The role of \( \text{BDNF} \) methylation and Val\(^{66}\)Met in amygdala reactivity during emotion processing

Ronny Redlich\(^1\) † | Ilona Schneider\(^{1,2}\) † | Nicole Kerkenberg\(^1\) | Nils Opel\(^1\) | Jonas Bauhaus\(^1\) | Verena Enneking\(^1\) | Jonathan Repple\(^1\) † | Elisabeth J. Leehr\(^1\) | Dominik Grotegerd\(^1\) | Claas Kähler\(^1\) | Katharina Förster\(^1\) | Katharina Dohm\(^1\) | Susanne Meinert\(^1\) | Tim Hahn\(^1\) | Harald Kugel\(^3\) | Kathrin Schwarte\(^1\) | Christiane Schettler\(^1\) | Katharina Domschke\(^{1,4}\) | Volker Arolt\(^{1,2}\) | Walter Heindel\(^3\) | Bernhard T. Baune\(^{1,5}\) | Weiqi Zhang\(^{1,2}\) | Christa Hohoff\(^1\) ‡ | Udo Dannlowski\(^{1,2}\) ‡

\( ^1 \)Department of Psychiatry, University of Münster, Münster, Germany
\( ^2 \)Otto Creutzfeldt Center for Cognitive and Behavioral Neuroscience, University of Münster, Münster, Germany
\( ^3 \)Department of Clinical Radiology, University of Münster, Münster, Germany
\( ^4 \)Department of Psychiatry and Psychotherapy, Medical Center—University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
\( ^5 \)Department of Psychiatry, Melbourne Medical School and The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia

Correspondence
Ronny Redlich, Department of Psychiatry, University of Muenster, Albert-Schweitzer-Campus 1, A9, 48149 Muenster, Germany. Email: r.redlich@uni-muenster.de

Funding information
Deutsche Forschungsgemeinschaft, Grant/ Award Numbers: FOR2107 DA1151/5-1, DA1151/5-2 to UD, SFB-TRR58, Project C09 to UD, SFB-TRR58, Projects C02/Z02 to KD; Innovative Medizinische Forschung, Grant/ Award Numbers: DA120903, DA111107 to UD, HO221003 to CH, RE111604 to RR, RE111722 to RR; Deanery of the Medical Faculty of the University of Münster; Interdisciplinary Centre for Clinical Research

Abstract
Epigenetic alterations of the brain-derived neurotrophic factor (BDNF) gene have been associated with psychiatric disorders in humans and with differences in amygdala BDNF mRNA levels in rodents. This human study aimed to investigate the relationship between the functional BDNF-Val\(^{66}\)Met polymorphism, its surrounding DNA methylation in BDNF exon IX, amygdala reactivity to emotional faces, and personality traits. Healthy controls (HC, \( n = 189 \)) underwent functional MRI during an emotional face-matching task. Harm avoidance, novelty seeking and reward dependence were measured using the Tridimensional Personality Questionnaire (TPQ). Individual BDNF methylation profiles were ascertained and associated with several BDNF single nucleotide polymorphisms surrounding the BDNF-Val\(^{66}\)Met, amygdala reactivity, novelty seeking and harm avoidance. Higher BDNF methylation was associated with higher amygdala reactivity (\( x = 34, y = 0, z = -26, t_{(166)} = 3.00, \text{TFCE} = 42.39, p_{\text{FWER}} = .045 \)), whereby the BDNF-Val\(^{66}\)Met genotype per se did not show any significant association with brain function. Furthermore, novelty seeking was negatively associated with BDNF methylation (\( r = -.19, p = .015 \)) and amygdala reactivity (\( r = -.17, p = .028 \)), while harm avoidance showed a trend for a positive association with BDNF...
1 | INTRODUCTION

The brain derived neurotrophic factor (BDNF) has been shown to play a crucial role in neural development, function and plasticity of the amygdala, mediating anxiety-like behaviors (Sagarkar et al., 2017). A wide range of studies have linked BDNF expression to the etiology and pathophysiology of several psychiatric disorders associated with deficient amygdala function, including mood disorders, anxiety disorders (Gottschalk & Domschke, 2017; Ikegame et al., 2013), eating disorders, and personality disorders (Thaler et al., 2014). Based on its broad neuronal impact, the genetic and epigenetic regulation of BDNF became a main topic in the field of molecular psychiatry. Various studies focused on a frequent single-nucleotide polymorphism (SNP) in the corresponding gene BDNF at nucleotide 196 (G/A; rs6265), which produces an amino acid substitution (valine to methionine) at codon 66 (Val66Met) in the proregion of the BDNF protein. The Met allele of this SNP has been shown to decrease activity-dependent intracellular trafficking and secretion of neuronal BDNF (Chen et al., 2004; Egan et al., 2003), leading to increased anxiety-related behaviors (Chen et al., 2006). In addition, studies revealed associations of the Val66Met SNP with amygdala reactivity (Lau et al., 2010; Montag, Reuter, Newport, Elger, & Weber, 2008), with a deficit in amygdala habituation, particularly for emotional pictures (Perez-Rodriguez et al., 2017), and anxiety-related endophenotypes, such as harm avoidance (Jiang et al., 2005; Montag et al., 2010b). However, the direction of Val66Met SNP impact on anxiety-related endophenotypes is still unclear, for instance controls carrying a Val66Met allele show lower neuroticism scores but also a trend for higher harm avoidance scores (Frustaci, Pozzi, Gianfagna, Manzoli, & Boccia, 2008). Taken together, although associations of the Val66Met polymorphism with anxiety traits were reported, the results remain inconclusive (Frustaci et al., 2008), suggesting further underlying variables and biological mechanisms involved in the regulation of the BDNF system.

Recently, the role of epigenetics, and in particular of DNA methylation, gained focus as one such mechanism. In an enrichment microarray analysis of the methylation status of several genetic BDNF regions, Mill et al. (2008) could identify an association of the Val66Met polymorphism and the methylation status of some of the surrounding CpG sites in exon IX. Carrying a guanine nucleotide (Val allele) resulted in an additional CpG site, which in turn lead to an increased methylation of surrounding CpG sites. Recent research revealed that DNA methylation of the BDNF gene broadly affects BDNF mRNA expression (Nagy, Vaillancourt, & Turecki, 2018), whereby high BDNF gene methylation goes along with low BDNF mRNA levels. Numerous studies have associated BDNF gene methylation with certain psychiatric disorders (anxiety disorder, major depression, bipolar disorder, borderline personality disorder, schizophrenia) (Zheleznyakova, Cao, & Schiöth, 2016) and personality traits like novelty seeking (Duclot & Kabbaj, 2013), highlighting the potential of BDNF methylation as a biomarker of psychiatric diseases. Focusing on amygdala functions, animal studies showed epigenetic modifications of BDNF to be associated with BDNF mRNA levels in the amygdala (Sagarkar et al., 2017). However, in humans, the associations of BDNF genotype, BDNF methylation, and amygdala reactivity have not been investigated yet.

Therefore, in the present study, we aimed to investigate the relationship between the BDNF Val66Met polymorphism, BDNF DNA methylation, amygdala reactivity and psychological phenotype in a large sample of 189 healthy participants. Furthermore, we additionally investigated the potential—confounding—effects of BMI, since neurotrophic factors, particularly the BDNF, is associated with the control of body weight and mutations in BDNF encoding genes lead to insatiable appetite and severe obesity (Xu & Xie, 2016). First, based on previous research, we hypothesized that the BDNF methylation in exon IX is associated with the Val66Met polymorphism. Second, we investigated possible main and interaction effects of BDNF methylation and the Val66Met polymorphism on amygdala reactivity. We hypothesized that amygdala reactivity to negative emotional stimuli is associated with the Val66Met polymorphism and limbic brain reactivity on novelty seeking, harm avoidance as well as reward dependence for the sake of completeness were exploratorily investigated, based on first evidence that have shown associations with BDNF in human and rodent studies (Duclot & Kabbaj, 2013; Jiang et al., 2005; Montag, Basten, Stelzel, Fiebach, & Reuter, 2010a; Montag, Markett, et al., 2010b).
2 | METHODS AND MATERIALS

2.1 | Subjects

In the present study n = 189 right-handed Caucasian healthy participants were analyzed. Participants responded to local newspaper ads and public notices. They were thoroughly investigated by experienced psychologists and free from any life-time history of psychiatric disorders according to DSM-IV criteria (American Psychiatric Association, 1994), as diagnosed with the SCID interview (Wittchen, Zaudig, & Fydrich, 1997). Exclusion criteria encompassed any neurological abnormalities, history of seizures, head trauma or unconsciousness, intake of any psychotropic medication, and the usual MRI-contraindications. Harm avoidance (HA), novelty seeking (NS), and reward dependence (RD) were measured using the Tridimensional Personality Questionnaire (TPQ) (Cloninger, Przybeck, & Svrakic, 1991). Table 1 lists sociodemographic and questionnaire data of study participants clear from fMRI movement effects (see below). The study was approved by the Ethics Committee of the University of Münster. After complete description of the study to the participants, written informed consent was obtained. Participants received a financial compensation.

2.2 | DNA analysis

Venous blood samples were taken from the 189 participants by default between 5 and 7 p.m., within 30 min postscanning. DNA was extracted as recommended by the manufacturer (FlexiGene DNA Kit; Qiagen, Germany) and dissolved in 25 mM Tris–HCL buffer (pH 7.8). Concentrations were ascertained by measurement of 260/280 nm absorbance (GENios Pro; Tecan, Germany), and DNAs diluted to 25 ng/μL.

DNA aliquots (500 ng) of participants were converted plus No Template Control with sodium bisulfite using EZ DNA Methylation Kit according to the manufacturer’s instructions (Zymo Research, HISS Diagnostics GmbH, Germany) with minor modifications: an incubation time of 5 min was included to step 12 after adding 10 μL M-Elution Buffer and prior to centrifugation; this modified step was repeated with 12 μL M-Elution Buffer (both eluates were pooled). For polymerase chain reaction (PCR) amplification of converted DNAs, Methyl Primer Express Software v1.0 and Primer Express Software v2.0 (Applied Biosystems by Thermo Fisher Scientific, Germany) were utilized for the design of bisulfite sequencing primers. These were chosen to encompass Val66Met SNP rs6265 and its closest surrounding CpG sites (Figure S1), tested for specificity via the BiSearch web server (Arányi, Váradi, Simon, & Tusnády, 2006; Tusnády, Simon, Váradi, & Arányi, 2005), and extended by 5’ tails enriched of C-bases for optimal PCR performance (F: 5’–TCCCCATTTTTAATTGTGTGTTAGAGTTG, R: 5’–GGGGAAAAACCTAATACAAACACCCCT). For standard PCRs of bisulfite converted DNA aliquots (30 ng), 0.8 μM of each extended primer and 1X ZymoTaq PreMix (Zymo Research, HiSS Diagnostics GmbH, Germany) were used in 20 μL final volumes with following conditions: 95°C for 10 min, 40 cycles of 94.5°C for 1 min + 58°C for 1 min + 72°C for 2 min, followed by 72°C for 7 min. After PCR clean-up with Vacuum Manifold and MultiScreen HTS Filter Plates following the manufacturer’s instructions (Millipore GmbH, Germany) sequencing reactions were performed with forward primer only using Big Dye Terminator chemistry (v3.1 Cycle Sequencing Kit, Applied Biosystems by Thermo Fisher Scientific, Germany). Ten microliters final volumes contained 3 μL cleaned PCR product and 7 μL Mastermix composed of 1 μL BigDye, 2 μL 5X Sequencing Buffer and 0.3 μM primer. Reaction conditions were 96°C for 1 min followed by 25 cycles of 96°C for 10 s + 50°C for 4 min. After removal of excess Dye Terminator using SephadeX-MultiScreen-HV plate system as recommended (Millipore GmbH, Germany), cleaned sequencing products were run on a 3,730 DNA analyser (Applied Biosystems by Thermo Fisher Scientific, Germany). Electropherograms were manually checked for genotypes of Val66Met SNP rs6265, mean fluorescence intensities, overall quality, and analyzability of CpG sites within the sequenced amplicon using sequence scanner software v1.0 (Applied Biosystems by Thermo Fisher Scientific, Germany). Additionally, genotypes of additional variants spanning the BDNF gene around rs6265, altogether eight variants, were determined: rs1519480, rs6265, rs11030101, rs11030104, rs7127507, rs988748, rs962369, rs12273363. Linkage disequilibrium (LD) analysis revealed that tightly linked variants rs1519480 and rs12273363 should thus provide additional and helpful information and are most likely to contribute to the relationship between genotype and DNA methylation status of the BDNF gene (for details see Supplemental Material).

For uncovering the individual methylation profiles, quantitative analysis of CpG site specific methylation (relative peak heights C/C + T) was performed with Epigenetic Sequencing Methylation analysis software (ESME) as recommended (Lewin, Schmitt, Adorjan, Hildmann, & Piepenbrock, 2004) and described previously (Domshke et al., 2012; Schartner et al., 2017; Tadić et al., 2014; Ziegler et al., 2016; Ziegler et al., 2018). This included quality control, correction for incomplete bisulfite conversions, normalization of signals, and alignment of own generated sequence trace files and reference sequences (public databases). The central CpG site at position 172–173 includes the Val66Met SNP rs6265 (at position 173) which allowed robust ESME data analysis only for participants homozygous for the frequent
G-allele (two CpG sites present), but not for heterozygous G/A participants (one CpG plus one CpA site) or homozygous A/A participants (two CpA sites). Therefore the methylation rates of this CpG site at position 172 bp were excluded for further analysis.

For quality control, standard PCRs and sequencing reactions were performed each in duplicate and checked for concordance (SD of mean methylation rate per participant to be ≤0.05) or extended to triplicate sequencing reactions, to include only mean data with SD ≤0.05 for further analysis (see below). Further, DNAs of seven random participants were independently three or four times sodium bisulfite converted followed by independent standard PCRs and sequencing reactions up to three times for each converted DNA. This resulted in at least quadruplicate (fourfold) sequence data sets up to twelvefold data sets (2 DNAs: 4 sets, 2 DNAs: 6 sets, 1 DNA: 8 sets, 2 DNAs: 12 sets) which revealed high concordance: SD of mean methylation rates within the same DNA <0.05 at all CpG sites. A boxplot depicting median and quartiles for all methylation CpG Sites can be found in Figure S2. All DNA analysis for quantitative investigation of individual methylation profiles and genotyping was performed analogous to previous research (Dannlowski et al., 2014) again by investigators blind for participant characteristics, structural or functional imaging data.

2.3 | fMRI methods

The experimental fMRI paradigm was frequently used to elicit a robust and replicable amygdala response across an array of imaging genetics studies (Dannlowski et al., 2016; Nikolova et al., 2014; Redlich et al., 2015b; Schneider et al., 2018). The paradigm, which utilized a face-processing task (faces with anger or fear expressions), alternating with a sensorimotor control task was conducted as described previously (Dannlowski et al., 2011; Redlich et al., 2015a) (see Supplementary Information and Figure S3). Functional images were realigned and unwarped, spatially normalized to standard Montreal Neurological Institute (MINI) space, and smoothed using a Gaussian kernel (6 mm Full Width Half Maximum; FWHM). Due to movement effects 16 individuals had to be excluded from further analysis (exclusion criterion >3 mm and/or 3’). Onsets and durations of the two experimental conditions (faces and shapes) were modeled using a canonical hemodynamic response function in the context of the general linear model (GLM). The model was corrected for serial correlations and a high-pass filter of 128 s was applied to reduce low frequency noise. An individual contrast image was generated in each fixed-effects first-level analysis comparing activation in response to fear-relevant faces with the control condition as baseline. The resulting contrast images were further used in second-level random-effects group analyses.

2.4 | Statistical analysis

Statistical analyses were conducted using SPSS (Version 23.0, IBM, Chicago, IL) with a consequent cut-off p-value of .05.

2.5 | Principal component analysis of BDNF methylation

Due to high intercorrelations of CpG sites (please see Table S2), leaving the statistical problem of multicollinearity, a principal component analysis (PCA) was used for data reduction of the six CpG sites, using components with an eigenvalue >1 as criteria. The PCA yielded two principal components (PC) with an eigenvalue >1. PC1 explained 49.8% and PC2 explained 19.3% of the total variance. All six CpG sites had factor loadings <0.35 (Table S1). To facilitate the analysis, both PCA factors were extracted to represent the overall BDNF exon IX methylation in the dataset. All assessed PCs and methylation values of the CpG sites were correlated with each other and checked for significant associations with the BDNF Val<sup>66</sup>Met polymorphism, age, gender, and BMI.

2.6 | BDNF methylation and genotype

According to our first study aim, we performed a multivariate analysis of variance (MANOVA) including both BDNF methylation PCA factors (PC1 and PC2) as dependent variables and the Val<sup>66</sup>Met polymorphism (val/val vs. val/met and met/met) as independent variable. Further, gender, age, and BMI where included as variables of no interest. As additional analyses, we investigated the associations between BDNF methylation, BMI, age and gender, each controlling for the remaining variables. In addition, the above applied model were also calculated for rs1519480 (CC and CT vs. TT) and rs12273363 (CC and CT vs. TT), according to the haplotype analysis (see supplementary material). Continuous predictors were standardized in order for their coefficients to be more comparable.

2.7 | fMRI analyses

Functional MRI analyses were conducted using Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm). In order to investigate the effects of BDNF methylation and the Val<sup>66</sup>Met polymorphism (BDNF-Val<sup>66</sup>Met) on amygdala reactivity (study aim 2), an ANCOVA was calculated using a SPM full factorial model, with genotype (val/val vs. val/met and met/met) and BDNF methylation as independent variables, again including sex, age, and BMI as covariates of no interest. Again, the above applied model were also calculated for rs1519480 (CC and CT vs. TT) and rs12273363 (CC and CT vs. TT). Given previous studies associating BDNF and the amygdala (Montag et al., 2008; Sagarkar et al., 2017) and its central role in emotion processing (Phelps & LeDoux, 2005), all calculations were restricted to the bilateral amygdala as defined by Tzourio-Mazoyer et al. (2002) using an anatomical mask created with the Wake Forest University (WFU) Pick Atlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). However, to cover for potential nonhypothesized effects on other brain regions, we also conducted additional explorative whole brain analyses. Significance thresholds for multiple testing were obtained at the cluster-level by threshold-free cluster enhancement as a nonparametric approach, which is implemented in the TFCE-toolbox (http://dbm.
neuro.uni-jena.de/tfce, Version 140). We consequently established a conservative FWE-corrected threshold of \( p < .05 \) obtained by 1,000 permutations per test. For each participant the mean contrast values of significant clusters were extracted from SPM and further analyzed in SPSS. The post hoc sensitivity analysis (http://www.gpower.hhu.de/) revealed that the sample size is suitable to detect (1) strong interaction or group based main effects (\( \eta^2 = .30, f = .66 \)), small to medium effects for post hoc group comparisons (\( \eta^2 = .04, d = .46 \)) and small effects for correlational main effects (\( r = .09 \)) with good statistical power (\( \alpha = .05\% \), 1 – \( \beta \) = 80%).

### 2.8 | Personality traits

According to our third study aim, we investigated associations between BDNF methylation, BDNF-Val\(^66\)Met, limbic brain function with the TPQ-scales using partial correlations controlling for age, gender, and BMI.

### 3 | RESULTS

#### 3.1 | BDNF methylation rates

Analyses of individual BDNF methylation profiles showed different methylation rates for all CpG sites (Table S1). The principal components analysis revealed two principle components, which accounts for 49.8% (PC1) and 19.3% (PC2) of the variation in methylation across the BDNF CpG sites. Correlations analyses and Mann-Whitney U tests revealed significant associations of high BDNF CpG methylation rates with BDNF-\(-66\)Met, high age and high BMI values (see Tables S2 and S3).

#### 3.2 | BDNF methylation and genotype

Using Pillai’s trace, the MANOVA predicting BDNF methylation PC1 and PC2 revealed a significant effect of BDNF-Val\(^66\)Met (\( V = .06, F_{[2,167]} = 5.17, p = .007, \eta^2 = .062 \)) and BMI (\( V = .04, F_{[2,167]} = 3.37, p = .037, \eta^2 = .038 \)), while the BDNF-\(rs1519480 \) (\( p = .414 \), BDNF-\(rs1519480 \)) model (\( p = .315 \)), gender (\( p = .753 \)), and age (\( p = .143 \)) were not significantly associated with BDNF methylation PC1 and PC2. Separate univariate ANOVAs revealed a significant effect of BDNF-Val\(^66\)Met on BDNF methylation PC2 (\( F[1,168] = 6.80, p = .01, \eta^2 = .043 \)), indicating higher BDNF methylation in the group of BDNF-Met carrier (Figure 1). An additional ANCOVA separating BDNF-Val\(^66\)Met into three groups (val/val, val/met, met/met) confirmed the main effect of BDNF genotype on BDNF methylation PC2 (\( F_{[2,167]} = 2.67, p = .24 \)). Post hoc analysis showed that this result was driven by the heterozygous group compared to the BDNF val/val homozygous group (\( T_{[2,165]} = 2.88, p = .004 \)) while the BDNF met/met homozygous group showing neither a significant difference to BDNF val/val homozygous nor BDNF heterozygous, which might be caused by the small sample size of \( n = 8 \) met homozygotes. Further, BMI showed significant effects on BDNF methylation PC1 (\( F[1,168] = 5.13, p = .025, \eta^2 = .029 \)) and on PC2 (\( F[1,168] = 3.90, p = .05, \eta^2 = .023 \)), with high BMI values associated with low BDNF methylation.

#### 3.3 | fMRI results

The analysis of brain function revealed a significant positive association of BDNF methylation PC1 (\( x = 34, y = 0, z = –26, t_{[166]} = 3.00, \text{TFCE} = 42.39, p_{\text{FWE}} = .045 \)) and on PC2 (\( x = 30, y = –2, z = –24, t_{[166]} = 2.75, \text{TFCE} = 56.95, p_{\text{FWE}} = .031 \)) with right amygdala reactivity to negative emotional faces. Including BDNF-Val\(^66\)Met as covariate to the model does not significantly alter the results for PC1 (\( t_{[165]} = 2.94, \text{TFCE} = 41.99, p_{\text{FWE}} = .046 \)) and PC2 (\( t_{[165]} = 2.73, \text{TFCE} = 56.34, p_{\text{FWE}} = .035 \)) indicating these association is independent from BDNF-Val\(^66\)Met genotype. To determine the amygdala subregions, the SPM Anatomy toolbox (Eickhoff et al., 2005) was used. According to the implemented probabilistic cytoarchitectonic (Amunts et al., 2005), the cluster were located in the basolateral amygdala. Neither a significant main effect of BDNF-Val\(^66\)Met nor an interaction effect with BDNF methylation PC1 or PC2 emerged. As for BDNF-Val\(^66\)Met no significant main effects or interaction effects with PC1 or PC2 emerged for rs1519480 and rs12273363. All abovementioned associations with amygdala reactivity were not significantly affected by sex, BMI and age, as analyzed by subsequent multiple regression with \( t \)-values ranging from \( t = -1.90 \) to \( t = 1.47 \). The whole-brain analyses did not reveal any additional significant results.

### 3.4 | Personality traits

The analysis of TPQ revealed a significant negative correlation of TPQ-NS with BDNF methylation PC1 (\( r = -.21, p = .007 \)), and a...
trend for a positive correlation of TPQ-HA and BDNF methylation PC1 ($r = .15, p = .059$). Further, TPQ-NS was associated with the amygdala reactivity in cluster of BDNF methylation PC1 ($r = -.17, p = .027$) and by tendency in PC2 ($r = -.15, p = .048$). BDNF-Val$^{66}$Met was not associated with any of the TPQ-scales. For details, please see Table 2.

### DISCUSSION

In the present study, we highlight a critical role of BDNF methylation in human amygdala response to negative emotional stimuli, whereby high BDNF methylation rates were for the first time shown to be associated with a high reactivity in the amygdala. Moreover, high BDNF...
methylation and high amygdala reactivity were associated with low novelty seeking. Although BDNF methylation was partly influenced by Val66Met, with Met allele carrier revealing higher BDNF methylation, there was no interaction or main effect of the Val66Met polymorphism on amygdala reactivity.

Our results add evidence to the hypothesis that epigenetic modification of BDNF methylation might play an important role in amygdala functions, presumably independently from BDNF genotype. Recently, a study in rodents showed that DNA hypermethylation of the BDNF exon IV and IX in the amygdala resulted in a down-regulation of BDNF mRNA levels in the amygdala and increased anxiety-like behaviors (Sagarkar et al., 2017). In humans, BDNF exon IV methylation in post-mortem brain tissue of patients who committed suicide revealed as well an inverse correlation of methylation and BDNF mRNA levels (Keller et al., 2010). Based on our data and previous research the question arises how epigenetically down-regulated BDNF levels could enhance amygdala reactivity. One possibility is that the BDNF down-regulation directly alters synaptic plasticity and fear learning via modifying amygdaloid synaptic strength and dendritic spines, thereby promoting amygdala excitability and environmental sensitivity (Agassandian, Gedney, & Cassell, 2006; Ehrlich & Josselyn, 2016).

Another way is the broad modification of other neurotransmitter systems via BDNF, like the GABAergic, glutamatergic, serotonergic, and neuropeptide Y system (Barnea & Roberts, 2001; Mamounas, Blue, Siuciak, & Altar, 1995; Matsumoto et al., 2006), which in turn have shown to modulate amygdala reactivity (Herman, Contet, Justice, Vale, & Roberto, 2013; Kirson, Oleata, Parsons, Ciccocioppo, & Roberto, 2018; Wood et al., 2016). Together, high BDNF exon XI methylation may lead to a downregulation of amygdala BDNF mRNA levels, which in turn could have modified the amygdala reactivity. Evidence supporting this hypothesis can also be derived from previous studies. First, higher BDNF DNA methylation has also been found in MDD patients (Kang et al., 2013), a diagnosis frequently associated with high amygdala reactivity (Redlich et al., 2017; Redlich et al., 2018; Stuhrmann et al., 2013). Second, it has been shown that the intake of epigenetic modifying medications like citalopram increases peripheral BDNF levels (Lopez et al., 2013) which goes along with reduced amygdala reactivity (Murphy, Norbury, O’Sullivan, Cowen, & Harmer, 2009). Third, a reduction of BDNF methylation could be achieved by psychotherapy (Perroud et al., 2013), which also results in decreased amygdala reactivity (Straub et al., 2015). Since altered amygdala reactivity has multiple times been associated with psychiatric disorders (Gaffrey et al., 2011; Goodman et al., 2014; Schneider et al., 2018; Schumann, Bauman, & Amaral, 2011), our data suggests high BDNF exon IX methylation as a potential risk factor for psychiatric disorders. However, since correlations do not prove causality, a direct link between human BDNF mRNA/protein levels, methylation, amygdala reactivity and psychiatric disorders is still missing, demanding further research. The fact that our results mainly involve the right amygdala is in line with previous studies. While early reviews particularly summarized a preponderance of left amygdala activations over right amygdala activations in functional neuroimaging studies of emotion processing (Baas, Aleman, & Kahn, 2004), more recent reviews suggest a general right hemisphere dominance for all kinds of emotions, and, more specifically, a critical role of the right amygdala in the early assessment of emotional stimuli (Gainotti, 2019). This is in line with a study that confirms a right amygdala’s key role in right anterior hemisphere cross-talk in subjects who are likely more stress-sensitive in general, and that high HA in particular is associated with a stronger right amygdala resting state functional connectivity with the dorsomedial prefrontal cortex, which is implicated in negative affect regulation (Baeken et al., 2014).

Furthermore, we found significant negative associations of NS with BDNF methylation and amygdala reactivity. Individuals with high NS are described as enthusiastic, impulsive and highly explorative to novel and rewarding situations. In animal models, low novelty seeking behavior is associated with higher vulnerability to depression-like behavior (Stendenfeld et al., 2011), while high novelty seeking is associated with resilience to negative effects of early life stress (Clinton, Watson, & Akil, 2014). Our findings align well with a study showing higher BDNF protein levels along with lower BDNF histone methylation in high NS compared to low NS rats (Duclot & Kabbaj, 2013). At the neurofunctional level, NS was negatively correlated with the right amygdala reactivity in the fMRI clusters associated with BDNF methylation. This is in line with studies showing amygdala affective processing might be linked with the temperament dimensions (Baeken et al., 2014), and that selective amygdala lesions in monkeys have been shown to increase NS personality traits like exploration and excitability (Machado, Kazama, & Bachevalier, 2009). In summary, the association of high BDNF methylation, high amygdala reactivity and low novelty seeking underlines again the possible role of BDNF methylation in psychiatric disorders. However, determining the underlying directions of the relations between BDNF methylation, amygdala reactivity, and NS cannot be accomplished based on our data and must await further research. Previous research indicates that other factors like brain injuries (Sagarkar et al., 2017), early caregiving environment and childhood maltreatment (Doherty, Forster, & Roth, 2016; Perroud et al., 2013), and the Val66Met polymorphism (Mill et al., 2008) might also determine BDNF methylation.

Furthermore, we found a negative association between BMI values and BDNF methylation. In addition to BDNF key roles in neuronal survival and development, it is important for the control of body weight (Xu & Xie, 2016). These results are in line with a previous study reporting BDNF hypomethylation in currently obese individuals compared to successful weight loss maintainers and normal weight individuals (Huang et al., 2015), and support the suggestion that the association between high BMI values and low BDNF methylation might reflect an epigenetic adaption of BDNF mRNA levels to the current nutrition status. However, since body weight was not a primary target in our study and we did not collect detailed nutrition status of our participants, this only provides small evidence and further research is needed to investigate the epigenetic BDNF regulation of energy balance in more detail.

The analysis of the Val66Met polymorphism revealed several implications. First, the association between the BDNF Val66Met polymorphism and methylation is in line with an earlier enrichment microarray
analysis from frontal-cortex brain tissue (Mill et al., 2008). However, while Mill et al. (2008) found a higher methylation in exon IX of two CpG sites (bp172 and bp112) in Val homozygotes, we found a higher methylation of two CpG sites (bp166 and bp209) in Met allele carriers. Based on the Met allele (T instead of C) Met homozygotes do not have the CpG site bp172, which likely explain the hypomethylation compared to Val homozygotes in the data of Mill et al. and the undetectable methylation for Met allele carriers in our data. The further differences could rely on tissue specific methylation rates, although studies reported similarity between blood and brain methylation rates (Klein et al., 2011). In addition, one third of the investigated participants by Mill et al. (2008) were patients with schizophrenia and bipolar disorder, which might have resulted in a different average methylation compared to healthy controls (Mill et al., 2008). As described above, the higher BDNF methylation in 66Met carriers might lead to lower BDNF mRNA levels (Keller et al., 2010; Sagarkar et al., 2017). Previous studies have likewise reported a reduction of activity-dependent BDNF release in Met allele carriers (Chen et al., 2005; Chen et al., 2006; Egan et al., 2003). Based on these results the hypothesis arises, that the inconclusive associations of the Val66Met polymorphism with psychiatric disorders and anxiety-related endophenotypes (Frustaci et al., 2008) might be explained by an additional impact of epigenetic influences on BDNF expression (Chen et al., 2015). Second, we did not find significant associations between Val66Met polymorphism and personality traits, which is consistent with previous negative findings in the literature (Frustaci et al., 2008; Montag, Basten, et al., 2010a; Wei et al., 2016). Finally, we did not find any genotype effect on amygdala reactivity. Although several fMRI studies reported associations of the BDNF val66met genotype with amygdala reactivity in response to emotional stimuli (Lau et al., 2010; Montag et al., 2008; Perez-Rodriguez et al., 2017), the results of these studies were limited by the single SNP approach, restricted generalizability of findings for females or MDD patients, and, in general, modest sample sizes. However, though the current study considered eight BDNF SNPs in a relatively large sample, we do not find a significant effect of BDNF genotype. Therefore, our findings add more evidence to Lau et al. (2010) results, revealing no direct Val66Met polymorphism effect on amygdala reactivity in healthy controls (Lau et al., 2010). Nevertheless, more research is required to analyze the relations between BDNF genotype, methylation and brain functions to create a clearer picture of the underlying relations, preferably using the GWAS approach.

Several limitations should be considered in interpreting the results. First, DNA methylation was measured using whole EDTA-blood. Inter-subject heterogeneity in blood cell type proportions might potentially confound methylation levels in our study (Jaffe & Irizarry, 2014). Furthermore, since determination of BDNF methylation in the brain of live patients is impractical, a direct correlation between BDNF methylation levels in the blood and brain cannot be assured. However, previous work indicates that BDNF can cross the blood–brain barrier, leading to detectable changes in peripheral blood (Hing, Sathyaputri, & Potash, 2017). Positive correlations between whole-blood BDNF levels and hippocampal BDNF in rats and pigs were observed (Klein et al., 2011), underlining peripheral BDNF measurements as a useful predictor of neuronal BDNF appearance (Hing et al., 2017; Kondakovic et al., 2015). The non significant BDNF polymorphism effects on the amygdala and personality trait level might be due to the low amount of Met/Met allele (n = 8) carriers and the resulting combination of Met/Met and Val/Met carriers into one group. Besides, influences of other BDNF exons, histone modifications, and functional polymorphisms could be biologically relevant and potentially confound our results. SLC6A4, for instance, has frequently been shown to interact with BDNF on behavioral, transcriptional, and epigenetic levels (Ignácio, Réus, Abelaira, & Quevedo, 2014). Last but not least, the cgp site (bp172) that includes the BDNF Val66Met SNP (rs6265) was excluded from our analysis, since it is only available in a part of subjects (BDNF met/met homozygotes and 50% of heterozygotes) leaving not enough power. In addition, other confounders like smoking status, physical exercises or stress could have influenced the BDNF methylation status and amygdala reactivity and should be taken into account for future studies. Finally, although we applied a computational and visual inspection of fMRI movement outliers and additionally used realignment, subtle movement effects cannot be completely ruled out.

In conclusion, we showed an association of BDNF methylation, amygdala reactivity and personality traits in humans, highlighting the multidimensional relations among genetics, epigenetics, and neuronal functions. Our data adds evidence to the hypothesis that epigenetic modifications of BDNF can result in an endophenotype associated with anxiety and mood disorders. Future more comprehensive epigenetic analyses are needed to examine further environmental, genetic, and epigenetic factors involved in the association of BDNF methylation and amygdala reactivity in detail.

ACKNOWLEDGMENTS

The study was supported by grants of Innovative Medizinische Forschung (IMF) of the Medical Faculty of Münster (RE111604 and RE111722 to RR, DA120903 and DA111107 to UD, and HO221003 to CH and UD), the German Research Foundation (DFG, grant FOR2107 DA1151/5-1 and DA1151/5-2 to UD; SFB-TRR58, Project C09 to UD and Projects C02/Z02 to KD), the Interdisciplinary Centre for Clinical Research (IZKF) of the medical faculty of Münster (grant Dan3/012/17 to UD), and by the Deanery of the Medical Faculty of the University of Münster.

DECLARATION OF INTEREST

VA is member of advisory boards and/or gave presentations for the following companies: Astra-Zeneca, Janssen-Organon, Lilly, Lundbeck, Servier, Pfizer, Otsuka, Trommsdorff, and Wyeth. He also receives funds from the German Ministry of Education and Research (BMBF) and from the European Union (EU-FP7). BTB is member of advisory boards, received funding and/or gave presentations for the following companies: AstraZeneca, Lundbeck, Pfizer, Servier, and Wyeth. He receives funding from the National Health and Medical Research
DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Ronny Redlich https://orcid.org/0000-0002-7018-4525
Jonathan Repple https://orcid.org/0000-0003-1379-9491

REFERENCES

Agassandian, K., Gedney, M., & Cassell, M. D. (2006). Neurotrophic factors in the central nucleus of amygdala may be organized to provide substrates for associative learning. Brain Research, 1076, 78–86.

American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders (4th ed.). Washington, DC: Author.

Amunts, K., Kedo, O., Kindler, M., Pieperhoff, P., Mohlberg, H., Shah, N. J., ..., Zilles, K. (2005). Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: Intersubject variability and probability maps. Anatomy and Embryology (Berlin), 210, 343–352. http://www.ncbi.nlm.nih.gov/pubmed/16208455

Arányi, T., Váradi, A., Simon, I., & Tusnády, G. E. (2006). The BiSearch web server. BMC Bioinformatics, 7, 431.

Baas, D., Aleman, A., & Kahn, R. S. (2004). Lateralization of amygdala activation: A systematic review of functional neuroimaging studies. Brain Research. Brain Research Reviews, 45, 96–103. http://www.ncbi.nlm.nih.gov/pubmed/15145620

Baeken, C., Marinazzo, D., Van Schuerbeeck, P., Wu, G.-R., De Mey, J., Luypaert, R., & De Raedt, R. (2014). Left and right amygdala—Medialfrontal cortical functional connectivity is differentially modulated by harm avoidance. PLoS One, 9, e95740. http://www.ncbi.nlm.nih.gov/pubmed/24760033

Barnea, A., & Roberts, J. (2001). Induction of functional and morphological expression of neuropeptide Y (NPY) in cortical cultures by brain-derived neurotrophic factor (BDNF). Evidence for a requirement for extracellular-regulated kinase (ERK)-dependent and ERK-independent mechanisms. Brain Research, 919, 57–69.

Chen, L., Pan, H., Tuan, T. A., Teh, A. L., Maclsaac, J. L., Mah, S. M., ..., Group TGS. (2015). Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism influences the association of the methyloyme with maternal anxiety and neonatal brain volumes. Development and Psychopathology, 27, 137–150.

Chen, Z.-Y., Ieraci, A., Teng, H., Dall, H., Meng, C.-X., Herrera, D. G., Lee, F. S. (2005). Sortilin controls intracellular sorting of brain-derived neurotrophic factor to the regulated secretory pathway. The Journal of Neuroscience, 25, 6156–6166.

Chen, Z.-Y., Jing, D., Bath, K. G., Ieraci, A., Khan, T., Siao, C.-J., ..., Lee, F. S. (2006). Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science, 314, 140–143.

Chen, Z.-Y., Patel, P. D., Sint, G., Meng, C.-X., Teng, K. K., Hempstead, B. L., & Lee, F. S. (2004). Variant brain-derived neurotrophic factor (BDNF) Met66 alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. The Journal of Neuroscience, 24, 4401–4411.

Clinton, S. M., Watson, S. J., & Akil, H. (2014). High novelty-seeking rats are resilient to negative physiological effects of the early life stress. Stress, 17, 97–107. http://www.ncbi.nlm.nih.gov/pubmed/24090131

Cloninger, C. R., Przybeck, T. R., & Svrakic, D. M. (1991). The dimensional personality questionnaire: U.S. normative data. Psychological Reports, 69, 1047–1057.

Dannowski, U., Kugel, H., Franke, F., Stuhrmann, A., Hofhoff, C., Zwanzger, P., ..., Domschke, K. (2011). Neuropeptide-S (NPS) receptor genotype modulates basolateral amygdala responsiveness to aversive stimulii. Neuropsychopharmacology, 36, 1879–1885. http://www.ncbi.nlm.nih.gov/pubmedcentral.nih.gov/articlerender.fcgi?artid=3154106&tool=pmcsearchrendertype=abstract

Dannowski, U., Kugel, H., Grotegerd, D., Redlich, R., Opel, N., Dohm, K., ... Baune, B. T. (2016). Disadvantage of social sensitivity: Interaction of oxytocin receptor genotype and child maltreatment on brain structure. Biological Psychiatry, 80, 398–405. http://www.ncbi.nlm.nih.gov/pubmed/26858213

Dannowski, U., Kugel, H., Redlich, R., Halik, A., Schneider, I., Opel, N., ... Hofhoff, C. (2014). Serotonin transporter gene methylation is associated with hippocampal gray matter volume. Human Brain Mapping, 35, 5356–5367. http://doi.wiley.com/10.1002/hbm.22555

Doherty, T. S., Forster, A., & Roth, T. L. (2016). Global and gene-specific DNA methylation alterations in the adolescent amygdala and hippocampus in an animal model of caregiver maltreatment. Behavioural Brain Research, 298, 55–61.

Domschke, K., Tidow, N., Kuitlan, H., Schwarte, K., Klauke, B., Ambriere, O., ... Deckert, J. (2012). Monoamine oxidase A gene DNA hypomethylation—A risk factor for panic disorder? The International Journal of Neuropsychopharmacology, 15, 1217–1228.

Duclot, F., & Kabbaj, M. (2013). Individual differences in novelty seeking predict subsequent vulnerability to social defeat through a differential epigenetic regulation of brain-derived neurotrophic factor expression. The Journal of Neuroscience, 33, 11048–11060.

Egan, M. F., Kojima, M., Callcott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., ... Weinberger, D. R. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell, 112, 257–269.

Ehrlich, D. E., & Josselyn, S. A. (2016). Plasticity-related genes in brain development and amygdala-dependent learning. Genes, Brain, and Behavior, 15, 125–143.

Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage, 25, 1325–1335. http://www.ncbi.nlm.nih.gov/pubmed/15850749

Frustaci, A., Pozzi, G., Gianfagna, F., Manzoli, L., & Boccia, S. (2008). Meta-analysis of the brain-derived neurotrophic factor gene (BDNF) Val66Met polymorphism in anxiety disorders and anxiety-related personality traits. Neuropsychobiology, 58, 163–170.

Gaffrey, M. S., Luby, J. L., Belden, A. C., Hirshberg, J. S., Volsch, J., & Barch, D. M. (2011). Association between depression severity and amygdala reactivity during sad face viewing in depressed preschoolers: An fMRI study. Journal of Affective Disorders, 129, 364–370.

Gainotti, G. (2019). Emotions and the right hemisphere: Can new data clarify old models? The Neuroscientist, 25, 258–270. http://www.ncbi.nlm.nih.gov/pubmed/29985120

Goodman, M., Carpenter, D., Tang, C. Y., Goldstein, K. E., Avedon, J., Fernandez, N., ... Hazlett, E. A. (2014). Dialectical behavior therapy alters emotion regulation and amygdala activity in patients with borderline personality disorder. Journal of Psychiatric Research, 57, 108–116. http://www.ncbi.nlm.nih.gov/pubmed/25038629

Gottschalk, M. G., & Domschke, K. (2017). Genetics of generalized anxiety disorder and related traits. Dialogues in Clinical Neuroscience, 19, 159–168.
severe depression. Human Brain Mapping, 43, 546–554. http://www.ncbi.nlm.nih.gov/pubmed/29039414

Redlich, R., Stacey, D., Opel, N., Grotegerd, D., Dohm, K., Kugel, H., ... Dannlowski, U. (2015b). Evidence of an IFN-γ by early life stress interaction in the regulation of amygdala reactivity to emotional stimuli. Psychoneuroendocrinology, 62, 166–173. http://www.ncbi.nlm.nih.gov/pubmed/26313134

Sagarkar, S., Bhambarkar, T., Shelkar, G., Choudhary, A., Kokare, D. M., & Sakharkar, A. J. (2017). Minimal traumatic brain injury causes persistent changes in DNA methylation at BDNF gene promoters in rat amygdala: A possible role in anxiety-like behaviors. Neurobiology of Disease, 106, 101–109.

Schartner, C., Ziegler, C., Schiele, M. A., Kollert, L., Weber, H., Zwanzger, P., ... Domschke, K. (2017). CRHR1 promoter hypomethylation: An epigenetic readout of panic disorder? European Neuropsychopharmacology, 27, 360–371.

Schneider, I., Kugel, H., Redlich, R., Grotegerd, D., Bürger, C., Bürkner, P.-C., ... Hohoff, C. (2018). Association of serotonin transporter gene AluJb methylation with major depression, amygdala responsiveness, 5-HTTLPR/rs25531 polymorphism, and stress. Neuropsychopharmacology, 43, 1308–1316. http://www.nature.com/doi/10.1038/npp.2017.273

Schoemann, C. M., Bauman, M. D., & Amaral, D. G. (2011). Abnormal structure of neurodevelopmental disorders. Neuropsychologia, 49, 745–759.

Stedenfeld, K. A., Clinton, S. M., Kerman, I. A., Akil, H., Watson, S. J., & Sved, A. F. (2011). Novelty-seeking behavior predicts vulnerability in a rodent model of depression. Physiology & Behavior, 103, 210–216. http://www.ncbi.nlm.nih.gov/pubmed/21303678

Straub, J., Plener, P. L., Sproebner, N., Sprenger, L., Koelch, M. G., Groen, G., & Abler, B. (2015). Neural correlates of successful psychotherapy of depression in adolescents. Journal of Affective Disorders, 183, 239–246. http://www.ncbi.nlm.nih.gov/pubmed/26025370

Stuhmann, A., Dohm, K., Kugel, H., Zwanzger, P., Redlich, R., Grotegerd, D., ... Dannlowski, U. (2013). Mood-congruent amygdala responses to subliminally presented facial expressions in major depression: Associations with anhedonia. Journal of Psychiatry & Neuroscience, 37, 249–258. http://www.ncbi.nlm.nih.gov/pubmed/23171695

Tadic, A., Muller-Engling, L., Schlicht, K. F., Kotsiari, A., Dreimuller, N., Kleimann, A., ... Frielings, H. (2014). Methylation of the promoter of brain-derived neurotrophic factor exon IV and antidepressant response in major depression. Molecular Psychiatry, 19, 281–283.

Thaler, L., Gauvin, L., Joobe, R., Groele, P., de Guzman, R., Ambalavanar, A., ... Steiger, H. (2014). Methylation of BDNF in women with bulimic eating syndromes: Associations with childhood abuse and borderline personality disorder. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 54, 43–49. http://www.ncbi.nlm.nih.gov/pubmed/24801751

Tusnady, G. b. E., Simon, I., Varadi, A., & Aranyi, T. (2005). BiSearch: Primer-design and search tool for PCR on bisulfite-treated genomes. Nucleic Acids Research, 33, e9–e9.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., ... Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage, 15, 273–289. http://www.ncbi.nlm.nih.gov/pubmed/11771995

Wei, S.-M., Eisenberg, D. P., Nabel, K. G., Kohn, P. D., Kippenhan, J. S., Dickinson, D., ... Berman, K. F. (2016). Brain-derived neurotrophic factor Val64Met polymorphism affects the relationship between an anxiety-related personality trait and resting regional cerebral blood flow. Cerebral Cortex, 27, bhw072.

Wittchen, H. U., Zaudig, M., & Fydrich, T. (1997). SKID—Strukturiertes Klinisches Interview DSM IV. Göttingen: Hogrefe.

Wood, J., Verma, D., Lach, G., Bonaventure, P., Herzog, H., Sperk, G., & Tasan, R. O. (2016). Structure and function of the amygdaloid NPY system: NPY Y2 receptors regulate excitatory and inhibitory synaptic transmission in the centromedial amygdala. Brain Structure & Function, 221, 3373–3391.

Xu, B., & Xie, X. (2016). Neurotrophic factor control of satiety and body weight. Nature Reviews. Neuroscience, 17, 282–292.

Zheleznyakova, G. Y., Cao, H., & Schloth, H. B. (2016). BDNF DNA methylation changes as a biomarker of psychiatric disorders: Literature review and open access database analysis. Behavioral and Brain Functions, 12, 17.

Ziegler, C., Richter, J., Mahr, M., Gajewska, A., Schiele, M. A., Gehrmann, A., ... Domschke, K. (2016). MAOA gene hypomethylation in panic disorder—Reversibility of an epigenetic risk pattern by psychotherapy. Translational Psychiatry, 6, e773–e773.

Ziegler, C., Wolf, C., Schiele, M. A., Feric Bojic, E., Kucukalic, S., Sabic Dzanovanic, E., ... Domschke, K. (2018). Monoamine oxidase A gene methylation and its role in posttraumatic stress disorder: First evidence from the South Eastern Europe (SEE)-PTSD study. The International Journal of Neuropsychopharmacology, 21, 423–432.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Redlich R, Schneider I, Kerkenberg N, et al. The role of BDNF methylation and Val64Met in amygdala reactivity during emotion processing. Hum Brain Mapp. 2020;41:594–604. https://doi.org/10.1002/hbm.24825
Minerva Access is the Institutional Repository of The University of Melbourne

Author/s: Redlich, R; Schneider, I; Kerkenberg, N; Opel, N; Bauhaus, J; Enneking, V; Repple, J; Leehr, EJ; Grotegerd, D; Kaehler, C; Foerster, K; Dohm, K; Meinert, S; Hahn, T; Kugel, H; Schwarte, K; Schettler, C; Domschke, K; Arolt, V; Heindel, W; Baune, BT; Zhang, W; Hohoff, C; Dannlowski, U

Title: The role of BDNF methylation and Val(66)Met in amygdala reactivity during emotion processing

Date: 2019-10-15

Citation: Redlich, R., Schneider, I., Kerkenberg, N., Opel, N., Bauhaus, J., Enneking, V., Repple, J., Leehr, E. J., Grotegerd, D., Kaehler, C., Foerster, K., Dohm, K., Meinert, S., Hahn, T., Kugel, H., Schwarte, K., Schettler, C., Domschke, K., Arolt, V., ... Dannlowski, U. (2019). The role of BDNF methylation and Val(66)Met in amygdala reactivity during emotion processing. HUMAN BRAIN MAPPING, 41 (3), pp.594-604. https://doi.org/10.1002/hbm.24825.

Persistent Link: http://hdl.handle.net/11343/246912

File Description: published version

License: CC BY-NC-ND