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Association between BDNF Val66Met polymorphism and trait depression is mediated via resting EEG alpha band activity

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ABSTRACT

A functional polymorphism of the brain-derived neurotrophic factor, BDNF Val66Met, is associated with risk for major depression alongside impairments in memory and selective attention. This study aims to identify the mediating neural mechanisms in links between BDNF and depression using highly heritable electroencephalographic (EEG) recordings. In 305 healthy subjects, BDNF Val66Met genotypes were compared in terms of trait depression, neural function (EEG during a resting state) and cognitive performance. The mediating effects of the EEG brain imaging endophenotypes were also examined using structural equation (path) modeling. A genotype–endophenotype–phenotype path model showed that Met homozygosity predicted elevated working memory commission errors and altered EEG activity; that is elevated relative theta and delta power coupled with reduced alpha power. In turn, reduced EEG alpha activity mediated the relationship between the Met/Met genotype and trait depression. These findings demonstrate the utility of an integrative endophenotype approach. They suggest that the BDNF Met/Met homozygote has a direct impact on memory systems, but impacts trait depression via the secondary effects of neural changes.

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a neurotrophin involved in the regulation of activity-dependent neural function (Pezawas et al., 2004), growth and survival (Black, 1999; Conner et al., 1997), facilitating learning and memory (Egan et al., 2003) and long-term alterations of the brain reward systems (Nestler et al., 2001, 2002). The BDNF Val66Met polymorphism impacts these processes by altering the regulated secretion of the mature peptide; the methionine (Met) variant being associated with inefficient secretion compared to the valine variant (Egan et al., 2003). More recently it has been suggested that BDNF-mediated mechanisms of cellular plasticity and resilience may underlie risk for depression (Duman et al., 1999; Manji and Duman, 2001). Indeed, the BDNF Met/Met (M/M) genotype has been associated with major depression (Hwang et al., 2006; Jiang et al., 2005), and with impairments in both emotional and general cognition which are characteristic of the depression phenotype (Hasler et al., 2004; Mayberg, 1997; Williams, 2006). Nonetheless, the mediating neural mechanisms of BDNF and depression remain to be understood.

There is increasing evidence that BDNF Met carriers demonstrate phenotypic characteristics of depression, including impairments in verbal memory (Dempster et al., 2005; Egan et al., 2003), working memory and related aspects of executive function (Gatt et al., 2007; Rybakowski et al., 2003) and visual declarative memory (Hariri et al., 2003). Moreover, M/M subjects show disturbances in hippocampal engagement during signal detection and declarative memory tasks (Hariri et al., 2003), as well as a loss of gray matter volume in the hippocampus and prefrontal areas to

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which they project (Pezawas et al., 2004). Similar deficits of Met carriers in memory and fronto-hippocampal dysfunction are seen in neurodegenerative disorders such as Alzheimer's disease (Kunugi et al., 2001) and Parkinson's disease (Momose et al., 2002). Indeed, recent evidence suggests that depression during adulthood is a significant risk factor for the development of Alzheimer's disease, even after controlling for co-morbid vascular risk factors (Dal Forno et al., 2005). Nevertheless, there is contrary evidence with some reporting associations between the BDNF *Val* allele and elevated neuroticism (Sen et al., 2003), and others reporting null effects (Lang et al., 2005; Willis-Owen et al., 2005). Moreover, some clinical studies report no associations between BDNF genotype and major depression (Tsai et al., 2003; Hong et al., 2003; Oswald et al., 2005), whereas others report associations with bipolar disorder or schizophrenia (Neves-Pereira et al., 2002, 2005). However, the robustness of the latter findings has been questioned, for instance with associations between BDNF and schizophrenia shown to be mainly attributable to the presence of comorbid depressive symptoms (Schumacher et al., 2005). In addition, discrepancies could arise due to sample variations in ethnicity (Tsai et al., 2003; Hong et al., 2003) or power (Oswald et al., 2005). Alternatively, it is possible that the link between genotypic variation and depression is indirect given that phenotypic measures are often crude measures reflecting the output from both genotypic and environmental influences (Gottesman and Gould, 2003).

A more direct and powerful approach entails mapping genotypes onto brain function endophenotypes that may mediate the genotype–phenotype relationship. Endophenotypes are internal phenotypes not obvious to the unaided eye, but observable by a biochemical or microscopic test (Gottesman and Gould, 2003). A good endophenotype should be (1) associated with the illness; (2) heritable; (3) be state-independent and stable over time; (4) co-segregate with illness within families; and (5) demonstrate a familial association by being evident in unaffected relatives at a higher rate than in the general population (Gould and Gottesman, 2006). Given these criteria and hence more defined genetic architecture, the use of these markers is considered to enhance power in gene finding approaches (Gottesman and Gould, 2003; Gould and Gottesman, 2006; Van Beijsterveldt and van Baal, 2002). The electroencephalogram (EEG) provides a good endophenotype because it is one of the most heritable complex traits in humans (Smit et al., 2005), and is stable over time (test–retest reliability of 0.83 for EEG power, Smit et al., 2005; higher with age controlled; Williams et al., 2005). Further, irregular EEG patterns have been identified in depressed patients, including reductions in fast EEG activity (Guidi et al., 1989) coupled with elevations in slow-wave EEG (Guidi et al., 1989; Kwon et al., 1996). In addition, EEG (such as alpha asymmetry) has been shown to vary as a function of familial loading of major depression (Bruder et al., 2005).

The EEG power spectrum is regulated by cortico-thalamic networks and feedback within these networks, with homeostatic regulation from inhibitory and excitatory neural action (Hughes and John, 1999; Rowe et al., 2004). Alpha activity is associated with excitatory cortico-thalamic efferents that synapse with relay nuclei to modulate sensory input to the cortex. This pathway has a time course of around 0.1 s (or 10 Hz) corresponding to the frequency of alpha (Rennie et al., 2002; Rowe et al., 2004). There is also a feedback pathway involving cortico-thalamic signals that pass through the inhibitory reticular nucleus of the thalamus before returning to the cortex. This pathway has a slower time scale associated with the theta frequency and results in an inversion of the positive signal associated with alpha (Rennie et al., 2002; Rowe et al., 2004). As BDNF has been shown to regulate both excitatory and inhibitory synaptic transmission, but with an overall net *increase* in neural activity (Bolton et al., 2000), it is possible that the lower activity-dependent BDNF secretion in M/M individuals leads to an imbalance in cortical excitation vs inhibition, and subsequent alterations in EEG power.

This study aims to examine whether the BDNF Met allele contributes to the phenotypic characteristics of depression (both memory problems and trait depression scores), and whether differences in electrical brain function (EEG), the brain function endophenotype, mediates these effects on behavior. These relationships were examined using structural equation (path) modeling; a form of statistical analysis that allows causal relationships to be tested while accounting for all other variables in the model, and has proved useful in elucidating neural networks in major depression (Seminowicz et al., 2004). We employed a healthy sample assessed for subclinical traits of depression, consistent with a dimensional approach which spans normal sadness to dysthymia to major depressive disorder (MDD; Hankin et al., 2005; Ruscio and Ruscio, 2000; Slade and Andrews, 2005). A monotonic increase in episodes, impairment, comorbidity and parental history of psychiatric disorders has been observed across the spectrum of subclinical depression to severe MDD (Kessler et al., 1997; Maier et al., 1997). Subclinical depression is also a significant risk factor for MDD in up to 33% of cases (Angst and Merikangas, 1997). Thus, links between BDNF status and subclinical depression in the current study will have implications for clinical depression. By studying trait depression in a subclinical sample, the possible confounds of overt illness such as medication and chronicity are controlled for.

2. Methods

2.1. Participants

305 healthy Caucasian participants of 100% European ancestry (mean age ± S.D.: 36.92 ± 12.57 years) participated in the Brain Resource International Database (BRID; http://www.brainresource.com). While these participants have volunteered from US, European and Australian sites, no differences between sites in neuropsychological and EEG measures are evident (Paul et al., 2007). Exclusion criteria included the presence of any psychiatric disorder, neurological disorder, other serious medical conditions, and/or a personal history of drug or alcohol dependence, using the SPHERE (based on DSM-IV criteria, and which encompasses depression and anxiety disorders; Hickie et al., 1998), General Health Questionnaire and AUDIT (World Health Organization: http://whqlibdoc.who.int/hq/2001/WHO_MSD_MSB_01.6a.pdf).

Informed written consent was provided in accordance with human research ethical requirements.

2.2. BDNF genotypes

DNA was extracted from cheek swab samples by a standard proteinase digestion and chloroform extraction procedure. PCR amplification of participant DNA was undertaken using primers 5′-TGTATTCCTCCAGCAGAAAGAGAA-3′ and 5′-AAA-GAAGCAAACATCCGAGGAC-3′ using standard conditions. The amplified fragment was digested with the restriction enzyme *Afl*III, which cleaves the Val allele and includes a positive digestion control in the PCR amplicon. PCR products were separated on 4% agarose gels. The genotype frequencies of the 305 Caucasian normals were 57.7% V/V ($n = 176$), 38% V/M ($n = 116$) and 4.3% M/M ($n = 13$). Allele frequencies were in Hardy-Weinberg equilibrium ($\chi^2 = 1.279$, $p > 0.20$). These genotype frequencies conform to expected population rates for the BDNF Val66Met genotype and are similar to previously reported distributions (Combarros et al., 2004; Jiang et al., 2005; Lang et al., 2005). No genotype differences were evident for the demographic variables age, sex, education or IQ (Table 1), or in terms of apolipoprotein E (APOE) ε4/4 ($\chi^2 = 3.08$, $p = .545$) or catechol-O-methyltransferase (COMT) Val108/158Met distribution ($\chi^2 = 5.62$, $p = .229$), genes associated with cognitive-related deficits (Alexander et al., 2007; Corder et al., 1993; Egan et al., 2001). BDNF genotype groups also did not differ in terms of caffeine consumption (beverages/day; $\chi^2 = 14.98$, $p = .133$) or nicotine intake (cigarettes smoked/day; $\chi^2 = 2.46$, $p = .873$), stimulants which may have an acute effect on the EEG.

2.3. Measures

Verbal memory and working memory were assessed using the tests of Verbal List Learning and Recall, and the 1-Back Working Memory test (see Supplementary Material for further details), derived from the computerized neuropsychological

Table 1
Means and statistical effects for BDNF genotypes on demographic and cognitive-emotion measures ($N = 305$)

Measure	Genotype group (mean ± S.E.)			Test of difference		
	V/V	V/M	M/M	Statistic	*p* Value	Cohen's *d*
Demographics						
Age	36.81 ± 0.95	37.01 ± 1.17	37.46 ± 3.60	$F = 0.02$	.979	–
Sex (M/F)	92/84	63/53	5/8	$\chi^2 = 1.18$	.553	–
Education (yrs)	13.30 ± 0.31	13.75 ± 0.36	14.77 ± 0.85	$F = 1.10$	.333	–
Estimated IQ[a]	106.62 ± 0.76	107.50 ± 0.80	108.23 ± 1.89	$F = 0.43$	.648	–
Cognition						
Working memory (commission errors)	0.69 ± 0.08	0.50 ± 0.09	1.39 ± 0.27	$F = 5.23$	.006** [b]	MM vs VV = .50 MM vs VM = .71
Mood						
Trait depression	3.89 ± 0.40	3.76 ± 0.49	5.12 ± 1.49	$F = 0.38$	.687[c]	MM vs VV = .22 MM vs VM = .26

Note. $^{**}p < .01$; $^{*}p < .05$ for univariate ANOVA. df for F tests = 2, 302.
[a] Estimated IQ was derived from Spot the Word total score (Paul et al., 2005).
[b] Contrasts were significant for M/M > V/V ($p = .013$) and M/M > V/M ($p = .002$).
[c] Contrasts were non-significant for M/M vs V/V ($p = .425$) and M/M vs V/M ($p = .386$).

test battery, 'IntegNeuro'. This test battery assesses core cognitive domains equivalent to those assessed by standard neuropsychological tests, and which form the basis of other available computerized batteries (Paul et al., 2005; Silverstein et al., 2007). IntegNeuro tests show sound test–retest reliability (Williams et al., 2005), cross-site consistency (Paul et al., 2007) and may be interpreted relative to robust age, sex and education norms (Clark et al., 2006) drawn from the Brain Resource International Database (Gordon et al., 2005).

Emotional function was assessed in terms of mood (experienced emotion). Trait depression was assessed using the DASS-21, a shortened version of the Depression Anxiety Stress Scale (DASS; Lovibond and Lovibond, 1995). This scale is a psychometrically sound measure of trait depression in non-clinical and clinical populations, has been validated against the commonly used Beck Depression Inventory (Beck et al., 1961), and has established norms that include Australian, US and UK populations (Antony et al., 1998; Crawford and Henry, 2003; Lovibond and Lovibond, 1995). Total scores were doubled for comparison with DASS-42 profiling. This scale assesses the severity of core symptoms of depression, with scores of 0–9, 10–13, 14–20, 21–27 and 28+ considered normal, mild, moderate, severe and extremely severe, respectively.

EEG data were recorded during two resting conditions: eyes open for 2 min, followed by eyes closed for 2 min (during which participants were seated in a comfortable, reclining chair in a dimly lit room). Average power spectra were computed for each condition, with each 2-min time block first divided into adjacent intervals of 4 s. Power spectral analysis was performed on each 4 s interval by first applying a Welch window to the data and then performing a Fast Fourier Transform (FFT). The resulting power spectra were then averaged for each electrode position in each of the two paradigms over four frequency bands: delta (1.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–13 Hz), and beta (14.5–30 Hz). These data were then log transformed to approximate the normal distributional assumptions required by parametric statistical methods. Absolute power (raw power of each frequency) and relative power (each relative to the total power of all frequencies) of each frequency band was examined here for both conditions (see Supplementary Material for further details).

2.4. Analyses

2.4.1. Group comparisons

BDNF genotype differences on the trait depression and memory measures were examined using univariate ANOVA, with age and sex included as covariates. Planned contrasts comparing M/M vs V/V, and M/M vs V/M were employed focusing on the effects of the BDNF M/M genotype (the additional comparison of V/M to V/V genotype groups was not examined in order to avoid Type I errors associated with the use of non-orthogonal comparisons). Cohen's *d* was calculated to examine the strength of pair-wise effects, with values of 0.20, 0.50, and 0.80 or above considered small, medium and large effects respectively (Cohen, 1988).

Repeated-measures ANOVA were undertaken for each of the four EEG bands: alpha, beta, theta and delta. The primary dependent measure of interest was relative power, given that this measure quantifies EEG power in each band relative to power in other bands. We also undertook parallel repeated measures with a secondary dependent measure, absolute power in each EEG band. BDNF genotype was the between-subjects factor, and brain region the within-subjects factor with four repeated measures (frontal, central, temporal and parietal-occipital regions), and age and sex included as covariates. For significant effects, planned contrasts comparing M/M to V/V, and M/M to V/M genotype groups were conducted. The electrode sites making up each region were as follows: frontal (Fp1, Fp2, F7, F3, Fz, F4, F8), central (FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4), temporal (T3, T4, T5, T6), and parietal-occipital regions (P3, Pz, P4, O1, Oz, O2). This regional division is consistent with previously published EEG depression research (Fingelkurts et al., 2006) and the relationship of EEG recording sites to lobe-based neuroanatomy (Gevins et al., 1999). We have recently demonstrated the corresponding trajectory of lobe-based EEG regions with neuroanatomical changes (assessed with MRI) over age (Whitford et al., 2007).

To confirm the localization of the EEG effects, contrast analyses comparing M/M to V/M and V/V genotypes were examined in the individual brain sites for significant brain regions identified in prior repeated-measures ANOVA.

ANOVAs were also undertaken to examine possible EEG laterality effects in the BDNF genotype groups, given theoretical models that argue negative mood is associated with left hypo-activity, and evidence that depression is characterized by frontal alpha asymmetry in particular (Davidson, 1998). An initial set of ANOVAs for each EEG band included an additional within-subjects factor of laterality (left vs right sides of each region, excluding midline sites): left frontal (Fp1, F7, F3), right frontal (Fp2, F4, F8), left central (FC3, C3, CP3), right central (FC4, C4, CP4), left temporal (T3, T5), right temporal (T4, T6), left parietal-occipital (P3, O1) and right parietal-occipital (P4, O2). Second, we compared genotype groups on frontal alpha asymmetry (for electrode pairs F3–F4 and F7–F8).

2.4.2. Equal-sized subgroup comparisons

To ensure that genotype differences in behavioral measures and EEG data were not due to spurious effects of unequal group sizes, a parallel set of analyses was performed in a subsample ($N = 39$) for which the genotype groups were matched on sample size ($n = 13$ each genotype group), mean age (V/V = 37.8 ± 13.28, V/M = 38.0 ± 12.52, M/M = 37.5 ± 13.00) and gender composition (8 females, 5 males per group).

2.4.3. Path model

To examine the direct and indirect effects of BDNF genotype on cognitive-emotion phenotypes via the brain function endophenotypes, structural equation modeling with maximum likelihood estimation (AMOS 5; Arbuckle and Wothke, 1999) was used to assess the fit of a genotype–endophenotype–phenotype path model. The variables included in the model were BDNF genotype (V/V vs M/M[1]), relative EEG power (eyes open), trait depression, and behavioral measures of verbal recall and working memory performance. Age and sex were also included to control for any variation in these factors. To establish mediation, we adopted the 'joint significance approach' (Fritz and MacKinnon, 2007; MacKinnon et al., 2002); a powerful causal-step approach with the highest reported accuracy for Type I error relative to other causal-step methods (MacKinnon et al., 2002). For mediation to be present, it has been specified that two conditions need to be satisfied: (1) there is a significant relationship between the independent variable and the mediating variable; and (2) there is a significant relationship between the mediating variable and the dependent variable, while controlling for the independent variable. Overall model fit was evaluated by observing the following goodness-of-fit (GOF) indices: the chi-square statistic (χ^2, 'good fit' = $p > 0.05$); the root mean square error of approximation (RMSEA, 'good fit' = RMSEA < 0.05, $p > 0.50$); and the comparative fit index (CFI, 'good fit' = CFI > 0.95; Byrne, 2001). Both standardized (β 'beta') and unstandardized (*b*) path coefficients were observed (see Supplementary Material for further details).

[1] While genotype cell sizes were unbalanced, path modeling analysis is a form of regression analysis, which treats each variable as a continuous variable, rather than a categorical variable.

3. Results

3.1. Cognitive-emotion measures

3.1.1. Memory

Univariate analyses suggested a significant difference for working memory commission errors, with M/M individuals demonstrating more commission errors compared to V/M and V/V individuals (see Table 1). No significant BDNF genotype differences for measures of verbal learning and memory recall were evident.

3.1.2. Trait depression

The full sample demonstrated a mean depressed mood of 3.87 (S.D. = 4.84; range = 0–20, or 'normal' to 'moderate' ranges). 85% (n = 223) of the sample scored within 'normal' severity ranges (0–9), 7% (n = 19) scored within 'mild' ranges (10–13), and 8% (n = 20) within 'moderate' ranges (14–20). No significant genotype differences were found for depressed mood (Table 1).

3.2. Resting brain function (EEG) – brain regions

3.2.1. 'Eyes open condition

For relative alpha power, repeated-measures ANOVA revealed significant main effects for BDNF genotype, with planned contrasts suggesting *reduced* relative alpha power in M/M individuals compared to V/M individuals for the parietal-occipital and central regions (Fig. 1 and Table 2). However, mean values show the consistent trend towards reduced relative alpha power in M/M vs V/M and V/V across all regions (Table 2). No significant 'BDNF × Region' interaction effects were evident.

For relative beta power, significant main effects of BDNF genotype for the frontal region were evident with M/M individuals demonstrating *reduced* relative beta power compared to V/M individuals (see Fig. 1 and Table 2). No significant 'BDNF × Region' interaction effects were evident.

For relative theta power, significant main effects of BDNF genotype were evident, with M/M individuals demonstrating *elevated* relative theta power compared to V/V individuals for temporal and parietal-occipital regions; and compared to V/M individuals for frontal, central, temporal, and parietal-occipital regions (Fig. 1 and Table 2). A significant interaction effect of 'BDNF × Region' was also evident for the temporal region ($F(6,864) = 2.24$, $p = .038$), with M/M individuals demonstrating elevated relative theta power compared to V/V individuals at sites T4 ($p = .001$) and T5 ($p = .020$); and compared to V/M individuals at sites T4 ($p < .000$), T5 ($p = .002$), and T6 ($p = .010$) (Fig. 1, Table 2).

For relative delta power, significant main effects for BDNF genotype were evident with planned contrasts demonstrating *elevated* relative delta power in M/M individuals compared to V/V individuals for frontal, temporal, and parietal-occipital regions; and compared to V/M individuals for frontal, central, temporal, and parietal-occipital regions (Fig. 1, Table 2). No significant 'BDNF × Region' interaction effects were evident.

Analyses of absolute EEG power confirmed that the distinctive effects of BDNF genotype on EEG were specific to each band relative to other bands, rather than representing an absolute increase or decrease in power. The only significant main effect was

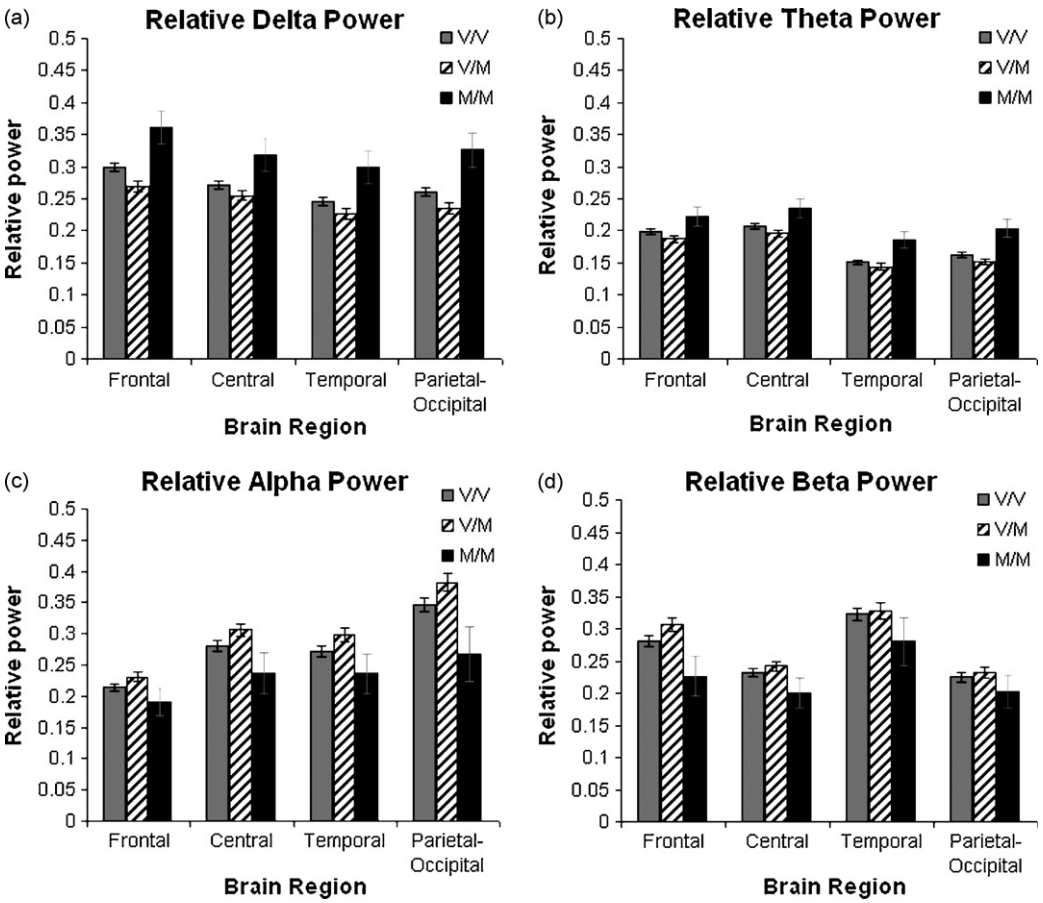

Fig. 1. Relative EEG power brain regions: mean differences (with S.E. bars) for the BDNF genotype groups in the frontal, central, temporal, and parietal-occipital regions for (a) relative delta power, (b) relative theta power, (c) relative alpha power and (d) relative beta power while resting (eyes open).

Table 2
Means, repeated measures and planned contrast effects for BDNF Val66Met genotypes in terms of relative and absolute EEG power for frontal, central, temporal and parietal-occipital brain regions for the 'eyes open' condition ($N = 305$)

Brain region	Genotype group (mean ± S.E.)			F statistic[c]	p Value	Cohen's d	
	V/V	V/M	M/M			M/M vs V/V	M/M vs V/M
RELATIVE POWER (eyes open)							
Alpha power							
Frontal	.214 ± .006	.231 ± .008	.191 ± .023	2.31	.102	.295	.462
Central	.281 ± .008	**.306 ± .011**	**.237 ± .032**[b]	3.00	*.052*	.375	.568
Temporal	.272 ± .009	.298 ± .011	.236 ± .033	2.77	*.065*	.333	.543
Parietal-occipital	.346 ± .012	**.382 ± .014**	**.268 ± .043**[b]	4.08	.018*	.571	.791
Beta power							
Frontal	.281 ± .008	**.306 ± .010**	**.226 ± .030**[b]	4.09	.018*	.396	.567
Central	.232 ± .006	.242 ± .008	.200 ± .023	1.62	.200	.312	.401
Temporal	.322 ± .010	.328 ± .012	.280 ± .037	0.76	.471	.263	.291
Parietal-occipital	.225 ± .007	.232 ± .008	.202 ± .026	0.68	.508	.226	.288
Theta power							
Frontal	.198 ± .004	**.187 ± .005**	**.222 ± .014**[b]	3.48	.032*	.386	.544
Central	.208 ± .004	**.196 ± .005**	**.235 ± .015**[b]	3.68	.026*	.479	.691
Temporal	**.151 ± .003**	**.144 ± .004**	**.186 ± .013**[a,b]	4.68	.010*	.655	.778
Parietal-occipital	**.163 ± .004**	**.151 ± .005**	**.204 ± .014**[a,b]	7.18	.001**	.904	1.12
Delta power							
Frontal	**.299 ± .007**	**.270 ± .008**	**.361 ± .025**[a,b]	7.71	.001**	.520	.784
Central	.271 ± .007	**.255 ± .008**	**.318 ± .026**[b]	3.12	.046*	.442	.612
Temporal	**.245 ± .007**	**.226 ± .009**	**.299 ± .026**[a,b]	4.13	.017*	.466	.655
Parietal-occipital	**.261 ± .007**	**.235 ± .009**	**.326 ± .027**[a,b]	6.34	.002**	.633	.929
ABSOLUTE POWER (eyes open)							
Alpha power							
Frontal	3.45 ± .045	3.55 ± .055	3.29 ± .168	1.55	.214	.224	.353
Central	3.90 ± .054	3.95 ± .067	3.57 ± .203	1.61	.202	.360	.417
Temporal	3.37 ± .052	3.44 ± .065	3.12 ± .196	1.37	.255	.265	.343
Parietal-occipital	3.90 ± .065	4.02 ± .080	3.48 ± .245[d]	2.52	.082	.435	.560
Beta power							
Frontal	3.69 ± .038	**3.79 ± .047**	**3.45 ± .142**[b]	3.20	.042*	.355	.510
Central	3.72 ± .037	3.70 ± .047	3.46 ± .141	1.64	.196	.418	.399
Temporal	3.54 ± .046	3.52 ± .057	3.27 ± .173	1.16	.316	.300	.282
Parietal-occipital	3.47 ± .037	3.50 ± .046	3.22 ± .141	1.81	.165	.373	.450
Theta power							
Frontal	3.39 ± .033	3.34 ± .040	3.50 ± .123	0.97	.379	.206	.322
Central	3.63 ± .035	3.53 ± .044	3.66 ± .132	1.67	.190	.068	.264
Temporal	2.81 ± .038	2.74 ± .047	2.94 ± .144	1.37	.255	.187	.328
Parietal-occipital	3.18 ± .039	3.12 ± .048	3.28 ± .147	0.74	.479	.150	.275
Delta power							
Frontal	3.79 ± .035	3.69 ± .043	3.97 ± .131[d]	2.71	.069	.295	.457
Central	3.86 ± .031	3.78 ± .039	3.96 ± .117	1.89	.153	.172	.339
Temporal	3.26 ± .042	3.15 ± .052	3.38 ± .157	1.89	.152	.160	.325
Parietal-occipital	3.61 ± .035	3.54 ± .044	3.72 ± .133	1.41	.246	.171	.331

Note. Means (and S.E.) are corrected for age and gender covariates. $^{**}p < .01$; $^{*}p < .05$; italics indicate non-significant trend effects ($.05 < p < .065$) for repeated-measures ANOVA. Bolding indicates significant planned contrast effects ($p < .05$).

[a] M/M vs V/V ($p < .05$).

[b] M/M vs V/M ($p < .05$).

[c] df = 2, 289.

[d] As overall ANOVA was not significant ($p < .05$), this significant contrast effect was considered marginal, and so has not been emphasized (bolded) here.

for absolute beta power for the frontal region. Planned contrasts indicated that M/M individuals had reduced beta power compared to V/M individuals (M/M: $M = 3.45$, S.E. = .142; V/M: $M = 3.79$, S.E. = .047; V/V: $M = 3.69$, S.E. = .038; Table 2).

3.2.2. 'Eyes closed' condition

For relative alpha power, repeated-measures ANOVA yielded significant main effects for BDNF genotype with M/M individuals demonstrating reduced relative alpha power compared to V/V individuals for the parietal-occipital region; and compared to V/M individuals for frontal, central, temporal and parietal-occipital regions (Table 3), consistent with findings for the eyes open condition. No significant 'BDNF × Region' interaction effects were evident.

For relative beta power, repeated-measures ANOVA revealed no significant main or interaction effects for any brain region (Table 3).

For relative theta power, significant main effects for BDNF genotype were evident with M/M individuals demonstrating elevated theta power compared to V/V individuals for central and parietal-occipital regions; and compared to V/M individuals for frontal, central and parietal-occipital regions (Table 3), consistent with the eyes open condition. No significant interaction effects of 'BDNF × Region' were evident.

For relative delta power, repeated-measures ANOVA again revealed significant main effects for BDNF genotype for frontal, central and parietal-occipital regions, consistent with the eyes open condition. M/M individuals demonstrated elevated relative

Table 3
Means, repeated measures and planned contrast effects for BDNF Val66Met genotype groups in terms of relative and absolute EEG power for frontal, central, temporal and parietal-occipital brain regions for the 'eyes closed' condition ($N = 305$)

Brain region	Genotype group (mean ± S.E.)			F statistic[c]	p Value	Cohen's d	
	V/V	V/M	M/M			M/M vs V/V	M/M vs V/M
RELATIVE POWER (eyes closed)							
Alpha power							
Frontal	.378 ± .012	**.421 ± .015**	**.320 ± .044**[b]	4.00	.019*	.375	.611
Central	.429 ± .011	**.464 ± .015**	**.359 ± .043**[b]	3.47	.032*	.444	.650
Temporal	.442 ± .011	**.472 ± .014**	**.370 ± .041**[b]	3.40	.035*	.450	.608
Parietal-occipital	**.549 ± .013**	**.571 ± .017**	**.424 ± .049**[a,b]	4.10	.018*	.667	.769
Beta power							
Frontal	.202 ± .006	.202 ± .008	.203 ± .024	0.00	1.000	.021	.025
Central	.190 ± .006	.191 ± .008	.196 ± .023	0.04	.964	.093	.086
Temporal	.223 ± .007	.214 ± .010	.223 ± .028	0.25	.779	.014	.095
Parietal-occipital	.161 ± .006	.166 ± .008	.185 ± .023	0.62	.536	.334	.234
Theta power							
Frontal	.188 ± .005	**.173 ± .007**	**.220 ± .019**[b]	3.44	.034*	.362	.526
Central	**.184 ± .005**	**.172 ± .006**	**.224 ± .019**[a,b]	3.78	.024*	.483	.612
Temporal	.146 ± .004	.138 ± .005	.171 ± .016	2.14	.120	.373	.474
Parietal-occipital	**.129 ± .004**	**.123 ± .006**	**.175 ± .017**[a,b]	4.44	.013*	.617	.695
Delta power							
Frontal	.222 ± .006	**.191 ± .008**	**.258 ± .023**[b]	6.66	.001**	.349	.706
Central	.194 ± .006	**.170 ± .008**	**.221 ± .024**[b]	3.73	.025*	.273	.573
Temporal	.186 ± .006	.164 ± .008	.204 ± .024	3.00	*.051*	.172	.406
Parietal-occipital	**.153 ± .006**	**.136 ± .008**	**.215 ± .025**[a,b]	4.81	.009**	.594	.781
ABSOLUTE POWER (eyes closed)							
Alpha power							
Frontal	4.31 ± .060	4.52 ± .076	4.19 ± .237	2.66	.072	.122	.374
Central	4.79 ± .061	4.93 ± .078	4.67 ± .254	1.12	.327	.090	.244
Temporal	4.30 ± .061	4.44 ± .077	4.20 ± .253	1.16	.315	.061	.203
Parietal-occipital	5.11 ± .074	5.27 ± .093	4.82 ± .305	1.58	.207	.245	.398
Beta power							
Frontal	3.65 ± .034	3.76 ± .043	3.58 ± .126	2.64	.073	.093	.327
Central	3.93 ± .037	4.00 ± .046	3.75 ± .138	1.89	.153	.301	.430
Temporal	3.53 ± .040	3.59 ± .049	3.47 ± .154	0.68	.509	.039	.136
Parietal-occipital	3.79 ± .040	3.94 ± .049	3.75 ± .154	3.07	.048*	.020	.284
Theta power							
Frontal	3.61 ± .040	3.62 ± .051	3.68 ± .153	0.09	.916	.101	.097
Central	3.93 ± .045	3.89 ± .056	3.91 ± .169	0.12	.888	.017	.040
Temporal	3.17 ± .047	3.18 ± .059	3.20 ± .178	0.03	.966	.054	.046
Parietal-occipital	3.59 ± .052	3.63 ± .065	3.57 ± .197	0.12	.890	.014	.050
Delta power							
Frontal	3.76 ± .034	3.72 ± .042	3.88 ± .127	0.83	.438	.182	.256
Central	3.93 ± .034	3.86 ± .042	3.91 ± .126	0.77	.465	.023	.095
Temporal	3.35 ± .042	3.31 ± .052	3.36 ± .157	0.23	.796	.014	.077
Parietal-occipital	3.70 ± .041	3.68 ± .050	3.68 ± .158	0.04	.959	.051	.010

Note. Means (and S.E.) are corrected for age and gender covariates. $^{**}p < .01$; $^{*}p < .05$; italics indicate non-significant trend effects ($.05 < p < .065$) for repeated-measures ANOVA. Bolding indicates significant planned contrast effects ($p < .05$).

[a] M/M vs V/V ($p < .05$).

[b] M/M vs V/M ($p < .05$).

[c] df = 2, 289.

delta power compared to V/V individuals for the frontal region; and compared to V/M individuals for frontal, central and parietal-occipital regions (Table 3). A significant 'BDNF × Region' interaction effect was also evident for the parietal-occipital region ($F(10,1370) = 2.65$, $p = .003$) with M/M individuals demonstrating elevated relative delta power compared to V/V individuals at occipital sites Oz ($p = .018$) and O2 ($p = .001$); and compared to V/M individuals at sites O1 ($p = .018$), Oz ($p = .002$), and O2 ($p < .0001$).

For the absolute EEG measures, repeated-measures ANOVA revealed no significant main effects for any frequency band (Table 3), but an interaction effect between genotype and the parietal-occipital region for absolute beta power ($F(10,1400) = 3.00$, $p = .001$).

3.3. Resting brain function (EEG) – individual brain sites

To confirm the precise localization of the above regional effects, planned contrasts for specific brain sites were performed. For the eyes open condition, the EEG findings of reduced fast-wave and elevated slow-wave relative power in M/M individuals compared to V/M and V/V individuals were confirmed in bilateral brain sites (Table S1). However, no significant effects for frontal absolute beta power were found for the eyes open condition. Fig. 2 provides a topographical brain representation of genotype differences for the individual brain sites for relative EEG. Similarly, for the eyes closed condition, all EEG findings were confirmed for bilateral brain sites for both relative and absolute power (Tables S2).

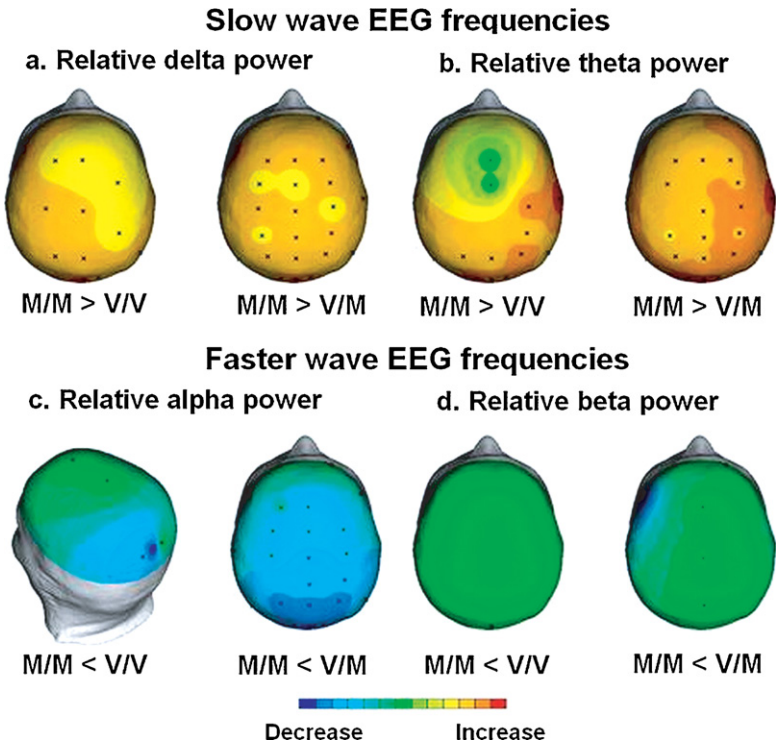

Fig. 2. Relative EEG power brain sites: topographical maps for BDNF genotype differences found in individual brain sites for (a) relative delta power, (b) relative theta power, (c) relative alpha power and (d) relative beta power while resting (eyes open). The headmaps illustrate magnitude of differences within each contrast. 'Warmer' (red) colors indicate an increase in activity, 'cooler' (blue) colors indicate a reduction in activity, and regions colored green indicate no significant difference. Means and contrast estimates are presented in Supplementary Table 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

3.4. EEG laterality effects

ANOVAs including the within-subjects factor, laterality, revealed no significant interactions between BDNF genotype and laterality, consistent with the results from planned contrasts above, which showed that EEG differences in M/M homozygotes were generally widespread and bilateral.

Similarly, BDNF genotype groups did not differ on frontal alpha asymmetry for either electrode pair.

3.5. Equal-sized subgroup comparisons

Parallel contrast analyses were performed on the equal-sized genotype subgroups ($N = 39$), age and sex-matched to the total genotype groups. Genotypes again differed on working memory commission errors ($F = 6.01$, $p = .006$), with M/M genotypes demonstrating elevated errors ($M = 1.39$, S.E. = 0.28) compared to V/M ($M = 0.23$, S.E. = 0.28, $p = .006$, Cohen's $d = .978$) and V/V genotypes ($M = 0.15$, S.E. = 0.28, $p = .004$, Cohen's $d = 1.053$). Similar EEG findings were found for the eyes open condition, with M/M genotypes demonstrating elevated slow-wave activity and reduced fast-wave activity compared to V/M and V/V genotypes (Table S3). The size of these effects was medium to large, consistent with the size of effects found in the full sample (Table 2). For the eyes closed condition, however, significant effects found for relative EEG in the full sample were not evident in the subsample (Table S4). This may be due to limited power as effect sizes were generally small in the subsample for the eyes closed condition.

3.6. Genotype–endophenotype–phenotype path model

The predictive relationships between BDNF genotype, trait depression and memory phenotypes in regard to EEG endophenotypes were examined using structural equation modeling with maximum likelihood estimation (AMOS 5; Arbuckle and Wothke, 1999). The initial matrix of correlations between the variables to be estimated in the path model is provided in Table S5. Results from path modeling suggested that the model had very good overall fit ($\chi^2 = 3.108$, $p = .375$; RMSEA = .009, $p = .722$; CFI = 1.000), indicating model respecifications were not required. The significant standardized and unstandardized estimates of this model are depicted in Fig. 3.[2]

BDNF Met homozygotes predicted lower relative alpha power (unstandardized $b = -.064$), but higher relative theta power ($b = .035$), delta power ($b = .062$) and working memory commission errors ($b = .579$). In addition, BDNF Met homozygotes predicted higher trait depressed mood via the mediating effects of alpha power (indirect $b = .415$). Age and sex also demonstrated several direct effects in the path model. Older age predicted a lower average theta ($b = -.001$) and delta power ($b = -.001$), lower depressed mood ($b = -.057$), and poorer performance on the verbal memory recall test ($b = -.064$), with fewer errors on the working memory test ($b = -.012$). Sex demonstrated a positive direct effect on average delta power ($b = .020$) and a negative direct effect on verbal memory recall ($b = -.860$); such that being male was predictive of higher delta power and poorer verbal memory recall.

The additional path model examining frontal alpha asymmetry confirmed a lack of BDNF genotype differences in asymmetry, and showed that alpha asymmetry did not mediate relationships between BDNF Met and trait depression.

[2] Note that the absence of paths between variables presented here does not necessarily imply a correlation of 'zero', but that a non-significant association was evident.

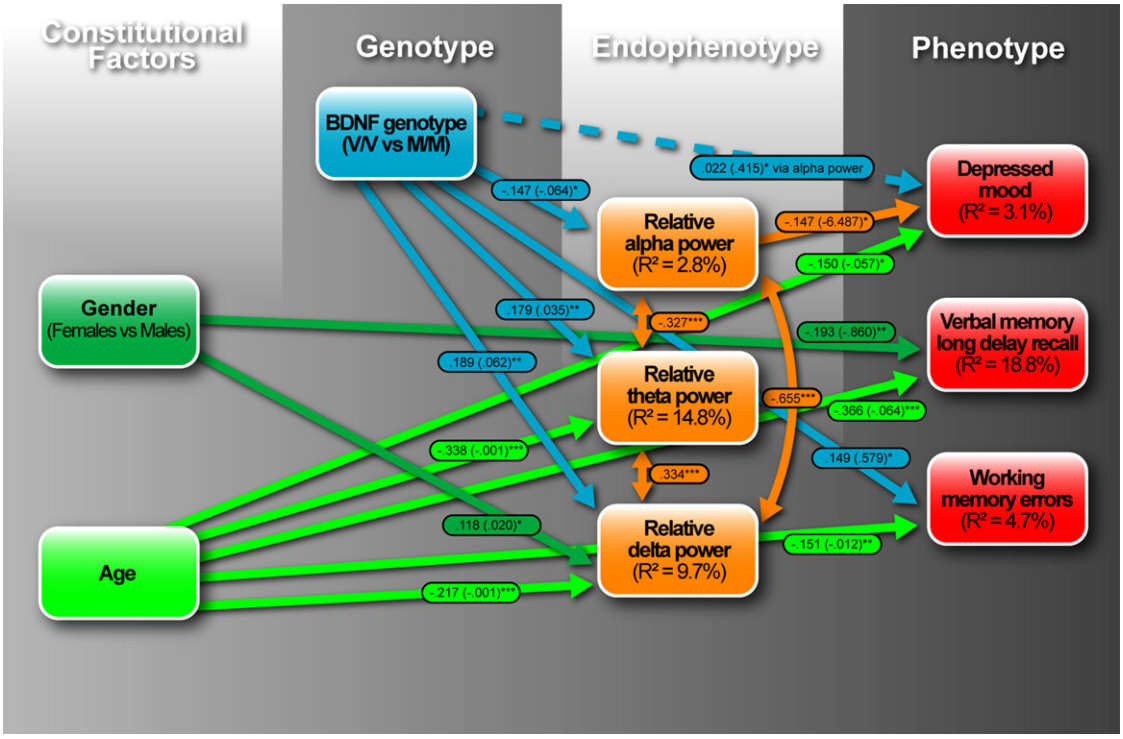

Fig. 3. Estimated BDNF-EEG-cognition/emotion path model with significant standardized and unstandardized estimates shown. Solid lines represent significant direct effects, and dashed lines represent significant indirect effects. Estimates associated with each path (one-headed arrow) represent standardized and unstandardized (within parentheses) path coefficients; estimates associated with the two-headed curved arrows represent correlations between two variables; and the values given within the boxes represent squared multiple correlations (R^2), that is, the proportion of variance of each variable in the network that is accounted for by preceding variables. Residual variances were estimated for the endogenous variables (relative alpha, theta, beta, depressed mood, verbal memory recall, and working memory errors) but are not presented here for simplicity. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

4. Discussion

We provide new evidence to suggest that the BDNF M/M genotype was a direct predictor of changes in working memory, while the effects of this polymorphism on trait depression were mediated by EEG alpha power. These predictive relationships were observed in the context of a marked shift in both alpha and slow-wave EEG, particularly during the eyes open condition, with effect sizes ranging from medium to large. Similar findings were found when analyses were repeated in the equal-sized genotype subgroups. These findings highlight the utility of using EEG measures to elucidate the pathway from genotype to phenotype.

The current findings support EEG power as a putative biological endophenotypic marker of depression. Consistent with the proposed criteria (Gould and Gottesman, 2006), we found evidence towards associations between EEG alpha power and depressive symptoms in the path model. In addition, the heritability of EEG was supported as demonstrated by links between BDNF variants and relative EEG power. This is also consistent with previous twin studies which have identified a common genetic factor that influences all EEG bands (Smit et al., 2005; Zietsch et al., 2007). Of note, previous studies have shown that alpha power demonstrates the highest heritability relative to all frequency bands with an average estimate of .902 across the brain (Smit et al., 2005); here, the specific EEG frequency that mediated BDNF and depressive symptoms. Our findings also support the endophenotypic criteria of state-independence, with particular EEG patterns predicting depressive symptoms in otherwise healthy individuals, suggesting that this EEG pattern may manifest in individuals whether or not the illness is active. However, as the current sample comprised unrelated individuals, the criteria of co-segregation and familial association still remain to be confirmed for future research.

Group comparisons suggested that BDNF M/M individuals demonstrated a shift towards a global elevation in slow-wave EEG activity (delta and theta) but a decrease in fast-wave activity (alpha and beta) compared to Val carriers. While there was a suggestion that M/M homozygotes may differ from V/M and V/V groups in anatomically distinct ways across the EEG power bands, it is likely that this apparent variation reflects differences in statistical power given that mean trends were consistent across brain sites for relative delta, theta and alpha power (see Fig. 1), consistent with a global neural effect of M/M status.

The presence of reduced alpha power and elevated slow-wave EEG in both eyes open and closed conditions suggests a generalized effect of BDNF Met status on neuronal excitability due to either an excess of inhibitory thalamic processing and/or a loss of excitatory activation, diminishing sensory input to the cortex (Hughes and John, 1999; Rennie et al., 2002). This is consistent with the overall excitatory effects of BDNF in neural activity (Bolton et al., 2000), and our proposal that the lower activity-dependent BDNF secretion in M/M individuals may be associated with a reduction in cortical excitability. This is also consistent with the observed elevations in theta power, which are typically inversely related to alpha power, and observed with a lack of cortical maturation (Klimesch, 1999). It seems thus reasonable to speculate that M/M individuals with deficient BDNF secretion are characterized by a surplus of inhibitory input from the thalamus to the cortex, which in effect, may cause alterations (or even deficits) in cognitive and emotional processing. Indeed, similar EEG alterations have been observed in depressed states which involve a loss of emotional arousal (Guidi et al., 1989), as well as memory disorders such as Alzheimer's disease (Duffy et al., 1984) which involve a loss of cortical integrity.

In terms of the cognitive-emotion measures, direct contrasts revealed a profile of differences between BDNF genotype groups in working memory which was further elucidated by predictive path modeling. Consistent with previous research (Rybakowski et al., 2003), M/M individuals demonstrated poorer working memory performance compared to Val carriers. However, there was no corresponding impairment in verbal learning recall, which is in contrast to previous findings (Egan et al., 2003; Hariri et al., 2003). This null result might reflect a ceiling effect in the current study being based on a healthy sample, or the related possibility that Met-related impairments in delayed recall are only revealed with more complex memory tasks. Alternatively, the effect of the BDNF genotype on delayed recall may reflect contributions from interactions with age and sex, given our observations that these demographic factors have significant direct effects on verbal memory. Variations with these factors accords with evidence that verbal memory performance has a relatively low heritability estimate of 21% (Tuulio-Henriksson et al., 2002).

M/M individuals also did not differ from either V/M or V/V individuals on level of trait depression, yet path modeling suggested that M/M homozygosity has a specific impact on neural activity, which in turn predicts level of trait depression. In this indirect relationship, M/M status predicted a lower level of generalized neuronal excitability (indexed by EEG alpha power), and this reduction was predictive of trait depression. The identification of these two significant pathways satisfies MacKinnon's (MacKinnon et al., 2002; Fritz and MacKinnon, 2007) criteria for establishing a mediating relationship. The reduction in EEG alpha may represent a neural susceptibility or risk factor in depression that is associated specifically with the M/M genotype, without being a sufficient condition for overt depressive illness to occur. Such a neural susceptibility mechanism may also involve changes in slow-wave activity that is coupled inversely with changes in alpha power.

Overall, our findings are the first to suggest that the BDNF M/M genotype impacts resting electrical brain function, and that this impact may be one mechanism by which it produces changes in mood and memory. Additional investigation of BDNF-EEG mechanisms in independent non-clinical and clinical samples will be important in verifying the present findings, and for understanding risk for particular depression phenotypes, such as depressed individuals who report concomitant memory problems vs those who do not (Marcos et al., 1994; Zakzanis et al., 1998). Other factors may also contribute to the role of BDNF in the pathways to depression such as stress, exercise and health behavior, as well as changes in brain structure or function not captured by the EEG. Elucidating the role of the BDNF polymorphism in the phenotype of depression will be valuable for treatment prediction, given animal evidence that anti-depressants up-regulate BDNF in the hippocampus (Nibuya et al., 1995), whereas immobilization stress lowers BDNF levels in the hippocampus (Smith et al., 1995).

Financial disclosures and potential conflicts of interest

The Brain Resource Company Ltd. (BRC) was the industry partner on the ARC-linkage grant which funded this study, but had no further role in design or implementation of the project. Partnership involved a cash contribution for a research assistant position and in-kind support from the Brain Resource International Database. Associate Professor Gordon is the CEO and Chairman of the BRC, and holds significant equity and stock options in the company. Professor Schofield holds stock options in the BRC. Professor Williams is a small equity holder in BRC. Dr Gatt and Dr Kuan are employed as postdoctoral researchers on the ARC-linkage grant which funded this study. Dr Kemp, Professor Rob Paul, Professor Russell Joffe, Dr Carol Dobson-Stone and Dr Andrew Kemp have no conflicts of interest for this study. Professor Paul and Dr Kemp have received fees from BRC for research development and coordination unrelated to the study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.biopsycho.2008.07.004.

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