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Brain-derived neurotrophic factor Val66Met genotype modulates amygdala habituation⋆

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Abstract

A deficit in amygdala habituation to repeated emotional stimuli may be an endophenotype of disorders characterized by emotion dysregulation, such as borderline personality disorder (BPD). Amygdala reactivity to emotional stimuli is genetically modulated by brain-derived neurotrophic factor (BDNF) variants. Whether amygdala habituation itself is also modulated by BDNF genotypes remains unknown. We used imaging-genetics to examine the effect of BDNF Val66Met genotypes on amygdala habituation to repeated emotional stimuli. We used functional magnetic resonance imaging (fMRI) in 57 subjects (19 BPD patients, 18 patients with schizotypal

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Declarations of interest

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Authors' contributions

M. Mercedes Perez-Rodriguez, Antonia S. New, and Erin A. Hazlett conceived of the study, lead the statistical analyses, interpreted the results and drafted the first version of the manuscript.
Kim E. Goldstein participated in the fMRI data acquisition and processing.
Qiaoping Yuan, Zhifeng Zhou, Colin Hodgkinson, and David Goldman performed the genotyping.
Kim E. Goldstein, Daniel Rosell, Qiaoping Yuan, Zhifeng Zhou, Colin Hodgkinson, David Goldman and Larry Siever participated in the statistical analysis and interpretation of results, and helped to draft the manuscript and revise it critically.
All authors read and approved the final manuscript.

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personality disorder [SPD] and 20 healthy controls [HC]) during a task involving viewing of unpleasant, neutral, and pleasant pictures, each presented twice to measure habituation. Amygdala responses across genotypes (Val66Met SNP Met allele-carriers vs. Non-Met carriers) and diagnoses (HC, BPD, SPD) were examined with ANOVA. The BDNF 66Met allele was significantly associated with a deficit in amygdala habituation, particularly for emotional pictures. The association of the 66Met allele with a deficit in habituation to unpleasant emotional pictures remained significant in the subsample of BPD patients. Using imaging-genetics, we found preliminary evidence that deficient amygdala habituation may be modulated by BDNF genotype.

Keywords

BDNF; Amygdala; Habituation; Borderline personality disorder; Extinction; Emotion regulation

1. Introduction

Borderline personality disorder (BPD) is a common mental disorder associated with severe and persistent functional impairment and a high risk of suicide (Leichsenring et al., 2011). Emotion dysregulation is a core feature of BPD (Kuo and Linehan, 2009), and it has been proposed as a potential endophenotype (Crowell et al., 2009), linked to abnormalities in neural circuits subserving emotion processing.

Amygdala hyper-reactivity to emotional stimuli is a putative neuroendophenotype (Gottesman and Gould, 2003) for BPD (Donegan et al., 2003; Koenigsberg et al., 2009). In our previous work, we extended prior replicated findings of amygdala hyper-reactivity in BPD by demonstrating an additional deficit in amygdala habituation, particularly to unpleasant emotional stimuli (Hazlett et al., 2012). In healthy individuals, the amygdala rapidly habituates to emotional stimuli with repeated stimulus exposure (i.e. the intensity of the activation decreases after repeated presentation of the same emotional stimulus) (Breiter et al., 1996). Conversely, in BPD patients the intensity of the amygdala activation remains unchanged or even increases after repeated presentation of the same emotional stimuli (Hazlett et al., 2012). Abnormal neural responses of amygdala networks during habituation have subsequently been replicated in independent studies in BPD patients (Koenigsberg et al., 2014).

Neural circuit abnormalities likely arise from the interaction of genetic and environmental factors. However, despite robust evidence from family, twin, and adoption studies supporting an underlying genetic vulnerability to BPD, its specific genetic underpinnings have not been thoroughly investigated (Amad et al., 2014; Calati et al., 2013; Siever et al., 2002).

Amygdala reactivity is under genetic control by brain-derived neurotrophic factor (BDNF) variants (Frielingsdorf et al., 2010; Soliman et al., 2010; Yu et al., 2012). However, despite evidence that BDNF genotype modulates amygdala activity during extinction learning (Soliman et al., 2010), whether amygdala habituation is itself under genetic control by BDNF genotype remains unexplored.

Brain derived neurotrophic factor (BDNF) is a neurotrophin growth factor essential for the development, functioning, neuronal plasticity, and well-being of the central nervous system (Numakawa et al., 2010). BDNF has been implicated in modulating reactivity to stress (Alexander et al., 2010) and in the pathophysiology of several psychiatric disorders (Balaratnasingam and Janca, 2012).

The most common and widely studied functional single nucleotide polymorphism (SNP) of the BDNF gene in humans is in exon 11 and results in an amino-acid substitution from valine (Val) to methionine (Met) at codon 66 (rs6265, also known as Val66Met) (Bath and Lee, 2006). The BDNF Val66Met SNP has been associated with risk for psychiatric disorders and suicide (Hong et al., 2011). This functional SNP prevents the activity-dependent release of BDNF (Egan et al., 2003) and some – but not all (Moreira et al., 2015; Tramontina et al., 2007) – studies have found that Met-carriers have lower serum BDNF levels (Ozan et al., 2010; Zakharyan and Boyajyan, 2014).

The 66Met allele is associated with increased neural reactivity to emotional stimuli in the amygdala and other areas involved in emotion processing (Lau et al., 2010; Montag et al., 2008; Outhred et al., 2012). Furthermore, in both mice and humans, the 66Met allele is associated with impaired extinction learning of a conditioned fear response (Frielingsdorf et al., 2010; Soliman et al., 2010; Yu et al., 2012). The involvement of BDNF genotype in modulating amygdala habituation is supported by research and theoretical evidence suggesting that extinction is accompanied by habituation-like processes (Delamater and Westbrook, 2014; McSweeney and Swindell, 2002). According to this theory, conditioned responding declines during extinction partly because habituation occurs to stimuli that support conditioned responding (McSweeney and Swindell, 2002). The fear extinction deficit in BDNF Val66Met Met carriers is associated with excessive amygdala reactivity - unsuppressed by the prefrontal cortex (Soliman et al., 2010). Although the exact molecular mechanism is still unknown, this amygdala hyper-reactivity may be caused by abnormal synaptic plasticity and glutamatergic transmission in amygdala-hypoccampus-prefrontal cortex pathways, which are modulated by the Val66Met polymorphism (Galvin et al., 2015). Some animal model data support this theory. For example, homozygous MetMet mice show a deficit in N-methyl-D-aspartate (NMDA) receptor-dependent synaptic plasticity in the hippocampus (Ninan et al., 2010). Moreover, mice carrying the Met allele of the BDNF Val66Met polymorphism show epigenetic changes that result in decreased expression of the glutamatergic mGlu2 receptor in the hippocampus (Nasca et al., 2015).

Although low platelet BDNF levels have been reported in BPD patients, (Koenigsberg et al., 2012) only one research group has examined a possible genetic association between the BDNF Val66Met SNP and BPD to date, and they reported no significant differences between BPD patients and healthy controls (HCs) in genotype distribution of the BDNF Val66Met SNP. However, the authors did find a gene-gene interaction suggesting increased susceptibility for BPD in subjects with the BDNF 66Met allele among those carrying the A-161 allele for the A-161T (rs130058) SNP in the promoter region of the serotonin receptor 1B gene (HTR1B) (Tadic et al., 2009). The A-161T SNP has a functional effect, and the A allele is associated with higher expression of the HTR1B gene (Conner et al., 2010). The same group also found that the BDNF Val66Met polymorphism modulated the

effects of serious life events on impulsive aggression in patients with BPD (Wagner et al., 2010).

Elucidating the neural systems and genetic modulators that contribute to the complex construct of BPD and fractionating it into neurobiologically defined pathophysiologic subtypes is crucial for refining testable models and discovering novel treatment targets. This approach - closely aligned with the Research Domain Criteria initiative of the National Institute of Mental Health (Insel et al., 2010) – is particularly relevant for BPD, a disorder with a highly heterogeneous categorical diagnosis (Gunderson, 2010).

One way to gain greater pathophysiologic resolution in psychiatric disorders is to combine dimensional neuroendophenotypes and genetics. Indeed, the role of functional genetic variants in modulating emotion processing is supported by the highly promising results of imaging genetics studies in other psychiatric disorders and in healthy volunteers (Gillihan et al., 2010; Lonsdorf et al., 2011; Meyer-Lindenberg, 2012; Pezawas et al., 2008). Surprisingly, imaging-genetics studies are lacking in BPD.

In the present study, we investigate for the first time the genetic underpinnings of amygdala habituation in psychiatric patients and healthy controls using an imaging-genetics framework (Pezawas and Meyer-Lindenberg, 2010). Specifically, we examined the effect of BDNF Val66Met SNP genotypes on functional magnetic resonance imaging (fMRI)-measured blood oxygen level–dependent (BOLD) amygdala habituation to repeated emotional and neutral pictures (i.e., fMRI BOLD activity within the amygdala ROI during novel vs repeated picture presentation). Our main hypothesis was that BDNF Val66Met genotypes would modulate amygdala habituation, such that 66Met allele carriers would show decreased habituation compared to non-Met (Val/Val) carriers across diagnoses.

As an exploratory aim, we examined interactions between Val66Met and psychiatric diagnosis on amygdala habituation. Since we had previously described the neural deficit of amygdala habituation in BPD patients, we chose to recruit a sample of BPD patients, healthy controls and a psychiatric control group of schizotypal personality disorder (SPD) patients. The inclusion of BPD patients without comorbid SPD and SPD patients without comorbid BPD allows better evaluation of diagnostic specificity or a potential diagnosis-by-genotype interaction (Lau et al., 2010).

2. Methods

2.1. Participants

A total of 57 subjects (37 patients and 20 healthy control subjects) participated in this study (See Table 1 for sociodemographic and genotype details). All patients met DSM-IV criteria for either BPD without SPD (n=19), or SPD without BPD (n=18) respectively.

For each subject, diagnosis was established via consensus meeting by a team of doctoral-level psychologists with high inter-rater reliability and expertise in evaluation of personality disorders. Diagnostic instruments included the Structured Clinical Interview for DSM-IV

Axis I disorders (SCID-I; (First et al., 2001)) and Structured Interview for DSM-IV Personality Disorders (SIDP-IV; (Pfohl et al., 1997)).

All patients were unmedicated for at least six weeks at the time of their fMRI scan and most were never previously medicated. Exclusion criteria included having a lifetime history of substance dependence, schizophrenia, other psychotic disorders, or bipolar disorder type I; a post-traumatic stress disorder (PTSD), anxiety disorder or major depressive disorder (MDD) episode within two months of study participation; or substance abuse within 6 months of participation (current substance use was excluded via urine toxicology). HCs had no Axis I or II diagnosis and no Axis I disorder in any first-degree relative. Exclusion criteria for all subjects included history of head trauma, neurological disease, organic mental syndrome, and mental retardation.

Patients and controls were matched by gender across BDNF Val66Met genotypes. Because there were significant differences in age across diagnostic groups and genotypes, we repeated all significant analyses including age as a covariate, and found that age was not significantly related to the dependent variable (data not shown). Four BPD patients had a lifetime history of PTSD. The rates of lifetime history of PTSD were not significantly different across diagnostic groups or genotypes.

Participants who participated in earlier fMRI studies were offered the opportunity to be genotyped. The study was approved by the Institutional Review Board at Icahn School of Medicine at Mount Sinai; after complete description of the study to the subjects, written informed consent was obtained.

2.2. Genotyping

The rs6265 or Val66Met SNP in exon 11 of the BDNF gene was one of the 130 candidate genes genotyped on a custom-designed Illumina 1536 SNP array, described in detail in prior publications (Perez-Rodriguez et al., 2010). Genotyping was carried out following Illumina GoldenGate assay protocols and the arrays were imaged on an Illumina Beadstation GX500. Details of the data analysis and quality controls have been described previously (Hodgkinson et al., 2008). Subjects were classified as Met-allele carriers or Non-Met allele carriers (ValVal homozygotes). (Frielingsdorf et al., 2010) Frequencies of all Val66Met genotypes and of Met allele carriers and Non-Met allele carriers are shown in Table 1.

2.3. Functional and structural MRI acquisition

The MRI scanner was a head-dedicated 3 T scanner (Siemens, Erlangen, Germany) and included a T2, echo planar image (EPI), and T1-weighted structural magnetization prepared rapid acquisition gradient-echo (MP-RAGE) scan. Echo Planar Images were acquired with a BOLD-EPI sequence (42-axial slices, 2.5 mm thick, skip =0.8 mm (33%), TR =3000 msec, TE =27 msec, flip angle =85°, FOV =210 mm, matrix =64 × 64). For high-resolution-structural-images that allowed accurate anatomical tracing of the amygdala, we acquired T1-weighted structural magnetization-prepared rapid gradient echo (MP-RAGE) imaging (208 slices for whole brain; axial acquisition, 0.82 mm slice thickness, TR =2500 msec, TE =4.38 ms, TI =1100 msec, flip angle =8°, FOV =210 mm, matrix size =256 × 256 × 208).

2.4. Event-related fMRI affective picture processing task

During the fMRI scan, participants viewed 96 intermixed unpleasant, neutral, and pleasant photographic pictures from the International Affective Picture System (IAPS). E-Prime software was used for the presentation of all stimuli in the scanner. The 96 pictures were presented twice within their respective run for a total of 192 picture trials. Each trial was 8 s long and included either 1) the presentation of a picture (for 6 s) followed by a three-choice button press response prompt (for 2 s; described in detail below) or 2) a fixation cross (8 s). The presentation of either a picture or fixation cross was semirandomized with the number of consecutive trials varying from one to six for pictures and one to three for fixation trials. Each run contained 24 unique pictures (eight unpleasant, eight neutral, eight pleasant) that were repeated once (48 picture events) and 16 non-picture (fixation cross) events (total of 64 contiguous trials per run). The contrast for generation of the BOLD images was the fixation point prior to picture onset as part of the time series. We used the Custom (3 column format) in FSL's FEAT for the basic shape of the waveform to model the stimulus. The first number was the onset of the stimulus. The second number was the duration of the stimulus which was 6 s. The third number was set to 1. The total scan time was 38 min and 12 s, which was divided into four runs with 30 s before and 31 s after each run (30+[8 × 64] +31=573 s; four runs =2292 s) (Hazlett et al., 2012).

Predominantly social pictures including faces and social interactions were included (Hazlett et al., 2012). Across the four runs, the unpleasant and pleasant pictures were matched based on the picture ratings from the standardized IAPS manual for arousal and opposite for valence. They were equally divergent from neutral in arousal and valence intensity. The neutral pictures were matched across each of the four runs on arousal and valence. All participants viewed the same stimulus sequence. Participants were instructed to attend to the pictures and think about their meaning for them personally.

2.5. Image processing

The FSL fMRI Expert Analysis Tool (FEAT) was used for image processing. We conducted an event-related analysis of the time-series of the BOLD response on the bilateral amygdala region of interest, which was hand-traced on structural MRI for each individual participant and co-registered to the BOLD images. BOLD data were preprocessed with motion correction using MCFLIRT (Jenkinson et al., 2002), nonbrain removal using Brain Extraction Tool (Smith, 2002), spatial smoothing (full-width at half maximum =5 mm), and a high-pass temporal filter (cutoff =70 s) to remove low-frequency signals. None of the subjects included in the sample were excluded for head motion. Prior to this final sample, two subjects were eliminated as they could not complete the scan due to claustrophobia (one healthy control and one BPD patient).

The MPRAGE and echo planar images were co-registered with a 7 degrees of freedom linear transformation followed by alignment to the Montreal Neurological Institute brain template using a 12 degrees of freedom linear fit.

Amygdala region of interest (ROI) tracing: For each participant, the amygdala volume was traced bilaterally on anterior commissure-posterior commissure positioned structural/

MPRAGE images using our published methods (Hazlett et al., 2012). Following the co-registration, we obtained the mean BOLD response time-series values 1–11 with each 3-second epoch beginning at picture onset and continuing to 33 s; 11 × 3 =33 s) for the fMRI hemodynamic response curves averaged across the voxels within the bilateral amygdala ROI for each of the key stimulus conditions (novel/unpleasant, repeated/unpleasant, novel/pleasant, repeated/pleasant, novel/neutral, repeated/neutral) averaged across all runs. We have previously published our methods for using a similar time series approach for the BOLD response (Hazlett et al., 2008, 2012).

We conducted a multivariate, repeated measures analysis of variance (MANOVA) using Statistica (StatSoft, Tulsa, Oklahoma). We included the following factors in the analysis: Diagnostic group (HC vs. BPD vs. SPD); Genotype (Met-carriers vs Non-Met carriers); Picture valence (Unpleasant, Neutral, Pleasant); Picture repetition (novel, repeated); Time (epochs 1 to 11=3 s, 6, 9…33 s following picture onset). Diagnostic group and Genotype were the between-group factors and the remaining factors were all repeated measures. We report multivariate *F* values (Wilks' lambda) and two-tailed p values. Significant interaction effects with Genotype were followed-up using Fisher's Least Significant Difference (LSD) tests.

The unique task design and data analytic plan allows to compare the longitudinal time course of amygdala BOLD activity (i.e., the shape of the curve) during habituation across diagnostic groups and genotypes.

3. Results

Main effects of diagnostic group, picture valence and repetition (novel vs repeated) have been reported previously, as well as the results of a whole-brain analysis confirming the amygdala ROI findings (Hazlett et al., 2012). What follows are the results describing the effect of BDNF Val66Met genotype on habituation (i.e., fMRI BOLD activity within the amygdala ROI during novel vs repeated picture presentation).

3.1. Effects of BDNF genotype on amygdala habituation across diagnoses

Consistent with our hypothesis, a significant Genotype × Picture repetition interaction (F[1,51] =4.48, p=0.039, Wilks) (Fig. 1) indicated that Met-carrying individuals had deficient amygdala habituation –or even a sensitization/potentiation-compared to non-Met allele carriers.

Among Met carriers across diagnostic groups, amygdala activation was higher for repeated compared to the novel picture presentations, representing a failure in habituation or a sensitization. Conversely, non-Met carriers showed the normal pattern of habituation, with higher amygdala activation for novel compared to repeated picture presentations. Met carriers had a lower amygdala response to the novel picture condition compared to the non-Met carrier group, although this difference did not reach statistical significance.

We further delineated the role of BDNF Val66Met genotypes in modulating amygdala habituation, described above, by exploring the effect of picture valence, time course of the

BOLD activity after picture onset, and diagnostic group through a series of interaction analyses reported below.

3.2. Effect of picture valence

A Genotype × Picture valence × Picture repetition interaction (F[2,50] =4.19, p=0.021, Wilks) (Fig. 2) indicated that carrying the 66Met allele was associated with a deficit in amygdala habituation particularly to emotional (unpleasant and pleasant) pictures.

3.3. Effect of time

When we included time in the analyses, we found that, both Met and Non-Met carriers show similar curves of BOLD activation during the novel picture presentation, with the Met carriers having a non-significantly smaller curve and a faster return to baseline. Among Non-Met carriers, the amygdala response curve was very reduced (almost flat) during the repeated presentation of the pictures, showing the normal habituation effect. Conversely, Met–carrying individuals showed significantly higher amygdala activation compared to Non-Met carriers during the repeated picture presentation, representing a failure to habituate (Fig. 3, Genotype × Novel/Repeat Picture repetition × Time interaction, F[10,42] =2.80, p=0.009, Wilks).

3.4. Effect of diagnostic group

A Diagnostic group × Genotype × Picture valence × Novel/Repeat Picture repetition × Time interaction (F[40,64] =1.68, p=0.032, Wilks) revealed that the 66Met allele remained significantly associated with deficient amygdala habituation to unpleasant emotional pictures in the subsample of BPD patients. Met-carrying BPD patients had increased and prolonged amygdala reactivity during repeated unpleasant pictures compared to Non-Met carrying BPD patients and both SPD and HC Met and non-Met carriers (Fig. 4). This was not true during the novel presentation (Data not shown).

4. Discussion

Using an imaging-genetics paradigm and building on replicated prior evidence of extinction learning modulation by BDNF Val66Met genotypes, our hypothesis-driven study shows for the first time that amygdala habituation is also modulated by BDNF Val66Met genotype.

Specifically, as we hypothesized, we found that BDNF 66Met allele carriers across diagnoses show decreased habituation (or even sensitization) to emotional stimuli (Fig. 1). This habituation deficit seems to be specific to emotional (unpleasant or pleasant), but not neutral pictures (Fig. 2).

Our findings support a link between the BDNF 66Met allele and the amygdala habituation deficit to unpleasant emotional pictures that we previously reported in BPD patients (Hazlett et al., 2012). Since habituation is likely required for extinction (Delamater and Westbrook, 2014; McSweeney and Swindell, 2002), the role of BDNF Val66Met genotypes in modulating amygdala habituation that we report here may be consistent with the previously replicated association of the BDNF 66Met allele with abnormal amygdala activity and

impaired extinction learning of a conditioned fear response (Frielingsdorf et al., 2010; Soliman et al., 2010; Yu et al., 2012). Consistent with this theory, PTSD patients carrying the BDNF 66Met allele had poorer responses to exposure therapy, which is believed to be based on extinction and habituation of fear responses (Felmingham et al., 2013; McGuire et al., 2014).

New therapies targeting BDNF pathways hold promise for disorders characterized by extinction/habituation deficits such as BPD or PTSD (Andero and Ressler, 2012). For example, the partial NMDA-receptor agonist d-cycloserine, which is a BDNF modulator, is a potential novel treatment that might normalize amygdala habituation in BPD. Both animal and human studies have shown that d-cycloserine enhances fear memory extinction, likely through its action on BDNF (Andero and Ressler, 2012; VanElzakker et al., 2014), so it may also enhance habituation. Furthermore, a single injection of d-cycloserine during extinction training reversed the deficit in extinction learning observed in BDNF 66Met homozygous mice (Yu et al., 2012). Of note, many commonly prescribed drugs for the treatment of schizophrenia and depression –often used off-label to treat symptoms of BPD-modulate BDNF, but the mechanism remains unknown (Price et al., 2007). Furthermore, growing evidence suggests that BDNF levels increase with antidepressant treatment (Sen et al., 2008).

When comparing the time course of the amygdala BOLD response after viewing novel and repeated pictures, we also found preliminary evidence of a genotype effect on habituation. Among Non-Met carriers, the amygdala response curve was almost flat during the repeated presentation of the pictures, representing the normal habituation effect. Conversely, Met–carrying individuals showed significantly higher amygdala activation compared to Non-Met carriers during the repeated picture presentation, representing a failure to habituate, or even a sensitization (Fig. 3).

We also found preliminary evidence of a diagnosis-by-genotype interaction, suggesting that the magnitude of the effect of BDNF Val66Met genotype on amygdala habituation differs across diagnostic groups. BPD patients carrying the BDNF 66Met allele showed decreased amygdala habituation to unpleasant emotional pictures compared to 66Met carriers in the HC or SPD groups (Fig. 4). This finding suggests that the risk effects of the 66Met allele may be more robustly expressed among BPD patients, leading to pathological out-comes, because of the presence of other risk factors (e.g., other gene polymorphisms, environmental factors such as childhood trauma or epigenetic factors), whereas they may be buffered by the presence of other protective factors in HCs (Lau et al., 2010). This diagnosis-by-genotype interaction is consistent with recent work showing that BPD diagnosis is associated with significantly higher methylation at select CpG sites in the BDNF gene and promoter (Perroud et al., 2013; Thaler et al., 2014), which may enhance the detrimental effects of the 66Met allele. Moreover, in BPD patients childhood maltreatment is associated with higher levels of methylation, and methylation decreases among BPD treatment responders after Dialectical Behavioral Therapy (DBT) (Perroud et al., 2013). Interestingly, DBT, an evidence-based psychotherapeutic treatment for BPD, targets emotional hyperreactivity and emotion dysregulation (Goodman et al., 2014, 2009), and also decreases amygdala reactivity in treatment responders (Goodman et al., 2014; Schnell and Herpertz, 2007). Furthermore,

growing evidence suggests that BDNF levels are state-dependent, likely regulated by epigenetic factors (Molendijk et al., 2011).

This study follows the RDoC approach since, rather than aiming to examine the neurobiology of the categorical diagnosis of BPD, it aims to elucidate the neurobiology underlying emotional hyperreactivity/dysregulation -which is a core dimension of BPD but is also found in other disorders-using multiple levels of analysis (neural activation using fMRI, and genetic factors –Val 66Met BDNF genotype-). Our results support the utility of the RDoC approach since they suggest that, rather than being a homogeneous group, within BPD patients there is significant heterogeneity in amygdala habituation, which may be modulated by BDNF Val66Met genotype. This may have important implications for treatment selection and outcomes.

Identifying genetically modulated neural biomarkers that contribute to emotion processing and habituation abnormalities in disorders characterized by emotional dysregulation, such as BPD, is key for developing etiopathological models, novel therapeutic targets and preclinical animal models, and to allow early diagnosis and intervention. This is particularly relevant for BPD because, notwithstanding the seriousness of this disorder, including a high suicide rate and use of mental health resources (Oldham, 2006; Skodol et al., 2002), there are no FDA approved pharmacologic treatments currently available, in part due to limited knowledge about its neurobiology.

Moreover, genetic and neuroimaging biomarkers of abnormal emotion processing, such as the BDNF-modulated deficit in amygdala habituation that we describe here, may in the future guide clinicians in selecting the best treatment for a given BPD patient. This has been done with promising results in patients with mood, anxiety disorders and PTSD (Doehrmann et al., 2012; Felmingham et al., 2013; Siegle et al., 2006).

4.1. Study strengths and limitations

This study has clear strengths, including using a robust neurobiological model of emotion-processing abnormalities in BPD grounded in prior consistently replicated findings (Donegan et al., 2003; Hazlett et al., 2012; Koenigsberg et al., 2009); a hypothesis-driven imaging-genetics approach based on replicated evidence of modulation of amygdala reactivity and extinction learning by BDNF genotypes (Hong et al., 2011); a sample of well-characterized unmedicated BPD patients; a psychiatric control group of SPD patients that allows to test the specificity of the findings; and gold-standard tracing of the amygdala. Moreover, the unique task design and data analytic plan allows to take into account the effect of time during habituation. Specifically, our study makes it possible to compare the longitudinal time course of amygdala BOLD activity (i.e., the shape of the curve) during habituation (see Figs. 3 and 4).

The main limitation of our study is the modest sample size for each diagnostic group. Although the sample sizes are within the range of other imaging genetics studies (Montag et al., 2008; Outhred et al., 2012), it should be noted that some of the subgroups defined by Val66Met genotypes have particularly small sample sizes. We addressed this limitation by employing an *a priori* hypothesis which allowed us to conservatively restrict our analysis to:

1) a single region of interest (the amygdala), in which hyperactivity in BPD has been consistently replicated across studies (Donegan et al., 2003; Hazlett et al., 2012; Koenigsberg et al., 2009); and 2) a single functional polymorphism in one candidate gene, the BDNF Val66Met SNP, for which there is robust evidence of its role in modulating the biological system that is the focus of our study (namely, amygdala reactivity as a biomarker of abnormal emotion processing and emotional hyperreactivity) (Montag et al., 2008; Outhred et al., 2012). Another limitation is that 4 BPD patients had a lifetime history of PTSD. However, the rate of PTSD did not differ across genotypes or diagnostic groups. Despite our limitations, significant results were obtained which are consistent with our *a priori* hypothesis and with the results of prior studies (Montag et al., 2008; Outhred et al., 2012), minimizing the risk of a false-positive finding. In fact, it has been noted (Outhred et al., 2012) that significant fMRI findings observed in smaller samples may be true, rather than false, positives, consistent with results in larger samples (Murphy and Garavan, 2004), particularly within the imaging genetics paradigm.

Despite the limitations described above, this study advances our knowledge by demonstrating for the first time that amygdala habituation is under genetic control by BDNF Val66Met genotypes. This finding is important because it points to examining BDNF pathways in disorders characterized by deficient habituation.

Future larger-scale studies are needed to replicate our hypothesis-generating findings and to test the effect of BDNF modulators such as d-cycloserine on amygdala habituation and behavioral symptoms in BPD patients.

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Abbreviations

BPD	borderline personality disorder
BDNF	brain-derived neurotrophic factor
fMRI	functional magnetic resonance imaging
SPD	schizotypal personality disorder
HC	healthy control

SNP	single nucleotide polymorphism
Val	valine
Met	methionine
PTSD	posttraumatic-stress disorder
MDD	major depressive disorder
MP-RAGE	magnetization prepared rapid acquisition gradient-echo
IAPS	International Affective Picture System
LSD	Least Significant Difference
DBT	Dialectical Behavior Therapy

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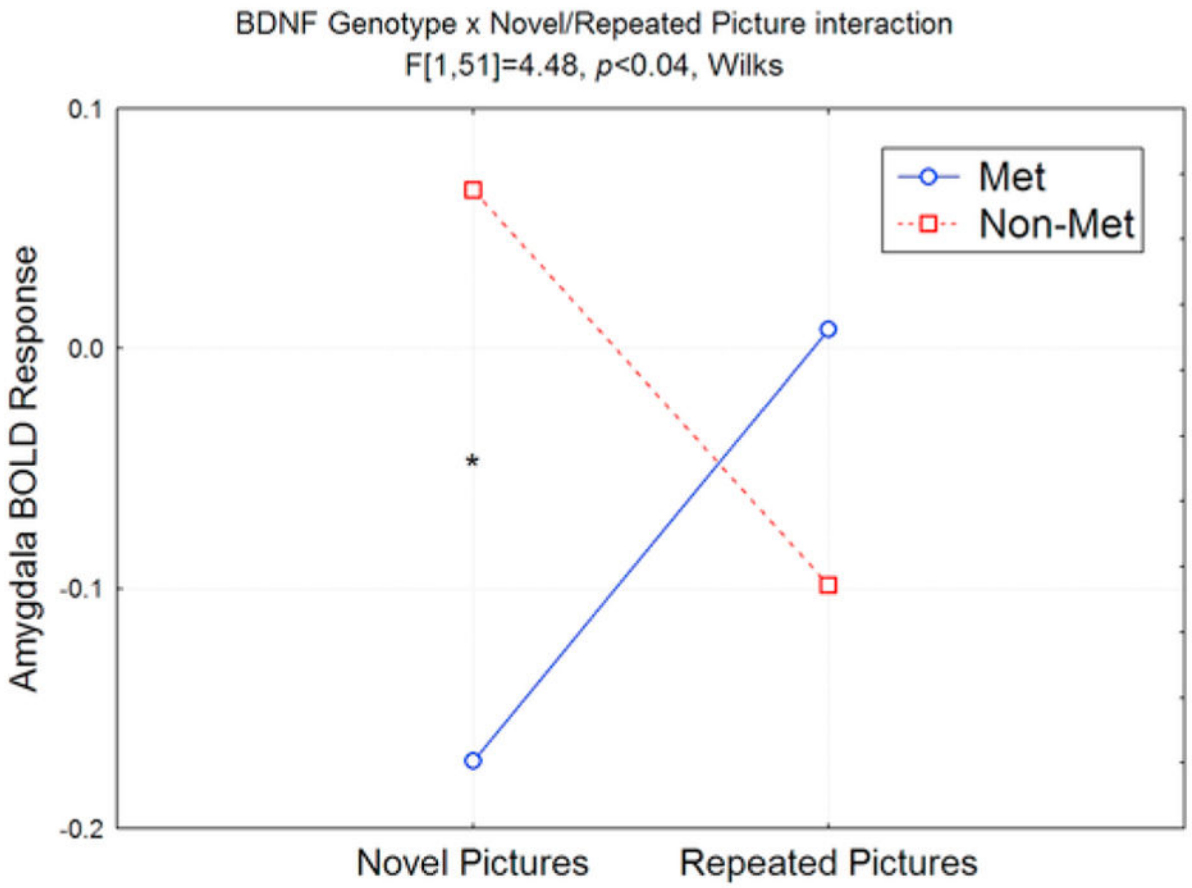

Fig. 1.

Genotype × Novel/Repeat Picture repetition interaction (F[1,51] =4.48, p=0.039, Wilks), indicating that Met-carrying individuals (collapsed across diagnoses) had a failure in amygdala habituation for repeated pictures compared to non-Met allele carriers. * Significant post-hoc analyses at p<0.05.

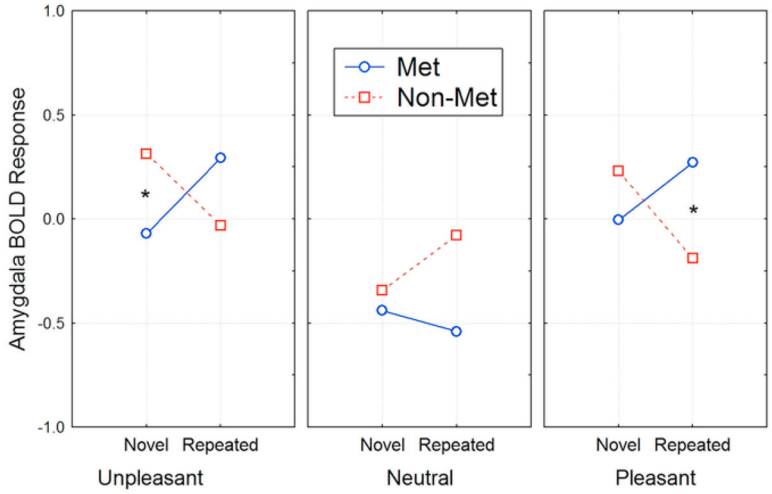

Fig. 2.

Genotype × Picture valence × Novel/Repeat Picture repetition interaction ($F[2,50] = 4.19$, $p=0.021$, Wilks), indicating that the failure in amygdala habituation for repeat emotional pictures among Met-carrying individuals (collapsed across diagnoses) compared to non-Met allele carriers was significant for unpleasant and pleasant, but not for neutral pictures. * Significant differences at $p<0.05$.

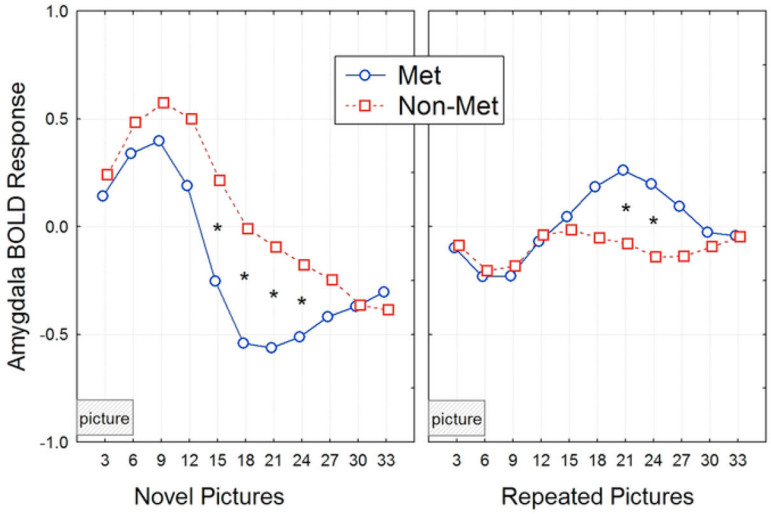

Fig. 3. Genotype × Novel/Repeat Picture repetition × Time interaction (F[10,42] =2.80, p=0.009, Wilks) (Fig. 3)

Both Met and Non-Met carriers show similar curves of BOLD activation during the novel picture presentation, with the Met carriers having a non-significantly smaller curve and a faster return to baseline. During the repeated presentation of the pictures, the amygdala response curve was almost flat among Non-Met carriers representing the normal habituation effect. Conversely, Met–carrying individuals showed significantly higher amygdala activation compared to Non-Met carriers during the repeated picture presentation, representing a failure to habituate. * Significant differences at $p<0.05$.

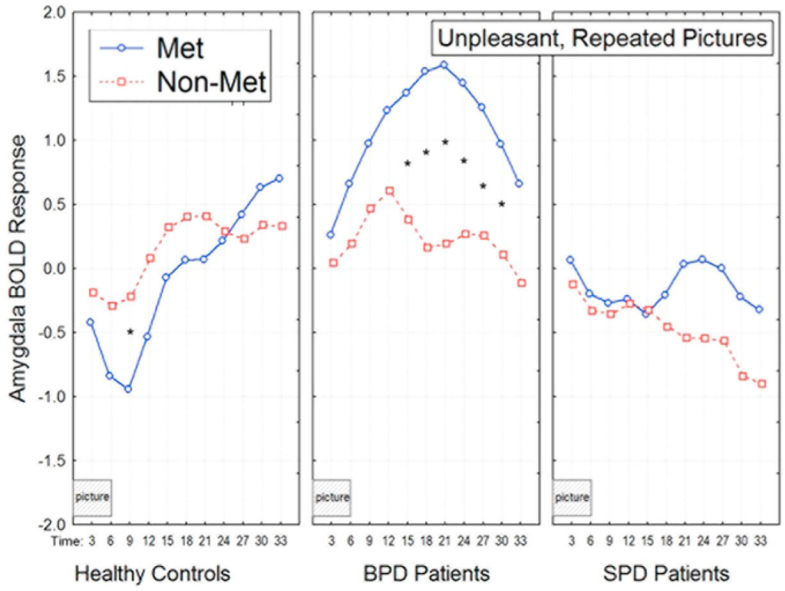

Fig. 4.

Diagnostic group × Genotype × Picture valence × Novel/Repeat Picture repetition × Time interaction (F[40,64] =1.68, p=0.032, Wilks): Met-carrying borderline personality disorder (BPD) patients had increased and prolonged amygdala reactivity during repeated unpleasant pictures compared to Non-Met allele carriers in all diagnostic groups, and Met carriers in the schizotypal personality disorder (SPD) and healthy control (HC) diagnostic groups. This represented a failure of habituation and was not true during the novel picture presentation (Data not shown). * Significant differences at $p<0.05$.

Table 1

Sociodemographic characteristics and Brain-Derived Neurotrophic Factor (BDNF) Val66Met genotype distribution (Met carriers vs Non-Met carriers) among healthy controls (HCs), borderline personality disorder (BPD) and schizotypal personality disorder (SPD) patients.

	HC (n=20)	BPD (n=19)	SPD (n=18)	Statistic
	n (%)	n (%)	n (%)	
Met carriers	7 (35)	4 (21)	9 (50)	n.s.[a]
Met/Met	1 (5%)	2 (10.5)	2 (11.1)	
Val/Met	6 (30)	2 (10.5)	7 (38.9)	
Non-Met carriers (Val/Val)	13 (65)	15 (79)	9 (50)	
Gender Male	7 (35)	7 (37)	11 (61)	
Female	13 (65)	12 (63)	7 (39)	
Education				
No high-school	4 (20)	6 (31.6)	2 (11.1)	
High-school/GED	7 (35)	8 (42.1)	11 (61.1)	
University degree	9 (45)	5 (26.3)	5 (27.8)	
	mean (m) (SD)	m (SD)	m (SD)	
Age	32.6 (9.2)	32.8 (9.4)	36.2 (11.7)	n.s.[a]

[a] n.s. = non statistically significant (Val66Met genotype distribution: Pearson Chi-Square 3.4; df=2; p=0.183 for Met carriers vs Val/Val; Pearson Chi-Square 4.7; df=4; p=0.322 for Met/Met vs Val/Met vs Val/Val; Sex: Pearson Chi-Square 3.2; df=2; p=0.203; Education: Pearson Chi-Square 4.6; df=4; p=0.329; Age: ANOVA F=0.745; df=2,54; p=0.480)