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ORIGINAL INVESTIGATION

The BDNF Val^{66}Met polymorphism is associated with escitalopram response in depressed patients

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Abstract
Background The brain-derived neurotrophic factor (BDNF) gene is a candidate gene in therapeutic responses to antidepressants. The aim of the study was to determine the effects of BDNF allelic variability on responses to escitalopram treatment at 3 weeks after treatment initiation and at a 6-week endpoint.
Methods We included 187 Caucasian subjects with depression; 153 completed the 6-week study. Clinical evaluation was performed using the Montgomery and Asberg Depression Rating Scale (MADRS) before and after 3–6 weeks of treatment.
Results After 3 weeks of treatment, we saw significantly better treatment responses in the Met carriers and greater antidepressant resistance among the Val/Val homozygotes. Relative to Val/Val homozygous (59.78 %), a significantly greater proportion of subjects Met-carriers (77.94 %) responded to escitalopram treatment (χ^2=5.88, p=0.015). After 6 weeks, we found the same pattern of results but this effect did not reach statistical significance (χ^2=2.07, p=0.15).
Conclusion These findings highlight a significant association between the BDNF valine to methionine substitution (Val^{66}Met) polymorphism and the treatment response to escitalopram in a Caucasian population of severely depressed inpatients.

Keywords Depression BDNF · Escitalopram · SSRI · Treatment-resistant depression

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Introduction

Major depressive disorder (MDD) has a heterogeneous etiology involving both environmental and genetic factors (El-Hage et al. 2009). It has a high prevalence worldwide in both developed and developing countries (Lépine and Briley 2011), and it will present one of the most serious public health problem in the coming years (Murray and Lopez 1997). Selective serotonin reuptake inhibitors (SSRIs) are first-line antidepressants with the most favorable adverse effect profiles, ease of administration, and acceptance by physicians across specialties (Steve et al. 2003). Among SSRIs, escitalopram offers an excellent balance between efficacy and acceptability (Cipriani et al. 2009). Nevertheless, initial treatment with SSRIs often fails to result in full remission from depressive episodes, resulting in more frequent episodes, worsened severity, and major disability (Keith and Matthews 1993; Philip et al. 2010). Factors affecting response to antidepressants are poorly understood, and few biomarkers are available to predict responses to pharmacotherapy (El-Hage et al. 2013; Zarate et al. 2013).

Although peripheral or central biomarkers that predict antidepressant treatment response have been proposed, no genetic predictors of antidepressant response have been

identified to date. Recently, Cattaneo et al. (2013) demonstrated dissociation between predictors and targets of antidepressant response. The authors showed that antidepressant response was associated with changes in genes (e.g., IL-6, FKBP5, BDNF, VGF), but these genes failed to predict antidepressant response. Thus, each of these biomarkers requires further investigation to clarify its role in predicting responses to antidepressants. Among genetic markers, the brain-derived neurotrophic factor (BDNF) gene plays a key role in neurodevelopment and in therapeutic responses to antidepressants (Ibarguen-Vargas et al. 2009). Antidepressants are associated with increase in BDNF expression in brain in animals and in serum in human (Warner-Schmidt and Duman 2006; Munno et al. 2013; Martocchia et al. 2014; Mikoteit et al. 2014). Upregulation of BDNF was observed after chronic, but not acute, administration of different classes of antidepressants (Nibuya et al. 1995; Saarelainen et al. 2003; Adachi et al. 2008; Monteggia et al. 2004). Treatment with antidepressants results in the phosphorylation of G-protein-mediated intracellular factors and stimulates the release of BDNF (Watanabe et al. 2010). The secretion and intercellular trafficking of BDNF are related to a single nucleotide polymorphism (SNP) in the BDNF gene that causes a valine to methionine substitution (Val^{66}Met) (Egan et al. 2003). BDNF is expressed as a precursor proBDNF consisting of an N-terminal prodomain and a C-terminal mature BDNF. The Val^{66}Met substitution located within the prodomain induces a shift in the secondary structure of the region surrounding the substitution (Anastasia et al. 2013). Both the mature BDNF protein and the cleaved prodomain are secreted by neurons. Very interestingly, the secreted prodomain containing the Met substitution promotes growth cone retraction in hippocampal neurons in culture, in contrast to inactive Val66 prodomain (Anastasia et al. 2013). Two recent meta-analyses (Kato and Serretti 2010; Zou et al. 2010b) indicated a better response to antidepressants in Met allele carriers. Considering that BDNF mediates the response to antidepressants (D'Sa and Duman 2002), it is possible that a polymorphism modifying the expression of the BDNF gene or different intracellular signaling pathways could play a major role in therapeutic and pharmacological responses to antidepressants.

Our primary hypothesis was that in depressed patients, therapeutic responses and pharmacological resistance to antidepressants would be associated with the BDNF Val^{66}Met polymorphism. An association of allelic variability with less efficient antidepressant action would add to the body of evidence that BDNF mediates the active mechanism of antidepressants. In a group of patients with major depression, we investigated the impact of BDNF allelic variability on responses to escitalopram treatment at 3 weeks after treatment initiation and at a 6-week endpoint.

Patients and methods

Ethics approval This study was approved by an independent research ethics committee (CCPPRB, Tours, France). The project was registered on the ClinicalTrials.gov website (NCT00308893) and was supervised by a clinical investigations monitoring committee (Inserm CIC 1415). All of the patients consented to participate after being informed of the study's purpose.

Study design and population This prospective, single-site cohort study consisted of 187 unrelated patients with MDD who were 18 years old and older. All of the subjects were inpatients and of Caucasian background. Patients were included if they had a principal diagnosis of MDD (DSM-IV) as assessed by the Mini-International Neuropsychiatric Interview (MINI), a semi-structured clinical interview (Sheehan et al. 1998). A Montgomery and Asberg Depression Rating Scale (MADRS) score of 21 was required to exclude milder cases of MDD, which might be less responsive to medication (Montgomery and Asberg 1979). Patients with any acute medical condition (e.g., hypothyroidism, anemia, etc.) were not included because such conditions could affect treatment response. All of the patients were physically healthy (body mass index=23.1±4.9 kg/m^2) without any abnormalities with regard to blood pressure, electrocardiogram, complete blood count, or electrolyte levels.

Antidepressant treatment The patients were treated with escitalopram for at least 6 weeks at doses ranging from 10 to 30 mg/day (11.7±4.7). During the first 2 weeks, all of the inpatients received a standard 10 mg/day dose of escitalopram. After week 2, the dose was increased if there was no improvement in clinical impressions. Other psychotropic medications were allowed (i.e., a naturalistic approach), but psychotherapy did not commence during the study period. The dosages of antidepressants and other psychotropic medications varied among patients and were not fixed for ethical reasons. Prior to treatment, 89 patients were drug-naïve. Escitalopram tablets were provided in unit-dose blister packs, allowing us to determine patient compliance.

Outcomes The patients' symptoms were studied prospectively for 6 weeks with MADRS ratings as the primary outcome measurement. Illness severity was assessed by MADRS scores before, 3 weeks after, and 6 weeks after the administration of escitalopram. An expert psychiatrist (WEH) who was blinded to genotype performed these ratings. Patients whose MADRS scores decreased by ≥50 % were defined as responders, those whose MADRS scores decreased to 12 or less were defined as remitters, and all others were defined as non-responders.

Genotyping The genetic analysis was performed by an investigator who was blinded to responder status. A 7 mL blood sample was obtained from each subject in the morning on the first day of treatment. Genomic DNA was extracted using the Qiasymphony system (Qiagen S.A.S., France). The rs6265 SNP in the BDNF gene was analyzed by high-resolution melting (HRM) using a LightCycler 480 instrument (Roche Diagnostics, Rotkreuz, Switzerland; software version 1.5). The PCR mixture contained 20 ng DNA, 3 mM $MgCl_2$, 250 nM of each primer (forward 5′-TGGCTGACACTTTCGAACAC-3′; reverse 5′-CCGAACTTTCTGGTCCTCAT-3′; Tm, 65 °C), and 1 U master mix (Roche). HRM analysis of the PCR product was performed by increasing the temperature by 0.02 °C/s from 70 to 95 °C. Two control DNA samples of each of the three genotypes were included in the experiments.

Statistical analysis Binary data are expressed as numbers and percentages, and continuous variables are reported as means and standard deviations. To compare responders and non-responders, the χ^2 test was used for qualitative analysis, and Student's *t* test was used for quantitative analysis. We used univariate logistic regression model to study the association between the treatment response and the polymorphism. The area under a ROC curve (AUC) measured the discrimination quality of the model. In order to control for confounding factors, we used logistic regression models adjusted on age, sex, comorbidities, and concomitant treatment. The level of significance for all of the analyses was 0.05. Statistical analyses were performed using SAS software, version 9.3 (SAS institute, Cary, NC, USA).

Results

Study population Of the 187 inpatients initially recruited, 77 were male and 110 were female (age range 19–86; mean±SD= 45±17). Of these patients, 160 patients completed 3 weeks of the study, and 153 completed the 6-week study (Fig. 1). Study withdrawal occurred when patients withdrew their consent, did not conform to the study protocol, or were lost to follow-up. At baseline, the mean MADRS score was high (34.2±6.6), revealing a sample of severely depressed patients. Comorbidities were evaluated using the MINI, which indicated the presence of suicidal risk in 152 patients and bipolarity in 28 patients (Table 1). At week 3, 108 patients were responders (67.5 %), and at week 6, 129 were responders (84.3 %). There were no age differences between responders and non-responders (week 3, p=0.19; week 6, p=0.46). At week 3, 86 (53.8 %) of the 160 patients achieved remission (MADRS score ≤12), whereas 111 (72.5 %) of the 153 patients achieved remission at week 6.

BNDF Val^{66}Met polymorphism and response The BDNF Val^{66}Met polymorphism was in Hardy-Weinberg equilibrium (χ^2=0.01, p=0.92). The allele frequencies of rs6265 in our sample were 75.3 and 24.7 % for the Val (G) and Met (A) alleles, respectively. The genotypes of these 176 patients were 100 Val/Val, 65 Val/Met, and 11 Met/Met in 58.8, 36.9, and 6.3 %, respectively.

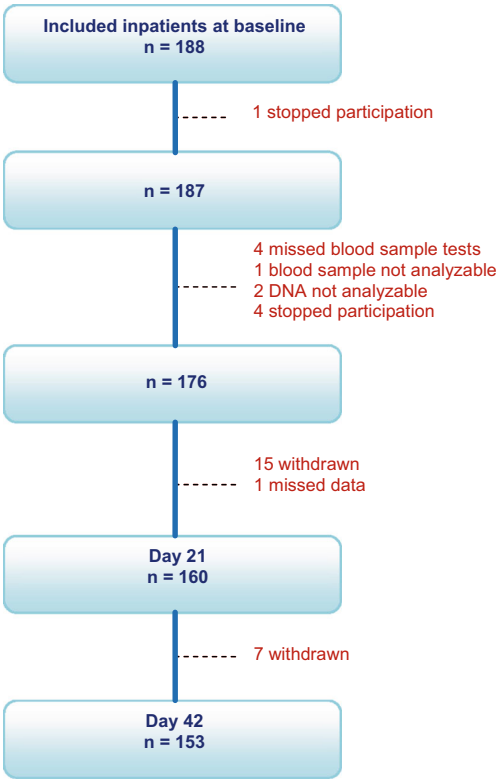

Fig. 1 Clinical trial profile of the study

Table 1 Clinical characteristics of the depressed inpatient sample at inclusion

	N=187
MADRS score, mean±SD	34.2±6.6
MINI 5.0.0	
MDD, current episode, *n* (%)	187 (100.0)
MDD with psychotic features, current episode, *n* (%)	6 (3.2)
Suicidality, previous month, *n* (%)	152 (81.3)
Manic episode, past episode, *n* (%)	28 (15.0)
Panic disorder, current episode, *n* (%)	7 (3.8)
Agoraphobia, current episode, *n* (%)	31 (16.7)
Social anxiety disorder, previous month, *n* (%)	12 (6.5)
Obsessive-compulsive disorder, previous month, *n* (%)	5 (2.7)
PTSD, previous month, *n* (%)	32 (17.2)
Alcohol abuse, previous 12 months, *n* (%)	7 (3.8)
Generalized anxiety disorder, previous 6 months, *n* (%)	26 (14.0)

MDD major depressive disorder, *MINI* Mini-International Neuropsychiatric Interview, *PTSD* posttraumatic stress disorder, *SD* standard deviation

We observed a significant association between the Met allele and response to escitalopram (χ^2=5.88, p=0.015) after 3 weeks. We found a difference in the BDNF Val^{66}Met genotype between responders and non-responders (Table 2). Relative to Val/Val homozygous (59.78 %), a significantly greater proportion of subjects Met carriers (77.94 %) responded to escitalopram treatment. This result remained significant after controlling for treatment compliance (χ^2= 4.96, p=0.026) and for bipolarity (χ^2=4.13, p=0.042). After 6 weeks of escitalopram treatment, this effect did not reach statistical significance (χ^2=2.07, p=0.15). There was no difference in the BDNF Val^{66}Met genotype between remitters and non-remitters (at week 3, p=0.27; at week 6, p=0.16).

To study the predictive value of this polymorphism, we explored the association between the treatment response and the polymorphism. We found a significant association at week 3 (OR=2.38, 95 % CI 1.17–4.83, p=0.016) but the genotype allows only poor discrimination between responders and non-responders (AUC=0.601). The significant association found between treatment response and the polymorphism at week 3 persists after adjustment on age, sex, and comorbidities.

Concomitant treatment During the study period, a total of 105 (56.1 %) of the depressed patients received benzodiazepine prescriptions, while 78 subjects (41.7 %) received hypnotic medications. A total of 21 patients (11.2 %) received mood stabilizers, and 20 subjects (10.7 %) received antipsychotic drugs. Each kind of treatment was included as a covariate in the logistic model to study the association between treatment response and the polymorphism at weeks 3 and 6: none of these treatments could be considered as a confounding factor.

Discussion

We studied the association between the BDNF Val^{66}Met polymorphism and responses to escitalopram in severely depressed patients. The data demonstrate that the BDNF Val^{66}Met polymorphism predicted escitalopram response, controlling for demographic and clinical confounders. After 3 weeks of treatment, we saw significantly better treatment responses in the Met carriers, greater antidepressant resistance among the Val/Val homozygotes, but no difference among the responders. After 6 weeks, we found the same pattern of results at a trend level. One possible explanation could be the decrease in the number of participants. However, different explanations are plausible as response to antidepressants can be driven and also altered at various levels (El-Hage et al. 2013).

This association of the BDNF Val^{66}Met polymorphism with escitalopram response is supported by a previous study showing that Met carriers were more likely to achieve remission than Val/Val homozygotes after 12 weeks of treatment with escitalopram (Alexopoulos et al. 2010). However, contradictory results regarding the BDNF Val^{66}Met polymorphism and antidepressant treatment response have been reported. For instance, Choi et al. (2006) found the same pattern of results with citalopram as reported here, with better responses to citalopram among Met allele carriers. In contrast, different studies have described an association between the Met allele and poorer responses to both venlafaxine and fluoxetine (Chi et al. 2010; Zou et al. 2010a). Yoshimura et al. (2011) found no correlation between the BDNF Val^{66}Met polymorphism and responses to paroxetine and sertraline. Similarly, Domschke et al. (2010) did not observe a major impact of BDNF in antidepressant treatment. In a recent meta-analysis, Zou et al. (2010b) demonstrated an association between the BDNF Val^{66}Met polymorphism and responses to different antidepressants in patients with major depressive disorder. These authors reported that BDNF Val^{66}Met heterozygous patients had a better response rate than Val/Val or Met/Met homozygotes, particularly in Asian populations.

Considering the duration of antidepressant treatment, Xu et al. (2012) suggested that the Met allele of the BDNF

Table 2 BNDF Val^{66}Met polymorphism and response to escitalopram

	Response rate	Val/Val	Met carriers	χ^2	p value
Week 3 (n=160)					
Remitters, n (%)	86 (53.75 %)	46 (50.00 %)	40 (58.82 %)	1.22	0.27
Responders, n (%)	108 (67.50 %)	55 (59.78 %)	53 (77.94 %)	5.88	0.015
Non-responders, n (%)	52 (32.50 %)	37 (40.22 %)	15 (22.06 %)		
Week 6 (n=153)					
Remitters, n (%)	111 (72.55 %)	60 (68.18 %)	51 (78.46 %)	1.98	0.16
Responders, n (%)	129 (84.31 %)	71 (80.68 %)	58 (89.23 %)	2.07	0.15
Non-responders, n (%)	24 (15.69 %)	17 (19.32 %)	7 (10.77 %)		

Remitters, MADRS score ≤12; responders, MADRS scores decreased by ≥50 %; %, the percentages indicate the rate of remission/response/non-response inside the group of allele carriers (Val/Val, Met carriers)

Val^{66}Met polymorphism might predict early responses to SSRI treatment. This suggestion is consistent with the findings of a European study in a Caucasian population, which reported that the Met allele was associated with better responses to 4 weeks of antidepressant treatment (Kocabas et al. 2011). Another study conducted in Taiwanese patients with MDD found that Val/Val homozygotes demonstrated a trend toward better responses to venlafaxine (Chi et al. 2010). In our Caucasian sample, the BDNF Val/Val genotype was associated with poorer responses after 3 and 6 weeks of escitalopram treatment.

The relation between antidepressant treatment and BDNF is not completely clear today. Studies support the idea that antidepressant treatment increases BDNF concentration in several brain regions. In the hippocampus, this increase in BDNF can result from a stimulation of the AMPA receptor pathway (Akinfiresoye and Tizabi 2013). The consequence of this increase could be a modification in activity-dependent neuroplasticity (Zhang et al. 2012). The mechanism by which Met^{66} BDNF is associated with antidepressant responses is unknown. Studies on other pathologies such as schizophrenia or hyperactivity disorder also reported a link between the Val^{66}Met substitution in BDNF and response to treatments (Nikolac Perkovic et al. 2014; Ramos-Quiroga et al. 2014). The Val^{66}Met SNP is located in the prodomain of the precursor proBDNF. It has been proposed that Met^{66} BDNF acts by modifying the activity-dependent release of the mature form of BDNF and its prodomain, both of which result in changes in synaptic plasticity (Chen et al. 2004). Indeed, a recent study reported that the Met^{66} prodomain, but not the Val^{66} prodomain, modified neuronal morphology, thereby inducing growth cone retraction (Anastasia et al. 2013).

Our study sample had satisfactory characteristics that were representative of the general population. Indeed, the allele frequencies of rs6265 in our sample were similar to those reported in a French control population (75.2 and 24.8 % for the G and A alleles, respectively) (Tabagh et al. 2010). Our sample was also representative of the depressed population, with a higher proportion of women (58.8 %). Moreover, the levels of response to antidepressant treatment were similar to that reported in the literature (Lin et al. 2013; Uher et al. 2011), with 67.5 % at 3 weeks and 84.3 % after 6 weeks of escitalopram treatment.

Nevertheless, this study had several limitations. First, this was a naturalistic, prospective, flexibly designed, uncontrolled, open study. Second, the present sample had limited power. Third, the study lasted only 6 weeks, so we cannot exclude the possibility that the effects of ongoing antidepressant treatment emerged later. Fourth, this study did not include measurements of HPA axis activity, cortisol, or plasma BDNF levels. Finally, this was a naturalistic study and limiting use of concomitant medications was not applied.

In conclusion, these findings highlight a significant association between the BDNF Val^{66}Met polymorphism and the treatment response to escitalopram in a Caucasian population of severely depressed inpatients. In response to escitalopram treatment of a major depressive episode, we found more non-responders among Val/Val homozygotes compared to Met carriers. Replication studies are needed to explore the relationship in a larger sample.

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Author contributions WEH, CB, and VC were involved in the design of the study and contributed to the interpretation of the current analysis. PG helped to develop the design of the study. WEH, PG, and VC were involved in data collection and performing experiments. YIV, PV, and CRA analyzed the genetic samples. JL and PV helped to draft the analysis plan of the current study and assisted in the creation of the initial draft of the manuscript. All authors contributed revisions to subsequent drafts of the manuscript and have contributed to and approved the final manuscript.

Conflict of interest The authors declare no conflict of interest.

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