

Modulatory effects of brain-derived neurotrophic factor Val66Met polymorphism on prefrontal regions in major depressive disorder

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Background

Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism contributes to the development of depression (major depressive disorder, MDD), but it is unclear whether neural effects observed in healthy individuals are sustained in MDD.

Aims

To investigate BDNF Val66Met effects on key regions in MDD neurocircuitry: amygdala, anterior cingulate, middle frontal and orbitofrontal regions.

Method

Magnetic resonance imaging scans were acquired in 79 persons with MDD (mean age 49 years) and 74 healthy volunteers (mean age 50 years). Effects on surface area and cortical thickness were examined with multiple comparison correction.

Results

People who were Met allele carriers showed reduced caudal

middle frontal thickness in both study groups. Significant interaction effects were found in the anterior cingulate and rostral middle frontal regions, in which participants in the MDD group who were Met carriers showed the greatest reduction in surface area.

Conclusions

Modulatory effects of the BDNF Val66Met polymorphism on distinct subregions in the prefrontal cortex in MDD support the neurotrophin model of depression.

Declaration of interest

None.

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Heritability estimates in major depressive disorder (MDD) are of the order of 48–75%.¹ A potential candidate gene is the brain-derived neurotrophic factor (BDNF) polymorphism which has been linked with an increased incidence of MDD.² The BDNF protein is the most common of the neurotrophins and has an important role in synaptic plasticity, neurogenesis, neural growth and differentiation.^{3,4} A common single nucleotide polymorphism (SNP) at codon 66 of the *BDNF* gene results in a valine to methionine (Val66Met) substitution, which has a functional impact on cellular packaging, transportation and secretion, and the neurotrophic model proposes that decreased BDNF expression contributes to the development of depression.⁵ Brain-derived neurotrophic factor is widely distributed within key regions in the neural circuitry of affective processing and in major depressive disorder, including in the anterior cingulate, prefrontal regions, hippocampus and amygdala.⁶ However, effects of the BDNF Val66Met polymorphism in healthy individuals have been variable. In subcortical limbic regions, reduced volumes of the hippocampus,^{7,8} and amygdala,⁸ as well as no significant difference,^{9,10} have been reported in a Met carrier group relative to a Val homozygous group. In prefrontal regions, individuals who were Met carriers showed reduced middle and inferior frontal cortical volumes,^{7,11} although no significant difference has been found in orbitofrontal volumes.¹²

Few studies have examined the effect of the BDNF polymorphism in depression; the main region of interest to date has been the hippocampus which has shown mixed findings, with reduced volume in people who are Met carriers,^{10,13} as well as reduced and increased volume in those homozygous for Val,^{14,15} whereas previously we found no difference between genotypes.¹⁶

However, studies in depression have been limited in their sample characteristics: absence of a healthy control group,¹³ specified regions of interest (namely, hippocampus and amygdala),^{10,14–16} and measures of white-matter tracts only.^{17,18} Moreover, the majority of studies have measured regional grey-matter, including grey-matter density. The determinants of grey-matter volume of a given cortical region are its surface area and cortical thickness, which have distinct developmental and genetic origins.¹⁹ Volumetric alterations are thus a product of independent or concurrent disparities in the two constituents. In a healthy sample Yang *et al* found a broad distribution of reduced cortical thickness in Chinese adults who were homozygous for Met compared with those homozygous for Val.²⁰ To our knowledge, BDNF Val66Met modulation of cortical thickness and surface area has not been investigated in MDD.

We sought to examine the effects of the BDNF Val66Met polymorphism on the neurocircuitry of depression, in particular the amygdala and the prefrontal regions of the anterior cingulate cortex (ACC), middle frontal and orbitofrontal cortices. We investigated the modulatory effects on regional brain volume and its components of surface area and cortical thickness. We expected to observe an effect of Met carrier status in reduced cortical volume in the middle frontal cortices,^{7,11} and perhaps in the corresponding cortical thickness,²⁰ in healthy participants, whereas it was uncertain whether the impact of the polymorphism would be sustained in MDD.

Method

The study was conducted in the UK and approved by the ethics research committee of the Institute of Psychiatry, King's College London; all participants provided written informed consent. All

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participants had previously participated in genetic association studies²¹ and were of White European ancestry. A total of 153 persons were included: 79 patients with a diagnosis of recurrent major depressive disorder and a healthy control group ($n=74$) matched for age, gender, handedness and IQ score. All participants in the MDD group met criteria for recurrent MDD, as characterised by the DSM-IV-TR using the Schedules for Clinical Assessment in Neuropsychiatry interview,²² and the control group was screened to ensure that its members had never experienced a depressive episode. All participants were screened for contraindications to magnetic resonance imaging (MRI), as well as any indication of neurological disorder such as head injury leading to loss of consciousness or conditions known to affect brain structure, such as alcohol or drug misuse. Potential participants were excluded if they or a first-degree relative had ever experienced an episode of mania, hypomania, schizophrenia or mood-incongruent psychosis. The IQ score was measured using the Wechsler Abbreviated Scale of Intelligence,²³ depressive symptoms with the Beck Depression Inventory²⁴ and anxiety symptoms with the State-Trait Anxiety Inventory.²⁵

Genotyping

Genotyping for the Val66Met BDNF polymorphism was performed using the TaqMan 5' exonuclease assay (www.appliedbiosystems.com).¹⁶ The BDNF genotypes were divided into three groups: Val/Val, Val/Met and Met/Met. For the purposes of this analysis the groups were combined into Val homozygotes (Val/Val) and Met carrier (Met-allele) groups owing to the small number of participants homozygous for Met.

Image acquisition

Magnetisation-prepared rapid gradient echo (MP-RAGE) T_1 -weighted scans were acquired at 1.5 T (Signa HDx 1.5 T system, General Electric, Wisconsin, USA) with the following parameters: time to echo 3.8 ms, repetition time 8.59 ms, flip angle 8°, field of view 24 × 24 cm², slice thickness 1.2 mm, number of slices 180, image matrix 256 × 256. The MP-RAGE volume was acquired using the Alzheimer's Disease Neuroimaging Initiative (ADNI) custom pulse sequence, with full brain and skull coverage.²⁶

Statistical analysis

Grey-matter volumes, surface area and average cortical thickness were measured using Freesurfer Pipeline version 5.1.0 (<http://surfer.nmr.mgh.harvard.edu>). The analysis involved removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of

the subcortical white-matter and deep grey-matter volumetric structures, intensity normalisation, tessellation of the grey matter–white matter boundary, automated topology correction and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defined the transition to the other tissue class. Once the cortical models were complete, registration to a spherical atlas took place using individual cortical folding patterns to match cortical geometry across individuals. This was followed by parcellation of the cerebral cortex into units based on gyral and sulcal structures (see online Fig. DS1). The pipeline generated 68 cortical thickness, cortical volume, surface area, mean curvature, gaussian curvature, folding index and curvature index measures (34 from each hemisphere) and 46 regional subcortical volumes. All volumetric measures from each participant were normalised by the participant's intracranial volume; cortical thickness measures were not normalised.

As *a priori* hypotheses, only the following regions were examined: amygdala, anterior cingulate (rostral and caudal ACC), middle frontal cortex (rostral and caudal) and orbitofrontal cortex (medial and lateral) bilaterally. A multivariate analysis of variance (ANOVA) in SPSS version 21 was used to assess differences between the MDD group and the control group and also between those homozygous for Val and those classified as Met carriers (Val/Met and Met/Met genotypes). False discovery rate (FDR) was used to adjust for multiple comparisons resulting from the ANOVA models with $\alpha=0.05$.²⁷

Results

The demographic characteristics of the sample are given in Table 1, and the clinical details of the participants with depression are summarised in Table 2. Most participants with depression were taking at least one antidepressant medication ($n=58$), although some were not taking any medication at the time of the MRI scan ($n=21$). The antidepressant medications encompassed selective serotonin reuptake inhibitors, serotonin–noradrenergic reuptake inhibitors, tricyclic antidepressants and other antidepressant classes. In addition, 7 patients were taking additional drugs for augmentation of the antidepressant medication: mood stabilisers, benzodiazepines, antipsychotic medication and thyroxine.

A significant effect of genotype that survived FDR correction for multiple comparisons was found in the left caudal middle frontal cortex (Brodmann's area 6) in cortical thickness, in which the Met carrier subgroup showed greater reduction in cortical thickness compared with the Val homozygote subgroup in both the MDD and control groups: Val/Val MDD group 2.474 mm (s.d. = 0.138); Met-allele MDD group 2.434 mm (s.d. = 0.177);

Table 1 Demographic features of the participants

	MDD group ^a ($n=79$)	Control group ($n=74$)	
Age, years: mean (s.d.)	49.09 (8.96)	50.92 (7.82)	$F=1.803, P=0.181$
Gender, n	27 M, 52 F	34 M, 40 F	$\chi^2=2.207, P=0.137$
Verbal IQ score: mean (s.d.)	117.44 (11.59)	119.04 (8.74)	$F=0.917, P=0.340$
Handedness, ^b n			
Right	69	63	$\chi^2=0.390, P=0.823$
Left	8	10	
BDNF status, n			
Met carrier	33	27	$\chi^2=0.448, P=0.503$
Val/Val	46	47	

BDNF, brain-derived neurotrophic factor; F, female; M, male; MDD, major depressive disorder.
a. Data were missing for one person in the MDD group.
b. One person in each group was ambidextrous.

Table 2 Clinical features of the participants with major depressive disorder

	Allele status ^a	
	Met carrier (n = 33)	Val/Val (n = 46)
Assessment scores: mean (s.d.)		
BDI	15.6 (11.6)	15.6 (11.1)
STAI	39.2 (11.1)	38.6 (10.2)
Age at onset, years: mean (s.d.)	20.3 (9.5)	20.3 (9.7)
Number of previous episodes: mean (s.d.)	4.4 (3.2)	4.2 (3.2)
History of suicide attempt, n (%)	14 (42)	19 (41)
History of ECT, n (%)	2 (6)	4 (9)
History of hospital admissions, n (%)	9 (27)	13 (28)
Current antidepressant medication, n (%)	26 (79)	32 (70)

BDI, Beck Depression Inventory; ECT, electroconvulsive therapy; MDD, major depressive disorder; STAI, State Trait Anxiety Inventory.
a. There was no significant difference between the two groups for any of the measures.

Val/Val control group 2.491 mm (s.d. = 0.158); Met-allele control group 2.36 mm (s.d. = 0.141); $F_{(1,149)} = 11.029$, $P = 0.001$ (Fig. 1). Significant interaction effects that survived multiple comparison correction were found in the surface area in three regions:

- (a) right caudal anterior cingulate (Fig. 2): Val/Val MDD 782.48 mm², s.d. = 140.17; Met-allele MDD 711.00 mm², s.d. = 150.61; Val/Val control 764.02 mm², s.d. = 153.13; Met-allele control 869.26 mm², s.d. = 186.70; $F_{(1,149)} = 11.73$, $P = 0.001$;
- (b) right rostral middle frontal cortex: Val/Val MDD 5975.30 mm², s.d. = 667.01; Met-allele MDD 5592.39 mm², s.d. = 611.78; Val/Val control 5673.02 mm², s.d. = 754.37; Met-allele control 6125.70 mm², s.d. = 671.12; $F_{(1,149)} = 13.49$, $P = 0.0003$;
- (c) left rostral middle frontal cortex: Val/Val MDD 5723.28 mm², s.d. = 633.79; Met-allele MDD 5383.06 mm², s.d. = 473.55; Val/Val control 5477.19 mm², s.d. = 677.13; Met-allele control 5890.04 mm², s.d. = 711.31; $F_{(1,149)} = 12.87$, $P = 0.0005$.

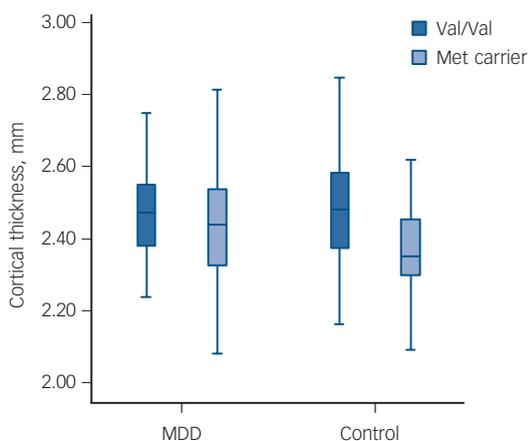


Fig 1 A significant main effect of BDNF Val66Met polymorphism which survived correction for multiple comparisons was found in the left caudal middle frontal region (Brodmann's area 6). Participants who carried the Met allele showed the greatest reduction in cortical thickness in both the major depressive disorder (MDD) and control groups. Boxplots indicate interquartile range, median and range.

In all of these regions reduced surface area was associated with Met carrier status relative to Val homozygosity in MDD, whereas the inverse was observed in the control group. No other main or interaction effect remained significant following multiple comparison correction, including in the amygdala: MDD left amygdala 1385.24 mm³, s.d. = 219.40, MDD right 1482.92 mm³, s.d. = 231.58; control left 1433.81 mm³, s.d. = 257.16, control right 1552.50 mm³, s.d. = 271.31; Val/Val left 1432.30 mm³, s.d. = 249.52, Val/Val right 1537.49 mm³, s.d. = 250.53; Met-allele left 1372.20 mm³, s.d. = 218.36, Met-allele right 1484.20 mm³, s.d. = 255.90 (all $P > 0.3$).

Discussion

Modulatory effects of the BDNF Val66Met polymorphism as well as genotype by diagnosis interactions were revealed in key nodes in the neurocircuitry of MDD. Distinct effects were observed in the anterior cingulate and subregions of the middle frontal cortices implicating converging yet separate influences of the disease process, genetic modulation and their interaction.

Changes in prefrontal cortical regions

Pezawas *et al* provided the first report of an effect of the BDNF Val66Met polymorphism in the caudal middle frontal cortex, revealing reduced grey-matter volume in healthy individuals who were Met carriers compared with those homozygous for Val.⁷ The potential contribution of cortical thinning to the volumetric reductions has recently been added,²⁰ and reduced middle frontal activity has also been observed in a healthy Met carrier group.⁹ In our study we found a main effect of Met carrier status on cortical thinning in the caudal middle frontal cortex in both healthy individuals and in people with depression. Our study extends both the observation by Yang *et al* in healthy Chinese adults,²⁰ and the original finding,⁷ by localising the contribution of cortical thinning to the reductions in caudal middle frontal volume. Moreover, this is the first report of the extent that Met carrier status leads to middle frontal cortical thinning, as the effect of the Met allele appears to supersede the disease process effects of MDD on cortical thickness. Grey-matter reductions in the caudal middle frontal region have been frequently observed in MDD,

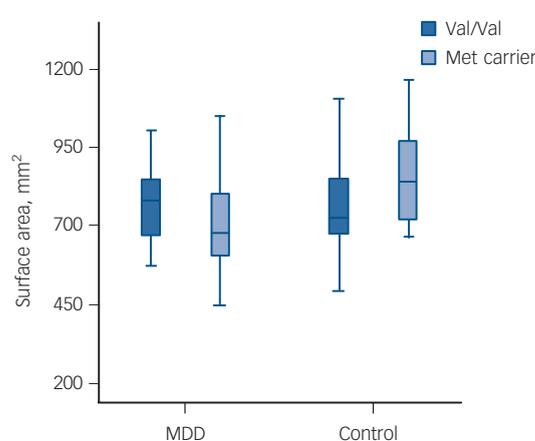


Fig 2 The significant interaction effect in the right caudal anterior cingulate. Participants with major depressive disorder (MDD) who carried the Met allele showed the greatest reduction in surface area compared with those homozygous for Val in both the MDD and control groups as well as with those who were Met carriers in the control group. Boxplots indicate interquartile range, median and range.

with further reductions in recurrent MDD.²⁸ Our findings indicate that the impact of the BDNF Val66Met polymorphism on cortical thinning in the caudal middle frontal region is even greater than that of recurrent MDD. It is possible that the influence of the Met allele in this region may not necessarily be causal in itself for MDD, but may be a predisposing, contributory factor in association with other neurogenic effects. Stress is linked to an increase in cortisol, which in turn causes a reduction in BDNF.²⁹ Individuals who are Met carriers are less able to compensate for this BDNF reduction owing to deficient transport of the BDNF preprotein which causes clumping around the nucleus, perhaps leading to neuronal atrophy in response to reduced BDNF levels.^{4,5}

We also observed a significant interaction effect in surface area in the caudal anterior cingulate and rostral middle frontal cortices. The anterior cingulate and middle frontal cortices are key regions in the neurocircuitry of mood disorders, and the anterior cingulate is a well-replicated predictive marker of clinical response in MDD,³⁰ which is evident at the individual level.³¹ Surface area and cortical thickness have independent genetic and developmental origins.¹⁹ The radial unit hypothesis proposes that cortical thickness is determined by the number of cells within a neuronal column, and cortical surface area is determined by the number of neuronal columns.³² There is support for a general regional expansion of surface area from childhood into adolescence, particularly in boys,³³ followed by subsequent decreases in adulthood with increasing age,³⁴ whereas cortical thinning is a pronounced feature of adolescence that continues into adulthood.³³ There is, however, some notable variability in the regional changes,^{33,34} for example the surface area of the anterior cingulate cortex may show relatively fewer changes in adulthood.³³ Modulation of grey-matter density by the BDNF Val66Met polymorphism in both the anterior cingulate and middle frontal cortices has been found in bipolar disorder,³⁵ and in the anterior cingulate in healthy individuals with a history of childhood abuse,¹² whereas no prefrontal regional effect has been reported in schizophrenia.³⁶ Our study localises the genetic influence to cortical surface area in its contribution to grey-matter volume, which had not been examined in previous studies in patient populations.^{35,36} It is possible that the surface area reduction we observed is an endophenotype for MDD, or more generally for mood disorders including bipolar disorder, or it may also be a feature in schizophrenia that has not been well captured by morphometric studies to date. The lack of an association of BDNF with schizophrenia,³⁷ however, suggests that the effect may be more strongly expressed in mood disorders.

Effects on amygdala volume

Contrary to our hypothesis, no significant interaction effect was found in the grey-matter volume of the amygdala. Our observations are consistent with findings in healthy individuals carrying the BDNF Met allele with a history of childhood adversity and in depression,^{10,12} but there have also been reports of reduced amygdala volume in healthy people with and without a history of stressful events.^{8,31} Similarly, studies of amygdala responsivity have been mixed, with reports of significant effects,^{38,39} but more frequently of no impact,^{9,40,41} of the BDNF polymorphism. The literature on amygdala volume in depression, however, is inconsistent, with some suggestion that amygdala volume is reduced in more chronic forms of depression.⁴² In our study, participants had a history of recurrent depression characterised by discrete acute depressive episodes with periods of euthymia rather than a more chronic, treatment-resistant type of depression. Our findings are most comparable with those of

Frodl *et al*, who similarly did not observe any effect of diagnosis or BDNF genotype on amygdala volume.¹⁰

Study limitations

We limited our analysis to *a priori* defined regions in the prefrontal cortex and the amygdala within the neurocircuitry of depression. However, our sample size was relatively modest and replication in an independent sample is required. Cortical thinning in the medial orbitofrontal region has been reported in first-episode depression,⁴³ and in a younger cohort of patients with MDD (mean age 34 years) than in our study.⁴⁴ Although there was evidence of left medial orbitofrontal cortical thinning in MDD patients relative to healthy controls in our sample, this difference did not survive correction for multiple comparisons. Furthermore, BDNF Val66Met effects have also been observed in the temporal and parietal cortices in healthy Chinese adults.²⁰ There may also be a modulatory effect of early life stress, as healthy individuals carrying the Met allele with a history of greater stressful events have shown reduced grey-matter volume in the amygdala and hippocampus,⁴⁵ and also in the anterior cingulate cortex,¹² compared with a group homozygous for Val. Another limitation of our study is the absence of data on the history of possible childhood trauma in our participants, although it is unclear whether these effects would persist alongside the pathophysiological effects of the illness. Moreover, most of the participants with MDD were taking antidepressant medication, which may have had an effect on BDNF levels,⁵ and in turn potentially on neural volumes.⁴⁶ The anterior cingulate region has been consistently identified as a predictive marker of clinical response,³⁰ and the BDNF polymorphism has shown an association with treatment response.⁴⁷ Furthermore, an interaction effect of BDNF and its high-affinity receptor, neurotrophic tyrosine kinase receptor 2 (NTRK2), gene polymorphisms has been associated with the development of treatment-resistant depression.⁴⁸ How these potentially complementary markers may interact at a neural level in predicting clinical response requires further investigation. Neural correlates of BDNF associations with clinical response in a sample of patients who were medication-free and perhaps in their first episode of depression would elucidate the effects of medication, recurrent episodes of depression and prediction of clinical response.

Concluding remarks

In summary, we demonstrated sustained effects of the BDNF Val66Met polymorphism on distinct subregions in the prefrontal cortex in depression. The effects in the caudal middle frontal regions exceeded those of the illness as Met carrier status was associated with greater cortical thinning in both MDD and control groups. Effects in the anterior cingulate and rostral middle frontal regions revealed an interaction with BDNF Val66Met genotype, in which the MDD Met carrier group showed the greatest reduction in surface area. Our findings specify the anterior cingulate and middle frontal regions as key regions within the neurotrophin hypothesis of depression.

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psychiatry in literature

Something nasty in the woodshed

Richard Leonard Symonds

Stella Gibbons' *Cold Comfort Farm* written in 1932 is a comic classic. Sensible, modern Flora visits her distant reclusive relatives on a farm in deepest rural Sussex, and resolves to bring some light and rationality to these appalling relics. She encounters the matriarch of the farm, Aunt Ada Doom.

“How d’ye do, Aunt Ada?” said Flora, pleasantly, putting out her hand. But Aunt Ada made no effort to take it . . . and observed in a low toneless voice: “I saw something nasty in the woodshed” “Mother . . . it’s Judith. I have brought Flora Poste to see you . . .” “Nay – I saw something nasty in the woodshed”, said Aunt Ada Doom, fretfully moving her great head from side to side. ‘Twas a burning noonday, sixty-nine years ago. And me no bigger than a titty-wren. And I saw something . . .” (p. 171)

The psychiatrist immediately recognises this situation, and I have been relying on Aunt Ada Doom for many years for an example of traumatic fallacy. Spread by post-war Hollywood, owing something to battle neurosis and more to psychoanalysis in the USA, the notion that all long-standing psychiatric symptoms must have been initiated by a traumatic incident in early childhood is so embedded in our culture that most patients, at least those with anxiety symptoms, take it for granted. Behind their distress, their language reveals the plea to find the ‘real’ cause, after which everything will magically improve. It may also relate to the depressive nature of some symptoms, that the sufferer is in some way bad in their essence, with their own original sin, and throws an emphasis on the past. It also reveals the passive and pessimistic nature of these patients, since the past cannot be changed.

By contrast, which is often illuminating, I have used the construction as follows: it is less important to know how you got into this situation – your illness – than how you can get out of it. Rather than concentrating on a distant origin, which could never be proved, you need to think where you are now and how you can move forward. This simple view has often come as a revelation to those who have ruminated about what they did or what had happened to them.

But Aunt Ada Doom carries another message, that of secondary gain and another familiar picture of a ‘black hole’, a family member who traps their relatives in a tight circle from which they can never escape. Gibbons has it exactly:

“You told them you were mad. You had been mad since you saw something nasty in the woodshed, years and years and years ago. If any of them went away, to any other part of the country, you would go much madder. Any attempt by any of them to get away from the farm made one of your attacks of madness come on. It was unfortunate in some ways but useful in others . . . The woodshed incident had twisted something in your child-brain seventy years ago. And seeing that it was because of that incident that you sat here ruling the roost and having five meals a day brought up to you as regularly as clockwork, it hadn’t been such a bad break for you, that day you saw something nasty in the woodshed.” (p. 115)

The author used the 2011 Penguin edition for the quotes.

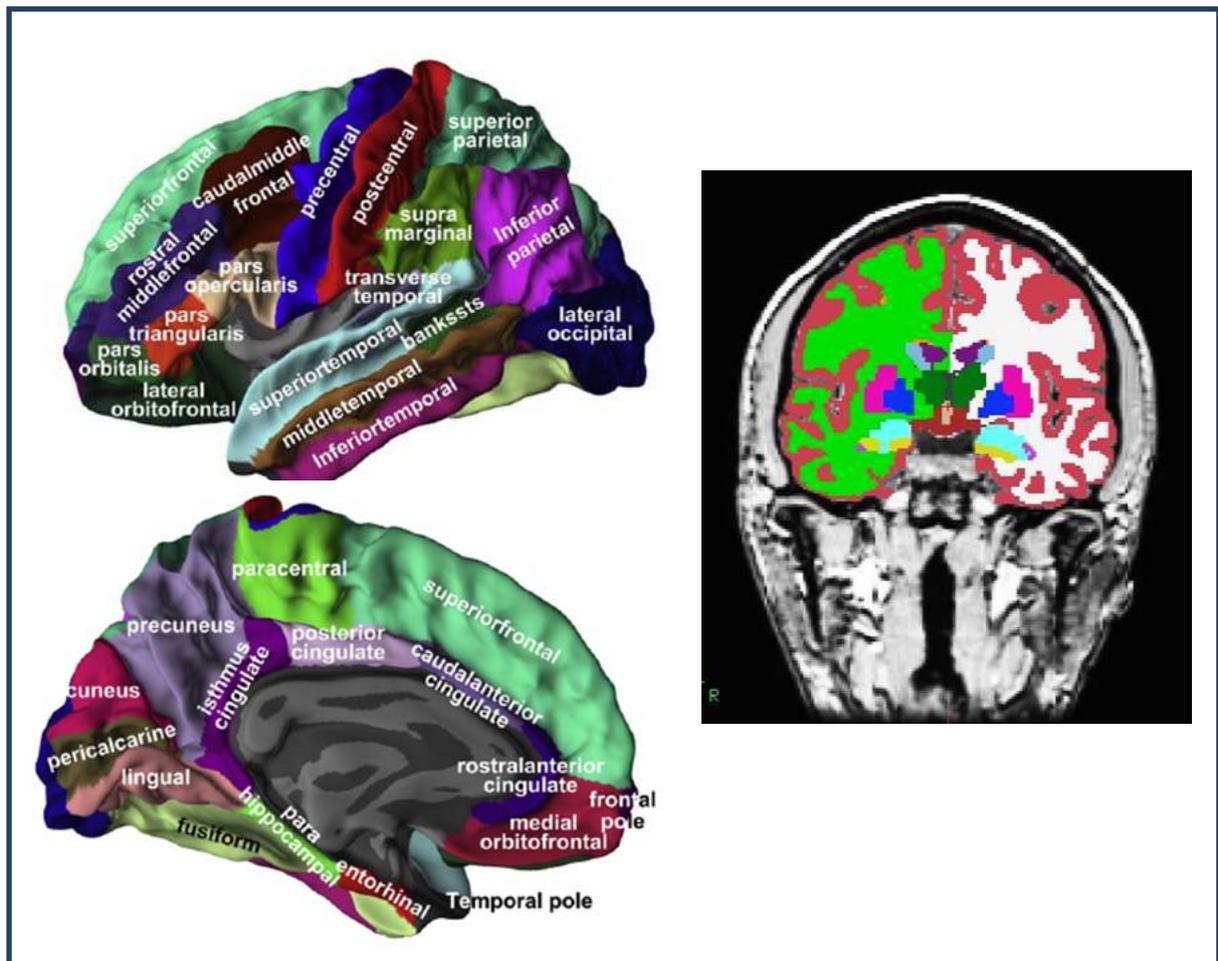
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Online data supplement

Fig. DS1

Depiction of the parcellation of cerebral regions onto lateral and medial hemispheres and coronal cross-section indicating location of subcortical regions and the grey matter–white matter boundary using Freesurfer version 5.1.0 (<http://surfer.nmr.mgh.harvard.edu/>). See supplementary references 48–50.



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Modulatory effects of brain-derived neurotrophic factor Val66Met polymorphism on prefrontal regions in major depressive disorder

Rebecca MacGregor Legge, Shahbaz Sendi, James H. Cole, Sarah Cohen-Woods, Sergi G. Costafreda, Andrew Simmons, Anne E. Farmer, Katherine J. Aitchison, Peter McGuffin and Cynthia H. Y. Fu
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**Supplementary
Material**

Supplementary material can be found at:
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