Journal of Affective Disorders 184 (2015) 239–244

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

BDNF Val66Met polymorphism in patterns of neural activation in individuals with MDD and healthy controls

Danuta M. Lisiecka [a,b,*], Erik O'Hanlon [c], Andrew J. Fagan [d,e], Angela Carballedo [f], Derek Morris [g], John Suckling [a,b,h], Thomas Frodl [f,i]

[a] Brain Mapping Unit, Department of Psychiatry, University of Cambridge, UK
[b] Behavioural and Clinical Neuroscience Institute, Department of Psychiatry, University of Cambridge, UK
[c] Department of Psychiatry, Faculty of Medicine and Health Sciences, Royal College of Surgeons, Dublin, Ireland
[d] Centre for Advanced Medical Imaging (CAMI), St James's Hospital, Dublin, Ireland
[e] Department of Clinical Medicine, Trinity College Dublin, Ireland
[f] Department of Psychiatry, Trinity College Dublin, Ireland
[g] Cognitive Genetics and Therapy Group, Discipline of Biochemistry and School of Psychology, National University of Ireland, Galway, Ireland
[h] Cambridge and Peterborough NHS Foundation Trust, Cambridge, UK
[i] Department of Psychiatry, University of Regensburg, Germany

ARTICLE INFO

Article history:
Received 13 February 2015
Received in revised form
4 June 2015
Accepted 4 June 2015
Available online 12 June 2015

Keywords:
Major depressive disorder
Brain-derived neurotrophic factor
Functional magnetic resonance imaging
Emotional response
Striatum
Prefrontal cortex

ABSTRACT

Background: Rs6265 single nucleotide polymorphism, which influences brain-derived neurotrophic factor (BDNF) levels in the cortical and subcortical brain structures, may result in distinguished patterns of neural activation during a major depressive disorder (MDD) episode. Valine homozygotes with high levels of BDNF and methionine carriers with lower levels of BDNF may present specific neural correlates of MDD. In our study we have tested differences in blood oxygen level dependant (BOLD) signal between individuals with MDD and healthy controls for both allelic variants.

Methods: Individuals with MDD ($N=37$) and healthy controls ($N=39$) were genotyped for rs6265 and compared separately in each allelic variant for BOLD response in a functional magnetic resonance imaging experiment examining appraisal of emotional scenes. The two allelic variants were also compared separately for both individuals with MDD and healthy controls.

Results: In the homozygous valine group MDD was associated with decreased neural activation in areas responsible for cognitive appraisal of emotional scenes. In the methionine group MDD was related to increased activation in subcortical regions responsible for visceral reaction to emotional stimuli. During an MDD episode methionine carriers showed more activation in areas associated with cognitive appraisal of emotional information in comparison to valine homozygotes.

Limitations: Small sample size of healthy controls carrying methionine ($N=8$).

Conclusion: Our results suggest that allelic variations in the rs6265 gene lead to specific neural correlates of MDD which may be associated with different mechanisms of MDD in the two allelic groups. This may have potential importance for screening and treatment of patients.

1. Introduction

According to the neuroplasticity theory, brain-derived neurotrophic factor (BDNF), a peptide responsible for neuronal growth, plays a significant role in the pathogenesis of major depressive disorder (MDD) (Brunoni et al., 2008; Castren et al., 2007; Groves, 2007). BDNF is associated with plasticity and long-term synaptic connectivity in neural networks including the hippocampus, frontal lobes and striatum (Fossati et al., 2004). Altered secretion of BDNF observed in MDD can lead to long-term changes in these regions and consequently to cognitive symptoms characteristic of MDD (Fossati et al., 2004). An increase of BDNF level in specific

Abbreviations: BDNF, brain-derived neurotrophic factor; MDD, major depressive disorder; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; BDI-II, Beck Depression Inventory II; SNP, single nucleotide polymorphism; *f*MRI, functional magnetic resonance imaging; IAPS, International Affective Picture System; RT, reaction time; DLPFC, dorsolateral prefrontal cortex

* Corresponding author at: Brain Mapping Unit, Department of Psychiatry, University of Cambridge, Douglas House, 18B Trumpington Road, Cambridge CB2 8AH, UK. Tel.: +44 1223746185; fax: +44 1223336581.
E-mail address: dml45@cam.ac.uk (D.M. Lisiecka).

http://dx.doi.org/10.1016/j.jad.2015.06.002
0165-0327/

neural areas can either promote or inhibit an antidepressant-like reaction (Castren et al., 2007; Groves, 2007).

In rodents a direct injection of BDNF into the hippocampus diminishes depressive symptoms (Shirayama et al., 2002). Patients with MDD have reduced volumes of the hippocampus and frontal lobes (Dwivedi et al., 2003; Knable et al., 2004; Stockmeier et al., 2004), a sign of neuronal atrophy associated with lower levels of BDNF (Martinowich et al., 2007). One mechanism of action of therapies for MDD involves an increase of BDNF concentration in the hippocampus and frontal lobes (Brunoni et al., 2008). Conversely, a high concentration of BDNF in the midbrain is depressogenic and in rodents its reduction eliminates a depressive-like behaviour (Berton et al., 2006; Eisch et al., 2003).

Substituting valine by methionine in the Val66Met BDNF gene (rs6265) reduces activity-dependent secretion of BDNF (Chen et al., 2004). This single-nucleotide polymorphism has been previously associated with MDD (Binder and Scharfman, 2004). Carriers of at least one methionine show increased depressive behaviours (Schumacher et al., 2005), while displaying reduced volumes of frontal lobes (Nemoto et al., 2006; Pezawas et al., 2004) and hippocampus (Bueller et al., 2006; Pezawas et al., 2004), similar to patients with MDD (Koolschijn et al., 2009). Conversely, homozygous valine individuals score higher on the neuroticism scale, which is symptomatic of liability to MDD (Hunnerkopf et al., 2007). This suggests that a different neuronal pathway may lead to developing MDD in the two genotypes.

Our study compares healthy controls and patients with MDD separately for both genotypes in neural correlates of emotional appraisal. Emotional appraisal is a part of the emotional regulation system monitoring approach-withdrawal behaviour, and in patients with MDD it could be altered in two ways. Firstly, according to emotional potentiation theory, patients with MDD would show a stronger visceral reaction during emotional appraisal (Bylsma et al., 2008). Alternatively, according to emotion context insensitivity theory, patients with MDD would be less-reactive to emotional stimuli (Rottenberg et al., 2005). Both of these theories are associated with emotional flexibility connected with the role of BDNF in the brain.

2. Methods

2.1. Subjects

Thirty-seven patients with MDD and 39 healthy controls – matched for age, gender and handedness (all right-handed) – participated in the study. Written informed consent was obtained from all study participants. The study protocol was approved by the local ethics committee of Trinity College Dublin, Ireland, and prepared in accordance to the ethical standards of the Declaration of Helsinki.

Participants with MDD were recruited from the Adelaide and Meath Hospital incorporating the National Children's Hospital, Dublin, and from the St James's Hospital, Dublin. The MDD diagnoses and lack of comorbidities for all the subjects were confirmed by the consensus of two consultant psychiatrists, one examining participants prior to the study and the other performing the structured Clinical Interview for Diagnostic Statistics Manual IV (First and Gibbon, 2004) two to three days prior to the assessment day. The medical exclusion criteria of the study included: previous or present head injury; a current or past psychiatric or neurological disease (apart from MDD in the case of the patient group); current medical disease influencing the nervous system; substance dependency. On the assessment day, participants' health was verified via the Hamilton Depression Rating Scale (HDRS), Montgomery Asberg Depression Rating Scale (MADRS) and Beck Depression Inventory II (BDI-II). Depressed individuals differed significantly from healthy controls in all depression ratings (Lisiecka et al., 2013). All healthy participants scored within the norm interval in HDRS, MDRS and BDI-II, and all subjects with MDD scored over the threshold characteristic for disease. Among patients, 12 were not medicated, 13 were being treated with selective serotonin reuptake inhibitors and 12 with dual action substances. Five patients had one previous episode of MDD, two patients had two previous episodes of MDD, while the remaining group were experiencing a first episode of MDD.

Both patients with MDD and healthy controls were genotyped for the variants of the rs6265 single nucleotide polymorphism (SNP). The Val66Met BDNF SNP (rs6265) was genotyped in the sample using a Taqman® SNP Genotyping Assay on a 7900HT Sequence Detection System (Applied Biosystems). The call rate for the Taqman genotyping was $>95\%$, and all samples were in Hardy–Weinberg equilibrium ($p>0.05$). Along with the test samples, a number of HapMap CEU DNA sample positive controls (www.hapmap.org) and non-template negative controls were genotyped for each SNP for quality control purposes. For positive controls, all genotypes were found to be concordant with the available online HapMap data. All non-template samples returned a negative result. As a result, participants were divided into three genotype groups: homozygous groups for methionine (bdnfmet66met) and valine alleles (bdnfval66val), and a heterozygous group carrying one methionine and one valine allele (bdnfval66met). Heterozygous individuals and subjects with two methionine alleles were combined into one group of methionine-carriers (bdnfval66met-or-bdnfmet66met), as has been done in previous functional magnetic resonance imaging (*f*MRI) studies investigating Val66Met polymorphism (Lau et al., 2010; Montag et al., 2008) since methionine homozygotes are infrequent (Shimizu et al., 2004), and having at least one methionine allele is associated with susceptibility to MDD (Frodl et al., 2007).

After *t* procedure, four groups of participants were distinguished: bdnfval66val patients with MDD ($N=23$; age$=41.3\pm12.4$ years; 17 females and 6 males; HDRS$=28.8\pm6.5$; MADRS$=29.6\pm7.4$; BDI-II$=30.7\pm12.2$), bdnfval66met-or-bdnfmet66met patients with MDD ($N=14$; age$=41.9\pm8.1$ years; 9 females and 5 males; HDRS$=28.3\pm6.9$; MADRS$=29.4\pm4.9$; BDI-II$=35.7\pm10.6$), bdnfval66val healthy controls ($N=31$; age$=38.3\pm13.3$ years; 19 females and 12 males; HDRS$=2.6\pm2.4$; MADRS$=1.5\pm2.6$; BDI-II$=1.9\pm2.3$), and bdnfval66met-or-bdnfmet66met healthy carriers ($N=8$; age$=33.5\pm14.1$ years; 4 females and 4 males; HDRS$=2.3\pm1.7$; MADRS$=3.3\pm4.8$; BDI-II$=4.3\pm4.9$). The groups did not differ in age ($p=0.369$) or gender ($p=0.623$). They differed in all applied ratings of MDD (HDRS $p<0.001$; MADRS $p<0.001$; BDI-II $p<0.001$). However, there was no significant difference in the depression ratings between the two groups of healthy controls (HDRS $p=0.998$; MADRS $p=0.82$; BDI-II $p=0.304$) and between the two groups of MDD patients (HDRS $p=0.988$; MADRS $p=1$; BDI-II $p=0.898$). Furthermore, the two patients groups did not differ in the method of treatment ($p=0.914$) and the number of previous episodes of MDD ($p=0.397$).

2.2. Design

The study utilized a four sample design with bdnfval66val patients with MDD, bdnfval66met-or-bdnfmet66met patients with MDD, bdnfval66val healthy controls, and bdnfval66met-or-bdnfmet66met healthy controls as comparison groups. An event-related *f*MRI experiment measuring emotional appraisal of scenes with standardized ratings of emotional valence from International Affective Picture System (IAPS) was used during the recording of blood oxygen level dependent signals for each subject (Lang et al.,