EEG Alpha Power as an Intermediate Measure Between Brain-Derived Neurotrophic Factor Val66Met and Depression Severity in Patients With Major Depressive Disorder

Harriët F. A. Zoon, C. P. M. Veth,*† Martijn Arns,*‡ W. H. I. M. Drinkenburg,§ Willem Talloen,§ Pieter J. Peeters,§ and J. L. Kenemans‡*

Summary: Major depressive disorder has a large impact on patients and society and is projected to be the second greatest global burden of disease by 2020. The brain-derived neurotrophic factor (*BDNF*) gene is considered to be one of the important factors in the etiology of major depressive disorder. In a recent study, alpha power was found to mediate between *BDNF Met* and subclinical depressed mood. The current study looked at a population of patients with major depressive disorder (N = 107) to examine the association between the *BDNF Val66Met* polymorphism, resting state EEG alpha power, and depression severity. For this purpose, repeated-measures analysis of variance, partial correlation, and multiple linear models were used. Results indicated a negative association between parietal-occipital alpha power in the eyes open resting state and depression severity. In addition, *Met*/*Met* patients showed lower global absolute alpha power in the eyes closed condition compared with *Val*-carriers. These findings are in accordance with the previously uncovered pathway between *BDNF Val66Met*, resting state EEG alpha power, and depression severity. Additional research is needed for the clarification of this tentative pathway and its implication in personalized treatment of major depressive disorder.

Key Words: Brain-derived neurotrophic factor, Val66Met polymorphism, Alpha rhythm, Depression, EEG.

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Major depressive disorder (MDD) is associated with a high global burden of disease (Mathers and Loncar, 2006), including high mortality and increasing socioeconomical costs. Increasing the understanding of the neurobiological background of MDD is critical as present-day treatments are inadequate for many patients (Rush et al., 2006; Trivedi et al., 2007). The heritability factor of this heterogenous disorder lies between 40% and 50% (Sullivan et al., 2000). Variations in genotype may thus explain some of the differences within MDD, including response to treatment. The genetic polymorphism brain-derived neurotrophic factor (*BDNF*) *Val66Met* is considered an important measure related to antidepressant treatment outcome (Zou et al., 2010). Furthermore, the *BDNF* gene and BDNF protein levels have been associated with MDD (Jiang et al., 2005; Molendijk et al., 2010; Verhagen et al., 2010) and MDD severity (Czira et al., 2011). However, the heterogenous nature of MDD makes it difficult to uncover the exact contribution of *BDNF* to the disease. Intermediate phenotypes captured in neurophysiologic measures reflect the combined influence of genes and can be used to determine the relationship between gene and disease (Gottesman and Gould, 2003). The aim of this study is to find an intermediate parameter that can aid in elucidating the association between *BDNF Val66Met* and depressive symptoms.

Brain-derived neurotrophic factor is a neurotrophic factor that is involved in neuronal proliferation and synaptic plasticity (Duman and Monteggia, 2006; Katz and Shatz, 1996). Activity-dependent secretion of BDNF was found to be affected by the *BDNF Val66Met* substitution *in vitro* (Egan et al., 2003). Depressive subjects carrying the *Met*-allele scored higher on depression severity than *Val* homozygotes (Ozan et al., 2010). In addition to this finding, healthy and depressed *Met*-allele carriers were found to have lower serum BDNF levels compared with *Val* homozygote individuals. Decreased expression of BDNF induced by stress is thought to be directly related to the pathophysiology of depression (Berton and Nestler, 2006; Groves, 2007). Normalization of BDNF levels (Molendijk et al., 2010; Sen et al., 2008) and dendritic arborization (specifically in hippocampal neurons; Berton and Nestler, 2006) is considered a hallmark of antidepressant treatment success.

Deficient neuronal connectivity and information processing are often reported as comorbid symptoms of MDD and other mood disorders (e.g., Castren, 2005). The effect of BDNF on neuronal plasticity can most likely be seen in neuronal activity, such as reflected in the highly heritable resting EEG alpha power (Enoch et al., 2008; Smit et al., 2005). The alpha rhythm, defined as ranging from 8 to 13 Hz, occurs in a state of relaxed alertness and is dominant during eyes closed conditions. The EEG in MDD characteristically shows increased alpha power (Bruder et al., 2005; Grin-Yatsenko et al., 2009; Itil, 1983). Furthermore, higher pretreatment alpha power is associated with improved SSRI treatment outcome (Bruder et al., 2008).

The previously discussed findings lead us to hypothesize that the *BDNF Val66Met* polymorphism causes a reduced secretion of BDNF, which subsequently negatively affects functional connectivity in neuronal systems that generate alpha oscillations and are involved in processes related to symptoms of MDD. The *Val*/*Val* genotype can be considered a protective factor for developing MDD. *Met*/*Met* patients who lack the protective effect of *Val* would in that case have an increased vulnerability for developing MDD and will presumably reach a higher depression severity. More specifically, this results in the following three hypotheses: (1) the *BDNF Val66Met* polymorphism is related to lower EEG alpha power, (2) lower

From the *Research Institute Brainclinics, Nijmegen, Netherlands; †Department of Cognitive Neuroscience, Radboud University, Nijmegen, Netherlands; ‡Department of Experimental Psychology and Psychopharmacology, Utrecht University, Utrecht, Netherlands; and §Janssen Pharmaceutical Research and Development, Pharmaceutical Companies of Johnson & Johnson, Beerse, Belgium.

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H. F. A. Zoon and C. P. M. Veth contributed equally to this work.

Address correspondence and reprint requests to Martijn Arns, PhD, Research Institute Brainclinics, Bijleveldsingel 34, 6524 AD Nijmegen, Netherlands; e-mail: martijn@brainclinics.com.

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EEG alpha power is related to symptom severity of major depression, and (3) a pathway is present that links the two previously mentioned associations. In other words, it was expected that a two-step relation between *BDNF Val66Met* and EEG alpha power on the one hand and EEG alpha power and depression severity on the other would be observed, rather than a direct significant association between *BDNF* genotype and depression severity. Recent research on a healthy population with subclinical features of depression revealed a pathway from *BDNF Val66Met* homozygosity via decreased relative alpha power to higher depressed mood (Gatt et al., 2008). The current study aims to extend those initial findings by investigating the relationship between the *BDNF Val66Met* polymorphism, EEG alpha power, and depression severity in a sample of MDD patients.

METHODS

Participants

For this study, 107 participants (mean age ± SD: 38.95 ± 13.13) with a medical diagnosis of MDD were included from the brain resource international database (Gordon et al., 2005). Further inclusion criteria were aged 18 to 65 years and complete genetic (BDNF), neurophysiologic (EEG), and depression severity (Hamilton Depression Rating Scale [HAM-D]) data. The study took place in Australia.

Major depressive disorder diagnosis was confirmed by trained research assistants at the pretreatment testing day using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) and the HAM-D (Hamilton, 1960; Williams, 1988). The Mini International Neuropsychiatric Interview was also used to rule out other current or present primary Diagnostic and Statistical Manual of Mental Disorders-IV disorders (e.g., posttraumatic stress disorder, obsessive-compulsive disorder, and bipolar disorder). Major depressive disorder subjects were excluded when an organic factor or substance use was indicated as the cause of the depression. Furthermore, it was ensured that treatment effects of previous medical or psychological treatment would not interfere with the primary aims of the study. A period of at least five half-lives was kept between ceasing use of antidepressant medication and the time of testing. Five half-lives as a washout is considered an appropriate period for excluding effects of medication on EEG measures (e.g., Pae et al., 2008).

Before the study commenced, all participants provided written informed consent. This study complied with the rules and regulations of the Sydney West Area Health Service and the University of Sydney Human Research Ethics Committees. In addition, the study protocol is in accordance with the ethical principles of the Declaration of Helsinki (2008) and the Guidelines of the International Conference on Harmonization.

BDNF Genotype

BDNF Val66Met genotypes were determined by genetic analysis of DNA that was extracted from cheek swab samples. Polymerase chain reaction amplification using intronic primers was used for the screening of single nucleotide polymorphisms. The *Afl*III restriction enzyme was used to cleave the *Val* allele, after which the polymerase chain reaction products were separated by mass spectrometry. Following the methods of Gatt et al. (2008), three genotype groups were maintained (*Val*/*Val* [n = 65]; *Val*/*Met* [n = 37]; *Met*/*Met* [n = 5]), even though the group size of the lowest prevalence *Met*/*Met* genotype group was small. No significant genotype differences were evident for demographic measures age, gender, and education (Table 1).

Measures

Depressive symptom severity was determined by trained research assistants with the aid of the HAM-D (Hamilton, 1960). This is a 17-item structured clinical interview with a score ranging between 0 and 52.

A 26-channel EEG system (Quickcap; NuAmps: 10–20 electrode international system) was used for data-acquisition during two consecutive resting state conditions: namely, eyes open and eyes closed. Scalp and electro-oculographic potentials were amplified and digitized continuously by a system (NuAmps, SCAN 4.3) having a frequency response from DC to 100 Hz and a sampling rate of 500 Hz. Offline settings entailed linked ear montage and electro-oculographic correction following a technique based on Gratton et al. (1983). During testing, participants were seated comfortably in a sound and light attenuated room. Both conditions had a duration of 2 minutes, which were divided into 4-second intervals. Spectral power analyses were performed on each 4-second interval by first applying a Welch window to the data and then performing a fast Fourier transformation. The power spectra were averaged for each electrode position, and power was then calculated for four frequency bands: delta (1.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–13 Hz), and beta (14.5–30 Hz). Relative power was calculated by dividing the

TABLE 1. Means and Statistical Effects for Brain-Derived Neurotrophic Factor Genotype on Demographics, Cognition, and Depression (N = 107)

	Genotype Groups, Mean (SE)			Test of Difference		
	Val/*Val*	*Val*/*Met*	*Met*/*Met*	*F* Statistics	*P**	Cohen *d*
Demographics						
Age	38.92 (1.65)	37.49 (2.07)	50.27 (4.92)	2.13	0.124	—
Gender (M/F)	27/38	16/21	2/3	—	1.000	—
Education (yrs)	13.89 (0.37)	13.92 (0.48)	14.60 (2.04)	0.13	0.880	—
Depression						
HAM-D	19.43 (0.64)	20.73 (0.79)	21.80 (1.11)	1.156	0.319	*Met*/*Met* vs. *Val*/*Val* = −0.47 *Met*/*Met* vs. *Val*/*Met* = −0.23

*Significance (two-sided).

absolute power of one frequency band by the average power across all four frequency bands. Calculations were performed for each individual electrode site. More details of the methods for EEG recording and analyses can be found elsewhere (Arns et al., 2007; Spronk et al., 2011; Williams et al., 2011).

Analyses

A one-way analysis of variance (ANOVA) for age, education, and depression severity was performed to examine the differences between the *BDNF* genotype groups. Differences in gender were analyzed using a Fisher exact probability test. Cohen *d* was calculated to express the size (0.20 = small; 0.50 = medium; and 0.80 = large) of the pairwise effects of "*Val*/*Val* versus *Met*/*Met*" and "*Val*/*Met* versus *Met*/*Met*."

Repeated-measures ANOVAs were conducted for the alpha frequency band with *BDNF* genotype as between-subjects factor, brain region as within-subjects factor, and covariates age and gender. The factor brain region was obtained by calculating the mean EEG power of all electrode sites within a region. The division of electrode sites over region was as follows: frontal (Fp1, Fp2, F7, F3, Fz, F4, and F8), central (FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, and CP4), temporal (T3, T4, T5, and T6), and parietal-occipital (P3, Pz, P4, O1, Oz, and O2). The repeated-measures ANOVAs were performed for the eyes open and for the eyes closed condition and included both absolute and relative power. Subsequently, one-way ANOVAs were performed to identify regional effects of *BDNF* genotype (Tables 2 and 3). Cohen *d* was calculated for the pairwise effects of "*Val*/*Val* versus *Met*/*Met*" and "*Val*/*Met* versus *Met*/*Met*."

Partial correlation analyses controlling for age and gender were used to test the relationship between EEG power measures and depression severity scores. Correlations were tested for the separate regions (frontal, central, temporal, and parietal-occipital).

Finally, based on the results of previously described analyses, eyes open absolute and relative EEG alpha power in the parietal-occipital region were selected to be tested for mediation between *BDNF Val66Met* and depression severity. Mediation analyses were performed according to the "joint significance approach" (MacKinnon et al., 2002). In this approach, two associations need to be significant for a variable to be considered a mediator: (1) the association between the independent variable and the mediator and (2) the relationship between the mediator and the dependent variable controlled for the independent variable. Both associations were analyzed using multiple linear models controlling for gender and age.

RESULTS

Depression Severity

No significant differences between *BDNF* genotypes were found in a one-way ANOVA for depression severity in MDD patients (Table 1).

BDNF and Resting Brain Function (EEG)—Eyes Open Condition

Repeated-measures analyses for the eyes open paradigm did not reveal any main effects for *BDNF* genotype, in relative (F [2,97] = 1.44, P = 0.242) nor in absolute power (F [2,97] = 1.84, P = 0.165) (Figs. 1A and 1B). Furthermore, no interaction effects for region × *BDNF* were present in absolute or relative alpha power. All one-way ANOVAs testing the effect of *BDNF* genotype on the separate regions are displayed in Table 2.

BDNF and Resting Brain Function (EEG)—Eyes Closed Condition

In the eyes closed condition, a main effect of *BDNF* genotype was found for absolute alpha power over all regions (F [2,101] = 3.26, P = 0.042) (Figs. 2A and 2B). *Post hoc* tests revealed that *Met*/*Met* individuals demonstrate a significantly lower absolute alpha power (P = 0.015) compared with *Val*/*Val* participants. The *Met*/*Met* group showed a near significant decrease in absolute alpha power when compared with the *Val*/*Met* group (P = 0.051). For relative alpha power, no significant effects were found (F [2,101] = 1.49, P = 0.230). No interaction effects for region × *BDNF* were

TABLE 2. Means, One-Way Analysis of Variance Effects for *BDNF* Genotype on Frontal, Central, Temporal, and Parietal-Occipital Brain Regions for the Eyes Open Condition (N = 107)

Brain Region	Genotype Group *Val*/*Val*			*Val*/*Met*						*F* Statistic	*P**	Cohen *d* *Met*/*Met* vs. *Val*/*Val*	*Met*/*Met* vs. *Val*/*Met*
	Mean	SE	N	Mean	SE	N	Mean	SE	N				
Relative power (eyes open)													
Alpha power													
Frontal	0.223	0.011	62	0.209	0.013	36	0.199	0.043	5	0.481	0.620	0.29	0.13
Central	0.294	0.014	62	0.269	0.019	36	0.245	0.053	5	0.892	0.413	0.45	0.21
Temporal	0.313	0.015	61	0.276	0.020	36	0.257	0.071	5	1.316	0.273	0.45	0.15
Parietal-occipital	0.390	0.020	62	0.341	0.026	36	0.271	0.056	5	2.108	0.127	0.76	0.45
Absolute power (eyes open)													
Alpha power													
Frontal	11.683	1.055	62	10.032	1.107	36	8.719	3.667	5	1.329	0.269	0.60	0.40
Central	19.377	1.988	62	15.063	1.905	36	12.642	6.171	5	1.950	0.148	0.73	0.49
Temporal	13.427	1.602	61	10.414	1.494	36	8.368	4.249	5	1.663	0.195	0.66	0.46
Parietal-occipital	27.722	3.365	62	19.674	3.020	36	11.697	5.394	5	2.300	0.106	0.82	0.62

*P < 0.05.

TABLE 3. Means, One-Way Analysis of Variance Effects for Brain-Derived Neurotrophic Factor Genotype on Frontal, Central, Temporal, and Parietal-Occipital Brain Regions for the Eyes Closed Condition (N = 107)

	Genotype Group											
Brain Region	**Val/Val**			**Val/Met**			**Met/Met**			***F* Statistic**	***P***	**Cohen *d* *Met/Met* vs. *Val/Val***	***Met/Met* vs. *Val/Met***
	Mean	SE	N	Mean	SE	N	Mean	SE	N				
Relative power (eyes closed)													
Alpha power													
Frontal	0.395	0.020	65	0.391	0.024	37	0.282	0.055	5	1.228	0.297	3.18	0.75
Central	0.436	0.018	65	0.435	0.023	37	0.337	0.061	5	1.107	0.334	2.63	0.71
Temporal	0.467	0.018	64	0.454	0.022	37	0.332	0.077	5	2.121	0.125	2.95	0.89
Parietal-occipital	0.550	0.020	65	0.550	0.026	37	0.391	0.066	5	2.406	0.095	3.92	1.02
Absolute power (eyes closed)													
Alpha power													
Frontal	33.870	3.260	65	34.916	6.576	37	12.481	5.681	5	3.347	0.039*	1.17	1.10
Central	48.784	4.860	65	41.862	5.091	37	20.632	10.501	5	3.105	0.049*	1.14	1.01
Temporal	43.800	5.853	64	29.732	3.542	37	13.062	7.168	5	4.095	0.019*	1.23	1.07
Parietal-occipital	89.133	11.279	65	68.065	9.944	37	20.048	9.160	5	4.047	0.020*	1.27	1.26

*$P < 0.05$.

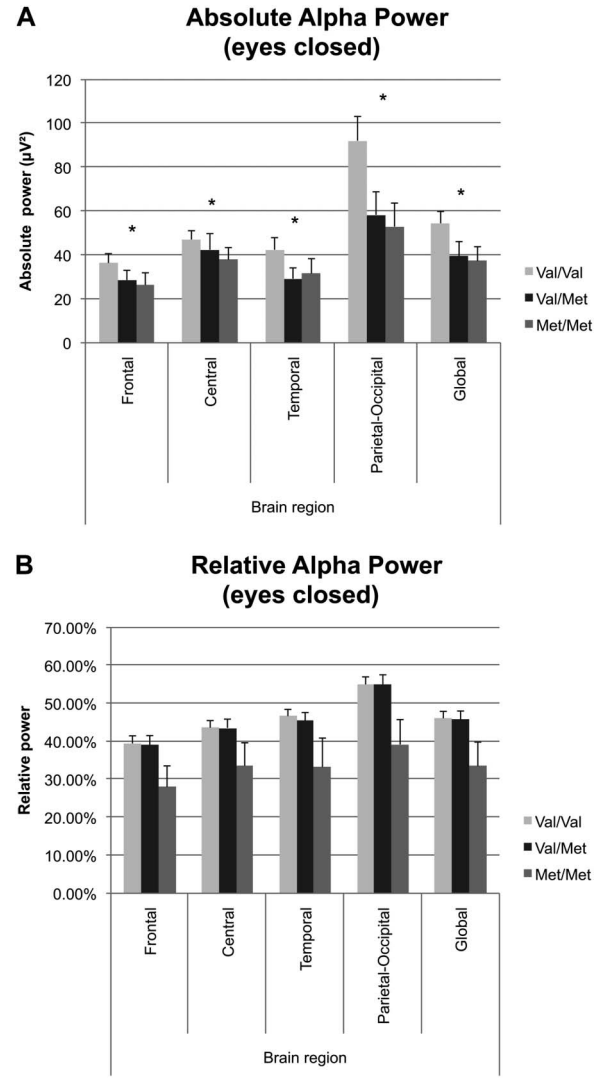

FIG. 1. Mean EEG alpha power for the brain-derived neurotrophic factor genetic groups (*Val/Val*, *Val/Met*, *Met/Met*) over separate brain regions (frontal, central, temporal, and parietal-occipital) and all regions taken together (global) displayed for eyes open resting state absolute alpha power (**A**) and relative alpha power (**B**).

present in absolute or relative alpha power. All one-way ANOVAs testing the effect of BDNF genotype on the separate regions are displayed in Table 3.

Resting Brain Function (EEG) and Depression Severity

Correlation analyses of the associations between EEG power in the eyes open condition and depression severity revealed a significant negative correlation between relative alpha power in the parietal-occipital region (r = -0.250, P = 0.013). In the same condition, a significant negative correlation was found for absolute alpha power in the parietal-occipital region (r = -0.258, P = 0.01). No significant correlations were found for relative and absolute alpha power in the eyes closed condition.

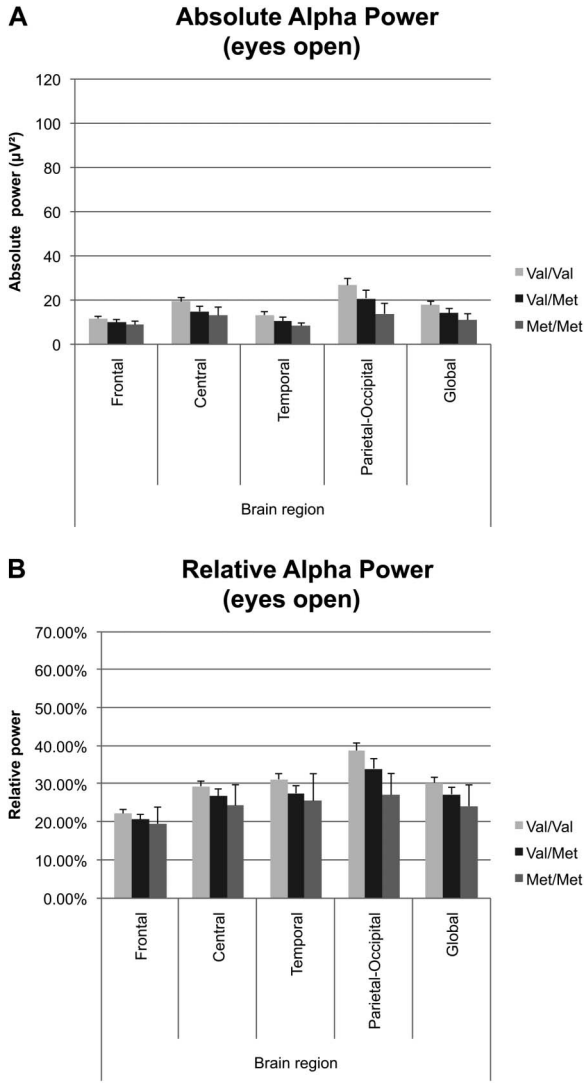

FIG. 2. Mean EEG alpha power for the brain-derived neurotrophic factor (*BDNF*) genetic groups (*Val*/*Val*, *Val*/*Met*, and *Met*/*Met*) over separate brain regions (frontal, central, temporal, and parietal-occipital) and all regions taken together (global) displayed for eyes closed resting state absolute alpha power (**A**) and relative alpha power (**B**). Repeated-measures reveal a significant main effect ($F\ [2,101] = 3.26$, $P < 0.05$) of the *BDNF Val66Met* single nucleotide polymorphism on absolute alpha power in the eyes closed condition. Results of the one-way analysis of variance (ANOVAs) show that this effect is present in all regions (*$P < 0.05$).

Genotype-Intermediate Measure-Phenotype—Eyes Open Condition (Absolute Power)

Multiple linear models were used to test for eyes open absolute EEG alpha power as a mediator in the relationship between *BDNF Val66Met* and depression severity. The first step of the analyses revealed that *BDNF Val66Met* adjusted for gender had significant predictive value for parietal-occipital absolute alpha power ($\beta = -0.20$, $t\ [100] = -2.09$, $P = 0.039$). However, the individual contribution of *BDNF Val66Met* independent of both gender and age was less significant ($\beta = -0.19$, $t\ [99] = -1.97$, $P = 0.051$). The second step of the analyses showed that parietal-occipital alpha power had a significant contribution in predicting depression severity, independent of *BDNF Val66Met*, gender, and age ($\beta = -0.25$, $t\ [98] = -2.53$, $P = 0.013$). Analyses aimed at uncovering interaction effects within the above analyses were nonsignificant, and no interaction effects were found.

Genotype-Intermediate Measure-Phenotype—Eyes Open Condition (Relative Power)

Mediation of relative EEG alpha power in the parietal-occipital region between *BDNF Val66Met* and depression severity was also tested with multiple linear regression models. The first step of the analyses showed that *BDNF Val66Met* adjusted for gender had a significant amount of predictive power for parietal-occipital relative alpha power ($\beta = -0.20$, $t\ [100] = -2.05$, $P = 0.043$) but, looking at the predictive value of *BDNF Val66Met* independent of gender and age, showed an association that was less strong ($\beta = -0.19$, $t\ [99] = -1.95$, $P = 0.054$). In the second part of the analyses, relative alpha power in the parietal-occipital area was found to contribute significantly in predicting depression severity independent of *BDNF Val66Met*, age, and gender ($\beta = -0.25$, $t\ [98] = -2.46$, $P = 0.015$). Analyses aimed at uncovering interaction effects within the above analyses were nonsignificant, and no interaction effects were found.

DISCUSSION

This study in a population of patients with MDD has unveiled several interesting associations between measures of genetics (*BDNF Val66Met* single nucleotide polymorphism), neurophysiology (EEG alpha power), and depression severity (Fig. 3). In line with the results of a study in a subclinical population by Gatt et al. (2008), increased depression severity was related to reduced relative parietal-occipital alpha power in the eyes open condition. In addition, this study revealed the same effect for absolute alpha power. Furthermore, in agreement with Gatt et al. (2008), an association was found between *BDNF Val66Met* and global alpha power. However, in this study, this effect was found for absolute alpha power specifically in the eyes closed condition, whereas Gatt et al. (2008) found this effect for eyes open relative alpha. The moderate P values and relatively large effect sizes (Cohen d) related to the eyes open EEG alpha in the parietal-occipital region (Table 2) and eyes closed relative alpha power (Table 3) indicate that this study was underpowered, most likely explaining differences with the results of Gatt et al. (2008). The same holds for the differences in depression severity between patient groups with the *Val*/*Val* and the *Met*/*Met* genotypes (Table 1). Large effect sizes (>0.80) indicate that the factor at hand (e.g., EEG alpha power or depression severity) has a high potential to assist in differentiating the *BDNF* genotype groups. In combination with low P values, this indicates that significant effects may be found in a larger sample. Moreover, the findings from the mediation analyses for eyes open alpha power in the parietal-occipital region follow the same direction of effect as in the pathway discovered by Gatt et al. (2008). There were strong indications for mediation by parietal-occipital alpha power. However, the predictive value of *BDNF Val66Met* on alpha power in the parietal-occipital region was limited when adjusted for age and gender. This suggests that, in addition to the influence of *BDNF Val66Met* on parietal-occipital alpha power, other factors account for a part of the relationship between this EEG measure and depression severity. In addition, the small *Met*/*Met* sample (n = 5) may have been a limitation

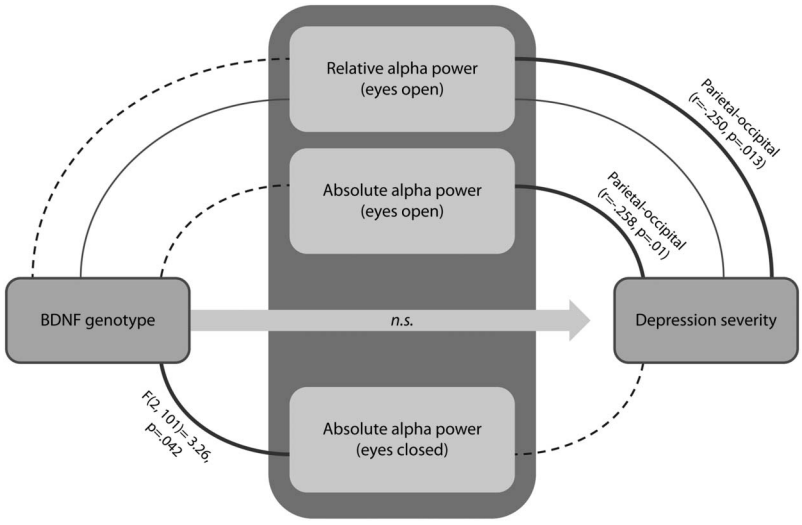

FIG. 3. Flowchart displaying the results of the associations studied with repeated-measures analysis of variances (ANOVAs) and partial correlation analyses. The lines represent significant results (bold line), nonsignificant results (dashed line), and the pathway as found by Gatt et al. (2008) (fine line). The brain-derived neurotrophic factor (BDNF) genotype is significantly related to absolute power in the eyes closed condition but not to alpha power in the eyes open condition. Depression severity is negatively correlated to alpha power in the eyes open condition but is not correlated to alpha power in the eyes closed condition.

for this study. Nevertheless, the significant effects and the nonsignificant ones combined with large effect sizes are in line with previous findings.

Parietal-occipital alpha power is often found to be higher in MDD (Bruder et al., 2005; Itil, 1983; Pollock and Schneider, 1990) and early depression (Grin-Yatsenko et al., 2009) compared with healthy controls. A recent study explains this increased alpha power as the result of a hyperstable vigilance regulation in depression (Hegerl et al., 2011). Different from the aforementioned research that showed differences between MDD and controls, our results demonstrate differences in alpha power within a population of depressive individuals. Increased depression severity is associated with decreased parietal-occipital alpha power in the eyes open condition but not in the eyes closed condition. Interestingly, the high heritability of alpha power as found by Smit et al. (2005) and Van Beijsterveldt et al. (1996) was only reported for eyes closed, suggesting that eyes closed provides a more stable condition, revealing "trait-like" alpha. The amount of alpha power observed in the EEG is generally more pronounced with eyes closed (Klimesch, 1999; Niedermeyer, 1997) and in MDD in the parietal-occipital region (Bruder et al., 2005; Itil, 1983; Pollock and Schneider, 1990). Therefore, the detection of variations in alpha power may have been facilitated by a higher signal-to-noise ratio in those conditions, making them ideal for finding effects of genetic factors such as *BDNF Val66Met*.

Alpha power in the eyes open resting state may be more susceptible to state-dependent effects such as mental alertness or mood, relevant in depression, making it more difficult to find genetic effects.

Decreased parietal-occipital alpha power or the inability to produce a classical posterior alpha rhythm was proposed to be related to defects in alpha synchronizing mechanisms (Niedermeyer, 1997). Furthermore, posterior alpha-band activity was found to have an inverse relationship with cortical excitability (Romei et al., 2008). In relation to our results, this would imply that *BDNF Met*-carriers and patients with a high depression severity are characterized by increased neuronal excitability and a less synchronized EEG. We speculate that the decreased alpha power found in the *BDNF Met*/*Met* group can be explained by a higher prevalence of low voltage alpha (LVA) power (Vogel, 1970). This autosomal-dominant heritable LVA trait was proposed to be caused by worse alpha synchronization in eyes closed and eyes open conditions (Niedermeyer, 1997). In studies of alcoholism and anxiety, LVA was associated with the *GABA-B* receptor gene (Winterer et al., 2003) and the *COMT Val158Met* gene (Enoch et al., 2003). Recently, a study by our group revealed a higher prevalence of both LVA and the *BDNF Met* allele in MDD compared with healthy controls (Veth et al., unpublished data). Future studies should investigate if *BDNF Met* is related to a defect in alpha synchronization mechanisms, reflected by LVA, and if this is associated with more severe MDD symptoms.

The limited secretion of the BDNF protein in *Met*-allele carriers (Ozan et al., 2010) and subsequent effects on functional connectivity may provide an additional explanation for the reduction in global alpha power in the *BDNF Met*/*Met* group. Being a *Met*-allele carrier was found to be associated with a reduction in cortical connectivity from hippocampal and parahippocampal regions within the default-mode network (Thomason et al., 2009). The extensive default-mode network is considered to show spontaneous and virtually continuous baseline brain activation, which is most pronounced in a resting state condition such as eyes closed (Raichle and Gusnard, 2005). It is plausible that effects of *BDNF Val66Met* on EEG alpha power were specifically detected during eyes closed resting state because of a main effect of *BDNF Val66Met* on functional connectivity within the default-mode network. Furthermore, the wide distribution of default-mode network across the brain would provide an explanation for the global effects of *BDNF Val66Met* on EEG alpha power.

In summary, the results of this study are largely in agreement with the findings of Gatt et al. (2008). The *BDNF Met*/*Met* genotype was associated with decreased alpha power, which was in turn associated with higher depression severity. There were strong indications that eyes open alpha power acted as a mediator between *BDNF Val66Met* and depression severity. Interestingly, higher depression severity predicted a longer time to remission after SSRI treatment (Frank et al., 2011). Moreover, *BDNF Val66Met* (Zou et al., 2010), lower serum BDNF levels (Wolkowitz et al., 2011), and decreased alpha power (Bruder et al., 2008) all have been associated with lower response to SSRI treatment. This suggests that a biological pathway including *BDNF Val66Met*, EEG alpha power and the depressive symptoms that determine depression severity might play a role in explaining treatment response to antidepressant treatment. Future studies should further investigate this tentative pathway in a larger MDD population and should consider the implication of this pathway in predicting treatment outcome.

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