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Nature *and* Nurture?
A review of the literature on Childhood Maltreatment and Genetic Factors in the pathogenesis of Borderline Personality Disorder

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Abstract

BACKGROUND:

Borderline Personality Disorder (BPD) is a psychiatric disorder associated with significant morbidity and mortality. However, the neurobiological alterations underlying the condition remain poorly understood. As a result, existing treatments remain inadequate. One of the main risk factors for the development of BPD is a history of childhood maltreatment. However, it is considered neither causative nor specific to the condition. Current theory is therefore increasingly moving toward a 'Gene x Environment' (GxE) model of the condition. The purpose of the current work was to conduct a systematic literature review, which comprehensively identifies all published molecular level GxE studies that have explored the role of specific genetic loci, in influencing the risk of BPD following exposure to childhood abuse or neglect.

METHODS:

Four electronic databases were used to systematically search for molecular level GxE studies of any design, which focused on the development of BPD following exposure to childhood abuse or neglect, without language or date restrictions. Articles were screened independently by two reviewers and results were synthesised narratively.

RESULTS:

A total of 473 articles were screened of which sixteen were selected for inclusion in our review. Implicated genes were categorised according to their influence on; Neurotransmitter Systems, Neurodevelopment and Neuroendocrine Systems.

CONCLUSIONS:

The identified studies have produced several relevant and statistically significant results. Of particular note, is the repeated finding that genes involved in HPA axis regulation, may be altered by exposure to childhood maltreatment, influencing subsequent susceptibility to BPD. This is both biologically plausible and of potential clinical significance.

Keywords: Child Abuse; Child Neglect; Adverse Childhood Experiences; Genetic Markers; Epigenetic Modifications; Borderline Personality Disorder.

Introduction

Borderline personality disorder (BPD) is a severe psychiatric disorder characterized by pervasive patterns of affective instability, self-image disturbances, instability of interpersonal relationships, impulsivity and suicidal behaviour (Lieb et al. 2004). It is common, with an estimated prevalence of 1-3 % of the general population, rising to 11-22% in psychiatric outpatients, and 33-49% amongst psychiatric inpatients (Chanen & McCutcheon, 2013; Sharp &Fonagy, 2015) and is known to seriously impair the quality of life of those who suffer (IsHak et al. 2013). Moreover, BPD is a condition which is associated with significant morbidity and a high mortality, with up to 10% of patients dying through completed suicide (Oldham, Skodol &Bender, 2005).

Despite these figures, and although an increasing amount of attention has been paid to the disorder in recent years, its aetiology and development pathways remain largely unexamined (Carpenter et al. 2013). As a result, existing treatments for patients remain inadequate with an indisputably unmet medical and psychological need for the development of novel therapeutic agents. This therapeutic stasis is partly a consequence of the fact that the neurobiological alterations underlying the condition remain poorly understood (Grambal et al. 2017).

Adverse Childhood Experiences in BPD

Several Adverse Childhood Experiences (ACEs) have now been identified as significant environmental risk factors for the development of BPD, including childhood illness (Bandelow et al. 2005), bullying (Sansone, Lam & Wiederman, 2010), maternal separation (Crawford et al. 2009), maladaptive parenting (Musser, Zalewski, Stepp & Lewis, 2018) and parental conflict or divorce (Porter et al. 2019).

However, of these ACEs, the impact of childhood maltreatment, including childhood sexual abuse and childhood physical or emotional abuse and neglect, is one of the most extensively studied (Stepp, Lazarus, &Byrd, 2016) and it has been repeatedly demonstrated that a diagnosis of BPD is associated

with child abuse and neglect more than any other personality disorder (Battle et al. 2004; Yen et al. 2002). Reflecting this, a recent meta-analysis of the literature identified that individuals with BPD are 13 times more likely to report childhood adversity than non-clinical controls and that of these adversities emotional abuse and neglect demonstrate the largest effect (Porter et al. 2019). Nonetheless, childhood maltreatment is currently considered to be neither causative nor specific to BPD (Hengartner et al., 2013; Paris, 2007). Indeed, 80% of subjects with a history of sexual abuse do not fulfil criteria for the disorder (Paris, 1998) and longitudinal follow-up studies of abused children showed high rates of resilience (McGloin and Widom, 2001).

Genetic Influences on BPD

Personality traits are highly heritable, with personality disorders showing similarly high genetic contribution (Newton-Howes, Clark & Chanen, 2015). Large twin studies suggest BPD has moderate to high heritability (Skodol et al. 2002) and genetic factors explain up to 42% of the variation in BPD symptomatology (Distel et al. 2008).

Most candidate gene studies of BPD have concentrated on functional genes that have biological consequences related to specific traits of the disorder, namely; impulsivity, suicidal behaviour and affective instability (Carpenter et al. 2013). Due to the identified contribution of reduced serotonergic function toward several of these traits, to date the genes which code for Tryptophan hydroxylase (TPH) and the Serotonin transporter gene (5-HTT), are the most studied candidate genes (Carpenter et al. 2013).However other implicated genes include those in which alterations could result in dopamine dysfunction, as this has previously been linked to emotional dysregulation, impulsivity and cognitive-perceptual impairment, three important dimensions of BPD (Friedel, 2004). Despite these findings, to date, no specific gene loci have been conclusively identified as causal or as conferring increased risk of BPD in isolation (Witt et al. 2017).

Gene-Environment (GxE) Interactions in BPD

As a result of these insights, it is now widely accepted that both genetic and environmental factors are at play in the pathogenesis of BPD. Current investigations are therefore increasingly moving towards an integrated Gene-Environment (GxE) model of the disorder, whereby genetic and epigenetic variability in the face of early childhood maltreatment might explain the trait-based construct (Tsuang et al. 2004; Newton-Howes et al. 2015).

While initial GxE research utilised latent, unmeasured indices of genetic influence to detect the possible presence of GxE interactions (namely through family, adoption and twin studies) (Distel et al. 2009; Reichborn-Kjennerud et al. 2010; Bornovalova et al. 2013), advances in the field have made the collection of deoxyribonucleic acid (DNA) and resultant genotyping relatively economical and straightforward (Gescher et al. 2018). As such, a growing body of molecular genetic studies has emerged, which hope to shed light on the biological processes through which exposure to environmental events could affect outcome and thus highlight potential targets for intervention (Gescher et al. 2018).

Aims

The purpose of the current work is to conduct a systematic literature review, which comprehensively identifies all published molecular level GxE studies that have explored the role of specific genetic loci, in influencing the risk of Borderline Personality Disorder following exposure to (a) childhood neglect or (b) emotional, physical or sexual childhood abuse.

Methods

The literature search was performed as a systematic review according the Preferred Recording Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009).

Eligibility Criteria

We searched for molecular level, GxE studies of any design, from any country, which focused on the development of Borderline Personality Disorder. Studies were subsequently deemed eligible for initial inclusion if they focused on: (a) genetic loci at a molecular level; in (b) human participants with a primary diagnosis of borderline personality disorder, determined by operationalised diagnostic criteria and (c) the environmental factors investigated included physical, sexual or emotional abuse or neglect occurring under the age of 18.

Search Strategy

Two researchers independently conducted a systematic literature search of PubMed, PsycINFO, EMBASE, and CINHAL, through February 2020, without date or language restrictions, using the search terms outlined in Table (1). This search was supplemented by a manual review of reference lists from eligible publications and relevant review articles.

[Table 1]

Study Selection

One reviewer (NW) screened all identified titles and abstracts of potential studies, and articles that clearly did not meet the eligibility criteria were excluded. Two reviewers (NW and ER) then independently assessed the full texts of all remaining studies against eligibility criteria. There was 100% agreement between reviewers in this process.

Data Extraction

Using a standardised template for data extraction, the following information was extracted from included studies by both principle researchers; study details (author, year of publication, country, primary aim), participant characteristics (sample size, age, gender, ethnicity), recruitment setting, methods used to assess BPD and childhood maltreatment (name of outcome measure) and study

results (where possible; odds ratios [OR], ANOVAs [F], regression analysis [R2], chi-squared tests [X2], standardised regression coefficients [b] and linear regression [β]). Where necessary and possible, study authors were contacted to clarify unclear data.

Assessment of Study Quality

The Newcastle-Ottawa Scale (NOS) (Wells et al., 2008) was used to assess the quality of included studies. This widely used measure is designed to assess the quality of observational studies, with versions available for case–control and cohort studies, as well as a recent adaptation for cross-sectional studies (Herzog et al., 2013). For the purposes of this review, a star-rating system was used to indicate the overall quality of studies, with a maximum of nine stars for cohort and case–control studies, and ten for cross-sectional studies.

Results

Searches identified 473 articles, excluding duplicates, which were screened according to title and abstract, following which 44 full articles were reviewed (Figure 1). Sixteen studies were finally included in this review.

[Figure 1]

Study Characteristics

Study characteristics are summarised in Table 2. Sample sizes ranged from 61 to 1051, with a combined sample size of 4961 from all the studies. Female participants comprised 70.2% of the total sample, which had a combined mean age of 35.2, ranging from 10.37 to 56.75 years.

[Table 2]

Results of Quality Assessment

The majority of studies scored between four and seven out of nine on the NOS, suggesting moderate to high quality (Table 3). However, common problems were no justification of sample sizes, no description of non-respondents, retrospective reporting of childhood maltreatment and inappropriate or poorly reported statistical tests.

Data Synthesis

A summary of the identified studies is provided in Table 3. A variety of methods were used to assess for childhood maltreatment, conversely Borderline Personality Disorder was assessed by the majority of studies, according to various versions of the Structured Clinical Interview for DSM-IV axis II disorders (SCID-II). The number of investigated genes also varied widely between the studies and ranged from single gene assays (Joyce et al. 2006; Martin-Blanco et al. 2014; Wagner et al. 2009, 2010a, 2010b, 2010c; Wilson et al. 2012; Perroud et al. 2011, 2013, 2016; Kolla et al. 2017; Amad et al. 2019) to genome-wide methylation analyses (Prados et al. 2015) with implications for statistical power.

As there was inadequate data available for meta-analysis, papers were alternatively collated and synthesized narratively according to the investigated genetic factor. The synthesis which emerged categorised papers according to their effect on; Neurotransmitter Systems, Neurodevelopment or Neuroendocrine Systems, as presented under subheadings below.

[Table 3]

Neurotransmitter Systems

Serotonergic System

Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine, widely regarded as a key neurotransmitter implicated in the development of normal personality (Hansenne, Pitchot & Ansseau, 2002). Its biological function is complex and multifaceted (Young, 2007); however key personality traits such

as impulsivity and impulsive aggression, common in patients with borderline personality disorder, have been shown to be associated with reduced serotonergic responsiveness (Coccaro et al. 2015). Thus, the serotonin system is a neurotransmitter system of significant interest in BPD patients (New et al. 2008).

Yet, while several studies have now identified a number of genes involved in the serotonergic system that might be linked to psychopathological changes in BPD '*per se*' (Lis et al. 2007; New et al. 2008), our review identified only three studies (Wagner et al. 2009; Wilson et al. 2012; Perroud et al. 2016) which have explored a gene-environment interaction between childhood abuse or neglect and serotonergic genes in the pathogenesis of the condition.

A potential association with childhood maltreatment and epigenetic methylation of the serotonin receptor 3A gene (5HTR3A) was explored by Perroud et al. (2016) by comparing DNA methylation levels within the 5HT3A gene in subjects with BPD, Attention Deficit Hyperactivity Disorder (ADHD) and Bipolar Disorder (BD). The authors identified that BPD subjects reported the highest levels of childhood maltreatment and that higher levels of childhood maltreatment were also significantly associated with a higher severity of illness, as determined by history of suicide attempt or having been hospitalized at least once. When compared with both BD and ADHD participants, BPD subjects had a higher $5\text{-HT}_{3A}R$ methylation status at several CpG sites (CpG2_II, CpG3_II, CpG1_III, CpG2_III and CpG4_IIII). In addition, for two CpG sites, this was mediated by a history of abuse. Specifically, the association between childhood physical abuse and severity of BPD was significantly mediated by methylation at CpG2_III and CpG5_III (Table 3).

A further study was identified, which explored the involvement of serotonin transporter gene (5-HTTLPR) polymorphisms. 5-HTTLPR is believed to play a role in suicide (Li & He, 2007), aggression (Beitchman et al., 2006), impulsivity (Frankle et al., 2005), and emotional liability (Hoefgen et al., 2005). To explore this association, Wagner and colleagues (2009) investigated the possible modulating effect of the 5-HTTLPR S/L polymorphism, which has previously been

associated with increased impulsivity (Paaver et al. 2007), on childhood sexual or physical abuse, amongst a cohort of BPD patients. The authors hypothesized that amongst individuals with this polymorphism exposure to childhood maltreatment, would increase impulsivity scores. However, using regression analysis, it was identified that when compared with 5-HTTLPR L/L-allele carriers, S-allele carriers exposed to childhood physical maltreatment and sexual abuse, actually had significantly lower impulsivity scores than those without these experiences (Table 3). Conversely in LL carriers, no marked significant association between impulsivity and childhood maltreatment was found. Despite this, their findings are noteworthy and do indicate that for 5-HTTLPR S-allele carriers, childhood maltreatment has a high effect on impulsivity, suggesting that it has a major effect on the regulation of BPD amongst those individuals, which warrants further investigation.

Finally, Wilson and colleagues (2012) explored whether Tryptophan Hydroxylase 1 (TPH1) genotypes or haplotypes moderated the relationship between childhood abuse history and BPD. TPH1 is an enzyme involved in the serotonin metabolic pathway which is responsible for catalyzing the conversion of tryptophan to 5-hydroxytryptophan, the rate-limiting step in the biosynthesis of serotonin (Swami & Weber, 2018). To explore whether TPH1 genotype has any moderating effect Wilson et al. (2012) compared self-reported history of childhood abuse and TPH1 G-6526A promoter polymorphism (rs4537731) and A218C intron 7 polymorphism (rs1800532) genotype amongst participants with a diagnosis of BPD, an Axis I mood disorder or an alternative personality disorder. Using chi-squared analysis, the authors demonstrated that patients with a diagnosis of BPD were more likely to be TPH1 risk allele carriers (A alleles at both of the above loci) than the non-BPD group (Table 3). In addition, they identified that the impact of childhood sexual and physical abuse, appeared to be significantly moderated by TPH1 genotype, with BPD being significantly more common among those with an AA/AG or AA/AC haplotype who had been exposed to childhood abuse compared with those who had not, as opposed to those with a GG or CC haplotype, where no such association was observed (Table 3).

Dopaminergic and Noradrenergic Systems

Dopamine is a catecholamine neurotransmitter, which plays a key role in regulating executive function, arousal, reward, and motor control (Grace, 2016). Through a variety of metabolic modifications within the central nervous system it can also be converted to noradrenaline (Marshall & Bangert, 2008), another catecholamine neurotransmitter, whose function has similarly been posited to be the mediation of stress responses, arousal and decision making (Stone et al. 2011). A growing interest in the role of these neurotransmitters in BPD potentially reflects increasing arguments from several authors, that the emotional dysregulation, impulsivity and cognitive-perceptual impairment commonly seen in individuals with BPD, are grounds for implicating catecholamine dysfunction in the pathogenesis of the disorder (Friedel, 2004). In keeping with this, we identified three studies (Joyce et al. 2006; Wagner et al 2010a; Martin-Blanco et al. 2015) which have explored the potential role of genes related to both the dopaminergic and noradrenergic systems and childhood maltreatment in the pathogenesis of BPD.

A 40-bp polymorphic variable number tandem repeats (VNTR) is present in the 3' untranslated region of the dopamine transporter gene SLC6A3 (DAT1), which and can vary from 3 to 12 repeats. The 9-repeat allele has previously been linked to a variety of psychiatric disorders (Heinz et al. 2004; Madras, Miller & Fischman, 2005). Therefore Joyce et al. 2006, explored the role of this 9-repeat allele in participants with major depressive disorder, with and without a co-morbid diagnosis of BPD. In doing so, they found a significant association between this allele and BPD, as well as between BPD and childhood maltreatment (Table 3). Moreover, they determined that the likelihood of BPD was significantly increased by the presence of the 9-repeat allele following exposure to childhood abuse plus neglect as a combined variable (Table 3). DAT1 functions to rapidly re-uptake dopamine from the synaptic cleft into the pre-synaptic terminals and thus acts as a key component in regulating dopaminergic neurotransmission (Kelsoe et al. 1996). The authors therefore concluded that their findings make biological sense and support a dopamine dysfunction hypothesis of the disorder.

Following this, Martin-Blanco et al. (2015) explored the potential influence on BPD risk, of over 40 polymorphisms within 4 noradrenergic genes, namely: the beta-2 adrenergic receptor gene (ADRB2); the dopamine beta (β)-hydroxylase (DBH) gene, the norepinephrine transporter (SLC6A2) gene and the Catechol-O-methyltransferase (COMT) gene, amongst BPD subjects with and without a history of childhood maltreatment. Using chi-squared analysis between patients and controls the authors identified associations between polymorphisms in COMT (rs5993882-G), DBH (rs77905-G) and SLC6A2 (rs1814270-C) and risk of BPD (Table 3). Moreover, one polymorphism within DBH (rs77905-G) was found to be significantly less frequent in BPD subjects with a history of childhood maltreatment, than in either BPD subjects with a history of abuse or controls for each type of childhood trauma (Table 3). It must be noted that this finding did not remain statistically significant after Bonferroni corrections. Nonetheless, the authors concluded that due to the conservative nature of Bonferroni corrections, the moderately large sample size and the biological plausibility of their findings, that their results would warrant replication

Finally, Wagner and colleagues (2010a; 2010b) similarly explored the moderating effects of the COMT Val158Met polymorphism on the association between childhood physical or sexual abuse, and impulsivity (Barratt Impulsiveness Scale) as well as impulsive aggression (Buss-Durke hostility inventory) respectively, amongst a sample of BPD subjects. Val158Met substantially reduces the activity of this COMT (Wagner et al. 2010b), thereby increasing levels of circulating catecholamine neurotransmitters. As such, it has previously been investigated for its potential role in the regulation of both impulsivity and aggression in several psychiatric disorders (Caspi et al. 2008). While measures of '*impulsivity*' are commonly understood to measure a predisposition toward rapid, unplanned reactions, '*impulsive aggression*' has conversely been defined as a predisposition toward aggressive behaviour produced in a deliberate, non-premeditated fashion (García-Forero et al. 2009). Using single regression procedures to look for modulating effects of COMT Val/Val, Val/Met and Met/Met, on the association between childhood maltreatment and impulsivity, Wagner (2010a) did not identify any modulating effects amongst any of these genotypes (Table 3). However, using

regression analysis, Wagner (2010b) did identify that amongst COMT Val/Val carriers, childhood sexual abuse was significantly associated with lower impulse aggression (Table 3). The authors of these papers subsequently concluded that this genotype may have a moderating effect on the relation between childhood maltreatment and impulsive aggression amongst BPD patients, yet also suggested that future studies should capitalize on other neurotransmitter systems when investigating GxE effects on impulsivity amongst this population.

Monoamine Oxidase-A

Monoamine oxidase-A (MAO-A), is an X-linked gene whose protein product degrades monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine. It is therefore relevant to all of these neurotransmitter systems and has previously been linked to aggressive, antisocial and impulsive behaviour (Beach et al. 2010).

However, although a wealth of literature has explored the role of MAO-A function in the development of Antisocial Personality Disorder (ASPD), there is a paucity of research surrounding its role in BPD (Kolla et al. 2017). This may be because MAO-A gene expression in females cannot be classified with absolute precision, due to difficulties in determining whether X-inactivation occurs at the MAO-A gene locus (Kolla et al. 2017). Nonetheless, its role in early development and association with increased impulsivity, indicate it is a gene which is clinically relevant in the study of BPD (Beach et al. 2010).

Our search identified only one study, which had explored any potential interaction between variants of this gene and childhood maltreatment in the development of BPD. A VNTR polymorphism in the human MAO-A promoter region has been shown to influence transcriptional efficiency in an allele-specific manner depending on the number of copies of the VNTR. High activity MAO-A alleles (MAOA-H), which comprise 3.5 or 4 VNTR copies, are transcribed 2–10 times more efficiently than low activity alleles (MAOA-L), which contain 2, 3, or 5 copies (Sabol, Hu & Hammer, 1998). Kolla,

Sanches and Charbonneau (2017) explored a potential interaction of the low activity variant (MAOA-L) and early childhood abuse or neglect on impulsivity scores amongst subjects with BPD, ASPD and controls. Using three-way ANOVAs, they identified a group ×genotype×abuse interaction was present for BPD patients, such that the interaction of MAOA-L and childhood abuse predicted greater impulsiveness in BPD (Table 3). Interestingly the same association was not observed in either ASPD or controls. The authors concluded that their results suggest that MAO-A gene variants may moderate the influence of early adverse experiences on risk for increased impulsivity among individuals with BPD.

Neurodevelopment

Brain Derived Neurotrophic Factor (BDNF)

Brain-derived Neurotrophic Factor (BDNF) is a protein which is important in neuronal growth, survival, synaptogenesis and neuroplasticity (Castrén & Kojima, 2017). Due to its involvement in neurodevelopment, BDNF is a natural candidate for investigating the biological correlates of early-life stress (Perroud et al. 2013). Consequently, a number of studies have now shown an association between the valine (Val)66-to-methionine (Met) variant (Val^{66}Met) within the BDNF sequence (also referred to as BDNF G196A or rs6265) in particular and a variety of mental health related disorders, including eating disorders, schizophrenia and substance misuse (Gratacòs et al. 2007). Gene environment-interaction studies have also shown that a history of maltreatment and the Val^{66}Met BDNF variant in particular, correlates positively with the development of depression (Kaufman et al, 2006) and a higher frequency of violent suicide attempts (Perroud et al. 2008).

To further investigate whether the BDNF Val^{66}Met polymorphism may also influence the effects of childhood maltreatment on BPD phenotype, Wagner et al. (2010c) compared BDNF genotype and impulsive aggression scores amongst a sample of BPD patients. Interestingly their results appeared to contradict those of Perroud and colleagues (2008), with t-tests identifying those with the Val^{66}Val genotype who had experienced childhood sexual abuse having significantly lower impulsive

aggression scores, compared to those who did not experience sexual abuse (Table 3). Conversely no difference in impulsive aggressions scores was observed for Val[66]Met carriers who experienced childhood sexual abuse compared to those who had not (Table 3). The authors proposed some of those who experienced childhood sexual abuse may have lower impulsive aggression scores due to an increased perception of danger and therefore the development of an increased ability to control their actions.

In 2013 Perroud and colleagues conducted research into the relationship between the percentage of methylation status at BDNF CpG exons I and IV, childhood maltreatment and response to psychotherapy in BPD patients. After controlling for age and gender they identified that those with BPD had a higher methylation status at both CpG regions and that the more childhood maltreatment reported, the higher the methylation status was (Table 3).

While further research is required, the results of both of these studies are significant and strengthen the findings of previous work which has indicated BDNF may play a role in a range of mood disorders (Castrén & Kojima, 2017). Further longitudinal studies are therefore essential to determine its role in the pathogenesis of BPD.

Neuroendocrine Systems

Hypothalamic-Pituitary-Adrenal-Axis

Hypothalamic-pituitary-adrenal (HPA) axis is a complex neuroendocrine system which acts as one of the main effectors of the bodies stress response (Simeon et al. 2007). However, it not only regulates peripheral body functions, but is also known to have profound effects on the brain (Simeon et al. 2007). For example, glucocorticoids regulate neuronal survival, neurogenesis, the sizes of complex anatomical structures such as the hippocampus, the acquisition of new memories and the emotional appraisal of events (Herbert et al. 2006). Unsurprisingly a concatenation of data now also implicates prolonged or excessive activity of the HPA-axis in the pathogenesis of numerous stress-

related psychiatric disorders, including BPD (van Rossum et al. 2006). We identified 6 studies (Perroud et al. 2011; Martin Blanco et al 2014; Cichetti et al. 2014; Prados et al. 2015; Martin-Blanco et al. 2016; Amad et al. 2019) which have indicated an interaction between HPA-axis related genes and childhood maltreatment in the pathogenesis of BPD.

The majority of these studies have focused on genes which regulate the systems responsivity to glucocorticoids, namely the glucocorticoid receptor gene (NR3C1) itself and FK506 binding protein 51 gene (FKPB5) which is known to be crucial in regulating the sensitivity and binding affinity of this receptor (Cichetti et al. 2104). Glucocorticoids are corticosteroid hormones, secreted under conditions of stress, which regulate HPA-axis activity through their action on glucocorticoid receptors (GR) throughout the body and within corticolimbic structures, such as the hypothalamus or hippocampus (Martin-Blanco et al. 2016). An impaired signalling pathway via GR, can lead to impaired negative feedback regulation within the HPA axis, which appears to act as the main precursor for HPA hyperactivity (Pariante &Miller, 2001). This makes genes which regulate GR availability or sensitivity, prime targets for exploring the different environmental associations with which they may interact, to increase susceptibility to a variety of stress related disorders, including BPD.

In 2011, Perroud and colleagues compared the percentage methylation of exon 1_F of the *NR3C1* promoter region, amongst subjects with BPD who had been exposed to childhood abuse or neglect, with subjects with a diagnosis of major depressive disorder who reported no history of childhood maltreatment. The authors report that significantly higher levels of methylation were found amongst subjects with a diagnosis of BPD who had been exposed to childhood sexual abuse and childhood physical neglect, when compared with the sample as a whole (Table 3). Moreover, they found that the severity of childhood maltreatment (as assessed by repetition of abuses and number of types of abuse and neglect, types of abuses) positively correlated with the degree of methylation (Table 3).

Following this, in 2014, Martin-Blanco and colleagues further explored the association between percentage methylation of exon 1_F of the NR3C1 promoter region, childhood maltreatment and current clinical severity of BPD, amongst a BPD cohort. Regression analysis similarly indicated a significantly higher mean methylation status, in subjects with a history of physical abuse or emotional neglect (Table 3). In addition, a positive correlation between methylation status and BPD clinical severity, as determined by rates of self-harm, hospitalisation and employment, was observed.

Finally, in the only identified whole-genome methylation scan of BPD subjects, Prados et al. (2015) assessed global methylation status amongst BPD subjects who reported varying levels of childhood maltreatment compared with a cohort of MDD subjects who reported low rates of child maltreatment. In doing so they identified a variety of CpGs, which were differently methylated in either BPD compared to MDD, or according to the severity of childhood maltreatment (Table 3). However, they report that their most noteworthy result was their finding that reduced methylation of CpG (cg04927004), close to the gene coding for microRNA (miR124-3), was found to be significantly associated with both the severity of childhood maltreatment and BPD (Table 3). MicroRNAs (miRNAs) are short non-coding RNAs which are responsible for modifying gene expression, through both the up regulation and down regulation of protein synthesis. This miRNA is of particular interest, as it is responsible for the regulation NR3C1, and its modification may therefore have a significant impact in HPA-axis regulation.

The authors of these studies (Perroud et al. 2011; Martin Blanco et al 2014; Prados et al. 2015) therefore hypothesize that excessive methylation of either NR3C1 or CpGs involved in its regulation, potentially as a consequence of childhood maltreatment, may permanently disturb the expression, availability or sensitivity of GR in the brain. Although such inferences are limited by the cross-sectional nature of the studies, they suggest this long-lasting effect on the HPA axis is one possible mechanism linking childhood maltreatment to the development of adulthood BPD (Perroud et al. 2011).

In 2014, Cicchetti, Rogosch, Hecht, Crick and Hetzel investigated the effects of FKPB5 haplotype (i.e. absence or presence of one or more CATT copies amongst four SNPs; rs3800373, rs9296158, rs1360780, rs9470080) in predicting child borderline personality disorder symptomatology, among maltreated and non-maltreated low-income children. In doing so they found interaction effects between maltreatment sub-types and the FKPB5 CATT haplotype in predicting BPD symptomatology when stratified by gender (Table 3). Specifically, BPD symptomatology was highest among boys with no CATT copies, who had experienced physical or sexual abuse, while for girls possessing 1 or 2 CATT copies was significantly more associated (Table 3).

Subsequently in 2016, Martin-Blanco and colleagues further explored the association between childhood maltreatment and forty-seven informative polymorphisms in ten HPA genes, amongst subjects with BPD and controls. In doing so, two FKBP5 alleles (rs3798347-T and rs10947563-A) were identified as significantly more frequent in BPD subjects with history of childhood physical abuse and childhood emotional neglect, than in BPD subjects with no abuse history.

Lastly in 2019, Amad and colleagues explored the moderating effects of five FKBP5 SNPs (rs3800373, rs9296158, rs737054, rs1360780, rs9470080) on childhood maltreatment in subjects with BPD compared to controls. Again, they identified that those with the minor allele of the rs9470080 SNP who had been exposed to physical abuse and those with the minor allele of the rs3800373 SNP who had been exposed to emotional abuse, were both significantly more likely to have a diagnosis of BPD (Table 3).

Other HPA-axis related genes which were also explored by the above studies include the Corticotropin-Releasing Hormone Receptor 2 Gene (CRHR2) and the Oxytocin Receptor Gene (OXTR) (Martin-Blanco et al. 2016; Cichetti et al. 2014). Two CRHR2 variants (rs4722999-C and rs12701020-C) were identified as significantly more frequent in BPD subjects with a history of childhood sexual abuse and childhood physical abuse, than in BPD subjects with no such history by Martin-Blanco et al. (2016). In addition, BPD symptoms were found to be significantly higher in girls

of an AA or AG OXTR SNP (rs53576) genotype and boys of a GG genotype who had been exposed to emotional abuse or physical neglect, by Cichetti et al. (2014). Involvement of either CRHR2 or OXTR in the development of BPD is plausible since both have been shown to significantly influence stress responses (De Kloet et al. 2005; Maud et al. 2018) and have previously been associated with a variety of other psychiatric disorders (Heim & Nemeroff, 2001; De Luca, Tharmalingam, & Kennedy, 2007; Maud et al. 2018). However, clearly research on the influence of these gene loci on risk of BPD is limited and further high-quality studies are warranted.

Summary

Overall, eleven papers were identified by this review which found key genetic loci that significantly moderate the relationship between childhood abuse or neglect and BPD, through predisposing genetic polymorphisms in genes involved in catecholamine neurotransmitter systems (Joyce et al. 2006; Wagner et al. 2009, 2010a, 2010b; Wilson et al. 2012; Martin-Blanco et al. 2015; Kolla et al. 2017), HPA-axis regulation (Cicchetti et al. 2014; Martin-Blanco et al. 2016; Amad et al. 2019) or neurodevelopment (Wagner et al. 2010c) (Table 5). Conversely, a mediating effect was observed in five of the identified papers, through epigenetic methylation (Martin-Blanco et al. 2014; Perroud et al. 2011, 2013, 2016; Prados et al. 2015) with implicated alterations in HPA-axis or Serotonin Receptor sensitivity (Table 4).

[Table 4]

Our results are presented according to the implications for the corresponding neurotransmitter system in isolation, and it must be noted that the effects of the identified genetic variations on gene, and subsequent neurotransmitter function remains unknown. However, if the identified variations were to confer into alterations in gene function, it must be recognised that the resultant change in any given neurotransmitter system may also have cascading consequences for others. For example, it is known that dopamine neuronal cell bodies are modulated by rich projections from serotonin neurons (Kapur

& Remington, 1996). Previous reviews have also suggested that dysfunctional interactions between serotonin and dopamine systems in the prefrontal cortex may be an important mechanism underlying the link between impulsive aggression and its comorbid disorders, including BPD (Seo, Patrick & Kennealy, 2008). Specifically, serotonin hypofunction may predispose individuals to impulsive aggression, with dopamine hyperfunction contributing in an additive fashion to the serotonergic deficit (Seo, Patrick & Kennealy, 2008). Similarly, while BDNF and serotonin are two seemingly distinct signalling systems, it has been identified that BDNF promotes the survival and differentiation of serotonin neurons, while administration of antidepressant selective serotonin reuptake inhibitors (SSRIs) enhances BDNF gene expression (Martinowich & Lu, 2008). The numerous complex interactions which may therefore be implicated by variation within a single genetic locus are beyond the scope of this review. However, it should be recognised that although we have presented the potential implications for each neurotransmitter system in isolation, any resultant changes may subsequently interact with one another.

Discussion

The objective of this review was to identify and summarize the existing GxE studies, which have sought to determine the specific genetic and epigenetic components, which influence sensitivity to BPD following exposure to childhood abuse.

Through a systematic review of the literature, we identified 16 studies, exploring the involvement of 14 different genetic loci amongst 4961 patients. Most of the identified studies were theory driven candidate gene association studies which focused on gene loci involved in the serotonergic, dopaminergic and noradrenergic neurotransmitter systems, the HPA-axis circuit, or those which code for BDNF. However, several SNPs and epigenetic modifications at specific genetic loci were found to have significant moderating or mediating effects on the association between childhood maltreatment and BPD. In addition, while only one genome-wide study was identified (Prados et al. 2015), it must be noted that it partially strengthened the findings of two other identified studies (Martin-Blanco et al.

2014, Perroud et al. 2011), all of which suggest NR3C1 activity, might play a mediating effect in the pathogenesis from childhood maltreatment to BPD. Moreover, the influence of alterations in genes related to the HPA-axis indicated by these findings, is further corroborated by several of the identified studies which suggest that FKBP5 polymorphisms may also be indicated (Cichetti et al. 2014; Martin-Blanco et al. 2016; Amad et al. 2019).

Unfortunately, all of the identified studies explored the role of specific genetic variants with unknown effects on gene function. As discussed previously, findings regarding single genetic variants are clearly not synonymous with changes in gene or subsequent neurotransmitter function and no subsequent studies exploring whether any of the identified genetic variants conferred into such alterations were found by this review. As such, the clinical significance of these findings remains unclear and further discussion on their role in influencing the relationship between childhood maltreatment and BPD is limited. However, given the crucial role of glucocorticoid receptor activity in HPA axis regulation, their implication in mediating this relationship is biologically plausible. A substantial body of evidence has identified clinically detectable alterations in HPA-axis activity amongst patients with BPD, as recognized through; reduced baseline serum, salivary and urinary cortisol (Thomas et al. 2018); blunted cortisol responses (Duesenberg et al. 2019) and volumetric reductions in the hippocampus, amygdala and medial temporal lobes bilaterally (Soloff et al. 2008) as compared to controls. Further investigation is therefore warranted to determine whether the identified epigenetic modification of NR3C1 or other CpG sites indirectly associated with its activity, do result in subsequent alterations in HPA-axis sensitivity. If so, this may represent a missing link in the pathogenesis of childhood abuse to adult borderline disorder symptomatology and would support the rethinking of BPD as a neurodevelopmental stress-related disorder.

Yet, despite these findings, GxE studies are often plagued with methodological and statistical problems, and unfortunately most of the studies we identified suffer from these limitations. Firstly, as this remains an area of emerging interest, to date there are relatively few studies available on the topic and the existing studies are significantly limited due to their relatively small sample size and often

through a lack of control group for comparison. BPD, as with the vast majority of psychiatric disorders, is likely to be highly polygenic, with thousands of independent genetic associations each of small effect (Witt et al. 2017). For example, Genome Wide Association Studies (GWAS) have indicated that genes influencing complex behavioural outcomes, such as BPD, likely have odds ratios (ORs) on the order of magnitude of 1.1 (Palk et al. 2019). This creates the need for incredibly large sample sizes, in order to determine the overall effect which contributes to meaningfully clinical risk (Palk et al. 2019).

Secondly, similar to previous reviews of GxE studies (Assary et al. 2018), a major limitation is that almost all of the identified studies lack replication samples. In particular, findings regarding: SLC6A3 VNTR 9 repeat allele carriers (Joyce et al. 2006); 5-HTTLPR S allele carriers (Wagner et al. 2009); BDNF Val/Val carriers (Wagner et al. 2010c); TPH1 SNP rs4537731 and rs1800532 carriers; CRHR2 SNP rs4722999, rs4722999 and rs12701020 carriers, MAOA-Low activity allele carriers (Kola et al. 2017); OXTR SNP rs53576 genotypes (Cichetti et al. 2014) and COMT SNP rs5993882-G, DBH SNP rs77905-G and SLC6A2 SNP rs1814270-C carriers (Martin-Blanco et al. 2015) were all without replication. While Wagner et al (2010a) and Wagner et al, (2010b) both explored the moderating effects of COMT Val/Val carrier status, the outcomes explored varied (impulsiveness vs impulse aggression). Similarly, although Martin Blanco et al. (2016) and Amad et al. (2019) both explored the moderating effect of FKBP5 SNPs, the SNPs explored varied. As such, the results of these studies were also without replication. Amad et al. (2019) and Cichetti et al (2014) both explored the moderating effects of several of the same FKBP5 SNPs (namely rs3800373, rs9296158, rs1360780, rs9470080) and both produced significant results. However, Cicchetti et al. (2014) reported only on the moderating effects of overall haplotype (number of CATT copies) amongst children, while Amad et al. (2019) explored moderating effects of individual SNPs amongst adults, limiting the comparability of these studies. A positive replication was found by Perroud et al. 2011 and Martin-Blanco et al. 2014, who both identified that increased methylation at exon 1F of NR3C1 following exposure to childhood maltreatment, was associated with increased risk of BPD and increased severity of BPD, respectively. Moreover, in Prados and colleagues (2015) subsequent genome wide

methylation analysis, reduced methylation at one CpG (cg04927004) implicated in the regulation of NR3C1 following exposure to childhood maltreatment was also identified. However, the previous findings related to exon 1F of NR3C1 specifically were not replicated, nor were findings regarding increased methylation at BDNF (Perroud et al. 2013) or 5-HT$_{3A}$R (Perroud et al. 2016). This is highly problematic. Studies of GxE interactions are likely to show a highly variable pattern of findings across studies which may be partly explained by, as discussed, the fact that the power to detect interaction effects can be small and is affected by a number of methodological artefacts (Aguinis & Stone-Romero, 1997) such as measurement error and measurement range restriction.

Thirdly, given their polygenic nature, another inherent shortcoming of investigating genetic influences on psychiatric disorders with candidate gene studies, is that they risk selecting inappropriate candidates for investigation and overlook the considerable probability that the same environmental factor will interact with multiple genetic loci (Assary et al. 2018). The identified studies widely varied regarding the particular gene site investigated and predominantly explored the influence of these variants in isolation. As such, they largely failed to investigate the potential effect of childhood maltreatment on multiple genetic loci within multiple neurotransmitter systems, simultaneously. While one genome wide study was identified, previous articles have highlighted that the SNP-by-SNP approach adopted by such studies, may also be considerably underpowered to detect the effects of multiple genetic variants acting in chorus across the genome (Assary et al. 2018). One alternative and emerging method of summarizing the risk of developing a psychiatric disorder is through Polygenic Risk Scores (Murray, 2020). Calculated on an individual basis, through combining the weighted counts of thousands of risk variants, it has been suggested that such scores could be used as a tool to represent the cumulative risk of inheriting a disorder, through aggregating contributions of the many DNA variants associated with a complex trait into a single quantitative metric (Palk et al. 2019; Murray, 2020).

Finally, despite limiting the scope of this review to the environmental impact of childhood abuse and neglect specifically, the inconstant consideration of this environmental factor is another methodical

deficit. Despite evidence that the timing and specificity of environmental factors appears to matter (Teicher & Samson, 2016), as evidenced in our review, there remains no consensus on how best to detect or assess childhood abuse or neglect and it is often still measured alongside other stressful or traumatic childhood events, to provide a single composite score (Lacey & Minnis, 2019). Assessing the impact of exposure to childhood maltreatment must take into context not just the forms of abuse or neglect experienced, but also the varying impact of exposure to additional or alternative environmental risk factors (including childhood bullying, parental separation etc.). Moreover, the self-reported, retrospective reporting of childhood maltreatment in almost all of the identified studies is problematic. This has implications for validity, as it is widely acknowledged such recall is likely to be affected by a variety of factors, including memory and mood at the time of reporting (Hardt & Rutter, 2004). It also limits the ability to control for confounding environmental variables or to draw inferences with regard to causal direction (Jaffee, & Price, 2008). As individuals actively shape their environments through heritable behaviour and inherited genotype, it is widely recognised that factors which are generally considered "environmental", may actually be under some degree of genetic influence (i.e., a gene-environment correlation) which creates obvious difficulties in establishing causality (Jaffee, & Price, 2008).

Conclusion

Clearly identifying the key genetic and epigenetic factors at play in the multi-factorial and multi-step genesis of BPD poses multiple, complex methodological challenges. However, the reviewed studies not only present biologically plausible explanations of genetically mediated susceptibility to BPD but have produced several statistically significant findings, which support the understanding of BPD as a neurodevelopmental stress-related disorder. As such they are both noteworthy and promising. They reveal several relevant gene loci that require further methodologically robust investigation but appear to support the existence of genetic and epigenetic risk and protective factors during the formation of personality structure in general, and in the pathogenesis of BPD specifically. Moreover, the pathophysiological principle of a gene-environment-interaction not only explains the obvious

differences in the severity and combination of symptoms in the BPD phenotype but may have implications for treatment. For example, while some of the reviewed studies identified specific genetic loci which were associated with alterations in impulsivity in particular amongst BPD patients (Kolla et al. 2017; Wagner et al. 2009, 2010b, 2010c), others unveiled genetic loci which were rather associated with increased rates of self-injury (Martin-Blanco et al. 2014) or hopelessness (Perroud et al. 2013). Identifying the genes which are potentially responsible for these distinct symptom clusters, may well represent a first step in identifying which treatments work best for which individuals.

We suggest future studies of GxE interactions in BPD should therefore ideally seek to be large scale, longitudinal genome wide association studies, which aim to establish polygenic risk scores for BPD that may have the potential to assist in more efficient risk identification, diagnosis and prognosis as well as improved treatment for those suffering from the condition.

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Table 1. Search Terms

Table 1.				
MeSH Search Terms				
Child abuse OR	**AND**	Genetic Phenomena OR	**AND**	Personality Disorders
Child sexual abuse OR		Genetic Markers OR		
Adult survivors of child abuse OR		Polymorphism, Genetic OR		
Child Neglect OR		Genotype OR		
Life Change Events OR		Genetics OR		
Adverse Childhood Experience		Epigenetic modification OR		
		Genes		

Table 2. Summary of Study Characteristics

Table 2.

Summary of Study Characteristics

Study	Country	Study Design	Sample Size	Female %	Age in Years (Mean, SD)	Ethnicity
Amad et al. 2019	France	CC	212	87.3%	29.2 (8.95)	Caucasian
Cicchetti et al. 2014	USA	CS	1051	50.2%	10.37 (1.30)	African American 61.2% Caucasian 10.4% Hispanic 19.7% Other 8.7%
Joyce et al. 2006	New Zealand	CC	335	63.8%	33.9 (10.9)	Caucasian
Kolla et al. 2017	Canada	CC	61	100%	35 (10.2)	Caucasian 55.7% African Canadian 12.3% Asian 20.3% Other 11.7%
Martin-Blanco et al. 2014	Spain	CC	281	85.1%	29.4 (7)	Caucasian
Martin-Blanco et al. 2015	Spain	CC	518	82.7%	41.8 (13)	Caucasian
Martin-Blanco et al. 2016	Spain	CC	596	82.66%	41.7 (12.95)	Caucasian
Perroud et al. 2011	Switzerland	CC	215	79.1%	36.57 (11)	Caucasian
Perroud et al. 2013	Switzerland	CC	167	79%	35.5 (10.6)	Caucasian
Perroud et al. 2016	Switzerland	CC	349	58.45%	38.13 (10.6)	Caucasian
Prados et al. 2015	Switzerland	CC	189	77.8%	36.78 (1.18)	Not reported
Wagner et al. 2009	Germany	CS	159	69%	33.0 (9.5)	Caucasian
Wagner et al. 2010a	Germany	CS	112	100%	33.0 (9.5)	Caucasian
Wagner et al. 2010b	Germany	CS	159	69%	33.0 (9.5)	Caucasian
Wagner et al. 2010c	Germany	CS	159	69%	32.0 (9.6)	Caucasian
Wilson et al. 2012	USA	CC	398	68.68%	38.6 (11.15)	Hispanic 20.9 % Caucasian 79.1%

(Note: CS=Cross Sectional; CC=Case Control)

Table 3. Study Summary Table.

Table 3.
Summary Table: GxE Studies exploring the Modulating Effect of Childhood Maltreatment on the Development of BPD

Author	Gene	Measure of Child maltreatment	Measure of BPD	Sample	Recruitment Setting	Results	NOS Rating
Neurotransmitter System							
Joyce et al. (2006)	DAT1 SNPs	Systematic enquiry by research nurse about childhood abuse.	SCID-II	43 subjects with BPD and MDD 292 subjects with MDD	Participants were recruited from outpatient psychiatric clinics.	Major risk factors for BPD were found to be both child abuse and neglect (OR=2.64, p<0.001) and the 9-repeat allele of the DAT1 gene (OR=3.10, p=0.002). When these were analysed together it was found that the likelihood of BPD, in the context of childhood maltreatment was significantly increased by the presence of the 9-repeat allele within DAT1 (OR=2.62, p<0.001). When the data was analysed according to age of patients it was found the presence of the 9-repeat allele was significant for those over 35 (OR= 9. 18, p=0. 007), but not for those under 35 (OR=2.03, p=0.098). This allowed for speculation that this SNP is associated with more persistent BPD.	Medium Quality (4/9)
Kolla et al. (2017)	MAOA SNPs	Childhood Trauma Questionnaire - Short Form (CTQ-SF) (Bernstein et al., 2003)	SCID-II	20 subjects with BPD 18 subjects with Antisocial Personality Disorder (ASPD) 23 subjects with no psychiatric diagnosis.	BPD subjects recruited from the community, psychiatric wards and outpatient DBT groups. ASPD subjects recruited from the community and correctional services. Controls recruited from the community.	Three-way ANOVAs identified a group×genotype×abuse interaction for motor impulsiveness (F=4.4, p=0.018), whereby BPD subjects with the MAOA-L genotype and a history of childhood abuse had significantly higher motor impulsiveness scores. The same was not observed for subjects with ASPD or no psychiatric diagnosis. Significant three-way interaction effects were not observed for attentional or non-planning impulsiveness.	Medium Quality (5/9)
Martin-Blanco et al. (2015)	ADRB2, DBH, SLC6A2 and COMT SNPs.	CTQ-SF	Spanish validated version of the SCID-II.	481 subjects with BPD 442 subjects with no psychiatric diagnosis	Recruited from 3 psychiatric hospitals in Catalonia, Spain, with specific BPD units. Controls were blood donors recruited from the general population.	Using chi-squared analysis, an association between risk of BPD and variants in the genes COMT (rs5993882-G, p=0.006), DBH (rs77905-G, p=0.04) and SLC6A2 (rs1814270-C, p=0.02) were found. In addition, when those with BPD and a history of childhood maltreatment were analysed separately, the association with COMT and DBH became more apparent. Rare variants of the COMT genes were more frequent in controls than in BPD patients (p<0.05 in all areas apart for emotional neglect). DBH rs77905-G was less frequent in BPD patients with a history of childhood maltreatment, than those without and controls (p<0.05). None of the findings retained significance after Bonferroni corrections.	High Quality (7/9)
Perroud et al. (2016)	5HTA Methylation	Childhood Trauma Questionnaire (CTQ)	SCID-II	116 subjects with BPD, 111 with attention deficit hyperactivity disorder (ADHD)	All participants recruited from a specialized outpatient centre for the treatment of BD, BPD, and ADHD	BPD patients suffered from more severe childhood maltreatment compared to the two other groups of patient (F =18.04, p< 0.0001). History of childhood maltreatment was associated with a higher severity of disorder characterized by: history of suicide attempt (OR=1.61; p=2.7×10−5), and having at least been hospitalized once (OR=1.82;	Medium Quality (4/9)

				122 with Bipolar Disorder (BD)		p=3.5×10−5). Childhood maltreatment and especially childhood physical abuse had a broad impact on 5-HT$_{3A}$R methylation levels, and BPD subjects showed a significantly higher methylation status at numerous CPG sites (CPG2_II, CpG3_II, CpG1_III, CpG2_III and CpG4_III; p<0.001) when compared with these other diagnoses, with physical abuse in particular, showing the strongest association with CpG3 II (*p*= 0.001), CpG2 III (*p*= 0.001), and CpG5 III (*p*=0.001).	
Wagner et al. (2009)	5-HTTLPR SNP	PTSD-section of the Munich-Composite International Diagnostic Interview (M-CIDI).	German version of the SCID-II. Barratt impulsiveness scale (BIS)	159 subjects with BPD	Recruited from outpatient psychiatry clinics in Germany.	Childhood sexual abuse (p=0.024) and the cumulative number of adverse experiences during childhood (p=0.028) were significantly associated with variance in impulsivity scores. No other measures of adverse childhood experiences were associated with impulsivity scores.\nHierarchical regression analysis found that in SS/SL carriers' physical maltreatment (R^2=0.09, p=0.002), childhood sexual abuse (R^2=0.073, p=0.006) and cumulative adverse childhood experiences (R^2=0.98, p=0.001) had a significant effect on impulsivity scores. Conversely in LL carriers no measure of childhood adversity was associated with variance in impulsivity scores.	Medium Quality (5/10)
Wagner et al. (2010a)	COMT SNP	DSM-IV version of the Munich-Composite International Diagnostic Interview.	Barratt Impulsiveness Scale	159 German Patients with BPD	Did not specifically state. Referred to other publications (Wagner 2010b).	Single regression procedures were used to look for a modulating effect of COMT Val/Val, Val/Met and Met/Met carriers on the effects of childhood maltreatment on BIS scores. No variance account of BIS score was found for any measure of childhood maltreatment (physical maltreatment, rape, childhood sexual abuse) for any of the different carriers. It did find that those who had experienced childhood sexual abuse had lower BIS scores (p0.022).	Low Quality (2/10)
Wagner et al. (2010b)	COMT SNP	PTSD section in the M-CIDI.	German version of the SCID-II. Buss-Durke hostility inventory (BDHI) assessed impulse aggression	112 female patients with BPD	Recruited from outpatient psychiatry clinics in Germany.	Hierarchical regression analyses identified that childhood sexual abuse explained a 26.1% variance account on BDHI sum score (*p*= 0.005). In addition, using regression analysis the authors identified that for COMT Val/Val carriers, but not Val/Met and Met/Met carriers, childhood sexual abuse was significantly associated with lower impulse aggression sum scores (R^2=0.693, *p*=0.001). Using hierarchical regression, they proposed that for Val/Val carriers, childhood sexual abuse could explain up to 69.3% (*p* = 0.001) increment in variance of impulse aggression sum scores.	Medium Quality (5/10)
Wilson et al. (2012)	TPH1 SNP	Response to 3 direct questions from the Columbia demographic and treatment history interview.	SCID-II	98 subjects with BPD\n226 subjects with no personality disorder (either MDD or Bipolar Affective Disorder)\n74 subjects with an alternative personality	All subjects were recruited through sequential psychiatric admissions.	Participants with a diagnosis of BPD were more likely to be TPH1 risk allele carriers (A alleles at both loci) than the non-BPD group (χ^2=100.32; *p*=.000). Chi-square tests also identified significant associations between TPH1 haplotype, childhood abuse history and BPD diagnosis. In participants with an AA/GA haplotype, a history of childhood physical or sexual abuse was significantly associated with BPD versus those with a GG haplotype, where no significant association was observed (χ^2=65.50; *p*<0.0001). Similarly, amongst those with an AA/AC haplotype, childhood physical and sexual abuse was significantly associated with BPD versus those with a CC haplotype, where no significant association was observed	Medium Quality (5/9)

				disorder.		$(\chi^2=100.32; p=.000)$.	

Neurodevelopment

Perroud et al. 2013	BDNF Methylation	CTQ	SCID-II	115 subjects with BPD 52 controls with no psychiatric diagnosis	BPD subjects recruited from a specialized DBT centre; controls recruited from dental clinics.	After adjustment for age and gender, using linear regression, the authors identified that BPD subjects had significantly higher methylation status in both investigated CpG regions compared with controls (32.84% vs 14.86%, β=0.61, P=0.002, 95% CI 0.22–0.99: and 11.27% vs 3.42%, β=0.66, P=0.001, 95% CI 0.24–0.99 for CpG exon IV and CpG exon I, respectively). In addition, amongst these subjects the greater the number of childhood maltreatments (sum of abuses and neglects) the higher the methylation status (b =0.12, p = 0.005). In addition, in BPD subjects there was a significant positive association between clinical severity and BDNF methylation status, as assessed by depression (b =0.02, p =0.0001), hopelessness (b =0.04; p =0.002) and impulsivity (b =0.02, p =2.32).	Medium Quality (4/9)
Wagner et al. (2010c)	BDNF SNP	PTSD section in the M-CIDI.	German Version of the SCID-II. BDHI	159 subjects with BPD	Recruited from outpatient psychiatry clinics in Germany.	Using ANOVAs the authors identified that amongst the total sample population, childhood sexual abuse accounted for 28.6% of the variance in impulsivity scores (F=9, 411; p=0.003). Regression analysis also identified that amongst Val/Val carriers a history of childhood sexual abuse (CSA) was associated with lower impulsivity scores (R^2=0.286; p=0.005). Conversely in met carriers' childhood maltreatment had no significant effect on impulsivity scores (R^2=0.133; p=0.290).	Medium Quality (5/10)

Neuroendocrine System

Amad et al. 2019	FKBP5	CTQ	French version of the structured clinical interview for DSM-IV axis II.	101 subjects with BPD 111 ethnically matched healthy controls	BPD subjects recruited from a psychiatric department of a French university hospital in Lille.	All the polymorphisms of the FKBP5 gene which were genotyped showed an association with BPD. The frequency distribution of FKBP5 AAACC haplotype was significantly different in BPD subjects than controls (p=0.02). SNP rs9470080 showed a gene environment interaction with physical abuse (p=0.01) and rs3800373 showed one with emotional abuse (p=0.03). After Bonferroni corrections none of the interactions remained significant.	Low Quality (3/9)
Cicchetti et al. (2014)	OXTR and FKBP5 SNPs	Maltreatment Classification System (MCS)	Borderline Personality Features Scale for Children (BPFS-C)	189 subjects with BPD 862 subjects with no psychiatric diagnosis.	All participants recruited from a summer camp research program designed for school-aged low-income children.	A series of initial ANCOVAS identified significant 3-way interactions between maltreatment status, gender and both OXTR (F= 4.53, p =0.01) and FKPB-5 genotype (F= 5.70, p =0.003) was found. However, this association occurred differently for boys and girls. Among maltreated girls the AG-AA OXTR genotype was significantly associated with high scores for BPD (p=0.016), when compared with the GG OXTR genotype. Conversely among maltreated boys the opposite was true, with the GG OXTR genotype being more associated with higher BPD scores (p<0.0001). Similar results were found for FKBP5-CATT haplotype. Among girls who had 1-2 CATT copies, childhood maltreatment status was significantly associated with BPD scores (p = .003), while for the 0 CATT group no difference according to maltreatment status was observed. In contrast, for boys, significant maltreatment status group differences were found for	High Quality (7/9)

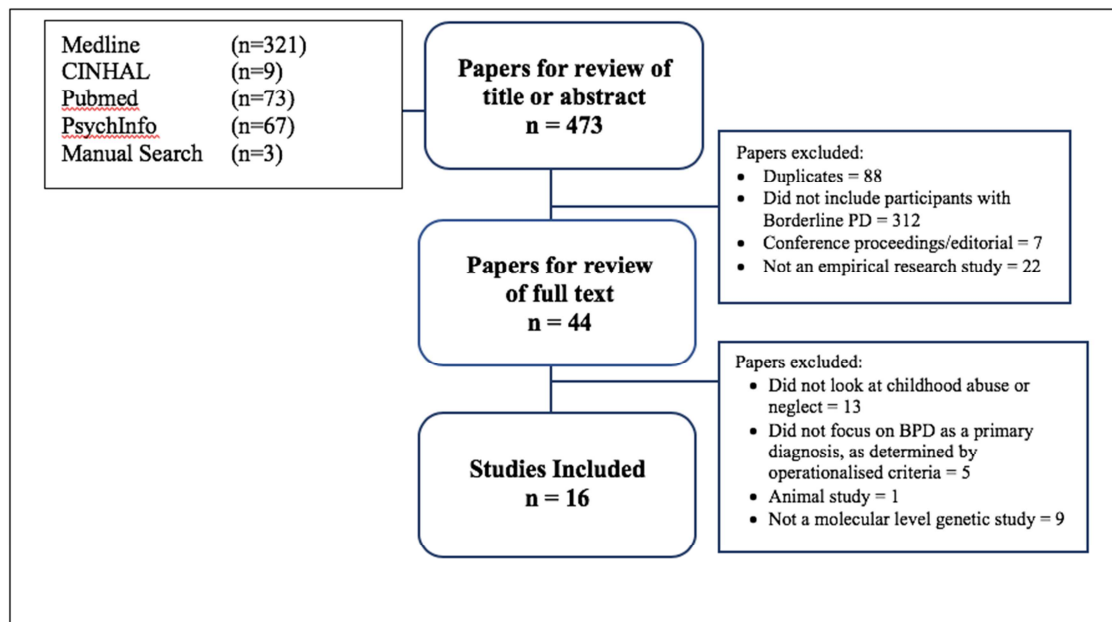|							
						the 0 CATT copies group, with maltreated boys having significantly higher BPD scores than non-maltreated boys ($p < .001$), whereas for boys with 1-2 copies of the CATT haplotype, maltreatment status groups did not differ significantly.	
Martin-Blanco et al. (2014)	NR3C1 Methylation	CTQ-SF	Structured Clinical Interview for DSM-IV [SCID-II] (First et al., 1996)	281 subjects with BPD	Recruited from 3 psychiatric hospitals in Catalonia, Spain, with specific BPD units.	Regression analysis identified an association between childhood physical abuse or emotional neglect and NR3C1 methylation status (R^2=0.10, p = 0.022). A significant positive correlation between overall NR3C1 methylation status and clinical severity, as determined by the Diagnostic Interview for Borderlines-Revised, rates of self-injury and hospitalisation, was also observed (R^2 = 0.13, p<0.001). A combined model of the association of childhood maltreatment and clinical severity with NR3C1 methylation in BPD was also statistically significant and was estimated to explain 16% of the variance.	Medium Quality (5/10)
Martin-Blanco et al. (2016)	FKBP5 and CRHR SNPs.	CTQ-SF	Spanish validated version of the SCID-II.	481 subjects with BPD. 442 subjects with no psychiatric diagnosis.	Recruited from 3 psychiatric hospitals in Catalonia, Spain, with specific BPD units. Controls were blood donors recruited from the general population.	Among BPD subjects, several CRHR2 variants were more frequent in patients with a history of childhood sexual abuse (rs4722999: β= 0.08, p=0.05) or childhood physical abuse (rs4722999: β=0.08, p=0.03 and rs12701020: β=-0.09, p=0.03) than in BPD patients with no maltreatment history or controls. Two FKBP5 polymorphisms were also relatively more frequent in BPD patients who reported childhood physical abuse (rs3798347: β=-0.08, p=0.03 and rs10947563: β=-0.08, p=0.02) and emotional neglect (rs3798347: β=-0.11, p=0.05 and rs10947563: β= −0.13, p=0.01).	High Quality (7/9)
Prados et al. (2015)	Genome Wide Methylation Analysis	CTQ	SCID-II	96 subjects with BPD 93 subjects with MDD	BPD subjects recruited in a specialized centre. MDD subjects recruited through consecutive psychiatric admissions.	10 CpGs were identified which were differently methylated in either BPD compared to MDD, or according to the severity of childhood maltreatment. In addition, one CpG was identified (cg04927004) which was found to have a significantly lower methylation status in BPD compared to MDD [0.22 (SD = 0.04) vs. 0.35 (SD = 0.04), p= 3.35×10^{-39}] and was also significantly associated with the severity of childhood maltreatment (p= 1.18×10^{-19}). The authors speculate that it may therefore have a modulating effect in the development of BPD following exposure to child abuse.	Medium Quality (4/9)
Perroud et al 2011	NR3C1 Methylation	CTQ	SCID-II	101 subjects with BPD 99 subjects with major depressive disorder (MDD) 15 participants with MDD and Post Traumatic Stress Disorder (PTSD)	BPD subjects recruited from a specialized dialectical behaviour therapy (DBT) centre; controls recruited via psychiatric hospital admissions.	Significantly more subjects with BPD reported a history of all forms of child abuse. In addition, significantly higher levels of NR3C1 methylation were found amongst subjects with a diagnosis of BPD who had been exposed to childhood sexual abuse (b =0.45; P=0.015), childhood physical neglect (b =0.38; P=0.017) and a higher number of types of child abuse in total (b =0.12; P=0.034) when compared with the sample as a whole. Finally, the severity of childhood sexual abuse (b=0.22; p=0.02) and the number of forms of abuse (b=0.28; p=0.043) positively correlated with the degree of NR3C1 methylation.	Medium Quality (4/9)

Table 4.

Childhood Exposure, Genetic Mediators, Genetic Moderators and BPD Outcome

Author	Childhood Exposure	Moderator	Outcome
Joyce et al 2006	Physical, emotional or sexual abuse	*SLC6A3* variable number tandem repeat (VNTR) - 9 repeat allele	Increased risk of BPD
Wagner et al 2009	Physical or sexual abuse	*5-HTTLPR* S allele carriers	Lower impulsivity in BPD subjects
Wagner et al 2010a	Sexual abuse	*COMT* Val/Val carriers	No significant effect observed
Wagner et al 2010b	Sexual abuse	*COMT* Val/Val carriers	Lower impulse aggression in BPD subjects
Wagner et al 2010c	Sexual abuse	*BDNF* Val/Val carriers	Lower impulsivity in BPD subjects
Wilson et al 2012	Physical or sexual abuse	*TPH1* SNPs (rs4537731; rs1800532) - AA genotype	Increased risk of BPD
Cichetti et al 2014	Emotional maltreatment or physical neglect.	*OXTR* SNP (rs53576) - AG-AA genotype (girls); GG genotype (boys). *FKPB5* CATT haplotype - 1-2 copies (girls); 0 copies (boys)	Increased risk of childhood BPD symptomatology
Martin-Blanco et al 2015	Physical or emotional abuse or neglect or sexual abuse.	*COMT* SNP (rs5993882-G) *DBH* SNP (rs77905-G) *SLC6A2* SNP (rs1814270-C).	Increased risk of BPD
Martin-Blanco et al. 2016	Physical abuse, sexual abuse or emotional neglect.	*CRHR2* SNPs (rs4722999-C; rs12701020-C) *FKBP5* SNPs (rs3798347-T; rs10947563-A)	Increased risk of BPD
Kolla et al 2017	Physical or sexual abuse	*MAOA*-Low activity allele carriers (2, 3, or 5 VNTR copies)	Increased impulsiveness in BPD subjects
Amad et al. 2019	Physical or emotional abuse	FKBP5 SNPs: rs9470080 and rs3800373	Increased risk of BPD

Author	Childhood Exposure	Mediator	Outcome
Perroud et al 2011	Sexual abuse or physical neglect	Higher methylation at exon 1F of *NR3C1*	Increased risk of BPD
Perroud et al 2013	Physical or emotional abuse or neglect or sexual abuse.	Higher BDNF methylation level	Increased risk of BPD
Martin-Blanco et al 2014	Physical abuse or emotional neglect	Higher methylation at exon 1F of *NR3C1*	Risk of increased severity of BPD
Prados et al 2015	Childhood maltreatment	Reduced methylation at Cg04927004	Increased risk of BPD
Perroud et al 2016	Physical or emotional abuse or neglect or sexual abuse.	Higher 5-HT$_{3A}$R metyhlation at CpG2_III and CpG5_III	Risk of increased severity of BPD

Figure 1. PRISMA Flow Diagram

<u>Highlights</u>

- 16 studies, exploring the involvement of 14 different genetic loci amongst 4961 patients were identified.

- Results indicated that predisposing genetic loci or subsequent epigenetic modifications exist within the serotonergic, dopaminergic and noradrenergic neurotransmitter systems, the HPA-axis circuit, or genes which code for BDNF, which may influence risk of BPD following exposure to childhood abuse or neglect.

- In particular, several studies identified that epigenetic modifications within genetic loci responsible for glucocorticoid receptor sensitivity might play a mediating effect in the pathogenesis from childhood maltreatment to BPD.

- These findings support a hypothesis of Borderline Personality Disorder as a neurodevelopmental stress-related disorder and indicate further investigation is warranted.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.