The Neurodevelopmental Trajectory of Borderline Personality Disorder: a review

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ABSTRACT

Borderline Personality Disorder (BPD) is a complex psychological condition characterised by affective instability, cognitive impairment, problematic behaviours and social dysfunction. Due to the variability in symptomatic profiles, efforts have recently been directed towards comprehending the disorder from a neurological standpoint within the aforementioned domains. Although adolescent-onset BPD is now reliably diagnosed as the adult-onset variant, a limited number of studies address the neural correlates of first presentation BPD. Moreover, research investigating the outcomes of therapeutic interventions on brain function and morphology is scarce. Preliminary findings consistently cite the involvement of grey matter deficiencies of the orbitofrontal cortex, hippocampus and amygdala in the neuropathology of BPD. Additionally, frontolimbic white matter deficits are thought to be implicated. Functionally, over-activity in limbic regions such as the cingulate cortices and amygdala are believed to partially account for emotion dysregulation though the neural correlates of cognitive, social and behavioural impairments are relatively poorly understood. The present review will endeavour to evaluate the existing neurobiological evidence for BPD in adolescence as well as adulthood. Finally, a rudimentary neurodevelopmental model of BPD will be proposed.

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ABBREVIATIONS

ACC – Anterior Cingulate Cortex

AI – Anterior Insula

BPD – Borderline Personality Disorder

DBT – Dialectical Behavioural Therapy

DMN – Default Mode Network

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)

DTI – Diffusion Tensor Imaging

FA – Fractional Anisotropy

fMRI – Functional Magnetic Resonance Imaging

IPS – Intraparietal Sulcus

OFC – Orbitofrontal Cortex

PET – Positron Emission Tomography

PFC – Prefrontal Cortex

RSFC – Resting State Functional Connectivity

VBM – Voxel Based Morphometry

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INTRODUCTION

Epidemiological evidence estimates Borderline Personality Disorder (BPD) to have a lifetime prevalence of around 1% (Coid et al., 2006) with a larger proportion of women (approximately 70%) affected than men (Lieb et al., 2004). The disorder is characterised by impairment in the following areas: emotion regulation, cognitive function, behaviour and interpersonal relationships; the consequences of which can be fatal, with up to 10% of patients committing suicide (American Psychiatric Association Practice, 2001). According to the DSM-IV (American Psychiatric Association, 2013), suspected sufferers of the condition must present with five or more symptoms including, but not limited to: identity disturbance, impulsivity, explosive episodes and suicidality, for the diagnostic criteria of BPD to be met. It is therefore considered to be an extremely heterogenous disorder as there are effectively over 100 permissible symptom combinations which would qualify for a clinical diagnosis (Herbort et al., 2016).

Typically, the onset of BPD is during early adulthood (American Psychiatric Association, 2013), though there is a growing body of evidence suggesting that symptoms of the disorder can be detected in adolescence with relatively high levels of reliability and validity (Chanen, Jovev et al., 2008). By identifying and treating the disorder at such an early stage; symptom severity can be reduced, leading to an overall improvement in functioning (Chanen, Velakoulis, et al., 2008). Furthermore, confounding variables such as treatment side effects and chronicity can be avoided by investigating the disorder in adolescence (Chanen, Velakoulis, et al., 2008). Despite the ever-increasing plethora of research into the aetiology of BPD, longitudinal data on the progression of the disorder from adolescence to adulthood is scarce.

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Concerning the aetiology of BPD, no definitive causal mechanism has been proposed but it is likely due to a result of complex interactions between several factors such as genetic predispositions, environmental stressors (for example, childhood adversity) and congenital or acquired neurobiological changes (Kaess et al., 2014). The latter is of particular interest owing to the wealth of research into the neural correlates of BPD carried out within the last two decades. Structural neuroimaging studies consistently report the occurrence of grey matter deficits associated with BPD in frontolimbic regions such as the orbitofrontal cortex (OFC) (Araujo et al., 2014; de Araujo Filho et al., 2014; Sato et al., 2012), hippocampus (Depping et al., 2016; Kimmel et al., 2016; Niedtfeld et al., 2013; O'Neill et al., 2013) and amygdala (Kimmel et al., 2016; Niedtfeld et al., 2013; Richter et al., 2014), suggesting that the disorder may have a distinct neurological profile.

It would appear that there are additional alterations in white matter tract coherence which have been examined in a few studies using the Diffusion Tensor Imaging (DTI) modality. Fractional anisotropy (FA), believed to be a measure of the myelination and organisational orientation of white matter tracts, has been also been found to be reduced in adult-onset and adolescent-onset BPD (Carrasco et al., 2012; Maier-Hein et al., 2014; New et al., 2013; Salvador et al., 2016). Moreover, studies using event-related measures such as fMRI have observed discrepant patterns of neural activation in the cognitive (Mensebach et al., 2009; Niedtfeld et al., 2017; O'Neill et al., 2015; Reitz et al., 2015) , behavioural (Herbort et al., 2016), social (Bungert et al., 2015; Domsalla et al., 2014; King-Casas et al., 2008) and affective processing (Bertsch et al., 2013; Hazlett et al., 2012; Lischke et al., 2017; Scherpiet et al., 2014) of BPD samples compared to healthy controls. However, it must be noted that the neurocircuitry of the disorder – though more

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widely researched at present – is still poorly understood and that which distinguishes BPD from other similar psychiatric disorders remains elusive.

Another area of somewhat unexplored territory are the neuroprotective biomarkers, despite the relatively high recovery rates such that ten years after the first diagnoses, 85% of patients no longer meet the diagnostic criteria for the disorder (Gunderson et al., 2011). Only three of the studies reviewed in the present work investigated the effects of therapy on the neural profiles of afflicted patients, with some promising preliminary results (Niedtfeld et al., 2017; Ruocco et al., 2016; Winter et al., 2017). It is therefore evident that a global understanding of BPD, spanning from first incidence to therapy-assisted remission is yet to be achieved.

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AIMS

The present review will endeavour to evaluate recent BPD literature and propose a neurodevelopmental profile of the condition from adolescence to adulthood. In addition, neuroprotective changes engendered by therapeutic measures such as DBT will be considered. To our knowledge, no prior paper has put forth a neurodevelopmental approach to BPD in the format of a systematic review as yet.

Moreover, the results of DBT from a neurological perspective in BPD have yet to be examined, despite its clinical utility. An understanding of the neural progression of BPD and how both functional and morphological brain changes can be remedied through DBT may enable clinicians to devise novel early interventions and refine existing treatments.

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METHODS

Potentially relevant research papers were retrieved using a broad PubMed search with "Borderline Personality Disorder" as a titular term, combined with ("neur*" or "imaging" or "brain") and ("adolescent", "child*", "adult*" or "longitudinal" or "therap*" or "remission"). The search, carried out on 27/11/17, yielded 180 papers and was then restricted using the *advanced search* tabs to return studies published exclusively within the past ten years (2007-2017). Further inspection of the titles and abstracts led to the exclusion of an additional 119 results due to general irrelevance, insufficient sample size (N<15) and inappropriate imaging modality (see section below). The methodology of the remaining literature was then reviewed and only the studies meeting the predetermined inclusion criteria were selected (N=45). Replicative articles of previous studies were also dismissed, providing they did not report any new findings. A visual representation of the present search methods can be observed in Figure 1 below:

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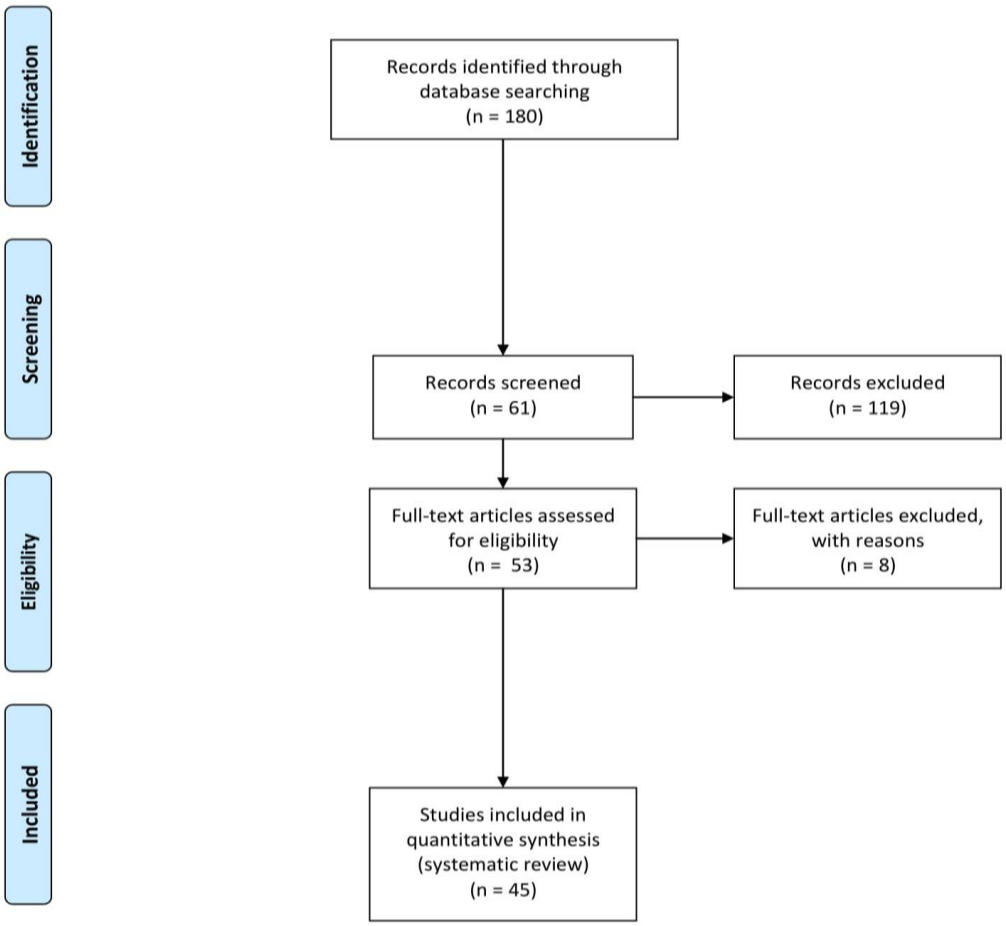

Figure 1. PRISMA flow diagram of search and selection method.

Exclusion Criteria

Following an initial PubMed search, non-applicable papers were screened out subject to several exclusion criteria such as insufficient sample size (N<15), imaging modalities other than fMRI, PET, MRI, DTI and NIRS and literature written in languages other than English. Furthermore, studies using samples of individuals with BPD who also suffered from comorbid Axis I disorders

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(specifically schizophrenia, schizoaffective disorder, affective psychoses (including bipolar I disorder), current alcohol/substance abuse or intellectual difficulties) were omitted.

RESULTS

A summary of all included studies is reported in Table 1, which can be found in the Appendices section.

STRUCTURAL BRAIN IMAGING

MRI of the Adolescent Cerebrum

According to Chanen and colleagues (2008), BPD can be as reliably diagnosed in adolescence as in adulthood; a claim which has received some experimental substantiation. The reduction of grey matter density in the orbitofrontal cortex (OFC) is seemingly the most discriminative deficit in first-presentation BPD relative to controls. Diminished grey matter volume in this area has been observed by two previous studies (Brunner et al., 2010; Chanen, Velakoulis, et al., 2008) albeit in contralateral hemispheres. Reductions in bilateral dorsolateral prefrontal cortex have also been reported, however at this early stage in the progression of the disorder, these alterations were not able to significantly discern BPD from other psychiatric diagnoses (Brunner et al., 2010).

The available research consistently observes no intergroup differences between BPD and control groups in the limbic and midline structures including the hippocampus, amygdala, insular cortices and the adhesio interthalamica (Brunner et al., 2010; Chanen, Velakoulis, et al., 2008; Takahashi et al., 2009a; Takahashi et al., 2009b).

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MRI of the Adult Cerebrum

A meta-analyses of nine voxel-based MRI studies comprising of a total of 256 BPD patients and 272 healthy controls, proposed that grey matter volume of the hippocampi and amygdalae decreases with age in BPD (Kimmel et al., 2016), hence the reason it does not present in the adolescent brain. The validity of VBM, however, can be called into question as the mapping of each brain, prior to analysis, onto a template is mandatory (Mechelli et al., 2005) and often lacks the robustness to accurately identify volumetric atypicalities in very small structures such as the hippocampus and amygdala (Kimmel et al., 2016). That said, Kimmel and colleagues' (2016) claims regarding hippocampal grey matter diminishment are consistently corroborated by the literature in adult samples (Depping et al., 2016; Niedtfeld et al., 2013; Richter et al., 2014; Soloff et al., 2008).

Additionally, Kimmel and associates (2016) speculate that hippocampal grey matter deficits may be attributable to comorbid PTSD as opposed to BPD in isolation. One study of 39 adults with BPD, reported concurrent findings as those with comorbid PTSD had a smaller hippocampal head and body. It is speculated that hippocampal deficits may be related to the trauma of childhood abuse specifically (Brambilla et al., 2004), which is present in up to 76% of BPD patients (Zanarini, 2000) thus explaining its synchronous presence in the neuropathology of PTSD. Unfortunately, decreased hippocampal volume as a biomarker of BPD with comorbid PTSD cannot be taken as more than conjecture, as some studies find no differences in the hippocampi or amygdalae across BPD-PTSD and BPD subgroups (Niedtfeld et al., 2013; Sato et al., 2012).

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Other limbic components such as the cingulate cortices are also thought to be involved in the neuropathology of BPD. The volume of the anterior cingulate cortex (ACC), a region which is theorised to be partly responsible for the modulation of emotional expression (New et al., 2012), is ostensibly reduced in the dorsal (Niedtfeld et al., 2013) and rostral (Sato et al., 2012) areas. Further, other investigators have found there to be volumetric asymmetry in the ACC, such that the left cortices are thinner than the right (Zhou et al., 2017). Dorsal ACC volume has also been found to predict BPD symptom severity (Niedtfeld et al., 2013), a correlation which could have great clinical utility (though some researchers find no between-group differences in this region (Muller et al., 2015)). Neighbouring regions such as the ventral cingulate gyrus have also shown bilateral decreases in volume (Soloff et al., 2008), whereas the middle and posterior cingulate cortices appear to have increased volume in BPD groups compared to healthy controls (Jin et al., 2016).

It would therefore seem that, consistent with adolescent research, the medial and lateral OFC are more reliable neural correlates of BPD, as volumetric deficits are also present in adult cerebrums (Araujo et al., 2014; de Araujo Filho et al., 2014; Sato et al., 2012). Lesion research suggests that the OFC is important for emotion regulation, the maintenance of social appropriateness and for curbing impulsivity (Malloy et al., 1993), where reductions in its volume could account for dysfunction of these behaviours in BPD. Other frontal regions such as the dorsolateral prefrontal (DLPFC) (O'Neill et al., 2013), inferior frontal gyrus (Kimmel et al., 2016) and ventrolateral prefrontal cortices (VLPFC) have been found to be reduced in BPD, with the latter again affected significantly by a history of childhood abuse (Morandotti et al., 2013). The left superior frontal gyrus however, was found to have increased cortical thickness and area (de Araujo Filho et al.,

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297 2014). Thus, due to the discord within the research community, MRI in isolation is not sufficient
298 to produce a steadfast neurodevelopmental profile of BPD.
299

300 ## Diffusion Imaging in BPD

301 Whilst structural MRI imaging focuses on neural grey matter changes, white matter tract
302 coherence and integrity is examined using DTI. The fractional anisotropy (FA) outcome measure
303 is believed to reflect axon directionality, myelination and fibre density (Carrasco et al., 2012;
304 Mädler, et al., 2008). Studies examining FA in the adolescent brain are limited but preliminary
305 research suggests that there may be decreased FA in the fornix compared to both healthy and
306 clinical controls (with other mixed diagnoses) (Maier-Hein et al., 2014). The inclusion of a
307 clinical control group in Maier-Hein and colleagues' work is a particular strength as the white
308 matter alterations found appear to be specific to BPD. Further changes have been observed
309 bilaterally in the inferior longitudinal fasciculi and temporal lobe white matter tracts (uncinated
310 and occipitofrontal fasciculi) of BPD adolescents compared to healthy adolescents (New et al.,
311 2013). The aforementioned work is of interest as the investigators recruited samples of both
312 healthy and disordered adolescents and adults to understand the pathological development of
313 white matter. As expected, FA was highest in healthy adolescents than the remaining samples
314 and it is noteworthy to mention that no differences in FA were found between BPD and healthy
315 adult groups (New et al., 2013).
316

317 On the contrary, consistent with New and associates' (2013) work in adolescent groups, one
318 study reports diminished FA in the uncinate and inferior fronto-occipital fasciculi in disordered
319 adults using diffusion MRI (Salvador et al., 2016). Similarly, Ninomiya et al. (2018) have found

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reduced axial diffusivity (which also determines axonal integrity) in the inferior front-occipital fasciculus, as well as the cingulum and inferior longitudinal fasciculus. The experimental sample of 35 BPD patients, also did not include medicated individuals nor individuals with comorbid conditions (Ninomiya et al., 2018), thus it could be that the white matter alterations of the inferior fronto-occipital fasciculus partly represent the core neuropathology of BPD. Nevertheless, such conclusions must be made tentatively as research suggests several other tracts (including the corpus callosum, corona radiata and prefrontal fasciculi) may be implicated in BPD (Carrasco et al., 2012; Ninomiya et al., 2018; Salvador et al., 2016), and diffusion modalities are more prone to artefacts than other imaging methods (Carrasco et al., 2012).

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FUNCTIONAL BRAIN IMAGING

fMRI is increasingly being used to determine the resting-state functional connectivity (RSFC) between various brain regions by examining contemporaneous patterns of neural activity (in the absence of goal-directed tasks) (Krause-Utz et al., 2014; Nierhaus et al., 2012). The RSFC observed within particular networks may also be referred to as the default mode network (DMN) (Kluetsch et al., 2012). One study exploring RSFC in BPD found there to be increased functional connectivity between the amygdala and insula as well as stronger amygdala-OFC and amygdala-putamen RSFC in individuals with BPD compared to controls (Krause-Utz et al., 2014). Additionally, decreased RSFC between the left ventral ACC and V1 cortex, lingual gyrus and cuneus was observed in the BPD sample relative to healthy controls. These findings should be interpreted with care though as they are yet to be endorsed by further research and signals from the amygdala can be confounded by venous drainage. Furthermore, due to the lack of adolescent-based functional imaging literature, the neural findings presented here refer only to the adult cerebrum.

Cognitive-Perceptual Differences

Functional connectivity has been explored within the default mode network as well as in the context of emotion processing and theory of mind (O'Neill et al., 2015). During rest, greater functional connectivity between the precuneus and the left inferior frontal lobe, left precentral gyrus, middle frontal gyrus, and left middle occipital and superior parietal lobes was observed; a conflicting pattern of activity to that reported by Krause-Utz et al. (2014). Additionally, during the theory of mind condition (which assessed the comprehension of visual puns and jokes), decreased functional connectivity between subgenual ACC and the left superior temp lobe, right

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supramarginal parietal lobes and right middle cingulate cortex was shown in the BPD sample relative to controls. As Krause-Utz and colleagues (2014) set the DMN seed as the amygdala whilst O'Neill and associates (2015) decided upon the precuneus, it is not surprising that the findings were not concurrent. Furthermore, O'Neill et al. (2015) procured DMN data during a ten second period of rest between task conditions, thus this is not a true exemplification of the default mode.

It is known that the processing of pain in BPD is atypical and is more than likely a direct result of the self-injurious behaviour that is present in approximately 60-80% of patients (Chapman, Specht, & Cellucci, 2005). Connectivity within DMN has therefore been investigated with respect to pain processing in BPD patients who partake in non-suicidal self-injury (Kluetsch et al., 2012). The left superior frontal gyrus and PCC were found to be less incorporated into the DMN in BPD, and the latter was ostensibly less integrated with the left DLPFC when the nociceptive stimuli were administered (Kluetsch et al., 2012). Furthermore, DMN response to painful stimuli was found to be negatively correlated with symptom severity (Kluetsch et al., 2012).

Nociceptive perception was also examined in a more ecologically valid study by Reitz and colleagues (2015), who demonstrated that for those with BPD, a small incision to the forearm is capable of reducing tension incurred by stressful tasks. This translated neurally to decreased amygdala activity and increased functional connectivity with the superior frontal gyrus in BPD patients following the incision, whereas the converse was observed in controls (Reitz et al., 2015). The objective of therapies targeting self-injurious behaviour in BPD is often to aid

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patients in finding means other than self-harm to reduce aversive tension. The effects of such treatments could therefore be assessed, taking the amygdala as a region of interest. One preliminary study exploring the effect of DBT on temperature pain perception and affect regulation shows promising results (see Niedtfeld et al., 2017).

Emotion Dysregulation

Both self-injurious behaviour and suicidality are typical examples of the dysfunctional behaviours that may arise as a result of the poor emotion regulation evident in BPD (Soloff et al., 2012; Stiglmayr et al., 2008). Region of interest studies researching emotion regulation in BPD at the neural level tend to focus on the amygdala and consistently report an increased response to negatively-valenced stimuli (Bertsch et al., 2013; Hazlett et al., 2012; Koenigsberg et al., 2009). Furthermore, one study suggests that amygdala activation may have some discriminative value across Axis II disorders, as it was shown to distinguish BPD from both healthy controls and those with schizotypal personality disorder, when viewing negative affect-inducing stimuli (Hazlett et al., 2012).

The anterior and posterior cingulate cortices also appear to "come online" when viewing negatively-valenced stimuli in BPD (Koenigsberg et al., 2009). Further, the mere anticipation of negative affect-inducing stimuli seems to be sufficient to cause a heightened response in the anterior and posterior cingulate cortices, as well as in the left visual areas (Scherpiet et al., 2014). Disparate findings, of reduced activation in the middle cingulate cortex projecting into the dorsolateral PFC, were observed when BPD samples anticipated ambiguously-valenced stimuli (Scherpiet et al., 2014). Emotion regulation hence, appears to be more disturbed with respect to

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negative emotions as there seems to be a bias toward potentially threatening information in BPD, which translates neurally to increased amygdala and cingulate cortex responses (Bertsch et al., 2013; Scherpiet et al., 2014). Encouragingly, one study investigating distraction (using negatively-valenced stimuli) and subsequent emotion regulation found positive treatment effects of DBT, reflected by reduced ACC activity in treatment responders (Winter et al., 2017); suggesting hyper-activation of particular brain areas may be reversible.

Psychological Distancing

As stipulated by the DSM-IV, severe dissociative symptoms are also present in the BPD psychopathological profile (American Psychiatric Association, 2013). A method of dissociation referred to as psychological distancing can be utilised by BPD patients in order to reduce negative affect induced by aversive stimuli (Koenigsberg et al., 2009; Silvers et al., 2016). Distancing as opposed to looking at negatively-valenced stimuli has been shown to correlate with increased activation of the PFC, PCC, precuneus and intraparietal sulcus (IPS) in both control groups and BPD samples (Koenigsberg et al., 2009). However, decreased activation of the dorsal ACC and IPS, as well as greater activation of the amygdala, superior temporal sulcus and superior frontal gyrus distinguished BPD from controls (Koenigsberg et al., 2009). Additionally, one study found that diminished precuneus activation when distancing may discriminate suicide attempters with BPD from non-attempters (Silvers et al., 2016). The precuneus may therefore be implicated in the lethality of poor emotion regulation in BPD. The aforementioned works differ in study design, however, as Silvers and colleagues (2016) chose to use aversive memories as negatively-valenced stimuli which prompted the activation of additional “memory” regions such as the hippocampus, whereas Koenigsberg et al. (2009) used

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images of negative interpersonal scenes. Moreover, there is no definitive way of assuring distancing took place as it is a very subjective psychological phenomenon.

Oxytocin Modulation

It is widely accepted that the neuropeptide oxytocin modulates prosociality and attachment formation (New et al., 2012), though its specific influence on human behaviour remains unclear (see Nave et al., 2015). Individuals with BPD tend to perceive others negatively and often lack empathy (American Psychiatric Association, 2013); providing the rationale for the study of the effects of oxytocin on the behaviour of those with BPD. Oxytocin has been found to dampen amygdala hyper-reactivity in response to negative affect-inducing stimuli in BPD samples, seemingly reducing the archetypal bias to threatening stimuli (Bertsch et al., 2013; Lischke et al., 2017). Greater amygdala activity was ostensibly related to less engagement with emotional scenes, which was regulated by oxytocin administration (Bertsch et al., 2013). Oxytocin therapy may therefore be beneficial for those with BPD who are hyper-reactive to aversive stimuli. It is necessary, however, to evaluate the role of oxytocin cautiously as it has also been shown to hinder affiliative behaviour in BPD (Bartz et al., 2011)

Opioid Function

Attachment and the regulation of the emotion and stress responses are thought to be mediated, in part, by the endogenous opioid system and μ-opioid receptors (Prossin et al., 2010). Binding potential is believed to measure neurotransmission facilitated by μ-opioid receptors and one PET study (using the radioligand ([11C] carfenatil) found that BPD patients, in a state of neutrality, exhibit greater μ-opioid receptor binding potential in the bilateral OFC, caudate, left amygdala

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and nucleus accumbens (Prossin et al., 2010). Activation of the endogenous opioid system was observed in the left posterior thalamus, left OFC, left ventral pallidum, left amygdala and left inferior temporal gyrus of BPD patients in states of sustained sadness, whereas controls showed activation only in the left anterior thalamus, left medial thalamus and the right hippocampus (Prossin et al., 2010). These results imply that BPD may be linked to greater activation the endogenous opioid system as a means to compensate for an intrinsic shortage of μ-opioid neurotransmission.

Interpersonal Dysfunction

Borderline personality disorder is also characterised by impaired interpersonal functioning, reflected by unstable relationships and preoccupation with abandonment (American Psychiatric Association, 2013). Despite the detrimental effects of interpersonal dysfunction, few studies explore the neural correlates of sociality in BPD; perhaps owing to the difficulty of recreating realistic social scenarios experimentally. Virtual ball tossing is a popular experimental paradigm which has been employed in the context of BPD by two studies. Domsalla and colleagues (2014) provide evidence that BPD patients tend to feel more excluded even when equally included by virtual teammates, which correlated neurally with greater activation of the precuneus, DLPFC, insula and medial PFC. Both healthy controls and BPD patients appeared to report similar levels of exclusion in the experimental condition, though BPD patients showed increased activation of the DLPFC relative to controls (Domsalla et al., 2014).[1] Using a similar study design exploring the relationship between rejection sensitivity and physical pain thresholds, social exclusion was found to lead to increasing reactivity to nociceptive stimuli in BPD patients and healthy controls (Bungert et al., 2015). At a neural level, this correlated with thalamic and anterior insular (AI)

[1] Some differences in neural activation across BPD and control samples were reported at a 10% significance level.

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activation in both samples and addition posterior AI was observed in BPD patients (Bungert et al., 2015). Interestingly, social inclusion engendered reduced relative activation of the amygdala in BPD patients following the administration of nociceptive stimuli (Bungert et al., 2015).

A landmark study, carried out by King-Casas and colleagues (2008), employed an economic exchange game as the experimental design in an effort to explore the neural correlates of social cooperation in BPD. Behaviourally, when interacting with healthy subjects, those with BPD reported lower levels of trust than did other healthy controls (King-Casas et al., 2008). Furthermore, BPD patients were less able to maintain co-operation and repair broken cyber relationships. Neurally, investigators observed activity of the anterior insula (AI) of BPD patients only when repaying money to their partners, whereas this region was activated in healthy controls when receiving monetary inputs from their partners. As AI activation often occurs in response to violations of social norms (New et al., 2012); this pattern of activation was interpreted as indication that those with BPD did not interpret low monetary offers as insulting due to their inherently negative perceptions of others (King-Casas et al., 2008). However, to our knowledge, this experimental paradigm has not been replicated more recently and more research on BPD interpersonal functioning using non-monetary incentives is necessary.

Abnormal Behaviour

Impulsive behaviours such as excessive spending, reckless driving and substance abuse are routinely observed in the symptom profile of individuals with BPD (American Psychiatric Association, 2013). Experimentally, investigators often utilise response inhibition as a measure of impulsivity, by way of Go/No-go, Stop Signal and Simon tasks. However, whether or not such experimental paradigms provide accurate depictions of pathological impulsivity is debateable.

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514 According to one study, fMRI BOLD signals did not differ across samples during each of the
515 three aforementioned tasks, as the inferior frontal gyrus, striatum and pre-supplementary motor
516 area was equally activated in both BPD and healthy control groups (van Eijk et al., 2015).
517 Moreover, BPD patients did not have shorter response latencies nor did they commit more errors
518 than did healthy individuals (van Eijk et al., 2015). Intriguingly, another study investigating the
519 effects of DBT on response inhibition in treatment completers and non-completers reported
520 increased activity in the bilateral medial and inferior frontal gyri during response inhibition after
521 seven months relative to pre-treatment levels (Ruocco et al., 2016). It is worth mentioning
522 though, that the investigators did not compare the performance of both BPD samples with
523 healthy controls, thus any disorder-specific performance differences cannot be ascertained from
524 this study.
525
526 Impulsivity and its relation to the processing of aversive and pleasant stimuli in BPD, has been
527 found to be mediated by the mesolimbic reward system, comprising the ventral striatum and
528 nucleus accumbens (Herbort et al., 2016). Rewarded tasks involving dopaminergic
529 neurotransmission ostensibly activate both of the aforementioned regions, which are also
530 believed to be crucial for both reward prediction and Bayesian prediction error (Schott et al.,
531 2008). Those with BPD appear to have a blunted neural response in both the striatum and
532 nucleus accumbens to reward and loss anticipation, as observed by Herbort and colleagues
533 (2016). The authors reported that, during a monetary incentive delay task, those with BPD
534 showed reduced activity in the nucleus accumbens and ventral striatum in response to reward and
535 loss predicting cues, where thrill-seeking behaviours were thought to arise as a means of
536 compensation. Due to the lack of clinical control group, however, it is difficult to determine

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whether these neurological changes are exclusive to BPD as muted striatal responses to losses and gains are reportedly present in those with depression (Ubl et al., 2015).

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DISCUSSION

Whilst the studies reviewed in the present paper report some interesting and informative findings, it must be borne in mind that a definitive neurological profile of borderline personality disorder is yet to be synthesised. However, in light of the recent research reviewed, a rudimentary neurodevelopmental model of BPD can be proposed.

Morphologically, it would seem that BPD is associated initially in adolescence with reduced grey matter volume in the orbitofrontal cortex (Brunner et al., 2010; Chanen, Velakoulis, et al., 2008), a region thought to partly mediate affect regulation, social appropriateness and inhibition (Malloy et al., 1993). Relative to adults, adolescents are ostensibly more prone to suffer acutely from symptoms such as impulsivity and inapposite anger (Kaess et al., 2014; Lawrence, Allen, & Chanen, 2010), which may therefore be attributable to a compromised OFC. Diminished white matter tract coherence in the inferior longitudinal and occipito-frontal fasciculi may also be implicated in the adolescent neuropathology of BPD (New et al., 2013); though due to the absence of a clinical control group and comorbid MDD in the BPD samples, the specificity of these results is questionable. Further replicative studies using large adolescent cohorts are therefore crucial to allow for the assessment of the influence of symptomatic variability (Brunner, 2010) and to increase the reliability of these preliminary findings. Longitudinal research within a developmental psychology framework would also allow for the verification of the abovementioned proposals.

Deficits in the OFC, inferior longitudinal and occipitofrontal fasciculi are also reported by studies using adult BPD samples (Araujo et al., 2014; de Araujo Filho et al., 2014; Ninomiya et al., 2018; Salvador et al., 2016; Sato et al., 2012); suggesting that these structural alterations may

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persist from adolescence into adulthood. Reductions of the hippocampus however, appear to present only with increasing age (Depping et al., 2016; Niedtfeld et al., 2013; Richter et al., 2014; Soloff et al., 2008) and is one of several regions purported to have discriminant clinical value (Sato et al., 2012). Future studies should aim to clarify whether comorbid PTSD, past childhood adversity and/or symptom severity modulate the volume of the hippocampus in BPD patients as is proposed by some investigators (Brambilla et al., 2004; Kreisel et al., 2015). Crucially, further investigations should also assess the relationship between structural brain changes and the corresponding functional impact.

Regarding resting-state functional connectivity in the default-mode network of those with BPD, further research is needed to replicate the few existing experimental designs and give credence to the small body of current evidence. Functionally, it seems as though BPD is mediated by hyperactivity of the cingulate cortices (Koenigsberg et al., 2009; Scherpiet et al., 2014) which has been interpreted by Mensebach et al. (2009) as a compensatory mechanism due to hippocampal shrinkage. Additionally, heightened amygdala responses are recurrently seen in BPD patients, particularly in relation to negatively-valenced stimuli (Bertsch et al., 2013; Hazlett et al., 2012; Koenigsberg et al., 2009). Further research should aim to investigate how the aforementioned regions interact during deliberate emotion regulation using strategies other than psychological distancing. In addition, future investigators should attempt to corroborate the notion that such neural hyper-activation can be remedied by DBT (Niedtfeld et al., 2017; Winter et al., 2017).

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Interpersonally, there is evidence to suggest that the anterior insula is additionally activated in BPD during social inclusion/exclusion paradigms (Bungert et al., 2015; Domsalla et al., 2014). More research, however, is needed due to the lack of a non-social control condition (such as tossing ball to oneself), to which neural activation across samples could be compared. Behaviourally, a blunted striatal response to reward and loss predicting cues may explicate impulsivity in BPD, where risky behaviours are carried out to compensate for the neural de-sensitisation. The findings with regard to response inhibition as a reflection of impulsivity in BPD are inconclusive. Further research should endeavour to different experimental designs to more reliably assess atypical behaviour in BPD.

Limitations

It is necessary to acknowledge that the present review is subject to publication bias, as only studies published in peer-reviewed journals were evaluated. Furthermore, the samples of the majority of the papers examined included only female subjects thus the findings cannot be generalised to males with BPD. Despite rather stringent exclusion criteria, many of the subjects in the included studied also presented with past histories of Axis I and II disorders, as is typical of BPD. Specificity of the results to BPD in isolation is therefore limited. Moreover, a neurodevelopmental model of BPD with respect to brain function within the four diagnostic domains (cognitive-perceptual differences, emotional dysregulation, interpersonal dysfunction and abnormal behaviour) was not put forth due to the non-existence of adolescent-based literature in these areas.

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CONCLUSION

To conclude, the current research reviewed presents fascinating results, though the degree to which they can be attributed to BPD alone remains elusive. Furthermore, the evidence base is not yet robust enough to have a strong clinical influence. A limited number of fMRI studies examining the neural aftereffects of psychological therapies offered to BPD patients are presently available; and further research is essential to corroborate the findings. The neural correlates of emotion dysregulation appear to be well-evaluated relative to other diagnostic domains such as interpersonal functioning, cognitive processing and atypical behaviours. Future investigators should therefore aim to devise ecologically valid methodologies to substantiate the existing evidence within these areas. It is crucial that the vast array of symptoms comprising the diagnostic criteria of BPD are eventually understood from a neurological perspective to aid in the development of person-centred therapies. Moreover, greater efforts to recruit larger cohorts of both adolescents and adults should be made to further our understanding of the neurological progression of this disorder.

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REFERENCES

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Washington, DC.

American Psychiatric Association Practice, G. (2001). Practice guidleline for the treatment of patients with borderline personality disorder. *The American Journal of Psychiatry, 158*(10), 2-52.

Araujo, T. B., Araujo Filho, G. M., Sato, J. R., Araujo, C. M., Lisondo, C. M., Carrete, H., Jr., . . . Jackowski, A. P. (2014). Cortical morphology changes in women with borderline personality disorder: a multimodal approach. *Rev Bras Psiquiatr, 36*(1), 32-38. doi:10.1590/1516-4446-2013-1120

Bartz, J., Simeon, D., Hamilton, H., Kim, S., Crystal, S., Braun, A., Vicens, V., Hollander, E. (2011) Oxytocin can hinder trust and cooperation in borderline personality disorder. *Social Cognitive and Affective Neuroscience*, 6(5), 556–563, https://doi.org/10.1093/scan/nsq085

Bertsch, K., Gamer, M., Schmidt, B., Schmidinger, I., Walther, S., Kastel, T., . . . Herpertz, S. C. (2013a). Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. *The American Journal of Psychiatry, 170*(10), 1169-1177.

Bertsch, K., Gamer, M., Schmidt, B., Schmidinger, I., Walther, S., Kastel, T., . . . Herpertz, S. C. (2013b). "Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder": Correction. *The American Journal of Psychiatry, 170*(10), 1218.

Brambilla, P., Soloff, P. H., Sala, M., Nicoletti, M. A., Keshavan, M. S., & Soares, J. C. (2004). Anatomical MRI study of borderline personality disorder patients. *Psychiatry Research: Neuroimaging, 131*(2), 125-133.

Brunner, R., Henze, R., Parzer, P., Kramer, J., Feigl, N., Lutz, K., . . . Stieltjes, B. (2010). Reduced prefrontal and orbitofrontal gray matter in female adolescents with borderline personality disorder: is it disorder specific? *Neuroimage, 49*(1), 114-120. doi:10.1016/j.neuroimage.2009.07.070

Bungert, M., Koppe, G., Niedtfeld, I., Vollstadt-Klein, S., Schmahl, C., Lis, S., & Bohus, M. (2015). Pain processing after social exclusion and its relation to rejection sensitivity in borderline personality disorder. *PLoS ONE Vol 10(8), 2015, ArtID e0133693, 10*(8).

Carrasco, J. L., Tajima-Pozo, K., Diaz-Marsa, M., Casado, A., Lopez-Ibor, J. J., Arrazola, J., & Yus, M. (2012). Microstructural white matter damage at orbitofrontal areas in borderline personality disorder. *J Affect Disord, 139*(2), 149-153. doi:10.1016/j.jad.2011.12.019

Chanen, A. M., Jovev, M., McCutcheon, L. K., Jackson, H. J., & McGorry, P. D. (2008). Borderline personality disorder in young people and the prospects for prevention and early intervention. *Current Psychiatry Reviews, 4*(1), 48-57.

Chanen, A. M., Velakoulis, D., Carison, K., Gaunson, K., Wood, S. J., Yuen, H. P., . . . Pantelis, C. (2008). Orbitofrontal, amygdala and hippocampal volumes in teenagers with first-presentation borderline personality disorder. *Psychiatry Research: Neuroimaging, 163*(2), 116-125.

Chapman, A. L., Specht, M. W., & Cellucci, T. (2005). Borderline personality disorder and deliberate self-harm: does experiential avoidance play a role? *Suicide and Life-Threatening Behavior, 35*(4), 388-399.

712 Coid, J., Yang, M., Tyrer, P., Roberts, A., & Ullrich, S. (2006). Prevalence and correlates of personality
713 disorder in Great Britain. *The British Journal of Psychiatry, 188*(5), 423-431.
714 doi:10.1192/bjp.188.5.423
715 Cuthbert, B. N. (2014). The RDoC framework: facilitating transition from ICD/DSM to dimensional
716 approaches that integrate neuroscience and psychopathology. *World Psychiatry, 13*(1), 28-35.
717 de Araujo Filho, G. M., Abdallah, C., Sato, J. R., de Araujo, T. B., Lisondo, C. M., de Faria, A. A., . . .
718 Jackowski, A. P. (2014). Morphometric hemispheric asymmetry of orbitofrontal cortex in women
719 with borderline personality disorder: a multi-parameter approach. *Psychiatry Res, 223*(2), 61-66.
720 doi:10.1016/j.pscychresns.2014.05.001
721 Depping, M. S., Wolf, N. D., Vasic, N., Sambataro, F., Thomann, P. A., & Wolf, R. (2016). Common and
722 distinct structural network abnormalities in major depressive disorder and borderline personality
723 disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 65*, 127-133.
724 Domsalla, M., Koppe, G., Niedtfeld, I., Vollstadt-Klein, S., Schmahl, C., Bohus, M., & Lis, S. (2014).
725 Cerebral processing of social rejection in patients with borderline personality disorder. *Soc Cogn*
726 *Affect Neurosci, 9*(11), 1789-1797. doi:10.1093/scan/nst176
727 Gunderson, J. G., Stout, R. L., McGlashan, T. H., & et al. (2011). Ten-year course of borderline
728 personality disorder: Psychopathology and function from the collaborative longitudinal
729 personality disorders study. *Archives of General Psychiatry, 68*(8), 827-837.
730 doi:10.1001/archgenpsychiatry.2011.37
731 Hazlett, E. A., Zhang, J., New, A. S., Zelmanova, Y., Goldstein, K. E., Haznedar, M. M., . . . Chu, K. W.
732 (2012). Potentiated amygdala response to repeated emotional pictures in borderline personality
733 disorder. *Biol Psychiatry, 72*(6), 448-456. doi:10.1016/j.biopsych.2012.03.027
734 Herbort, M. C., Soch, J., Wustenberg, T., Krauel, K., Pujara, M., Koenigs, M., . . . Schott, B. H. (2016). A
735 negative relationship between ventral striatal loss anticipation response and impulsivity in
736 borderline personality disorder. *Neuroimage Clin, 12*, 724-736. doi:10.1016/j.nicl.2016.08.011
737 Jin, X., Zhong, M., Yao, S., Cao, X., Tan, C., Gan, J., . . . Yi, J. (2016). A Voxel-Based Morphometric
738 MRI Study in Young Adults with Borderline Personality Disorder. *PLoS One, 11*(1), e0147938.
739 doi:10.1371/journal.pone.0147938
740 Kaess, M., Brunner, R., & Chanen, A. (2014). Borderline Personality Disorder in Adolescence.
741 *Pediatrics, 134*(4), 782-793. doi:10.1542/peds.2013-3677
742 Kimmel, C. L., Alhassoon, O. M., Wollman, S. C., Stern, M. J., Perez-Figueroa, A., Hall, M. G., . . .
743 Radua, J. (2016). Age-related parieto-occipital and other gray matter changes in borderline
744 personality disorder: A meta-analysis of cortical and subcortical structures. *Psychiatry Research:*
745 *Neuroimaging, 251*, 15-25.
746 King-Casas, B., Sharp, C., Lomax-Bream, L., Lohrenz, T., Fonagy, P., & Montague, P. R. (2008). The
747 rupture and repair of cooperation in borderline personality disorder. *Science, 321*(5890), 806-810.
748 doi:10.1126/science.1156902
749 Kluetsch, R. C., Schmahl, C., Niedtfeld, I., Densmore, M., Calhoun, V. D., Daniels, J., . . . Lanius, R. A.
750 (2012). Alterations in default mode network connectivity during pain processing in borderline
751 personality disorder. *Arch Gen Psychiatry, 69*(10), 993-1002.
752 doi:10.1001/archgenpsychiatry.2012.476
753 Koenigsberg, H. W., Fan, J., Ochsner, K. N., Liu, X., Guise, K. G., Pizzarello, S., . . . Siever, L. J. (2009).
754 Neural correlates of the use of psychological distancing to regulate responses to negative social

PeerJ Preprints | https://doi.org/10.7287/peerj.preprints.27414v1 | CC BY 4.0 Open Access | rec: 5 Dec 2018, publ: 5 Dec 2018

cues: a study of patients with borderline personality disorder. *Biol Psychiatry, 66*(9), 854-863. doi:10.1016/j.biopsych.2009.06.010

Krause-Utz, A., Veer, I. M., Rombouts, S. A., Bohus, M., Schmahl, C., & Elzinga, B. M. (2014). Amygdala and anterior cingulate resting-state functional connectivity in borderline personality disorder patients with a history of interpersonal trauma. *Psychol Med, 44*(13), 2889-2901. doi:10.1017/s0033291714000324

Kreisel, S. H., Labudda, K., Kurlandchikov, O., Beblo, T., Mertens, M., Thomas, C., . . . Driessen, M. (2015). Volume of hippocampal substructures in borderline personality disorder. *Psychiatry Res, 231*(3), 218-226. doi:10.1016/j.pscychresns.2014.11.010

Lawrence, K. A., Allen, J. S., & Chanen, A. M. (2010). Impulsivity in borderline personality disorder: reward-based decision-making and its relationship to emotional distress. *Journal of Personality Disorders, 24*(6), 785-799.

Lenzenweger, M. F. (2006). The Longitudinal Study of Personality Disorders: History, Design Considerations, and Initial Findings. *Journal of Personality Disorders, 20*(6), 645-670.

Lieb, K., Zanarini, M. C., Schmahl, C., Linehan, M. M., & Bohus, M. (2004). Borderline personality disorder. *The Lancet, 364*(9432), 453-461. doi:https://doi.org/10.1016/S0140-6736(04)16770-6

Lischke, A., Herpertz, S. C., Berger, C., Domes, G., & Gamer, M. (2017). Divergent effects of oxytocin on (para-)limbic reactivity to emotional and neutral scenes in females with and without borderline personality disorder. *Soc Cogn Affect Neurosci, 12*(11), 1783-1792. doi:10.1093/scan/nsx107

Mädler, B., Drabycz, S. A., Kolind, S. H., Whittall, K. P., & MacKay, A. L. (2008). Is diffusion anisotropy an accurate monitor of myelination?: Correlation of multicomponent T2 relaxation and diffusion tensor anisotropy in human brain. *Magnetic resonance imaging, 26*(7), 874-888.

Maier-Hein, K. H., Brunner, R., Lutz, K., Henze, R., Parzer, P., Feigl, N., . . . Stieltjes, B. (2014). Disorder-specific white matter alterations in adolescent borderline personality disorder. *Biol Psychiatry, 75*(1), 81-88. doi:10.1016/j.biopsych.2013.03.031

Malloy, P., Bihrle, A., Duffy, J., & Cimino, C. (1993). The orbitomedial frontal syndrome. *Archives of Clinical Neuropsychology, 8*(3), 185-201.

Mechelli, A., Price, C. J., Friston, K. J., & Ashburner, J. (2005). Voxel-based morphometry of the human brain: methods and applications. *Current medical imaging reviews, 1*(2), 105-113.

Mensebach, C., Beblo, T., Driessen, M., Wingenfeld, K., Mertens, M., Rullkoetter, N., . . . Woermann, F. G. (2009). Neural correlates of episodic and semantic memory retrieval in borderline personality disorder: an fMRI study. *Psychiatry Res, 171*(2), 94-105. doi:10.1016/j.pscychresns.2008.02.006

Morandotti, N., Dima, D., Jogia, J., Frangou, S., Sala, M., Vidovich, G. Z., . . . Brambilla, P. (2013). Childhood abuse is associated with structural impairment in the ventrolateral prefrontal cortex and aggressiveness in patients with borderline personality disorder. *Psychiatry Res, 213*(1), 18-23. doi:10.1016/j.pscychresns.2013.02.002

Muller, L. E., Schulz, A., Andermann, M., Gabel, A., Gescher, D. M., Spohn, A., . . . Bertsch, K. (2015). Cortical Representation of Afferent Bodily Signals in Borderline Personality Disorder: Neural Correlates and Relationship to Emotional Dysregulation. *JAMA Psychiatry, 72*(11), 1077-1086. doi:10.1001/jamapsychiatry.2015.1252

Nave, G., Camerer, C., & McCullough, M. (2015). Does Oxytocin Increase Trust in Humans? A Critical Review of Research. Perspectives on Psychological Science, 10(6), 772–789. https://doi.org/10.1177/1745691615600138

New, A. S., Carpenter, D. M., Perez-Rodriguez, M., Ripoll, L. H., Avedon, J., Patil, U., . . . Goodman, M. (2013). Developmental differences in diffusion tensor imaging parameters in borderline personality disorder. *Journal of Psychiatric Research, 47*(8), 1101-1109.

New, A. S., Carpenter, D. M., Perez-Rodriguez, M. M., Ripoll, L. H., Avedon, J., Patil, U., . . . Goodman, M. (2013). Developmental differences in diffusion tensor imaging parameters in borderline personality disorder. *J Psychiatr Res, 47*(8), 1101-1109. doi:10.1016/j.jpsychires.2013.03.021

New, A. S., Perez-Rodriguez, M. M., & Ripoll, L. H. (2012). Neuroimaging and borderline personality disorder. *Psychiatric Annals, 42*(2), 65-71.

Niedtfeld, I., Schmitt, R., Winter, D., Bohus, M., Schmahl, C., & Herpertz, S. C. (2017). Pain-mediated affect regulation is reduced after dialectical behavior therapy in borderline personality disorder: A longitudinal fMRI study. *Social Cognitive and Affective Neuroscience Vol, 12*(5), 739-747.

Niedtfeld, I., Schulze, L., Krause-Utz, A., Demirakca, T., Bohus, M., & Schmahl, C. (2013). Voxel-based morphometry in women with borderline personality disorder with and without comorbid posttraumatic stress disorder. *PLoS One, 8*(6), e65824. doi:10.1371/journal.pone.0065824

Nierhaus, T., Margulies, D., Long, X., & Villringer, A. (2012). fMRI for the assessment of functional connectivity. In *Neuroimaging-Methods*: InTech.

Ninomiya, T., Oshita, H., Kawano, Y., Goto, C., Matsuhashi, M., Masuda, K., . . . Akiyoshi, J. (2018). Reduced white matter integrity in borderline personality disorder: A diffusion tensor imaging study. *J Affect Disord, 225*, 723-732. doi:10.1016/j.jad.2017.09.007

O'Neill, A., D'Souza, A., Carballedo, A., Joseph, S., Kerskens, C., & Frodl, T. (2013). Magnetic resonance imaging in patients with borderline personality disorder: a study of volumetric abnormalities. *Psychiatry Res, 213*(1), 1-10. doi:10.1016/j.pscychresns.2013.02.006

O'Neill, A., D'Souza, A., Samson, A. C., Carballedo, A., Kerskens, C., & Frodl, T. (2015). Dysregulation between emotion and theory of mind networks in borderline personality disorder. *Psychiatry Res, 231*(1), 25-32. doi:10.1016/j.pscychresns.2014.11.002

Prossin, A. R., Love, T. M., Koeppe, R. A., Zubieta, J. K., & Silk, K. R. (2010). Dysregulation of regional endogenous opioid function in borderline personality disorder. *Am J Psychiatry, 167*(8), 925-933. doi:10.1176/appi.ajp.2010.09091348

Reitz, S., Kluetsch, R., Niedtfeld, I., Knorz, T., Lis, S., Paret, C., . . . Schmahl, C. (2015). Incision and stress regulation in borderline personality disorder: neurobiological mechanisms of self-injurious behaviour. *Br J Psychiatry, 207*(2), 165-172. doi:10.1192/bjp.bp.114.153379

Richter, J., Brunner, R., Parzer, P., Resch, F., Stieltjes, B., & Henze, R. (2014). Reduced cortical and subcortical volumes in female adolescents with borderline personality disorder. *Psychiatry Res, 221*(3), 179-186. doi:10.1016/j.pscychresns.2014.01.006

Ruocco, A. C., Amirthavasagam, S., Choi-Kain, L. W., & McMain, S. F. (2013). Neural correlates of negative emotionality in borderline personality disorder: an activation-likelihood-estimation meta-analysis. *Biol Psychiatry, 73*(2), 153-160. doi:10.1016/j.biopsych.2012.07.014

Ruocco, A. C., Rodrigo, A. H., McMain, S. F., Page-Gould, E., Ayaz, H., & Links, P. S. (2016). Predicting treatment outcomes from prefrontal cortex activation for self-harming patients with borderline personality disorder: A preliminary study. *Frontiers in Human Neuroscience Vol 10 2016, ArtID 220, 10*.

Salvador, R., Vega, D., Pascual, J. C., Marco, J., Canales-Rodriguez, E. J., Aguilar, S., . . . Pomarol-Clotet, E. (2016). Converging Medial Frontal Resting State and Diffusion-Based Abnormalities in

PeerJ Preprints | https://doi.org/10.7287/peerj.preprints.27414v1 | CC BY 4.0 Open Access | rec: 5 Dec 2018, publ: 5 Dec 2018

Borderline Personality Disorder. *Biol Psychiatry, 79*(2), 107-116. doi:10.1016/j.biopsych.2014.08.026

Sato, J. R., de Araujo Filho, G. M., de Araujo, T. B., Bressan, R. A., de Oliveira, P. P., & Jackowski, A. P. (2012). Can neuroimaging be used as a support to diagnosis of borderline personality disorder? An approach based on computational neuroanatomy and machine learning. *J Psychiatr Res, 46*(9), 1126-1132. doi:10.1016/j.jpsychires.2012.05.008

Scherpiet, S., Bruhl, A. B., Opialla, S., Roth, L., Jancke, L., & Herwig, U. (2014). Altered emotion processing circuits during the anticipation of emotional stimuli in women with borderline personality disorder. *Eur Arch Psychiatry Clin Neurosci, 264*(1), 45-60. doi:10.1007/s00406-013-0444-x

Schott, B. H., Minuzzi, L., Krebs, R. M., Elmenhorst, D., Lang, M., Winz, O. H., . . . Zilles, K. (2008). Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. *Journal of Neuroscience, 28*(52), 14311-14319.

Silvers, J. A., Hubbard, A. D., Chaudhury, S., Biggs, E., Shu, J., Grunebaum, M. F., . . . Stanley, B. (2016). Suicide attempters with Borderline Personality Disorder show differential orbitofrontal and parietal recruitment when reflecting on aversive memories. *J Psychiatr Res, 81*, 71-78. doi:10.1016/j.jpsychires.2016.06.020

Soloff, P., Nutche, J., Goradia, D., & Diwadkar, V. (2008). Structural brain abnormalities in borderline personality disorder: a voxel-based morphometry study. *Psychiatry Res, 164*(3), 223-236. doi:10.1016/j.pscychresns.2008.02.003

Soloff, P. H., Pruitt, P., Sharma, M., Radwan, J., White, R., & Diwadkar, V. A. (2012). Structural brain abnormalities and suicidal behavior in borderline personality disorder. *J Psychiatr Res, 46*(4), 516-525. doi:10.1016/j.jpsychires.2012.01.003

Stiglmayr, C., Ebner-Priemer, U., Bretz, J., Behm, R., Mohse, M., Lammers, C. H., . . . Kleindienst, N. (2008). Dissociative symptoms are positively related to stress in borderline personality disorder. *Acta Psychiatrica Scandinavica, 117*(2), 139-147.

Takahashi, T., Chanen, A. M., Wood, S. J., Walterfang, M., Harding, I. H., Yucel, M., . . . Pantelis, C. (2009). Midline brain structures in teenagers with first-presentation borderline personality disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 33*(5), 842-846.

Takahashi, T., Chanen, A. M., Wood, S. J., Yucel, M., Tanino, R., Suzuki, M., . . . McGorry, P. D. (2009). Insular cortex volume and impulsivity in teenagers with first-presentation borderline personality disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 33*(8), 1395-1400.

Ubl, B., Kuehner, C., Kirsch, P., Ruttorf, M., Diener, C., & Flor, H. (2015). Altered neural reward and loss processing and prediction error signalling in depression. *Soc Cogn Affect Neurosci, 10*(8), 1102-1112.

van Eijk, J., Sebastian, A., Krause-Utz, A., Cackowski, S., Demirakca, T., Biedermann, S. V., . . . Tuscher, O. (2015). Women with borderline personality disorder do not show altered BOLD responses during response inhibition. *Psychiatry Res, 234*(3), 378-389. doi:10.1016/j.pscychresns.2015.09.017

Winter, D., Niedtfeld, I., Schmitt, R., Bohus, M., Schmahl, C., & Herpertz, S. C. (2017). Neural correlates of distraction in borderline personality disorder before and after dialectical behavior therapy. *Eur Arch Psychiatry Clin Neurosci, 267*(1), 51-62. doi:10.1007/s00406-016-0689-2

PeerJ Preprints | https://doi.org/10.7287/peerj.preprints.27414v1 | CC BY 4.0 Open Access | rec: 5 Dec 2018, publ: 5 Dec 2018

885 Zanarini, M. C. (2000). Childhood experiences associated with the development of borderline personality
886 disorder. *Psychiatric Clinics of North America*, *23*(1), 89-101.
887 Zhou, Q., Zhong, M., Yao, S., Jin, X., Liu, Y., Tan, C., . . . Yi, J. (2017). . *Acta Psychiatr Scand*, *136*(6),
888 637-647. doi:10.1111/acps.12823
889
890
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892
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APPENDIX

Table 1.

Summary of the aims, results and limitations of the selected articles.

Author(s)	Imaging Modality	Participants	Aims	Results	Limitations/Future Directions
Araujo et al., 2014	MRI	25 BPD, 25 HC (F) Those with a current Axis I or II disorder were excluded.	To investigate whether structural atypicalities of the cortex are present in BPD patients.	Reduced unilateral thickness of the l. lat OFC, r. mid. front. gyrus, area of l. med. oFC and r. insula and increased area and thickness of the bilateral parietal gyri, r. postcentral gyrus thickness and area l. sup frontal gyrus in BPD compared to HC.	All patients taking at least one psychotropic agent. Small sample size. Not generalizable to males with disorder nor to typical BPD patient who will likely have several comorbid conditions. No clinical control.
Bertsch et al., 2013	fMRI	40 BPD, 41 HC (F) Those with IQ <85; pregnancy; endocrine or neurological disorders; use of any type of regular medication except contraceptives; lifetime diagnoses of schizophrenia, schizoaffective disorder, or bipolar disorder; and current alcohol or drug dependence were excluded.	To investigate effect of oxytocin on amygdala response during an emotion classification task.	Quicker initial gaze fixation to eyes of angry faces in BPD group and increased amygdala response to angry faces relative to HCs, hyper-reactivity dampened after oxytocin. Increased amygdala activity positively correlated with quicker disengagement from eyes of angry faces in BPD group.	No clinical control. Focused on amygdala, no whole brain changes reported. Limited sample size.

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Brunner et al., 2010	MRI	20 BPD, 20 other MHD (mixed diagnoses) , 20 HCs adolescents (F)	To investigate structural changes in brain volume present in adolescent-onset BPD.	Reduced bilateral DLPFC and left OFC grey matter density in BPD compared to HCs. Decreased grey matter in right DLPFC in clinical controls compared to HCs. No significant grey matter alterations in BPD relative to clinical control. No intergroup differences in limbic system and WM structures.	Small sample size. Gender bias. Comorbid diagnoses may influence brain morphology. Larger cohort studies may allow for examination of symptomatic variability within groups.
Bungert et al., 2015	fMRI	20 BPD, 20 HC (F) Those with a lifetime history of psychotic disorder, current major depression, substance abuse or addiction, pregnancy, organic brain disease, a history of skull or brain damage, severe neurological illnesses, and currently using psychotropic medication were excluded.	Investigated experience of physical pain in BPD compared to controls following social inclusion/exclusion during a virtual ball-tossing game. Examined effect of rejection sensitivity on experience and neural processing of physical pain post inclusion/exclusion.	Social exclusion in ball tossing game led to hypersensitivity to physical pain in both groups (subjective measures) as well as increased AI and thalamic activation. Exclusion linked to additional posterior AI activation, inclusion linked to reduced amygdala activation in response to nociceptive stimuli in BPD group relative to HCs. Increasing rejection sensitivity related to less difference in	Within subjects so all patients experienced inclusion as well as exclusion, which may have dampened/enhanced the effects of each. Gender bias. Excluded major depression which may reduce generalisability to the average individual with BPD. Future studies may wish to use this paradigm on subgroups of BPD patients (i.e. high impulsivity, non-suicidal self-injury etc). Small sample size.

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				amygdala and insula activation in response to pain after inclusion and exclusion.	
Carrasco et al., 2012	DTI	28 BPD (13M, 15F), 26 HCs Those with current major depression, substance dependence, life-time diagnosis of schizophrenia, bipolar disorder or organic mental disorders, and those using psychotropic medication in the two weeks prior to study were excluded.	To investigate microstructural damage to white matter tracts of PFC in a representative sample of BPD patients.	Decreased fractional anisotropy (FA) in genu and rostral corpus callosum, bilateral prefrontal white matter fasciculi and orbitofrontal white matter in BPD group compared to controls. No increased FA in relation to controls.	Small sample size. Some patients on long term medications which could have altered brain morphology. Decreased FA cannot be specifically linked to BPD as comorbid conditions, disorder severity and additional complications could influence white matter development. DTI more prone to artefacts than other modalities.
Chanen et al., 2008	MRI	20 BPD (15F, 5M), 20 (15F, 5M) HCs Those with schizophrenia or affective psychotic disorders, anorexia nervosa, current alcohol dependence, history of head injury, loss of consciousness for 10 min or more, seizures, thyroid	To investigate the hippocampal, orbitofrontal and amygdala volumes of teenagers with first-presentation BPD.	Right side OFC grey matter loss relative to controls, no significant differences in hippocampal and amygdala grey matter. Smaller amygdala bilaterally in males with BPD (sample size incredibly small). Correlations between right amygdala volume and symptoms (i.e. inappropriate	Longitudinal studies needed to observe whether or not hippocampal/amygdala deficits appear later in course of disorder Controversial diagnostic criteria for BPD in youth. Structural changes over time cannot be determined from this paper. Comorbidity may influence brain morphology. Large number of statistical analyses used

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		disorder or other significant medical illness were excluded.		anger, externalisation/internalisation, impulsivity) in females.	increasing possibility of Type I error. Small sample size.
de Araujo Filho et al., 2014	MRI	25 BPD, 25 HCs (F) Those with any other psychiatric comorbidity at time of investigation were excluded.	To investigate differences between volumes of OFC in BPD and HC samples.	Reduced cortical thickness bilaterally in medial OFC, decreased curvature and depth of sulcus in right medial OFC and increased curvature of left in BPD compared to control.	High rates of past psychiatric comorbidity which could confound results. High levels of psychotropic use. Cannot generalise to males nor to those with comorbidities. Small sample size.
Depping et al., 2016	MRI	22 MDD, 17 BPD, 22 HCs (F) Those with medical/ neurological disorders, drug or alcohol abuse, a history of head trauma, lifetime or current comorbid Axis I and II disorders (for MDD), lifetime schizophrenia or bipolar disorder diagnosis or ADHD were exluded.	To investigate and compare the structural networks that are shared and distinct in MDD and BPD to healthy controls (MRI).	Reduced volume of bilateral frontostriatal network in MDD compared to BPD and HC. Reductions in medial/temporal frontal network (hippocampus, parahippocampus and amygdala) volumes in BPD relative to HCs and MDD. Structural pattern of lateral PFC and cingulate significantly related to depressive symptoms in MDD and BPD	Limited sample size across groups. Differential therapeutic measures taken across clinical groups. Small sample size.
Domsalla et al., 2014	fMRI	20 BPD and 20 HCs (F). Those with a lifetime history of psychotic or bipolar I disorder,	To develop an understanding of rejection sensitivity in BPD at the neural level using a	Both BPD and HCs felt excluded to similar degree in exclusion groups but BPD felt more excluded during inclusion and control than	Brain structures activated may not be exclusive to social-emotional processes, should add a non-social control condition to further examine (i.e. tossing and catching)

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		current major depressive episode, current substance abuse or addiction, pregnancy, organic brain disease, psychotropic medication use skull/brain damage, or severe neurological illness were excluded.	virtual ball-tossing paradigm.	HCs; more dissociative symptoms in BPD across conditions compared to HC. Greater activation of medial PFC and dACC in BPD group across conditions. Cortical activation differences: Greater activation in precuneus, dlPFC, insula and mPFC in BPD brain during control task (equal tosses between participants), greater dlPFC activation in BPD during exclusion conditions (other activation comparisons failed to reach statistical sig).	No clinical control group, findings may not be specific to BPD. Some differences in activation reported at 10% significance level. Small sample size.
Hazlett et al., 2012	fMRI	33 BPD (20F, 13M) 28 SPD (12F, 16M) 32 HC (20F, 12M) Those with a history of psychotic disorder, bipolar I affective disorder, or current MDD, medical/ neurological illness, head injury, substance dependence/abuse (in past 6 months) and those using psychotropic	To investigate differences in amygdala response to neutral and affect-inducing (positive/negative in valence) stimuli in BPD, schizotypal personality disorder and HC groups.	Greater amygdala activation in BPD compared to SPD and HCs to affect-inducing stimuli (no group difference for neutral stimuli), increased time to return to baseline activation levels in BPD group relative to HCs and SPD. Greater amygdala response to repeated pictures in BPD suggesting impaired amygdala habituation relative to SPD and HCs.	Several BPD patients had history of antidepressant, neuroleptic and benzodiazepine use which could confound results. Limited sample size.

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		medication were excluded.			
Herbort et al., 2016	fMRI	21 BPD, 23 HCs (F) Those with a history of schizophrenia, bipolar disorder, schizoaffective disorder, lifetime diagnosis of adult ADHD, substance abuse and currently using psychotropic medication were excluded.	To examine the relationship between striatal responses to rewards/losses and impulsivity in those with BPD.	Reduced activity in nucleus accumbens and ventral striatum in response to reward and loss predicting cues compared to neutral cues in BPD group. Negative correlation between ventral striatum loss anticipation cues and self-reported impulsivity scores in BPD, converse relationship observed in HCs. Positive correlation between striatal response to both losses/gains and impulsivity scores in BPD. Blunted neural response to reward/loss anticipation may lead individual to thrill-seek more to compensate?	Insufficient sample size to examine regions other than striatum. Used monetary rewards only, future research may want to investigate social reward/punishment. No clinical control group, muted striatal response to losses/gains apparent also in depression and bipolar II disorder (Ubl et al., 2015; Yip et al., 2015)
Jin et al., 2016	MRI	34 HCs (15M, 19F), 34 BPD (17F, 17F) Those with past or current diagnosis of schizophrenia, paranoid disorder, schizoaffective	To investigate grey matter differences across experimental groups and its relationship to childhood trauma and attachment	Increased bilateral volume of middle cingulate cortex, posterior cingulate cortex and precuneus compared to HCs, no other significant differences in grey matter concentration.	Used lower accuracy widespread voxel-by-voxel univariate analyses. Not generalisable to patients with comorbid conditions.

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		disorder, bipolar disorder, physical disorder with psychiatric consequence (e.g., hypothyroidism, seizure disorder, brain injury) were excluded.	styles.	Childhood trauma not correlated with grey matter volume across groups. HCs with more insecure attachments had less grey matter in precuneus, MCC and middle occipital gyrus but no negative correlations between insecure attachment and volume in BPD group.	
Kimmel et al., 2016	MRI	Meta-analyses: 256 BPD and 272 HCs	To investigate age-related neural changes in BPD.	Greater r. sup. motor area volume in BPD relative to controls. Smaller grey matter volume in r. sup./midd. temp gyri, inferior frontal gyrus pars opercularis, left hippocampus compared to controls. Left superior parietal-occipital volumes increase with age in BPD (younger patients show reduced parieto-occipital volumes). Right amygdala volume decreases with age. Grey matter deficits in limbic areas ostensibly worsen with age in BPD.	Meta-analyses examine summarised, compiled data rather than raw, experimental data. Voxel-based morphometry may not be powerful enough to accurately detect differences in very small structures such as hippocampus and amygdalae. Publication bias (unpublished data not included).

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				Psychotropic medications not correlated with regional grey matter volume differences between BPD and HC groups.	
King-Casas et al., 2008	fMRI	55 BPD (37F, 1M) 38 HCs (51F, 4M)	To investigate cooperation in BPD using an economic exchange game.	Behavioural: BPD less able to maintain co-operation and repair broken co-operation Neurological: positive association between in AI activity and input/output responses (value of monetary offers received/money offered as repayment to partner respectively) AI activity only related to output (money repaid to partner) and not input (relationship independent of medication status). Indicates BPD have low expectations of others such that low offers not seen as violation of social norms Investments levels lower for pairs with BPD player than for HC vs HC (indicator of untrustworthiness/non-cooperation) Lower levels of self-reported	Economic exchange games are not an exact replica of real-world social interaction. Monetary element may compel subjects to behave more antisocially than normal (in a bid to maximise earnings). Lack of clinical control – difficult to attribute mode of gameplay specifically to BPD.

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				trust in BPD compared to control	
Kluetsch et al., 2012	fMRI	25 BPD and 22 HCs (F) Those with a history of head trauma, chronic pain, serious medical/neurological illness, current MDD, alcohol or substance abuse/dependence, lifetime diagnosis of bipolar disorder and schizophrenia, and pain disorders, and those taking medication within two weeks of scan.	Evaluate connectivity of the default mode network (DMN; comprising the mPFC, PCC including the precuneus, inferior parietal lobule, lateral temporal cortex, and hippocampal formation) with respect to nociceptive or neutral stimuli in BPD and HC individuals.	L. retrosplenial cortex and l. sup. front. gyrus less integrated into DMN in BPD Lower DMN response to nociceptive stimuli was associated with greater symptom severity in those with BPD. L. DLPFC less connected to pCC seed region during painful vs neutral stimuli in BPD.	No non-NSSI control group – is the effect specific to BPD or BPD with self-injurious behaviour? Higher temperature used for BPD condition due to greater reported tolerance to pain, so group differences may be due to stimulus intensity as opposed to brain connectivity. Comorbid conditions may have confounded results. Further research should look at DMN connectivity in response to social/autobiographical stimuli (group differences here mediated by appraisal of stimuli as more or less self relevant/aversive).
Koenigsberg et al., 2009	fMRI	18 BPD (10F, 8M), 16 HC (9F, 7M) Those with bipolar I disorder, schizophrenia, schizoaffective disorder, substance dependence, organic mental syndromes, or substance abuse disorder in past 6 months were excluded	To understand affective instability in BPD through psychological distancing from aversive stimuli.	Distancing vs looking at negative stimuli caused increased activation of DLPFC, IPS areas, ventrolateral prefrontal cortex, and posterior cingulate/precuneus regions in both groups (both groups reported less negative affect when distancing). When viewing negative stimuli, BPD show greater activation sup. temporal gyrus,	Very small sample size so little statistical power. BPD sample also met criteria for PTSD, GAD and other Axis II disorders so results may not be exclusive to BPD. No way of definitively tested that "distancing" took place. Future studies should look at other reappraisal strategies (reinterpretation etc).

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		as were those taking psychotropic medication within two weeks of scan.		PCC, ACC, and cerebellum vs the HC. Increased amygdala activation in BPD relative to baseline during distancing vs looking. Less activation in DACC and IPS, less amygdala deactivation, greater sup. temp sulcus and sup. front. gyrus in BPD during distancing relative to looking.	
Krause-Utz et al., 2014	fMRI	20 BPD, 17 HC (F) Those with current MDD, lifetime psychotic disorder, bipolar affective disorder, mental retardation, developmental disorder, and in suicidal crisis were excluded.	To investigate resting state functional connectivity in ROIs (frontolimbic regions).	BPD showed evidence of increased amygdala-insula (as well as oFC and putamen) resting state functional connectivity (RSFC). Stronger functional connectivity between ACC and dmPFC in BPD, whereas HCs showed diminished connectivity. Decreased RSFC in between left vACC and V1, lingual gyrus and cuneus in BPD compared to controls.	Large proportion of BPD subjects reported trauma in past, associations may be linked to trauma as oppose to condition. BOLD responses of amygdala can be confounded by physiological factors such as venous drainage. Small sample size.
Kreisel et al., 2015	MRI	39 BPD (33F, 6M) and 39 HC (33F, 6M)	To investigate whether there are differences in	Hippocampal volumes did not differ across groups.	History of psychotropic use in sample – possible confounder.

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		Those with current/previous medical conditions (e.g., stroke, ischemic heart disease), history of anorexia, schizophrenia, schizoaffective disorder, major depressive episodes with psychotic symptoms, or substance abuse within the 6 months were excluded.	hippocampal grey matter volume between HCs and BPD groups.	Exploratory analyses revealed that comorbid PTSD with BPD gave rise to smaller hippocampi (head and body) than BPD without PTSD. Those with >7 DSM-IV BPD criteria showed reduced volume of head of hippocampus than those with fewer symptoms.	Several comorbid conditions in patient past including anorexia and bulimia (starvation leads to general cortical shrinkage). Further studies should look to examine whether numbers of symptom criteria fulfilled affects morphology of other structures.
Lischke, Herpertz, Berger, Domes, & Gamer, 2017	fMRI	51 BPD, 48 HCs (F) Those with schizoaffective disorder, schizophrenia or intellectual disability or taking regular medication within past 8 weeks of the scan.	To examine paralimbic activity to emotional and neutral scenes after intranasal administration of oxytocin.	OT decreased amygdala reactivity in BPD but increased reactivity in HCs. Greater baseline paralimbic activation in BPD (after placebo administration) Negative correlation between amygdala activity and gaze behaviour (greater amygdala activity implied less looking at emotive stimuli). No abnormal activity in PFC, nor atypical connectivity between paralimbic and prefrontal regions in BPD.	Did not report symptom profile nor comorbid conditions of sample thus generalisability is questionable.

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				OT regulated atypical relationship between amygdala activity and gaze behaviour across scenes in BPD group, irrespective of the valence.	
Maier-Hein et al., 2014	DTI	20 BPD adolescents, 20 HCs and 20 clinical control (mixed diagnoses) (F) Those with lifetime diagnosis of SCZ, schizoaffective disorder, bipolar disorder, pervasive developmental disorder, alcohol/drug dependence, significant neurological disease, BMI of 16.0 or lower, and IQ <85 were excluded.	To highlight BPD-specific white matter changes in adolescents	Decreased FA in fornix in BPD group compared to CC as well as white matter alterations in thalamus-hippocampus connecting tracts. No changes in FA of inferior frontal WM.	High levels of psychotropics usage in samples. Comorbid disorders such as PTSD present in BPD group so BPD-specific changes difficult to specify. Small sample size. Tractography still lacks experiential validation. Cannot generalise to male patients.
Mensebach et al., 2009	fMRI	18 BPD, 18 HCs (F) Those with infectious diseases, anorexia, SCZ, schizoaffective disorders, and MDD with psychotic symptoms, alcohol or drug dependence were	To assess whether deficits in episodic/semantic memory are present in BPD through free-recall and verbal fluency tasks.	No differences in performance across groups, both groups showed activation of bilateral frontal, temporal and limbic neocortical areas during episodic and left lateral frontal and temporal, bilateral medial frontal and left parietal neocortical regions during	Small sample size. High rates of comorbid disorders, namely PTSD, depressive and panic disorders - result cannot be exclusively due to BPD. All patients treated by DBT and psychotropics – possible confounder.

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		excluded.		semantic memory Neurally, during episodic task, BPD showed increased activation of bilateral PCC, left mid, sup temp gyri, r. inf. front. gyrus and r. ang. gyrus. During semantic memory task, BPD showed increased activation of PCC, r. fusiform gyrus, l. ACC and l. postcentral gyrus Those with BPD need to recruit additional brain structures to carry out tasks which are less neurally taxing for controls. Post hoc analyses showed no differences in performance for BPD-PTSD subjects compared to BPD.	Future research should use larger cohorts to allow for subgroup analysis by comorbidity.
Morandotti et al., 2013	MRI	18 BPD, 19 HC (F) Those with current or lifetime personality disorders, schizophrenia, schizoaffective disorder, bipolar or a	To investigate grey matter volume of vPFC in BPD and its relation to child abuse.	Right VLPFC reduced in BPD with history of childhood abuse compared to non-abuse BPD (no other pairwise comparisons significant). Aggression self-report scores (as well as irritability and	Comorbid depressive disorders present – possible confounder. Incredibly small subsample sizes, future work should carry out larger cohort studies. Child abuse history measured in hindsight using patient self-report (memories subject to

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		history of alcohol or substance abuse within the 6 months preceding the study were excluded.		negativism subscale scores) positively correlated with VLPFC volume in BPD with child abuse group. Self-reported irritability higher in abused subgroup than non-abused. Total intracranial did not differ between groups, no overall main effect of diagnosis on grey matter volume.	distortion) Child abuse in itself may relate to diminished PFC volume as no differences between BPD and HCs found.
Muller et al., 2015	MRI	34 BPD (20 F, 14M) 31 HC (16F, 15M) 17 BPD-Remission (F) Those with neurological disorders, current alcohol or drug abuse, SCZ, schizoaffective disorder, or bipolar disorder; severe medical illness, including heart problems; psychotropic medication were excluded.	To reveal neural activity underpinning distorted interoception and its relationship with emotional dysregulation in BPD.	Reduced amplitude in heart-rate evoked potentials in BPD compared to HC, BPD-remission lies between. Heart-rate evoked potentials negatively correlated with emotional dysregulation and positively correlated with AI and bilateral dACC volume. No sig relationship between HEP amplitude and amygdala/hippocampal volumes across groups and no sig. AI or ACC volume diff between both BPD groups and HC.	Only women comprise the BPD-R group so difficult to compare results from mixed group groups to same sex. Level of statistical significance taken as 0.01. No evidence as to what, if any, therapies contributed to remission status Exploratory analyses for smaller BPD-R subgroup were not corrected for multiple tests
New et al., 2013	DTI	38 BPD (14 adolescents, 24-adults)	To investigate development	Decreased bilateral FA in inf. long. fasciculus in BPD	More males in adult sample than adolescent samples – possible confounder

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		32 HCs (13 adolescents, 19-adults) (mixed gender) Those with serious head injury or neurological disorder, schizphrenia, any other psychotic disorder, bipolar disorder I or pervasive developmental disorder, and those taking medication prior to scan were excluded.	changes in WM tracts in BPD from adolescence to adulthood.	adolescents relative to HC adolescents. Higher FA in HC adolescents compared to all other groups. Lower FA in BPD adolescents compared to HC adolescents in uncinated and occipitofrontal fasciculi (temp lobe WM tracts). No between group FA differences in adults.	MDD very prevalent in BPD samples, FA may be due in part to this. Future research should include clinical control to assess whether this is disorder specific. Adult BPD unmedicated but adolescents on variety of medications (ethical concern).
Nicol, Pope, Romaniuk, & Hall, 2015	fMRI	20 BPD (17F, 3M) 16 HC (14 F, 2M) Those with bipolar I disorder or SCZ, current alcohol/drug dependency, or any neurological illness.	Examine relationships between child abuse, psychotic symptoms and brain activation to fearful stimuli in BPD	Decreased activation of r. cuneus in BPD group Sig positive correlation between physical childhood abuse (as reported by CTQ) and activation of midbrain, pulvinar, cerebellum and med. front. gyrus in response to fearful vs neutral faces. No correlation between emotional abuse and activation. Positive correlation between midbrain activation and reported psychotic symptoms.	Upwards of 60% sample on antidepressants and/or neuroleptics. 85% of sample had comorbid conditions including depressive disorders and PTSD so difficult to determine whether activation pattern specific to BPD. Disproportionately female samples. Insufficient range of CTQ scores from HCs thus cannot conclude this pattern of activation is exclusive to BPD child abuse population relative to general child abuse population.

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				No differences in activation between those treated with antipsychotics, antidepressants and other treatments.	
Niedtfeld et al., 2013	MRI	60 HC, 21 BPD-PTSD, 39 BPD (F) Those with severe medical or neurological illnesses, organic brain disease, mental retardation, medical history of skull- and/or brain-damage, pregnancy, left-handedness, pieces of metal in the body, claustrophobia, as well as those using psychotropic medication two weeks prior to the study we excluded.	To examine grey matter volume differences in BPD groups with and without comorbid PTSD relative to controls.	Smaller r. amygdala, r. hippocampus, fusiform, lingual and cingulate gyri observed in BPD relative to HC Comorbid PTSD with BPD linked to increased grey matter volume in sup. temp. gyrus and DLPFC. No subgroup differences in volume of hippocampi/amygdalae. BPD symptom severity predictor of amygdala and dorsal ACC volume (negative correlation) irrespective of comorbidity as well as smaller grey matter volume in cerebellum and fusiform gyrus.	No PTSD without BPD control group to determine whether changes specific to comorbid condition or PTSD alone. Non-PTSD group may have experienced trauma but was not considered "traumatic" enough to meet PTSD criteria. Lacked statistical corrections for multiple comparisons increasing probability of type I error.
Niedtfeld et al., 2017	fMRI	28 BPD-DBT, 15 BPD-C, 23 HC Those who are left-handed or have experienced traumatic brain injury, lifetime	To alter the neural processing of pain-mediated affect regulation post-DBT To determine the	Reduced activation of amygdala and altered left amygdala and dorsal ACC connectivity following nociceptive stimuli in BPD (inhibitory coupling), attenuation of this effect post	High percentages of BPD groups receiving pharmacotherapy – possible confounder. IQ was not controlled for. Low statistical power due to small sample size.

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		SCZ or bipolar I disorder, mental or developmental disorders, substance dependence during the last year, current severe depressive episode, and those using benzodiazepines were excluded from partaking.	effect of DBT on hot/cold pain thresholds.	DBT treatment. No main effect of treatment on pain thresholds in BPD groups.	Did not assess inter-patient variability in picture evaluation and pain perception. Future studies should aim for a double blind RCT design. Gender of sample unspecified.
Ninomiya et al., 2018	DTI	35 BPD (11F, 24M), 50 HC (17F, 33M) Those with comorbid Axis I disorders, using medication, and those suffering from alcohol or drug abuse were excluded.	To examine the effect of borderline personality disorder on white matter tract integrity.	BPD reported higher levels of anxiety, emotional abuse/neglect, self-denial, anger-hostility and depression-dejection Lower axial diffusivity in BPD cingulum, inf. fronto-occipital fasciculus and inf. long. Fasciculus AD of cingulum positively correlated with depression in BPD Physical neglect negatively correlated with AD of inf. fronto-occipital fasciculus	Small sample size. Subjects were un=medicated without comorbid conditions thus not a very representative of the average individual with BPD.
O'Neill et al., 2013	MRI	20 BPD, 21 HC (F) Those suffering from substance dependency	To examine volumetric abnormalities in hippocampus (as	BPD group scored higher on both depression scales than HCs.	All patients treated with psychotropics in past/present Future research may wish to incorporate a

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		and additional psychiatric disorders (aside from current/past comorbid medical conditions) were excluded.	well as its sub-regions), basal ganglia and ACC in BPD vs healthy conytols	No intergroup differences in total intracranial volume. Smaller bilateral hippocampal tails and l. head and body in BPD. Reductions in caudate and DLPFC of BPD group. No correlation between hippocampal volume and depression nor impulsivity scores in BPD group.	memory task to see whether hippocampal differences directly affect performance. Did not assess trauma levels in group (also known to affect size of hippocampus). Small sample size. Future studies may wish to use MRS to see how volumetric deficits influence neurometabolites in hippocampus (N-acetylaspartate (tNAA) and creatine (Cr)).
O'Neill et al., 2015	fMRI	19 HC, 17 BPD (F) Those with neurological disorders, severe medical illness, head injury, and alcohol or substance dependency were excluded (other clinical comorbidities were not reported).	To investigate between group differences in functional connectivity between emotional and ToM networks as well as in the default mode network (DMN).	Higher impulsivity, neuroticism, depression and lower extraversion in BPD group. Fewer ToM trials were reportedly understood by BPD. Decreased functional connectivity between subgenual ACC and l. sup. temp lobe, r. supramarginal parietal lobes and r. mid. CC in BPD during ToM task condition. Increased functional connectivity seen between	DMN data taken from 10s rest period within task, so not truly representative of resting state. BPD received fewer years of education than HCs thus understanding of jokes could have been impaired by this (not known if there is an interaction between years of education and ToM).

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				precuneus and l. inf. front. lobe, l. precentral/mid. front., and l. mid. occipital/superior parietal lobes particularly during rest Psychotropic usage as co-variate did not influence data.	
Prossin, Love, Koeppe, Zubieta, & Silk, 2010	PET	18 BPD, 14 HC (F) Those with any concurrent axis I and III diagnoses (except for mood disorder); history of psychosis or head trauma; and current or recent (within 3 months) illicit substance use, abuse, or dependence were exlcluded	To investigate extent to which opioid system (Mu-opioid receptors) in BPD accounts for emotion dysregulation.	Significant effect of condition on PANAS scores and of diagnosis, with BPD patients reporting more sadness after vignette. BPD showed greater binding potential than HCs in neutral state in bilateral OFC, caudate, l. amygdala and nucleus accumbens, lower binding potential in pos. thalamus. Endogenous activation for HCs observed in l. ant. thalamus, l. medial thalamus, r. hippocampus during sadness. Endogenous system activation in l. pos. thalamus, l. OFC, l. ventral pallidum, l. amygdala and l. inf. temp. cortex during sadness state for BPD group. Greater endogenous opioid	Very small sample size. Difficult to know whether neutral task conditions were adhered to.

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				system activation in BPD relative to comparison subjects during sadness in the pregenual ACC, left OFC, left ventral pallidum, left amygdala, and left ITC.	
Reitz et al., 2015	fMRI	21 BPD, 17 HC (F) Those experiencing a current episode of MDD, lifetime diagnosis of schizophrenia, bipolar, acute suicidal tendencies, major medical or neurological illness and those using psychotropic medication were excluded.	To investigate neural correlates of NSSI in BPD.	Decreased amygdala activity and regulation of functional connectivity with SFG after incision in BPD group Increase in amygdala activity for HCs over time after stress induction. HCs showed reduced amygdala-sup. front. gyrus connectivity in response to incision over sham, whereas amygdala- sup. front. gyrus connectivity increased in BPD group after incision. Steeper decline in aversive tension in BPD following incision vs sham compared to controls whereas HCs showed greater decrease in aversive tension following sham. Heart rate stayed higher in BPD after sham vs incision.	Incision was not inflicted by oneself so not truly representative of NSSI Cannot say incision directly affected stress during task as it was administered afterwards Looked at changes in ROIs, not activation produced by NSSI Cannot generalise to men nor to the average individual with BDP and depression or other comorbidities.
Richter et	MRI	20 HC, 20 BPD, 20	To investigate	No group differences in	Many concurrent disorders in both BPD and CC

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al., 2014		clinical control (F) Those with schizophrenia, schizoaffective disorder, bipolar disorder, pervasive developmental disorder, alcohol/drug dependence, or neurological disease, a BMI<16 or IQ≤85 were excluded.	differences in brain volume between adolescent BPD patients relative to healthy and clinical controls.	cortical thickness. Smaller r.hippocampus, l. orbital inf. front. gyrus in BPD and CC compared to HC. Smaller l. hippocampus, r. amygdala, r. mid. front. gyrus, and r. sup temp gyrus in BPD compared to HC (other pairwise comparisons not significant for these areas). BPD and CC differed only in r. orbital front. gyrus and l. sup parietal gyrus volume.	groups such as mood disorders, anxiety and eating disorders thus difficult to attribute results to BPD alone. Several psychotropics used in BPD group.
Ruocco et al., 2016	fNIRS	31 BPD (F) Those with psychotic disorder, current substance dependence, illness that may impact brain function (e.g., significant head trauma) or an estimated IQ <80 were excluded.	To determine factors which may predict treatment response and attrition by examining neural activation during response inhibition. To ascertain whether activation in pFC pre-DBT was associated with either reductions in self-harm with treatment or	Activation in bilateral medial/inf. frontal gyri reduced during response inhibition prior to treatment. Activity increased in these regions 7mo post treatment. Completers showed less DLPFC activation during response inhibition than non-completers (showed higher activation in mPFC and r. inf. front. gyrus.	ROI study focusing only on the frontal cortices. Prelim. Study so cannot definitively conclude that fNIRS can predict treatment outcomes. Replications using larger cohorts and RCTs necessary to validate results – may lead to clinical measure of identification of at-risk groups and early self-harm intervention.

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			treatment attrition.		
Salvador et al., 2016	Diffusion MRI	103 HC, 103 BPD (F) Those with brain trauma, neurological diseases, alcohol/ substance abuse or dependence in 6 months, current comorbid Axis I disorders or previous bipolar or psychotic disorder diagnosis.	To examine global brain connectivity (GBC) in BPD relative to HCs.	High resting state activity (fluctuations) found in the l. hippocampus and amygdala, increased functional connectivity of these regions with the anterior cingulated. White matter reductions of fractional anisotropy in corpus callosum (genu/body) but also involving part of the corona radiata, external capsule (including uncinate fasciculus and inf. fronto-occipital fasciculus), l. ant. limb of int. capsule in BPD. Greater global brain connectivity in BPD located in ant. cingulate, reduced GBC found in r. temp. lobe only, correlated with emotion regulation Reductions in global brain connectivity was not correlated with diagnosis as measured by (Diagnostic Int. for Borderlines)	Pharmacological treatment permitted. Correlations were not corrected for multiple tests. Diagnostic measures used did not explain severity of condition. Results cannot be generalised to males as sample consists solely of women. MRI sequences not powerful enough to detect changes in small brain structures.
Sato et al., 2012	MRI	25 BPD, 25 HC (F)	To explore how MRI can be used in	L. med. orbitofrontal, rostral ACC, PCC, middle temporal	Antidepressant, antipsychotic and mood stabilisers in use amongst the clinical

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		Those with axis I and II (aside from BPD) disorders were excluded.	the clinical diagnoses of BPD.	cortices and r. parahippocampal areas contain most discriminative alterations compared to HCs (volumetric differences in grey matter). Above areas purported to have discriminant clinical value.	population. No clinical control so extent to which these changes are exclusive to BPD is debatable. Cannot generalise results to males .
Scherpiet et al., 2014	fMRI	18 BPD, 18 HC (F) Those with present or previous bipolar I disorder, schizophrenia, or schizoaffective disorder were excluded.	To examine how brain activity changes when anticipating stimuli of known or ambiguous valence in BPD vs HCs.	Observed reduced signal change in l. dACC and l. MCC in BPD vs HCs when anticipated negatively-valenced stimuli Increased activation in l. pregenual ACC, l. PCC and l. visual areas such as lingual gyrus in BPD compared to HC When valence of anticipated stimuli was ambiguous compared to neutral, BPD group showed less activation in l. MCC projecting into the med. and bilateral DLPFC and caused r.inf. front. gyrus within the VLPFC and insula activation. When anticipating negative stimuli relative to neutral, BPD	Occasional usage of cannabinoids, alcohol and current depressive episodes permitted in BPD groups. Small sample size.

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				showed increased activation in r. vACC, med. front. gyrus, MPFC, r. lingual gyrus, cuneus, l. PCC	
Silvers et al., 2016	fMRI	46 attempters, 14 non-attempters (F) Those with past or present bipolar I or psychotic disorder were excluded.	To examine that which differentiates non-attempters from suicide attempters at a neural level during emotion regulation.	Both BPD groups experienced less negative affect when distancing compared to immersing. Aversive memories activated the lat. prefrontal, temp. (including the hippocampus and amygdala) and occipital cortex irrespective of diagnosis. Attempters recruited thalamus more than non-attempters, but non-attempters recruited occipital cortex more than attempters during recall. Greater activation of lat. OFC in attempters when both distancing and immersing compared to non-attempters whereas attempters showed diminished signal from the precuneus when distancing. Attempters who were successfully able to distance	Not generalisable to men. Participants simply instructed to recall aversive memories thus difficult to ensure whether or not this was adhered to. Clinical control group of attempters would have been beneficial to include. Comorbid depression present in BPD condition, no mention of other comorbidities (no demographics). Non-attempter group much smaller than attempter.

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				themselves showed recruitment of precuneus akin to non-attempters.	
Soloff, Nutche, Goradia, & Diwadkar, 2008	MRI	34 BPD (22F, 12M), 30 HC (19F, 11M) Those with a past or current Axis I diagnosis of schizophrenia, delusional (paranoid) disorder, schizoaffective disorder, bipolar disorder or psychotic depression were excluded.	To assess structural brain changes associated with BPD relative to HCs.	Bilateral reductions grey matter reductions in ventral cingulate gyrus and med. temp. lobe (such as hippocampus, amygdala, parahippocampal gyrus, and uncus). Reductions unilaterally in right insula, l. sup. temp. gyrus in BPD. Increases in grey matter volume for BPD in r. med. front. gyri, r. parietal and precuneus, l. sup. front. and l. inf. parietal gyri, l. insula and l. putamen. Gender differences within the BPD group: women had reductions in the med. temp. lobe, including the amygdala; men had less grey matter in ACC compared to HCs. When partialling out depression scores, differences in ventral cingulate became non-significant but differences	Data can be confounded by Axis I comorbidities. Larger sample studies needed to control for gender, clinical characteristics, Axis I and Axis II co-morbidities.

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				in med. temp. cortex remained.	
Soloff et al., 2012	MRI	68 BPD (16M, 52F) of whom 44 had attempted suicide. 52 HC (28M, 24F) Those with any past or current Axis I diagnosis of schizophrenia, delusional (paranoid) disorder, schizoaffective disorder, bipolar disorder, or psychotic depression, physical disorders of known psychiatric consequence and significantly reduced IQ were excluded.	To determine brain structures in BPD which differentiate attempters from non-attempters.	History of child abuse more prevalent in attempters than non-attempters. Smaller conc. of grey matter in l. insula in attempters relative to non-attempters. Greater grey matter volume of l. lingual and l. mid. temp. gyrus. Attempters with high lethality had diminished r. mid-sup. temp. gyrus, r. mid. inf. orbitofront. Gyrus, r. insular cortex, l. fusiform gyrus, l. lingual gyrus, r. parahippocampal gyrus in comparison to low lethality.	Global brain differences cannot be ascertained from ROI studies. Imbalanced gender proportions for BPD group. Comorbidities included MDD and PTSD. Structural brain changes may be an effect of consequences of suicide attempt (i.e coma etc) Results may indicate changes due to predisposition for suicidality irrespective of clinical diagnosis. ROI structural MRI studies do not imply functional impairment.
Takahashi, Chanen, Wood, Walterfang, et al., 2009	MRI	20 BPD (5M, 15F) 20 HC (5M, 15F) Those with schizophrenia spectrum disorders or affective psychoses, anorexia nervosa, or current alcohol dependence (≥ 2 months).	To examine region specific structural changes in first presentation BPD.	Shorter AI observed in BPD relative to controls, larger third ventricle, no differences in cavum septum pellucidum AI length did not differ between those with and without comorbid disorders. No significant effect of gender on midline structures.	Control sample significantly older than BPD. Small number of males could confound results. Future research needed to examine whether or not these differences limited to BPD (clinical control groups necessary).

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				Exclusions of those with reported past substance addictions did not alter findings.	
Takahashi, Chanen, Wood, Yucel, et al., 2009	MRI	20 BPD (5M, 15F), 20 HC (5M, 15F) Those with schizophrenia spectrum disorders or affective psychoses, anorexia nervosa, or current alcohol dependence (≥ 2 months).	To examine region specific structural changes in first presentation BPD.	No significant difference between groups in volume of insular cortex. No correlation between insular volume and episodes of parasuicidality, trauma, or comorbid Axis I disorders. Negative correlation between insular volume and impulsivity. Bilateral reductions in AI as well as posterior insula volume in BPD pps with violent episodes in past six months compared to non-violent BPD. Exclusions of males and participants taking antidepressants did not alter findings.	Controls significant older than BPD groups. Small sample size. BPD more heterogenous in adolescents (diagnostic methods less coherent). Impulsivity measured by way of violent episodes, manifests itself in a variety of other ways.
van Eijk et al., 2015	fMRI	Sample 1 – 18 BPD, 18 HC (F) Sample 2 – 26 BPD, 25 HC (F)	To assess response inhibition and neural correlates in BPD (without	No significant differences in fMRI BOLD signal during response inhibition across groups for all three tasks.	Small sample size (reliability improved however by two samples). Response inhibition only one aspect of

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		Those with a lifetime diagnosis of ADHD, schizophrenia or bipolar disorder, substance abuse within the last three years, or a current depressive episode in the BPD group were excluded.	ADHD) vs HC.	No significant group differences in activation of neural inhibitory network (including r. inf. front. gyrus, striatum, pre-supp. motor area), activated in both groups. Both samples differed significantly from control on self-reported impulsivity scales (UPPS and BIS-11), BPD more impulsive across all measures. Samples did not differ from controls in terms of reaction times nor commission error rate across all three tasks (no performance deficit).	impulsivity. Future work should clearly define area of impulsivity that is of interest.
Winter et al., 2017	fMRI	31 BPD-DBT, 15 BPD-C (without DBT treatment), 22 HCs (F) Left-handed subjects and those with traumatic brain injury, lifetime schizophrenia or bipolar I disorder diagnoses, mental or developmental disorders, substance	To investigate the notion that neural correlates of distraction in BPD can be altered through DBT.	BPD-DBT group showed decreased activity in right inf. parietal lobe/supramarginal gyrus during distraction with negative relative neutral stimuli, compared to HCs and BPD without treatment groups where this decrease correlated with reduction in self-reported symptom severity (DBT group greater reduction in severity than	BPD-DBT group received residential treatment compared to BPD-C group who had outpatient services. Adherence to DBT program regulations were not reported. Not generalisable to males. Small sample size of BPD-C group. Further research using another measure of

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		dependence during the last year, drug consumption in the last 2 months, current diagnosis of a severe depressive episode, and benzodiazepine use were excluded.		BPD-C). Treatment responders shown less perigenual ACC activity when viewing negative over neutral stim (less sensitive to emotionality during distraction). Non-responders showed elevated activity in AI when viewing negative over neutral stimuli (not shown in DBT responders)	emotion regulation separate from distraction needed.
Zhou et al., 2017	MRI	30 BPD, 32 HC Those with past or current Axis I diagnosis (e.g., schizophrenia, delusional (paranoid) disorder, schizoaffective disorder or bipolar disorder were excluded.	To investigate the notion that those with BPD have reduced volume of the fronto-limbic cortices.	Greater instance of insecure attachment as well as emotional and physical neglect, emotional and physical abuse in BPD. Greater frontolimbic cortex asymmetry observed in BPD than HC: thinner cortices in l. ACC and less surface area and grey matter volume in l. AI of BPD groups. Asymmetry of ACC and AI positively correlated with attentional impulsivity.	Cross-sectional rather than longitudinal study. Future work should aim to confirm whether volumetric differences are congenital or acquired after illness onset. Study focused on ACC and AI which are two small regions in larger frontolimbic network of brain.

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