the insula is particularly important as this is suggestive of the insula's role in inducing dissociative symptoms and emotions even in the absence of external triggers. Taken

together, these findings indicate possible associations between RSFC of the DMN and core BPD symptomatology.

Three further studies sought to extend the findings by Wolf et al. 2011. Firstly, in an all-female study, Krause et al. (2014) not only investigated RSFC of the DMN in 20 individuals with BPD and 17 healthy controls, they also included the salience network, responsible for monitoring both internal and external sensory information before initiating cascading responses influencing other vital networks (Menon, 2011). In this study, reduced RSFC between the DMN and salience network in BPD was postulated to result in reduced modulation of attention (Kluetsch et al., 2012; Lis & Bohus, 2013). Based on a sample of 14 BPD participants and 16 healthy controls, the second study by Doll et al. (2013) investigated the DMN, salience network, as well as the central executive network (CEN); the latter is thought to be involved in cognitive processes such as attention and working memory (Menon, 2011). Similar to Wolf et al. (2011), Doll et al. (2013) obtained reduced RSFC between the DMN and CEN, which was associated with reduced cognitive control and increased emotional reactivity and increased intra RSFC of the insula and insula-PFC connectivity. The final study seeking to extend research the research by Wolf et al. (2011) found that compared to the 19 female controls, the 17 females with BPD displayed increased RSFC between the precuneus and the following DMN regions: left inferior frontal gyrus, left precentral/middle frontal, and left middle occipital/superior parietal lobes (O'Neil et al., 2014). Apart from these four studies, Kluetsch et al. (2012) also explored RSFC of the DMN in relation to pain processing. The researchers found that the 25 females with BPD had lower inter RSFC amongst the left retrosplenial cortex, right inferior temporal and left superior frontal gyrus when compared to the 22 female healthy controls, which was in turn associated with

increased dissociative symptoms and reduced processing of both pain and emotions in BPD (Kluetsch et al., 2012). Overall, these studies suggest preliminary evidence of aberrant RSFC of the DMN, with the possibility that aberrant RSFC in BPD might constitute a potential biomarker in BPD. However, the lack of emphasis on the influence of co-morbidities and core BPD symptomatology unfortunately limits clinical utility of current findings.

Current Gaps in the DMN Literature in BPD

Firstly, it is apparent that to date, research investigating RSFC of the DMN in BPD are primarily informed by a neuroscience paradigm in which the main focus is neural connectivity patterns of the brain, with less emphasis on understanding and relating these findings to an overarching clinical framework. Thus, whilst it is interesting to observe aberrant RSFC, how do we make sense of congruent and divergent findings? Also, what are the associations between RSFC, core symptomatology and co-morbidities? Lastly, how can these findings inform clinical formulation and intervention?

Current Study

The present study aims to characterize RSFC of the DMN in individuals with BPD as compared to healthy controls, and to further elucidate the associations between RSFC of the DMN, early traumatic experiences, dissociation and difficulties in managing emotions. In contrast to the study by Wolf et al. (2011), the clinical participants in this study will be better characterised in terms of comorbid PDs and will comprise of a larger sample. In addition, this study will use a different resting state analytic approach: seed-based analysis with eight a priori-defined regions of interest (ROIs; further elaborated in the method section). This study will also add to the current literature by taking into consideration self-reported emotional

dysregulation, dissociation and traumatic experiences in order to better understand the links between DMN, emotional regulation, dissociation and trauma in BPD as well as associations with general clinical symptomatology and personality psychopathology. Resultantly, this study aims to address two hypothesis, firstly, differences in RSFC are expected between participants with BPD and healthy controls. Secondly, it is predicted that differences in RSFC will in turn be associated with self-reported trauma, dissociation, emotional dysregulation, general clinical symptomatology and personality psychopathology.

Method

Design

This study is part of an on-going large research (Montague and Fonagy, Wellcome Trust) investigating neurobiological and behavioural underpinnings of BPD and Anti-Social Personality Disorder (ASPD) within a computational psychiatry framework. Approval for the study was granted by the Research Ethics Committee for Wales (REC reference 12/WA/0283; Appendix B1). Adolescents with emerging personality psychopathology, adults diagnosed with BPD and/or ASPD, as well as healthy controls completed self-report measures, structured interviews, and MRI of brain structure and function during a task battery comprising several neuroeconomics-based social exchange paradigms as well as a resting state scan. In this study, a cross-sectional design was used to explore group differences between adult healthy controls and adult participants with BPD, specifically in relation to RSFC and associations with emotional dysregulation, dissociation and trauma.

Sample Size and Statistical Power

Assuming equal group sizes, power calculation using the "G*Power 3" computer program (Faul, Erdfelder, Lang & Buchner, 2007), specifying alpha =5% and desired power = 80% estimated an adequate sample size of 48 individuals per group. However, estimation of sample size in fMRI studies is not as straightforward. Firstly, due to external factors such as access to equipment, duration of scans, costs (Murphy & Garavan, 2004), rather than considering statistical power, most fMRI studies rely on anecdotal guidelines of approximately 12 to 16 participants per group (Guo et al., 2014) or preferred guidelines of 20 participants per group for whole brain analyses or 15 to 20 participants per group if there is a priori evidence for selected ROIs (Carter, Heckers, Nichols, Pine, & Strother, 2008).

Secondly, where present, power calculations in fMRI is often computed using complex statistical models requiring specification of expected neural activation, considerations regarding ROIs (Bhaumik et al., 2009), between and within participants' variance and specific temporal indices of fMRI (Desmond & Glover, 2002, Hayasaka, Peiffer, Hugenschmidt, & Laurienti, 2007; Mumford, 2012). Even then, these statistical models are designed for task-based fMRI which therefore limits applicability in rs-fMRI studies (Mumford & Nichols, 2008). In view of these constraints and to ensure adequate power, the current study aimed to obtain a sample size of at least 40 participants per group, double the normative fMRI guidelines. The achieved sample size was 30 healthy controls and 44 BPD participants. The shortfall of healthy controls was because eight participants were excluded from further analyses as they scored above the threshold on the Standardised Assessment of Personality-Abbreviated Scale and overall recruitment focused mainly on PD participants.

Participants

Clinical participants were recruited from outpatient specialist PD services across London and London Probation Services. Advertisements on internet sites and public places were used to recruit healthy control participants across London. In order to be eligible, participants had to be fluent in writing and understanding English, able to attend two testing sessions and have normal corrected vision. In addition, clinical participants had to meet diagnostic criteria for BPD whilst healthy controls are required to have negative screening results for personality psychopathology based on scores on the Standardised Assessment of Personality-Abbreviated Scale. Despite stipulations in the research protocol, SCID-II was omitted for eight healthy controls who scored above the threshold. These participants were therefore excluded. Participants were also excluded if they had current or past history of neurological disorders or learning disabilities requiring specialised support.

Overall Procedures

Participants were assessed by trained researchers at the Wellcome Trust Centre for Neuroimaging at UCL. Before the initial testing session, participants were emailed an information sheet describing the study, which was also discussed during the initial session (Appendix B2). Prior to participation, all participants provided written informed consent (Appendix B3). Participants were reimbursed for their time at £10 per hour and for any travel expenses incurred. At the end of participation, a participant debrief sheet was provided (Appendix B4).

rs-fMRI Procedures

DMN activation, endogenous oscillations and connectivity were measured using a multi-echo echoplanar imaging sequence which facilitated subsequent

disambiguation of movement and physiological effects from endogenous hemodynamic contrast. Prior to the rs-fMRI scan, participants completed both structural and functional MRI scans whilst playing five social exchange games. Total scanning time for rs-fMRI was five minutes. To encourage resting state, a stationary standard *Windows* screen was used as a neutral background and participants were given the following verbal instruction: "For the next five minutes, please keep your eyes open and let your mind wander, think of whatever that comes to mind". As the MRI scanning environment is noisy, earplugs were provided. In addition, researchers would periodically check in with participants to ensure that they remain comfortable throughout the scanning. Participants were scanned for a maximum of 60 minutes each time and were informed that they can request for a break or to stop scanning at any point.

Measures

Socio-demographics and Intellectual Functioning

Socio-demographic information pertaining to age, ethnicity, education level, years in education, employment status and household income were obtained for all participants. In addition, BPD participants were also asked to list their currently prescribed medication. Participants also completed the Raven's Standard Progressive Matrices (Raven, Raven, & Court, 2003), which measures abstract reasoning abilities using 60 multiple-choice questions of increasing difficulty, yielding a total score of 60. Participants were presented with patterns that have a missing element and were required to identify the correct response from a choice of six or eight options. Raven's Matrices has been found to possess high test-retest and split-half reliability of above .80 and convergent validity of .49 to .81 with Wechlser Adult Intelligence (Raven, 2000).

Self-report Measures of Personality Psychopathology

In order to assess presence and severity of personality psychopathology, all participants were administered the Personality Assessment Inventory-Borderline Features scale (PAI-BOR, Appendix B5) and Standardised Assessment of Personality-Abbreviated Scale (SAPAS, Appendix B6). The 24-item PAI-BOR required participants to rate themselves on four core features of BPD: affective instability, identity problems, negative relationships and self-harm (Morey, 1991). Participants rated statements such as "My moods get quite intense" and "Sometimes I feel terribly empty inside" on a four-point scale of 0 to 3, which directly correspond to descriptors of false, slightly true, mainly true and very true. Apart from a total score of 0 to 72, the PAI-BOR also yields four sub-scale scores corresponding to the core features. Prior studies suggests that the PAI-BOR has good test re-test reliability ($r = .86$), internal consistency ($\alpha = .84$) and is valid for assessing BPD features in both healthy and clinical participants (Kurtz, Morey, & Tomarken, 1993; Morey, 1991; Trull, 1995).

The SAPAS consists of eight questions that screens for likelihood of PDs (Moran et al., 2003). Participants have to answer yes or no to questions such as "In general, do you trust other people?" and "In general, are you a perfectionist?". A total score of four and above suggests increased likelihood of PD(s). Correlation between scores on the SAPAS and diagnoses of PDs ranges from low to high, depending on the diagnosis, with a moderate correlation obtained for BPD (Moran et al., 2003).

Self-report Measures of Specific Clinical Symptomatology

Participants also completed the Childhood Trauma Questionnaire (CTQ, Appendix B7), Dissociative Experience Scale (DES, Appendix B8) and Difficulties

in Emotion Regulation Strategies Scale (DERS, Appendix B9). The 28-item CTQ consists of five scales assessing categories of childhood trauma and a minimization scale that detects individuals who might be under-reporting traumatic experiences (Bernstein et al., 1994). Using a five-point scale of 1 to 5 which correspond to the response set of never true, rarely true, sometimes true, often true and very often true, participants had to answer questions such as "I got hit so hard by someone in my family that I had to see a doctor or go to hospital" and "Someone tried to make me do sexual things or watch sexual things". Obtained raw scores ranging from 5 to 25 are then classified into levels of maltreatment: none, low, moderate and severe. The CTQ is a brief self-report inventory that has good test-retest reliability (r = .88), internal consistency reliability (r = .80 to .97) and criterion validity (Fink, Bernstein, Handelsman, Foote, & Lovejoy, 1995).

In addition, the 28-item DES was used to assess dissociative experiences using questions such as "Some people sometimes have the experience of feeling that other people, objects, and the world around them are not real" (Bernstein & Putnam, 1986). Participants had to rate the frequencies of dissociative experiences on a 11 point scale ranging from never (0%) to always (100%), which was then used to obtain an overall average score. The DES has a test-retest reliability coefficient of .84 and construct validity of .70 (Bernstein & Putnam, 1986).

Participants also completed the DERS which encompasses six features of emotional dysregulation: non-acceptance of emotional responses, difficulties engaging in goal-oriented behaviours, difficulties controlling impulses, lack of emotional awareness, lack of access to emotion regulation strategies and lack of emotional clarity (Gratz & Roemer, 2004). The DERS comprises of 36 questions, including "I experience my emotions as overwhelming and out of control" and

"When I'm upset, I believe there is nothing I can do to make myself feel better". Participants had to rate themselves on a five-point scale of 1 to 5 which directly corresponded to a response set of almost never (0-10%), sometimes (11-35%), about half the time (36-65%), most of the time (66-90%) and almost always (91-100%). The DERS has demonstrated good test-retest reliability of .88 and high internal consistency within both clinical and non-clinical populations (Gratz, Tull, Baruch, Bornovalova, & Lejuez, 2008). Specifically, individuals with BPD were shown to score higher on the DERS (Gratz, Rosenthal, Tull, Lejuez, & Gunderson, 2006).

Lastly, participants also completed the Brief Symptom Inventory (BSI, Appendix B10), a 53-item symptom inventory assessing somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism (Derogatis & Melisaratos, 1983). Participants were required to rate their distress on a five-point scale ranging from not at all, a little bit, moderately, quite a bit and extremely, using scenarios such as "The idea that someone else can control your thoughts" and "Feeling lonely even when you are with people". The BSI has demonstrated internal consistency range of .71 to .85 and test-retest reliability of .68 to .91 (Derogatis, 1993; Wood, 1986).

Structured Clinical Interview for DSM-IV PDs (SCID-II)

SCID-II (First, Gibbon, Spitzer, Williams, & Benjamin, 1997) was administered to all clinical participants as well as healthy controls who had a SAPAS score of four and above. Core symptoms are scored using a three point scale where a score of 1 suggests the absence of symptoms, while scores of 2 and 3 suggest sub-threshold and threshold presence of symptoms, respectively. In addition, assessors can also indicate that there was insufficient information required for scoring; as denoted by the symbol "?". Questions assessing BPD included "Have you often

become frantic when you thought that someone you really cared about was going to leave you". The SCID-II has been found to possess high inter-rater reliability kappa scores of .77 to .94 across all the PD diagnoses (Lobbestael, Leurgans, & Arntz, 2011).

fMRI Data Acquisition

A 3.0 Tesla Siemens Trio scanner was used to acquire anatomical and functional images. High resolution T1-weighted scans (1.0 × 1.0 × 1.0 mm) were acquired using a MP-RAGE sequence. The resting state scan lasted five minutes with a repetition time (TR) = 2000 ms, echo time (TE) = 25 ms, flip angle = 90°, axially oriented slices = 37 and voxel size = 3.4 × 3.4 × 4.0 mm. 150 functional images were acquired.

Pre-processing of rs-fMRI Data

After acquisition, pre-processing of the rs-fMRI data is necessary in order to minimize data variability and to ensure spatial and temporal accuracy (VanDijk et al., 2010; Weissenbacher et al., 2009). This was done using standard statistical parametric mapping (SPM12 v6225; Wellcome Department of Imaging Neuroscience; http://www.fil.ion.ucl.ac.uk/spm/) and MATLAB 2014b. Functional images were motion-corrected using a six parameter rigid-body transformation to the first functional scan and un-warped using nonlinear basis functions. Using a 12-parameter affine transformation, the mean functional images for each subject were co-registered to the subject's high-resolution T1 structural scan. Structural T1 images were segmented into grey and white matter and normalized using nonlinear basis functions to the Montreal Neurological Institute (MNI) template whilst functional images were normalized to the template, with re-sampled 3 × 3 × 3mm functional

voxels. Functional images were also spatially smoothed using an isotropic 8-mm full-width at half-maximum Gaussian kernel.

Data Analysis

Questionnaire measures were explored for missing values and relevant reversed scoring was applied before data analysis. Distribution of data and multicollinearity was investigated using SPSS 22 (IBM Corp, 2013). Multivariate analysis of covariance (MANCOVA) was used to analyse group differences in measures of personality and clinical psychopathology. Initial RSFC data analyses were performed using the connectivity toolbox, CONN v.15, a MATLAB based software (available from http://www.nitrc.org/projects/conn). RSFC between brain regions and associations between RSFC and questionnaire measures were then explored using general linear model (GLM) within SPM12.

Missing Value Analysis (MVA) and Single Imputation

In order to establish if responses were missing at random, MVA was conducted using SPSS. Non-significant results from the Little's "Missing Completely at Random Test" suggests that data were missing at random. Across the measures, missing values were within the range of 1.33% to 3.15%, with the highest number of missing values obtained in the CTQ and BSI, and across BPD participants. Appendix B11 provides the breakdown of missing values. Since there were less than 5% of missing values, single imputation based on the expectation-maximization algorithm within SPSS was used to compute values for missing questionnaire items.

Distribution of Data

In order to assess whether normality assumptions for parametric testing were met, demographic and questionnaire data were explored for normality, skewness, kurtosis and outliers (Appendix B12). Significant Kolmogorov-Smirnov for age was

obtained only for healthy controls. For healthy controls, age and all measures except for DERS were positively skewed. In addition, healthy controls also displayed significant kurtosis for age, DES and BSI. On the other hand, BPD participants showed negative skewness for SAPAS and PAI-BOR. BPD participants' PAI-BOR scores also indicated presence of kurtosis. Therefore, transformation was applied to the total scores of these scales and used in subsequent rs-fMRI analyses.

Demographic Data

In the current study, chi-square analyses indicate that BPD participants and healthy controls differed significantly in terms of gender, $\chi^2(1, 74) = 10.05$, $p = .002$ and household income, $\chi^2(1, 74) = 18.89$, $p = .002$. In relation to age and IQ, independent samples T-tests showed that there were significant differences between BPD participants and healthy controls for IQ scores, $t(72) = 2.70$, $p = .008$ but, not age, $t(72) = 1.621$, $p = .10$. Thus, in all subsequent analyses, gender, household income and IQ were included as covariates. Table 1 summarizes the demographic data of all participants. 44 BPD participants (8 males and 36 females) and 30 healthy controls (16 males and 14 females) participated in the research. Participants were aged between 18 and 54 years. Participants were mainly White British (56.75%), 12.16% were of other White ethnicity, 6.75% were Black British, 10.81% were Mixed and 10.81% Asian. In general, 50% of BPD participants reported family household income of less than £10000 as compared to 23.33% of healthy controls. Healthy controls obtained higher scores on Raven's Matrices ($M = 51.50$, $SD = 5.48$) as compared to BPD participants ($M = 47.80$, $SD = 5.97$). In addition, 10% of healthy controls reported that they had attained post graduate education as compared to 4.55% of BPD participants. However, BPD participants reported spending more

years in education (*M* = 14.89, *SD* = 4.65) as compared to healthy controls (*M* = 13.80, *SD* = 3.05). 43.33% of healthy controls and 25% of BPD participants reported that they were employed. Conversely, prevalence of unemployment was 56.82% and 23.33% for BPD participants and healthy controls, respectively. All BPD participants were considered to be receiving psychological therapy since recruitment was conducted via specialist PD services. Of the 65.90% of BPD participants who were prescribed medication, anti-depressants was most common (86.20%), jointly followed by anti-psychotics and anxiolytics (both 24.13%); Table 2.

Multicollinearity Check

To assess multicollinearity, partial correlations between all six questionnaire measures were explored whilst controlling for the influence of gender, IQ and income. As seen in table 3, strong correlations of above .7 were obtained between PAI-BOR and DERS (*r* =.80), PAI-BOR and BSI (*r* =.78), DERS and BSI (*r* = .76), SAPAS and DERS (*r* =.76), PAI-BOR and SAPAS (*r* =.73), CTQ and BSI (*r* =.72) as well as DES and BSI (*r* = .72). In view of these correlations, subsequent rs-fMRI analyses elucidated associations between RSFC and individual questionnaire measure, whilst controlling for the influence of all other measures.

Table 1. Demographic Data of Sample (Total N=74)

	Healthy Controls N (%)	**BPD Participants N (%)**	**Test Statistic**	**Significance Level (*p*-value)**
N	30	44		
Gender				
Male	16 (53.33%)	8 (18.18%)		
Female	14 (46.66%)	36 (81.81%)	$\chi^2(1, 74)= 10.05$	.002**
Age	mean (SD)	mean (SD)		
	26.50 (8.65)	29.98 (9.32)		
18-25	18 (60%)	18 (40.91%)	$t(72)=1.621$	.10
26-35	8 (26.67%)	13 (29.55%)		
36-45	1 (3.33%)	11 (25%)		
46-55	3 (10.00%)	2 (4.55%)		
Ethnicity				
White British	14 (46.67%)	28 (63.64%)	$\chi^2(1, 74)=6.44$	.265
White Other	6 (20%)	3 (6.82%)		
Black British	2 (6.67%)	3 (6.82%)		
Mixed	5 (16.67%)	3 (6.82%)		
Asian	3 (10%)	5 (11.36%)		
Any Other Background not Stated	-	2 (4.55%)		
Family Income				
Less than £10,000	7 (23.33%)	22 (50%)	$\chi^2(1, 74)=18.89$	.002**
£10,000-20,000	2 (6.67%)	12 (27.27%)		
£20,000-35,000	12 (40%)	4 (9.09%)		
£35,000-50,000	1 (3.33%)	3 (6.82%)		
£50,000-75,000	4 (13.33%)	2 (4.55%)		
£75,000-100,000	1 (3.33%)	0		
More than £100,000	0	0		
IQ	Mean (SD)	Mean (SD)		
	51.50 (5.48)	47.80 (5.97)		
Intellectually impaired	2 (6.67%)	4 (9.09%)	$t(72)=2.70$	.008**
Definitely below average	8 (26.67%)	21 (47.72%)		
Average	16 (53.33%)	18 (40.90%)		
Definitely above average	1 (3.33%)	1 (2.27%)		
Intellectually Superior	3 (10%)	0		
Education Level				
No Qualifications	2 (6.67%)	7 (15.91%)	$\chi^2(1, 74)=3.17$	6.73
Less than 5 GCSEs	3 (10%)	7 (15.91%)		
More than 5 GCSEs	6 (20%)	9 (20.45%)		
A Level	9 (30%)	9 (20.45%)		
Higher Education or Professional/Vocational Equivalent	7 (23.33%)	10 (22.73%)		
Post Graduate Education	3 (10%)	2 (4.55%)		
Years in Education	Mean (SD)	Mean (SD)	$t(72)=1.02$	.310
	13.80 (3.05)	14.89 (4.65)		
Not Stated	5 (16.67%)	8 (18.18%)		
Employment Status				
Employed	13 (43.33%)	11 (25%)	$\chi^2(1, 74)=8.18$	.042**
Student	9 (30%)	7 (15.91%)		
Carer	1 (3.33%)	1 (2.27%)		
Unemployed	7 (23.33%)	25 (56.82%)		

Note: ** represents significant p-values (<.05)

Table 2. Profile of Prescribed Medication in BPD Participants

Prescribed Medication (sorted by categories)	N (% out of 29 BPD participants who are prescribed medication)
Anti-depressants	25 (86.20%)
Anti-psychotics	7 (24.13%)
Anxiolytics	7 (24.13%)
Other	10 (34.48%)

Table 3. Partial Correlations (r) Between Total Scores of Self-report Measures after Controlling for Gender, Income and IQ

	PAI-BOR	SAPAS	CTQ	DES	DERS	BSI
PAI-BOR	-	.732**	.612	.700**	.802**	.777**
SAPAS	.732**	-	.537	.566	.760**	.694
CTQ	.612	.537	-	.653	.581	.658
DES	.700**	.566	.653	-	.618	.720**
DERS	.802**	.760**	.581	.618	-	.762**
BSI	.777**	.694	.720**	.720**	.762**	-

Note: ** indicates partial correlation of .7 and above

Seed-based RSFC Analyses

Strength of RSFC between ROIs (seeds) and Whole Brain

Strength of RSFC between a priori defined ROIs and the whole brain was performed in CONN using seed-based analysis. These ROIs are commonly termed "seeds" whilst all the other areas constituting the 'whole brain' are referred to as "voxel". In fMRI analyses, voxels are in turn denoted by the Montreal Neurological Institute (MNI) coordinates, which consists of three series of values. Identifying the corresponding brain region was accomplished by visually inspecting the results

within SPM12 and with the use of MRIcron 6/2013 programme in order to map the MNI coordinates onto brain regions (available from http://www.nitrc.org/frs/?group_id=152). Based on existing rs-fMRI BPD literature (Doll et al., 2013; Kluetsch et al., 2012; Krause-Utz et al., 2014; O' Neil et al., 2014; Wolf et al., 2011), eight core DMN regions were chosen as seeds for the current study in order to explore potential connectivity with other voxels (Appendix B13): left posterior cingulate cortex (lPCC), right PCC, left temporal parietal junction (lTPJ), right TPJ, both right and left anterior medial prefrontal cortex (ramPFC and lamPFC, respectively), dorsal medial prefrontal cortex (dmPFC) and ventromedial PFC (vmPFC).

Within Subject and Between Group Seed-whole Brain RSFC Analyses

For each seed, within-subject RSFC with head motion as a covariate was calculated using CONN, yielding a beta-value **(β).** Thus, each participant will have eight βs corresponding to the eight seeds. In order to determine whether RSFC differed between BPD participants and healthy controls, that is, between-group RSFC, the previously obtained β is transferred into SPM12 for further statistical analyses.

To address the first hypothesis that BPD participants will display atypical RSFC between core DMN regions (our selection of eight seeds) and other brain regions, between-group RSFC analysis for the eight seeds was performed using the GLM function within SPM, with gender, IQ and income as covariates. Unlike SPSS, the GLM function in SPM requires the researcher to set up a design specification whereby the level of contrast is defined using a matrix where 1 and 0 symbolize the presence and absence of contrast, respectively (please refer to Appendix B14 for elaboration of SPM design specification and statistical analysis). In the event that

non-significant between-group differences were found for any of the eight seeds, the seed(s) will be removed from the second stage of analyses which seeks to investigate our second hypothesis that seed-voxel RSFC is associated with indices of clinical and personality psychopathology. This exploratory analysis was done using the GLM function within SPM where all six questionnaires as well as the above mentioned three socio-demographic covariates were included (Appendix 15). By including all the questionnaires in the design, this enables us to investigate the unique variance of each questionnaire in association to obtained RSFC.

To facilitate interpretation of results, it is worth explaining key concepts in fMRI findings. In fMRI analyses, two sets of significance levels are produced. The first, $P_{uncorrected}$, does not correct for multiple comparisons, thereby increasing the risk of false positives and chance findings. The second and more stringent threshold which incorporates multiple comparisons correction procedures, $P_{family\ wise\ error\ corrected\ (fwe)}$ is therefore preferable (Friston et al., 1994). Lastly, these two significance levels exist at three levels of inferences; voxel, cluster and set. So, each significance level can be associated with an individual voxel or a cluster of voxels or a set of clusters. In the current study, only cluster level findings will be reported. Lastly, when making cluster level inference, the statistic of interest is the size of cluster/number of voxels in the cluster, denoted by the value of the extent threshold (K_e). Thus, all fMRI results will be reported by stipulating the brain region that displayed the strongest RSFC with the seed, followed by the corresponding MNI coordinates, P_{fwe} and lastly the K_e. In cases of non-significant P_{fwe}, the less stringent $P_{uncorrected}$ will be reported instead; with threshold for both P_{fwe} and $P_{uncorrected}$ set at .05.

Results

Personality Psychopathology

18 clinical participants who did not meet SCID-II diagnostic criteria for BPD were excluded from this study. 14% of the clinical group met criteria for only BPD whilst 15% and 11% met criteria for one and two additional PDs, respectively, with paranoid and avoidant PD being the most prevalent (Table 4). As expected, BPD participants had higher total scores on the PAI-BOR (M = 44.89, SD = 8.19) as compared to healthy controls (M = 23.57, SD = 7.52), $F(1,74) = 31.28$, $p < .0001$, $\eta^2p = .64$ as well as on all the four PAI-BOR sub-scales (Table 5). In the SAPAS, in which a score of four and above suggests increased likelihood of PD, BPD participants scored higher (M = 5.93, SD = 1.45) than healthy controls (M = 1.93, SD = 1.17), $F(1,74) = 43.11$, $p < .0001$, $\eta^2p = .71$ as shown in Table 5. Overall these results indicate the presence of significant differences in personality psychopathology between the groups, with BPD participants endorsing higher personality psychopathology.

Table 4. Profile of BPD Participants (n=44) who met SCID-II PD Diagnostic Criteria

	N (%)
Cluster A	
Paranoid	15 (34.09)
Schizoid	1 (2.27%)
Schizotypal	-
Cluster B	
Narcissistic	1 (2.27%)
Histrionic	-
Antisocial	11 (25%)
Cluster C	
Obsessive Compulsive	3 (6.81%)
Avoidant	15 (34.09%)
Dependant	-
SCID data absent except for BPD section	2 (4.54%)
Lack of reliability for SCID data except for BPD section	1 (2.27%)
Participants who met criteria for only BPD	14 (31.81%)
Participants who met criteria for BPD and 1 additional PD	15 (34.09%)
Participants who met criteria for BPD and 2 additional PDs	11 (25%)
Participants who met criteria for BPD and 3 additional PDs	2 (4.54%)
Participants who met criteria for BPD and 4 additional PDs	1 (2.27%)

Clinical Symptomatology

With gender, IQ and household income as covariates, Levene's test indicated that apart from the minimization scale of the CTQ, all total scores and sub-scale scores of the CTQ, DES, DERS and BSI differed significantly between the groups (Table 5). Expectedly, BPD participants had higher CTQ total scores (M = 76.25, SD = 23.11) as compared to healthy controls (M = 37.37, SD = 11.93), with $F(1,74)$ = 19.83, p <.0001, η^2p =.53. As seen in Table 5, BPD participants reported significantly higher emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. BPD participants also reported more dissociative experiences (M = 111.86, SD = 57.06) than healthy controls (M = 32.97, SD = 30.22), $F(1,74)$ = 12.15, p <.0001, η^2p =.41. Based on the DERS, BPD participants also had greater difficulties in emotional regulation (M = 139.27, SD = 18.60), in comparison to healthy controls (M = 75.03, SD = 21.25), which corresponded to results of the Levene's test $F(1,74)$ = 46.57, p <.0001, η^2p =.73. This corresponded with BPD participants scoring significantly higher on all the six sub-scales of DERS as compared to healthy controls (Table 6). Lastly, higher averaged scores on the BSI suggest that BPD participants (M = 2.33, SD = .81) experienced greater severity of clinical symptoms, including psychoticism and anxiety (Table 6) as compared to healthy controls (M = .43, SD = .52), $F(1,74)$ = 30.57, p <.0001, η^2p =.63. In summary, as compared to healthy controls, BPD participants reported more experiences of trauma, increased tendencies to dissociate, greater difficulties in emotional regulation as well as higher general clinical symptomatology, with these differences meeting the significance threshold.

Table 5. Profile of PAI-BOR, SAPAS, CTQ and DES in Participants (controlled for gender, IQ and household income)

	Healthy Controls Mean (SD)	**BPD participants Mean (SD)**	**Test Statistic (*f*)**	**Significance Level (*p*-value)**	**η^2p**
Personality Psychopathology					
PAI-BOR					
Affective Instability	6.03 (1.95)	10.61 (2.41)	18.27	<.0001**	.51
Identity Problems	6.27 (3.29)	12.95 (3.29)	19.59	<.0001**	.53
Negative Relationships	7 (2.77)	10.77 (2.64)	9.00	<.0001**	.34
Self-Harm	4.27 (1.94)	10.55 (3.45)	20.17	<.0001**	.53
Total Score	23.57 (7.52)	44.89 (8.19)	31.28	<.0001**	.64
SAPAS					
Total Score	1.93 (1.17)	5.93 (1.45)	43.11	<.0001**	.71
Clinical Symptomatology					
CTQ					
Emotional Abuse	8.17 (3.64)	19.27 (5.36)	24.37	<.0001**	.58
Physical Abuse	6.37 (2.76)	12.95 (7.25)	6.73	<.0001**	.28
Sexual Abuse	5.70 (2.15)	12.20 (8.30)	7.39	<.0001**	.30
Emotional neglect	10.20 (4.99)	19.09 (4.46)	16.62	<.0001**	.49
Physical Neglect	6.93 (2.34)	12.73 (4.91)	9.45	<.0001**	.35
Minimization	.40 (.894)	.07 (.25)	1.42	.23	.07
Total Score	37.37 (11.93)	76.25 (23.11)	19.83	<.0001**	.53
DES					
Total Score	32.97 (30.22)	111.86 (57.06)	12.15	<.0001**	.41

Note: ** represents significant p-values (<.05)

Table 6. Profile of DERS and BSI in Participants (controlled for gender, IQ and household income)

	Healthy Controls Mean (SD)	**BPD participants Mean (SD)**	**Test Statistic (*f*)**	**Significance Level (*p*-value)**	η^2p
DERS					
Non-acceptance of Emotional Responses	10.93 (5.07)	23.39 (5.32)	25.65	<.0001**	.59
Difficulties Engaging in Goal-oriented Behaviours	14.43 (5.03)	22.14 (3.12)	16.98	<.0001**	.49
Difficulties Controlling Impulses	10 (3.82)	24.50 (5.55)	37.48	<.0001**	.68
Lack of Emotional Awareness	14.97 (5.79)	18.64 (4.22)	4.46	.003**	.20
Lack of Access to Emotion Regulation Strategies	15.20 (6.15)	32.89 (5.39)	41.57	<.0001**	.70
Lack of Emotional Clarity	9.50 (3.81)	17.73 (4.35)	17.47	<.0001**	.50
Total Score	75.03 (21.25)	139.27 (18.60)	46.57	<.0001**	.73
				<.0001**	
BSI					
Somatization	.38 (.48)	1.82 (.99)	14.35	<.0001**	.45
Obsessive Compulsive	.75 (.81)	2.58 (1.00)	16.94	<.0001**	.49
Interpersonal Sensitivity	.42 (.55)	2.76 (1.00)	32.16	<.0001**	.65
Depression	.59 (.85)	2.95 (.83)	34.35	<.0001**	.66
Anxiety	.41 (.64)	2.35 (1.06)	19.22	<.0001**	.52
Hostility	.32 (.42)	2.35 (1.06)	15.55	<.0001**	.47
Phobic Anxiety	.22 (.47)	2.03 (1.17)	16.12	<.0001**	.48
Paranoid	.44 (.69)	2.18 (1.05)	16.05	<.0001**	.48
Psychoticism	.30 (.54)	2.25 (.86)	29.87	<.0001**	.63
General Severity index	.43 (.52)	2.33 (.81)	30.57	<.0001**	.63

Note: ** represents significant p-values (<.05)

Hypothesis 1: Group Differences in Seed-Whole Brain RSFC

Partially in line with the first hypothesis, after controlling for the influence of gender, IQ and income, group differences in RSFC were present for five of the eight seeds: lPCC, lTPJ, ramPFC, lamPFC and dmPFC, but not rPCC, rTPJ and vmPFC. Only significant findings for each of the five seeds will be reported here as well as summarized in Table. Figures 3 to 8 provide a pictorial representation of these results. Appendix 16 presents all the original tables of results produced in SPM12.

BPD participants displayed higher RSFC between five of the seeds and six brain regions. However, only one of this six seed-whole brain RSFC analyses survived Family Wise Error correction; that of the dmPFC seed and left middle temporal gyrus (-54 -76 16), $P_{fwe} = .016$, $K_e = 220$. At the $P_{uncorrected}$ level, BPD participants displayed higher RSFC between the:

lPCC seed and left cerebellar lobule Crus 1 (-24 -66 -32), $P_{uncorrected} = .005$, $K_e = 145$

lTPJ seed and right superior medial frontal gyrus (6 46 52), $P_{uncorrected} = .004$, $K_e = 158$

ramPFC seed and right middle frontal gyrus (44 15 50), $P_{uncorrected} = .034$, $K_e = 88$

lamPFC seed and left middle temporal gyrus (14 34 64), $P_{uncorrected} = .017$, $K_e = 120$

dmPFC seed and left middle frontal gyrus (-36 54 8), $P_{uncorrected} = .008$, $K_e = 126$

Table 7. Significant Between-group Differences in Seed-whole Brain RSFC, Controlled for Gender, IQ and Income

	Cluster Level						
	$P_{uncorrected}$	**$P_{family\ wise\ error\ corrected}$ (P_{fwe})**	**Extent Threshold (K_e)**	**MNI Coordinates of Voxel**			**MNI Coordinate Region**
				x	y	z	
Left precuneus (lPCC)	.005**	.082	145	-24	-66	-32	Left cerebellar lobule Crus 1
Left temporal parietal junction (lTPJ)	.004**	.062	158	6	46	52	Right superior frontal gyrus, medial
Right anterior medial prefrontal cortex (ramPFC)	.034**	.402	88	44	15	50	Right middle frontal gyrus
Left anterior medial prefrontal cortex (lamPFC)	.017**	.219	120	14	34	64	Right superior frontal gyrus, medial
Dorsal medial prefrontal cortex (dmPFC)	.001**	.016**	220	-54	-76	16	Left middle temporal gyrus
	.008**	.132	126	-36	54	8	Left middle frontal gyrus

Note: The set-up in SPM12 specify that results reflect higher RSFC in BPD participants as compared to healthy control. $P_{uncorrected:}$ excludes correction for multiple comparisons. $P_{family\ wise\ error\ corrected:}$ takes into consideration multiple comparisons and therefore, is recommended over $P_{uncorrected}$. Extent threshold: number of voxels in the cluster that is correlated with the seed region. ** indicates significant p-values at threshold of .05

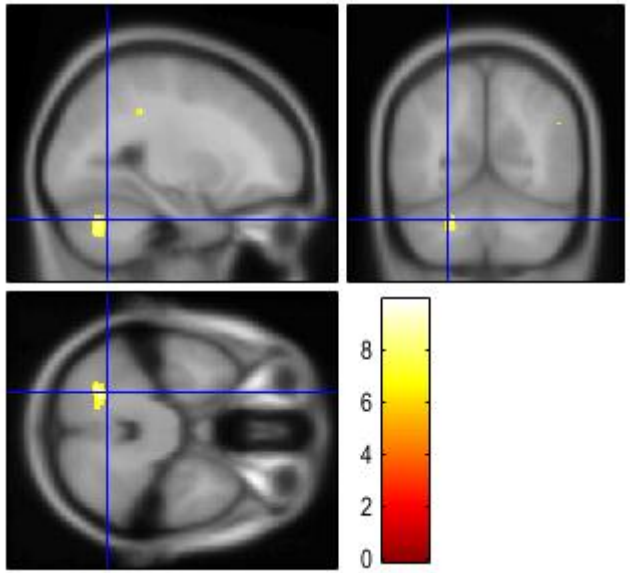

Figure 3. Higher RSFC between lPCC seed and peak voxel of left cerebellar lobule Crus 1 in BPD participants; with the crosshair depicting location of voxel

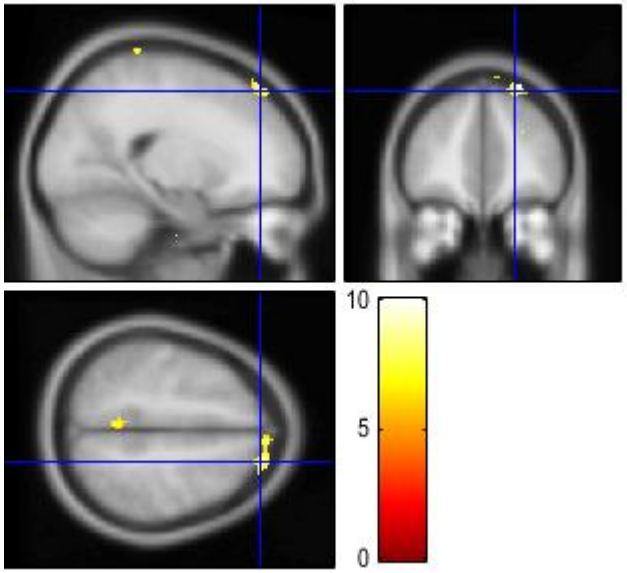

Figure 4. Higher RSFC between lTPJ seed and peak voxel of right superior frontal gyrus, medial in BPD participants; with the crosshair depicting location of voxel

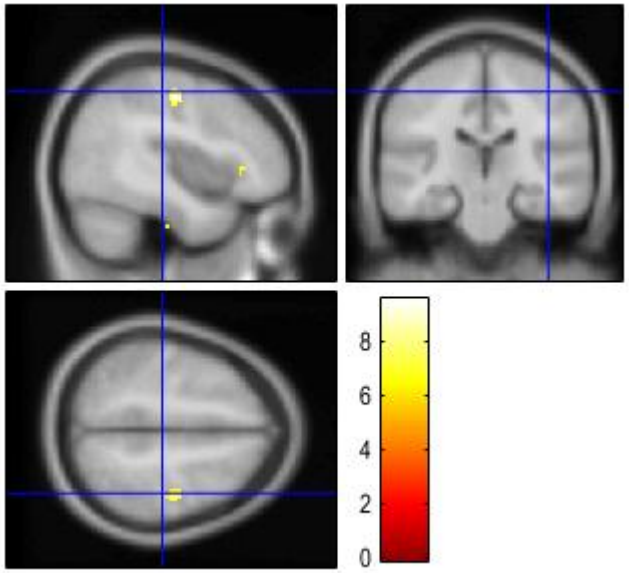

Figure 5. Higher RSFC between ramPFC seed and peak voxel of right middle frontal gyrus in BPD participants; with the crosshair depicting location of voxel

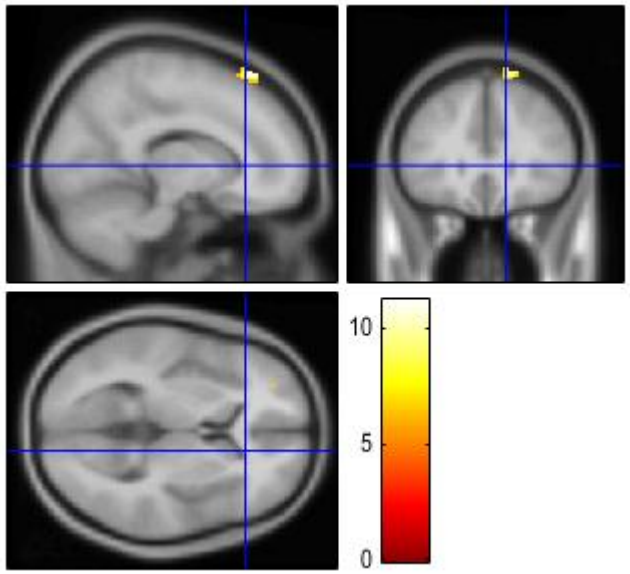

Figure 6. Higher RSFC between lamPFC seed and peak voxel of right superior frontal gyrus, medial in BPD participants; with the crosshair depicting location of voxel

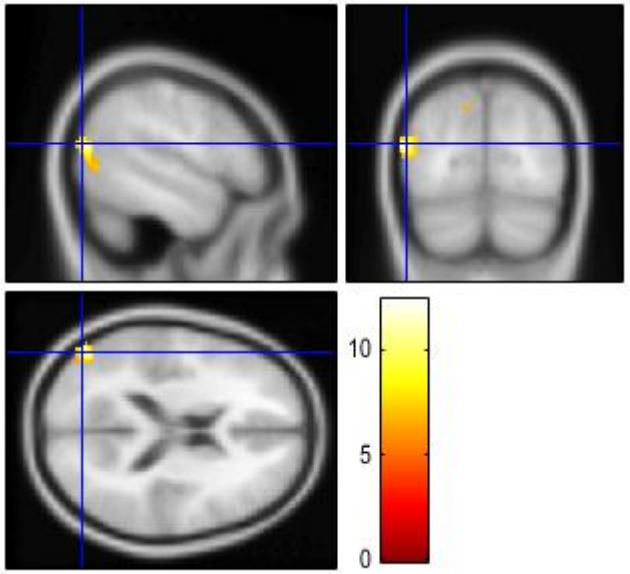

Figure 7. Higher RSFC between dmPFC seed and peak voxel left middle temporal gyrus in BPD participants; with the crosshair depicting location of voxel

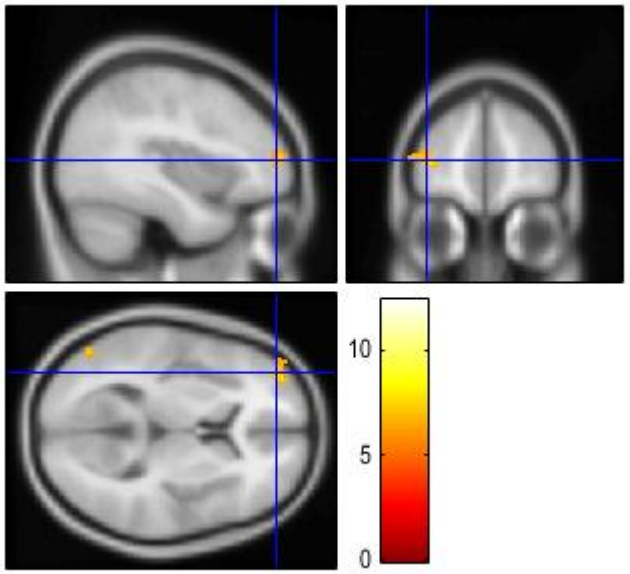

Figure 8. Higher RSFC between dmPFC seed and peak voxel left middle frontal gyrus in BPD participants; with the crosshair depicting location of voxel

Hypothesis 2: Exploratory Analysis of RSFC and Associations with Indices of Psychopathology in BPD Participants

In terms of the second hypothesis, the current study found that in BPD participants, RSFC for all five seeds were in turn associated with selected indices of psychopathology, even after controlling for the potential influence of the three sociodemographic covariates and other questionnaire measures. However, it is crucial to highlight that none of these associations were significant at the P_{fwe} level, and therefore should be interpreted cautiously. The following paragraphs will further elaborate on these findings, which are also summarized in Tables 8 to 10.

Personality Psychopathology and Seed-Whole Brain RSFC

In this study, SAPAS and PAI-BOR were included as indices of personality psychopathology. However, results suggest that in BPD participants, there were no significant associations between both measures and RSFC arising from any of the five seeds.

Clinical Psychopathology and Seed-Whole Brain RSFC

Firstly, in BPD participants, except for DERS, all the other measures were found to be significantly associated with RSFC across one or more seeds at the $P_{uncorrected}$ level. More importantly, these associations remained significant even after covariation for sociodemographic variables and the rest of the questionnaires.

Childhood Trauma (CTQ) and Seed-Whole Brain RSFC

Across four of the five seeds, significant findings between RSFC and total CTQ scores were obtained, in that stronger seed-voxel RSFC was associated with higher self-reported childhood trauma. This includes RSFC between 1. lPCC seed and both left inferior temporal gyrus (-52 -50 -20), $P_{uncorrected} = .010$, $K_e = 139$ and left fusiform gyrus (-38 -42 -22), $P_{uncorrected} = .010$, $K_e = 139$; 2. lTPJ seed and left middle frontal gyrus (-20 40 26), $P_{uncorrected} = .021$, $K_e = 266$; 3. lamPFC and both left

and right supramarginal gyrus (-64 -22 40/ 70 -26 24), $P_{uncorrected}$ = .018/.023, K_e = 147/132 as well as with the right postcentral gyrus (66 -16 18), $P_{uncorrected}$ = .023, K_e = 132 and 4. dmPFC seed and both right postcentral gyrus (66 -14 18), $P_{uncorrected}$ = .006, K_e = 172 as well as right inferior frontal gyrus (28 34 -20), $P_{uncorrected}$ = .038, K_e = 87. Figures 9 to 16 provide a pictorial representation of these associations.

Dissociative Experiences (DES) and Seed-Whole Brain RSFC

Within the BPD group, higher RSFC between two seeds and left precentral gyrus were found to be associated with scores on the DES. Namely, RSFC between the ramPFC seed and left precentral gyrus (-38 -10 50), $P_{uncorrected}$ = .013, K_e = 159 as well as between the lamPFC seed and left precentral gyrus (-40 -10 52), $P_{uncorrected}$ = .035, K_e = 111 were associated with higher self-reported dissociative experiences, as illustrated in Figure 17 and 18.

BSI and Seed-Whole Brain RSFC

To reiterate, the BSI is a self-report measure encompassing eight categories of clinical symptoms, including depression and anxiety. As seen in figures 19 to 21, BPD participants displayed higher RSFC between the dmPFC seed and three brain regions, including left cerebellar lobule Crus 2 (-16 -92 -28), $P_{uncorrected}$ = .007, K_e = 165, left inferior parietal lobule (-36 -76 50), $P_{uncorrected}$ = .008, K_e = 154 and right cerebellar lobule Crus 1 (34 -82 -28), $P_{uncorrected}$ = .039, K_e = 86. These three patterns of higher RSFC in BPD participants were in turn linked to higher averaged BSI scores indicated by the “general severity index”.

Table 8. Profile of the lPCC and lTPJ Seeds and Associations with the Six Questionnaire Measures; Controlled for other Questionnaire Measures, Gender, IQ and Income

	Cluster Level						
	$P_{uncorrected}$	P_{fwe}	K_e	MNI Coordinates of Voxel			MNI Coordinate Region
				x	y	z	
lPCC							
PAIBOR	.483	-	-	-	-	-	-
SAPAS	.257	-	-	-	-	-	-
CTQ	.010**	.139	143	-52	-50	-20	Left inferior temporal gyrus
				-38	-42	-22	Left fusiform gyrus
DES	.190	-	-	-	-	-	-
DERS	.395	-	-	-	-	-	-
BSI	.115	-	-	-	-	-	-
lTPJ							
PAIBOR	.189	-	-	-	-	-	-
SAPAS	.256	-	-	-	-	-	-
CTQ	.021**	.266	110	-20	40	26	Left middle frontal gyrus
DES	.135	-	-	-	-	-	-
DERS	.211	-	-	-	-	-	-
BSI	.228	-	-	-	-	-	-

Note: ** indicates significant p-values at threshold of .05. For non-significant findings at $P_{uncorrected}$ level, P_{fwe}, K_e, MNI Coordinates of Voxel and MNI coordinate region will not be reported, as indicated by (-)

Table 9. Profile of the ramPFC and lamPFC Seeds and Associations with the Six Questionnaire Measures; Controlled for other Questionnaire Measures, Gender, IQ and Income

	Cluster Level						
	$P_{uncorrected}$	**P_{fwe}**	**K_e**	**MNI Coordinates of Voxel**			**MNI Coordinate Region**
				x	y	z	
ramPFC							
PAIBOR	.256	-	-	-	-	-	-
SAPAS	.337	-	-	-	-	-	-
CTQ	.314	-	-	-	-	-	-
DES	.013**	.149	159	-38	-10	50	Left precentral gyrus
DERS	.173	-	-	-	-	-	-
BSI	.072	-	-	-	-	-	-
lamPFC							
PAIBOR	.126	-	-	-	-	-	-
SAPAS	.280	-	-	-	-	-	-
CTQ	.018**	.191	147	-64	-22	40	Left supramarginal gyrus
	.023**	.244	132	70	-26	24	Right supramarginal gyrus
				66	-16	18	Right postcentral gyrus
DES	.035**	.344	111	-40	-10	52	Left precentral gyrus
DERS	.059	-	-	-	-	-	-
BSI	.087	-	-	-	-	-	-

Note: ** indicates significant p-values at threshold of .05. For non-significant findings at $P_{uncorrected}$ level, P_{fwe}, K_e, MNI Coordinates of Voxel and MNI coordinate region will not be reported, as indicated by (-)

Table 10. Profile of the dmPFC Seed and Associations with the Six Questionnaire Measures; Controlled for other Questionnaire Measures, Gender, IQ and Income

	Cluster Level						
	$P_{uncorrected}$	**P_{fwe}**	**K_e**	**MNI Coordinates of Voxel**			**MNI Coordinate Region**
				x	y	z	
dmPFC							
PAIBOR	.142	-	-	-	-	-	-
SAPAS	.137	-	-	-	-	-	-
CTQ	.006**	.081	172	66	-14	18	Right postcentral gyrus
	.038**	.425	87	28	34	-20	Right Inferior frontal gyrus, orbital part
DES	.133						
DERS	.060	-	-	-	-	-	-
BSI	.007**	.092	165	-16	-92	-28	Left cerebellar lobule Crus 2
	.008**	.114	154	-36	-76	50	Left inferior parietal lobule
	.039**	.433	86	34	-82	-28	Right cerebellar lobule Crus 1

Note: ** indicates significant p-values at threshold of .05. For non-significant findings at $P_{uncorrected}$ level, P_{fwe}, K_e, MNI Coordinates of Voxel and MNI coordinate region will not be reported, as indicated by (-)

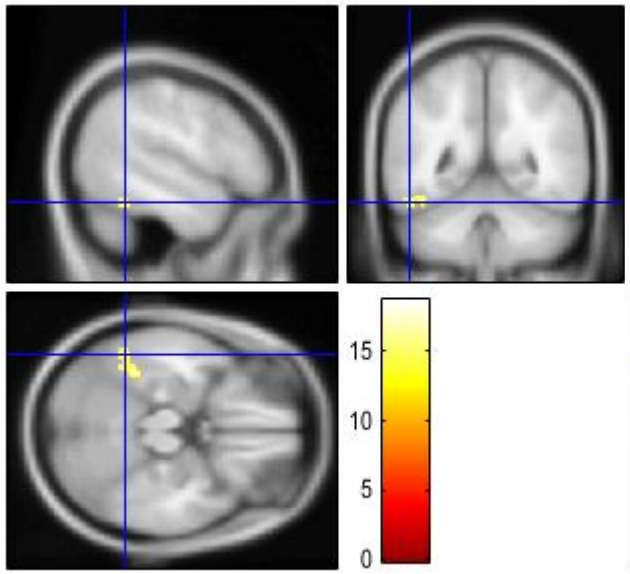

Figure 9. Higher RSFC between lPCC seed and peak voxel of left inferior temporal gyrus in BPD participants in association with CTQ scores; with the crosshair depicting location of voxel

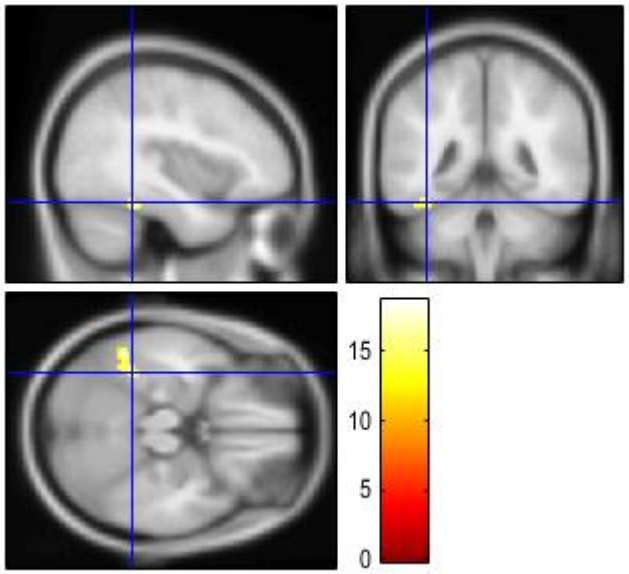

Figure 10. Higher RSFC between lPCC seed and peak voxel of left fusiform gyrus in BPD participants in association with CTQ scores; with the crosshair depicting location of voxel

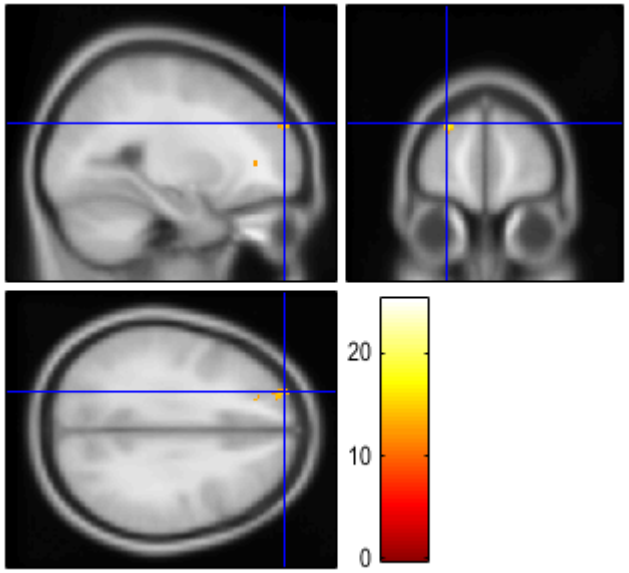

Figure 11. Higher RSFC between lTPJ seed and peak voxel of left middle frontal gyrus in BPD participants in association with CTQ scores; with the crosshair depicting location of voxel

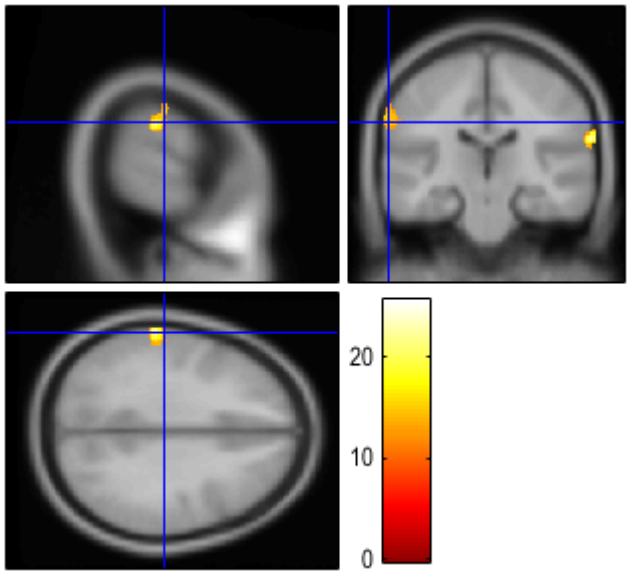

Figure 12. Higher RSFC between lamPFC seed and peak voxel of left supramarginal gyrus in BPD participants in association with CTQ scores; with the crosshair depicting location of voxel

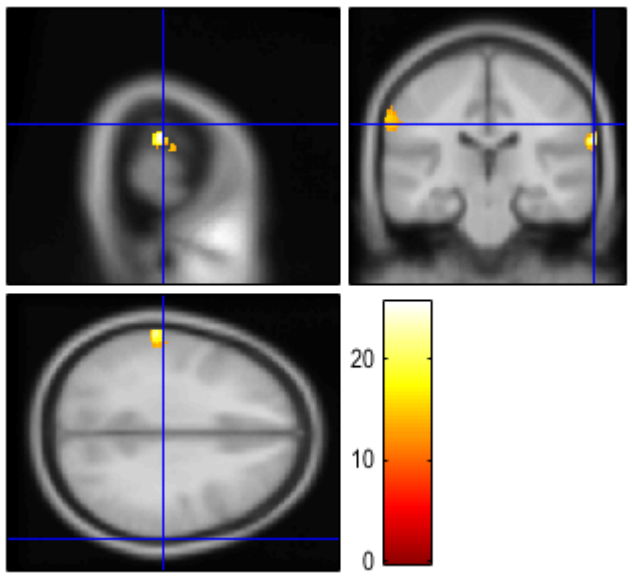

Figure 13. Higher RSFC between lamPFC seed and peak voxel of right supramarginal gyrus in BPD participants in association with CTQ scores; with the crosshair depicting location of voxel

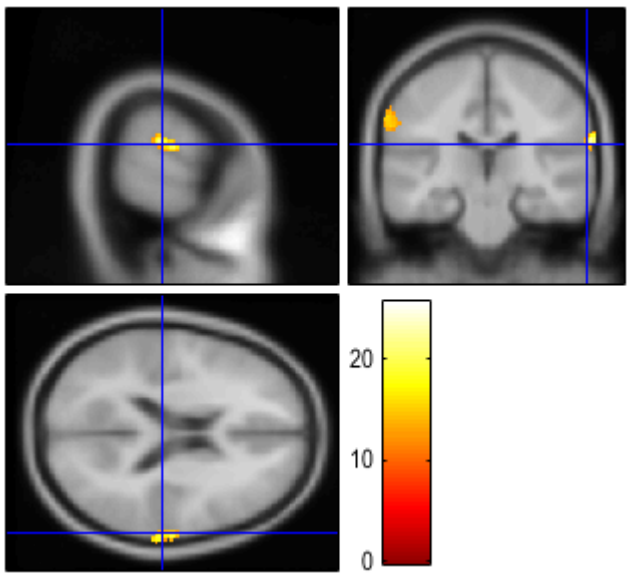

Figure 14. Higher RSFC between lamPFC seed and peak voxel of right postcentral gyrus in BPD participants in association with CTQ scores; with the crosshair depicting location of voxel

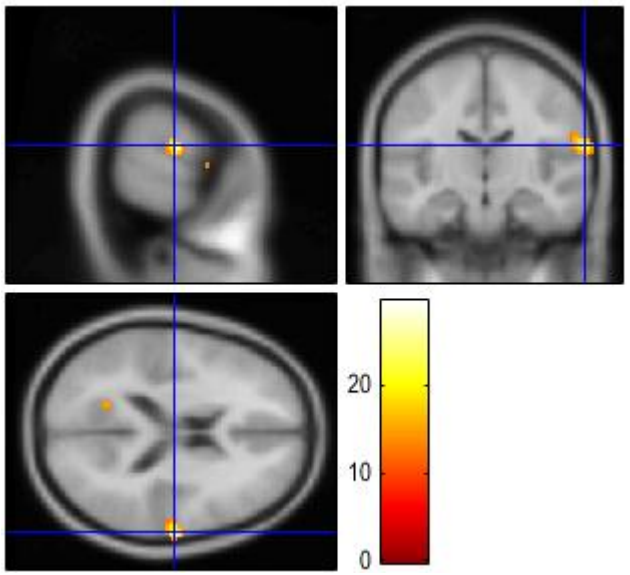

Figure 15. Higher RSFC between dmPFC seed and peak voxel of right postcentral gyrus in BPD participants in association with CTQ scores; with the crosshair depicting location of voxel

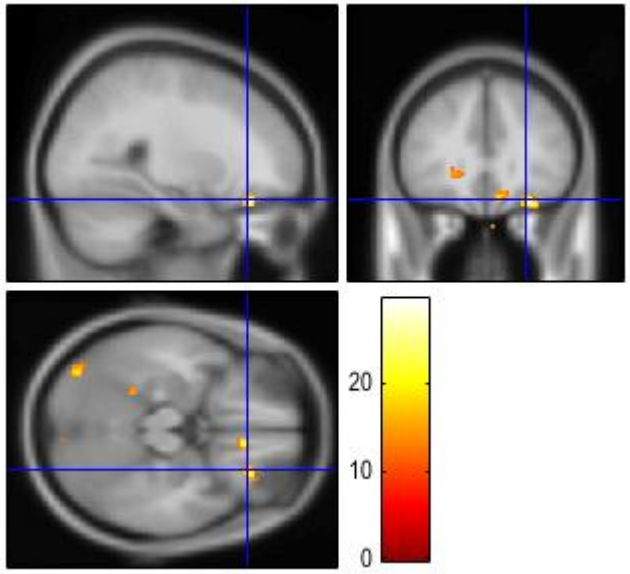

Figure 16. Higher RSFC between dmPFC seed and peak voxel of right inferior frontal gyrus, orbital part in BPD participants in association with CTQ scores; with the crosshair depicting location of voxel

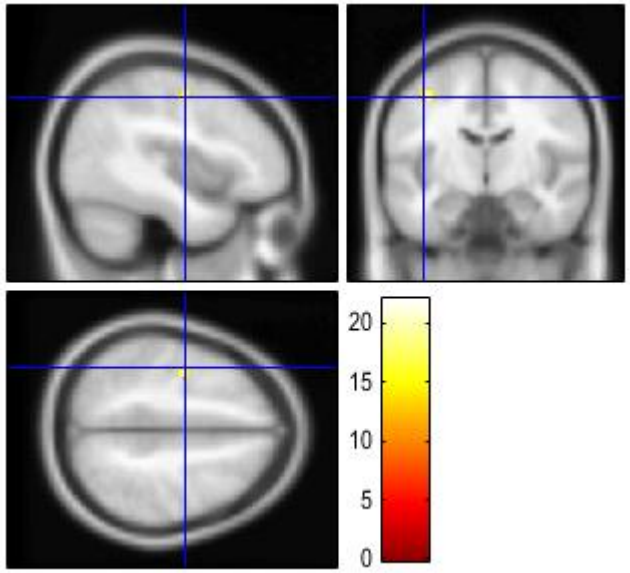

Figure 17. Higher RSFC between ramPFC seed and peak voxel of left precentral gyrus in BPD participants in association with DES scores; with the crosshair depicting location of voxel

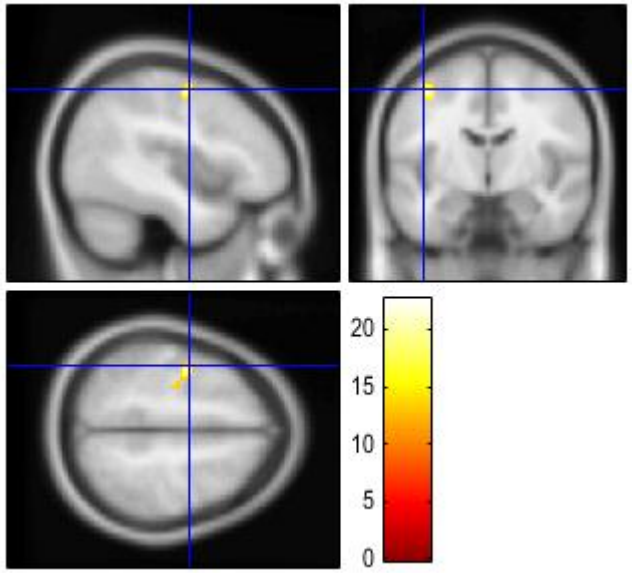

Figure 18. Higher RSFC between lamPFC seed and peak voxel of left precentral gyrus in BPD participants in association with DES scores; with the crosshair depicting location of voxel

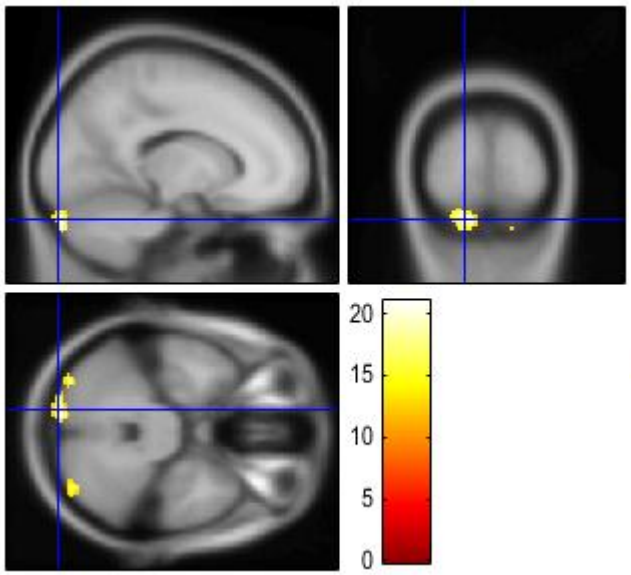

Figure 19. Higher RSFC between dmPFC seed and peak voxel of left cerebellar lobule Crus 2, orbital part in BPD participants in association with BSI scores; with the crosshair depicting location of voxel

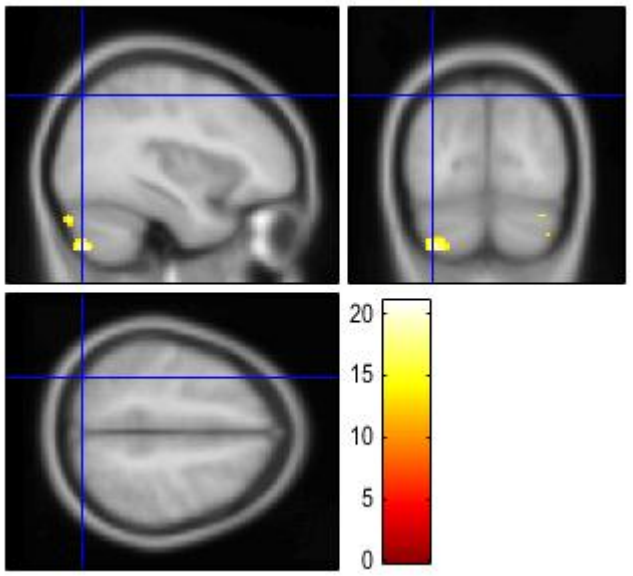

Figure 20. Higher RSFC between dmPFC seed and peak voxel of left inferior parietal lobule in BPD participants in association with BSI scores; with the crosshair depicting location of voxel

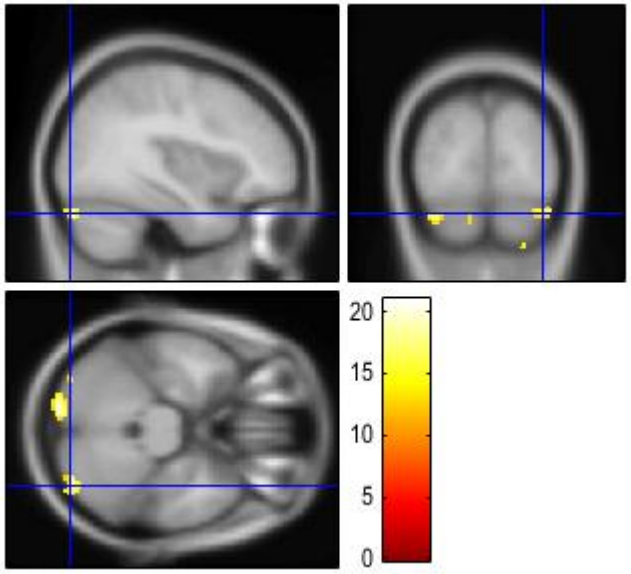

Figure 21. Higher RSFC between dmPFC seed and peak voxel of right cerebellar lobule Crus 1 in BPD participants in association with BSI scores; with the cross0hair depicting location of voxel

Discussion

The first aim of the current study is to investigate the hypothesis that compared to healthy controls, BPD participants will display atypical RSFC. The second aim is to address the hypothesis that observed RSFC is associated with indices of personality and clinical psychopathology. This section will first discuss the obtained findings in relation to current literature and the wider theoretical context. Alternative explanations and limitations of the present study will also be considered along with implications for future research and clinical psychology.

Atypical Seed-whole brain RSFC in BPD Participants

In the absence of external demands, and controlling for the influence of gender, IQ and income, this study found that as compared to healthy controls, BPD participants displayed higher RSFC between five of the eight seeds and specific voxels. However, it is crucial to highlight that only RSFC between the dmPFC seed and left middle temporal gyrus (lMTG) remained significant after correcting for multiple comparisons. Therefore, this finding will be further elaborated followed by a brief discussion of findings that were only significant before controlling for multiple comparisons.

Significant RSFC between dmPFC seed and lMTG at P_{fwe} Level

The temporal lobe subserves a myriad of functions including memory and sensory processing. With the use of independent component analysis (ICA), a method that investigates RSFC without a prior selected region, Wolf et al. (2011) found reduced RSFC within the right middle temporal lobe in BPD participants. In contrast, the current study found increased RSFC between the dmPFC and left middle temporal lobe. Interestingly, two separate task-based fMRI studies found that

as compared to healthy controls, BPD participants displayed atypical neural activity in the temporal lobe. In the first study based on an emotional stroop task, BPD participants exhibited lower neural activity in the temporal lobe, which was hypothesized to be associated with reduced attentional and emotional modulation, consistent with their scores on the task (Wingenfeld et al., 2009). In the second study where participants had to identify an emotional face amongst neutral faces, BPD participants were found to display higher neural activity within the temporal lobe, which was in turn correlated with higher impulsivity scores (Guitart-Masip et al., 2009). Thus, while existing findings suggest atypical connectivity within the temporal lobe in BPD, results from current rs-fMRI and task-based fMRI studies remain inconclusive.

Despite the contradictory findings, the current study found that BPD participants displayed higher RSFC between the dmPFC seed and lMTG, an association that remained significant after correction for multiple comparisons. The dmPFC is established to be a core DMN region underpinning social cognition and mental simulations relevant to oneself (Buckner et al., 2008; Dutta et al., 2014). On the other hand, the lMTG has been hypothesized to be involved in emotional processing, episodic memory and sensory integration (Guitart-Masip et al., 2009). Interestingly, several task-based fMRI studies suggest the presence of atypical activity of the lMTG in BPD. Firstly, BPD participants were found to display higher activation of the lMTG as compared to healthy controls in response to both negative and positive affective stimuli (Frick et al., 2012). In addition, the researchers also found that BPD participants were better at discriminating between the affective stimuli, which was in turn hypothesized to be associated with hypervigilance of affective social cues in BPD (Frick et al., 2012). In a separate study by Schulze,

Schmahl & Niedtfeld (2015), as compared to healthy controls, BPD participants displayed higher connectivity in lMTG when processing negative stimuli. Moving away from the domain of emotional processing, a study by Mensebach et al. (2009) found that during an episodic memory recall task, BPD participants displayed increased activation of the lMTG as compared to healthy controls. Episodic memory constitutes event related and contextual memory (Cabeza and Nyberg, 2000). Lastly, apart from fMRI studies, a MRI study by Rossi et al. (2013) was used to investigate the presence of structural abnormalities in BPD participants as compared to participants with bipolar disorder. The researchers found reduced grey matter volume of the lMTG in BPD participants (Rossi et al., 2013).

Taken together, these findings suggest the presence of atypical activation of the lMTG in emotional processing and recall of episodic memory, along with reduced grey matter volume of lMTG in BPD participants. Thus, one plausible explanation for the significant finding of higher RSFC between the dmPFC seed and lMTG obtained in the current study is that in the absence of external tasks, BPD participants might experience higher self-generate internal activities related to episodic memories or of emotional valence. In summary, findings from the current study and existing literature suggest neurobiological aberration of the lMTG in BPD, an area that warrants future research.

Significant RSFC within the Frontal Lobe and Cerebellum at $P_{uncorrected}$ Level

The findings discussed in this section were only significant prior to correction for multiple comparisons and therefore should be interpreted cautiously. Several seed-voxels associations were located within the frontal lobe, including that of dmPFC seed and left middle frontal gyrus (lMFG), lTPJ seed and right superior frontal gyrus, medial part (rSFG) as well as between the ramPFC seed and right

middle frontal gyrus (rMFG). Lastly, higher RSFC between lPCC and prefrontal projecting cerebellar lobule 1 was also found in BPD participants. To briefly explicate these findings, these RSFC will be explored with reference to existing MRI literature.

In line with the hypothesis by Wolf et al. (2011) that BPD participants will exhibit higher RSFC in the frontal lobe, a region hugely involved in executive control, the current study found higher RSFC in rSFG and bilateral MFG across four seeds. Interestingly, Wolf et al. (2011) did not obtain findings concordant with their hypothesis, and hypothesized that this could be because BPD participants were less likely to be emotionally aroused or require executive control during resting state thereby resulting in minimal connectivity within the frontal lobe. However, two other studies found evidence of increased RSFC within the frontal lobe. In the first study, O'Neil et al. (2014) found that BPD participants displayed higher RSFC between the PCC seed, left inferior frontal gyrus and left middle frontal lobe. In the second study, Doll et al. (2003) found that BPD participants displayed the highest RSFC within the frontal lobe. In summary, the uncorrected significant results of the current study and contradictory findings of existing literature suggest the need for further research in order to investigate RSFC of frontal lobe in BPD.

With PCC as a seed, increased RSFC between PCC and left cerebellar lobule Crus 1 (part of the cerebellum) was obtained in the current study. To make sense of the finding, we direct our attention to the study by Das, Calhoun, & Malhi (2014) in which participants with bipolar disorder displayed the highest RSFC between the PCC and DMN as compared to BPD participants and healthy controls. In the study by Das, Calhoun, & Malhi (2014), the DMN comprised of the cerebellum ($K_e = 72$) and seven other voxel regions, including ACC ($K_e = 1719$) and left inferior parietal

lobule (K_e = 719). Looking at the K_e values, it is evident that the cluster size for cerebellum is extremely low as compared to the other clusters. In addition, it is imperative to highlight that similar to the current study, these findings did not meet the significance threshold upon correction for multiple comparisons. Therefore, the uncorrected results from the current study in conjunction with Das, Calhoun, & Malhi (2014) would strongly suggest that increased RSFC with the cerebellum observed in BPD participants might be due to chance.

Implications of Seed-whole brain RSFC Findings

It is evident from the findings discussed thus far that not all voxels in the obtained RSFC findings are core DMN regions. As mentioned, core DMN regions includes PCC, precuneus, ACC, mPFC, inferior parietal lobe and medial temporal lobe (Andrews-Hanna, Reidler, Sepulcre, Poulin & Buckner, 2010; Buckner, Andrews-Hanna, & Schacter, 2008; Greicius et al., 2003). Consequently, one possible explanation is that atypical intrinsic connectivity in BPD participants might extend beyond the DMN, a position that warrants further investigation. Notwithstanding the different analytical methods and chosen seeds, the second observation pertains to the implications associated with the directionality of obtained RSFC; in this case what does higher or lower RSFC obtained for BPD participants signify? Unfortunately, this remains an area that attracts much speculation.

In relation to the current findings, almost all of the aforementioned frontal and temporal voxel regions are situated within the core DMN. However, as only the RSFC between the dmPFC seed and lMTG remained significant after correction for family wise error, these findings should be cautiously interpreted. For now, higher RSFC with the aforementioned frontal and temporal regions observed in BPD participants might tentatively reflect atypical intrinsic connectivity, an area that

warrants further research. As readers might recall from the introduction section, the mentalization framework was used to explain core mechanisms and dysregulation. Unfortunately in the current study, none of the obtained atypical RSFC findings corresponded to brain regions associated with mentalization. In the next section, we explore the associations between RSFC findings and indices of personality and clinical psychopathology.

RSFC and Associations with Personality Psychopathology

Exploratory analysis revealed that neither the SAPAS nor PAI-BOR were associated with seed-voxel RSFC. Furthermore, even though four previous studies had included the borderline symptom list, none investigated the associations with RSFC (Doll et al., 2013; Kluetsch et al., 2012; Krause-Utz et al., 2014; Wolf et al., 2011). A hypothesis that might be relevant here pertains to an increasingly popular position in clinical psychology where psychopathology is understood using a dimensional rather than categorical approach (Krueger, Chentsova-Dutton, Markon, Goldberg, & Ormel, 2003). Thus, this stance emphasizes individual symptomatology and difficulties which might be less represented in diagnosis-led measures. To address this, future rs-fMRI studies have to explicitly investigate the associations between RSFC and indices of personality psychopathology.

RSFC and Associations with Clinical Symptomatology

In BPD participants, with the exception of DERS, higher RSFC between four seeds and specific voxels were associated with higher scores on three indices of clinical symptomatology. However, as none of these associations were significant after correction for multiple comparisons procedures, results should be interpreted cautiously. Firstly, childhood experienced trauma as indicated in the self-report CTQ was associated with higher RSFC between the 1. lPCC seed, left inferior temporal

gyrus (part of temporal lobe) and left fusiform gyrus (part of temporal and occipital lobe) 2. lTPJ seed and left middle frontal gyrus (part of frontal lobe) 3. lamPFC seed, bilateral supramarginal gyrus and right postcentral gyrus (the latter two are part of parietal lobe) 4. dmPFC seed and right post central gyrus. Moving away from trauma, increased prevalence of dissociative experiences as measured with the DES was related to higher RSFC in BPD participants, particularly between left precentral gyrus (part of frontal lobe) and two seed regions of ramPFC and lamPFC. Lastly, increased severity of general clinical symptomatology based on averaged scores on the BSI was associated with higher RSFC between the dmPFC seed, left cerebellar lobule Crus 2 (part of cerebellum), left inferior parietal lobule (part of parietal lobe) and right cerebellar lobule Crus 1 (part of cerebellum). The proceeding paragraphs will elaborate on these associations.

Difficulties in Emotional Regulation

Whilst the present study did not find any associations between difficulties in emotional regulation, this was not the case for Das, Calhoun, & Malhi (2014). The researchers found that reduced RSFC between the salience network and right fronto-parietal region was correlated with impulse control difficulties measured using DERS. In addition, they found that reduced emotional clarity and emotional awareness of DERS was associated with increased RSFC between salience network and vmPFC in bipolar disorder participants, but not BPD participants. The overarching mentalization framework asserts the centrality of emotional dysregulation in BPD symptomatology. Yet, based on current findings, the relationship between RSFC in BPD and emotional dysregulation remains unclear. Thus, further research is warranted.

Trauma Experienced in Childhood

Even though two previous rs-fMRI BPD (Das, Calhoun, & Malhi, 2014; Krause-Utz et al., 2014) and three rs-fMRI PTSD (Bluhm et al., 2009; Philip et al., 2013a; Philip et al., 2013b) incorporated the CTQ, none investigated corresponding associations with obtained RSFC findings, thereby limiting comparisons. Despite this, existing rs-fMRI have established atypical RSFC in PTSD and experienced trauma, mainly for ACC, mPFC, insula and amygdala (Bluhm et al., 2009; Sripada et al., 2012). Furthermore, these RSFC are linked to PTSD symptomatology, such as hyper-arousal, impaired memory processes, hypervigilance and dissociation (Brown et al., 2013; Lanius et al., 2010; Paulus & Stein, 2006). It follows that, similar to the preceding section on emotional dysregulation, current literature concerning associations between trauma and RSFC in BPD is still inconclusive.

Dissociative Experiences

In line with the current study, two previous BPD studies confirmed associations between scores on the DES and RSFC of selected regions. Firstly, Wolf et al. (2011) found that higher dissociative tendencies were positively correlated with increased RSFC of the insula. The second study, by Krause-Utz et al. (2014) also found positive correlation between dissociation and higher RSFC, albeit within disparate regions, including amygdala, occipital lobe, cuneus and fusiform gyrus. Comparing these studies with the present one, it is clear that whilst dissociative tendencies is associated with higher RSFC, a range of brain regions are implicated. Therefore, it is essential to revert to theoretical understanding as well as relevant task-based fMRI studies. As discussed in the introduction, dissociation is best conceptualized as an over-modulation of emotions and has been associated with increased neural activity within the ACC, mPFC, thalamus and inferior frontal gyrus

(Lanius et al., 2002) as well as insula (Lanius et al., 2005; Ludäscher et al., 2010; Niedtfeld et al., 2010). Although dissociation is a relatively common transdiagnositic phenomena, our understanding is still limited. If further corroborating evidence in this area is obtained, this might suggest that BPD participants are prone to dissociation even in the absence of external triggers.

General Clinical Symptomatology

Thus far, the current study remains the only research that explored the associations between RSFC and BSI-based general clinical symptomatology. Since these results did not survive correction for multiple comparison, they are at best preliminary and require further investigation by future studies.

Implications of Clinical Psychopathology and Seed-Whole Brain RSFC

This paper begun by emphasizing that the functional significance of neuroscience findings has greater clinical relevance when embedded within an overarching theoretical framework as well as focusing on associations with clinical psychopathology. Thus, the second aim of the current study is to explore the associations between RSFC and three highly prevalent clinical phenomena in individuals with BPD. Not only is BPD, trauma and dissociation highly co-morbid, the overarching mentalization framework detailed at the start of this paper posits closely linked developmental pathways and emotional dysregulation mechanisms between these clinical phenomena. To understand the lack of significant associations between RSFC and indices of clinical psychopathology, the proceeding section will elaborate on alternative explanations and limitations of the current study.

Alternative Explanations and Limitations

It should be acknowledged that a major limitation in the current study is that only one of the RSFC finding remained significant after correction for multiple

comparisons, meaning that it is highly probable that the rest of the results are chance findings. That said, the very nature of resting state generates a myriad of uncontrollable and unknown variables, including the content (if any) of participants' internal experiences, such as their emotional state, cognitions and memories (O'Neill & Frodl, 2012). Related to this, readers are reminded that in the current study, participants completed social exchange tasks lasting approximately an hour whilst in the scanner. This cross-over effect of task might in turn influence the focus of participants' inner experiences, for example thoughts about task performance (Cole, Smith, & Beckmann, 2010). In the absence of external demands, our mind has the capacity to self-generate inner experiences not based on the present moment. One should bear in mind that the wide array of self-generated experiences is not limited to mind-wandering, reminiscing, thoughts of self, others and future and problem solving (Callard, Smallwood, Golchert, & Margulies, 2013). In turn, these phenomena may be characterized by distinct or overlapping neural connectivity (Buckner, Krienen, & Yeo, 2013). Perhaps in order to be able to attribute RSFC findings to intrinsic functional organization of the brain rather than to between-subject variations in state-dependent factors, there is a need to understand these self-generated activities and consider ways of maximizing the resting state. Apart from cognitive processes, emotional fluctuations between participants constitutes another state-dependent factor that might influence RSFC.

Information obtained in clinical and research settings converge on the high prevalence of co-morbid disorders in individuals with BPD, including MDD, PTSD bipolar disorder and eating disorder (Grant et al., 2008). In the present study, since only diagnostic screening for PDs was conducted, we are therefore unable to exclude the influence of non-PD co-morbidities on obtained RSFC findings. Accordingly,

this limits the specificity of RSFC findings to BPD symptomatology. This is pertinent since past literature have established the influence of various disorders on RSFC, including PTSD and MDD (Bluhm et al., 2009; Duuta et al., 2014; Kennis, Rademaker, Van Rooij, Kahn, & Geuze, 2014; Kerestes, Davey, Stephanou, Whittle, & Harrison, 2014; Lanius et al., 2010; Zhu et al., 2012). Moreover, while the heterogeneity of our clinical sample maximizes ecological validity, it might well have implications in our investigations of the associations between RSFC and indices of psychopathology. Related to the issue of specificity, as all the BPD participants in the current study were undergoing therapy, we should question if therapy influences RSFC. For example, third wave Cognitive Behaviour Therapies focuses on creating a different relationship with one's inner experiences, by emphasizing mindfulness and adopting a non-judgmental stance; could this then have an impact on RSFC? Lastly, several studies have suggested that psychotropic drugs influence RSFC (Lui et al., 2010; Sambataro et al., 2010), further questioning the specificity of current findings to BPD symptomatology.

Functional connectivity is essentially statistically computed correlations between temporally synchronous brain regions (Toga, 2015). Thus, the very nature of RSFC precludes causality and does not address mediation or moderation effects. In addition, even though we might observe higher or lower seed-voxel RSFC, there is no indication whether these signify modulation by the seed or that they are simply a cascading connectivity between the seed and voxel. However, a plausible solution to these conundrums is to investigate effective connectivity using dynamic casual modelling and augment with task-based fMRI. Additionally, as the resting state scan lasted only five minutes, there is also a possibility that cascading connectivity with various regions and networks was not fully captured within this timeframe.

Whilst seed-based analysis is suited to address hypothesis driven research aims, there is another limitation of this methodology apart from the aforementioned preclusion of causality. Since the seeds are a priori selected, seed-based analysis restricts the investigation only to RSFC stemming from those seeds, thereby obscuring RSFC between non-seed regions. Additionally, as seed-based analysis focuses on regions displaying the most connectivity with the seed, this might favour overlapping brain networks in close proximity rather than larger and widespread networks (Buckner, Andrews-Hanna, & Schacter, 2008). Contrastingly, ICA enables investigation of RSFC without limitations to particular regions. Interestingly, of the six rs-fMRI BPD studies, there seems to be a preference for ICA whilst all but one rs-fMRI PTSD study utilized seed-based analysis. In the current study where included BPD participants are heterogeneous in terms of medication use and co-morbidities, it might have been useful to consider ICA.

Implication for Future Research and Clinical Psychology

Future research can enhance specificity of RSFC findings in relation to clinical psychopathology by incorporating screening for non-PD co-morbidities and to include comparison clinical samples, for example that of PTSD and MDD. Despite our limited understanding of the DMN, prospective research should not be deterred from exploring and investigating this fundamental neural architecture of our brain. The ability to generate inner experiences not anchored to the present is essential to our sense of self and "human consciousness" (Greicius, Krasnow, Reiss, & Menon, 2003). As aforementioned, the DMN has been linked with a multitude of cognitive phenomena, it would therefore be useful for future research to further explore these phenomena so as to understand the influence on resting state. This can be done using psychoanalytic techniques of introspection and free association (Fell, 2013) and

asking participants to report their inner experiences. In addition, there is also potential for future research to investigate the impact of treatment on the DMN as well as the longitudinal effects of psychopathology on the DMN. It is still a long way before we can conclude that atypical RSFC patterns constitute a neurobiological marker for BPD, a research domain that will benefit from considering multiple levels of analyses and collaborative working. One observation is that all of the current rs-fMRI BPD studies adopted different seeds or focused on disparate brain regions. Seeing that this is a relatively new field, exploratory analyses as such is interesting, but in order to synthesize research findings and maximize clinical relevance, it is essential that replication studies are conducted and that non-significant findings are understood and not simply added to the "file drawer effect". Furthermore, future research will also benefit from considering findings from structural and task-based fMRI studies (Schmahl et al., 2009; Weniger, Lange, Sachsse, & Irle, 2009) and studies focused on key neurotransmitters (Dixon-Gordon, Gratz, Breetz, & Tull, 2013; Wingenfeld et al., 2007). As it stands, the current literature is still lacking at adequately understanding how RSFC is in turn associated with psychopathology. Despite some studies including clinical measures, it is often the case that no further analyses are conducted to explore associations with obtained RSFC findings. Thus, future research should explicitly investigate the relationship (if any) between RSFC with psychopathology. At the same time, it is also pertinent that research does not lapse into "reverse inference" (Poldrack, 2006), simply explaining psychopathology by locating it within brain region(s) displaying atypical RSFC, without discerning core mechanisms, such as well-established frontal-limbic impairments in BPD (Koenigsberg et al., 2009; Malhi et al., 2013; Mauchnik & Schmahl, 2010)

In the realm of clinical psychology, our understanding of BPD can be further enhanced by considering multiple level of analyses including the individual, social and biological as well as the interactions amongst these levels (Bradley, Jenei, & Westen, 2005; Carpenter, Tomko, Trull, & Boomsma, 2013; Zanarini & Frankenburg, 1997). Accordingly, rather than focusing on disparate symptoms, it will also be integral to employ an overarching framework that seeks to understand BPD on the various levels, such as the mentalization framework discussed extensively at the start of this paper. The mentalization framework posits that disruptions to early attachment, such as with early traumatic experiences, impact on the ability to mentalize and regulate one's emotions, along with core behavioural and self dysregulation, and interpersonal difficulties (Fonagy, Luyten, & Strathearn, 2011). Secure attachment is linked with effective down-regulation of the stress arousal and affect as well as facilitation of mentalization (Fonagy, Luyten, & Strathearn, 2011). Conversely, the lack of a good enough attachment impairs the ability to mentalize and manage arousal while at the same time increases vulnerability to arousal. Interestingly, apart from prevalence of trauma in BPD, dissociation is most commonly associated with BPD (Zanarini, Frankenburg, Jager-Hyman, Reich, & Fitzmaurice, 2008). It was therefore the aim of the current study to investigate BPD, trauma and dissociation by focusing on the DMN, an area established to be associated with mentalization (Satpute & Lieberman, 2006). Based on current understanding of the DMN, coupled with what we know about psychopathological processes, clinical psychology is essentially targeting the DMN in our treatment when we formulate and work with our clients' cognitions, judgments, ruminations, attentional control, memories and the broader category of social cognition. For this reason, clinical psychology will greatly benefit if we

continue to explicate the psychopathological and therapeutic factors influencing the DMN across disorders.

Conclusion

The field of using rs-fMRI to investigate intrinsic functional connectivity underlying clinical psychopathology is a very new one. As discussed in the preceding sections, before we can confidently mobilize the use of RSFC to elucidate underlying neurobiological mechanisms of clinical psychopathology, there are still a multitude of unanswered questions which necessitates further research. In turn, this will better facilitate clinical psychologists to evaluate the utility of RSFC findings in aiding us to understand, formulate and treat BPD.

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Part 3: Critical Appraisal

Introduction

This critical appraisal seeks to reflect on the key issues that arose over the course of the research. Before highlighting important areas for future research to consider, I briefly describe personal and professional influence on the current research. This is then followed by three main focuses, namely implications of the current research, integral issues to consider in multilevel research and barriers to address in order to maximize clinical utility of resting state functional connectivity (RSFC) findings. The aim is that these reflections will be beneficial for future research investigating the neurobiological basis of clinical psychopathology.

Influences on Current Research

This research project was ideal as it offered me the opportunity to pursue my interest in clinical psychopathology and the brain. Prior to commencing training, I was involved in an Electroencephalography (EEG) project and was considering opportunities that will allow me to gain knowledge and experience in my two main areas of interest. The research process required that I maintain multiple focuses including the neuroscience aspects, psychological mechanisms, clinical psychopathology as well as the technicalities and implications of using neuroimaging. This was interesting as it facilitated thinking across domains whilst still adopting clinical psychology as the overarching perspective.

Implications of Current Research

Linking Therapy to Underlying Neurobiology

My involvement in this research has made me think a lot more about the links between the therapy I provide as a clinician and neurobiological underpinnings of clinical psychopathology. Until recently, most clinical neuroscience research has focused on associated abnormalities in mental health disorders. However, there is

huge potential in using neuroimaging techniques to investigate treatment outcomes or inform therapy development. In particular, the default mode network (DMN) and its purported functions is fascinating as it is implicated in a multitude of symptom profiles across numerous psychological disorders such as autism, schizophrenia and depression (Philippi & Koenigs, 2014; Whitfield-Gabrieli & Judith, 2012; Zhao, Luo, Li, & Kendrick, 2013).

Understanding of BPD, Trauma, Dissociation and Emotional Dysregulation

The literature review focused on resting state- functional magnetic resonance imaging (rs-fMRI) studies investigating RSFC of the DMN across borderline personality disorder (BPD), post traumatic stress disorder (PTSD) and dissociation. Overall, the current literature suggests that RSFC of the DMN has the most functional utility in PTSD because on the whole, the 12 studies considered the influence of co-morbid MDD, experienced trauma in the absence of PTSD diagnosis and the predictive value of the DMN in trauma symptomatology. In comparison, the five existing BPD literature are still in their infancy and lacked synthesis. At the start of the empirical paper, mentalization framework was used to understand BPD along with common co-morbidity of PTSD, with dissociation subsumed under emotional dysregulation. However, due to the complexity of BPD, core dysregulation is also pervasive across interpersonal relationships, behaviour and cognitions, with the majority of existing studies focusing on specific dysregulation, thereby limiting current understanding. Thus, this study sought to investigate if BPD participants displayed atypical RSFC as compared to healthy controls. Next, observed RSFC was further investigated to elucidate associations with self-reported trauma, dissociation, emotional dysregulation and personality psychopathology. While only the finding that BPD participants displayed higher RSFC between the dorsal medial prefrontal

cortex (dmPFC) seed and left middle temporal gyrus (lMTG) remained significant after correction for multiple comparisons, this study is the first to utilize an overarching clinical framework to investigate the underlying neurobiological basis of BPD and the links with core dysregulation. Fundamentally, the incorporation of the mentalization framework is aimed at maximizing clinical utility, by focusing on mechanisms underlying neurobiological findings.

Investigation of BPD symptomatology is slightly more established in task-based fMRI studies, with most converging on increased activation within the limbic regions accompanied by decreased activation in the prefrontal regions during emotional dysregulation (Ochsner, Silvers, & Buhle, 2012; Ochsner, Bunge, Gross, & Gabrieli, 2002; Phan et al., 2005). Firstly, task-based fMRI has been used to investigate emotional sensitivity, with Donegan et al. (2003) and Minzenberg, Fan, New, Tang, & Siever (2007) reporting increased amygdala activation when BPD participants were shown emotional facial expressions, but this was not replicated by Guitart-Masip et al. (2009). Emotional sensitivity was further investigated using emotional scenes in eight studies, with four studies obtaining increased amygdala activity (Arntz et al., 2015; Herpertz et al., 2001; Koenigsberg et al., 2009; Schulze et al., 2011) and two studies obtaining decreased activation in anterior insula, ventral lateral prefrontal cortex (vlPFC), dorsal lateral prefrontal cortex (dlPFC), and dmPFC (Koenigsberg et al., 2009; Schulze et al., 2011) in BPD participants. Despite inconsistencies, these findings are generally concordant with the theoretical understanding of heightened emotional experiences accompanied by reduced modulation of inhibitory and regulatory responses observed in BPD (Rosenthal et al., 2008; Schmahl et al., 2014). Of note, even though emotional dysregulation is at the core of the BPD diagnostic criteria and leading theoretical orientation, to date, there

has only been three neuroimaging studies in this area (Konigsberg et al., 2009; Lang et al., 2012; Schulze et al., 2011). In these studies, BPD participants were shown emotional stimuli and asked to modulate their emotions. It was found that BPD participants displayed increased activity in the amygdala (Koenigsberg et al., 2009) and anterior insula as well as decreased activity in the orbitofrontal cortex (OFC; Schulze et al., 2011). These areas are involved in generating emotions while the anterior insula has been implicated in self-awareness and empathy (Craig, 2009; Singer, Critchley, & Preuschoff, 2009). In terms of areas responsible for emotional regulation, contradictory results were found for anterior cingulate cortex (ACC) and dlPFC, with Koenigsberg et al. (2009) and Lang et al. (2012) reporting lower activity in ACC and higher activity in dlPFC whilst Schulze et al. (2011) found the opposite. Similar to BPD research on emotional sensitivity, these findings are congruent with clinical understanding of emotional dysregulation. However, the presence of inconsistencies and the small number of studies support the need for future studies in this domain. More importantly, almost all of these task-based fMRI studies had the same issue as the current study, namely low statistical power and findings reported at significance level uncorrected for multiple comparisons, an issue that is further elaborated in the next section.

Interestingly, dissociation was put forth as a moderator in explaining the disparate activation patterns obtained in emotional modulation studies (Ebner-Priemer et al., 2005). Despite the high prevalence of BPD, PTSD and dissociation, there is a dearth of fMRI studies covering all three areas, with majority of studies focusing on either PTSD or BPD. Seeing that dissociation is a common transdiagnostic phenomena, future research in this area will be beneficial in enhancing our clinical understanding. Moving on to current literature on PTSD and

BPD, the only task-based fMRI study that included BPD participants with and without PTSD found that BPD participants without PTSD displayed bilateral OFC and Broca area activation whilst BPD participants with PTSD had higher right lateralized activation in the OFC, amygdale, anterior temporal lobes, mesio-temporal areas, posterior cingulate gyrus, occipital areas, and cerebellum (Driessen et al., 2004). Based on these findings, the authors hypothesized that this might provide support for the dual representation theory of PTSD (Brewin, Dalgleish, & Joseph, 1996). In comparison, several task-based fMRI studies focusing only on participants with PTSD found that participants displayed greater activation of limbic, paralimbic regions and lower activation of the mPFC and Broca's areas (Lanius et al., 2001; Lanius et al., 2003). However, despite these findings, our understanding of the underlying mechanisms is still limited and with most MRI research, contradictory findings suggest the need for replication studies and research complemented with other techniques such as positron emission tomography.

Current Status of Neuroimaging Studies

Since only one of the RSFC finding in this study remained significant after controlling for multiple comparisons, an extremely lenient uncorrected significance threshold of .05 was used to discuss the results. The major flaw of this approach is that this inflates likelihood of chance findings/ false positives. On the whole, low statistical power seems to be the norm in neuroimaging studies, averaging between 8 to 31% (Button et al., 2013), highlighting the pertinence of implementing sound research principles. From conducting the literature review and writing the empirical paper, it was observed that most studies do not disclose key decisions and processes related to sample size and power, data exclusion, data analysis plans and whether findings were a priori or exploratory (Carp, 2012; Fanelli, 2012). Clarity of research

processes will only increase the interpretability of and confidence in the findings. Interestingly, a UCL research associate asked if I had pre-registered my analysis plan. Upon further reading, pre-registration is one initiative to minimize biasness and differentiate between hypothesis testing and hypothesis generating (Button et al., 2013). Thus, even though pre-registration was omitted for the current study, future studies should consider doing so.

Another observation is the lack of replication studies. This is not unusual since rs-fMRI DMN research has only recently came into the attention of researchers. However, replication studies are essential to separate true positives from false positives (Moonesinghe, Khoury, & Janssens, 2007). Going back to the point of low statistical power, apart from increasing sample size, another consideration is to enhance the signal to noise ratio; however, the technical details are beyond the scope of the study and readers are referred to articles by Frost & Goebel (2012), Liu, Frank, Wong, E.C, & Buxton (2001) and Weiskopf, Hutton, Josephs, & Deichmann (2006). Lastly, in the current study, participants are excluded from MRI scanning if they do not meet the safety requisites and are instead offered to complete the social exchange tasks on a laptop. Notably, some BPD and healthy control participants requested to opt out from scanning, with some citing fear of confined spaces, intense general anxiety and concerns about the scan. Hence, there could potentially have been differences between participants who consented to scanning and those who did not, for example in terms of severity of psychopathology. Unfortunately, this was not a focus of the current research but is nonetheless a consideration for prospective research.

Heterogeneity of Sample and Implications

Heterogeneity seems to be commonplace not just in the current study but also in the existing literature. Here, I will focus on heterogeneity within the sample, specifically in terms of medication use and co-morbidities. Two out of six of the BPD studies included in the literature review required participants to cease medication use prior to participation. In a separate review of task-based fMRI studies, 10 out of 15 studies excluded participants who were taking medication on the basis that medication use has been found to influence brain connectivity (Hafeman, Chang, Garrett, Sanders, & Phillips, 2012). Notwithstanding the influence on the brain, medication use might well imply heterogeneity in terms of severity and co-morbidities, potentially impacting on specificity of findings. Several methods such as post hoc statistical analyses (Hafeman et al., 2012) and arterial spin labelling (Wang, Chen, Fernandez-Seara, & Detre, 2011) can be used to minimize the confounding effects of medication but this is still an area that warrants further attention. Heterogeneity of BPD participants extends to the high occurrence of co-morbidities such as major depressive disorder (MDD), PTSD, substance abuse, eating disorders and other personality disorders, with estimated prevalence rates between the range of 16 to 83%, depending on the disorder (McGlashan et al., 2000; Zanarini et al., 2008; Zimmerman & Mattia, 1999), suggesting that co-morbidities seem to be the norm rather than exception. Therefore, increasing specificity and confidence of our findings whilst maximizing ecological validity necessitates the inclusion of comparison clinical groups and centering findings not just on observed connectivity, but on the underlying psychopathological mechanisms.

In the preceding paragraph, the importance of specificity was highlighted. That said, the complexity related to the issue of specificity extends beyond ways of maximizing specificity. Essentially, specificity implies distinct psychopathology linked to diagnosis, a notion not reflected in reality as seen by huge overlaps in psychopathology between diagnoses, for example impulsivity and emotional dysregulation observed in BPD, attention deficit hyperactivity disorder and anti social personality disorder (ASPD) (Gross, 2007; Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). This has led to debates surrounding the utility of categorical classification of psychopathology as compared to a dimensional approach (Cuthbert, 2014; National Institute of Mental Health, 2008). Based on my experience in conducting this research, I am more aware of the research implications of simply using a categorical classification as it obscures the complexity of psychopathology and associated symptomatology. Future research can consider investigating underlying psychopathological processes across disorders which will enable us to identify distinct and overlapping features of disorders. The last point relating to heterogeneity pertains to the lack of understanding in relation to sub-types of BPD and PTSD as well as the implications when these two disorders are co-morbid. A review by Frías & Palma (2015) highlighted the complexity by discussing four positions: 1. Presence of either disorder increases the risk for the other disorder 2. The existence of a pool of common risk factors related to both PTSD and BPD 3. Distinctions between the two disorders occur across psychosocial, neurobiological and clinical psychopathological domains 4. There are no underlying differentiations between the two disorders, instead, there is a lack of distinction between the diagnostic criteria of PTSD and BPD. This review makes it clear that there are still important but unanswered questions that have both research and clinical

implications. Lastly, the use of DES and CTQ in this study raises the question of whether there are sub-types of BPD, for example, those who do/ do not dissociate as well as those who meet/do not meet the criteria for PTSD/complex PTSD. In summary, this research and the current literature not only highlight the complexity of this research domain, but also the vast opportunities for future research.

Multilevel Research: What to Consider

Levels of Analyses and Operational Definition

In the current research and existing rs-fMRI literature, several variables of interest are usually present, including DMN, RSFC, clinical psychopathology and measures of psychopathology. This then results in multiple levels of analyses which are linked by hypotheses and investigated for purported connections. However, multilevel analyses are advantageous and valid only if the respective constructs are effectively operationally defined (Cacioppo & Decety, 2011). Over the course of the research, it is apparent that these constructs are highly complex and not necessarily operationally defined or separated into distinct components. Consequently, it becomes more challenging to be confident of the connections we observe and when we seek to explain them. Thus, as an initial step, future research should carefully operationalize constructs which would in turn facilitate understanding of psychopathology based on observed neurobiological processes. Additionally, despite the complexities of multilevel analyses, our understanding and treatment of clinical psychopathology can be enhanced if research seeks to understand the complementary sum of different levels of analyses rather than merely focusing on individual parts (Ilardi & David, 2001).

Levels of Inference and Collaborative Working

Reading and synthesizing the current literature brought to the fore the levels of inference, made by both researchers and readers. Depending on one's training, philosophical views and biases, presented RSFC findings could be interpreted as 1. Absence or presence of associations between psychological and neurobiological constructs 2. Observed associations are informative of underlying mechanisms 3. Neurobiological processes are responsible for psychological processes (Insel & Quirion, 2005) 4. Neurobiological processes are but one of the determinant of psychological processes (Cacioppo & Decety, 2011). It was interesting to find myself moving between the levels of inferences during the course of the research and when reading the research articles. My opinion is that these level of inferences have a profound impact on how one receives/ rejects the influence of neurobiological findings in clinical psychopathology, with some arguing that it is either too reductionist or too encompassing (Kandel & Squire, 2000). Additionally, levels of inference have been and are still prominent in the dichotomy of clinical psychopathology as either a disorder of the brain or mind; with further implications on whether treatment warrants medication or therapy (Peres & Nasello, 2008). As stated in the preceding section, RSFC research in the domain of clinical psychopathology entails multiple constructs across two primary levels of psychology and neurobiology. Based on my limited experience undertaking this research area, I think sound inference is best achieved by incorporating expertise across relevant disciplines. Particularly for clinical psychology, interdisciplinary neuroscience research will allow the exploration of interactions within the biopsychosocial model. The final two thoughts about inferences, in relation to "reverse inference" were also raised in the discussion section (Poldrack, 2006). These pertain to the practice of

explaining psychological processes within brain anatomy and/or connectivity. Future research can circumvent this problem by placing an emphasis on plausible mechanisms embedded within an overarching psychological framework, for example, the mentalization framework. It was also apparent as I read existing DMN literature and when I considered my findings with the existing literature, that an extremely common approach of interpreting obtained RSFC findings was to look for a direct one to one mapping of clinical psychopathology and brain region. Rather, what tended to emerge was in direct contrast to this one to one mapping as most brain regions are associated with more than one psychopathology/ processes, and vice versa (Poldrack 2006). This is a far cry from physiological disorders where one to one mapping is commonplace. Hence, a shift in thinking might be warranted for both researchers as well as consumers of research.

Translational Research: Barriers of Current RSFC Research

Whilst neuroimaging techniques such as fMRI allows us to investigate underlying neurobiological circuitry, as highlighted in the discussion section, there are limitations to its use. Apart from the correlational nature of RSFC, the use of oxygenated blood flow as a proxy for neural activities is not without controversy. This is particularly an issue with a clinical sample consuming prescribed medication, such as in the current study, since psychotropic medication can result in either vasoconstriction or vasodilation (Schleim & Roiser, 2009). Despite its limitations, neuroimaging studies still has huge utility in enhancing our understanding of psychopathology, co-morbidities and transdiagnostic phenomena when used in combination with clinical and behavioural measures. Concurrent with conducting the research, I was also working in a specialist personality disorder (PD) service, and it was common for clinicians to share with clients the neurobiological aspects of PD.

Often, this entailed explaining the neurobiological antecedents, how symptoms are maintained as well as changes to the neurobiological circuitry/ structures post treatment. Often, this aids clients to recognize that PD is multi-faceted, that they are not deliberately being difficult and that improvements can occur not only at the symptomatic level but also biologically. As a clinician, this reinforces the utility and valuableness of research seeking to enhance our neurobiological understanding of clinical psychopathology.

However, before neuroimaging studies, including rs-fMRI DMN literature can be regarded as translational research with actual clinical utility in diagnosis and treatment outcomes, several barriers have to be acknowledged. Firstly, the highly complex nature of the research is often accompanied with an equally complex way of presenting the findings. Without prior knowledge or further reading, these findings can come across as jargonistic and almost impossible to comprehend. Therefore, one suggestion is to ensure that key clinical mechanisms and implications are emphasized rather than merely focusing on the technical findings. Secondly, as it stands, the DMN literature in clinical psychopathology is very much segregated into separate research studies lacking synthesis, thereby limiting its impact on clinical utility. Therefore, future research should consider integrating existing literature and clinical implications (Ilardi & David, 2001).

Conclusions

Despite the limitations of the current research, it is the intention of this critical appraisal to discuss pertinent areas for future RSFC research to consider. As stated, the use of rs-fMRI to understand clinical psychopathology is still in its infancy and before it can be regarded as translational research, emphasis should be

placed on sound research principles, understanding and investigating heterogeneity within sample, considering multiple levels of analysis in conjunction with adequate operational definition and conducting inter-disciplinary collaborative research.

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Appendix A1

Methods of Analysis for RSFC

There are two main methods of analysing RSFC, namely, seed-based analysis and independent component analysis (ICA). The main idea behind seed-based analysis of RSFC involves identifying a priori selected region of interest (ROI) within the brain, also referred to as the seed (Fox & Raichle, 2007). This can be limited to one or more brain regions. Temporally synchronous RSFC within the selected seed is then compared with brain regions we are interested in. Obtained RSFC can then be numerically quantified and therefore statistically analysed, for example using correlation or general linear model with the aid of programs such as Statistical Parametric Mapping (SPM). As compared to seed-based analysis, ICA does not rely on a priori selected ROI. Instead, ICA is a multivariate mathematical approach where obtained RSFC is used to identify regions of the brain that seems to be simultaneously active over a specified time course (Fox & Raichle, 2007). Therefore, the primary aim of ICA is to maximize statistical independence amongst identified regions showing increased RSFC activation. Similar to seed-based analysis, the use of programs such as the SPM would then allow one to perform further statistical analyses.

Appendix A2

Arguments against the DMN

Despite the purported functions and corresponding evidence, the field of the DMN is not without controversy, with some researchers arguing against the concept and utility of the DMN (Morcom & Fletcher, 2007). Firstly, there is a lack of consensus regarding the origins of the low frequency BOLD signals observed during resting state. Critics of the DMN do not concur that these signals are a proxy measure of intrinsic neural activity, instead, they argue that these signals are merely due to cardiac and respiratory processes (Birn, Smith, Jones, & Bandettini, 2008; Shmueli et al., 2007; Wise, Ide, Poulin, & Tracey, 2004) and/or spurious findings arising from a lack of head motion correction (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Satterthwaite et al., 2012; Van Dijk, Sabuncu, & Buckner, 2012). However, evidence against this line of reasoning stems from findings that these non-neural processes have a higher frequency of .3 Hz (Cordes et al., 2001) as compared to the .01 to .1 Hz usually obtained for intrinsic neural activity (Callard & Margulies, 2011; Cordes et al., 2001). Therefore, this implies that the elicited BOLD signals cannot be wholly attributed to these non-neural processes nor considered merely as artefacts. That said, it should be acknowledged that these non-neural processes does have an influence on BOLD signals (Van den Heuvel & Hulshoff Pol, 2010) and should therefore be addressed during the pre-processing of the fMRI data so as to ensure validity of findings (Lee, Smyser, & Shimony, 2013; Van Buuren et al., 2009; Weissenbacher et al., 2009). Further evidence stems from a series of studies in which both EEG and fMRI were used to investigate the relationship between electrical and hemodynamic indices underlying neural activity. These studies found that during resting state, strong and distinct correlations were obtained between electrical and fMRI indices, particularly in regions of the DMN (Laufs et al., 2003; Meyer, Oort, & Barth, 2013;

Scheeringa, Petersson, Kleinschmidt, Jensen, & Bastiaansen, 2012). In conclusion, these research findings provides necessary evidence that the DMN exists as an empirically derived brain region network.

Appendix A3

Supporting Evidence for the DMN

The first line of evidence supporting the existence of the DMN pertains to the replicated findings of consistently demarcated brain regions across a range of fMRI processing methods and samples (Sambataro, Wolf, Giusti, Vasic, & Wolf, 2013; Shehzad et al., 2009; Snyder & Raichle, 2012). Secondly, in terms of brain-behaviour links, over a specified temporal duration, RSFC has been found to exist across regions with overlapping functions (Damoiseaux et al., 2006; De Luca, Smith, De Stefano, Federico, & Matthews, 2005; Van den Heuvel et al., 2010). In addition, proponents of the DMN argue for the importance of intrinsic neural activities by factoring in the brain's energy consumption. Despite only constituting two per cent of total body weight, the brain consumes approximately 60 to 80 per cent of energy in the absence of external tasks engagement and stimuli (Raichle & Snyder, 2007). Related to this, one might naturally expect large increase in energy consumption during task engagement, but, Raichle & Mintun et al. (2006) found that there was only an additional five to ten per cent increase. Apart from the three main psychopathologies elaborated in this review, aberrant RSFC has also been found in other mental health disorders, including MDD (Auerbach, Webb, Gardiner, & Pechtel, 2013; Belleau, Taubitz, & Larson, 2014; Northoff, Wiebking, Feinberg, & Panksepp, 2011), autism (Broyd et al., 2009; Fox & Greicius, 2010), Alzheimer's disease (Buckner et al., 2005; Zhang & Raichle, 2010) and schizophrenia (Calhoun, Kiehl, & Pearlson, 2008; Garrity et al., 2007; Williamson, 2007). Some researchers put forth the centrality of self-referential processing (Philippi & Koenigs, 2014; Qin & Northoff, 2011), for example, increased self-referential processing has been associated with increased functional connectivity of the mPFC in MDD (Berman et al., 2011; Greicius et al., 2007; Zhu et al., 2012) as well as anxiety (Etkin, 2009; Liao

et al., 2010; Zhao et al., 2007). Conversely, reduced self-referential processing has been correlated with reduced functional connectivity of mPFC in autism (Cherkassky, Kana, Keller, & Just, 2006; Kennedy & Courchesne, 2008; Lombardo, et al., 2010) and anti-social PD (Motzkin, Newman, Kiehl, & Koenigs, 2011; Pujol et al., 2012). Thus, the study of the DMN has the potential of increasing our understanding of psychopathologies and possible trans-diagnostic phenomena which could in turn inform diagnosis and treatment.

Lastly, further support for the role of the DMN stems from research investigating the impact of psycho-social interventions. Changes in RSFC of the DMN has been correlated with improved self-reported symptoms and clinical indices of psychopathologies (Yoshimura et al., 2014) after patients received meditation-based interventions (Beason-Held, Kraut, & Resnick, 2009), trauma focused therapy (Landin-Romero et al., 2013) and medication (Li et al., 2013; Liston et al., 2014; Posner et al., 2013; Yoshimura et al., 2014;).

Appendix A4

QualySyst Quality Critical Appraisal Tool

No.	Criteria	No (0)	Partial (1)	Yes (2)	Not applicable
1.	Question / objective sufficiently described?				
2.	Study design evident and appropriate?				
3.	Method of subject/comparison group selection or source of information/input variables described and appropriate?				
4.	Subject (and comparison group, if applicable) characteristics sufficiently described?				
5.	If interventional and random allocation was possible, was it described?				
6.	If interventional and blinding of investigators was possible, was it reported?				
7.	If interventional and blinding of subjects was possible, was it reported?				
8.	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?				
9.	Sample size appropriate?				
10.	Analytic methods described/justified and appropriate?				
11.	Some estimate of variance is reported for the main results?				
12.	Controlled for confounding?				
13.	Results reported in sufficient detail?				
14.	Conclusions supported by the results?				

Appendix A5

Total QualSyst Score of Shortlisted Studies (n= 19)

Research Paper (listed according to order presented in review)	Total Qualsyst Score
Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma (Bluhm et al., 2009)	20
A preliminary study of alterations in default network connectivity in post-traumatic stress disorder patients following recent trauma. (Qin et al., 2012)	19
Neural Dysregulation in Posttraumatic Stress Disorder: Evidence for Disrupted Equilibrium Between Salience and Default Mode Brain Networks (Sripada et al., 2012)	21
Resting state Functional Connectivity of the Anterior Cingulate Cortex in Veterans With and Without Post-traumatic Stress Disorder (Kennis et al., 2014)	22
Altered Resting-State Functional Connectivity of Basolateral and Centromedial Amygdala Complexes in Posttraumatic Stress Disorder. (Brown et al., 2014)	22
Altered amygdala resting-state functional connectivity in post-traumatic stress disorder. (Rabinak et al., 2011)	21
Altered functional connectivity in posttraumatic stress disorder with versus without comorbid major depressive disorder: a resting state fMRI study. (Kennis et al., 2013)	22
Default mode network connectivity as a predictor of post-traumatic stress disorder symptom severity in acutely traumatized subjects. (Lanius et al., 2010)	20

Research Paper (listed according to order presented in review)	Total Qualsyst Score
Quantitative Prediction of Individual Psychopathology in Trauma Survivors Using Resting-State fMRI. (Gong et al., 2014)	21
Decreased default network connectivity is associated with early life stress in medication-free healthy adults (Philip et al., 2013)	20
Regional homogeneity and resting state functional connectivity: Associations with exposure to early life stress. (Philip et al., 2014)	21
Resting-state functional connectivity in adults with childhood emotional maltreatment. (Van der Werff et al., 2013)	22
Aberrant connectivity of resting-state networks in borderline personality disorder (Wolf et al., 2011)	22
Amygdala and anterior cingulate resting-state functional connectivity in borderline personality disorder patients with a history of interpersonal trauma. (Krause-Utz et al., 2014)	21
Shifted intrinsic connectivity of central executive and salience network in borderline personality disorder. (Doll et al., 2013)	21
Dysregulation between emotion and theory of mind networks in borderline personality disorder (O'Neill et al., 2014)	20
Bipolar and borderline patients display differential patterns of functional connectivity among resting state networks (Das et al., 2014)	20
Alterations in Default Mode Network Connectivity During Pain Processing in Borderline Personality Disorder. (Kluetsch et al., 2013)	22
Dissociative Part-Dependent Resting-State Activity in Dissociative Identity Disorder: A Controlled fMRI Perfusion Study. (Yolanda et al., 2014)	19

Appendix A6

DSM-5 Criteria for PTSD

Criterion A: stressor

The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, as follows: **(one required)**

1. Direct exposure.
2. Witnessing, in person.
3. Indirectly, by learning that a close relative or close friend was exposed to trauma. If the event involved actual or threatened death, it must have been violent or accidental.
4. Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (e.g., first responders, collecting body parts; professionals repeatedly exposed to details of child abuse). This does not include indirect non-professional exposure through electronic media, television, movies, or pictures.

Criterion B: intrusion symptoms

1. The traumatic event is persistently re-experienced in the following way(s): **(one required)**
2. Recurrent, involuntary, and intrusive memories. Note: Children older than six may express this symptom in repetitive play.
3. Traumatic nightmares. Note: Children may have frightening dreams without content related to the trauma(s).
4. Dissociative reactions (e.g., flashbacks) which may occur on a continuum from brief episodes to complete loss of consciousness. Note: Children may reenact the event in play.
5. Intense or prolonged distress after exposure to traumatic reminders.
6. Marked physiologic reactivity after exposure to trauma-related stimuli.

Criterion C: avoidance

Persistent effortful avoidance of distressing trauma-related stimuli after the event: **(one required)**

1. Trauma-related thoughts or feelings.
2. Trauma-related external reminders (e.g., people, places, conversations, activities, objects, or situations).

Criterion D: negative alterations in cognitions and mood

Negative alterations in cognitions and mood that began or worsened after the traumatic event: **(two required)**

1. Inability to recall key features of the traumatic event (usually dissociative amnesia; not due to head injury, alcohol, or drugs).
2. Persistent (and often distorted) negative beliefs and expectations about oneself or the world (e.g., "I am bad," "The world is completely dangerous").
3. Persistent distorted blame of self or others for causing the traumatic event or for resulting consequences.
4. Persistent negative trauma-related emotions (e.g., fear, horror, anger, guilt, or shame).
5. Markedly diminished interest in (pre-traumatic) significant activities.
6. Feeling alienated from others (e.g., detachment or estrangement).
7. Constricted affect: persistent inability to experience positive emotions.
8. Criterion E: alterations in arousal and reactivity

Trauma-related alterations in arousal and reactivity that began or worsened after the traumatic event: **(two required)**

1. Irritable or aggressive behavior
2. Self-destructive or reckless behavior
3. Hypervigilance
4. Exaggerated startle response
5. Problems in concentration
6. Sleep disturbance

Criterion F: duration

Persistence of symptoms (in Criteria B, C, D, and E) for more than one month.

Criterion G: functional significance

Significant symptom-related distress or functional impairment (e.g., social, occupational).

Criterion H: exclusion

Disturbance is not due to medication, substance use, or other illness.

Specify if: With dissociative symptoms.

In addition to meeting criteria for diagnosis, an individual experiences high levels of either of the following in reaction to trauma-related stimuli:

1. **Depersonalization**: experience of being an outside observer of or detached from oneself (e.g., feeling as if "this is not happening to me" or one were in a dream).
2. **Derealization**: experience of unreality, distance, or distortion (e.g., "things are not real").

Specify if: With delayed expression.

Full diagnosis is not met until at least six months after the trauma(s), although onset of symptoms may occur immediately.

Table A7: Main DMN Findings in PTSD

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with PTSD/ trauma (unless otherwise stated)	Main functions of listed brain regions
Bluhm et al., 2009	All females – 17 with PTSD and 15 healthy controls Exclusion criteria: neurologic disorders or a history of drug or alcohol abuse in the 6months preceding the scan, bipolar disorder and schizophrenia MDD and panic disorder was most common co-morbidity in clinical participants Use of medication allowed	Structured Clinical Interview for DSM-IV non -PDs (SCID-I) Clinician Administered PTSD Scale (CAPS) Dissociative Experiences Scale (DES) Toronto Alexithymia Scale Childhood Trauma Questionnaire (CTQ) – Short Form	Seed-based analysis with a priori-defined seed ROI of PCC/precuneus	Reduced RSFC between the PCC, precuneus and mPFC	PCC- self-referential processing (Bluhm et al., 2009) Precuneus - self-referential processing and autobiographical memory (Das, Calhoun, & Malhi, 2014) mPFC - social cognition and mental simulations relevant to oneself (Buckner, Andrews-Hanna, & Schacter, 2008; Dutta, Mckie, & Deakin, 2014)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with PTSD/ trauma (unless otherwise stated)	Main functions of listed brain regions
Qin et al., 2012	17 with PTSD (5 females and 12 males) and 15 trauma exposed controls (3 females and 12 males) Exclusion criteria: acute stress disorder inventory score of less than 3, neurological abnormalities during emergency department evaluation, loss of consciousness longer than several seconds during the accident, current mental health disorders at the time of the accident, drug or alcohol abuse/dependence 6 months prior to the accident, psychotropic medications within 4 weeks of scan	Mini-International Neuropsychiatric Interview (M.I.N.I) Acute stress disorder inventory CAPS	Seed-based analysis with 3 priori-defined seed ROIs of mPFC and bilateral amygdala	Participants with PTSD displayed lower RSFC in the right lingual and right middle temporal gyrus, and the PCC as well as increased RSFC within the left inferior temporal gyrus, right middle temporal gyrus, left middle temporal gyrus/insula, left medial frontal lobe/ACC, and right medial frontal gyrus	right lingual, right middle temporal gyri and left inferior temporal gyrus - visual processing (Baddeley et al., 1997) PCC - self-referential processing (Bluhm et al., 2009) right middle temporal gyrus - cognitive processes e.g. attention (Qin et al., 2012) left middle temporal gyrus/insula - emotional regulation, pain sensitivity, dissociation, perception and monitoring of internal states (Ludäscher et al., 2010; Niedtfeld et al., 2010) left medial frontal lobe - motor control (Dum & Strick, 1991) ACC - cognitive control, conflict monitoring, self-referential processing, emotional regulation (Kennis, Rademaker, Van Rooij, Kahn, & Geuze, 2014) right medial frontal gyrus - self-awareness (Qin et al., 2012)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with PTSD/ trauma (unless otherwise stated)	Main functions of listed brain regions
Sripada et al., 2012	All males – 15 veterans with PTSD, 15 veterans without PTSD and 15 healthy controls Exclusion criteria: psychosis, alcohol or substance abuse or dependence in the past 3 months, any psychoactive medication other than sleep aids, left-handedness	M.I.N.I CAPS – only for veterans	Seed-based analysis with 4 a priori-defined seed ROIs of PCC, vmPFC, right anterior insula and left anterior insula	Veterans with PTSD had reduced RSFC within the DMN, specifically when considering the rostral ACC and vmPFC	rostral ACC - emotional regulation and self-referential processing (Kennis et al, 2014) vmPFC - social cognition and mental simulations relevant to oneself (Buckner et al., 2008; Dutta et al., 2014)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with PTSD/ trauma (unless otherwise stated)	Main functions of listed brain regions
Kennis et al., 2014	All males – 37 veterans with PTSD, 27 veterans without PTSD and 26 healthy controls Use of medication allowed	SCID-I CAPS	Seed-based analysis with 5 a priori-defined seed ROIs of Caudal ACC, Dorsal ACC Rostral ACC, Perigenual ACC and Subgenual ACC	Veterans with and without PTSD displayed lower RSFC between the caudal ACC and the precentral gyrus, and between the perigenual ACC, superior medial gyrus and middle temporal gyrus Veterans without PTSD were observed to have increased connectivity between the rostral ACC and precentral/middle frontal gyrus	Caudal ACC - motor control (Dum & Strick, 1991) Precentral gyrus - motor control (Dum & Strick, 1991) Perigenual ACC - self-referential and social processing (Amodio & Frith, 2006; Kelley et al., 2002) Superior medial gyrus - self-awareness (Qin et al., 2012) Middle temporal gyrus – cognitive processes (Qin et al., 2012) Precentral/middle frontal gyrus - response inhibition (Qin et al., 2012)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with PTSD/ trauma (unless otherwise stated)	Main functions of listed brain regions
Brown et al., 2014	All males – 22 veterans with PTSD and 22 trauma exposed veterans Apart from MDD, all other mental health disorders were excluded Use of medication allowed	SCID-I Alcohol Use Disorders Test Beck Depression Inventory (BDI) CAPS Combat Exposure Scale Drug Abuse Screening Test Traumatic Life Events Questionnaire	Seed-based analysis with 4 a priori-defined seed ROIs of bilateral centromedial amygdala and bilateral basolateral amygdala (BLA)	Veterans with PTSD had higher RSFC between the BLA and pregenual ACC, dmPFC and dorsal ACC as compared to the trauma exposed veterans	BLA - emotional processing (Brown et al., 2013) Pregenual ACC - self-referential and social processing (Amodio & Frith, 2006; Kelley et al., 2002) dmPFC - social cognition and mental simulations relevant to oneself (Buckner et al., 2008; Dutta et al., 2014) Dorsal ACC - cognitive control (Chouinard & Paus, 2006; Paus, 2001)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with PTSD/ trauma (unless otherwise stated)	Main functions of listed brain regions
Rabinak et al., 2011	All males - 17 veterans with PTSD and 17 combat exposed veterans without PTSD Use of medication allowed	SCID-I CAPS PTSD Checklist-Military Combat Exposure Scale Hamilton Depression Inventory BDI	Seed-based analysis with 2 a priori-defined seed ROIs of bilateral amygdala	Higher RSFC between the amygdala and insula for veterans with PTSD	Amygdala - emotional processing (Brown et al., 2013) Insula - emotional regulation, pain sensitivity, dissociation, perception and monitoring of internal states (Ludäscher et al., 2010; Niedtfeld et al., 2010)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with PTSD/ trauma (unless otherwise stated)	Main functions of listed brain regions
Kennis et al., 2013	All males- 27 veterans with PTSD and MDD and 23 veterans with PTSD but not MDD Use of medication allowed	SCID-I CAPS Mood and Anxiety Symptoms Questionnaire	Seed-based analysis with 4 a priori-defined seed ROIs of bilateral subgenual ACC and two distinct anterior insula subdivisions	For veterans with PTSD and MDD, increased RSFC between the ACC and insula as well as decreased RSFC between the ACC and thalamus was found	ACC - cognitive control (Chouinard & Paus, 2006; Paus, 2001), self-referential processing (Amodio & Frith, 2006; Kelley et al., 2002) emotional regulation (Drevets et al., 1997; Phan, Wager, Taylor, & Liberzon, 2002) Insula - emotional regulation, pain sensitivity, dissociation, perception and monitoring of internal states (Ludäscher et al., 2010; Niedtfeld et al., 2010) Thalamus - attention and arousal (Portas et al., 1998)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with PTSD/ trauma (unless otherwise stated)	Main functions of listed brain regions
Lanius et al., 2010	6 females and 5 males who had experienced either a motor vehicle crash or workplace accident Exclusion criteria: loss of consciousness greater than several seconds during the accident, mental health disorders, drug or alcohol abuse/dependence in the past 6 months, use of psychotropic medications within 4 weeks of scan, analgesics (including opioids), non-steroidal anti-inflammatories, or acetaminophen, all within 2 weeks of scan, lifetime history of bipolar disorder or schizophrenia	CAPS M.I.N.I Acute Stress Disorder Interview Acute Stress Disorder Scale Beck Depression and Anxiety Inventories DES	Seed-based analysis with a priori-defined seed ROIs of PCC/precuneus	Strength of RSFC between PCC/precuneus of the DMN and amygdala was found to predict severity of PTSD	PCC - self-referential processing (Bluhm et al., 2009) Precuneus – self-referential processing and autobiographical memory (Das et al., 2014) Amygdala - emotional processing (Brown et al., 2013)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with PTSD/ trauma (unless otherwise stated)	Main functions of listed brain regions
Gong et al., 2014	121 survivors of an earthquake (40 males and 81 females) Excluded if they have a history of mental health disorders, drug abuse or alcohol abuse	PTSD checklist Non-clinician version of the PTSD checklist	Multivariate Approach	Investigated the RSFC of the whole brain. Found that the left superior parietal lobule, right angular gyrus, right superior and middle occipital gyri, right cerebellum and the right uncus was able to predict PTSD severity	Parietal and occipital regions - Involved in attention and perception (Gong et al., 2013)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with PTSD/ trauma (unless otherwise stated)	Main functions of listed brain regions
Philip et al., 2014	All females - 8 participants without mental health disorders but had experienced ELS and 4 healthy controls without experiences of ELS Exclusion criteria: current use of psychotropic medications	CTQ SCID-I Perceived Stress Scale	Seed-based analysis with 3 priori-defined seed ROIs of PCC and bilateral amygdala	Individuals with ELS were found to have reduced RSFC between the PCC, mPFC and inferior temporal cortex	PCC - self-referential processing (Bluhm et al., 2009) mPFC - social cognition and mental simulations relevant to oneself (Buckner et al., 2008; Dutta et al., 2014) inferior temporal cortex – dissociation (Herath, Kinomura, & Roland, 2001; Ludäscher et al., 2010; Mesulam, 1998)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with PTSD/ trauma (unless otherwise stated)	Main functions of listed brain regions
Philip et al., 2013	14 participants without mental health disorders but had experienced ELS (7 males and 7 females) and 13 healthy controls without experiences of ELS (4 males and 9 females) Exclusion criteria: current use of psychotropic medications	SCID-I and SCID-II CTQ Inventory of Depressive Symptomatology (self-report) State-Trait Anxiety Inventory	Seed-based analysis with 2 priori-defined seed ROIs of Inferior parietal lobule and superior temporal gyrus	ELS participants displayed reduced RSFC between the inferior parietal lobule and right precuneus/PCC, left fusiform gyrus, cerebellum and caudate	Inferior parietal lobule - hypervigilance (Singh-Curry & Husain, 2009) PCC - self-referential processing (Bluhm et al., 2009) Left fusiform gyrus - memory (Singh-Curry & Husain, 2009) Cerebellum - motor control of emotional processing (Timmann & Daum, 2007) Caudate - reward processing (Epstein et al., 2006; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with PTSD/ trauma (unless otherwise stated)	Main functions of listed brain regions
Van der Weff et al., 2013	44 participants who had experienced emotional maltreatment (22 males and 22 females) and 44 participants who had no experiences of emotional maltreatment (20 males and 24 females)	Netherlands Mental Health Survey and Incidence Study trauma interview Neuroticism Extroversion Openness Five-Factor Inventory Beck Anxiety Inventory Montgomery–Asberg Depression Rating Scale Inventory of Depressive Symptomatology	Seed-based analysis with 5 priori-defined seed ROIs of bilateral amygdala, dorsal ACC, PCC and left dmPFC	Participants who had experienced of emotional maltreatment were found to display decreased RSFC between the amygdala and the following regions: precuneus, insula and putamen. In addition, decreased RSFC was also found between the ACC and precuneus, mPFC and the frontal pole	Amygdala - emotional processing (Brown et al., 2013) Precuneus - self-referential processing and autobiographical memory (Das et al., 2014) Insula - emotional regulation, pain sensitivity, dissociation, perception and monitoring of internal states (Ludäscher et al., 2010; Niedtfeld et al., 2010) Putamen - goal directed activity (Bennett, 2011) ACC - cognitive control, conflict monitoring, self-referential processing, emotional regulation (Kennis et al, 2014) mPFC and frontal pole – cognitive functions (Van Der Werff et al., 2013)

Appendix A8: DSM-5 Criteria for BPD

The essential features of a personality disorder are impairments in personality (self and interpersonal) functioning and the presence of pathological personality traits. To diagnose borderline personality disorder, the following criteria must be met:

A**)** Significant impairments in personality functioning manifest by:

1. Impairments in self functioning (a or b)

   a) Identity: Markedly impoverished, poorly developed, or unstable self-image, often associated with excessive self-criticism; chronic feelings of emptiness; dissociative states under stress.
   b) Self-direction: Instability in goals, aspirations, values, or career plans.

   AND

2. Impairments in interpersonal functioning (a or b)

   a) Empathy: Compromised ability to recognize the feelings and needs of others associated with interpersonal hypersensitivity (i.e. prone to feeling slighted or insulted) perceptions of others selectively biased toward negative attributes or vulnerabilities.
   b) Intimacy: Intense, unstable, and conflicted close relationships, marked by mistrust, neediness, and anxious preoccupation with real or imagined abandonment; close relationships often viewed in extremes of idealization and devaluation and alternating between over involvement and withdrawal.

B**)** Pathological personality traits in the following domains:

1. Negative Affectivity, characterized by

   a) Emotional lability: Unstable emotional experiences and frequent mood changes; emotions that are easily aroused, intense, and/or out of proportion to events and circumstances.
   b) Anxiousness: Intense feelings of nervousness, tenseness, or panic, often in reaction to interpersonal stresses; worry about the negative effects of past unpleasant experiences and future negative possibilities; feeling fearful, apprehensive, or threatened by uncertainty; fears of falling apart or losing control.
   c) Separation insecurity: Fears of rejection by – and/or separation from – significant others, associated with fears of excessive dependency and complete loss of autonomy.
   d) Depressivity: Frequent feelings of being down, miserable, and/or hopeless; difficulty recovering from such moods; pessimism about the future; pervasive shame; feeling of inferior self-worth; thoughts of suicide and suicidal behavior.

2. Disinhibition, characterized by

   a) Impulsivity: Acting on the spur of the moment in response to immediate stimuli; acting on a momentary basis without a plan or consideration of outcomes; difficulty establishing or following plans; a sense of urgency and self-harming behavior under emotional distress.
   b) Risk taking: Engagement in dangerous, risky, and potentially self-damaging activities, unnecessarily and without regard to consequences; lack of concern for one's limitations and denial of the reality of personal danger.

3. Antagonism, characterized by

   a) Hostility: Persistent or frequent angry feelings; anger or irritability in response to minor slights and insults.

C) The impairments in personality functioning and the individual's personality trait expression are relatively stable across time and consistent across situations.

D) The impairments in personality functioning and the individual's personality trait expression are not better understood as normative for the individual's developmental stage or socio-cultural environment.

E) The impairments in personality functioning and the individual's personality trait expression are not solely due to the direct physiological effects of a substance (e.g. substances of abuse or medication) or a general medical condition (e.g. severe brain injury).

Appendix A9: Main DMN Findings in BPD

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with BPD (unless otherwise stated)	Main functions of listed brain regions
Wolf et al., 2011	All females - 17 with BPD and 17 healthy controls Clinical participants with no co-morbid schizophrenia, drug and alcohol abuse six months prior to their participation, bipolar disorder and PTSD and absence of active suicidal ideation Use of medication allowed	SCID-II Barratt Impulsiveness Scale (BIS) Borderline Symptom List (BSL)-23 Dissociative Tension Scale	ICA	Increased RSFC in the FPC and the left insula Decreased RSFC in the left cuneus Decreased RSFC in the lateral frontoparietal networks and medial-frontal networks	FPC – processing of intentional thoughts, self-referential information and social interactions (Den Ouden, Frith, Frith, & Blakemore, 2005; Saxe, 2006) Left insula – emotional regulation, pain sensitivity, dissociation, perception and monitoring of internal states (Ludäscher et al., 2010; Niedtfeld et al., 2010) Left cuneus – dissociation (Gardini, Cornoldi, De Beni, & Venneri, 2006; Sander et al., 2005) Lateral frontoparietal networks and medial-frontal networks – attention, memory, behavioural inhibition (Smith et al., 2009)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with BPD (unless otherwise stated)	Main functions of listed brain regions
Krause-Utz et al., 2014	All females - 20 participants with BPD (9 of whom were diagnosed with PTSD) and 17 healthy controls Exclusion criteria for BPD group: current major depression, lifetime diagnoses of psychotic disorder, bipolar affective disorder and life threatening suicidal crisis Participants with BPD were free of medication for 14 days prior to scanning (28 days in the case of fluoxetine)	SCID-I International Personality Disorder Examination BSL-95 Post-traumatic Stress Diagnostic Scale CTQ DES BDI BIS Difficulties in Emotion Regulation Scale (DERS) Affect Intensity Measure	Seed-based analysis with three a priori-defined seed ROIs of amygdala, dACC and vACC	Increased RSFC between dACC and dmPFC, vACC and occipital cortex/ lingual gyrus/ cuneues	ACC - cognitive control, conflict monitoring, self-referential processing, emotional regulation (Kennis et al., 2014)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with BPD (unless otherwise stated)	Main functions of listed brain regions
Doll et al., 2013	14 participants with BPD (1 of whom is male) and 16 healthy controls (1 of whom is male) Exclusion criteria: psychosis, schizophrenia, schizoaffective disorder, bipolar disorder Use of medication allowed	SCID-I and II for clinical participants BDI Hamilton Depression Scale BSL Global Assessment of Functioning Scale	ICA	Lower RSFC between the CEN, salience network and DMN Higher RSFC of salience network in relation to interactions with CEN and DMN Increased intra RSFC for CEN, salience network and DMN (Specifically in relation to the DMN, these increases occurred in the PFC and insula)	CEN - cognitive processes such as attention and working memory (Menon, 2011) salience network - monitors both internal and external inputs before signals are sent to activate or de-activate either the DMN or CEN (Menon, 2011) PFC - self-related and social cognitive functions (Buckner, Andrews-Hanna, & Schacter, 2008; Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010) Insula - emotional regulation, pain sensitivity, dissociation, perception and monitoring of internal states (Ludäscher et al., 2010; Niedtfeld et al., 2010)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with BPD (unless otherwise stated)	Main functions of listed brain regions
O'Neill et al., 2014	All females – 17 with BPD and 19 healthy controls MDD was the only co-morbidity allowed for participants with BPD Use of medication allowed	SCID-I Hamilton Rating Scale for Depression BDI Eysenck Personality Questionnaire BIS	Seed-based analysis with a priori-defined seed ROI of precuneus	Increased RSFC between the precuneus and left inferior frontal gyrus, left precentral/middle frontal, and left middle occipital/superior parietal lobes	Precuneus - self-referential processing and autobiographical memory (Das, Calhoun, & Malhi, 2014) left inferior frontal gyrus - processing of intentional thoughts, self-referential information and social interactions (Den Ouden et al., 2005; Saxe, 2006) left precentral/middle frontal, and left middle occipital/superior parietal lobes - Theory of mind (O'Neill et al., 2014)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with BPD (unless otherwise stated)	Main functions of listed brain regions
Das et al., 2014	All females - 14 with BPD, 16 with euthymic bipolar disorder and 13 healthy controls Use of medication allowed	CTQ BIS BDI The Depression Anxiety Stress Scales DERS	ICA	Participants with bipolar disorder displayed higher RSFC between the DMN and precuneus network as compared to participants with BPD and healthy controls	Precuneus – self-referential processing and autobiographical memory (Das et al., 2014)

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings for participants with BPD (unless otherwise stated)	Main functions of listed brain regions
Kluetsch et al., 2013	All females – 25 with BPD and 22 healthy controls Exclusion criteria: MDD, alcohol or substance abuse or dependence in the last six months, bipolar disorder, schizophrenia, and pain disorders All participants free of psychotropic and pain medications for at least 2 weeks prior to scanning	SCID-I and II International Personality Disorder Examination DES BSL	ICA	Lower RSFC between the left retrosplenial cortex, right inferior temporal, left superior frontal gyrus and that of the DMN	Left retrosplenial cortex – processing of emotions and memory (Maddock, 1999; Nielsen, Balslev, & Hansen, 2005) Right inferior temporal gyrus - multisensory integration, and dissociation (Herath, Kinomura, & Roland, 2001; Ludäscher et al., 2010) Left superior frontal gyrus – self-referential processing (Van Buuren, Gladwin, Zandbelt, Kahn, & Vink, 2010)

Appendix A10: DSM-5 Criteria for Dissociative Disorders

A. Disruption of identity characterised by two or more distinct personality states, which may be described in some cultures as an experience of possession. The disruption in identity involves marked discontinuity in sense of self and sense of agency, accompanied by related alterations in affect, behaviour, consciousness, memory, perception, cognition, and/or sensory-motor functioning. These signs and symptoms may be observed by others or reported by the individual.

B. Recurrent gaps in the recall of everyday events, important personal information, and /or traumatic events that are inconsistent with ordinary forgetting.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The disturbance is not a normal part of a broadly accepted cultural or religious practice. Note: In children, the symptoms are not better explained by imaginary playmates or other fantasy play.

E. The symptoms are not attributable to the physiological effects of a substance (e.g., blackouts or chaotic behaviour during alcohol intoxication or other medical condition, e.g., complex partial seizures.)

<u>Depersonalisation/Derealisation Disorder</u>

A. The presence of persistent or recurrent experiences of depersonalisation, derealisation or both.

1. Depersonalisation: Experiences of unreality, detachment, or being an outside observer with respect to one's thoughts, feelings, sensations, body, or actions (e.g., perceptual alterations, distorted sense of time, unreal or absent self, emotional and/or physical numbing)
2. Derealisation: Experiences of unreality or detachment with respect to surroundings (e.g., individuals or objects are experienced as unreal, dreamlike, foggy, lifeless, or visually distorted.)

B. During the depersonalisation or derealisation experiences, reality testing remains intact.

C. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, medication) or other medical condition (e.g., seizures).

D. The disturbance is not better explained by another mental disorders

Dissociative Amnesia with or without Dissociative Fugue

A. An inability to recall important autobiographical information, usually of a traumatic or stressful nature, that is inconsistent with ordinary forgetting. Note: Dissociative Amnesia most often consists of localised or selective amnesia for a specific events or events; or generalised amnesia for identity and life history.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The disturbance is not attributable to the physiological effects of a substance.

D. The disturbance is not better explained by Dissociative Identity Disorder.

- Specify if: With Dissociative Fugue: Apparently purposeful travel or bewildered wandering that is associated with amnesia with Dissociative Fugue.

Appendix A11: Main DMN Findings in Dissociative Disorders

Research Article	Characteristics of Participants	Formal diagnostic/ screening and self-report measures for all participants (unless otherwise stated)	Resting State Analysis Method	Main Findings	Main functions of listed brain regions
Yolanda et al., 2014	All females - 15 with DID and 15 healthy controls Exclusion criteria: psychosis, drug abuse and addiction, anti-social personality disorder and histrionic personality disorder Use of medication allowed	SCID-I for clinical participants Healthy controls completed the Posttraumatic Diagnostic Scale and the BDI	ICA	For participants with DID, higher RSFC was found in the temporal pole of the middle temporal gyrus, precuneus, angular gyrus, and dmPFC	middle temporal gyrus - cognitive processes e.g. attention (Qin et al., 2012) precuneus - self-referential processing and autobiographical memory (Das et al., 2014) angular gyrus - attention and perception (Gong et al., 2013) dmPFC - social cognition and mental simulations relevant to oneself (Buckner, Andrews-Hanna, & Schacter, 2008; Dutta, Mckie, & Deakin, 2014)

Appendix A12: Scanner Model of Reviewed Research Articles

Research Article	Scanner Model
Bluhm et al., 2009	4.0 Tesla UNITY INOVA whole-body imaging system (Varian)
Qin et al., 2012	3.0 Tesla MRI scanner (GE Signa HDxt 3 T, USA)
Sripada et al., 2012	3.0 Tesla General Electric Signa Excite scanner (Milwaukee, WI)
Kennis et al., 2014	3.0 Tesla MRI scanner (Philips Medical System, Best, The Netherlands)
Brown et al., 2014	3.0 Tesla GE Signa EXCITE scanner
Rabinak et al., 2011	3.0 Tesla GE Signa System (General Electric; Milwaukee, WI, USA)
Kennis et al., 2013	3.0 Tesla MRI scanner (Philips Medical System, Best, the Netherlands)
Lanius et al., 2010	4.0 Tesla INOVA UNITY Varian (Palo Alto, CA, USA)
Gong et al., 2014	3.0 Tesla MRI system (EXCITE, General Electric, Milwaukee, WI, USA)
Philip et al., 2014	3.0 Tesla Siemens TIM TRIO scanner (Siemens, Erlangen, Germany)
Philip et al., 2013	3.0 Tesla Siemens TIM TRIO scanner (Siemens, Erlangen, Germany)

Research Article	Scanner Model
Van der Weff et al., 2013	3.0 Tesla Philips MR systems (Philips Healthcare, The Netherlands)
Wolf et al., 2011	3.0 Tesla MAGNETOM Allegra (Siemens)
Krause-Utz et al., 2014	3.0 Tesla Siemens TRIO MRI scanner (Siemens Medical Solutions, Germany)
Doll et al., 2013	3.0 Tesla whole body MR scanner (Achieva, Philips, Netherlands)
O'Neill et al., 2014	Philips Achieva MRI scanner (Philips Medical System, Netherland BV, Veenphuis 4–6, 5684 PC Best, The Netherlands)
Das et al., 2014	3.0 Tesla Siemens Magnetom Trio Scanner
Kluetsch et al., 2013	1.5 Tesla magnetic resonance scanner (Siemens Medical Solutions)
Yolanda et al., 2014	3.0 Tesla Philips Achieva whole body magnetic resonance imaging

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Appendix B1: Ethical Approval Letter

Part of the research infrastructure for Wales funded by the National Institute for Social Care and Health Research, Welsh Government.
Yn rhan o seilwaith ymchwil Cymru a ariannir gan y Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd, Llywodraeth Cymru

NISCHR
Gwasanaeth Moeseg Ymchwil | RES | Research Ethics Service

Research Ethics Committee (REC) for Wales
Sixth Floor, Churchill House
17 Churchill Way
Cardiff CF10 2TW
Telephone : 029 2037 6829
Fax : 029 2037 6824

E-mail : corinne.scott@wales.nhs.uk

Website : www.nres.nhs.uk

09 October 2012

Professor Peter Fonagy
HoD, Department of Clinical, Educational and Health Psychology, UCL
UCL
Gower Street
London WC1N 3BG

Dear Professor Fonagy

Study title: **Probing Social Exchanges – A Computational Neuroscience Approach to the Understanding of Borderline and Anti-Social Personality Disorder**
REC reference: **12/WA/0283**

Thank you for your letter of 25 September 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered by a sub-committee of the REC at a meeting held on 05 October 2012. A list of the sub-committee members is attached.

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites
NHS sites
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the

R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

- *The Clinical / Probation Service information sheet, page two paragraph one, has the phrase "which is a psychiatric interview" twice; one of these instances should be removed;*
- *The word "However" should be removed from the start of the first paragraph of page three under "What are the possible disadvantages and risks of taking part?";*
- *The second paragraph of the same section is the same sentence repeated twice, and one of these instances should be removed;*
- *The Healthy volunteers information page three, the word "However" should be removed from the start of the first paragraph of page three under "What are the possible disadvantages and risks of taking part?"*

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation.

Approved documents
The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Advertisement	Letter of invitation = advertisement material as well; version 1.1	22 August 2012
Covering Letter	signed Tobias Nolte, Anna Freud Centre	22 August 2012
Evidence of insurance or indemnity	Arthur J Gallagher International certificate of insurance - University College London - expires 01 August 2013	30 July 2012
GP/Consultant Information Sheets	1	22 August 2012
Investigator CV	Professor Fonagy; version 1.1	22 August 2012
Investigator CV	Dr Feigenbaum; version 1.1	22 August 2012
Investigator CV	Tobias Nolte; version 1.1	22 August 2012
Investigator CV	P Read Montague; no version or date	
Letter from Sponsor	signed David Wilson, University College London	21 August 2012
Letter of invitation to participant		22 August 2012
Other: Risk and Safety Protocol	1.1	22 August 2012
Other: Data Protection Form	no version or date	
Other: Additional details regarding MRI data	1.1	22 August 2012
Other: Consent to contact form	1.1	22 August 2012
Participant Consent Form: Healthy volunteers	1.2	
Participant Consent Form: Clinical / Probation service	1.2	
Participant Information Sheet: Genetics	1.1	22 August 2012
Participant Information Sheet: Healthy volunteers	1.2	

Participant Information Sheet: Clinical / Probation service	1.2	
REC application	signed electronically by Professor Fonagy, and electronically by Mr David Wilson, sponsor's representative	21 August 2012
Response to Request for Further Information	signed Dr Nolte	25 September 2012

Statement of compliance
The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements
The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback
You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/WA/0283	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Gordon Taylor
Chairman

Email: corinne.scott@wales.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: David Wilson, University College London
Dr Janet Feigenbaum, North East London Foundation Trust

Appendix B2: Information Sheet

Understanding the Social Brain in Healthy Volunteers and People with Psychological Difficulties.

This study has been approved by the Research Ethics Committee for Wales (Project ID Number): 12/WA/0283.

We would like to invite you to participate in this research project.

You are being invited to take part in a research study. You should only participate if you want to. Before you decide whether to take part, this sheet will give you some more information about why the study is being carried out, what you would be asked to do if you decide to take part, and how the study will be conducted. Please take some time to read this sheet, and to discuss it with other people if you wish. You are also very welcome to ask any further questions about the study, or if you find anything on this sheet unclear.

Why is this study being done?

With the proposed project we plan to investigate the brain activation patterns of people suffering from personality disorders (both in adults and adolescents) or similar traits and compare them with healthy control participants. Only little is known about the neurobiology of Borderline and Antisocial Personality Disorders. Our study design will address some of these. This will hopefully allow us to gain a better understanding of the disorders and to develop more informed and effective treatments from which clients will benefit.

Why have you been invited to take part?

You have been invited to take part in the study because you have recently been assessed by a clinician at one of the clinical or probation services currently collaboration with the research team.

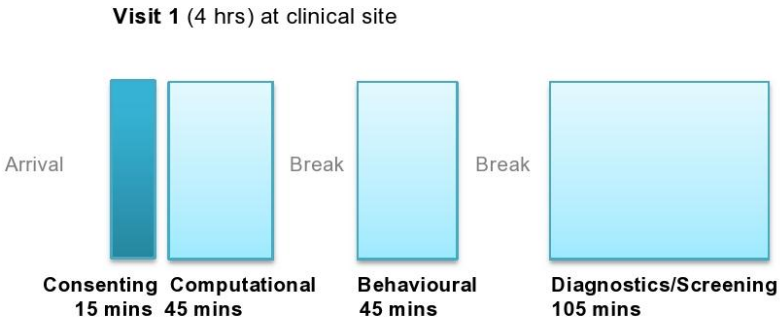
Do I have to take part?

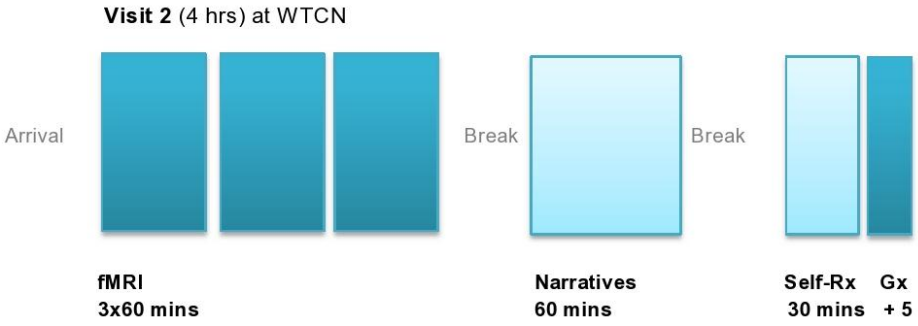
No. Taking part in the study is entirely voluntary. It is your choice whether or not you would like to participate. Deciding not to take part in the study will not affect the care you receive from services either now or in the future. If you do decide to participate, you will be given this information sheet to keep, and you will later be asked to sign a consent form stating that you wish to take part. If you do give consent to take part in the study, you are still free to leave the study at any point, without giving a reason. This will not affect the care you are currently receiving, or will receive in the future. If you leave, any information that we have already collected from you will be destroyed.

What will happen if I decide to take part?

If you wish to take part in the study, then you can get in touch with the research team or provide your contact details so that we can arrange a time to discuss the study in more detail and to book in the assessments if consent is obtained. We can then contact you to arrange a convenient time to meet. At this meeting you will meet a member of the research team and you can ask any other questions you may have. You will then be asked to sign a consent form to say that you wish to take part in the study. You will also be asked about your eligibility for brains scans as not every person can undergo these.

Study overview:





There will be two or three assessments with approximately 8 hours in total duration. In the first assessment, which will be held at the clinical site or the probation service, you will be asked to fill in questionnaires on personality functioning, developmental history, symptomatology etc. You will then perform several computer-based cognitive tasks and have a SCID I and II (relevant sections only) which is a psychiatric interview that takes approximately 30 to 60 minutes to complete. Any of these measures that have already been routinely obtained at your service will not be repeated if you are happy for your service to share the data with us (your consent provided).

If you agree to participate in this study you will be asked to come to the Wellcome Trust Centre for Neuroimaging on one occasion. The experiment will consist of 5 computerised tasks (which you will do whilst lying in a magnetic resonance imaging (MRI) brain scanner). In the tasks you will have to perform some tasks such as responding to written cues using different buttons to estimate or compare different events or conditions (similar to simple computer games) In some of them you will play another person who is being scanned at a different laboratory at the Principal Investigator's second laboratory at Virginia Tech University.. This phase will last roughly 3 hours but it is broken down into 3 sections of 60 minutes maximum with lots of breaks. After each hour you will have a longer break and leave the scanner. Most people find the tests quite straightforward and interesting to do. After the scanning, we will ask you to answer some further questions regarding the same or similar events or

conditions, fill out several questionnaires and you will be administered an interview regarding experiences in your childhood which usually takes another 45 minutes and which will be audio-recorded and transcribed before being coded for attachment by a reliable and experienced member of the research team. Before coding, all identifiable information will be removed from the audio file for anonymity.

If you have a tattoo, we will ask you to participate in a study that investigates any adverse effects which may occur as a result of MRI, such as heating or pulling on the tattoo.

No part of the study is compulsory and there will be separate consent sections for each part of the study.

What is functional magnetic resonance (fMRI) and what are the potential risks?

An MRI scanner takes pictures of your brain and measures the activity of different parts of it. The MRI scan procedure is painless and safe – these procedures are done hundreds of times a day all over the world. However, the MRI scanner makes loud noises while it is operating; we will provide you with headphones or earplugs to reduce the noise to safe levels. Some people find being in an MRI scanner makes them feel anxious and/or claustrophobic, even if they have not experienced claustrophobia before. A member of staff will be in constant contact with you via the intercom, and if you feel uncomfortable in any way the scanning can be stopped. Before you get into the MRI scanner the person who operates the scanner will explain the procedure to you and answer your questions. There is no radiation involved. MRI scans work using very strong magnetic fields. Therefore it would be dangerous for anyone with any magnetic metal in their body to go near the scanner, since that metal might move towards the magnet. You will not be able to participate in the MRI scan if you do have such metal in your body. Examples include: pace-makers; piercings; certain tattoos (which are sometime made with metallic inks) and screws from surgery. Fillings are not magnetic and are therefore not a problem. **If you are not sure whether you are able to participate in the MRI scan due to the presence metal in your body, please ask a researcher.**

What are the possible disadvantages and risks of taking part?

We will support you if you become upset. A specific Risk and Safety protocol for this study has been developed. You will be given time at the end of the study to be fully debriefed with a member of the research team and provided with a handout on emotional regulation skills, and crisis phone numbers and details of clinical services to contact. Your personal therapist or probation officer will also be aware of your participation in the study and able to support you should you find discussing your experiences difficult. Should you feel overwhelmed or acutely distressed during or at the end of the assessments, we you will be appropriately looked after by an experienced clinician.

Some people find the experience of being in the brain scanner uncomfortable or distressing as it is very noisy in you will have to lie still for a long time in a narrow tube.

Should any abnormalities be found during the scan a qualified Neurologist will be asked to review the image and if necessary contact your GP regarding any concerns.

What are the possible benefits of taking part?

You may find it interesting to complete these tasks and the information gathered during this study will also help to inform our understanding of treatment for Personality Disorders, which will hopefully be a step towards helping improve interventions in the future.

Will I be paid for taking part in the study?

As an acknowledgement of your time, we will be offering you a flat rate of £10 for your participation with additional compensation depending on your performance on some of the tasks. If you agree to give a saliva and blood sample, we will be offering you an additional £30.

Who will know you are taking part in the study?

We will inform your personal therapist or probation officer if you have been recruited via these services. We will inform your GP of your participation in this study, but information collected during all stages of the study will be kept strictly confidential. All information will only be viewed by members of the research teams at University College London and Virginia Tech University in the US.. However, if through the course of the study it was found that you are at immediate risk of harm to yourself or others, this information will be shared with your therapist or GP and, if necessary, emergency services.

Your consent form will be kept in a separate location from all your other data, ensuring that this remains anonymous. All data will be stored in secure locations whereby a participant ID will be assigned to your data, not identifiable personal information and the results of your tasks will be recorded on computers or flash drives which are password protected. Any published data will also be entirely anonymous meaning individuals cannot be identified.

Some of the MRI data will be transferred for analysis to the Principal Investigator's second laboratory at Virginia Tech University in the US. Those data will be anonymised and no identifiable personal information will be shared or transferred.

The data from this study will be stored in accordance with the UCL and NHS Data Protection and Records Management policies.

All data will be collected and stored in accordance with the Data Protection Act 1998.

What will happen to the results of the research study?

The results will be written up in the form of reports to be submitted to scientific journals or presented at conferences. As mentioned, you will not be identifiable from these results. On completion and if you request it you will be sent a report of the study.

What if there is a problem?

Every care will be taken in the course of this study. However, in the unlikely event that you are injured by taking part, compensation may be available.

If you suspect that the injury is the result of the Sponsor's (University College London) negligence then you may be able to claim compensation. After discussing with your research doctor, please make the claim in writing to Dr. Janet Feigenbaum or Dr Tobias Nolte on behalf of the Chief Investigators (Profs Read Montague and Peter Fonagy) who are based at University College

London. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff you may have experienced due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you. Please ask your research doctor if you would like more information on this. In the unlikely event that you are harmed by taking part in this study, compensation may be available to you. If you suspect that the harm is the result of the Sponsor's (University College London) or the hospital's negligence then you may be able to claim compensation. After discussing with your research doctor, please make the claim in writing to the Prof Fonagy who is the Chief Investigator for the research and is based at UCL, Research Department of Clinical, Educational and Health Psychology, 1-19 Torrington Place, London, WC1E 7HB. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this

Who has reviewed this study?

This study has been reviewed by the **REC for Wales 12/WA/0283**

Contact Details

If you wish to contact the research team to discuss any of the information further or any concerns you have about the study, then please do so by getting in touch with the members of the research team listed below:

If you feel that we have not addressed your questions adequately or if you have any concerns about the conduct of the research team, then please contact my supervisor Dr. Janet Feigenbaum (Strategic and Clinical Lead for Personality Disorder Services, North East London NHS Foundation Trust and Senior Lecturer, Research Department of Clinical, Educational and Health Psychology, UCL) on 07957 919 961or by email at janet.feigenbaum@nhs.net.

Janet Feigenbaum, PhD
Research Department of Clinical, Educational and Health Psychology
General Office, Room 436, 4th Floor
1-19 Torrington Place, London, WC1E 7HB

Tobias Nolte MD

Wellcome Trust Centre for Neuroimaging & Research Department of Clinical, Educational and Health Psychology
12 Queen Square
London
WC1N 3BG

Tobias.nolte@annafreud.org

Thank you very much for taking the time to read this information sheet.

Appendix B3: Written Consent

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Project Title:

Understanding the Social Brain in Healthy Volunteers and People with Psychological Difficulties.

This study has been approved by the Research Ethics Committee for Wales (Project ID): 12/WA/0283.

Thank you for your interest in taking part in this research. Before you agree to take part, the person organising the research must explain the project to you.

If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you to decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

Participant's Statement

I

- have read the notes written above and the Information Sheet, and understand what the study involves. I am also aware that I can consent to certain aspects of the study in order to participate in them whereas I can withhold my consent for others parts.
- understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately.
- consent to the processing of my personal information for the purposes of this research study.
- understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- understand that some of the MRI data will be transferred for analysis to the Principal Investigator's second laboratory at Virginia Tech University in the USA and will therefore no longer be subject to EEA data protection laws but that this data will be anonymised and no identifiable personal information will be shared or transferred.
- agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study.
- I agree that my non-personal research data may be used by others for future research. I am assured that the confidentiality of my personal data will be upheld through the removal of identifiers.

- I understand that part of my participation will be audio-recorded (the interviews) and I consent to the anonymous use of this material as part of the project.
- I agree to be contacted in the future by UCL researchers who would like to invite me to participate in follow-up studies.
- I understand that the information I have submitted will be published as a report and that I can request a copy. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications.
- I agree that the research team might re-contact me in case that additional data has to be obtained or for follow-up studies.

Please initial the statements below if you agree with them:	**Initial here**
I agree to take part in the general part of the PD-CPA study as outlined in the information Sheet and to all points listed above. (a separate consent for the MRI, tattoo component, and genetics component follows below).	
I agree to the audio recording of interviews and I consent to the anonymous use of this material as part of the project.	
I agree that some of the study data will be shared with the collaborating laboratory at Virginia Tech University in the USA.	
I understand that relevant sections of medical and or probation notes and data collected during my clinical assessment and during the study from me, may be looked at by individuals from the PD-CPA research team, my clinician or from the NHS Trust, where it is relevant to our taking part in this research. I give permission for these individuals to have access to my records.	
I agree that the PD-CPA research team can contact me about coming in for up to two follow-up sessions over the next three years.	
I agree that I can be contacted after the end of this study about possible future research and follow-up with PD-CPA and related groups.	
I agree that my GP can be told that I am participating in this study.	

GP's name: _____ Surgery: _____

Address: _____

MRI and Cognition:

I agree to have an MRI scan and I understand what will happen in the scan.	☐
I have had an MRI safety check and I am confident that there is no reason why I can't have a scan, such as a recent operation.	☐
I agree that my test results can be held by the Wellcome Trust and shared with other research groups, and I understand that this data will be anonymous and not contain any personal information.	☐

Genetics:

You do not have to agree to provide blood or saliva samples to take part in the research. You do not have to agree that any samples you do give can be stored for future testing.
By giving a sample, you consent to be contacted by BioResource about the possibility of joining their panel, but you are under no obligation to join BioResource.

I agree to give a sample of **blood and saliva** (delete as appropriate) for medical research and for details about me and any samples I provide to be kept on a secure database. I agree that BioResource, the study collaborator on genetics, can store my samples and can contact me to invite me to join their panel.	☐
I agree that the samples and information I provide can be stored for use in future medical research, subject to ethical approval.	☐
I understand that I will not benefit financially if my samples are used in research leading to a new treatment or medical test being developed.	☐
In the unlikely event that an abnormality is picked up from tests carried out on my sample, I agree to be informed, and with my consent my GP can be told.	☐

Thank you for your help.

By completing and returning this form, you are giving us your consent that the personal information you provide will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.

Participant:

Signed: Date:

Researcher:

Signed: Date:

Appendix B4: Debrief Sheet

Version 1.0 **[Debriefing Sheet]**

PD – CPA

Personality Disorders – a Computational Psychiatry Approach

Understanding the Social Brain in Healthy Volunteers and People with Psychological Difficulties.

Thank you for taking part in our study, we appreciate that you gave up your time to take part and hope that you found it interesting.

Summary of the Research Project

The aim of our study is to understand how mind and brain work in order to better understand patients with psychological difficulties. We hope that this will have an impact on the development of specific treatment interventions.

Most of our tasks are designed to look at how we think about ourselves and others (called "mentalisation"), how we regulate our emotions, value co-operation or experience close relationships and how problems can sometimes develop in these relationships.

Getting a better sense of the different strategies that people apply in these areas can help us understand more about when people experience mental health problems that can lead them to find certain social interactions and situations challenging. We hope to use these findings so that treatments can be tailored to help improve the domains where a patient's difficulties may lie.

We are also interested in how someone's experiences in childhood and his or her parenting at that time impact on the performances in the tasks and the functioning of the brain areas that underpin them. For instance, the long interview can tell us more about the quality of your bonding with parents.

Some of the topics discussed in the course of the study may have brought about thoughts or feelings which you had not previously considered or may have made you recall memories which could be perceived as distressing or lead you to feel tense or ruminate on thoughts. Therefore, we have provided some exercises at the back of this sheet which may help you to cope with any such feelings which you may experience.

What to do if you continue to feel concerned

If you continue to feel concerned after taking part in the study it may be useful to talk to a family member, a friend or your GP. Your Lead Clinician (care co-ordinator) or Probation Worker will also be able to support you, if you have one.

In addition to this support there is also free and confidential advice provided by the Mental Health charity Mind which can be found on their website: http://www.mind.org.uk/ or by calling their advice line 0300 123 3393.

If you feel at immediate risk do not hesitate to contact Dr Janet Feigenbaum (details overleaf).

Contact Details

If you still have concerns or wish to contact the research team to discuss any of the information further or any concerns you have about the study, then please do so by getting in touch with the members of the research team listed below:

If you feel that we have not addressed your questions adequately or if you have any concerns about the conduct of the research team, then please contact my supervisor Dr. Janet Feigenbaum (Strategic and Clinical Lead for Personality Disorder Services, North East London NHS Foundation Trust and Senior Lecturer, Research Department of Clinical, Educational and Health Psychology, UCL) on 07957 919 961 or by email at janet.feigenbaum@nhs.net.

Janet Feigenbaum, PhD

Research Department of Clinical, Educational and Health Psychology

General Office, Room 436, 4th Floor
1-19 Torrington Place, London, WC1E 7HB

telephone: 07957 919 961

Tobias Nolte MD

Wellcome Trust Centre for Neuroimaging & Research Department of Clinical, Educational and Health Psychology

12 Queen Square

London

WC1N 3BG

Tobias.nolte@annafreud.org

Thank you very much for taking the time to read this information sheet.

Relaxation Exercises

Progressive Muscle Relaxation Technique
{Pause between instructions}

Begin by finding a comfortable position either sitting or lying down in a location where you will not be interrupted.
Allow your attention to focus only on your body. If you begin to notice your mind wandering, bring it back to the muscle you are working on.

Take a deep breath through your abdomen, hold for a few seconds, and exhale slowly. Again, as you breathe notice your stomach rising and your lungs filling with air.

As you exhale, imagine the tension in your body being released and flowing out of your body.
And again inhale…..and exhale. Feel your body already relaxing.

As you go through each step, remember to keep breathing .

Now let's begin. Tighten the muscles in your forehead by raising your eyebrows as high as you can. Hold for about five seconds. And abruptly release feeling that tension fall away.

Now smile widely, feeling your mouth and cheeks tense. Hold for about 5 seconds, and release, appreciating the softness in your face.

Next, tighten your eye muscles by squinting your eyelids tightly shut. Hold for about 5 seconds, and release.

Gently pull your head back as if to look at the ceiling. Hold for about 5 seconds, and release, feeling the tension melting away.

Now feel the weight of your relaxed head and neck sink.

Breath in…and out.

In…and out.

Let go of all the stress

In…and out.

Now, tightly, but without straining, clench your fists and hold this position until I say stop. Hold for about 5 seconds, and release.

Now, flex your biceps. Feel that buildup of tension. You may even visualize that muscle tightening.

Hold for about 5 seconds, and release, enjoying that feeling of limpness.

Breath in...and out.

Now tighten your triceps by extending your arms out and locking your elbows. Hold for about 5 seconds, and release.

Now lift your shoulders up as if they could touch your ears. Hold for about 5 seconds, and quickly release, feeling their heaviness.

Tense your upper back by pulling your shoulders back trying to make your shoulder blades touch.

Hold for about 5 seconds, and release.

Tighten your chest by taking a deep breath in, hold for about 5 seconds, and exhale, blowing out all the tension.

Now tighten the muscles in your stomach by sucking in. Hold for about 5 seconds, and release.

Gently arch your lower back. Hold for about 5 seconds, relax.

Feel the limpness in your upper body letting go of the tension and stress, hold for about 5 seconds, and relax.

Tighten your buttocks. Hold for about 5 seconds…, release, imagine your hips falling loose.

Tighten your thighs by pressing your knees together, as if you were holding a penny between them.

Hold for about 5 seconds…and release.

Now flex your feet, pulling your toes towards you and feeling the tension in your calves. Hold for about 5 seconds, and relax, feel the weight of your legs sinking down.

Curl your toes under tensing your feet. Hold for about 5 seconds, release.

Now imagine a wave of relaxation slowly spreading through your body beginning at your head and going all the way down to your feet.

Feel the weight of your relaxed body.

Breathe in…and out…in…out….in…out.

Mindfulness Exercise

Read the following instructions

Sit comfortably, with your eyes closed and your spine reasonably straight.

Bring your attention to your breathing.

Imagine that you have a balloon in your tummy. Every time you breathe in, the balloon inflates. Each time you breathe out, the balloon deflates. Notice the sensations in your abdomen as the balloon inflates and deflates. Your abdomen rising with the in-breath, and falling with the out-breath.

Thoughts will come into your mind, and that's okay, because that's just what the human mind does. Simply notice those thoughts, then bring your attention back to your breathing.

Likewise, you can notice sounds, physical feelings, and emotions, and again, just bring your attention back to your breathing.

You don't have to follow those thoughts or feelings, don't judge yourself for having them, or analyse them in any way. It's okay for the thoughts to be there. Just notice those thoughts, and let them drift on by, bringing your attention back to your breathing.

Whenever you notice that your attention has drifted off and is becoming caught up in thoughts or feelings, simply note that the attention has drifted, and then gently bring the attention back to your breathing.

It's okay and natural for thoughts to enter into your awareness, and for your attention to follow them. No matter how many times this happens, just keep bringing your attention back to your breathing.

Appendix B5

PAI-BOR

This exercise contains a number of statements. Read each statement and decide if it is an accurate statement about you. Select whether the statement is FALSE (NOT AT ALL TRUE) or SLIGHTLY TRUE or MAINLY TRUE or VERY TRUE.

Work quickly and give your immediate answer, and try to answer every question. There are no right or wrong answers since this is simply a measure of the way you react.

	False	Slightly True	Mainly True	Very True
My mood can shift quite suddenly.				
My attitude about myself changes a lot.				
My relationships have been stormy.				
My moods get quite intense.				
Sometimes I feel terribly empty inside.				
I want to let certain people know how much they've hurt me.				
My mood is very steady.				
I worry a lot about other people leaving me.				
People once close to me have let me down.				
I have little control over my anger.				
I often wonder what I should do with my life.				
I rarely feel very lonely.				
I sometimes do things so impulsively that I get into trouble.				

	False	Slightly True	Mainly True	Very True
I've always been a pretty happy person.				
I can't handle separation from those close to me very well.				
I've made some real mistakes in the people I've picked as friends.				
When I'm upset, I typically do something to hurt myself.				
I've had times when I was so mad I couldn't do enough to express all my anger.				
I don't get bored very easily.				
Once someone is my friend, we stay friends.				
I'm too impulsive for my own good.				
I spend money too easily.				
I'm a reckless person.				
I'm careful about how I spend my money.				

Appendix B6

SAPAS

Only circle Y (yes) or N (no) in the case of question 3) if you think that the description applies most of the time and in most situations.

1. In general, do you have difficulty making and keeping friends? . . . . . Y / N

2. Would you normally describe yourself as a loner? . . . . . Y / N

3. In general, do you trust other people? . . . . . .Y / N

4. Do you normally lose your temper easily? . . . . . .Y / N

5. Are you normally an impulsive sort of person? . . . . . .Y / N

6. Are you normally a worrier?. . . . . .Y / N

7. In general, do you depend on others a lot? . . . . . .Y / N

8. In general, are you a perfectionist? . . . . . .Y / N

Appendix B7

CTQ:

These questions ask about some of your experiences growing up as a child and a teenager. Although these questions are of a personal nature, please try to answer as honestly as you can. For each question select the circle under the response that best describes how you feel.

	Never True	Rarely True	Sometimes True	Often True	Very Often True
I didn't have enough to eat.					
I knew there was someone to take care of me and protect me.					
People in my family called me things like "stupid", "lazy", or "ugly".					
My parents were too drunk or high to take care of the family.					
There was someone in my family who helped me feel that I was important or special.					
I had to wear dirty clothes.					
I felt loved.					
I thought that my parents wished I had never been born.					
I got hit so hard by someone in my family that I had to see a doctor or go to hospital.					
There was nothing I wanted to change about my family.					
People in my family hit me so hard that it left me with bruises or marks.					
I was punished with a belt, a board, a cord, or some other hard object.					
People in my family looked out for each other.					
People in my family said hurtful or insulting things to me.					
I believe that I was physically abused.					
I had the perfect childhood.					
I got hit or beaten so badly that it was noticed by someone like a teacher, neighbour, or doctor.					

	Never True	Rarely True	Sometimes True	Often True	Very Often True
I felt that someone in my family hated me.					
People in my family felt close to each other.					
Someone tried to touch me in a sexual way, or tried to make me touch them.					
Someone threatened to hurt me or tell lies about me unless I did something sexual with them.					
I had the best family in the world.					
Someone tried to make me do sexual things or watch sexual things.					
Someone molested me.					
I believe that I was emotionally abused.					
There was someone to take me to the doctor if I needed it.					
I believe that I was sexually abused.					
My family was a source of strength and support.					

Appendix B8

DES:

This questionnaire consists of twenty-eight questions about experiences that you may have in your daily life. We are interested in how often you have these experiences. It is important, however, that your answers show how often these experiences happen to you when you are not under the influence of drugs or alcohol.

To answer the questions, please determine to what degree the experience described in the question applies to you and select the number to show what percentage of the time you have the experience. 100% means ' always', 0% means 'never' with 10% increments in between. This assessment is not intended to be a diagnosis. If you are concerned about your results in any way, please speak with a qualified health professional.

	Never 0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	Always 100%
Some people have the experience of driving in a car and suddenly realising that they don't remember what happened during all or part of the trip.											
Some people find that sometimes they are listening to someone talk and they suddenly realise that they did not hear all or part of what was said.											
Some people have the experience of finding themselves in a place and having no idea how they got there											
Some people have the experience of finding themselves dressed in clothes that they don't remember putting on.											
Some people have the experience of finding new things among their belongings that they do not remember buying.											

	Never 0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	Always 100%
Some people sometimes find that they are approached by people that they do not know who call them by another name or insist that they have met them before.											
Some people sometimes have the experience of feeling as though they are standing next to themselves or watching themselves do something as if they are were looking at another person.											
Some people are told that they sometimes do not recognise friends or family members.											
Some people find that they have no memory for some important events in their lives (for example, a wedding or graduation).											
Some people have the experience of being accused of lying when they do not think that they have lied.											
Some people have the experience of looking in a mirror and not recognizing themselves.											
Some people sometimes have the experience of feeling that other people, objects, and the world around them are not real.											
Some people sometimes have the experience of feeling that their body does not belong to them.											

	Never 0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	Always 100%
Some people have the experience of sometimes remembering a past event so vividly that they feel as if they were reliving that event.											
Some people have the experience of not being sure whether things that they remember happening really did happen or whether they just dreamed them.											
Some people have the experience of being in a familiar place but finding it strange and unfamiliar.											
Some people find that when they are watching television or a movie they become so absorbed in the story that they are unaware of other events happening around them.											
Some people sometimes find that they become so involved in a fantasy or daydream that it feels as though it were really happening to them.											
Some people find that they sometimes are able to ignore pain.											
Some people find that that they sometimes sit staring off into space, thinking of nothing, and are not aware of the passage of time.											

	Never 0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	Always 100%
Some people sometimes find that when they are alone they talk out loud to themselves.											
Some people find that in one situation they may act so differently compared with another situation that they feel almost as if they were two different people.											
Some people sometimes find that in certain situations they are able to do things with amazing ease and spontaneity that would usually be difficult for them (for example, sports, work, social situations, etc.).											
Some people sometimes find that they cannot remember whether they have done something or have just thought about doing it (for example, not knowing whether they have just mailed a letter or have just thought about mailing it).											
Some people find evidence that they have done things that they do not remember doing.											
Some people sometimes find writings, drawings, or notes among their belongings that they must have done but cannot remember doing.											

	Never 0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	Always 100%
Some people sometimes find that they hear voices inside their head that tell them to do things or comment on things that they are doing.											
Some people sometimes feel as if they are looking at the world through a fog so that people and objects appear far away or unclear.											

Appendix B9

DERS

Please indicate how often the following statements apply to you by writing the appropriate number from the scale below on the line beside each item.

1----------2----------3----------4----------5

almost never (0-10%) | sometimes (11-35%) | about half the time (36-65%) | most of the time (66-90%) | almost always (91-100%)

1) I am clear about my feelings.	1	2	3	4	5
2) I pay attention to how I feel.	1	2	3	4	5
3) I experience my emotions as overwhelming and out of control.	1	2	3	4	5
4) I have no idea how I am feeling.	1	2	3	4	5
5) I have difficulty making sense out of my feelings.	1	2	3	4	5
6) I am attentive to my feelings.	1	2	3	4	5
7) I know exactly how I am feeling.	1	2	3	4	5
8) I care about what I am feeling.	1	2	3	4	5
9) I am confused about how I feel.	1	2	3	4	5
10) When I'm upset, I acknowledge my emotions.	1	2	3	4	5
11) When I'm upset, I become angry with myself for feeling that way.	1	2	3	4	5
12) When I'm upset, I become embarrassed for feeling that way.	1	2	3	4	5
13) When I'm upset, I have difficulty getting work done.	1	2	3	4	5
14) When I'm upset, I become out of control.	1	2	3	4	5
15) When I'm upset, I believe that I will remain that way for a long time.	1	2	3	4	5
16) When I'm upset, I believe that I will end up feeling very depressed.	1	2	3	4	5
17) When I'm upset, I believe that my feelings are valid and important.	1	2	3	4	5
18) When I'm upset, I have difficulty focusing on other things.	1	2	3	4	5
19) When I'm upset, I feel out of control.	1	2	3	4	5
20) When I'm upset, I can still get things done.	1	2	3	4	5
21) When I'm upset, I feel ashamed at myself for feeling that way.	1	2	3	4	5
22) When I'm upset, I know that I can find a way to eventually feel better.	1	2	3	4	5
23) When I'm upset, I feel like I am weak.	1	2	3	4	5

24) When I'm upset, I feel like I can remain in control of my behaviours.	1	2	3	4	5
25) When I'm upset, I feel guilty for feeling that way.	1	2	3	4	5
26) When I'm upset, I have difficulty concentrating.	1	2	3	4	5
27) When I'm upset, I have difficulty controlling my behaviours.	1	2	3	4	5
28) When I'm upset, I believe there is nothing I can do to make myself feel better.	1	2	3	4	5
29) When I'm upset, I become irritated at myself for feeling that way.	1	2	3	4	5
30) When I'm upset, I start to feel very bad about myself.	1	2	3	4	5
31) When I'm upset, I believe that wallowing in it is all I can do.	1	2	3	4	5
32) When I'm upset, I lose control over my behaviour.	1	2	3	4	5
33) When I'm upset, I have difficulty thinking about anything else.	1	2	3	4	5
34) When I'm upset I take time to figure out what I'm really feeling.	1	2	3	4	5
35) When I'm upset, it takes me a long time to feel better.	1	2	3	4	5
36) When I'm upset, my emotions feel overwhelming.	1	2	3	4	5

Appendix B10

BSI:

Instructions

The BSI test consists of a list of problems people sometimes have. Read each one carefully and tick the box of the response the best describes how much that problem has distressed or bothered you during the past seven days including today.

Do not skip any items.

If you have any questions, please ask them now.

In the last 7 days, how much were you distressed by:

	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Nervousness or shakiness inside					
2. Faintness or dizziness					
3. The idea that someone else can control your thoughts					
4. Feeling others are to blame for most of your troubles					
5. Trouble remembering things					
6. Feeling easily annoyed or irritated					
7. Pains in the heart or chest					
8. Feeling afraid in open spaces					
9. Thoughts of ending your life					
10. Feeling that most people cannot be trusted					
11. Poor appetite					

	Not at all	A little bit	Moderately	Quite a bit	Extremely
12. Suddenly scared for no reason					
13. Temper outbursts that you could not control					
14. Feeling lonely even when you are with people					
15. Feeling blocked in getting things done					
16. Feeling lonely					
17. Feeling blue					
18. Feeling no interest in things					
19. Feeling fearful					
20. Your feelings being easily hurt					
21. Feeling that people are unfriendly or dislike you					
22. Feeling inferior to others					
23. Nausea or upset stomach					
24. Feeling that you are watched or talked about by others					
25. Trouble falling asleep					

	Not at all	A little bit	Moderately	Quite a bit	Extremely
26. Having to check and double check what you do					
27. Difficulty making decisions					
28. Feeling afraid to travel on buses, subways, or trains					
29. Trouble getting your breath					
30. Hot or cold spells					
31. Having to avoid certain things, places, or activities because they frighten you					
32. Your mind going blank					
33. Numbness or tingling in parts of your body					
34. The idea that you should be punished for your sins					
35. Feeling hopeless about the future					
36. Trouble concentrating					
37. Feeling weak in parts of your body					
38. Feeling tense or keyed up					
39. Thoughts of death or dying					

	Not at all	A little bit	Moderately	Quite a bit	Extremely
40. Having urges to beat, injure, or harm someone					
41. Having urges to break or smash things					
42. Feeling very self-conscious with others					
43. Feeling uneasy in crowds					
44. Never feeling close to another person					
45. Spells of terror or panic					
46. Getting into frequent arguments					
47. Feeling nervous when you are left alone					
48. Others not giving you proper credit for your achievements					
49. Feeling so restless you couldn't sit still					
50. Feelings of worthlessness					
51. Feeling that people will take advantage of you if you let them					
52. Feeling of guilt					
53. The idea that something is wrong with your mind					

Appendix B11

Breakdown of Missing Values across Questionnaires

	Healthy Controls N (% within total sample)	BPD Participants N (% within total sample)
Across all Questionnaires	5 (1.33%)	14 (3.15%)
Questionnaire		
PAI-BOR	-	1 (1.35%)
SAPAS	-	-
CTQ	1 (1.35%)	4 (5.40%)
DES	3 (4.05%)	2 (2.70%)
DERS	-	3 (4.2%)
BSI	1 (1.35%)	4 (5.40%)

Appendix B12

Test of Normality for Demographic Data and Questionnaires

	Kolmogorov-Smirnov		Skewness	Kurtosis
	Statistic	Significance Level (*p*-value)		
Age				
Healthy controls	.25	<.0001**	4.62**	3.42**
BPD participants	.14	.017	1.71	-.72
Years in Education				
Healthy controls	.10	.200	.34	.31
BPD participants	.11	.200	-.27	1.07
IQ				
Healthy controls	.10	.200	-1.57	.54
BPD participants	.08	.200	-.54	-1.44
DERS Total				
Healthy controls	.16	.040	1.52	-.007
BPD participants	.14	.028	-1.59	-.25
DES Total				
Healthy controls	.17	.016	3.43**	3.64**
BPD participants	.12	.119	.70	-1.16
CTQ Total				
Healthy controls	.17	.015	3.03**	1.70
BPD participants	.10	.200	.12	-1.61
SAPAS Total				
Healthy controls	.17	.017	2.25**	.40
BPD participants	.22	<.0001**	-2.05**	.25
PAI-BOR Total				
Healthy controls	.20	.003**	2.50**	.52
BPD participants	.14	.026	-3.88**	5.11**
BSI GSI				
Healthy controls	.28	<.0001**	5.22**	6.29**
BPD participants	.09	.200	-.78	-1.28

** indicates significant values <.05

Appendix B13

Eight Seed Regions Chosen Based on Existing Literature

Seed Region	Hemisphere	Abbreviation	MNI Coordinates		
			x	y	z
Ventral medial prefrontal cortex	midline	vmPFC	0	26	-18
Dorsal medial prefrontal cortex	midline	dmPFC	0	52	26
Temporal parietal junction	left	lTPJ	-54	-54	28
	right	rTPJ	54	-54	28
Posterior cingulate cortex	left	lPCC	-8	-56	26
	right	rPCC	8	-56	26
Anterior medial prefrontal cortex	left	lamPFC	-6	52	-2
	right	ramPFC	6	52	-2

Note: Coordinates were obtained from masks used in McCormick et al, 2013[a] and are based on the Montreal Neurological Institute (MNI) system (Evans et al, 1993[b]) and represent the center of 8mm spheres.

[a] McCormick, C., Quraan, M., Cohn, M., Valiante, T. A., & McAndrews, M. P. (2013). Default mode network connectivity indicates episodic memory capacity in mesial temporal lobe epilepsy. Epilepsia, *54,* 809–818.

[b] Evans, A.C., Collins, D.L., Mills, S.R., Brown, E.D., Kelly, R.L., & Peters, T.M. (1993). 3D statistical neuroanatomical models from 305 MRI volumes. Proceedings of IEEE-Nuclear Science Symposium and Medical Imaging Conference, 1813–1817.

Appendix B14

Design Specification in SPM

Information presented in this appendix is based on the SPM manual (http://www.fil.ion.ucl.ac.uk/spm/doc/manual.pdf). In order to investigate the first hypothesis that there are differences in RSFC between healthy controls and BPD participants, a GLM design matrix was specified within the SPM program by defining the weights matrix. Essentially, the design matrix mathematically models the experimental design and hypothesis. To assess the presence of between group differences, contrast vectors are used. Thus, these contrast vectors are used to test against the null hypothesis (no difference exist). Additionally, specification of multiple vectors allows the testing of multiple main and interaction effects.

Design Specification to Investigate Hypothesis One

The design matrix used to test the first hypothesis in relation to the lPCC seed is shown in Figure 22. In this design matrix, the first two columns correspond with the scans that are uploaded into SPM, in this case, the first 44 scans are for BPD participants followed by the next 30 scans for healthy controls. In these two columns, a contrast vector was defined to distinguish the two groups of participants; white column represents BPD participants whilst black column represents healthy controls. Since this study found significant differences between the groups in relation to gender, income and IQ, these three variables were also entered into the design matrix, as reflected by the next three columns. To specify the contrast, we then create a weights matrix (Figure 23). This then generate statistical parametric maps, such as the one depicted in Figure 24 as well as statistical results reflected in Figure 25. The statistical results reflected in Figure 25 is in descending order of statistical

significance. Once the design specification is set up and saved, analyses for the rest of the seeds can be completed by uploading the scans for the respective seed.

Figure 22. Design matrix created to test the first hypothesis, with the first two columns corresponding to the two groups and next three columns corresponding to IQ, gender and income.

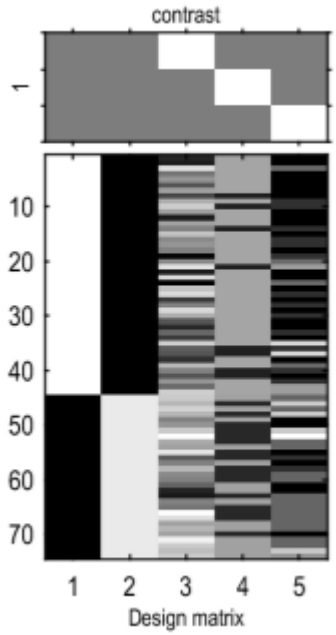


Figure 23. Weights matrix used to test the first hypothesis, with the rows corresponding to IQ, gender and income, respectively

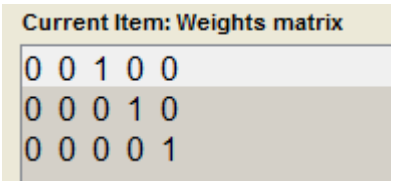


Figure 24. Statistical parametric map for between-subject differences in relation to the lPCC seed after controlling for the influence of IQ, gender and income

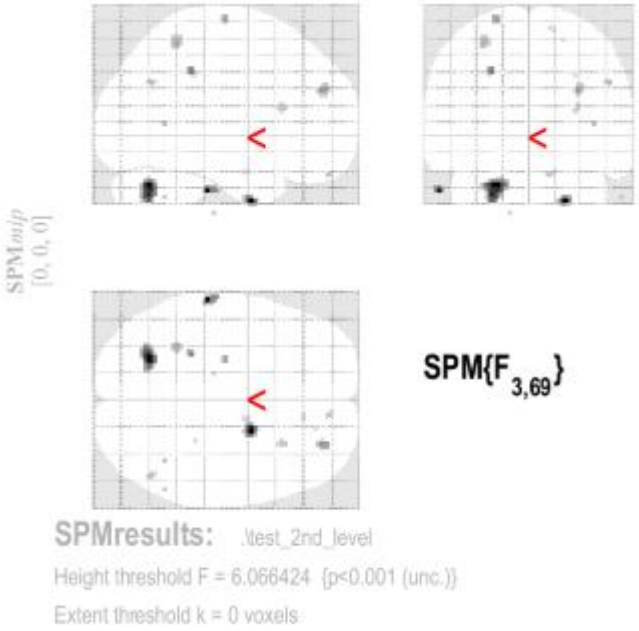


Figure 25. Statistical results for between-subject differences in relation to the lPCC seed after controlling for the influence of IQ, gender and income

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	$(Z_=)$	p_{uncorr}	
0.639	17	0.952	0.824	28	0.167	0.500	0.323	9.90	4.15	0.000	22 0 -42
		0.082	0.080	145	0.005	0.510	0.323	9.87	4.15	0.000	-24 -66 -32
		0.997	0.824	14	0.324	0.605	0.323	9.56	4.07	0.000	-60 -28 -36
		1.000	0.824	8	0.460	0.987	0.912	7.75	3.61	0.000	-26 -38 38
		0.993	0.824	17	0.277	0.999	0.959	7.27	3.47	0.000	30 46 26
		1.000	0.824	7	0.491	1.000	0.959	7.08	3.41	0.000	-22 -16 70
		0.981	0.824	22	0.218	1.000	0.959	6.94	3.37	0.000	-32 -48 56
		1.000	0.824	1	0.824	1.000	0.959	6.78	3.32	0.000	40 -56 6
		1.000	0.824	5	0.567	1.000	0.959	6.74	3.31	0.000	50 -64 32
		1.000	0.824	3	0.668	1.000	0.959	6.52	3.24	0.001	12 50 -26
		1.000	0.824	1	0.824	1.000	0.959	6.50	3.23	0.001	58 -56 -40
		1.000	0.824	5	0.567	1.000	0.959	6.47	3.22	0.001	30 20 16
		1.000	0.824	2	0.735	1.000	0.959	6.32	3.18	0.001	14 -2 -24
		1.000	0.824	1	0.824	1.000	0.959	6.32	3.17	0.001	-14 -24 -50
		1.000	0.824	2	0.735	1.000	0.959	6.25	3.15	0.001	12 34 66
		1.000	0.824	1	0.824	1.000	0.983	6.09	3.10	0.001	20 42 58
		1.000	0.824	1	0.824	1.000	0.983	6.09	3.10	0.001	28 -36 36

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 6.07, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 15.537
Expected number of clusters, <c> = 18.17
FWEp: 13.037, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [3.0, 69.0]
FWHM = 12.4 12.2 12.1 mm mm mm; 6.2 6.1 6.1 {voxels}
Volume: 2044216 = 255527 voxels = 1045.6 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 230.13 voxels)

Appendix B15

Design Specification to Investigate Hypothesis Two

In the second hypothesis, it was thought that RSFC between groups will be associated with indices of personality and clinical psychopathology. Thus, the design specification set up for hypothesis one was retained but additional contrasts corresponding to the six self-report measures were added. The weights matrix used to investigate hypothesis two, specifically in relation to CTQ is shown in Figure 26. These six additional contrasts can be seen in the last 12 columns of Figure 27.

Figure 26. Weights matrix used to test the second hypothesis, specifically for CTQ

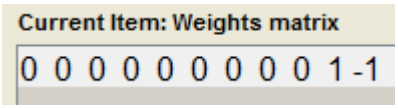
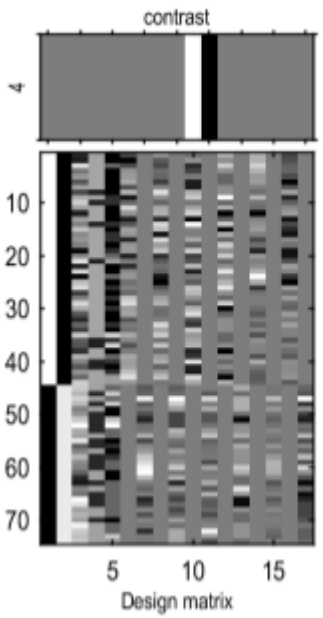


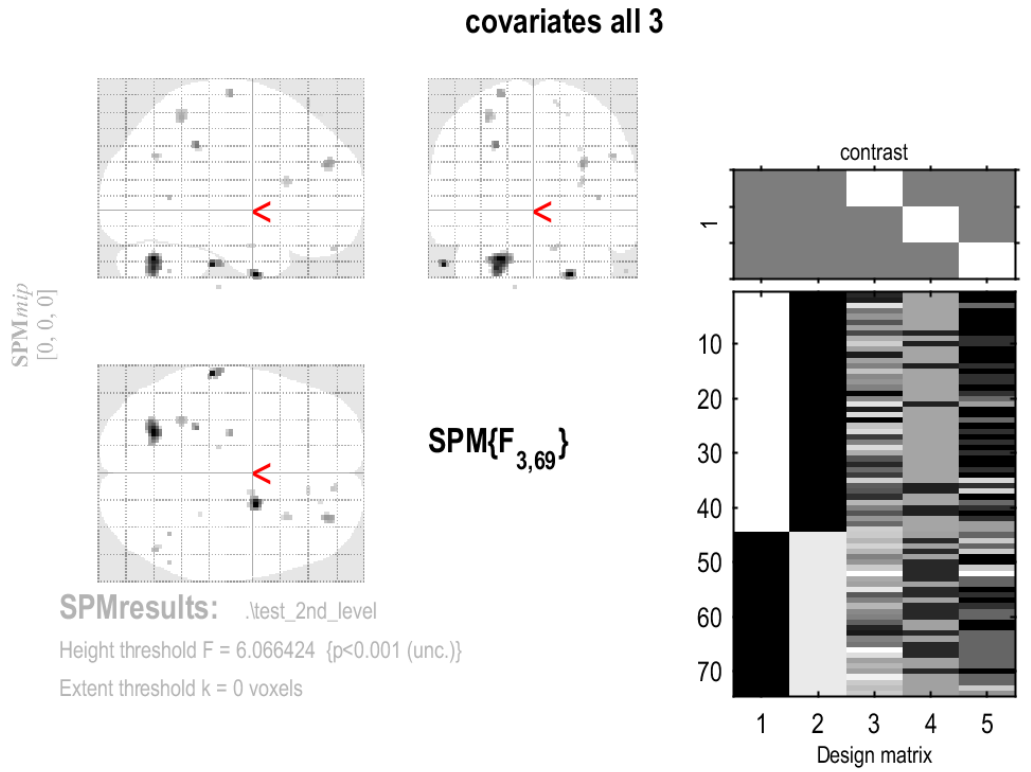
Figure 27.



Design matrix created to test the second hypothesis, with the first two columns corresponding to the two groups, next three columns to the covariates and last 12 columns corresponding to self-report measures in order of DERS, DES, CTQ, SAPAS, PAI-BOR and BSI. Beneath the label "contrast", the location of the white bar (representing scores of BPD participants) and black bar (representing scores for healthy controls) depicts that this design set up is for the investigation of RSFC in relation to that specific measure (in this case, the CTQ) whilst controlling for the influence of the rest of the five measures and the three covariates.

Appendix B16

Original Tables Generated by SPM12; RSFC to the lPCC whilst controlling for gender, income and IQ



Statistics: ***p-values adjusted for search volume***

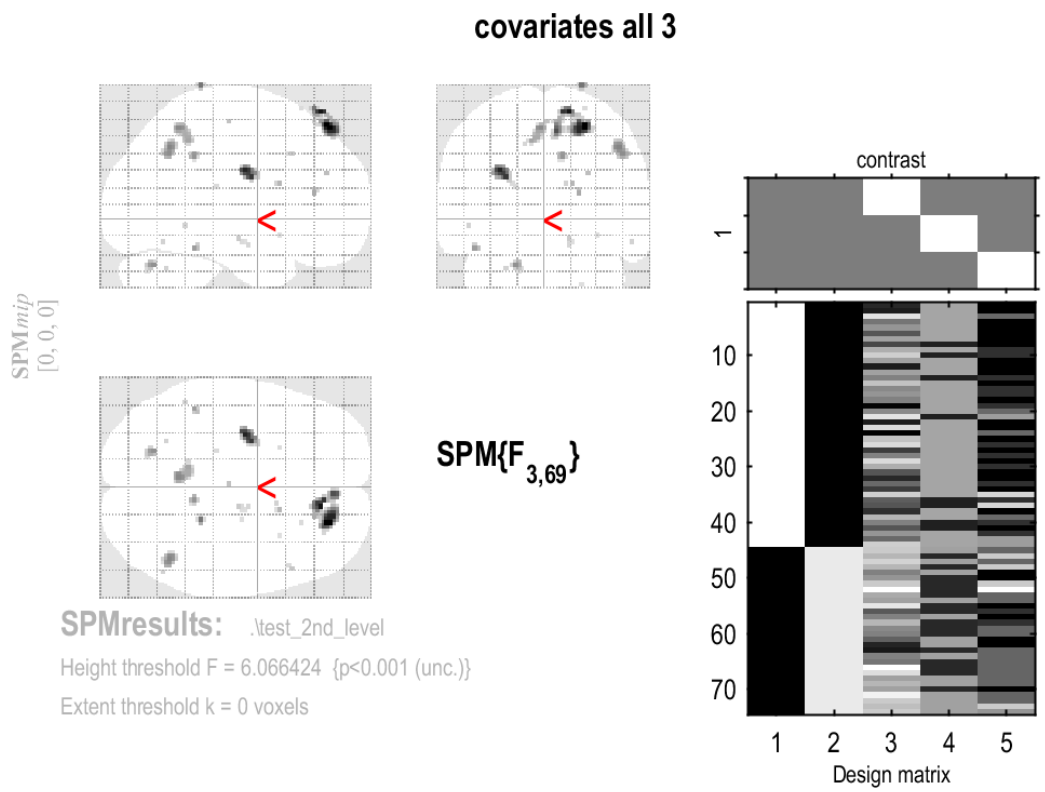
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	$(Z_{\equiv})$	p_{uncorr}			
0.639	17	0.952	0.824	28	0.167	0.500	0.323	9.90	4.15	0.000	22	0	-42
		0.082	0.080	145	0.005	0.510	0.323	9.87	4.15	0.000	-24	-66	-32
		0.997	0.824	14	0.324	0.605	0.323	9.56	4.07	0.000	-60	-28	-36
		1.000	0.824	8	0.460	0.987	0.912	7.75	3.61	0.000	-26	-38	38
		0.993	0.824	17	0.277	0.999	0.959	7.27	3.47	0.000	30	46	26
		1.000	0.824	7	0.491	1.000	0.959	7.08	3.41	0.000	-22	-16	70
		0.981	0.824	22	0.218	1.000	0.959	6.94	3.37	0.000	-32	-48	56
		1.000	0.824	1	0.824	1.000	0.959	6.78	3.32	0.000	40	-56	6
		1.000	0.824	5	0.567	1.000	0.959	6.74	3.31	0.000	50	-64	32
		1.000	0.824	3	0.668	1.000	0.959	6.52	3.24	0.001	12	50	-26
		1.000	0.824	1	0.824	1.000	0.959	6.50	3.23	0.001	58	-56	-40
		1.000	0.824	5	0.567	1.000	0.959	6.47	3.22	0.001	30	20	16
		1.000	0.824	2	0.735	1.000	0.959	6.32	3.18	0.001	14	-2	-24
		1.000	0.824	1	0.824	1.000	0.959	6.32	3.17	0.001	-14	-24	-50
		1.000	0.824	2	0.735	1.000	0.959	6.25	3.15	0.001	12	34	66
		1.000	0.824	1	0.824	1.000	0.983	6.09	3.10	0.001	20	42	58
		1.000	0.824	1	0.824	1.000	0.983	6.09	3.10	0.001	28	-36	36

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 6.07, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 15.537
Expected number of clusters, <c> = 18.17
FWEp: 13.037, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [3.0, 69.0]
FWHM = 12.4 12.2 12.1 mm mm mm; 6.2 6.1 6.1 {voxels}
Volume: 2044216 = 255527 voxels = 1045.6 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 230.13 voxels)

Original Tables Generated by SPM12; RSFC to the lTPJ whilst controlling for gender, income and IQ



Statistics: ***p-values adjusted for search volume***

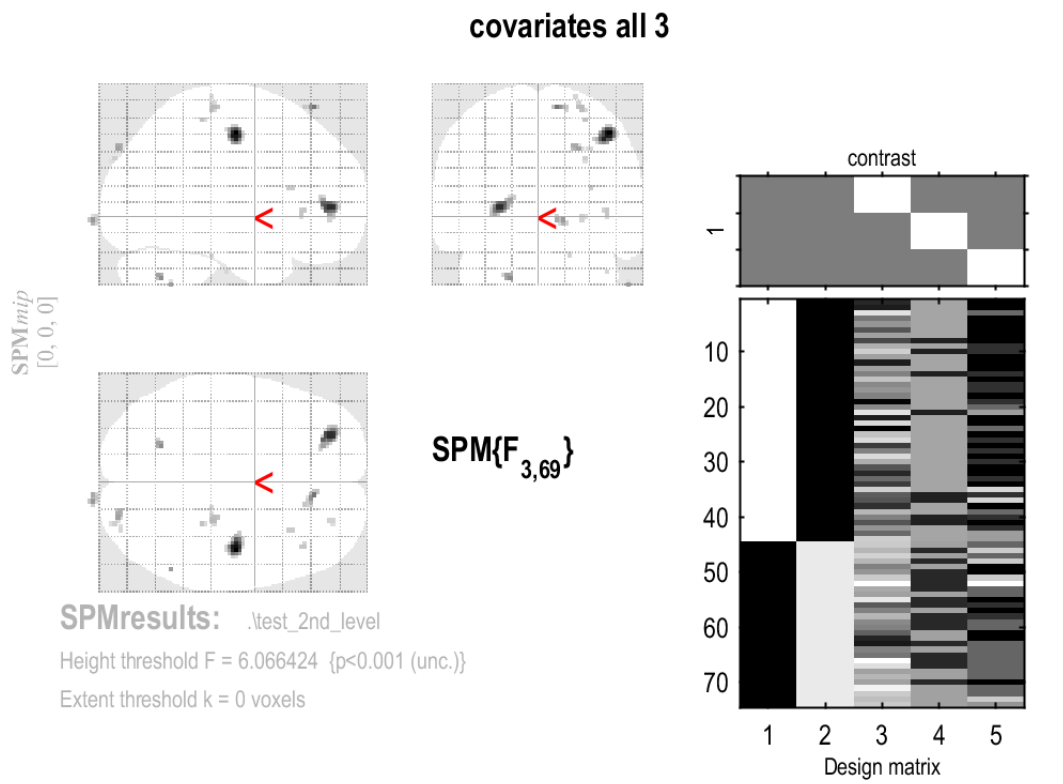
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	$(Z_{\equiv})$	p_{uncorr}			
0.102	24	0.062	0.085	158	0.004	0.470	0.569	10.00	4.18	0.000	24	42	56
						0.601	0.569	9.56	4.07	0.000	14	38	64
						0.891	0.655	8.53	3.82	0.000	6	46	52
		0.631	0.407	58	0.055	0.687	0.569	9.29	4.01	0.000	-30	-10	28
		1.000	0.824	6	0.529	0.980	0.908	7.87	3.64	0.000	22	-38	80
		0.706	0.407	52	0.068	0.991	0.908	7.64	3.57	0.000	46	-58	42
		0.644	0.407	57	0.057	0.995	0.908	7.52	3.54	0.000	-4	-52	54
						1.000	0.963	7.06	3.40	0.000	-10	-46	46
		0.995	0.824	16	0.293	0.997	0.908	7.37	3.50	0.000	-20	-68	-30
		0.999	0.824	12	0.363	0.998	0.908	7.34	3.49	0.000	10	-42	36
		1.000	0.824	5	0.569	0.999	0.926	7.22	3.45	0.000	-46	-42	-20
		1.000	0.824	3	0.669	1.000	0.963	7.01	3.39	0.000	20	34	14
		1.000	0.824	2	0.736	1.000	0.983	6.82	3.33	0.000	16	12	20
		1.000	0.824	1	0.824	1.000	0.983	6.62	3.27	0.001	26	42	26
		1.000	0.824	1	0.824	1.000	0.983	6.57	3.25	0.001	0	-20	58
		1.000	0.824	2	0.736	1.000	0.983	6.48	3.23	0.001	52	20	38
		1.000	0.824	4	0.615	1.000	0.983	6.44	3.21	0.001	14	-14	-14
		1.000	0.824	1	0.824	1.000	0.983	6.32	3.17	0.001	12	10	20
		1.000	0.824	1	0.824	1.000	0.983	6.30	3.17	0.001	-50	-48	-6

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 6.07, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 15.665
Expected number of clusters, <c> = 18.02
FWEp: 13.027, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [3.0, 69.0]
FWHM = 12.5 12.2 12.1 mm mm mm; 6.3 6.1 6.1 {voxels}
Volume: 2044216 = 255527 voxels = 1037.0 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 232.04 voxels)
Page 1

Original Tables Generated by SPM12; RSFC to the ramPFC whilst controlling for gender, income and IQ



Statistics: ***p-values adjusted for search volume***

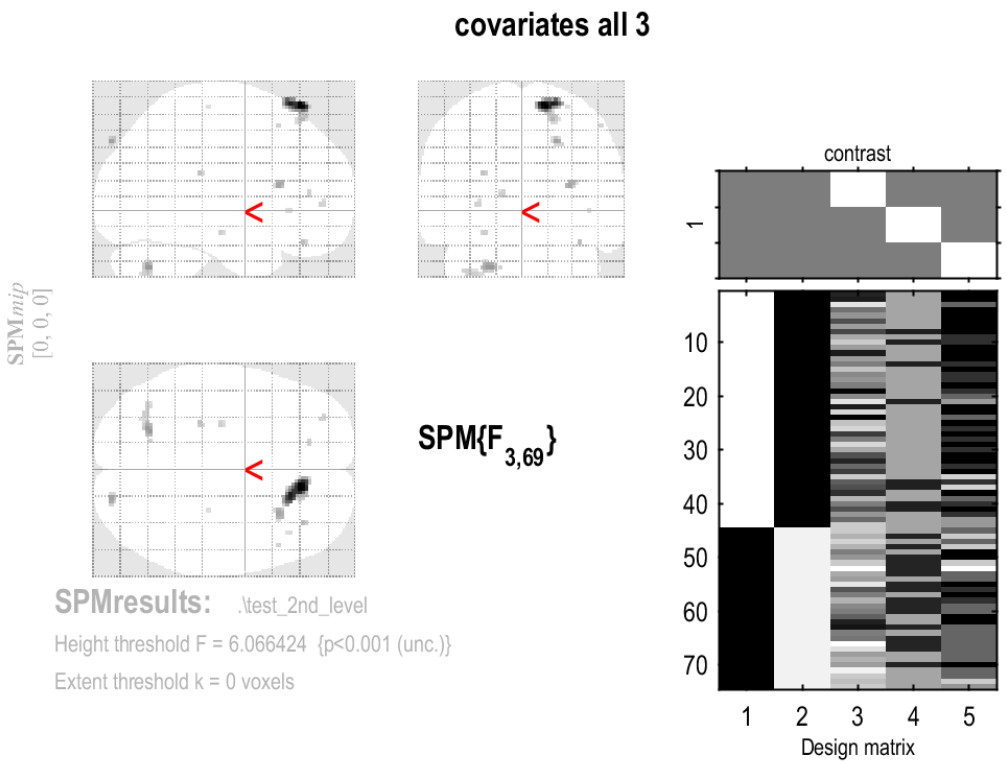
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	$(Z_{=})$	p_{uncorr}			
0.354	17	0.402	0.490	88	0.034	0.545	0.903	9.54	4.07	0.000	44	-14	50
		0.584	0.490	68	0.058	0.784	0.903	8.76	3.87	0.000	-26	46	4
						0.999	0.903	7.02	3.39	0.000	-20	42	8
		0.999	0.843	11	0.429	0.977	0.903	7.71	3.59	0.000	10	36	66
						1.000	0.903	6.45	3.22	0.001	16	30	66
		0.999	0.843	9	0.477	0.995	0.903	7.31	3.48	0.000	-20	-62	-40
		0.999	0.843	11	0.429	0.998	0.903	7.10	3.42	0.000	14	-106	-4
		1.000	0.843	2	0.762	0.999	0.903	7.06	3.41	0.000	56	-56	-44
		0.998	0.843	12	0.408	0.999	0.903	6.99	3.39	0.000	24	-90	40
		0.999	0.843	9	0.477	1.000	0.903	6.66	3.28	0.001	26	-28	66
		1.000	0.843	2	0.762	1.000	0.903	6.50	3.23	0.001	28	-36	58
		1.000	0.843	5	0.606	1.000	0.903	6.48	3.23	0.001	42	30	2
		1.000	0.843	2	0.762	1.000	0.903	6.38	3.20	0.001	32	22	16
		1.000	0.843	2	0.762	1.000	0.903	6.32	3.17	0.001	28	-92	34
		1.000	0.843	3	0.700	1.000	0.903	6.30	3.17	0.001	26	46	-4
		1.000	0.843	1	0.843	1.000	0.903	6.25	3.15	0.001	18	-30	-26
		1.000	0.843	2	0.762	1.000	0.903	6.21	3.14	0.001	32	-88	40
		1.000	0.843	1	0.843	1.000	0.903	6.20	3.14	0.001	22	-30	72
		1.000	0.843	1	0.843	1.000	0.903	6.19	3.13	0.001	42	-20	-36

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 6.07, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 18.764
Expected number of clusters, <c> = 15.19
FWEp: 12.812, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [3.0, 69.0]
FWHM = 13.3 13.1 12.8 mm mm mm; 6.6 6.5 6.4 {voxels}
Volume: 2044216 = 255527 voxels = 865.8 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 277.94 voxels)

Original Tables Generated by SPM12; RSFC to the lamPFC whilst controlling for gender, income and IQ



Statistics: ***p-values adjusted for search volume***

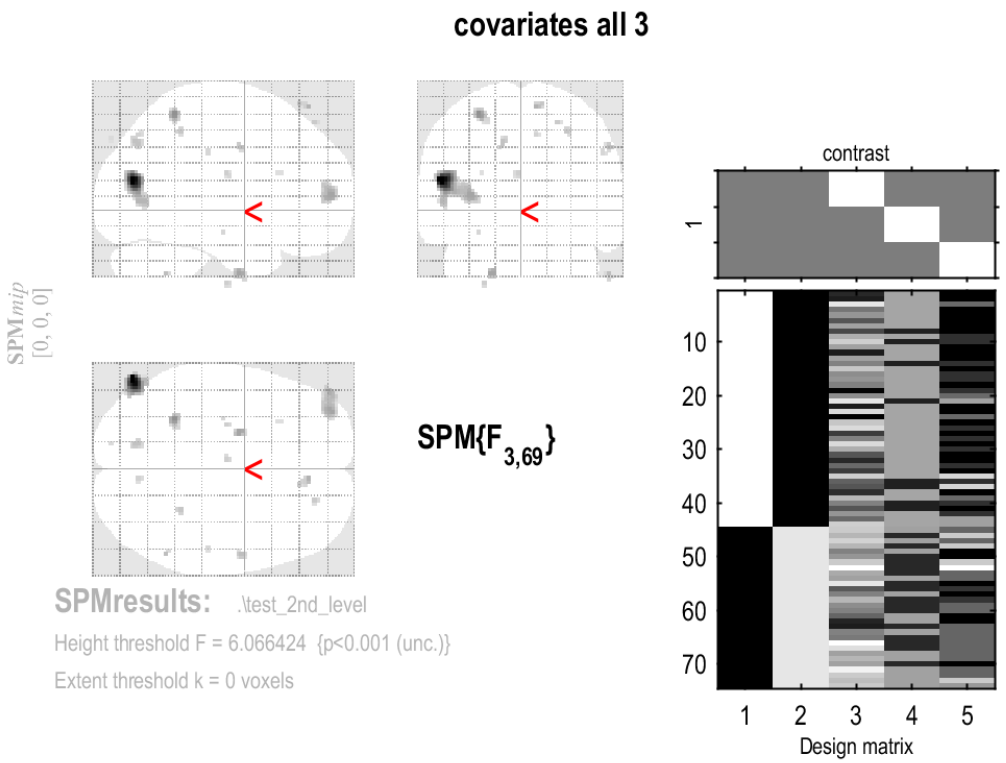
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	$(Z_{\equiv})$	p_{uncorr}			
0.719	13	0.219	0.216	120	0.017	0.179	0.207	11.15	4.43	0.000	14	34	64
						0.999	0.903	6.97	3.38	0.000	18	36	56
		0.865	0.845	41	0.135	0.979	0.903	7.65	3.58	0.000	-22	-64	-38
						1.000	0.903	6.49	3.23	0.001	-32	-68	-42
		0.998	0.845	12	0.414	0.991	0.903	7.42	3.51	0.000	20	-90	42
		0.998	0.845	11	0.435	0.993	0.903	7.36	3.50	0.000	30	20	14
		1.000	0.845	2	0.765	1.000	0.903	6.79	3.32	0.000	36	36	-22
		1.000	0.845	3	0.704	1.000	0.903	6.69	3.29	0.000	-28	-32	22
		1.000	0.845	4	0.654	1.000	0.903	6.50	3.23	0.001	-26	-18	-16
		1.000	0.845	4	0.654	1.000	0.903	6.46	3.22	0.001	-16	40	8
		1.000	0.845	4	0.654	1.000	0.903	6.37	3.19	0.001	-32	50	2
		1.000	0.845	1	0.845	1.000	0.903	6.34	3.18	0.001	50	20	52
		1.000	0.845	1	0.845	1.000	0.903	6.34	3.18	0.001	-16	-64	-38
		1.000	0.845	2	0.765	1.000	0.981	6.16	3.12	0.001	42	28	-2
		1.000	0.845	1	0.845	1.000	0.981	6.09	3.10	0.001	28	-26	64

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 6.07, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 19.236
Expected number of clusters, <c> = 14.84
FWEp: 12.783, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [3.0, 69.0]
FWHM = 13.4 13.2 12.9 mm mm mm; 6.7 6.6 6.4 {voxels}
Volume: 2044216 = 255527 voxels = 844.5 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 284.93 voxels)

Original Tables Generated by SPM12; RSFC to the dmPFC whilst controlling for gender, income and IQ



Statistics: ***p-values adjusted for search volume***

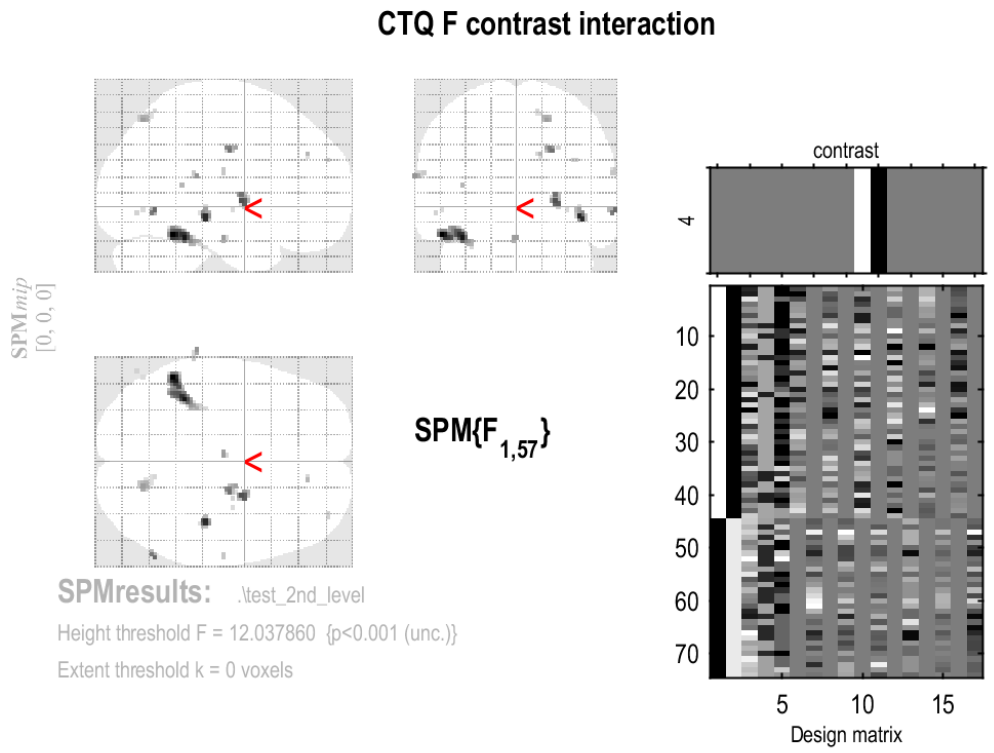
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	$(Z_{\equiv})$	p_{uncorr}			
0.528	18	0.016	0.016	220	0.001	0.087	0.117	12.32	4.67	0.000	-54	-76	16
						0.999	0.931	7.23	3.46	0.000	-54	-70	4
		0.932	0.780	31	0.149	0.945	0.931	8.21	3.73	0.000	-30	-48	60
		0.132	0.071	126	0.008	0.989	0.931	7.70	3.59	0.000	-36	54	8
						0.997	0.931	7.39	3.50	0.000	-46	54	10
						1.000	0.931	6.76	3.31	0.000	-40	50	14
		0.987	0.780	20	0.242	0.991	0.931	7.65	3.58	0.000	-22	-6	-42
		1.000	0.780	8	0.463	0.998	0.931	7.35	3.49	0.000	8	40	64
		1.000	0.780	7	0.494	1.000	0.931	7.00	3.39	0.000	56	-4	38
		1.000	0.780	2	0.736	1.000	0.931	6.99	3.39	0.000	56	-54	-42
		0.995	0.780	16	0.294	1.000	0.931	6.92	3.36	0.000	-14	-72	40
		1.000	0.780	6	0.529	1.000	0.931	6.76	3.31	0.000	28	-44	48
		1.000	0.780	3	0.670	1.000	0.931	6.63	3.27	0.001	22	44	54
		1.000	0.780	6	0.529	1.000	0.931	6.55	3.25	0.001	-4	-14	22
		1.000	0.780	4	0.615	1.000	0.931	6.53	3.24	0.001	-26	-14	-48
		1.000	0.780	4	0.615	1.000	0.931	6.42	3.21	0.001	8	-72	46
		1.000	0.825	1	0.825	1.000	0.931	6.32	3.17	0.001	-30	-16	-16
		1.000	0.780	3	0.670	1.000	0.931	6.32	3.17	0.001	52	-26	36
		1.000	0.780	3	0.670	1.000	0.931	6.29	3.16	0.001	56	-2	-46

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 6.07, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 15.718
Expected number of clusters, <c> = 17.97
FWEp: 13.023, FDRp: Inf, FWEc: 220, FDRc: 220

Degrees of freedom = [3.0, 69.0]
FWHM = 12.5 12.3 12.1 mm mm mm; 6.3 6.1 6.1 {voxels}
Volume: 2044216 = 255527 voxels = 1033.5 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 232.82 voxels)
Page 1

Original Tables Generated by SPM12; RSFC to the lPCC and associations with CTQ whilst controlling for all measures, gender, income and IQ



Statistics: ***p-values adjusted for search volume***

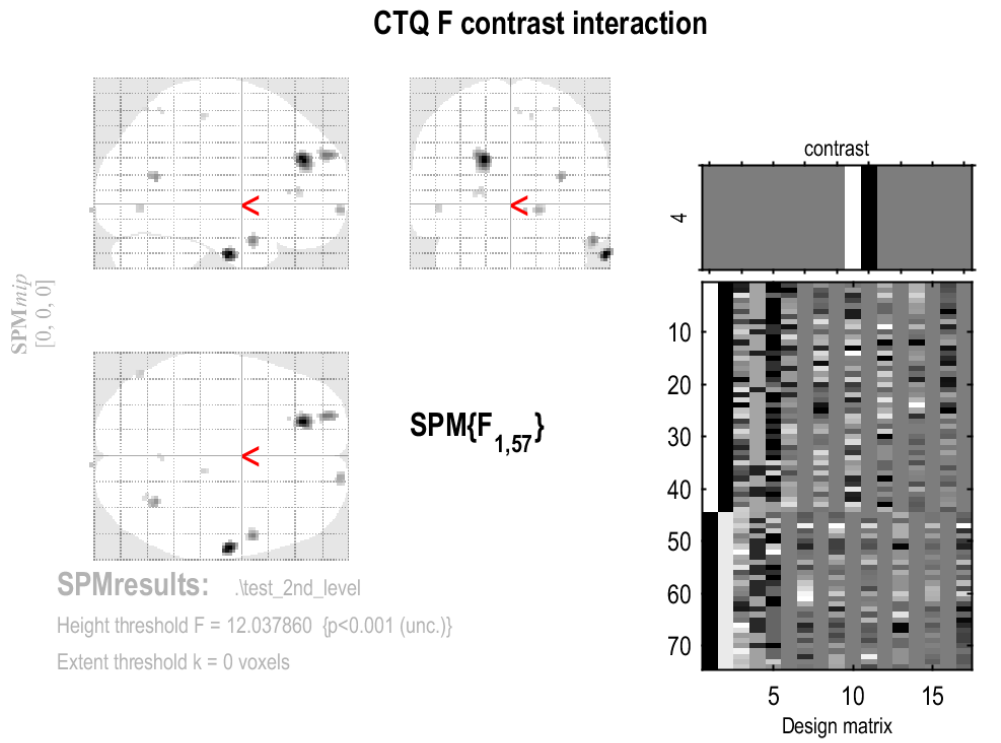
set-level		cluster-level				peak-level					mm mm mm
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	$(Z_{=})$	p_{uncorr}	
0.412	16	0.139	0.161	143	0.010	0.835	0.958	18.59	3.83	0.000	-52 -50 -20
						0.899	0.958	17.82	3.75	0.000	-38 -42 -22
						1.000	0.958	12.38	3.13	0.001	-32 -30 -28
		0.966	0.845	26	0.229	0.939	0.958	17.21	3.69	0.000	40 -28 -8
		0.986	0.845	20	0.290	0.981	0.958	16.10	3.57	0.000	24 -4 2
		1.000	0.845	6	0.574	0.993	0.958	15.40	3.50	0.000	64 -62 -4
		0.995	0.845	15	0.360	0.995	0.958	15.20	3.47	0.000	22 -12 34
		1.000	0.845	6	0.574	0.999	0.958	14.14	3.35	0.000	-70 -34 18
		1.000	0.845	4	0.655	1.000	0.958	13.96	3.33	0.000	-2 -16 -22
		0.978	0.845	23	0.257	1.000	0.958	13.96	3.33	0.000	18 -70 54
						1.000	0.958	12.27	3.12	0.001	12 -62 60
		1.000	0.845	1	0.845	1.000	0.958	13.30	3.25	0.001	-38 -44 12
		1.000	0.845	3	0.705	1.000	0.958	13.19	3.24	0.001	14 40 32
		1.000	0.845	4	0.655	1.000	0.958	12.74	3.18	0.001	64 -16 22
		1.000	0.845	1	0.845	1.000	0.958	12.45	3.14	0.001	-56 -74 -6
		1.000	0.845	2	0.766	1.000	0.958	12.40	3.14	0.001	38 54 28
		1.000	0.845	1	0.845	1.000	0.958	12.39	3.14	0.001	26 -10 36
		1.000	0.845	1	0.845	1.000	0.958	12.20	3.11	0.001	32 -10 -4
		1.000	0.845	1	0.845	1.000	0.958	12.17	3.11	0.001	-52 -70 -4

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 12.04, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 19.281
Expected number of clusters, <c> = 14.81
FWEp: 30.315, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 57.0]
FWHM = 12.4 12.2 12.1 mm mm mm; 6.2 6.1 6.0 {voxels}
Volume: 2044216 = 255527 voxels = 1053.6 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 228.39 voxels)

Original Tables Generated by SPM12; RSFC to the lTPJ and associations with CTQ whilst controlling for all measures, gender, income and IQ



Statistics: ***p-values adjusted for search volume***

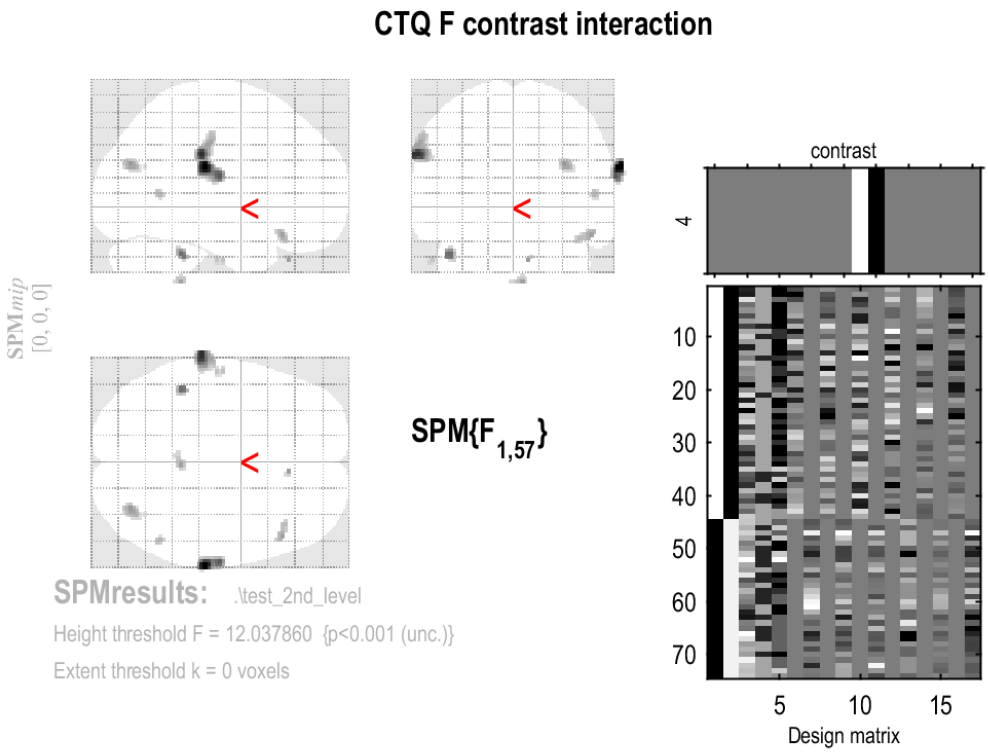
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	$(Z_{=})$	p_{uncorr}			
0.521	15	0.266	0.312	110	0.021	0.211	0.152	25.15	4.40	0.000	-20	40	26
		0.758	0.662	52	0.095	0.234	0.152	24.75	4.37	0.000	62	-10	-34
		0.882	0.662	39	0.144	0.894	0.593	17.90	3.76	0.000	-24	54	30
		0.927	0.662	33	0.176	0.925	0.593	17.45	3.71	0.000	54	6	-26
		0.996	0.845	14	0.375	0.977	0.720	16.28	3.59	0.000	32	-60	16
		0.994	0.845	16	0.343	0.997	0.924	15.03	3.45	0.000	16	64	-6
		1.000	0.845	2	0.765	1.000	0.955	13.71	3.30	0.000	8	-104	-6
		1.000	0.845	7	0.540	1.000	0.955	13.28	3.25	0.001	-52	-70	-4
		1.000	0.845	4	0.654	1.000	0.955	12.91	3.20	0.001	-24	36	6
		1.000	0.845	3	0.704	1.000	0.955	12.78	3.19	0.001	12	-28	56
		1.000	0.845	1	0.845	1.000	0.955	12.72	3.18	0.001	-22	30	6
		1.000	0.845	1	0.845	1.000	0.955	12.29	3.12	0.001	4	-56	58
		1.000	0.845	2	0.765	1.000	0.955	12.26	3.12	0.001	28	-66	60
		1.000	0.845	1	0.845	1.000	0.955	12.21	3.11	0.001	-20	36	4
		1.000	0.845	1	0.845	1.000	0.955	12.18	3.11	0.001	2	-58	60

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 12.04, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 19.197
Expected number of clusters, <c> = 14.87
FWEp: 30.329, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 57.0]
FWHM = 12.4 12.1 12.0 mm mm mm; 6.2 6.1 6.0 {voxels}
Volume: 2044216 = 255527 voxels = 1058.2 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 227.39 voxels)

Original Tables Generated by SPM12; RSFC to the lamPFC and associations with CTQ whilst controlling for all measures, gender, income and IQ



Statistics: ***p-values adjusted for search volume***

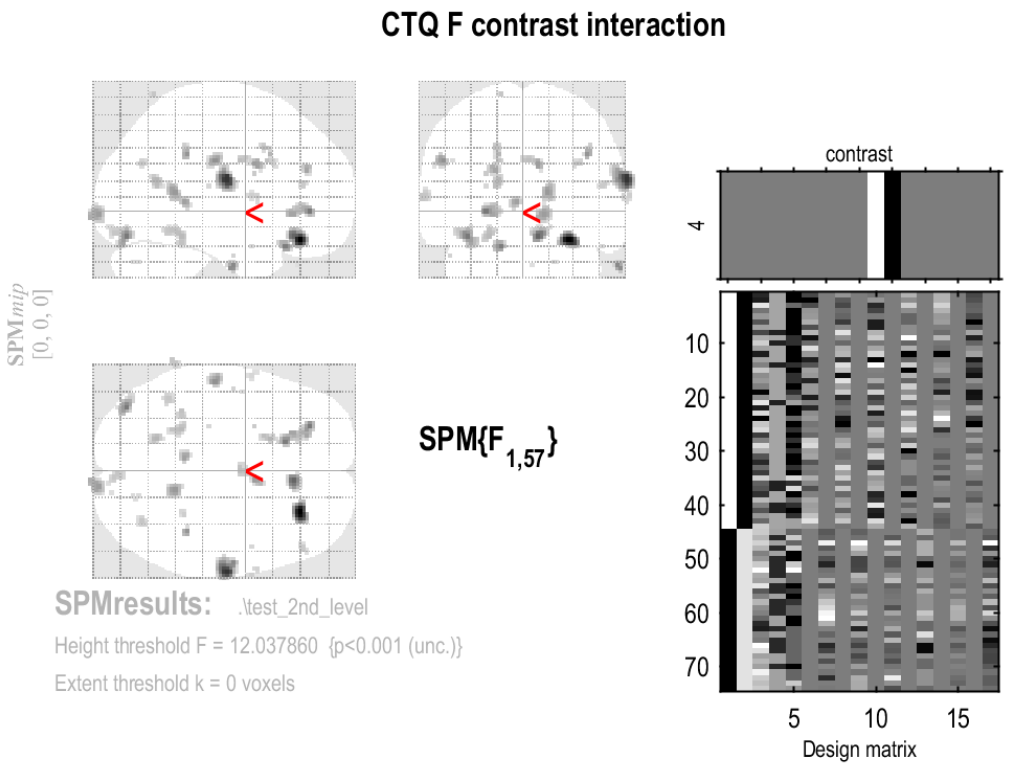
set-level		cluster-level				peak-level					mm mm mm
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	$(Z_{=})$	p_{uncorr}	
0.758	10	0.244	0.117	132	0.023	0.156	0.239	25.54	4.43	0.000	70 -26 24
						0.611	0.446	19.96	3.96	0.000	66 -16 18
		0.191	0.117	147	0.018	0.355	0.310	22.42	4.17	0.000	-68 -28 32
						0.983	0.578	15.37	3.49	0.000	-64 -22 40
		0.965	0.560	26	0.280	0.738	0.475	18.85	3.85	0.000	-44 -42 -32
		0.853	0.533	45	0.160	0.962	0.578	16.05	3.57	0.000	32 -76 26
		1.000	0.822	3	0.740	0.971	0.578	15.82	3.54	0.000	8 30 -36
		0.965	0.560	26	0.280	0.972	0.578	15.79	3.54	0.000	50 26 -20
						0.997	0.646	14.21	3.36	0.000	42 28 -22
		0.986	0.594	19	0.356	0.974	0.578	15.73	3.53	0.000	4 -42 -50
						1.000	0.909	12.52	3.15	0.001	-4 -44 -50
		0.996	0.610	12	0.468	0.995	0.635	14.54	3.40	0.000	52 -56 6
		0.997	0.610	11	0.488	0.999	0.646	13.80	3.31	0.000	-56 -14 -36
		1.000	0.865	1	0.865	1.000	0.981	12.10	3.10	0.001	36 -66 24

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 12.04, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 24.085
Expected number of clusters, <c> = 12.00
FWEp: 29.573, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 57.0]
FWHM = 13.5 13.2 12.9 mm mm mm; 6.7 6.6 6.4 {voxels}
Volume: 2044216 = 255527 voxels = 843.5 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 285.29 voxels)

Original Tables Generated by SPM12; RSFC to the dmPFC and associations with CTQ whilst controlling for all measures, gender, income and IQ



Statistics: ***p-values adjusted for search volume***

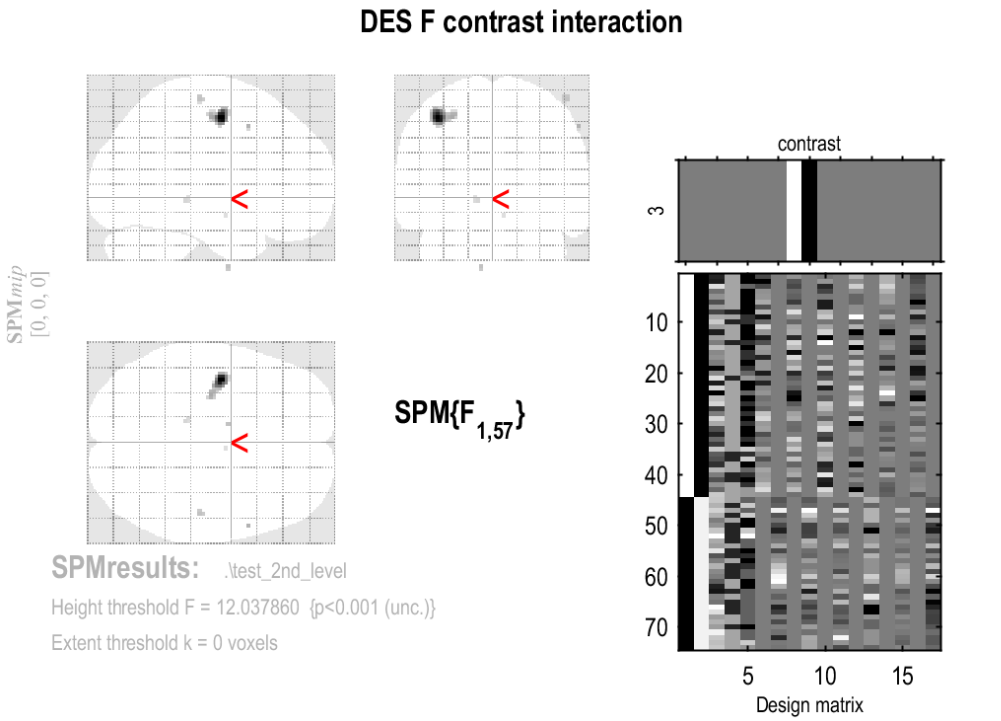
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	$(Z_{=})$	p_{uncorr}			
0.000	37	0.425	0.527	87	0.038	0.065	0.218	29.37	4.71	0.000	28	34	-20
		0.081	0.212	172	0.006	0.213	0.392	25.06	4.39	0.000	66	-14	18
		0.761	0.532	52	0.098	0.538	0.757	21.24	4.07	0.000	8	30	-18
		0.648	0.527	63	0.071	0.714	0.757	19.70	3.93	0.000	-38	-80	-18
		0.567	0.527	71	0.057	0.717	0.757	19.68	3.93	0.000	-26	40	-2
						0.975	0.757	16.30	3.59	0.000	-22	28	-4
		0.946	0.646	30	0.200	0.754	0.757	19.35	3.90	0.000	-16	24	-24
		0.986	0.646	20	0.292	0.842	0.757	18.48	3.82	0.000	60	-10	-36
		0.830	0.560	45	0.121	0.881	0.757	18.02	3.77	0.000	-54	-22	30
		0.992	0.646	17	0.332	0.911	0.757	17.63	3.73	0.000	40	-40	34
		0.771	0.532	51	0.101	0.937	0.757	17.21	3.69	0.000	14	-48	10
		0.875	0.584	40	0.142	0.948	0.757	17.00	3.67	0.000	8	4	28
						0.998	0.865	14.69	3.42	0.000	2	-6	30
		0.607	0.527	67	0.064	0.953	0.757	16.88	3.65	0.000	12	-98	-4
		0.974	0.646	24	0.249	0.964	0.757	16.64	3.63	0.000	-6	-42	4
		0.992	0.646	17	0.332	0.972	0.757	16.42	3.61	0.000	-20	38	24
		0.957	0.646	28	0.215	0.994	0.865	15.30	3.48	0.000	-18	-60	18
		0.988	0.646	19	0.305	0.995	0.865	15.19	3.47	0.000	-18	14	34
		0.946	0.646	30	0.200	0.997	0.865	14.91	3.44	0.000	-24	-44	-18

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 12.04, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 19.492
Expected number of clusters, <c> = 14.66
FWEp: 30.278, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 57.0]
FWHM = 12.5 12.2 12.1 mm mm mm; 6.2 6.1 6.0 {voxels}
Volume: 2044216 = 255527 voxels = 1042.2 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 230.89 voxels)
Page 1

Original Tables Generated by SPM12; RSFC to the lamPFC and associations with DES whilst controlling for all measures, gender, income and IQ



Statistics: ***p-values adjusted for search volume***

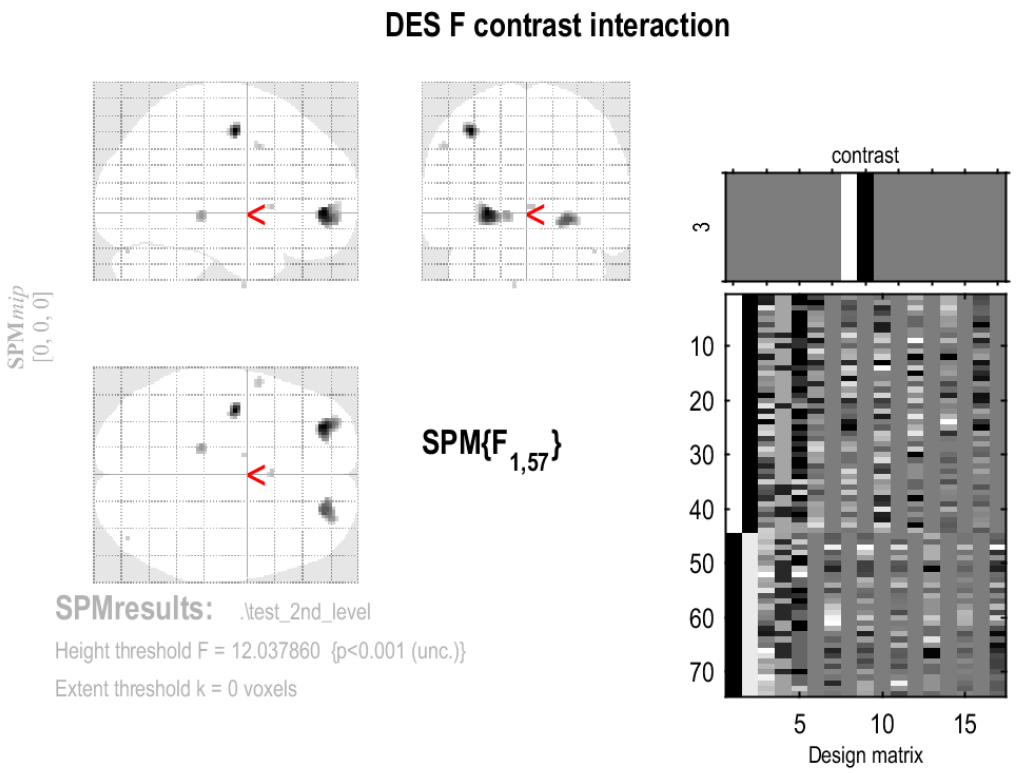
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	($Z_{\equiv}$)	p_{uncorr}			
0.980	6	0.344	0.211	111	0.035	0.346	0.248	22.51	4.18	0.000	-40	-10	52
						0.996	0.897	14.50	3.39	0.000	-30	-16	52
		1.000	0.865	2	0.794	0.998	0.897	14.12	3.35	0.000	58	10	46
		1.000	0.865	2	0.794	0.999	0.897	13.49	3.27	0.001	-10	-4	-48
		0.999	0.865	6	0.620	1.000	0.897	13.41	3.26	0.001	50	-24	64
		1.000	0.865	4	0.694	1.000	0.959	12.48	3.15	0.001	-12	-34	-4
		1.000	0.865	1	0.865	1.000	0.959	12.17	3.11	0.001	6	-6	-14

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 12.04, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 24.085
Expected number of clusters, <c> = 12.00
FWEp: 29.573, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 57.0]
FWHM = 13.5 13.2 12.9 mm mm mm; 6.7 6.6 6.4 {voxels}
Volume: 2044216 = 255527 voxels = 843.5 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 285.29 voxels)

Original Tables Generated by SPM12; RSFC to the ramPFC and associations with DES whilst controlling for all measures, gender, income and IQ



Statistics: ***p-values adjusted for search volume***

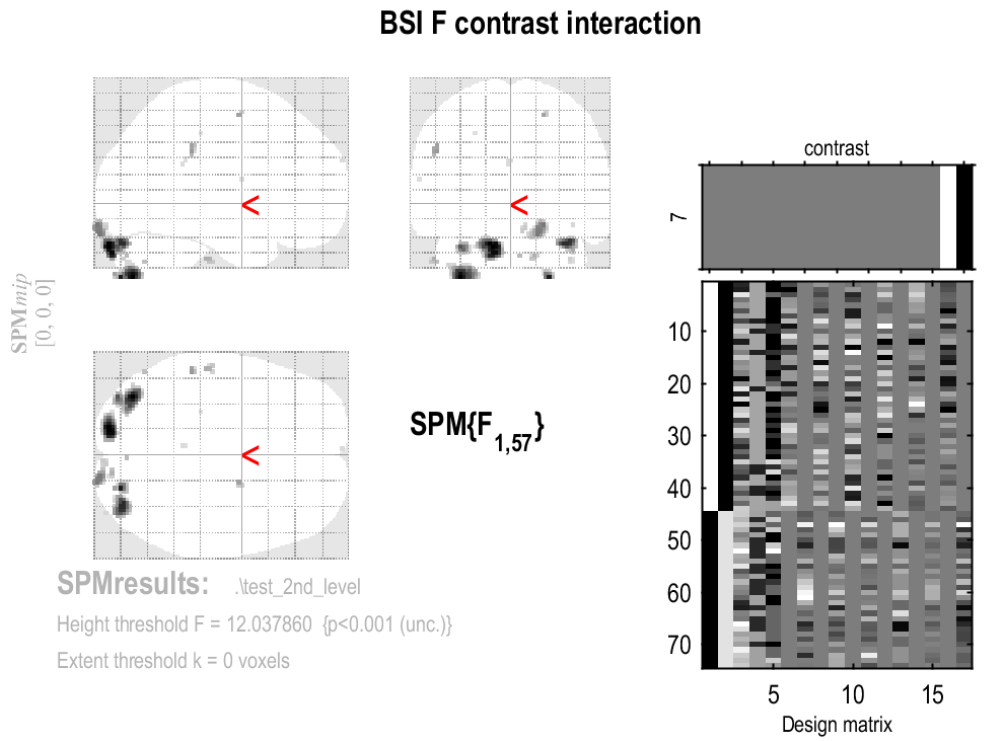
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	$(Z_{=})$	p_{uncorr}			
0.924	8	0.827	0.379	48	0.142	0.411	0.194	21.89	4.13	0.000	-38	-10	50
		0.149	0.105	159	0.013	0.450	0.194	21.50	4.10	0.000	-28	48	-2
		0.581	0.283	76	0.071	0.847	0.406	17.88	3.76	0.000	26	48	-6
		0.982	0.650	21	0.325	0.991	0.764	15.01	3.45	0.000	-14	-32	-4
		1.000	0.863	3	0.735	1.000	0.764	13.32	3.25	0.001	2	14	2
		0.999	0.863	7	0.582	1.000	0.764	13.25	3.24	0.001	-56	6	40
		1.000	0.863	1	0.863	1.000	0.764	12.97	3.21	0.001	42	-80	-26
		1.000	0.863	2	0.791	1.000	0.764	12.87	3.20	0.001	-10	-4	-48

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 12.04, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 23.420
Expected number of clusters, <c> = 12.32
FWEp: 29.666, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 57.0]
FWHM = 13.3 13.0 12.8 mm mm mm; 6.7 6.5 6.4 {voxels}
Volume: 2044216 = 255527 voxels = 867.4 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 277.41 voxels)

Original Tables Generated by SPM12; RSFC to the dmPFC and associations with BSI whilst controlling for all measures, gender, income and IQ



Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*F*	$(Z_{\equiv})$	p_{uncorr}			
0.157	19	0.092	0.079	165	0.007	0.577	0.544	20.89	4.04	0.000	-16	-92	-28
		0.114	0.079	154	0.008	0.581	0.544	20.86	4.04	0.000	-36	-76	-50
		0.966	0.732	26	0.231	0.732	0.544	19.54	3.92	0.000	24	-84	-50
		0.433	0.245	86	0.039	0.797	0.544	18.94	3.86	0.000	34	-82	-28
		0.914	0.637	35	0.168	0.930	0.755	17.33	3.70	0.000	-36	-86	-30
		0.792	0.508	49	0.107	0.982	0.810	16.05	3.57	0.000	20	-100	-16
		0.999	0.846	9	0.486	0.998	0.892	14.68	3.41	0.000	-52	-36	32
		1.000	0.846	3	0.707	0.999	0.892	14.42	3.38	0.000	20	-4	56
		1.000	0.846	6	0.576	1.000	0.931	14.03	3.34	0.000	-54	-26	-38
		1.000	0.846	6	0.576	1.000	0.931	13.84	3.32	0.000	14	-90	-36
		1.000	0.846	1	0.846	1.000	0.950	13.49	3.27	0.001	4	-80	-36
		1.000	0.846	1	0.846	1.000	0.950	13.39	3.26	0.001	-52	-68	-40
		1.000	0.846	5	0.614	1.000	0.985	12.95	3.21	0.001	6	-96	-20
		1.000	0.846	4	0.657	1.000	0.985	12.66	3.17	0.001	38	-82	-38
		1.000	0.846	1	0.846	1.000	0.985	12.34	3.13	0.001	40	-94	-16
		1.000	0.846	2	0.767	1.000	0.985	12.25	3.12	0.001	-4	-42	24
		1.000	0.846	1	0.846	1.000	0.985	12.22	3.11	0.001	-2	66	26
		1.000	0.846	1	0.846	1.000	0.985	12.14	3.10	0.001	-26	-30	44
		1.000	0.846	1	0.846	1.000	0.985	12.08	3.10	0.001	-64	-2	14

table shows 3 local maxima more than 8.0mm apart

Height threshold: F = 12.04, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 19.492
Expected number of clusters, <c> = 14.66
FWEp: 30.278, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 57.0]
FWHM = 12.5 12.2 12.1 mm mm mm; 6.2 6.1 6.0 {voxels}
Volume: 2044216 = 255527 voxels = 1042.2 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 230.89 voxels)

Appendix B17: List of Abbreviations

ACC	-	anterior cingulate cortex
ASPD	-	Anti-Social Personality Disorder
BDI	-	Beck Depression Inventory
BIS	-	Barratt Impulsiveness Scale
BLA	-	basolateral amygdala
BOLD	-	blood oxygen level dependent
BPD	-	Borderline Personality Disorder
BSI	-	Brief Symptom Inventory
BSL	-	Borderline Symptom List
CAPS	-	Clinician Administered PTSD Scale
CEN	-	central executive network
CTQ	-	Childhood Trauma Questionnaire
DERS	-	Difficulties in Emotion Regulation Scale
DES	-	Dissociative Experiences Scale
DID	-	Dissociative Identity Disorder
DMN	-	default mode network
dlPFC	-	dorsal lateral prefrontal cortex
dmPFC	-	dorsal medial prefrontal cortex
EEG	-	electroencephalography
ELS	-	early life stress
fMRI	-	functional magnetic resonance imaging
FPC	-	frontopolar cortex
GLM	-	General Linear Model
Hz	-	hertz
ICA	-	independent component analysis
K_e	-	extent threshold
lamPFC	-	left anterior medial prefrontal cortex
lMTG	-	left middle temporal gyrus
lTPJ	-	left temporal parietal junction
M.I.N.I	-	Mini-International Neuropsychiatric Interview
MANCOVA	-	Multivariate Analysis of Covariance
MDD	-	Major Depressive Disorder
MNI	-	Montreal Neurological Institute
mPFC	-	medial prefrontal cortex
MTL	-	medial temporal lobe
MVA	-	Missing Value Analysis
OFC	-	orbitofrontal cortex
PAI-BOR	-	Personality Assessment Inventory-Borderline Features Scale
PCC	-	posterior cingulate cortex
PD	-	personality disorder
P_{fwe}	-	$P_{\text{family wise error corrected}}$
PTSD	-	Post Traumatic Stress Disorder
ramPFC	-	right anterior medial prefrontal cortex
rMFG	-	right middle frontal gyrus
ROI	-	region of interest
RSFC	-	resting state functional connectivity

rSFG	-	right superior frontal gyrus, medial part
rs-fMRI	-	resting state fMRI
rTPJ	-	right temporal parietal junction
SAPAS	-	Standardised Assessment of Personality-Abbreviated Scale
SCID-I	-	Structured Clinical Interview for DSM-IV non-PDs
SCID-II	-	Structured Clinical Interview for DSM-IV PDs
SPM	-	Statistical Parametric Mapping
STS	-	superior temporal sulcus
T		tesla
TE	-	echo time
TOM	-	theory of mind
TPJ	-	temporal parietal junction
TR	-	repetition time
vmPFC	-	ventral medial prefrontal cortex
vlPFC	-	ventral lateral prefrontal cortex
β	-	beta-value