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Brief Report

BRIEF REPORT

The Impact of BDNF Polymorphisms on Suicidality in Treatment-Resistant Major Depressive Disorder: A European Multicenter Study

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Abstract

Background: Numerous studies have reported associations between the brain-derived neurotrophic factor (*BDNF*) gene and psychiatric disorders, including suicidal behavior, although with conflicting results.
Methods: A total of 250 major depressive disorder patients were collected in the context of a European multicenter resistant depression study and treated with antidepressants at adequate doses for at least 4 weeks. Suicidality was assessed using the Mini International Neuropsychiatric Interview and Hamilton Rating Scale for Depression, and treatment response using the HAM-D. Genotyping was performed for the functional Val66Met polymorphism (rs6265) and 7 additional tagging single nucleotide polymorphisms within the *BDNF* gene.
Results: Neither BDNF single markers nor haplotypes were found to be associated with suicide risk and lifetime history of suicide attempts. Gender-specific analyses revealed nonsignificant single marker (rs908867) and haplotypic association with suicide risk in males after multiple testing correction. Analyzing treatment response phenotypes, the functional Val66Met polymorphism as well as rs10501087 showed significant genotypic and haplotypic association with suicide risk in remitters (n = 34, 13.6%).

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Conclusions: Considering the sample size, the present findings need to be replicated in larger samples to confirm or refute a role of BDNF in the investigated suicidal behavior phenotypes.

Keywords: BDNF, suicidality, depression, pharmacogenetic

Introduction

Suicide is a significant public health issue and a major cause of death, with the WHO estimating that suicide accounts for 1.5% of the deaths throughout the world. Suicidal behavior refers to the occurrence of suicide attempts that range from suicide death, to highly lethal but failed suicide attempts, to suicide attempts of low lethality (Mann, 2002). It is strongly linked with psychiatric disorders, in particular mood disorders and substance abuse (Arsenault-Lapierre, 2004). Approximately 90% of suicide attempters are estimated to have a psychiatric disorder. Patients suffering from MDD have an estimated 6% to 15% lifetime risk of suicide (Davies et al., 2001).

Major depressive disorder (MDD) constitutes a major clinical problem with a mean lifetime prevalence of 16% (Wittchen, 2011). Treatment-resistant depression is usually seen as the failure to reach response after an adequate treatment, and different definitions that need to be validated before their application in clinical practice have been proposed (Souery et al., 2007).

Family, twin, and adoption studies all support a genetic contribution to suicidal behavior, with an estimated heritability of suicide death of approximately 43% (McGuffin et al., 2001).

Neurotrophic factors such as brain derived neurotrophic factor (*BDNF*) gene are hypothesized to be markers of suicidality (Sher, 2011), and altered BDNF levels may play a role in the pathogenesis of suicidal behavior by resulting in long-term changes in the brain that can lead to neuropsychological deficits (for review, see Eisen et al., 2015). In a large meta-analysis based on 12 studies, the *BDNF* Val66Met polymorphism (rs6265) was found to have a statistically significant effect on the risk of suicide, with the Met allele and Met-allele carriers being associated with a history of suicide attempt (Zai et al., 2012). In a systematic review and meta-analysis to explore associations between BDNF levels and suicidal behavior, the meta-analysis of studies examining serum BDNF levels and attempted suicide revealed no significant association. Similarly, the qualitative review of the literature revealed that the current evidence does not provide consistent support for an association between BDNF and suicidal behavior phenotypes (completed suicide, suicidal ideation, suicide attempt) (Eisen et al., 2015); however, both cases had significant methodological limitations, thus making it difficult to draw sound conclusions.

We carried out an association study investigating 8 *BDNF* single nucleotide polymorphisms (SNPs) in a sample of 250 MDD patients collected in the context of a European multicenter treatment-resistant depression study. The functional Val66Met SNP (rs6265) as well as 7 additional tagging SNPs, covering the *BDNF* genomic region, were selected for genotyping. This is the first study investigating *BDNF* modulation of suicidality in treatment-resistant depression patients. The primary aim of the study was to test for association between *BDNF* SNPs and suicide risk and/or lifetime history of suicide attempts, and the secondary aim was to investigate possible associations between *BDNF* SNPs with and treatment response phenotypes.

Methods

Sample collection was performed in the context of the European multicenter project "Patterns of Treatment Resistance and Switching Strategies in Unipolar Affective Disorder" (Schosser et al. 2012a). Seven centers took part in this large multicenter study on treatment-resistant depression: (1) Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria; (2) Department of Psychiatry, Chaim Sheba Medical Center Tel-Hashomer, Israel; (3) Department of Psychiatry, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium; (4) Department of Psychiatry, University Hospital Gasthuisberg, Leuven, Belgium; (6) Hôpital la Salpetriere, INSERM U302, Paris, France; and (7) Sint-Truiden, Psychiatric center, Sint-Truiden, Belgium.

Subjects and Diagnostic Interviews

A total of 250 unrelated MDD patients were recruited, diagnosed by experienced psychiatrists using the Mini-International Neuropsychiatric Interview version 5.0.0 (MINI) (Sheehan et al., 1998), and modified for the European Group for the Study of Resistant Depression (Souery et al., 2007). The Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1967) 17-item version was administered to all patients at the end of the last antidepressant treatment for the current episode.

Inclusion criteria were: (1) male or female inpatients or outpatients ≥18 years of age, (2) patients with primary diagnosed MDD (i.e., mood disorder preexisting to any other psychiatric disorder), and (3) having received at least one adequate antidepressant treatment (that is at least 4 weeks of treatment at a dosage at optimal range of an antidepressant) during the current or last episode of depression.

Treatment resistance was defined as not reaching a HAM-D-17 score ≤17 after at least 2 adequate consecutive antidepressant trials administered during the last episode (Schosser et al. 2012a). Nonresistance was defined as a HAM-D-17 score ≤17 after a single antidepressant treatment or at the second trial after one failure. It was not required that drugs from 2 different classes of medication were used in order to define resistance status.

Exclusion criteria were: (1) patients with a mood disorder secondary to any primary "nonaffective" psychiatric condition, (2) patients not receiving at least one adequate antidepressant treatment during the last depressive episode, (3) patients unwilling to participate in the study, and (4) patients unwilling to give an informed consent. Detailed information on the diagnosis, the recruiting method, and treatment response phenotypes is described elsewhere (Souery et al., 2007; Schosser et al., 2012a).

Suicidality was assessed using the MINI section on suicidality and the HAM-D item 3 on suicidality (score 0–4: 0= absent, 1= feels life is not worth living, 2= wishes he were dead or any thoughts of possible death to self, 3= suicidal ideas or gestures, 4= attempt at suicide [any serious attempt rates 4]) as described previously (Schosser et al., 2012b; Höfer et al., 2013, 2016; Carlberg et al., 2015). The MINI defines a current suicidal risk as presence of at least one of the following suicide related items: having in the past month thought that it would be better being dead or wishing to die (item C1), wanting to harm oneself (item C2), thinking about suicide (item C3), having a suicide plan (item C4), attempting suicide (item C5), and ever attempted suicide at least once in the lifetime (item C6a). Assessment of the item "lifetime history of suicide attempt" was performed using the MINI item C6a, and the item "suicide risk" was assessed using the MINI item C6c (current suicide risk).

As described previously (Souery et al., 2007; Schosser et al., 2012a), treatment response was defined as HAM-D ≤ 17 and remission as HAM-D ≤ 7. The study protocol was approved by ethical committees of all participating centers. Written informed consent was obtained from all participants.

Genotyping

Genomic DNA was extracted from the whole blood using standard phenol-chloroform extraction procedure. Genotypes of 8 *BDNF* SNPs (rs11030096, rs925946, rs10501087, rs6265, rs12273363, rs908867, rs1491850, and rs1491851) were obtained using the Sequenom iPLEX genotyping technology by Cogenics (Morrisville) as previously described (Kocabas et al., 2011).

Statistical Analyses

To test for deviation from Hardy-Weinberg Equilibrium (HWE), the computer program FINETTI (https://ihg.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl) was used to perform exact statistics, and cases and controls were separately considered.

To test for genotypic association with each SNP, a standard chi-square (χ^2) statistic was calculated using PASW Statistics version 18 for MAC. The computer program FINETTI was used to calculate the Cochran-Armitage trend statistic to test for allelic association. UNPHASED version 3.0.10 program (Dudbridge, 2003) was applied using 3-marker slide windows to analyze for haplotypic association. UNPHASED uses the standard Expectation-Maximisation algorithm to estimate haplotypes from genotypes. The rare haplotype frequency threshold was taken as 0.01. UNPHASED uses unconditional logistic regression to perform likelihood ratio tests under a log-linear model of the probability that an allele or haplotype belongs to the case rather than control group. The global null hypothesis is that the odds ratios of all haplotypes are equal between cases and controls. Individual haplotypes were also tested for association by grouping the frequencies of all other haplotypes together. Haploview 4.0 program (Barrett et al., 2005) was used to perform linkage disequilibrium analysis of all SNPs in our sample (data not shown).

To calculate the power of our case-control sample, we used the PS program (Dupont and Plummer, 1990). Assuming a disease allele and/or genotype with a population frequency of 0.3, which confers risk of disease at an odds ratio of 1.3, we have 17.4% or 15.4% power of our MDD sample to detect association at $P = .05$ for suicide risk or lifetime history of suicide attempt, respectively.

All *P* values reported in this study were 2-tailed, and the statistical significance was set at the 0.05 level. Multiple testing corrections were performed by application of the false discovery rate (FDR; Benjamini et al., 2001) to both single-marker and haplotype analyses. In the case of single-marker analyses, it was assumed that 8 independent tests were performed when testing 8 SNPs. Haplotype analyses were corrected for the number of sliding windows used.

Results

We investigated a total of 250 MDD patients (as previously described, Schosser et al., 2012b, Höfer et al., 2013, 2016, Carlberg et al., 2015) (females: 72.8%, males: 27.2%; mean age: 50.97 ± 15.2; Caucasians: 97.2%, Asians: 0.8%, Africans: 1.6%, North Americans: 0.4%; mean HAM-D-17-score: 17.33 ± 7.81) in the context of a European multicenter resistant depression study. The minor allele frequencies (MAFs) of the investigated polymorphisms did not differ between Caucasian (C) and non-Caucasian (NC) patients (rs11030096: MAF-C = 0.46, MAF-NC = 0.50; rs925946: MAF-C = 0.23, MAF-NC = 0.21; rs10501087: MAF-C = 0.20, MAF-NC = 0.14; rs6265: MAF-C = 0.19, MAF-NC = 0.14; rs12273363: MAF-C = 0.16, MAF-NC = 0.14; rs908867: MAF-C = 0.08, MAF-NC = 0.07; rs1491850: MAF-C = 0.40, MAF-NC = 0.43; rs1491851: MAF-C = 0.44, MAF-NC = 0.43).

The primary aim of the current study was to test for association of 8 *BDNF* SNPs with either suicide risk or lifetime history of suicide attempts. We previously reported (Schosser et al., 2012b) that 21.9% of MDD patients with but only 10.7% without a lifetime history of suicide attempts had a family history (first-degree relatives) of suicide death or suicide attempts ($P = .021$).

Suicide risk (yes/no, 59.1% yes) was analyzed as dichotomous trait applying a standard chi-square (χ^2) statistics, finding neither genotypic nor allelic association with any of the tested SNPs. The same holds true for haplotypic association analysis using 3-marker slide windows (data not shown). Gender-specific analyses revealed nonsignificant genotypic ($P = .046$ [FDR $P = .184$]) and allelic ($P = .046$ [FDR $P = .184$]) association between the rs908867 SNP and suicide risk in male MDD subjects (n = 68) after multiple testing correction (FDR *P* values in brackets). Three-marker haplotypes containing this SNP showed significant individual *P* values even after multiple testing correction [FDR $P \leq .036$] but nonsignificant global *P* values (see Table 1). Two different 3-marker haplotypes, G-C-G of rs925946-rs10501087-rs6265 and C-G-T of rs10501087-rs6265-rs12273363, showed significant individual

Table 1. Suicide Risk Males: Haplotypic Association Analyses

SNP	Haplotypes					
rs11030096	T					
rs925946	T	G				
rs10501087	T	C	C			
rs6265		G	G	G		
rs12273363			T	T	T	
rs908867				A	A	A
rs1491850					T	T
rs1491851						T
Global *P*	.326	**.0068 (.014)**	**.014 (.021)**	.313	.228	.650
Individual *P*	.119	**.003 (.009)**	**.003 (.009)**	**.042 (.050)**	.039	.015
Frequency cases/controls	0.31/0.19	0 / 0.11	0 / 0.11	0.12/0.02	0.12/0.02	0.03/0.0

Abbreviations: BDNF, brain-derived neurotrophic factor; HWE, Hardy Weinberg equilibrium SNP, single nucleotide polymorphism.
3-marker slide windows are shown.
False discovery rate (FDR) *P* values after multiple testing correction in brackets. Significant *P* values in bold.

(*P* = .003 in both cases [FDR *P* = .009]) and global (*P* = .0068 and *P* = .014 [FDR *P* = .014 and FDR *P* = .018]) *P* values.

Investigating the lifetime history of suicide attempts (yes/no, 29.8% yes), we found neither single marker nor haplotypic association with any of the tested SNPs. The same holds true for gender-specific analyses (uncorrected individual *P* = .for T-G-T haplotype of rs11030096-rs925946-rs10501087 in females) after multiple testing correction (data not shown).

The secondary aim of the study was to further perform subanalyses to test for association of the 2 suicide phenotypes with either treatment response/nonresponse or remission/nonremission, as described previously (Schosser et al., 2012b). Treatment response was defined as an HAM-D score ≤ 17 after 4 weeks of treatment with antidepressants at adequate dose, and 42.8% of our 250 MDD cases were defined responders (n = 107), whereas 57.2% were defined as nonresponders (n = 143). Remission was defined as an HAM-D score ≤7 after 4 weeks of treatment with antidepressants at adequate dose, thus 13.6% (n = 34) of MDD patients remitted, whereas 86.4% (n = 216) were nonremitters. Association analyses of between *BDNF* SNPs with and treatment response in MDD were previously published (Kocabas et al., 2011).

Regarding suicide risk, there was neither single marker nor haplotypic association with any of the SNPs tested in treatment responders (n = 107, data not shown). In nonresponders (n = 143), a *P* value of 0.036 was found for allelic association with the functional Val66Met polymorphism (rs6265), however, not resisting multiple testing correction and was thus taken as nonsignificant finding. Similarly, neither the genotypic *P* value of the same SNP (*P* = .111) nor the haplotypes including this SNP were significant. The same holds true for the other *BDNF* SNPs tested. Investigating suicide risk in nonremitters (n = 216), neither single marker nor haplotypic association was found (data not shown). However, in remitters (n = 34), the rs10501087 and the functional Val66Met polymorphism (rs6265) showed significant genotypic association with suicide risk (*P* = .009 [FDR *P* = .024] for rs10501087 and *P* = .003 [FDR *P* = .016] for rs6265, FDR *P* values in brackets), as well as significant haplotypic association (Table 2). Of note, MDD patients without suicide risk were out of HWE for both SNPs (*P* = .015 [FDR *P* = .031] for rs10501087 and *P* = .0039 [FDR *P* = .016] for rs6265), but not those with suicide risk.

Discussion

Since mental disorders, especially depression, are present in more of 90% of suicides (Asenault-Lapierre et al., 2004), analyzing suicidal behavior in a cohort of depression cases provides an a priori high-risk group for suicidal behavior that is appropriate for uncovering the genetic contribution to this complex phenotype.

There is evidence that neurotrophins such as BDNF are involved in the neurobiology of suicidal behavior (Deveci et al., 2007; Kim et al., 2007). Associations between the *BDNF* gene and suicidality phenotypes were reported in some (Kim et al., 2008; de Luca et al., 2011; Pregelj et al., 2011; Zai et al., 2012) but not all studies (Zarrilli et al., 2009; Murphy et al., 2011).

In the present study, we further elucidated the impact of *BDNF* gene on suicidal behavior (suicide risk and lifetime history of suicide attempt) in a sample of 250 MDD cases collected in the context of a treatment-resistant depression study and treated with antidepressants at adequate doses for at least 4 weeks. MDD subjects were genotyped for 8 tagging SNPs covering the *BDNF* genomic region, including the functional Val66Met polymorphism. Response, remission, and treatment resistance as well as suicidality information derived from the MINI and the HAM-D were recorded.

Neither *BDNF* single markers nor haplotypes were found to be associated with suicide risk. In gender-specific analyses, a nonsignificant trend towards single-marker association between rs908867 SNP and suicide risk in males was observed after correction for multiple testing. Of note, we also found an association between suicide risk in males and haplotypes containing this SNP, as well as 2 significant adjacent 3-marker haplotypes that resisted multiple testing correction, although the sample size is a limiting factor (68 male subjects). No significant single marker or haplotypic association was identified between *BDNF* SNPs and lifetime history of suicide attempts, neither in the whole sample nor in gender-specific analyses.

Analyzing treatment response phenotypes, no association with suicide risk was found in responders, nonresponders, and nonremitters after multiple testing correction. As for remitters, the functional Val66Met polymorphism (rs6265) as well as rs10501087 SNP showed significant genotypic and haplotypic association with suicide risk. However, although resisting multiple testing correction, this finding should be interpreted with caution, since the sample size in this subgroup is a clear limitation (34 subjects). Therefore, confirmation in larger samples is essential. As for personal lifetime history of suicide attempts and treatment response phenotypes, neither single-marker nor haplotypic association was identified after multiple testing correction.

Table 2. Suicide Risk, Remitters: Haplotypic Association Analyses

SNP	Haplotypes					
rs11030096	T					
rs925946	T	G				
rs10501087	T	C	C			
rs6265		A	A	A		
rs12273363			T	T	C	
rs908867				G	G	A
rs1491850					C	T
rs1491851						T
Global *P*	.341	**.014 (.017)**	**.002 (.004)**	**.035 (.035)**	.254	.840
Individual *P*	.182	**.009 (.014)**	**.002 (.004)**	**.002 (.004)**	.106	.473
Frequency cases/controls	0.13/0.29	0.31/0.06	0.35/0.06	0.35/0.06	0.05/0.21	0.00/0.10

Abbreviations: BDNF, brain-derived neurotrophic factor; HWE, Hardy Weinberg equilibrium SNP, single nucleotide polymorphism.
2- and 3-marker slide windows are shown.
False discovery rate (FDR) *P* values after multiple testing correction in brackets. Significant *P* values in bold.

The current study has several limitations. First, suicide risk and lifetime history of suicide attempts were defined from items of the MINI and HAM-D-17 scale. Neither the instruments nor our treatment-resistant depression study were primarily designed to address suicidality. Another limitation of the current study is that our sample of MDD cases had limited power to identify genes of small effect size that are assumed to be involved in suicidal behavior. This issue especially holds true for our association signal with suicide risk in remitters, but also for our association finding with suicide risk in males. Therefore, it is possible that the reported findings are false positives, and replications in independent samples are essential to confirm or refute their role. Our investigation was performed within a single disorder (MDD), which could be seen as a further limitation of this study. However, focusing on suicidal behaviour within a single disorder allows the distinction between genes relating to suicide per se from those associated with the disorder itself (Schosser et al., 2011).

In conclusion, considering the small sample size, the present findings need to be replicated in larger samples to confirm or refute a role of BDNF in the investigated suicidal behaviour phenotypes.

Conflict of Interest

Raffaella Calati received a grant from FondaMental Foundation, France. Alessandro Serretti is or has been consultant/speaker for: Abbott, Astra, Zeneca, Clinical Data, Boheringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Pfizer, Sanofi, and Servier. Christoph Spindelegger received a travel grant from Lundbeck and speaker's fees from Bristol Myers Squibb. Julien Mendlewicz is a member of the Board of the Lundbeck International Neuroscience Foundation and of the Advisory Board of Servier. Daniel Souery has received grant/research support from GlaxoSmithKline and Lundbeck; has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Lundbeck. Joseph Zohar has received grant/research support from Lundbeck, Servier, and Pfizer; has served as a consultant or on advisory boards for Servier, Pfizer, Solvay, and Actelion; and has served on speakers' bureaus for Lundbeck, GSK, Jazz, and Solvay. Stuart Montgomery has been a consultant or served on advisory boards for: AstraZeneca, Bionevia, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Grunenthal, Intellect Pharma, Johnson & Johnson, Lilly, Lundbeck, Merck, Merz, M's Science, Neurim, Otsuka, Pierre Fabre, Pfizer, Pharmaneuroboost, Richter, Roche, Sanofi, Sepracor, Servier, Shire, Synosis, Takeda, Theracos, Targacept, Transcept, UBC, Sytis, and Wyeth. Siegfried Kasper received grants/research support, consulting fees, and/or honoraria within the last 3 years from Angelini, AOP Orphan Pharmaceuticals AG, AstraZeneca, Eli Lilly, Janssen, KRKA-Pharma, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe, and Servier. All other authors, no conflicts of interest.

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