DE GRUYTER Reviews in the Neurosciences

A Systematic Review of the Neurobiological Underpinnings of Borderline Personality Disorder (BPD) in Childhood and Adolescence

Journal:	*Reviews in the Neurosciences*
Manuscript ID	RNS.2016.0026.R1
Manuscript Type:	REVIEW
Date Submitted by the Author:	n/a
Complete List of Authors:	Winsper, Cathy Marwaha, Steven Lereya, Tanya Thompson, Andrew Eyden, Julie Singh, Swaran
Keywords:	Systematic Review, Borderline Personality Disorder, Childhood, Adolescence

A Systematic Review of the Neurobiological Underpinnings of Borderline Personality Disorder (BPD) in Childhood and Adolescence

RUNNING HEAD: NEUROBIOLOGY OF YOUTH BPD

Catherine Winsper, Ph.D., Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick;

Steven Marwaha, Ph.D., MRCPsych, MSc, MBBS, Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick;

Suzet Tanya Lereya, Ph.D., Evidence Based Practice Unit (EBPU), University College London and the Anna Freud Centre, London, UK;

Andrew Thompson, MD, MBBS, MedSci, FRCPsych, Division of Mental Health and Wellbeing Warwick Medical School, University of Warwick;

Julie Eyden, MSc. Department of Psychology, University of Warwick;

Swaran P Singh, DM. Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick.

Correspondence: Dr Cath Winsper, Warwick Medical School, University of Warwick, Coventry, UK, CV4 7AL email: catherine.winsper@warwick.ac.uk; tel: 024 765 74886.

Funding: Prof. Singh receives funding from the National Institute for Health Research (NIHR) Collaborations for Leadership in Applied Health Research and Care West Midlands (CLAHRC-WM) initiative. The views expressed are those of the authors and not necessarily those of the CLAHRC-WM collaborative organisations, the NIHR, or the Department of Health.

Declaration of Interest: C.W; S.M; S.T.L; A.T; J.E; & S.P.S report no conflict of interest.

Word count (excluding references and abstract):

Abstract: 244; **Body text:** 6, 951

Abstract

Contemporary theories for the aetiology of Borderline Personality Disorder (BPD) take a lifespan approach asserting that inborn biological predisposition is potentiated across development by environmental risk factors. In this review we present and critically evaluate evidence on the neurobiology of BPD in childhood and adolescence, compare this evidence to the adult literature, and contextualise within a neurodevelopmental framework. A systematic review was conducted to identify studies examining the neurobiological (i.e., genetic, structural neuroimaging, neurophysiological and neuropsychological) correlates of BPD symptoms in children and adolescents aged 19 years or under. We identified, quality assessed, and narratively summarised 34 studies published between 1980 and June 2016. Similar to findings in adult populations, twin studies indicated moderate to high levels of heritability of BPD, and there was some evidence for gene-environment interactions. Also consistent with adult reports, some adolescents with BPD demonstrated structural (grey and white matter) alterations in frontolimbic regions, and neuropsychological abnormalities (i.e., reduced executive function and disturbances in social cognition). These findings suggest that neurobiological abnormalities observed in adult BPD may not solely be the consequence of chronic morbidity or prolonged medication use. They also provide tentative support for neurodevelopmental theories of BPD by demonstrating that neurobiological markers may be observed from childhood onwards, and interact with environmental factors to increase risk of BPD in young populations. Prospective studies with a range of repeated measures are now required to elucidate the temporal unfurling of neurobiological features, and further delineate the complex pathways to BPD.

Keywords: Neurobiology; Borderline Personality Disorder; Childhood; Adolescence; Systematic Review

Introduction

Borderline Personality Disorder (BPD) is a serious and enduring mental disorder affecting from 1 to 6% of the general population (Grant et al., 2008; Lenzenweger, Lane, Loranger, & Kessler, 2007; Trull, Jahng, Tomko, Wood, & Sher, 2010). Contemporary theories for the aetiology of BPD take a lifespan approach, proposing that an inborn tendency towards emotionality is potentiated across early development by environmental risk factors (Crowell, Beauchaine, & Linehan, 2009; Hughes, Crowell, Uyeji, & Coan, 2012). Within this context, BPD is unlikely to appear *de novo* in early adulthood (Paris, 2013), but may be considered as the continuation of a collection of BPD precursor symptoms that first emerge during childhood or early adolescence (Crowell et al., 2009; Winsper, Marwaha, et al., 2015).

A growing body of studies have demonstrated the clinical utility, validity and reliability of the adolescent (Kaess, Brunner, & Chanen, 2014; Sharp & Fonagy, 2015; Winsper et al., 2016) and to a lesser extent child (Hawes, 2014; Winsper et al., 2016) BPD phenotype. Recent systematic evidence indicates that the diagnostic stability of BPD in adolescence is largely comparable (though slightly attenuated) to that in adulthood, and that a considerable proportion of adolescents continue to manifest BPD symptoms up to 20 years later (Winsper, Marwaha, et al., 2015). Reflecting these findings, national treatment guidelines and classification systems have recently confirmed the legitimacy of the BPD diagnosis in adolescence (American Psychiatric Association, 2013; NICE, 2009; Tyrer, Crawford, & Mulder, 2011). Nevertheless, many clinicians remain reluctant to diagnose the disorder prior to age 18 (Griffiths, 2011; Laurenssen, Hutsebaut, Feenstra, Van Busschbach, & Luyten, 2013), meaning that adolescents manifesting BPD symptoms may be misdiagnosed (Paris, 2013) and opportunities for early intervention missed (Newton-Howes,

Clark, & Chanen, 2015). Increasing awareness and understanding of the biological correlates of youth BPD may help to reduce clinical reluctance, and further our understanding of the aetiological mechanisms and pathological processes germane to the development of BPD (Goodman, Mascitelli, & Triebwasser, 2013).

Our understanding of the potential neurobiological underpinnings of BPD in adulthood has grown rapidly over the past few decades (Krause-Utz, Winter, Niedtfeld, & Schmahl, 2014; van Zutphen, Siep, Jacob, Goebel, & Arntz, 2015). However, the extant literature remains relatively underdeveloped in comparison to that of other mental disorders (e.g., dementias, depression, and schizophrenia). Over recent years a number of reviews have been published collating evidence on the genetic (Amad, Ramoz, Thomas, Jardri, & Gorwood, 2014), and structural and functional brain abnormalities (Krause-Utz et al., 2014; Ruocco, 2005; Ruocco, Amirthavasagam, & Zakzanis, 2012; van Zutphen et al., 2015) associated with adult BPD. While reviews have pointed towards several inconsistencies across studies (Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013), there are some replicated findings (Krause-Utz et al., 2014; van Zutphen et al., 2015). Familial and twin studies indicate a genetic component to adult BPD (Amad et al., 2014). Candidate genes have been investigated largely within the serotonin system, though no clear gene has been identified highlighting the need to consider epigenetic variability (Newton-Howes et al., 2015) and “plasticity” genes (Amad et al., 2014). Neuroimaging studies suggest structural and functional abnormalities in the frontolimbic network, including hyper-reactivity of regions involved in emotional processing (e.g., insula, amygdala, hippocampus) and diminished recruitment of regulatory control processes, e.g., anterior cingulate cortex, medial frontal cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex (Krause-Utz et al., 2014; Christian Schmahl & Bremner, 2006). On a neurochemical level, altered function in

neurotransmitter systems including the serotonin, glutamate and GABA systems has been observed in BPD patients (Krause-Utz et al., 2014). In a synthesis of 10 studies, Ruocco (2005) reported that adult BPD patients performed more poorly than controls across several neuropsychological domains (i.e., cognitive flexibility, planning, attention, learning and memory). Studies also suggest disturbances in social cognition including the recognition (i.e., negative bias) of facial emotions (Domes, Schulze, & Herpertz, 2009), thoughts, and intentions (Preißler, Dziobek, Ritter, Heekeren, & Roepke, 2010). Studies examining mentalisation (i.e., recognition of the mental states of social interaction partners), however, indicate that adults with BPD may have superior abilities (Arntz & Veen, 2001; Fertuck et al., 2009; Franzen et al., 2011).

Examining the neurobiological correlates of BPD features in younger populations in the early stages of the disorder may help reduce the likelihood of confounders, including duration of illness, prolonged use of medication, and cumulative trauma experiences (Chanen, Velakoulis, et al., 2008; Richter et al., 2014). Furthermore, considering younger populations will allow for the prospective assessment of neurobiological and environmental precursors (and their interactions) to shed light on the developmental pathways to BPD at both the biological and behavioural level (Hughes et al., 2012).

In 2013, a narrative review examined aspects of the neurobiological basis of adolescent-onset BPD (Goodman et al., 2013). Although the authors' conclusions were very tentative due to the limited number of available studies at the time, they emphasised the importance of studying the biological basis of adolescent BPD to inform screening, treatment and preventive strategies. In the current study we expand on this review by taking advantage of the recent wave of research on BPD in childhood and adolescence, and

present a systematic evaluation of all studies examining the neurobiological correlates of BPD in individuals 19 years of age and under. Specifically, we aimed to:

1) Ascertain the extent to which adolescents with BPD share similar neurobiological features (i.e., genetic underpinnings, neurophysiology, brain structures, and neuropsychological processes) to adults with BPD.
2) Situate our findings within a neurodevelopmental perspective of BPD.
3) Critically evaluate the extant literature to set out a framework for future research.

Methods

Search strategies

We used PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009) to describe our procedures and results. We searched MEDLINE, EMBASE, PsychINFO and PubMed databases to identify studies reporting on BPD features in children and adolescents (i.e., individuals 19 years and under) published in English between 1980 and 28th January 2014. We chose 1980 as the earliest date for inclusion to parallel when BPD was first introduced as a disorder in the Diagnostic and Statistical Manual (APA., 1980). The search terms (borderline* OR "emotionally unstable personality disorder" OR BPD) AND (adolescen* OR child* OR young* OR youth* OR teen* OR student*) were entered. To ensure comprehensive coverage of the neurobiological literature we updated our search to include studies published between 1980 and 4th June 2016, and cross-referenced returns against our previous search. For the updated search we used the following search strings: (BPD OR "emotionally unstable personality" OR borderline*) AND (child* OR adolescen* OR youth* OR young* OR teen* OR

student*) AND (genes OR gene OR genetic* OR neuro* OR imaging OR biological). Reference lists of included studies were inspected for relevant titles. We also examined the reference lists of related narrative reviews as a cross check (Brunner, Henze, Richter, & Kaess, 2015; Chanen, Jovev, McCutcheon, Jackson, & McGorry, 2008; Goodman et al., 2013).

Study Selection

A study was considered for selection if it met all the following a priori criteria:

(1) Original research was presented;

(2) Participants were 19 years of age or younger at initial assessment (based on the World Health Organisation (2016) definition of childhood and adolescence);

(3) The study was published in English;

(4) The study provided any information on the neurobiological (i.e., genetic, neurophysiological, structural brain characteristics, neuropsychological) correlates of BPD.

Studies were excluded if:

(1) BPD was not the primary focus of the study (e.g., associations pertained to all Cluster B personality disorders rather than BPD specifically);

(2) They were case studies without statistical analysis;

Screening procedure

After removal of all duplicates, abstracts were retrieved using the initial search strategy. If a title appeared potentially eligible but no abstract was available, the full-text article was retrieved. C.W and T.L independently scanned 100% of the titles and abstracts to identify relevant articles for full text retrieval, and these were read by C.W to assess for inclusion in the review. S.M independently reviewed 50% of the full text articles as a reliability check.

Data extraction and quality assessment

A data extraction form was developed prior to full text review. It included author details, country of study, sample characteristics (i.e., age, sex, and clinical status), study design, BPD assessment tool, methodology of neurobiological assessment, and main findings. A quality assessment form was also produced based on the Newcastle-Ottawa Scale (NOS) (Wells et al., 2000), which can be adapted for the assessment of non-randomised cross-sectional and case control studies. For case control studies we assessed the quality domains of selection (maximum of 4 stars), comparability (maximum of 2 stars) and exposure (maximum of 3 stars). For cross-sectional studies which did not use a case control design we used the adapted scale by Herzog et al. (2013), covering the domains of selection (maximum of 5 stars), comparability (maximum of 2 stars), and outcome (maximum of 3 stars).

Results

Search results

Of the original 8,195 abstracts scanned, 209 text articles were selected for full text retrieval (**Figure 1**). There was a high level of agreement between raters (Kappa = 0.82). The authors met to discuss discrepancies regarding selected articles, which were largely due to uncertainty regarding sample characteristics (e.g., the sample was primarily defined according to another mental illness) or age (the age was not reported in the abstract). If there was doubt over whether an abstract should be included for full text retrieval, the decision was made to include. Of the 209 full text articles reviewed, we identified 25 studies providing information on the neurobiological correlates of BPD. We identified a further three relevant studies via hand search (Coolidge, Thede, & Jang, 2001; Houston, Ceballos, Hesselbrock, & Bauer, 2005; Jovev et al., 2008). The 50% full text reliability check indicated a high level of agreement between raters (Kappa=0.80). The cross-referenced updated search

conducted on June 4th 2016 yielded a total of 12, 367 abstracts (i.e., when the original and updated searches were combined and all duplicates removed). We identified a further 6 articles from the updated search (Cicchetti, Rogosch, Hecht, Crick, & Hetzel, 2014; Conti et al., 2013; Kaess, Parzer, Koenig, Resch, & Brunner, 2016; Kalpakci, Vanwoerden, Elhai, & Sharp, 2016; Richter et al., 2014; Zhang et al., 2015). Therefore, a total of 34 studies are included in the review. Please see **Table 1** for a description of studies and summary of main findings.

Studies comprised a mix of clinical, high-risk and non-clinical populations. Distribution of gender within samples varied across studies, with most studies having a preponderance of female participants (with the exception of two early studies which had a majority of male participants (Paris, Zelkowitz, Guzder, Joseph, & Feldman, 1999; Zelkowitz, Paris, Guzder, & Feldman, 2001)). All studies, with the exception of two longitudinal studies (Belsky et al., 2012; Bornovalova, Hicks, Iacono, & McGue, 2009) were cross-sectional in design. Cross-sectional studies were a mix of case control studies and those assessing associations between neurobiological features and continuous BPD outcome measures (i.e., scales of BPD symptoms).

Twenty six studies utilised adolescent samples (i.e., youth aged 12 years or older), and eight child samples (or a mixture of children and adolescents) ranging from 4 to 17 years of age (Cicchetti et al., 2014; Coolidge, Segal, Stewart, & Ellett, 2000; Coolidge et al., 2001; Hankin et al., 2011; Jovev et al., 2013; Paris et al., 1999; Rogosch & Cicchetti, 2005; Zelkowitz et al., 2001). The majority of the adolescent studies assessed BPD features with the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II), commonly used in adult BPD studies (Maffei et al., 1997). Studies with children used a range of validated BPD assessment tools, some of which had been adapted from widely used adult

diagnostic tools, i.e., the Child version of the Diagnostic Interview for Borderlines (C-DIB), which has five sub-scales incorporating social adaptation, impulsivity, affect, psychosis and interpersonal relations (Paris et al., 1999; Zelkowitz et al., 2001). Others were adapted from dimensional assessments used in adult BPD populations. The Borderline Personality Features Scale for Children (BPFS-C) developed by Crick, Murray–Close, and Woods (2005) covered the four domains of: affective instability, identity problems, self-harm, and negative relationships. The Children in the Community-Self Report described in Crawford et al. (2005) was based on the DSM-IV conceptualisation of BPD.

We organised the studies into three main types:

(1) Those reporting on the genetic underpinnings (i.e., heritability, molecular genetic studies; gene-environment interactions) of BPD;

(2) Those exploring neurophysiological correlates (i.e., electrophysiological measures, physiological measures) and brain structures of BPD;

(3) Those examining performance on neuropsychological (i.e., cognition, emotion recognition, mentalisation) tasks.

Quality assessment of studies

Table 2 presents a summary of the quality assessment for case control studies, and **Table 3** a summary of cross-sectional studies (e.g., those assessing associations with continuous BPD scales). Studies varied widely in quality according to the Newcastle Ottawa Scale (NOS), with scores ranging from 2 to 7 (out of a possible 9/10). Most studies demonstrated some degree of *selection bias*, usually in terms of issues with the representativeness of cases (e.g., self-

selection bias). A number of studies also demonstrated *comparability bias* by not sufficiently controlling for pertinent confounding variables (e.g., whole brain volume).

The genetic underpinnings of BPD in childhood and adolescence

Family studies

We identified three studies examining the heritability of BPD in young twin populations. Coolidge et al. (2001) reported that the monozygotic (MZ) correlation for BPD symptoms in a sample of 4 to 15 years olds was significantly greater than the dizygotic (DZ) correlation (r_{MZ} = 0.70; r_{DZ} =0.39). Structural equation modelling confirmed a substantial genetic component, with a heritability figure of 0.76. In the first of two prospective studies, Bornovalova et al. (2009) examined heritability rates at 4 discrete periods from 14 to 24 years of age. MZ correlations were higher than DZ correlations: 14 years (r_{MZ} = 0.48; r_{DZ} =0.38); 17 years (r_{MZ} = 0.50; r_{DZ} =0.30); 20 years (r_{MZ} = 0.43; r_{DZ} =0.35) and 24 years (r_{MZ} = 0.48; r_{DZ} =0.22). Heritability figures ranged from a moderate 0.3 to 0.5 across the four time points, with a trend towards increased heritability from age 14 to 24. Finally, in a twin sample of 12 year olds, Belsky and colleagues (2012) found a higher correlation of BPD symptoms between MZ (0.66) than DZ twins (0.29). Biometric modelling indicated that genetic factors accounted for 66% of the variance in BPD symptoms.

Molecular genetic studies

We identified two molecular genetic studies examining associations between candidate genes and BPD symptoms in childhood and adolescence (Cicchetti et al., 2014; Hankin et al., 2011). Hankin and colleagues (2011) used two independent samples of 9 to 15 year olds to assess the association between the 5-HTTLPR serotonin transporter gene and BPD symptoms. Participants were divided into groups according to variants of the 5-HTTLPR gene

(2 short alleles; 2 long alleles; or 1 short and 1 long allele). In both samples, mean BPD traits significantly differed as a function of 5-HTTLPR polymorphism (Sample 1, $F_{2, 239}$ =4.33, p = .01; Sample 2, $F_{2, 144}$ =4.97, p= .008). Participants with two short alleles exhibited significantly higher BPD trait scores than participants with two long alleles. Participants carrying one short and one long allele (S/L) exhibited intermediate BPD traits.

Cicchetti et al. (2014) examined associations between two candidate genes (oxytocin receptor gene and FKBP5) and BPD symptoms in a sample of 8 to 12-year-old children. The authors selected the oxytocin receptor gene (OXTR) due to its relation to variation in social behaviour, attachment, affiliation and aggression; and the FKBP5 gene due to its role in the pathogenesis of stress-related psychopathology. There were no significant main effects of OXTR or FKBP5 on BPD symptoms in childhood.

Gene-environment interactions

Belsky et al. (2012) prospectively demonstrated the impact of genetic vulnerability in combination with environmental risk on the development of BPD in early adolescence. Young adolescents with a genetic risk (i.e., a family history of psychiatric disorder) and exposed to physical maltreatment had a 13-fold increased risk of being in the extreme (>95th percentile of symptoms) BPD group. In contrast, those without a genetic risk but exposed to harsh parenting had only a two-fold increased risk of being in the extreme BPD group. A similar effect was observed for high maternal negative expressed emotion, with a 15-fold increased risk for adolescents with genetic risk and exposure to negative expressed emotion compared to a five-fold increased risk for those just exposed to high expressed emotion.

Cicchetti et al. (2014) tested three-way interactions between variations in genotype (OXTR and FK506), environmental risk, and gender on the development of BPD symptoms in late childhood. Results indicated differential effects for males and females. For girls, effects

were most consistent with a stress-diathesis effect, i.e., genotype (OXTR: AG-AA genotype; FK506: 1 to 2 copies of the CATT haplotype) was associated with BPD symptoms in the presence of maltreatment only. For boys, observed effects were most consistent with a differential susceptibility effect (i.e., genetic predisposition increased susceptibility for both better and worse outcomes). Boys exposed to maltreatment had significantly higher BPD scores than non-maltreated boys if they had the GG genotype of OXTR (there was no difference between maltreatment groups for those with the AG-AA genotype). For FK506, maltreated boys had significantly higher BPD scores than non-maltreated boys if they had the zero copy CATT haplotype (maltreatment groups did not differ for boys with the one to two copies of the CATT haplotype).

Neurophysiological correlates and brain structures

Neurophysiological correlates

We identified 2 studies using P300 Event Related Potential (ERP) measurements to examine differences in brain maturation between adolescents with and without BPD (Ceballos, Houston, Hesselbrock, & Bauer, 2006; Houston et al., 2005). In a sample of 14 to 19 year old girls, Houston et al. (2005) used a visual oddball task to compare P300 amplitudes between 4 groups (BPD <16.5 years; BPD>16.5 years; no BPD <16.5 years; no BPD>16.5 years). ANCOVAs, adjusting for comorbid conduct disorder and depression symptoms, demonstrated a significant interaction. Girls with BPD features did not evidence the expected age-related reductions in P300 amplitude, suggesting impairment in brain maturation. Ceballos et al. (2006) failed to find similar neurophysiological abnormalities in BPD adolescents in the absence of co-morbid conduct disorder symptoms. Again using the visual oddball paradigm in a sample of 14 to 19 year olds, P300 amplitudes were compared

across 4 groups (BPD only, Conduct Disorder only, BPD plus CD, no BPD or CD). With increasing age, abnormal brain maturation (i.e., lack of age related reductions) was only observed in the BPD plus CD and CD groups. The authors attributed the discrepancy in results (i.e., lack of impairment in BPD only subjects) to sex. Indeed, when they reanalysed their data with the females only (Houston's study used females only) they observed the expected impairment in brain maturation in the BPD only group.

We identified one study examining dysfunction of the neurosteroid system in adolescents with BPD (Conti et al., 2013). The authors compared BPD patients (M_{age}=15.5; SD=1.2) to healthy controls on diazepam binding inhibitor (DBI) and dehydroepiandrosterone sulphate (DHEA-S) plasma levels, and also cortisol to DHEA-S molar ratio (CDR). There was no difference between groups in DBI plasma levels; however, BPD patients had significantly increased (approx. 70%) DHEA-S levels (t=3.023; p=.0054) and decreased CDR (t=2.401; p=.0235). The authors hypothesised that DHEA-S may represent a trait marker for the altered stress response observed in BPD.

Brain structures

We identified fourteen structural neuroimaging studies examining whether adolescents with BPD demonstrate brain abnormalities. Eight studies were derived from the Orygen Youth Health Research Centre in Melbourne (Chanen, Velakoulis, et al., 2008; Garner et al., 2007; Jovev et al., 2008; Takahashi, Chanen, Wood, Walterfang, et al., 2009; Takahashi et al., 2010; Takahashi, Chanen, Wood, Yücel, et al., 2009; Walterfang et al., 2010; Whittle et al., 2009) and three from the University of Heidelberg (Brunner et al., 2010; Maier-Hein et al., 2014; Richter et al., 2014). These two study groups used the same respective cohort of patients for each study, but examined different brain structures or utilised varying imaging technologies. Two studies were derived from the Mount Sinai Hospital in New York

(Goodman et al., 2011; New et al., 2013). Of note, the adolescents in these two studies were all (with the exception of one) co-morbid for Major Depressive Disorder. In view of the very high levels of comorbidity observed between BPD and depression in adolescence (Glenn & Klonsky, 2013), and because these studies adjusted for depression symptoms within the analysis, they were included in the review. Results from these two studies should be interpreted with caution, however, as they are not directly generalisable to all adolescents with BPD features (i.e., the patients in these studies likely represent the severe end of the spectrum of BPD psychopathology (Goodman et al., 2011)). The final study utilised a high risk sample selected from sixth grade students in Melbourne, Australia (Jovev et al., 2013).

Grey matter structures of the frontolimbic network

Two studies reported reductions in Orbitofrontal Cortex (OFC) volume in BPD compared to control groups (Brunner et al., 2010; Chanen, Velakoulis, et al., 2008), while one study reported no difference in OFC between groups (Goodman et al., 2011).

Using Region of Interest (ROI) methodology, Chanen, Velakoulis, et al. (2008) found that 15-19 year old BPD patients demonstrated significant OFC grey matter loss in comparison to healthy controls (HCs): $F_{1.35}$=8.62, p=.006. Inspection of the data indicated a reversal of the normal asymmetry associated with BPD, with a reduction in the *right* OFC. Brunner et al. (2010), using Voxel-Based Morphometry (VBM) techniques, found that BPD patients aged 14-18 years exhibited significant volume reductions in the *left* OFC in comparison to healthy (but not clinical) controls: t =6.11, p=.002. Conversely, Goodman et al. (2011) found no difference in OFC grey matter volume between BPD patients with co-morbid major depressive disorder (M_{age}=15.8, SD=1.1) and HCs using ROI methodology.

Two studies reported anterior cingulate (AC) volume reductions (Goodman et al., 2011; Whittle et al., 2009) in adolescents with BPD in comparison to controls, while one study did not find any significant difference between groups (Brunner et al., 2010). Using a subsample of female patients from the Melbourne group, Whittle et al. (2009) reported a decrease in left AC cortex volume (across limbic and paralimbic regions) in patients with BPD compared to HCs: t_{29} =5.82, p=.023. Post hoc partial correlations controlling for age and whole brain volume indicated that volumetric change was significantly correlated with parasuicidal behaviour: r_s = -.675 and impulsivity: r_s=.575. Goodman et al. (2011) found that BPD/MDD patients had smaller relative volume (averaged across grey and white matter) in Brodmann area 24 (i.e., part of the anterior cingulate) in comparison to HCs: $F_{4, 96}$ =3.43, p=.03. Of note, smaller BA 24 volume was associated with BPD (r= -.45, p=.022) but not MDD indices. Conversely, Brunner et al. (2010) did not report any ACC abnormalities in BPD patients in comparison to healthy or clinical controls (CCs).

Two studies assessed dorsolateral cortex (DLPFC) volume in adolescents with BPD. Brunner et al. (2010) reported bilateral volume reduction of the DLPFC in adolescents compared to healthy, but not clinical, controls. In contrast, Goodman et al. (2011) did not find any difference in DLPFC volume in BPD/MDD patients compared to HCs.

In another Orygen research group study, Takahashi, Chanen, Wood, Yücel, et al. (2009) found no significant difference in insular cortex volume (a frontolimbic integration cortex) between BPD patients and HCs. BPD patients reporting violent episodes during the previous 6 months, however, had a smaller insular volume bilaterally than those who had not been violent: $F_{1, 16}$ = 5.56, p=.031.

Only one (Richter et al., 2014) of three studies comparing amygdala volume in adolescents with BPD to controls reported a significant group difference. Chanen,

Velakoulis, et al. (2008) did not find any differences in amygdala volume between patients with BPD and HCs (p>.05). Sub-analysis with female BPD patients only, however, demonstrated a significant negative correlation between right amygdala volume and BPD total symptom score: r= -.613, p=.026. Similarly, Brunner et al. (2010) found no significant difference in amygdala volume between BPD patients, CCs and HCs. In a follow-up to Brunner et al. utilising *FreeSurfer* software to reanalyse the data, Richter et al. (2014) found volumetric reductions in the right amygdala of BPD patients compared to healthy and clinical controls. These differences only reached significance for comparison with the HC group: BPD=1613 (49.58) mm^3; HC=1777 (38.16) mm^3; p =.024. There was no significant difference between CC and HC groups in amygdala volume: CC=1712.45 (33.78) $mm.^3$

Four studies assessed hippocampal volume in adolescents with BPD; two reported significant differences between BPD patients and controls (Jovev et al., 2013; Richter et al., 2014) and two reported no difference (Brunner et al., 2010; Chanen, Velakoulis, et al., 2008). Chanen, Velakoulis, et al. (2008) found no difference in hippocampal volume between patients with BPD and HCs (p<.05) using ROI methodology. Similarly, Brunner et al. (2010) reported no hippocampal volume differences between BPD, CC and HC groups using VBM methodology. In re-analysis with the same sample, but using *FreeSurfer* technology, Richter et al. (2014) demonstrated group (i.e., BPD, CC, HC) differences in right and left hippocampal volumes, with BPD patients evincing the smallest hippocampal volume. Post hoc tests revealed significant group differences between patients with BPD and HCs in both the right (BPD=3977.65 [70.49] mm^3 versus HC=4339. 8 [74.66] mm^3; p=.003) and left (BPD= 3748.75 [82.26] mm^3 versus HC=4167.5 [81.87] mm^3; p=.008) hippocampus, as well as group differences between the CC (4066.35[66.47] mm^3; p=.033) and HC in the right hippocampus. Finally, Jovev et al. (2013) reported an association between atypical

rightward hippocampal asymmetry and BPD symptoms in 11-13 year olds, but only via the moderating effects of temperament (i.e., there was no significant main effect of hippocampal asymmetry on BPD symptoms). Two significant three-way interactions (i.e., sex, temperament and hippocampal asymmetry) were observed. Boys were more likely to have BPD symptoms if they were high on affiliation (representing a desire for closeness with others) and had atypical rightward hippocampal asymmetry. Girls were more likely to have elevated BPD symptoms if they were low in effortful control (representing poor self-regulation) and had atypical rightward hippocampal asymmetry.

White matter structures of the frontolimbic network

Brunner et al. (2010) failed to find any differences in white matter structures between BPD, CC, and HC groups using VBM. In a follow-up study, Maier-Hein et al. (2014) analysed the same data using Diffusion Tensor Imaging (DTI). Tractography methods were used to explore group differences in the fornix (white matter tract of the limbic system), cingulum (a major frontolimbic tract) and uncinate fasciculus (a major frontotemporal tract). Tract-Based Spatial Statistics (TBSS) analysis was used for a global (exploratory) assessment. The BPD group demonstrated significantly lower fractional anisotropy (reflecting lower myelination and organised directionality of white matter tracts) in the bilateral fornices in comparison to clinical (x^2 =13.11, p=.009) and healthy (x^2=4.52, p=.097) controls. TBSS indicated disorder specific white matter alterations in the long association bundles interconnecting the heteromodal association cortex, and in connections between the thalamus and hippocampus. The authors concluded that a large-scale network of emotion processing is disrupted in adolescents with BPD. In a second DTI study examining adolescents with BPD, New et al. (2013) reported bilateral tract specific decreased fractional anisotropy (FA) in the inferior longitudinal fasciculus (ILF) (i.e., a fibre bundle

connecting the temporal lobe and occipital lobe) of BPD adolescents (M_{age}=15.8 [1.1]) in comparison to HCs (left ILF: t=3.13; p<.005; right ILF: t=2.92; p<.008). Follow-up TBSS analysis indicated a lower FA in BPD adolescents in comparison to HCs in the uncinate and occipitofrontal fasciculi (i.e., the white matter tracts connecting parts of the limbic system to the OFC among other frontal regions). The authors hypothesised that these findings indicate a possible neural substrate for the previously reported OFC-amygdala disconnect in adults with BPD (New et al., 2007).

Using the Orygen sample, Walterfang et al. (2010) failed to find a significant difference in corpus callosum size or shape between BPD and HC groups.

Other brain regions

Again using the sample from the Orygen research group, Takahashi, Chanen, Wood, Walterfang, et al. (2009) examined several midline brain structures, including the adhesio interthalamica (AI), the cavum septum pellucidum (CSP), and the third ventricular. Compared to the HCs, the length of the AI was significantly shorter ($F_{1, 34}$ = 11.45, p=.002) and the third ventricle significantly larger ($F_{1, 34}$ = 4.56, p=.040) in the BPD group. In a subsequent study led by Takahashi (Takahashi et al., 2010), BPD patients and healthy controls did not significantly differ in superior temporal gyrus (STG) volumes (p>.05). BPD patients with a history of violent episodes, however, had a smaller left caudal STG volume than those without violent histories ($F_{4, 72}$= 2.81, p=.032). Walterfang et al. (2010) found no group differences in lateral ventricular volume between BPD and HC groups.

Indicators of neuroendocrine functioning

Only two studies have considered potential markers of Hypothalamic-Pituitary-Adrenal (HPA) axis functioning. In the first from the Orygen research group, Garner et al. (2007) examined whether adolescent patients with BPD differed from HCs in pituitary gland

volume (PGV). There were no significant differences in PGV between BPD patients and HCs ($F_{1, 39}$ = 0.5, p=.5). In an extension to this study with just the BPD patient group, Jovev et al. (2008) found that lifetime parasuicidal events significantly predicted increased PGV (β = 71.76 [29.78], p=.029) following adjustment for age, sex and internalising problems.

The neuropsychological correlates of BPD in childhood and adolescence

Neurological soft signs/executive function

Seven studies examined neuropsychological soft signs (NSS) in youth with BPD (Belsky et al., 2012; Coolidge et al., 2000; Kaess et al., 2016; Paris et al., 1999; Rogosch & Cicchetti, 2005; Zelkowitz et al., 2001; Zhang et al., 2015).

Belsky et al. (2012) examined the prospective association between executive functioning (maze task, non-verbal Stroop task, and sentence working memory task) in early childhood and BPD symptoms. Executive functioning at 5 years was significantly negatively (though weakly) correlated with BPD symptoms at 12 years (r= - .06, p < .05).

In two related studies (Paris et al., 1999; Zelkowitz et al., 2001), Paris and colleagues examined deficits in executive function using the Wisconsin Card Sorting Task (WCST) and Continuous Performance Test (CPT). Children with BPD aged 7 to 12 years of age significantly differed from clinical controls on a number of WCST (i.e., poorer learning efficiency, more perseverative responses and more errors) and CPT (i.e., more risk taking, slower and more inconsistent responses) tasks (Paris et al., 1999). Extending these findings, Zelkowitz et al. (2001) reported that the CPT index (OR=1.12; 95% CI=1.01, 1.23) and WCST learning efficiency (OR=7.08; 95% CI=1.98, 25.35) remained significant predictors of borderline pathology after adjustment for psychosocial risk factors (i.e., sexual abuse and witnessing violence).

Coolidge et al. (2000) compared the parent-reported neurocognitive skills of 5 to 17 year olds with BPD to those with other personality disorders. Children and adolescents with BPD demonstrated significantly higher scores on the executive function deficits (M=63.1 [SD=10.6] vs. M=52.3 [SD=9.8], *p*=.001) and mild neurocognitive disorder (M=66.3 [SD=14.7] vs. M=54.4 [SD=10.7], *p*=.005) scales than controls with other personality disorders. Rogosch and Cicchetti (2005) compared low income children aged 6-12 high in BPD traits to those low in BPD traits on alerting, orienting and conflict attention network tasks. There were no group differences for alerting and orienting; however, children with BPD had significantly higher conflict network scores ($F_{1, 359}$ = 10.66, *p* =.001) interpreted as less efficient processing of the executive attention network.

Zhang and colleagues (Zhang et al., 2015) examined the prevalence and severity of neurological soft signs (NSS) in adolescents aged 14 to 18 with BPD. Using the soft sign subscales of the Cambridge Neurological Inventory (i.e., motor coordination - MC, sensory integration - SI, and disinhibition - DI), they examined group differences between 14 to 18 years olds' with BPD traits versus those without any personality disorder. Five NSS (i.e., go-no go-test, mirror movements [left], finger agnosia [right; left], left-right orientation) were significantly more frequent in adolescents with BPD traits. In total, 59.6% of adolescents with BPD traits exhibited at least one neurological soft sign, while 42.7% exhibited at least two. In comparison, 34.8% of adolescents in the control group exhibited one soft sign and just 16.9% exhibited at least two soft signs.

In a recent study, Kaess and colleagues (2016) presented adolescent females with a dual-task paradigm to examine functioning of the central executive system within stress and non-stress conditions. There were no group differences in task performance between adolescents with BPD and healthy controls (HCs). Under stress conditions, performance on

the auditory (but not visual) task decreased for both groups, but there were no significant group differences. HCs (but not the BPD group) showed an increase in heart rate following stress induction. The authors hypothesised that this finding may contradict current theories suggesting that the affective hyper-responsivity in BPD is biologically based.

Social cognition

Facial emotion recognition

Three studies assessed emotion processing as a likely attentional bias in BPD in adolescence (Robin et al., 2012; von Ceumern-Lindenstjerna et al., 2009, 2010). Using a visual dot paradigm and emotional face stimuli, von Ceumern-Lindenstjerna et al. (2009) reported an interaction between current mood and hypervigilance towards negative emotional stimuli in 13 to 19 year olds with BPD (i.e., an attentional bias towards negative emotional stimuli was observed when BPD patients were in a negative mood). In a second study with the same sample, groups were compared on attentional orienting to negative emotional faces (von Ceumern-Lindenstjerna et al., 2010). Adolescents with BPD perceived more negative faces than healthy controls; however, adolescents with mixed psychiatric diagnoses also demonstrated this bias. Finally, Robin et al. (2012) used a dynamic paradigm in which neutral faces were morphed into fully expressed emotions (i.e., sadness, anger, happiness, disgust, surprise and fear) to examine whether 15 to 19 year olds with BPD process facial expressions differently to healthy matched controls. There were no significant differences in the accuracy of responses between groups; however, adolescents with BPD were less sensitive to facial expressions of anger and happiness (i.e., they required more intense expressions to be able to accurately label emotions).

Mentalisation

Four studies reported disturbances in aspects of mentalisation (i.e., understanding others behaviour in mental state terms, also referred to as "theory of mind") in child or adolescent BPD populations.

Belsky et al. (2012) examined the prospective association between theory of mind (ToM) at 5 years and BPD symptoms at 12 years. ToM, measured with a battery of tests to determine the child's ability to attribute first and second order false beliefs, was significantly negatively correlated with BPD features (r= - .11, p<.001).

Sharp and colleagues conducted a series of studies to examine mentalisation abilities in adolescents with BPD (Kalpakci et al., 2016; Sharp et al., 2013; Sharp et al., 2011). In the first, the authors examined associations between mentalisation, emotion regulation, and BPD traits in adolescent inpatients. Mentalisation (i.e., undermentalising, no mentalisation, and excessive or hypermentalising reflecting an over-interpretation of mental states) was assessed with the Movie Assessment for Social Cognition (MASC) task. Emotion regulation and psychopathology were assessed via self-report. The authors found that hypermentalising (but not undermentalising) was independently associated with BPD traits (B=0.91, p=.002) and diagnosis (B=0.17, p=.04) following adjustment for age, sex, externalising, internalising, and psychopathy symptoms. In cross-sectional analysis (thus not indicative of temporal ordering), the association between hypermentalising and BPD was significantly mediated (i.e., partly explained) by difficulties in emotion regulation.

In a subsequent study, Sharp et al. (2013) investigated whether a reduction in hypermentalisation may be achieved between the admission and discharge of adolescent inpatients. They found that hypermentalisation (but not other forms of social-cognitive reasoning) was responsive to milieu-based inpatient treatment (i.e., treatment placing an emphasis on forming close relationships with mental health workers to provide structure

and discipline). The effect was significantly more pronounced for patients with BPD in comparison to psychiatric controls (interaction effect for BPD and hypermentalising: *F*=5.30, *p*=.02, partial eta squared = .03).

Finally, Kalpakci et al. (2016) examined associations between emotion regulation, hypermentalisation (assessed with the MASC), and cognitive and affective empathy (assessed with the Basic Empathy Scale: BES) in female adolescent inpatients. Adolescents with BPD had greater affective (but not cognitive) empathy than non-BPD adolescents (Mean = 3.70, SD =0.70 vs Mean = 3.48, SD =0.65, *p* = .01). Emotional dysregulation was associated with increased affective empathy in BPD patients (β= 0.01, SE: 0.00, *p*=.01), while hypermentalisation was related to decreased cognitive empathy (β= - 0.03, SE: 0.01, *p*=.01). There was no relation between hypermentalisation and either type of empathy for the psychiatric controls.

Discussion

As far as we are aware this is the first systematic review of studies examining the neurobiological correlates of BPD features in child and adolescent populations. Before we evaluate individual study findings, compare them with the adult literature, and contextualise within a neurodevelopmental framework, a consideration of methodological limitations observed across studies is warranted.

First, as observed within the adult literature (van Zutphen et al., 2015), findings regarding brain abnormalities (e.g., structural volumes and emotional processing) were somewhat inconsistent. This is unsurprising given the small sample sizes (meaning that some studies could have been underpowered); variance in sample characteristics; divergence in imaging techniques (potentially varying in sensitivity); and variations in BPD

assessment tools (though the majority of imaging studies with adolescent patients tended to use the SCID-II for BPD diagnosis). A number of studies used exclusively female participants (e.g., von Ceumern et al., 2010) or a majority of female participants (e.g., Walterfang et al., 2010) making generalisations to males difficult (Grant et al., 2008). Some study samples encompassed a wide age range (e.g., 5 to 17 years) spanning both childhood and adolescence (Coolidge et al., 2000), which is problematic in view of likely developmental differences in neurobiological features across development (e.g., changes in gray and white matter, executive functioning, and social cognition (Blakemore & Choudhury, 2006)). In two of the studies we included in our review, *all* participants had co-morbid depression, limiting the comparability (and generalisability) of the findings. Our formal quality assessment using the NOS indicated variations in risk of bias across studies, with some studies scoring low in the domains of selection (impacting on the generalisability of findings), and comparability (failure to control for important confounding factors, such as whole brain volume). This, along with the observation that a number of studies used healthy controls only, indicates that future studies should focus on corroborating the specificity of findings for BPD by carefully controlling for co-morbid symptomatology (Goodman et al., 2013) and selecting appropriate clinical control groups.

Second, although samples comprised young individuals in the very early stages of the disorder, the confounding effects of treatment cannot be totally ruled out; a substantial proportion of young participants in some of the identified studies were taking a variety of psychotropic medications. Furthermore, as nearly all of the studies were cross-sectional, it was not possible to ascertain whether neurobiological features predated the development of the disorder, or elucidate the progression of neurobiological perturbations across development (e.g., whether alterations in some brain structures or biological processes had

a cascade effect, see Selby and Joiner Jr (2009)). Cross-sectional studies do not allow us to disentangle the core pathophysiological processes of BPD from the effects of pre-existing illness and adverse life experiences on brain development (Mazzone & Curatolo, 2010), or allow for the study of intra-individual change over time (Crone & Elzinga, 2015). Just two of the included studies were prospective, and only one examined prospective pathways to BPD involving gene-environment interactions, and neuropsychological dysfunction (Belsky et al., 2012).

Third (and related to the previous point), although there is growing evidence for the validity of BPD in adolescence (Ensink, Biberdzic, Normandin, & Clarkin, 2015; Kaess et al., 2014; Winsper, Marwaha, et al., 2015), it is recognised that a proportion of youths demonstrating the BPD phenotype will not be diagnosed with BPD in adulthood. Thus, findings from the cross-sectional literature (although suggestive) will require further elaboration from longitudinal studies to identify the neurobiological underpinnings of chronic BPD symptom trajectories.

Fourth, neuroimaging findings were based on a limited number of independent cohorts utilising the same patient groups (i.e., the 14 neuroimaging studies drew on only four independent cohorts), thus limiting replication of specific findings. Further, all of these studies utilised structural neuroimaging techniques. While we can speculate regarding associations between alterations to frontolimbic structures and BPD pathology, functional imaging studies are needed to more explicitly determine links between brain activity and the clinical features of BPD (Weber & Thompson-Schill, 2010).

Overview of main findings and comparison with the adult literature

Twin studies indicated a moderate to high level of heritability for BPD symptoms in adolescent and child populations ranging from.30/.50 to.76 (Belsky et al., 2012; Bornovalova et al., 2009; Coolidge et al., 2001). These figures are largely similar to those reported in adult BPD (.40) and overlap with bipolar (.79) populations (Amad et al., 2014; Cardno et al., 1999; Kendler, Myers, & Reichborn-Kjennerud, 2011; Torgersen, 2000). Also congruent with some of the adult literature (Lis, Greenfield, Henry, Guilé, & Dougherty, 2007; Lynch et al., 2006), a significant association between the serotonin transporter gene 5-HTTLPR (specifically the short allele) and BPD traits in 9 to 15 year olds was reported (Hankin et al., 2011). Previous adult studies have reported that risk-allele carriers with a history of childhood abuse show increased probability of BPD diagnosis (Wilson et al., 2012). Two studies included in this review support that gene-environment (i.e., childhood maltreatment) interactions may play a role in the early development of BPD (Belsky et al., 2012; Cicchetti et al., 2014), though there may be complex variations in effects according to gender (Cicchetti et al., 2014).

Both structural and functional neuroimaging studies in adult populations suggest that the frontolimbic network (encompassing the anterior cingulate cortex [ACC], orbitofrontal cortex [OFC], dorsolateral prefrontal cortex [DLPFC], amygdala, and hippocampus) is dysfunctional in individuals with BPD and that this dysfunction mediates most BPD symptomatology (Ensink et al., 2015; Krause-Utz et al., 2014). The neuroimaging studies we identified in adolescent populations examined only structural aspects of this network, including both grey (i.e., cells involved in processing and cognition) and white (i.e., neural substrates of connectivity) matter structures. Congruent with findings from adult studies (Hazlett et al., 2005; Tebartz van Elst et al., 2003) there was some evidence of volumetric reduction in grey matter structures of the frontolimbic network, including the

OFC, ACC, hippocampus and to a lesser degree, amygdala. Two studies (utilising different methodologies) reported reductions in OFC volume in comparison to healthy, but not clinical, controls (Brunner et al., 2010; Chanen, Velakoulis, et al., 2008). Findings regarding ACC alterations followed a similar pattern, with two studies reporting reductions in ACC volume in comparison to HCs (Goodman et al., 2011; Whittle et al., 2009). In contrast to the adult literature (Driessen et al., 2000; C. Schmahl, Vermetten, Elzinga, & Douglas Bremner, 2003; Tebartz van Elst et al., 2003), initial studies using Voxel Based Morphology and Region Of Interest methodologies found no difference between hippocampal or amygdala volumes in BPD and control groups (Brunner et al., 2010; Chanen, Velakoulis, et al., 2008). These findings led the authors to conjecture that alterations in these structures may be acquired later on in development as a consequence of changes to the OFC (Chanen, Velakoulis, et al., 2008). More recent studies utilising different methodologies or considering interactional effects (with temperament) indicate that hippocampal and amygdala abnormalities may be present early on in the course of the disorder (Jovev et al., 2013; Richter et al., 2014), suggesting that previous null findings could potentially reflect insufficient sensitivity in neuroimaging techniques (Dewey et al., 2010). Whether discrepancies in findings between adolescent and adult studies reflect methodological artefacts or developmentally sensitive alterations in amygdala and hippocampus regions requires further explication (e.g., prospective studies with repeated assessments).

While there were no functional brain imaging studies in adolescent populations, studies denoting alterations in white matter structures were compatible with adult functional studies (Silbersweig et al., 2007) in suggesting possible regions of disconnect between brain structures in the frontolimbic system. New et al. (2013), for example, reported decreased fractional anisotropy in white matter tracts between the limbic system

and frontal brain regions, which may manifest as diminished top-down control of affective and aggression responses (Leichsenring, Leibing, Kruse, New, & Leweke, 2011). Similarly, Maier-Hein et al. (2014) reported white matter alterations in a large-scale network (i.e., limbic system, bilateral fornices) of emotion processing in adolescents with BPD.

Findings from the neuropsychological studies are somewhat consistent with those from adult studies. Studies utilising a variety of methodologies (e.g., questionnaires, behavioural tasks) demonstrated that children and adolescents (like adults) with BPD evince problems in executive functioning (Belsky et al., 2012; Coolidge et al., 2000; Paris et al., 1999; Rogosch & Cicchetti, 2005; Zelkowitz et al., 2001; Zhang et al., 2015). Comparisons with adult studies (Bazanis et al., 2002; Posner et al., 2003; Ruocco, 2005); however, should be considered through a developmental lens, as executive processes develop throughout childhood to adolescence (Ensink et al., 2015).

Results regarding social cognition suggested a tendency towards hypervigilance in adolescents with BPD. Two studies indicated a hypervigilance towards negative emotional faces at both the initial (von Ceumern-Lindenstjerna et al., 2010) and later stages (von Ceumern-Lindenstjerna et al., 2009) of emotional processing. There was an indication that this tendency may be mood dependent (von Ceumern-Lindenstjerna et al., 2010). Congruent with these findings, Sharp and colleagues (2011; 2013) found that adolescents with BPD tended to "hypermentalise" or over-interpret the actions of others (i.e., make negative assumptions about other people's mental states). Studies with BPD adults have suggested atypical or superior mentalisation ability (Arntz & Veen, 2001; Fertuck et al., 2009; Franzen et al., 2011), though superior awareness appears to relate to explicit, external features (e.g., face, behaviour) rather than internal (e.g., putative thoughts and feelings) features (Sharp et al., 2013).

Study findings contextualised within a neurodevelopmental framework

Several pathways to BPD incorporating various neurobiological markers (i.e., genetic, structural, neuropsychological) are indicated by the included studies (see **Figure 2**), though these hypotheses remain tentative pending future prospective research. Indeed, the current literature does not provide information on the temporality of the neurobiological underpinnings of adolescent BPD (with the exception of Belsky et al., 2012), thus our interpretations are guided by current neurodevelopmental models (Ensink et al., 2015; Hughes et al., 2012).

Contemporary theories for the development of BPD assert that an inborn biological vulnerability is potentiated across development by environmental risk factors giving rise to more extreme emotional, behavioural, interpersonal, and cognitive dysregulation until these precursors eventuate in clinically relevant BPD (Crowell et al., 2009; Selby & Joiner Jr, 2009). Pathways to adolescent BPD are likely overlapping, encompassing genetic, biological, and environmental influences which make reciprocal contributions to the development of the disorder (Judd, 2005).

At the genetic level, polymorphisms, such as the short allele of the 5-HTTLPR genotype (Hankin et al., 2011) and the OXTR genotype (Cicchetti et al., 2014), may underpin problems with self-and interpersonal-regulation, both of which may be exacerbated across development by environmental risk factors (e.g., childhood maltreatment, Belsky et al., 2012; Cicchetti et al., 2014). Epigenetic mechanisms, in turn, may impact on gene expression. Prenatal maternal depression, for example, may modulate infant stress responsiveness through the methylation of glucocorticoid receptors (Steele & Siever, 2010) increasing risk of adolescent BPD (Winsper, Wolke, & Lereya, 2015). Of note, individuals

who inherit a genetic predisposition to BPD are also at heightened risk of environmental adversity (e.g., insecure attachment), as observed in the children of mothers with BPD (Eyden, Winsper, Wolke, Broome, & MacCallum, 2016).

At the structural level, alterations to frontolimbic structures (associated with BPD) may begin as early infancy within the context of poor mother-child attachment experiences (Schore, 2000). We cannot glean from the current literature when in the developmental trajectory (or in what order) the observed alterations to frontolimbic structures occurred. Overall, however, findings of grey and white matter alterations are consistent with diminished top-down control of the limbic system. At the neuropsychological level, frontolimbic dysfunction may impact on attentional control, executive function, and mentalisation domains (Ensink et al., 2015). Consistent with this theory, studies in our review indicated child or adolescent markers of diminished executive function (e.g., Zelkowitz et al., 2001), impaired mentalisation (e.g., Sharp et al., 2011), and biases in emotion recognition (e.g., von Ceumern-Lindenstjerna, et al., 2009).

At the phenotypic (or BPD precursor) level, frontolimbic dysregulation may contribute to dysregulation of the interpersonal, emotional, behavioural, and cognitive domains, via an exacerbation of “cascades of emotion” in a self-amplifying positive feedback loop of rumination, negative emotions, and dysregulation during the day (Selby & Joiner Jr, 2009) and night via increased risk of nightmares (Lereya, Winsper, Tang, & Wolke, 2016).

As mentioned, neurobiological features (e.g., at the neuropsychological and phenotypic level) are believed to interact with one another in complex (reciprocal) ways on the pathway to BPD (Lenzenweger & Castro, 2005), and a number of possible routes are suggested by the reviewed literature. Diminished executive function, for example, could increase the risk of impulsive behaviours (Pharo, Sim, Graham, Gross, & Hayne, 2011), and

thus subsequent BPD. Hyper-mentalisation could increase risk of BPD by exacerbating levels of emotional dysregulation (Sharp et al., 2011). Attentional bias to negative faces may be moderated by mood states (von Ceumern-Lindenstjerna et al., 2010), and further exacerbate a tendency to hyper-mentalise.

Conclusions and future research directions

The main aims of this review were to ascertain whether the neurobiological abnormalities associated with BPD in adulthood are also observed in child and adolescent populations, and to contextualise findings within a neurodevelopmental framework to highlight areas for future research.

Accepting limitations of the extant studies, we found that BPD symptoms in adolescence are associated with similar neurobiological features (e.g., structural frontolimbic abnormalities, neurocognitive deficits) to BPD in adulthood. This suggests that these features are not simply a non-specific consequence of chronic illness, nosological overlap, or prolonged medication use.

The cross-sectional findings summarised in this review provided an important platform from which we could hypothesise about the neurodevelopment of adolescent BPD. However, there remain a number of gaps in our knowledge particularly regarding the temporal unfurling of neurobiological features. Thus, an important next step is the use of longitudinal studies with repeated, prospective assessments of biological and environmental risk indicators for adolescent BPD. These studies could help clarify how, and in what order, various life experiences impact on neurobiological factors (e.g., child maltreatment may produce “limbic scars” on brain functioning and structure) across development. Further, they would facilitate the statistical examination of complex reciprocal effects between

environment and biology. For a fuller understanding of BPD pathology, the effects of epigenetic programming (e.g., the impact via methylation of child maltreatment on the expression of stress-related genes) should also be considered (Perroud et al., 2013). Genome wide studies are indicated as multiple genes (e.g., MAOA, BDNF, DRD2, and COMT) are thought to play a role in moderating the impact of early life stress on the development of BPD (Prados et al., 2015).

There has been debate regarding the conceptualisation of BPD. The DSM-5 (Section III: Emerging Models and Measures) now presents an alternative hybrid dimensional-categorical model for further research. The new model emphasises dimensional functional impairment criteria and personality traits mapping onto six categorical personality disorders, including BPD (Anderson & Sellbom, 2015). This, and emerging data on the meta-structure of psychopathology (Ofrat & Krueger, 2012), challenge the notion of BPD as a categorical construct. A neurodevelopmental approach to the aetiology of BPD may sit well with these developments, as it seeks to elucidate the neurobiological correlates of dysfunction (associated with BPD) at varying levels of explanation (e.g., endophenotypic: executive dysfunction; phenotypic: emotional dysregulation), which may underlie multiple disorders.

A neurobiological understanding of adolescent BPD offers promise for the development of refined treatment programmes, which can be implemented early on when traits may be more malleable (Lenzenweger & Cicchetti, 2005). For example, findings from neurocognitive studies may directly inform social-cognitive therapies, i.e., adolescents may be taught to replace emotionally driven interpretations (Sharp et al., 2013), while neurochemical studies could underpin pharmacological regimens (Conti et al., 2013).

Table 1. Summary of neurobiological studies of youth with BPD features

First Author	Year	Country	Sample *n* (age)	Percent female	Sample frame (control group)	Design	BPD assessment (cut-point)	Neurobiology assessment	Main Findings
Belsky	2012	UK	1,116 pairs of twins 12 years	51%	Community (N/A)	Prospective cohort	BPRC 95th percentile	Twin study	Genetic factors accounted for 66% of the variance in BPD symptoms.
Bornovalova	2009	USA	1118 14-17 years	100%	Community (N/A)	Prospective (4 assessment points)	MPQ (continuous)	Twin study (heritability estimate)	Heritability co-efficient for BPD symptoms ranged from .3 to .5
Brunner	2010	Germany	60 14 - 18 years	100%	Clinical (CC; HC)	Cross-sectional (case control)	SCID-II (≥5)	MRI (VBM)	BPD subjects exhibited reduced grey matter in the OFC (left) and DLPFC (bilateral) in comparison to HCs but not CCs
Ceballos	2006	USA	213 14 - 19 years	57%	High risk (CD; CD/BPD; HC)	Cross-sectional (case control)	SCID-II (≥5)	P300 task (visual oddball)	With increasing age BPD and HCs showed a decline in P300 amplitude. Those with CD & CD/BPD did not show the typical decline
Chanen	2008	Australia	40 15-19 years	75%	Clinical (HC)	Cross-sectional (case control)	SCID-II (≥5)	MRI (ROI)	BPD patients exhibited reduced grey matter in the OFC (right) compared to HCs. No amygdala or hippocampus differences
Cicchetti	2014	USA	1, 051 8-12 years	50.2%	High risk (N/A)	Cross-sectional	BPFS-C (continuous)	Molecular genetic study	OXTR and FKBP5 genes moderated associations between child maltreatment and BPD symptoms
Coolidge	2000	USA	42 5-17 years	57% (BPD) 31% (PD)	Clinical (other PDs)	Cross-sectional (case control)	CPNI (≥ 70)	Questionnaire (neuropsychological)	BPD group scored higher on executive function deficits & neurocognitive disorder
Coolidge	2001	USA	112 (twins) 4-15 years	Not given	Community (N/A)	Cross-sectional	CPNI (T score)	Twin study (heritability estimate)	Heritability co-efficient for BPD symptoms was 0.76
Conti	2013	Italy	30 M_{age}=15.5 (1.2)	47% (BPD) 69% (HC)	Clinical (HC)	Cross-sectional (case control)	DSM-IV-TR	Fasting plasma tests (neurosteroid system)	Adolescents with BPD had significantly increased dehydroepiandrosterone sulphate (DHEA-S) plasma levels and decreased cortisol-to-DHEA-S molar ratio in comparison to HCs
Garner	2007	Australia	40 15-19 years	75%	Clinical (HC)	Cross-sectional (case control)	SCID-II (≥5)	MRI (ROI)	No difference in PGV between BPD and HCs. BPD subjects with childhood trauma had smaller PGV
Goodman	2011	USA	26 Mage=15.8 (1.1)	84.6% (BPD) 69.2% (HC)	Clinical (HC)	Cross-sectional (case control)	SCID-II (≥5) DIB-R	MRI (ROI)	BPD/MDD patients had smaller BA 24 volume in grey but not white matter. Smaller BA24 volume was associated with BPD (but not depressive) symptoms
Hankin	2011	USA	242/144 9-15 years	57%	Community (N/A)	Cross-sectional	CIC-SR (continuous)	Molecular genetic study	Carriers of the short allele of 5-HTTLPR exhibited significantly higher BPD traits
Houston	2005	USA	123 14-19 years	100%	High-risk (BPD vs. no BPD)	Cross-sectional (case control)	SCID-II (≥5)	P300 task (visual oddball)	BPD subjects did not exhibit the typical age related decline in P300
Jovev	2008	Australia	20 15-19 years	75%	Clinical (no controls)	Cross-sectional	SCID-II (≥5)	MRI (ROI)	Number of parasuicidal behaviours was a predictor of increased PGV?
Jovev	2013	Australia	153 11-13 years	46%	High-risk (N/A)	Cross-sectional	CIC-SR (continuous)	MRI (ROI)	Boys: low affiliation was a predictor of BPD in the presence of atypical rightward hippocampal asymmetry. Girls: low effortful control was associated with BPD in the presence of atypical rightward hippocampal asymmetry

HC=Healthy Controls; CC=Clinical Controls; BPRC= Borderline Personality Related Characteristics; MPQ = Multidimensional Personality Questionnaire; SCID-II = Structured Clinical Interview for DSM-IV Axis II Disorders; BPCFS-C= Borderline Personality Features Scale for Children; CPNI=Coolidge Personality and Neuropsychological Inventory; BPDCL=Borderline Personality Disorder Check List; CIC-SR=Children in the Community Self-Report; C-DIB=Child Diagnostic Interview for Borderlines; VBM=Voxel Based Morphology; MRI=Magnetic Resonance Imaging; ROI=Region of Interest; DTI=Diffusion Tensor Imaging; TBSS=Tract Based Spatial Statistics; WCST=Wisconsin Card Sorting Task; CPT=Continuous Performance Test; OFC=Orbitofrontal Cortex; DLPFC=Dorsolateral Prefrontal Cortex; PGV=Pituitary Gland Volume

Table 1. Summary of neurobiological studies of youth with BPD features

First Author	Year	Country	Sample *n* (age)	Percent female	Sample frame (control group)	Design	BPD assessment (cut-point)	Neurobiology assessment	Main findings
Kaess	2016	Germany	64 13-19 years	100%	Clinical (CC; HC)	Cross-sectional	SCID-II (≥5)	Computerised dual-task paradigm	No group differences in dual-task performance. Under stress conditions, performance on the auditory task decreased in both groups.
Kalpakci	2016	USA	252 12-17 years	100%	Clinical (CC)	Cross-sectional (case control)	CI-BPD (≥5)	MASC, BES (mentalisation, empathy)	Patients with BPD had greater affective empathy. Hypermentalisation was associated with decreased cognitive empathy in the BPD group
Maier-Hein	2014	Germany	60 14-18 years	100%	Clinical (CC; HC)	Cross-sectional (case control)	SCID-II (≥5)	MRI (DTI; TBSS)	BPD patients exhibited decreased fractional anisotropy in the fornix (white matter of the limbic system) compared to HC and CC
New	2013	USA	27 Mage=15.8 (1.1)	85.7% (BPD) 69.2%(HC)	Clinical (HC)	Cross-sectional (case control)	SCID-II (≥5) DIB-R	MRI (DTI; TBSS)	BPD patients exhibited decreased fractional anisotropy in the inferior longitudinal fasciculus, uncinate, and occipitofrontal fasciculi
Paris	1999	Canada	89 7-12 years	14.6%	Clinical (CC)	Cross-sectional (case control)	C-DIB (≥7)	WCST; CPT (Neuropsychological)	Children with BPD had abnormal scores on the WCST and CPT suggesting executive function deficits
Richter	2014	Germany	60 14-18 years	100%	Clinical (CC; HC)	Cross-sectional (case control)	SCID-II (≥5)	MRI (FreeSurfer)	BPD patients exhibited significantly smaller amygdala and hippocampal volumes than HCs but not CCs. Also showed reductions in the right middle frontal gyrus and inferior frontal gyrus
Robin	2012	Europe	44 15-19 years	100%	Clinical (HC)	Cross-sectional (case control)	SCID-II (≥5)	Emotional recognition task (facial expressions)	BPD subjects were less sensitive to facial expressions of happiness and anger than HCs
Rogosch	2005	USA	360 6-12 years	48.6%	High-Risk (N/A)	Cross-sectional	BPD precursors composite (1 SD>Mean)	ANT task (neuropsychological)	BPD subjects demonstrated less efficient processing of the conflict attention network in comparison to high risk controls
Sharp	2011	USA	111 12-17 years	55.9%	Clinical	Cross-sectional	BPFSC (continuous) CI-BPD (≥5)	MASC (mentalisation)	Overmentalising was associated with BPD traits. The association between overmentalising and BPD traits was mediated by problems with emotion regulation
Sharp	2013	USA	164 12-17 years	55.9%	Clinical	Cross-sectional	As Sharp 2011	As Sharp 2011	Hypermentalisation was responsive to a mileu-based inpatient treatment
Takahashi	2009a, b 2010	Australia	40 15-19 years	75%	Clinical (HC)	Cross-sectional (case control)	SCID-II (≥5)	MRI (ROI)	BPD patients exhibited shorter AIs and larger third ventricles than HCs. No significant difference in insular cortex or superior temporal gyrus volumes between BPD patients and HCs
von Ceumern	2009	Germany	89 13-19 years	100%	Clinical (CC; HC)	Cross-sectional (case control)	SCID-II (≥5)	Visual dot probe task (emotional faces)	BPD patients exhibited mood dependent attentional bias towards negative emotional stimuli
von Ceumern	2010	Germany	89 13-19 years	100%	Clinical (CC; HC)	Cross-sectional (case control)	SCID-II (≥5)	Visual dot probe task (emotional faces)	BPD patients perceived more negative faces than HCs but not CCs
Walterfang	2010	Australia	40 15-19 years	75%	Clinical (HC)	Cross-sectional (case control)	SCID-II (≥5)	MRI (ROI)	BPD patients did not exhibit differences in corpus callosum size in comparison to HCs
Whittle	2009	Australia	30 15-19 years	100%	Clinical (HC)	Cross-sectional (case control)	SCID-II (≥5)	MRI (ROI)	Female BPD patients exhibited reduced ACC volume in comparison to HCs

HC=Healthy Controls; CC=Clinical Controls; SCID-II = Structured Clinical Interview for DSM-IV Axis II Disorders; C-DIB=Child Diagnostic Interview for Borderlines; ANT=Attention Network Task; MRI=Magnetic Resonance Imaging; ROI=Region of Interest; WCST=Wisconsin Card Sorting Task; MASC=Movie for Assessment of Social Cognition; BES= Basic Empathy Scale

Table 1. Summary of neurobiological studies of youth with BPD features

Author	Year	Country	Sample n (age)	Percent female	Sample frame (control group)	Design	BPD assessment (cut-point)	Neurobiological assessment	Main findings
Zelkowitz	2001	Canada	86 7-12 years	13%	Clinical (CC)	Cross-sectional (case control)	C-DIB (≥7)	WCST; CPT (Neuropsychological)	After control for psychosocial confounders BPD patients exhibited executive function deficits in comparison to CCs
Zhang	2015	China	178 14-18 years	69.7%	High-BPD traits (HC)	Cross sectional (case control)	PDQ-4+ (≥6)	CNI (Neuropsychological)	59.6% of the BPD trait group exhibited one NSS, while 42.7% exhibited at least two NSS. In comparison, 34.8% ($p<0.01$) of controls exhibited one and 16.9% ($p<0.001$) at least two NSS.

HC=Healthy Controls; CC=Clinical Controls; C-DIB=Child Diagnostic Interview for Borderlines; ANT=Attention Network Task; MRI=Magnetic Resonance Imaging; ROI=Region of Interest; WCST=Wisconsin Card Sorting Task; CPT=Continuous Performance Test; CNI = Cambridge Neurological Inventory; NSS = Neurological Soft Signs;

Table 2. Summary of the Quality Assessment of Case Control Studies included in the Review*

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Exposure (max 3 stars)	Total score (out of 9)
Brunner 2010	*	**	*	4
Ceballos 2006	*	N/A	*	2
Chanen 2008	*	**	**	5
Conti 2014	N/A	N/A	**	2
Coolidge 2000	N/A	*	**	3
Garner 2007	*	**	**	5
Goodman 2011	**	N/A	*	3
Houston 2005	*	*	*	3
Kaess 2016	*	N/A	**	3
Kalpakci 2016	N/A	**	*	3
Maier-Hein 2014	*	*	*	3
New 2013	**	*	*	4
Paris 1999	**	*	*	4
Richter 2014	*	**	*	4
Robin 2012	*	*	*	3
Sharp 2011/2013	N/A	**	*	3
Takahashi 2009a	*	**	**	4
Takahashi 2009b	*	**	**	5
Takahashi 2010	*	**	*	4
von Ceumern 2009	**	**	**	6
von Ceumern 2010	*	*	*	3
Walterfang 2010	**	**	**	6
Whittle 2009	*	**	**	5
Zelkowitz 2001	**	*	**	5
Zhang 2015	**	*	*	4

*Based on Wells et al. (2000).

Table 3. Summary of the Quality Assessment of Cross Sectional Studies included in the Review*

Study	Selection (max 5 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)	Total score (out of 10)
Cicchetti 2014	***	*	**	6
Coolidge 2001	*	N/A	**	3
Hankin 2011	****	*	**	7
Jovev 2008	**	**	**	6
Jovev 2013	***	**	**	7
Rogosch 2004	***	*	**	6

*Based on Herzog et al. (2013)

References

Amad, A., Ramoz, N., Thomas, P., Jardri, R., & Gorwood, P. (2014). Genetics of borderline personality disorder: systematic review and proposal of an integrative model. *Neuroscience & Biobehavioral Reviews, 40*, 6-19.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders. 5th ed.* Arlington, VA: American Psychiatric Publishing.

Anderson, J. L., & Sellbom, M. (2015). Construct Validity of the DSM–5 Section III Personality Trait Profile for Borderline Personality Disorder. *Journal of personality assessment, 97*(5), 478-486.

APA. (1980). *Diagnostic and Statistical Manual of Mental Disorders (3rd ed.).* Washington, DC: American Psychiatric Association.

Arntz, A., & Veen, G. (2001). Evaluations of others by borderline patients. *The Journal of nervous and mental disease, 189*(8), 513-521.

Bazanis, E., Rogers, R., Dowson, J., Taylor, P., Meux, C., Staley, C., . . . Sahakian, B. (2002). Neurocognitive deficits in decision-making and planning of patients with DSM-III-R borderline personality disorder. *Psychological medicine, 32*(8), 1395-1405.

Belsky, D. W., Caspi, A., Arseneault, L., Bleidorn, W., Fonagy, P., Goodman, M., . . . Moffitt, T. E. (2012). Etiological features of borderline personality related characteristics in a birth cohort of 12-year-old children. *Development and psychopathology, 24*(01), 251-265.

Blakemore, S. J., & Choudhury, S. (2006). Development of the adolescent brain: implications for executive function and social cognition. *Journal of child psychology and psychiatry, 47*(3-4), 296-312.

Bornovalova, M. A., Hicks, B. M., Iacono, W. G., & McGue, M. (2009). Stability, change, and heritability of borderline personality disorder traits from adolescence to adulthood: A longitudinal twin study. *Development and psychopathology, 21*(04), 1335-1353.

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.

Brunner, R., Henze, R., Richter, J., & Kaess, M. (2015). Neurobiological findings in youth with borderline personality disorder. *Scandinavian Journal of Child and Adolescent Psychiatry and Psychology, 3*(1), 22-30.

Cardno, A. G., Marshall, E. J., Coid, B., Macdonald, A. M., Ribchester, T. R., Davies, N. J., . . . Sham, P. C. (1999). Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. *Archives of General Psychiatry, 56*(2), 162-168.

Ceballos, N. A., Houston, R. J., Hesselbrock, V. M., & Bauer, L. O. (2006). Brain maturation in conduct disorder versus borderline personality disorder. *Neuropsychobiology, 53*(2), 94-100.

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.

Cicchetti, D., Rogosch, F., Hecht, K., Crick, N., & Hetzel, S. (2014). Moderation of maltreatment effects on childhood borderline personality symptoms by gender and oxytocin receptor and FK506 binding protein 5 genes. *Development and psychopathology, 26*(3), 831-849.

Conti, E., Nacinovich, R., Bomba, M., Uccellini, O., Rossi, M. S., Casati, M., . . . Tremolizzo, L. (2013). Diazepam Binding Inhibitor and Dehydroepiandrosterone Sulphate Plasma Levels in Borderline Personality Disorder Adolescents. *Neuropsychobiology, 69*(1), 19-24.

Coolidge, F. L., Segal, D. L., Stewart, S. E., & Ellett, J. A. (2000). Neuropsychological dysfunction in children with borderline personality disorder features: A preliminary investigation. *Journal of Research in Personality, 34*(4), 554-561.

Coolidge, F. L., Thede, L. L., & Jang, K. L. (2001). Heritability of personality disorders in childhood: a preliminary investigation. *Journal of Personality Disorders, 15*(1), 33-40.

Crawford, T. N., Cohen, P., Johnson, J. G., Kasen, S., First, M. B., Gordon, K., & Brook, J. S. (2005). Self-reported personality disorder in the children in the community sample: convergent and prospective validity in late adolescence and adulthood. *Journal of Personality Disorders, 19*(1), 30-52.

Crick, N. R., Murray–Close, D., & Woods, K. (2005). Borderline personality features in childhood: A short-term longitudinal study. *Development and psychopathology, 17*(04), 1051-1070.

Crone, E. A., & Elzinga, B. M. (2015). Changing brains: how longitudinal functional magnetic resonance imaging studies can inform us about cognitive and social-affective growth trajectories. *Wiley Interdisciplinary Reviews: Cognitive Science, 6*(1), 53-63.

Crowell, S. E., Beauchaine, T. P., & Linehan, M. M. (2009). A biosocial developmental model of borderline personality: Elaborating and extending linehan's theory. *Psychological bulletin, 135*(3), 495.

Dewey, J., Hana, G., Russell, T., Price, J., McCaffrey, D., Harezlak, J., . . . Navia, B. (2010). Reliability and validity of MRI-based automated volumetry software relative to auto-assisted manual measurement of subcortical structures in HIV-infected patients from a multisite study. *Neuroimage, 51*(4), 1334-1344.

Domes, G., Schulze, L., & Herpertz, S. C. (2009). Emotion recognition in borderline personality disorder-a review of the literature. *Journal of personality disorders, 23*(1), 6.

Driessen, M., Herrmann, J., Stahl, K., Zwaan, M., Meier, S., Hill, A., . . . Petersen, D. (2000). Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Archives of general psychiatry, 57*(12), 1115-1122.

Ensink, K., Biberdzic, M., Normandin, L., & Clarkin, J. (2015). A Developmental Psychopathology and Neurobiological Model of Borderline Personality Disorder in Adolescence. *Journal of Infant, Child, and Adolescent Psychotherapy, 14*(1), 46-69.

Eyden, J., Winsper, C., Wolke, D., Broome, M. R., & MacCallum, F. (2016). A systematic review of the parenting and outcomes experienced by offspring of mothers with borderline personality pathology: potential mechanisms and clinical implications. *Clinical psychology review*.

Fertuck, E., Jekal, A., Song, I., Wyman, B., Morris, M., Wilson, S., . . . Stanley, B. (2009). Enhanced'Reading the Mind in the Eyes' in borderline personality disorder compared to healthy controls. *Psychological medicine, 39*(12), 1979.

Franzen, N., Hagenhoff, M., Baer, N., Schmidt, A., Mier, D., Sammer, G., . . . Lis, S. (2011). Superior 'theory of mind'in borderline personality disorder: an analysis of interaction behavior in a virtual trust game. *Psychiatry research, 187*(1), 224-233.

Garner, B., Chanen, A. M., Phillips, L., Velakoulis, D., Wood, S. J., Jackson, H. J., . . . McGorry, P. D. (2007). Pituitary volume in teenagers with first-presentation borderline personality disorder. *Psychiatry Research: Neuroimaging, 156*(3), 257-261.

Glenn, C. R., & Klonsky, E. D. (2013). Reliability and validity of borderline personality disorder in hospitalized adolescents. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 22*(3), 206.

Goodman, M., Hazlett, E. A., Avedon, J. B., Siever, D. R., Chu, K.-W., & New, A. S. (2011). Anterior cingulate volume reduction in adolescents with borderline personality disorder and co-morbid major depression. *Journal of psychiatric research, 45*(6), 803-807.

Goodman, M., Mascitelli, K., & Triebwasser, J. (2013). The neurobiological basis of adolescent-onset borderline personality disorder. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 22*(3), 212.

Grant, B. F., Chou, S. P., Goldstein, R. B., Huang, B., Stinson, F. S., Saha, T. D., . . . Pickering, R. P. (2008). Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *The Journal of clinical psychiatry, 69*(4), 533.

Griffiths, M. (2011). Validity, utility and acceptability of borderline personality disorder diagnosis in childhood and adolescence: Survey of psychiatrists. *The Psychiatrist, 35*(1), 19-22.

Hankin, B. L., Barrocas, A. L., Jenness, J., Oppenheimer, C. W., Badanes, L. S., Abela, J. R., . . . Smolen, A. (2011). Association between 5-HTTLPR and borderline personality disorder traits among youth. *Frontiers in Psychiatry, 2*.

Hawes, D. J. (2014). Does the concept of borderline personality features have clinical utility in childhood? *Current opinion in psychiatry, 27*(1), 87-93.

Hazlett, E. A., New, A. S., Newmark, R., Haznedar, M. M., Lo, J. N., Speiser, L. J., . . . Siever, L. J. (2005). Reduced anterior and posterior cingulate gray matter in borderline personality disorder. *Biological Psychiatry, 58*(8), 614-623.

Herzog, R., Álvarez-Pasquin, M. J., Díaz, C., Del Barrio, J. L., Estrada, J. M., & Gil, Á. (2013). Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? a systematic review. *BMC public health, 13*(1), 154.

Houston, R. J., Ceballos, N. A., Hesselbrock, V. M., & Bauer, L. O. (2005). Borderline personality disorder features in adolescent girls: P300 evidence of altered brain maturation. *Clinical Neurophysiology, 116*(6), 1424-1432.

Hughes, A. E., Crowell, S. E., Uyeji, L., & Coan, J. A. (2012). A developmental neuroscience of borderline pathology: Emotion dysregulation and social baseline theory. *Journal of abnormal child psychology, 40*(1), 21-33.

Jovev, M., Garner, B., Phillips, L., Velakoulis, D., Wood, S. J., Jackson, H. J., . . . Chanen, A. M. (2008). An MRI study of pituitary volume and parasuicidal behavior in teenagers with first-presentation borderline personality disorder. *Psychiatry Research: Neuroimaging, 162*(3), 273-277.

Jovev, M., Whittle, S., Yücel, M., Simmons, J. G., Allen, N. B., & Chanen, A. M. (2013). The relationship between hippocampal asymmetry and temperament in adolescent borderline and antisocial personality pathology. *Development and psychopathology*, 1-12.

Judd, P. H. (2005). Neurocognitive impairment as a moderator in the development of borderline personality disorder. *Development and psychopathology, 17*(04), 1173-1196.

Kaess, M., Brunner, R., & Chanen, A. (2014). Borderline personality disorder in adolescence. *Pediatrics, 134*(4), 782-793.

Kaess, M., Parzer, P., Koenig, J., Resch, F., & Brunner, R. (2016). Dual-task performance under acute stress in female adolescents with borderline personality disorder. *European child & adolescent psychiatry*, 1-9.

Kalpakci, A., Vanwoerden, S., Elhai, J. D., & Sharp, C. (2016). The Independent Contributions of Emotion Dysregulation and Hypermentalization to the " Double Dissociation" of Affective and Cognitive Empahty in Female Adolescent Inpatients with BPD. *JOURNAL OF PERSONALITY DISORDERS, 30*(2), 242-260.

Kendler, K., Myers, J., & Reichborn-Kjennerud, T. (2011). Borderline personality disorder traits and their relationship with dimensions of normative personality: a web-based cohort and twin study. *Acta Psychiatrica Scandinavica, 123*(5), 349-359.

Krause-Utz, A., Winter, D., Niedtfeld, I., & Schmahl, C. (2014). The latest neuroimaging findings in borderline personality disorder. *Current psychiatry reports, 16*(3), 1-13.

Laurenssen, E. M. P., Hutsebaut, J., Feenstra, D. J., Van Busschbach, J. J., & Luyten, P. (2013). Diagnosis of personality disorders in adolescents: a study among psychologists. *Child and adolescent psychiatry and mental health, 7*(1), 3.

Leichsenring, F., Leibing, E., Kruse, J., New, A. S., & Leweke, F. (2011). Borderline personality disorder. *The Lancet, 377*(9759), 74-84.

Lenzenweger, M. F., & Castro, D. D. (2005). Predicting change in borderline personality: Using neurobehavioral systems indicators within an individual growth curve framework. *Development and psychopathology, 17*(04), 1207-1237.

Lenzenweger, M. F., & Cicchetti, D. (2005). Toward a developmental psychopathology approach to borderline personality disorder. *Development and Psychopathology, 17*(04), 893-898.

Lenzenweger, M. F., Lane, M. C., Loranger, A. W., & Kessler, R. C. (2007). DSM-IV personality disorders in the National Comorbidity Survey Replication. *Biological psychiatry, 62*(6), 553-564.

Lereya, S. T., Winsper, C., Tang, N. K., & Wolke, D. (2016). Sleep problems in childhood and borderline personality disorder symptoms in early adolescence. *Journal of abnormal child psychology*, 1-14.

Lis, E., Greenfield, B., Henry, M., Guilé, J. M., & Dougherty, G. (2007). Neuroimaging and genetics of borderline personality disorder: a review. *Journal of psychiatry & neuroscience, 32*(3), 162.

Lynch, T. R., Rosenthal, M. Z., Kosson, D. S., Cheavens, J. S., Lejuez, C., & Blair, R. (2006). Heightened sensitivity to facial expressions of emotion in borderline personality disorder. *Emotion, 6*(4), 647.

Maffei, C., Fossati, A., Agostoni, I., Barraco, A., Bagnato, M., Deborah, D., . . . Petrachi, M. (1997). Interrater reliability and internal consistency of the structured clinical interview for DSM-IV axis II personality disorders (SCID-II), version 2.0. *Journal of personality disorders, 11*(3), 279-284.

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. *Biological psychiatry, 75*(1), 81-88.

Mazzone, L., & Curatolo, P. (2010). Conceptual and methodological challenges for neuroimaging studies of autistic spectrum disorders. *Behavioral and Brain Functions, 6*(1), 6-17.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine, 151*(4), 264-269.

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. *Journal of psychiatric research, 47*(8), 1101-1109.

New, A. S., Hazlett, E. A., Buchsbaum, M. S., Goodman, M., Mitelman, S. A., Newmark, R., . . . Flory, J. (2007). Amygdala–prefrontal disconnection in borderline personality disorder. *Neuropsychopharmacology, 32*(7), 1629-1640.

Newton-Howes, G., Clark, L. A., & Chanen, A. (2015). Personality disorder across the life course. *The Lancet, 385*(9969), 727-734.

NICE. (2009). *Borderline Personality Disorder: Treatment and Managment*. Retrieved from London:

Ofrat, S., & Krueger, R. F. (2012). How research on the meta-structure of psychopathology aids in understanding biological correlates of mood and anxiety disorders. *Biology of mood & anxiety disorders, 2*(1), 1.

Paris, J. (2013). Personality Disorders Begin in Adolescence. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 22*(3), 195.

Paris, J., Zelkowitz, P., Guzder, J., Joseph, S., & Feldman, R. (1999). Neuropsychological factors associated with borderline pathology in children. *Journal of the American Academy of Child & Adolescent Psychiatry, 38*(6), 770-774.

Perroud, N., Salzmann, A., Prada, P., Nicastro, R., Hoeppli, M., Furrer, S., . . . Malafosse, A. (2013). Response to psychotherapy in borderline personality disorder and methylation status of the BDNF gene. *Translational psychiatry, 3*(1), e207.

Pharo, H., Sim, C., Graham, M., Gross, J., & Hayne, H. (2011). Risky business: executive function, personality, and reckless behavior during adolescence and emerging adulthood. *Behavioral neuroscience, 125*(6), 970.

Posner, M. I., Rothbart, M. K., Vizueta, N., Thomas, K. M., Levy, K. N., Fossella, J., . . . Kernberg, O. (2003). An approach to the psychobiology of personality disorders. *Development and psychopathology, 15*(04), 1093-1106.

Prados, J., Stenz, L., Courtet, P., Prada, P., Nicastro, R., Adouan, W., . . . Dayer, A. (2015). Borderline personality disorder and childhood maltreatment: a genome-wide methylation analysis. *Genes, Brain and Behavior, 14*(2), 177-188.

Preißler, S., Dziobek, I., Ritter, K., Heekeren, H. R., & Roepke, S. (2010). Social cognition in borderline personality disorder: evidence for disturbed recognition of the emotions, thoughts, and intentions of others. *Frontiers in behavioral neuroscience, 4*(182), 1-8.

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 Research: Neuroimaging, 221*(3), 179-186.

Robin, M., Pham-Scottez, A., Curt, F., Dugre-Le Bigre, C., Speranza, M., Sapinho, D., . . . Kedia, G. (2012). Decreased sensitivity to facial emotions in adolescents with Borderline Personality Disorder. *Psychiatry research, 200*(2), 417-421.

Rogosch, F. A., & Cicchetti, D. (2005). Child maltreatment, attention networks, and potential precursors to borderline personality disorder. *Development and psychopathology, 17*(04), 1071-1089.

Ruocco, A. C. (2005). The neuropsychology of borderline personality disorder: a meta-analysis and review. *Psychiatry research, 137*(3), 191-202.

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. *Biological psychiatry, 73*(2), 153-160.

Ruocco, A. C., Amirthavasagam, S., & Zakzanis, K. K. (2012). Amygdala and hippocampal volume reductions as candidate endophenotypes for borderline personality disorder: a meta-analysis of magnetic resonance imaging studies. *Psychiatry Research: Neuroimaging, 201*(3), 245-252.

Schmahl, C., & Bremner, J. D. (2006). Neuroimaging in borderline personality disorder. *Journal of psychiatric research, 40*(5), 419-427.

Schmahl, C., Vermetten, E., Elzinga, B. M., & Douglas Bremner, J. (2003). Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. *Psychiatry Research: Neuroimaging, 122*(3), 193-198.

Schore, A. N. (2000). Attachment and the regulation of the right brain. *Attachment & human development, 2*(1), 23-47.

Selby, E. A., & Joiner Jr, T. E. (2009). Cascades of emotion: The emergence of borderline personality disorder from emotional and behavioral dysregulation. *Review of General Psychology, 13*(3), 219.

Sharp, C., & Fonagy, P. (2015). Practitioner Review: Borderline personality disorder in adolescence–recent conceptualization, intervention, and implications for clinical practice. *Journal of Child Psychology and Psychiatry, 56*(12), 1266-1288.

Sharp, C., Ha, C., Carbone, C., Kim, S., Perry, K., Williams, L., & Fonagy, P. (2013). Hypermentalizing in adolescent inpatients: Treatment effects and association with borderline traits. *Journal of personality disorders, 27*(1), 3-18.

Sharp, C., Pane, H., Ha, C., Venta, A., Patel, A. B., Sturek, J., & Fonagy, P. (2011). Theory of mind and emotion regulation difficulties in adolescents with borderline traits. *Journal of the American Academy of Child & Adolescent Psychiatry, 50*(6), 563-573. e561.

Silbersweig, D., Clarkin, J. F., Goldstein, M., Kernberg, O. F., Tuescher, O., Levy, K. N., . . . Pavony, M. T. (2007). Failure of frontolimbic inhibitory function in the context of negative emotion in borderline personality disorder. *American Journal of Psychiatry, 164*(12), 1832-1841.

Steele, H., & Siever, L. (2010). An attachment perspective on borderline personality disorder: Advances in gene–environment considerations. *Current psychiatry reports, 12*(1), 61-67.

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

Takahashi, T., Chanen, A. M., Wood, S. J., Yücel, M., Kawasaki, Y., McGorry, P. D., . . . Pantelis, C. (2010). Superior temporal gyrus volume in teenagers with first-presentation borderline personality disorder. *Psychiatry Research: Neuroimaging, 182*(1), 73-76.

Takahashi, T., Chanen, A. M., Wood, S. J., Yücel, 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 and Biological Psychiatry, 33*(8), 1395-1400.

Tebartz van Elst, L., Hesslinger, B., Thiel, T., Geiger, E., Haegele, K., Lemieux, L., . . . Ebert, D. (2003). Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. *Biological psychiatry, 54*(2), 163-171.

Torgersen, S. (2000). Genetics of patients with borderline personality disorder. *Psychiatric Clinics of North America, 23*(1), 1-9.

Trull, T. J., Jahng, S., Tomko, R. L., Wood, P. K., & Sher, K. J. (2010). Revised NESARC personality disorder diagnoses: gender, prevalence, and comorbidity with substance dependence disorders. *Journal of personality disorders, 24*(4), 412.

Tyrer, P., Crawford, M., & Mulder, R. (2011). Working Group for the Revision of Classification of Personality Disorders. Reclassifying personality disorders. *Lancet*(377), 1814–1815.

van Zutphen, L., Siep, N., Jacob, G. A., Goebel, R., & Arntz, A. (2015). Emotional sensitivity, emotion regulation and impulsivity in borderline personality disorder: a critical review of fMRI studies. *Neuroscience & Biobehavioral Reviews*.

von Ceumern-Lindenstjerna, I.-A., Brunner, R., Parzer, P., Mundt, C., Fiedler, P., & Resch, F. (2009). Attentional bias in later stages of emotional information processing in female adolescents with borderline personality disorder. *Psychopathology, 43*(1), 25-32.

von Ceumern-Lindenstjerna, I.-A., Brunner, R., Parzer, P., Mundt, C., Fiedler, P., & Resch, F. (2010). Initial orienting to emotional faces in female adolescents with borderline personality disorder. *Psychopathology, 43*(2), 79-87.

Walterfang, M., Chanen, A. M., Barton, S., Wood, A. G., Jones, S., Reutens, D. C., . . . Pantelis, C. (2010). Corpus callosum morphology and relationship to orbitofrontal and lateral ventricular volume in teenagers with first-presentation borderline personality disorder. *Psychiatry Research: Neuroimaging, 183*(1), 30-37.

Weber, M. J., & Thompson-Schill, S. L. (2010). Functional neuroimaging can support causal claims about brain function. *Journal of cognitive neuroscience, 22*(11), 2415-2416.

Wells, G., Shea, B., O'connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2000). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.

Whittle, S., Chanen, A. M., Fornito, A., McGorry, P. D., Pantelis, C., & Yücel, M. (2009). Anterior cingulate volume in adolescents with first-presentation borderline personality disorder. *Psychiatry Research: Neuroimaging, 172*(2), 155-160.

Wilson, S. T., Stanley, B., Brent, D. A., Oquendo, M. A., Huang, Y.-y., Haghighi, F., . . . Mann, J. J. (2012). Interaction between Tryptophan Hydroxylase I (TPH1) polymorphisms and childhood

abuse is associated with increased risk for borderline personality disorder in adulthood. *Psychiatric genetics, 22*(1), 15.

Winsper, C., Lereya, S. T., Marwaha, S., Thompson, A., Eyden, J., & Singh, S. P. (2016). The aetiological and psychopathological validity of borderline personality disorder in youth: A systematic review and meta-analysis. *Clinical psychology review, 44*, 13-24.

Winsper, C., Marwaha, S., Lereya, S., Thompson, A., Eyden, J., & Singh, S. (2015). Clinical and psychosocial outcomes of borderline personality disorder in childhood and adolescence: a systematic review. *Psychological medicine*, 1-15.

Winsper, C., Wolke, D., & Lereya, T. (2015). Prospective associations between prenatal adversities and borderline personality disorder at 11–12 years. *Psychological medicine, 45*(05), 1025-1037.

World Health Organisation. (2016). Maternal, newborn, child and adolescent health Retrieved from http://www.who.int/maternal_child_adolescent/topics/adolescence/dev/en/

Zelkowitz, P., Paris, J., Guzder, J., & Feldman, R. (2001). Diatheses and stressors in borderline pathology of childhood: The role of neuropsychological risk and trauma. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*(1), 100-105.

Zhang, J., Cai, L., Zhu, X., Yi, J., Yao, S., Hu, M., . . . Wang, Y. (2015). Neurological soft signs in adolescents with borderline personality traits. *International journal of psychiatry in clinical practice, 19*(1), 40-44.

We would like to thank the editor for inviting us to revise our manuscript. We also thank the reviewers for their positive comments, and helpful suggestions to improve the manuscript. Please find our responses to each of the reviewers' points below. We have also typed our changes in purple text within the manuscript for ease of identification.

Reviewer: 1

Comments to the Author
This is an excellent systematic review of a literature that has not been examined in a synthetic fashion.
My only suggestion is that the authors do not discuss gene-environment interactions. I know this is not the purpose of the review, but it would put the findings in a broader context and potentially guide future research,

We thank the reviewer for these positive comments, and the useful suggestion. We have added to the manuscript:

Page 2:

Similar to findings in adult populations, twin studies indicated moderate to high levels of heritability of BPD, and there was some evidence for gene-environment interactions.

Page 12, 2nd paragraph:

Gene-environment interactions

Belsky et al. (2012) prospectively demonstrated the impact of genetic vulnerability in combination with environmental risk on the development of BPD in early adolescence. Young adolescents with a genetic risk (i.e., a family history of psychiatric disorder) and exposed to physical maltreatment had a 13-fold increased risk of being in the extreme (>95th percentile of symptoms) BPD group. In contrast, those without a genetic risk but exposed to harsh parenting had only a two-fold increased risk of being in the extreme BPD group. A similar effect was observed for high maternal negative expressed emotion, with a 15-fold increased risk for adolescents with genetic risk and exposure to negative expressed emotion compared to a five-fold increased risk for those just exposed to high expressed emotion.

Cicchetti et al. (2014) tested three-way interactions between variations in genotype (OXTR and FK506), environmental risk, and gender on the development of BPD symptoms in late childhood. Results indicated differential effects for males and females. For girls, effects were most consistent with a stress-diathesis effect, i.e., genotype (OXTR: AG-AA genotype; FK506: 1 to 2 copies of the CATT haplotype) was associated with BPD symptoms in the presence of maltreatment only. For boys, observed effects were most consistent with a differential susceptibility effect (i.e., genetic predisposition increased susceptibility for both better and worse outcomes). Boys exposed to maltreatment had significantly higher BPD scores than non-maltreated boys if they had the GG genotype of OXTR (there was no difference between maltreatment groups for those with the AG-AA genotype). For FK506, maltreated boys had significantly higher BPD scores than non-maltreated boys if they had the zero copy CATT haplotype (maltreatment groups did not differ for boys with the one to two copies of the CATT haplotype).

Page 27, 1st paragraph:

Previous adult studies have reported that risk-allele carriers with a history of childhood abuse show increased probability of BPD diagnosis (Wilson et al., 2012). Two studies included in this review support that gene-environment (i.e., childhood maltreatment) interactions may play a role in the early development of BPD (Belsky et al., 2012; Cicchetti, Rogosch, Hecht, Crick, & Hetzel, 2014), though there may be complex variations in effects according to gender (Cicchetti et al., 2014).

Page 30, 3rd paragraph:

At the genetic level, polymorphisms, such as the short allele of the 5-HTTLPR genotype (Hankin et al., 2011) and the OXTR genotype (Cicchetti et al., 2014), may underpin problems with self-and interpersonal-regulation, both of which may be exacerbated across development by environmental risk factors (e.g., childhood maltreatment, Belsky et al., 2012; Cicchetti et al., 2014). Epigenetic mechanisms, in turn, may impact on gene expression. Prenatal maternal depression, for example, may modulate infant stress responsiveness through the methylation of glucocorticoid receptors (Steele & Siever, 2010) increasing risk of adolescent BPD (Winsper, Wolke, & Lereya, 2015). Of note, individuals who inherit a genetic predisposition to BPD are also at heightened risk of environmental adversity (e.g., insecure attachment), as observed in the children of mothers with BPD (Eyden, Winsper, Wolke, Broome, & MacCallum, 2016).

Page 32, 3rd paragraph:

For a fuller understanding of BPD pathology, the effects of epigenetic programming (e.g., the impact via methylation of child maltreatment on the expression of stress-related genes) should also be considered (Perroud et al., 2013). Genome wide studies are indicated as multiple genes (e.g., MAOA, BDNF, DRD2, and COMT) are thought to play a role in moderating the impact of early life stress on the development of BPD (Prados et al., 2015).

Please also see **Figure 2,** which incorporates findings on gene-environment interactions into our summary model.

Reviewer: 2

Comments to the Author
I generally applaud the authors for their overall work! This systematic review is written on an emerging topic in the field of mental health, namely adolescent borderline personality disorder (BPD). Since the past years have led to a first set of studies on the neurobiological underpinnings of adolescent BPD, I think that the review is timely and deserves publication in a good journal. In addition, the review shows sound and well-described methodology and is nicely written.

However, some issues need to be targeted during a revision:

First of all, my major concern: Since we have now May 2016, the review needs an urgent literature update since articles are only included before January 2014 (almost two and a half years are not included in this review which is a far too long period of time). The field of adolescent BPD is growing; thus, there may be some new articles that should also be included in systematic review. As one example, the Heidelberg group around Romuald Brunner and Michael Kaess recently published on neurocognition and autonomous stress reactivity in adolescent BPD. The abstract and literature search for the past 28 months should be a feasible task.

Thank you for highlighting this. We agree that the field of adolescent BPD is growing, and that we should provide the most up-to-date review of the literature. We conducted an updated search on June 4th 2016. This yielded an additional 6 studies (Cicchetti et al., 2014; Conti et al., 2013; Kaess, Parzer, Koenig, Resch, & Brunner, 2016; Kalpakci, Vanwoerden, Elhai, & Sharp, 2016; Richter et al., 2014; Zhang et al., 2015).

Please see page 6, 2nd paragraph:

To ensure comprehensive coverage of the neurobiological literature we updated our search to include studies published between 1980 and 4th June 2016, and cross-referenced returns against our previous search.

Please see page 8, 2nd paragraph:

The cross-referenced updated search conducted on June 4th 2016 yielded a total of 12, 367 abstracts (i.e., when both searches were combined and all duplicates removed). We identified a further 6 articles from this search (Cicchetti et al., 2014; Conti et al., 2013; Kaess et al., 2016; Kalpakci et al., 2016; Richter et al., 2014; Zhang et al., 2015). Therefore, a total of 34 studies are included in the review.

Second, the authors could still be more critical of the methodology and the implications of the research conducted so far.

We have now added additional critical points regarding methodology to our limitations section, and more on future research directions (please see below). Please also see our response to reviewer 3, which outlines the implications of the research in terms of a neurodevelopmental theory of BPD.

Page 25, 2nd paragraph:

Furthermore, as nearly all of the studies were cross-sectional, it was not possible to ascertain whether neurobiological features predated the development of the disorder, or elucidate the progression of neurobiological perturbations across development (e.g., whether alterations in some brain structures or biological processes had a cascade effect, see Selby and Joiner Jr (2009)).

Page 26, 3rd paragraph:

Further, all of these studies utilised structural neuroimaging techniques. While we can speculate regarding associations between alterations to fronto-limbic structures and BPD pathology, functional imaging studies are needed to more explicitly determine links between brain activity and the clinical features of BPD (Weber & Thompson-Schill, 2010).

Page 32, 3rd paragraph:

Thus, an important next step is the use of longitudinal studies with repeated, prospective assessments of biological and environmental risk factors (Crone & Elzinga, 2015). These studies could help clarify how, and in what order, various life experiences impact on neurobiological factors (e.g., child maltreatment may produce "limbic scars" on brain functioning and structure) across development. Further, they would facilitate the statistical examination of complex reciprocal effects between environment and biology. For a fuller understanding of BPD pathology, the effects of epigenetic programming (e.g., the impact via methylation of child maltreatment on the expression of stress-related genes) should also be considered (Perroud et al., 2013). Genome wide studies are indicated as multiple genes (e.g., MAOA, BDNF, DRD2, and COMT) are thought to play a role in moderating the impact of early life stress on the development of BPD (Prados et al., 2015).

Third, why were individuals until the age of 19 included?

We included individuals up to the age of 19 as we were specifically interested in the neurobiological correlates of children and adolescents with BPD. We selected this threshold as commensurate with the WHO (2016) definition of childhood and adolescence.

Please see page 7, 1st paragraph:

(2) Participants were 19 years of age or younger (based on the World Health Organisation (2016) definition of childhood and adolescence;

And in addition, I doubt that this is entirely correct since to the best of my knowledge the imaging papers from the Melbourne group around Andrew Chanen include youth up to the age of 25!

Thank you for highlighting this potential for confusion. Although Andrew Chanen's early intervention service for BPD in Melbourne (Helping Young People Early: HYPE) caters for youth between the ages of 15 and 25 years (Chanen et al., 2009), the studies from Chanen's group included in this review had BPD participants with a maximum age of 19 years.

For example in Chanen et al. (2008) the ages of the 20 BPD participants were 19.2, 18.2, 18, 16.8, 18.9, 17.4, 17.2, 15.6, 18.2, 15.4, 17.2, 17.5, 18.2, 17.6, 18.2, 16.2, 17.5, 17.4, 16.2, and 16.0.

Please see **Table 1** for verified details on the age ranges of participants in the included studies.

One minor remark: Why does the specific research question 1 focus on brain regions only. This is misleading since it reads as if this was an imaging review. However, this review includes genetic and neuropsychological data as well.

Thank you for highlighting this omission.

Please see page 6, 1st paragraph:

Ascertain the extent to which adolescents with BPD share similar neurobiological features (i.e., genetic underpinnings, neurophysiology, brain structures, and neuropsychological processes) to adults with BPD.

Reviewer: 3

Comments to the Author
This paper presents the results of a systematic review of the literature on the neurobiology of BPD in youth. The review appears to be well-conducted and the paper is well-written. Enthusiasm was diminished slightly by some conceptual issues and a concern that the review does not do enough to chart future research. Specifically a neuro-developmental perspective is lacking and the paper will be significantly enhanced if literature can be contextualized thus. Below I provide more specific details:

1. The authors aims are (1) to ascertain the extent to which the same brain regions and processes affected in adult BPD is also affected in youth BPD and (2) critically evaluate the extant literature to test out a framework for future research. Both these aims are only partly realized. While a decent review was undertaken and while the authors discuss whether findings in adolescent samples are congruent with those in adult samples, the authors do not provide any developmentally sensitive explanation for discrepancies or overlap. The reader is left with a good summary of what is discrepant but no resolution of what this might mean. Similarly, with regard to the second aim, the authors evaluate some methodological limitations of current studies, and make some suggestions for future research, but do not provide an integrated perspective to guide future research. I feel an opportunity is missed and that the paper could have a much larger impact if it provides an integrative review rather than just a systematic one.

Thank you for this suggestion. We agree that contextualising the results within a neurodevelopmental framework will enhance the review. We now situate our review findings within a neurodevelopmental perspective of BPD, and consider future research directions from within this framework.

Please see:

Page 2, 1st paragraph:

In this review we present and critically evaluate evidence on the neurobiology of BPD in childhood and adolescence, compare this evidence to the adult literature, and contextualise within a neurodevelopmental framework.

They also provide tentative support for neurodevelopmental theories of BPD by demonstrating that neurobiological markers may be observed from childhood onwards, and interact with environmental factors to increase risk of BPD in young populations. Prospective studies with a range of repeated measures are now required to elucidate the temporal unfurling of neurobiological features, and further delineate the complex pathways to BPD.

Page 6, 2nd paragraph:

Furthermore, considering younger populations will allow for the prospective assessment of neurobiological and environmental precursors (and their interactions) to shed light on the developmental pathways to BPD at both the biological and behavioural level (Hughes, Crowell, Uyeji, & Coan, 2012).

Page 6, 1st paragraph:

3) Situate our findings within a neurodevelopmental perspective of BPD.

Page 24, 2nd paragraph:

Before we evaluate individual study findings, compare them with the adult literature, and contextualise within a neurodevelopmental framework, a consideration of methodological limitations observed across studies is warranted.

Page 25, 2nd paragraph:

Furthermore, as nearly all of the studies were cross-sectional, it was not possible to ascertain whether neurobiological features predated the development of the disorder, or elucidate the progression of neurobiological perturbations across development (e.g., whether alterations in some brain structures or biological processes had a cascade effect, see Selby and Joiner Jr (2009)).

Page 28, 1st paragraph:

Whether discrepancies in amygdala and hippocampus findings between adolescent and adult studies reflect methodological artefacts or developmentally sensitive alterations requires further explication (e.g., prospective, longitudinal studies with repeated assessments).

Page 29, 3rd paragraph onwards:

Study findings contextualised within a neurodevelopmental framework

*Several pathways to BPD incorporating various neurobiological markers (i.e., genetic, structural, neuropsychological) are indicated by the included studies (see **Figure 2**), though these hypotheses remain tentative pending future prospective research. Indeed, the current literature does not provide information on the temporality of the neurobiological underpinnings of adolescent BPD (with the exception of Belsky et al., 2012), thus our interpretations are guided by current neurodevelopmental models (Ensink, Biberdzic, Normandin, & Clarkin, 2015; Hughes et al., 2012).*

Contemporary theories for the development of BPD assert that an inborn biological vulnerability is potentiated across development by environmental risk factors giving rise to more extreme emotional, behavioural, interpersonal, and cognitive dysregulation until these precursors eventuate in clinically relevant BPD (Crowell, Beauchaine, & Linehan, 2009; Selby & Joiner Jr, 2009). Pathways to adolescent BPD are likely overlapping, encompassing genetic, biological, and environmental influences which make reciprocal contributions to the development of the disorder (Judd, 2005).

At the genetic level, polymorphisms, such as the short allele of the 5-HTTLPR genotype (Hankin et al., 2011) and the OXTR genotype (Cicchetti et al., 2014), may underpin problems with self-and interpersonal-regulation, both of which may be exacerbated across development by environmental risk factors (e.g., childhood maltreatment, Belsky et al., 2012; Cicchetti et al., 2014). Epigenetic mechanisms, in turn, may impact on gene expression. Prenatal maternal depression, for example, may modulate infant stress responsiveness through the methylation of glucocorticoid receptors (Steele & Siever, 2010) increasing risk of adolescent BPD (Winsper et al., 2015). Of note, individuals who inherit a genetic predisposition to BPD are also at heightened risk of environmental adversity (e.g., insecure attachment), as observed in the children of mothers with BPD (Eyden et al., 2016).

At the structural level, alterations to frontolimbic structures (associated with BPD) may begin as early infancy within the context of poor mother-child attachment experiences (Schore, 2000). We cannot glean from the current literature when in the developmental trajectory (or in what order) the observed alterations to frontolimbic structures occurred. Overall, however, findings of grey and white matter alterations are consistent with diminished top-down control of the limbic system. At the neuropsychological level, frontolimbic dysfunction may impact on attentional control, executive function, and mentalisation domains (Ensink et al., 2015). Consistent with this theory, studies in our review indicated child or adolescent markers of diminished executive function (e.g., Zelkowitz et al., 2001), impaired mentalisation (e.g., Sharp et al., 2011), and biases in emotion recognition (e.g., von Ceumern-Lindenstjerna, et al., 2009).

At the phenotypic (or BPD precursor) level, frontolimbic dysregulation may contribute to dysregulation of the interpersonal, emotional, behavioural, and cognitive domains, via an exacerbation of "cascades of emotion" in a self-amplifying positive feedback loop of rumination, negative emotions, and dysregulation during the day (Selby & Joiner Jr, 2009) and night via increased risk of nightmares (Lereya, Winsper, Tang, & Wolke, 2016).

As mentioned, neurobiological features (e.g., at the neuropsychological and phenotypic level) are believed to interact with one another in complex (reciprocal) ways on the pathway to BPD (Lenzenweger & Castro, 2005), and a number of possible routes are suggested by the reviewed studies. Diminished executive function, for example, could increase the risk of impulsive behaviours (Pharo, Sim, Graham, Gross, & Hayne, 2011), and thus subsequent BPD. Hyper-mentalisation could increase risk of BPD by exacerbating levels of emotional dysregulation (Sharp et al., 2011). Attentional bias to negative faces may be moderated by mood states (von Ceumern-Lindenstjerna et al., 2010) and further exacerbate a tendency to hyper-mentalise.

*Please also see **Figure 2** for our summary model of research findings*

2. Here and there references are used incorrectly. For instance, Cichetti is not the author of the BPFSC (rather Crick et al., 2005) and the definition of hypermentalizing as provided by the authors is the Sharp et al definition, not the way Franzen intended ("superior mindreading).

Many thanks for highlighting these discrepancies. We have now made the following changes to the manuscript.

Page 10, 1st paragraph:

The Borderline Personality Features Scale for Children (BPFS-C) developed by Crick, Murray–Close, and Woods (2005) covered the four domains of: affective instability, identity problems, self-harm, and negative relationships.

The Children in the Community-Self Report described by Crawford et al. (2005) was based on the DSM-IV conceptualisation of BPD.

Page 30, 2nd paragraph:

Congruent with these findings, Sharp and colleagues (2011; 2013) found that adolescents with BPD tended to "hypermentalise" or over-interpret the actions of others (i.e., make negative assumptions about other people's mental states). Studies with BPD adults have suggested atypical or superior mentalisation ability (Arntz & Veen, 2001; Fertuck et al., 2009; Franzen et al., 2011), though superior awareness appears to relate to explicit, external features (e.g., face, behaviour) rather than internal (e.g., putative thoughts and feelings) features (Sharp et al., 2013).

3. The inclusion of emotion recognition but not social cognition was curious. Both may be seen as neurocognitive/neuropsychological functions in addition to more traditional neuropsychological functions of memory, attention, executive function. The authors may decide to justify the exclusion of emotion recognition; or alternatively include social cognition in their review.

Thank you for highlighting this point. We have now incorporated studies on social cognition into our review.

Page 5, 1st paragraph:

Studies also suggest disturbances in social cognition including in the recognition (i.e., negative bias) of facial emotions (Domes, Schulze, & Herpertz, 2009), thoughts, and intentions (Preißler, Dziobek, Ritter, Heekeren, & Roepke, 2010). Studies examining mentalisation (i.e., recognition of the mental states of social interaction partners), however, indicate that adults with BPD may have superior abilities (Arntz & Veen, 2001; Fertuck et al., 2009; Franzen et al., 2011).

Page 22, 2nd paragraph:

Mentalisation capacity

Four studies reported disturbances in aspects of mentalisation (i.e., understanding others behaviour in mental state terms, also referred to as "theory of mind") in child or adolescent BPD populations.

Belsky et al. (2012) examined the prospective association between theory of mind (ToM) at 5 years and BPD symptoms at 12 years. ToM, measured with a battery of tests to determine the child's ability to attribute first and second order false beliefs, was significantly negatively correlated with BPD features ($r=-.11$, $p < .001$).

Sharp and colleagues conducted a series of studies to examine mentalisation abilities in adolescents with BPD (Kalpakci et al., 2016; Sharp et al., 2013; Sharp et al., 2011). In the first, the authors examined associations between mentalisation, emotion regulation, and BPD traits in adolescent inpatients. Mentalisation (i.e., undermentalising, no mentalisation, and excessive or hyper-mentalising reflecting an over-interpretation of mental states) was assessed with the Movie Assessment for Social Cognition (MASC) task. Emotion regulation and psychopathology were assessed via self-report. The authors found that hyper-mentalising (but not undermentalising) was independently associated with BPD traits (B=0.91, p=.002) and diagnosis (B=0.17, p=.04) following adjustment for age, sex, externalising, internalising, and psychopathy symptoms. In cross-sectional analysis (thus not indicative of temporal ordering), the association between hypermentalising and BPD was significantly mediated by difficulties in emotion regulation.

In a subsequent study, Sharp et al. (2013) investigated whether a reduction in hypermentalisation may be achieved between the admission and discharge of adolescent inpatients. They found that hypermentalisation (but not other forms of social cognitive reasoning) was responsive to milieu-based inpatient treatment (i.e., treatment placing emphasis on forming close relationships with mental health workers to provide structure and discipline). The effect was significantly more pronounced for patients with BPD in comparison to psychiatric controls (interaction effect for BPD and hypermentalising: F=5.30, p=.02, partial eta squared = .03).

Finally, Kalpakci et al. (2016) examined associations between emotion regulation, hypermentalisation (assessed with the MASC), and cognitive and affective empathy (assessed with the Basic Empathy Scale: BES) in female adolescent inpatients. Adolescents with BPD had greater affective (but not cognitive) empathy than non-BPD adolescents (Mean = 3.70, SD =0.70 vs Mean = 3.48, SD =0.65, p = .01). Emotional dysregulation was associated with increased affective empathy in BPD patients (β= 0.01, SE: 0.00, p=.01), while hypermentalisation was related to decreased cognitive empathy (β= - 0.03, SE: 0.01, p=.01). There was no relation between hypermentalisation and either type of empathy for the psychiatric controls.

Page 29, 2nd paragraph:

Results regarding social cognition suggested a tendency towards hypervigilance in adolescents with BPD. Two studies indicated a hypervigilance towards negative emotional faces at both the initial (von Ceumern-Lindenstjerna et al., 2010) and later stages (von Ceumern-Lindenstjerna et al., 2009) of emotional processing. There was an indication that this tendency may be mood dependent (von Ceumern-Lindenstjerna et al., 2010). Congruent with these findings, Sharp and colleagues found that adolescents with BPD tended to "hypermentalise" or over-interpret the actions of others (i.e., make negative assumptions about other people's mental states). Studies with BPD adults have suggested a superior mentalisation ability (Arntz & Veen, 2001; Fertuck et al., 2009; Franzen et al., 2011), though superior awareness appears to relate to explicit, external features (e.g., face, behaviour) rather than internal (e.g., putative thoughts and feelings) features (Sharp et al., 2013).

4. The review ignores the most important current debate in PD research which is the fact that the notion of BPD as we know it is currently being challenged by DSM-5 Section III and emerging data on the metastructure of psychopathology. To be a truly cutting-edge review the authors must acknowledge that any future research on the neurobiology of BPD will have to take into account changing approaches to the behavioral phenotype.

Thank you for this salient point. Please see Page 33, 1st paragraph:

There has been debate regarding the conceptualisation of BPD. The DSM-5 (Section III: Emerging Models and Measures) now presents an alternative hybrid dimensional-categorical model for further research. The new model emphasises dimensional functional impairment criteria and personality traits mapping onto six categorical personality disorders, including BPD (Anderson & Sellbom, 2015). This, and emerging data on the meta-structure of psychopathology (Ofrat & Krueger, 2012), challenge the notion of BPD as a categorical construct. A neurodevelopmental approach to the aetiology of BPD may sit well with these developments, as it seeks to elucidate the neurobiological correlates of dysfunction (associated with BPD) at varying levels of explanation (e.g., endophenotypic: executive dysfunction; phenotypic: emotional dysregulation), which may underlie multiple disorders.

References

Anderson, J. L., & Sellbom, M. (2015). Construct Validity of the DSM–5 Section III Personality Trait Profile for Borderline Personality Disorder. *Journal of personality assessment, 97*(5), 478-486.

Arntz, A., & Veen, G. (2001). Evaluations of others by borderline patients. *The Journal of nervous and mental disease, 189*(8), 513-521.

Belsky, D. W., Caspi, A., Arseneault, L., Bleidorn, W., Fonagy, P., Goodman, M., . . . Moffitt, T. E. (2012). Etiological features of borderline personality related characteristics in a birth cohort of 12-year-old children. *Development and psychopathology, 24*(01), 251-265.

Chanen, A. M., Mccutcheon, L. K., Germano, D., Nistico, H., Jackson, H. J., & Mcgorry, P. D. (2009). The HYPE Clinic: an early intervention service for borderline personality disorder. *Journal of Psychiatric Practice®, 15*(3), 163-172.

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.

Cicchetti, D., Rogosch, F., Hecht, K., Crick, N., & Hetzel, S. (2014). Moderation of maltreatment effects on childhood borderline personality symptoms by gender and oxytocin receptor and FK506 binding protein 5 genes. *Development and psychopathology, 26*(3), 831-849.

Conti, E., Nacinovich, R., Bomba, M., Uccellini, O., Rossi, M. S., Casati, M., . . . Tremolizzo, L. (2013). Diazepam Binding Inhibitor and Dehydroepiandrosterone Sulphate Plasma Levels in Borderline Personality Disorder Adolescents. *Neuropsychobiology, 69*(1), 19-24.

Crawford, T. N., Cohen, P., Johnson, J. G., Kasen, S., First, M. B., Gordon, K., & Brook, J. S. (2005). Self-reported personality disorder in the children in the community sample: convergent and prospective validity in late adolescence and adulthood. *Journal of Personality Disorders, 19*(1), 30-52.

Crick, N. R., Murray–Close, D., & Woods, K. (2005). Borderline personality features in childhood: A short-term longitudinal study. *Development and psychopathology, 17*(04), 1051-1070.

Crone, E. A., & Elzinga, B. M. (2015). Changing brains: how longitudinal functional magnetic resonance imaging studies can inform us about cognitive and social-affective growth trajectories. *Wiley Interdisciplinary Reviews: Cognitive Science, 6*(1), 53-63.

Crowell, S. E., Beauchaine, T. P., & Linehan, M. M. (2009). A biosocial developmental model of borderline personality: Elaborating and extending linehan's theory. *Psychological bulletin, 135*(3), 495.

Domes, G., Schulze, L., & Herpertz, S. C. (2009). Emotion recognition in borderline personality disorder-a review of the literature. *Journal of personality disorders, 23*(1), 6.

Ensink, K., Biberdzic, M., Normandin, L., & Clarkin, J. (2015). A Developmental Psychopathology and Neurobiological Model of Borderline Personality Disorder in Adolescence. *Journal of Infant, Child, and Adolescent Psychotherapy, 14*(1), 46-69.

Eyden, J., Winsper, C., Wolke, D., Broome, M. R., & MacCallum, F. (2016). A systematic review of the parenting and outcomes experienced by offspring of mothers with borderline personality pathology: potential mechanisms and clinical implications. *Clinical psychology review*.

Fertuck, E., Jekal, A., Song, I., Wyman, B., Morris, M., Wilson, S., . . . Stanley, B. (2009). Enhanced'Reading the Mind in the Eyes' in borderline personality disorder compared to healthy controls. *Psychological medicine, 39*(12), 1979.

Franzen, N., Hagenhoff, M., Baer, N., Schmidt, A., Mier, D., Sammer, G., . . . Lis, S. (2011). Superior 'theory of mind'in borderline personality disorder: an analysis of interaction behavior in a virtual trust game. *Psychiatry research, 187*(1), 224-233.

Hankin, B. L., Barrocas, A. L., Jenness, J., Oppenheimer, C. W., Badanes, L. S., Abela, J. R., . . . Smolen, A. (2011). Association between 5-HTTLPR and borderline personality disorder traits among youth. *Frontiers in Psychiatry, 2*.

Hughes, A. E., Crowell, S. E., Uyeji, L., & Coan, J. A. (2012). A developmental neuroscience of borderline pathology: Emotion dysregulation and social baseline theory. *Journal of abnormal child psychology, 40*(1), 21-33.

Judd, P. H. (2005). Neurocognitive impairment as a moderator in the development of borderline personality disorder. *Development and psychopathology, 17*(04), 1173-1196.

Kaess, M., Parzer, P., Koenig, J., Resch, F., & Brunner, R. (2016). Dual-task performance under acute stress in female adolescents with borderline personality disorder. *European child & adolescent psychiatry*, 1-9.

Kalpakci, A., Vanwoerden, S., Elhai, J. D., & Sharp, C. (2016). The Independent Contributions of Emotion Dysregulation and Hypermentalization to the " Double Dissociation" of Affective and Cognitive Empahty in Female Adolescent Inpatients with BPD. *JOURNAL OF PERSONALITY DISORDERS, 30*(2), 242-260.

Lenzenweger, M. F., & Castro, D. D. (2005). Predicting change in borderline personality: Using neurobehavioral systems indicators within an individual growth curve framework. *Development and psychopathology, 17*(04), 1207-1237.

Lereya, S. T., Winsper, C., Tang, N. K., & Wolke, D. (2016). Sleep problems in childhood and borderline personality disorder symptoms in early adolescence. *Journal of abnormal child psychology*, 1-14.

Ofrat, S., & Krueger, R. F. (2012). How research on the meta-structure of psychopathology aids in understanding biological correlates of mood and anxiety disorders. *Biology of mood & anxiety disorders, 2*(1), 1.

Perroud, N., Salzmann, A., Prada, P., Nicastro, R., Hoeppli, M., Furrer, S., . . . Malafosse, A. (2013). Response to psychotherapy in borderline personality disorder and methylation status of the BDNF gene. *Translational psychiatry, 3*(1), e207.

Pharo, H., Sim, C., Graham, M., Gross, J., & Hayne, H. (2011). Risky business: executive function, personality, and reckless behavior during adolescence and emerging adulthood. *Behavioral neuroscience, 125*(6), 970.

Prados, J., Stenz, L., Courtet, P., Prada, P., Nicastro, R., Adouan, W., . . . Dayer, A. (2015). Borderline personality disorder and childhood maltreatment: a genome-wide methylation analysis. *Genes, Brain and Behavior, 14*(2), 177-188.

Preißler, S., Dziobek, I., Ritter, K., Heekeren, H. R., & Roepke, S. (2010). Social cognition in borderline personality disorder: evidence for disturbed recognition of the emotions, thoughts, and intentions of others. *Frontiers in behavioral neuroscience, 4*(182), 1-8.

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 Research: Neuroimaging, 221*(3), 179-186.

Schore, A. N. (2000). Attachment and the regulation of the right brain. *Attachment & human development, 2*(1), 23-47.

Selby, E. A., & Joiner Jr, T. E. (2009). Cascades of emotion: The emergence of borderline personality disorder from emotional and behavioral dysregulation. *Review of General Psychology, 13*(3), 219.

Sharp, C., Ha, C., Carbone, C., Kim, S., Perry, K., Williams, L., & Fonagy, P. (2013). Hypermentalizing in adolescent inpatients: Treatment effects and association with borderline traits. *Journal of personality disorders, 27*(1), 3-18.

Sharp, C., Pane, H., Ha, C., Venta, A., Patel, A. B., Sturek, J., & Fonagy, P. (2011). Theory of mind and emotion regulation difficulties in adolescents with borderline traits. *Journal of the American Academy of Child & Adolescent Psychiatry, 50*(6), 563-573. e561.

Steele, H., & Siever, L. (2010). An attachment perspective on borderline personality disorder: Advances in gene–environment considerations. *Current psychiatry reports, 12*(1), 61-67.

von Ceumern-Lindenstjerna, I.-A., Brunner, R., Parzer, P., Mundt, C., Fiedler, P., & Resch, F. (2009). Attentional bias in later stages of emotional information processing in female adolescents with borderline personality disorder. *Psychopathology, 43*(1), 25-32.

von Ceumern-Lindenstjerna, I.-A., Brunner, R., Parzer, P., Mundt, C., Fiedler, P., & Resch, F. (2010). Initial orienting to emotional faces in female adolescents with borderline personality disorder. *Psychopathology, 43*(2), 79-87.

Weber, M. J., & Thompson-Schill, S. L. (2010). Functional neuroimaging can support causal claims about brain function. *Journal of cognitive neuroscience, 22*(11), 2415-2416.

WHO. (2016). Maternal, newborn, child and adolescent health Retrieved from http://www.who.int/maternal_child_adolescent/topics/adolescence/dev/en/

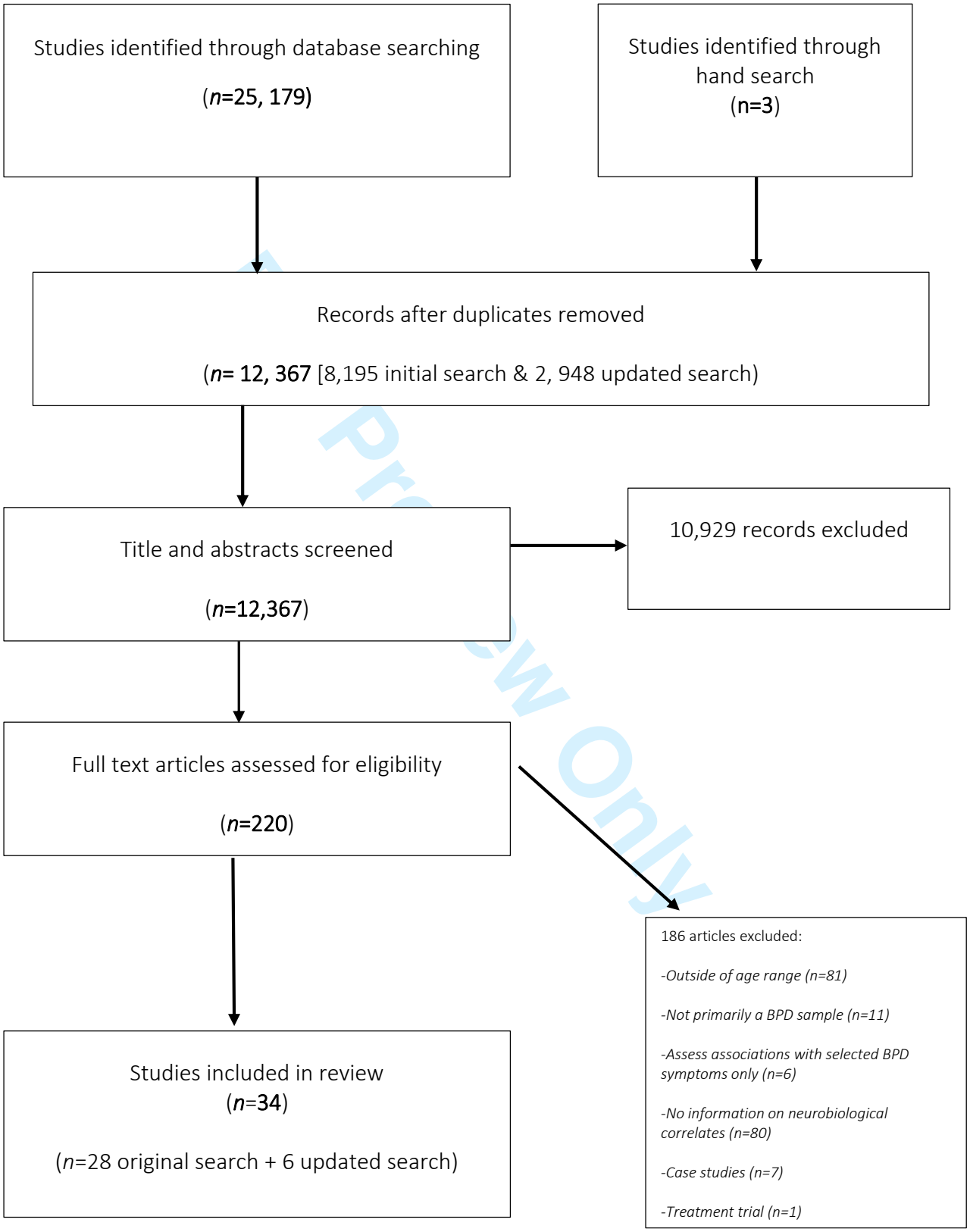
Wilson, S. T., Stanley, B., Brent, D. A., Oquendo, M. A., Huang, Y.-y., Haghighi, F., . . . Mann, J. J. (2012). Interaction between Tryptophan Hydroxylase I (TPH1) polymorphisms and childhood abuse is associated with increased risk for borderline personality disorder in adulthood. *Psychiatric genetics, 22*(1), 15.

Winsper, C., Wolke, D., & Lereya, T. (2015). Prospective associations between prenatal adversities and borderline personality disorder at 11–12 years. *Psychological medicine, 45*(05), 1025-1037.

World Health Organisation. (2016). Maternal, newborn, child and adolescent health Retrieved from http://www.who.int/maternal_child_adolescent/topics/adolescence/dev/en/

Zhang, J., Cai, L., Zhu, X., Yi, J., Yao, S., Hu, M., . . . Wang, Y. (2015). Neurological soft signs in adolescents with borderline personality traits. *International journal of psychiatry in clinical practice, 19*(1), 40-44.

Figure 1 Flowchart outlining the search and selection strategy



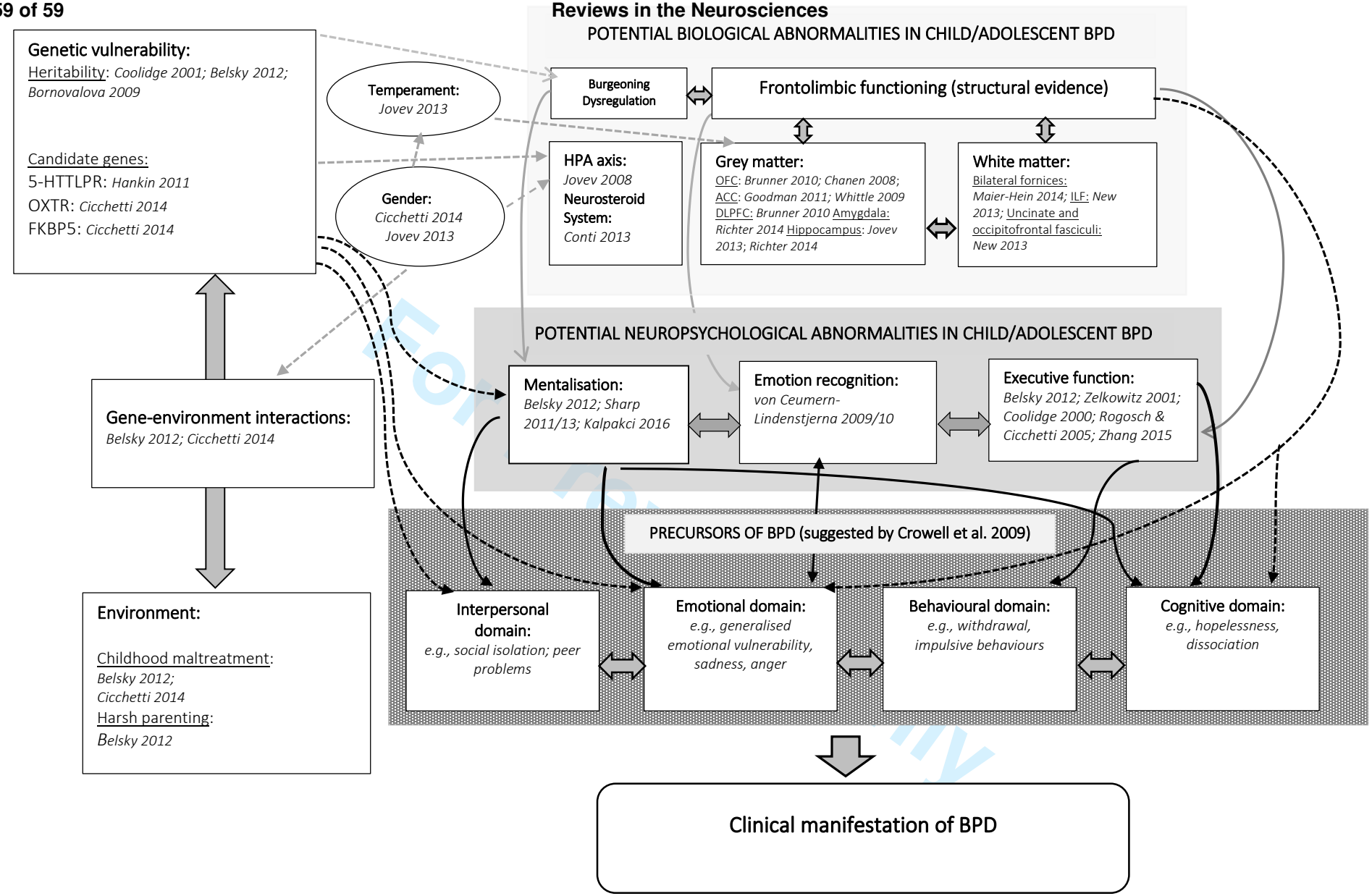


Figure 2

Results presented within a developmental psychopathology model of Borderline Personality Disorder (BPD)

Based on the biosocial developmental model of BPD (Crowell et al., 2009) and the developmental neuroscience of borderline pathology (Hughes et al., 2012); Relevant studies from the review offering support for the model are included within the figure; Black arrows represent suggested links between neuropsychological factors and BPD precursors; grey arrows represent suggested links between biological abnormalities and neuropsychological factors; black dotted arrows represent links between genetic/biological abnormalities and neuropsychological abnormalities or BPD precursors; grey dotted lines represent links between genetic vulnerability, temperament, gender, and neurobiological factors