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ARTICLE

BDNF gene polymorphism, cognition and symptom severity in a Brazilian population-based sample of first-episode psychosis subjects

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Abstract
Objective: To investigate the influence of brain-derived neurotrophic factor (BDNF) gene variations on cognitive performance and clinical symptomatology in first-episode psychosis (FEP). *Methods*: We performed BDNF val66met variant genotyping, cognitive testing (verbal fluency and digit spans) and assessments of symptom severity (as assessed with the PANSS) in a population-based sample of FEP patients (77 with schizophreniform psychosis and 53 with affective psychoses) and 191 neighboring healthy controls. *Results*: There was no difference in the proportion of *Met al*lele carriers between FEP patients and controls, and no significant influence of BDNF genotype on cognitive test scores in either of the psychosis groups. A decreased severity of negative symptoms was found in FEP subjects that carried a *Met al*lele, and this finding reached significance for the subgroup with affective psychoses ($p < 0.01$, ANOVA). *Conclusions*: These results suggest that, in FEP, the BDNF gene Val66Met polymorphism does not exert a pervasive influence on cognitive functioning but may modulate the severity of negative symptoms.

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Introduction

Brain derived neurotrophic factor (BDNF) is a neurotrophin of key relevance in the central nervous system, being crucial for neurodevelopment, the formation of neural networks and neuronal plasticity. A functional polymorphism (rs6265) in the human BDNF gene producing an amino acid substitution of valine to methionine at codon 66 (Val66Met) has been shown to alter the intracellular trafficking and processing of BDNF, having as consequence an impaired secretion of BDNF.[1] Some studies suggest that the presence of the M*et al*lele in healthy individuals is associated with cognitive deficits,[2,3] although this has not been confirmed in recent meta-analytic investigations.[4]

Several authors have proposed that BDNF expression may influence the pathogenesis of schizophrenia and mood disorders.[5-11] An association between the Met BDNF allele and impaired cognitive performance has been found in individuals with mood disorders[12] or schizophrenia,[13] although there has been no clear demonstration of an excess of Met BDNF allele carriers in patients with those mental disorders relative to healthy controls.[10,14] On the other hand, some studies have reported an over-transmission of the Val allele to affected offspring both in schizophrenia[15] and bipolar disorder patients,[16] suggesting that the presence of the M*et al*lele may have a protective effect for individuals at risk for those psychiatric disorders. Furthermore, Chang et al.[17] have shown that the M*et al*lele may be associated with reduced severity of negative symptoms of schizophrenia. Taken together, these findings hint at the possibility that the Val66Met BDNF polymorphism may exert an important influence on the variability of specific clinical features of schizophrenia and mood disorders.[10]

We have previously detected structural brain deficits as assessed with morphometric magnetic resonance imaging[18] and cognitive impairment[19,20] in a population-based sample of patients presenting a first episode of psychosis (FEP) compared to environmentally-matched healthy controls, and demonstrated that brain volume deficits and cognitive performance were significantly inter-related in FEP subjects.[21] In the present study, we investigated the influence of the Val66Met polymorphism on cognitive performance and clinical symptomatology in a larger group of FEP sample, which substantially overlapped with the FEP sample investigated in our previous studies. As we aimed to investigate the relationship between the Val66Met BDNF polymorphism and clinical/cognitive features of psychosis, it was of critical importance to assess patients with a recent onset of illness, in order to minimize the confounding influence of continued medication use and effects of illness chronicity on the expression of symptoms.

Methods

The psychosis group (age 18-64) was drawn from a sample of 200 patients with FEP identified for an epidemiological study on the incidence of psychotic disorders in a circumscribed area of São Paulo, Brazil.[22] Subjects were assessed with the Structured Interview for DSM-IV,[23] the Positive and Negative Syndrome Scale (PANSS),[24] the Alcohol Use Disorders Identification Test,[25] the South Westminster Questionnaire[26] and Annett's handedness questionnaire.[27]

In order to obtain a population-based psychosis-free sample of controls, next-door neighbors were contacted and screened to exclude the presence of psychotic symptoms using the Psychosis Screening Questionnaire.[28] The additional exclusion criteria outlined above also applied to the control group. Further details on the selection and recruitment of FEP and control subjects have been described previously.[19,22]

A short neuropsychological battery was applied both to FEP patients and controls,[19] including the forward and backward digit span tests from the Wechsler Memory Scale – Third Edition,[29] and the Controlled Oral Word Association Test[30] to measure verbal fluency. The G196A/Val66Met (rs 6265) polymorphism in BDNF gene was genotyped according to the methods of Egan et al.[3]

Between-group comparisons were conducted using Pearson's chi-square test for categorical variables and univariate ANOVAs for continuous variables using the Statistical Package for Social Sciences (SPSS), and the level of significance adopted was $p < 0.05$.

The study was approved by local ethics committees, and all subjects gave informed written consent.

Results

From the original sample of 200 FEP patients and 400 controls enrolled in the epidemiological study (Menezes *et al.*[27]), the total number of individuals who underwent BDNF genotyping was 130 FEP patients (77 with schizophreniform psychosis and 53 with affective psychoses) and 191 controls. The remaining subjects were excluded either because they were recruited for the overall project before we were able to start the molecular genetics arm of the investigation, or because they refused to participate. The FEP group recruited for the present study was representative of the overall FEP sample, as there were no statistical differences between the FEP patients who underwent BDNF genotyping and those who did not in regard to gender distribution ($p = 0.17$), handedness ($p = 0.41$), schooling ($p = 0.10$), alcohol ($p = 0.37$) and/or drug abuse ($p = 0.51$), except for a marginal difference in age ($p = 0.02$, with mean ages of genotyped and non-genotyped cases equal to 30.98 and 34.76, respectively). For the purposes of the following analyses, Met/Met homozygous and Val/Met heterozygous individuals were grouped together as Met carriers.

Table 1 shows the demographic, clinical and genotype characteristics of the subjects in the FEP and healthy control groups, divided by their BDNF Val66Met polymorphism profile. Genotype distributions had no deviation from Hardy Weinberg equilibrium in either of the two groups. There was no significant difference in the frequency of BDNF alleles between FEP patients and controls, or between the different subtypes of psychosis (schizophreniform *versus* affective psychoses) (Table 1). No interaction was found between genotypes and age, handedness, alcohol abuse, drug abuse, schooling, mean age of disease onset, use of benzodiazepines or use of antipsychotics either for the whole group or when the healthy controls and patients were examined separately, except for a higher presence of Met carriers among healthy women (Table 1). Separate analyses stratified by gender demonstrated no significant influence of this parameter on cognitive and clinical assessment in any group (data not shown). There were significant differences in schooling, and in the prevalence of alcohol and drug abuse between FEP and controls subjects, but no significant differences were seen in regard to sex, age and handedness (Table 1).

Table 1 Demographic features in relation to diagnosis, BDNF genotype and their interaction

	Mean (SD)								
				Diagnostic X Genotype interaction					
	Main effect of diagnosis			Controls			Patients		
	Controls N = 191	Patients with FEP N = 130	p value	VAL/VAL N = 142	VAL/MET N = 44 or MET/MET N = 5	p value	VAL/VAL N = 88	VAL/MET N = 37 or MET/MET N = 5	p value
BDNF VAL66MET genotype VAL/VAL (%) VAL/MET OR MET/MET (%)	74.3 25.7	67.7 32.3	0.19	NA	NA		NA	NA	
Age; years	33.51 (11.58)	31.12 (10.88)	0.06	33.05 (12.13)	34.86 (9.72)	0.34	30.81 (10.47)	31.79 (11.78)	0.63
Gender Female (%) Male (%)	58.6 41.4	52.3 47.7	0.26	53.5 46.5	73.5 26.5	0.02	51.1 48.9	54.8 45.2	0.70
Handedness Right (%) Left(%)	92.7 6.3	94.6 5.4	0.47	91.5 7	95.9 4.1	0.53	96.6 3.4	90.5 9.5	0.15
Schooling[a] Less than 8 years (%) 9 years or more (%)	35.6 64.4	50 50	0.01	39.4 60.6	24.5 75.5	0.06	51.1 48.9	47.6 52.4	0.71
Alcohol abuse/ Dependence Yes (%) No (%)	9.9 90.1	20 80	0.01	9.9 90.1	89.8 10.2	0.94	20.5 79.5	19 81	0.85
Drug abuse/ Dependence Yes (%) No (%)	2.1 97.9	16.2 83.8	< 0.001	2.8 97.2	0 100	0.23	12.5 87.5	23.8 76.2	0.10
Mean age of disease onset; years	NA	29.38 (11.28)	NA	NA	NA	NA	28.99 (11.07)	30.21 (11.79)	0.56
Benzodiazepine use Yes (%) No (%)	NA	13.7 86.3	NA	NA	NA	NA	12 88	17.1 82.9	0.44
Use of antipsychotics Typical (%) Atypical (%) Both (%) None (%)	NA	60.5 16.9 16.1 6.5	NA	NA	NA	NA	65.1 15.7 14.5 4.8	51.2 19.5 19.5 9.8	0.46

Group differences in categorical variables were assessed with x^2 tests, while differences in continuous variables were investigated using ANOVA. [a]Number of years of formal education.
SD: standard deviation; FEP: first-episode psychosis; NA: not applicable; VAL: valine; MET: methionine.

Table 2 shows the relationship between BDNF Val66Met genotype and cognitive variables in FEP patients and controls. No genotype x diagnosis interaction was found on cognitive performance. When comparisons were performed using the separate categories for schizophreniform and affective psychoses, there were again no significant differences for the three cognitive tests between the subgroups divided according to the Val66Met genotype (Table 2).

Table 3 summarizes the pattern of relationship between psychopathological assessments in FEP patients and BDNF Val66met genotype. FEP patients who had the *Met al*lele showed reduced negative symptomatology. The subgroup analyses conducted using the separate categories for schizophreniform and affective psychoses indicated that such difference was evident for the mood disorder subgroup but not for the schizophreniform psychosis subgroup (Table 3).

Discussion

In the present study, we found no significant association of the BDNF Val66Met polymorphism (rs 6265) either with the overall diagnosis of FEP, or with specific diagnostic categories of schizophreniform and affective psychoses. These results are consistent with the findings of previous studies that used similar methods and included samples of size similar to ours or larger.[14,31]

Table 2A Comparison of cognitive test scores of first-episode psychosis patients and controls divided according to BDNF Val66Met genotyping

Cognitive Mean Scores (SD)									
				Diagnostic X Genotype interaction					
	Main effect of diagnosis			Controls			Patients		
	Controls N = 191	Patients with FEP N = 130	p value	VAL/VAL N = 142	VAL/MET N = 44 or MET/MET N = 5	p value	VAL/VAL N = 88	VAL/MET N = 37 or MET/MET N = 5	p value
Verbal Fluency	25.76(10.65)	23.19(10.61)	0.03	24.92(10.58)	28.20 (10.59)	0.06	22.51(10.79)	24.62(10.20)	0.29
Digit span forward	5.32 (2.43)	4.49 (2.00)	0.001	5.18(2.26)	5.73(2.87)	0.17	4.41 (1.97)	4.67 (2.07)	0.49
Digit span backward	4.89(2.04)	3.95(2.01)	0.001	4.77(2.01)	5.22(2.11)	0.18	4.02(2)	3.81(2.05)	0.57

Table 2B Comparison of cognitive test scores of first-episode psychosis diagnostic subcategories and controls divided according to BDNF Val66Met genotyping

Cognitive Mean Scores (SD)									
				Subdiagnosis of FEP X Genotype interaction					
	Main effect of subdiagnosis			Non-affective psychosis			Affective psychosis		
	Non-affective psychosis N = 77	Affective psychosis N = 53	p value	VALVAL N = 55	VAL/MET N = 20 or MET/MET N = 2	p value	VAL/VAL N = 33	VAL/MET N = 18 MET/MET N = 2	p value
Digit span forward	4.56(2.16)	4.40(1.75)	0.65	4.60(2.18)	4.45(2.15)	0.79	4.09(1.52)	4.90(2.00)	0.10
Digit span backward	3.94(2.91)	3.98(1.73)	0.90	4.15(2.11)	3.41(2.34)	0.18	3.82(1.81)	4.25(1.61)	0.39
Verbal fluency	22.64(9.77)	24.00(11.78)	0.47	22.42(9.26)	23.18(11.13)	0.76	22.67(13.10)	26.20(9.09)	0.29

Group differences were investigated using ANOVA. SD: standard deviation; FEP: first-episode psychosis; NA: not applicable; VAL: valine; MET: methionine.

Table 3 Comparison of PANSS scores of first-episode psychosis diagnostic subcategories divided according to BDNF Val66Met genotyping

PANSS Mean Scores (SD)									
				Subtype of FEP X Genotype interaction					
	Main effect of subdiagnosis			Non-affective psychosis			Affective psychosis		
	Non-affective psychosis N = 77	Affective psychosis N = 53	p value	VAL N = 55	VAL/MET N = 20 or MET/MET N = 2	p value	VAL N = 33	VAL/MET N = 18 MET/MET N = 2	p value
Total symptom scores	46.13 (13.59)	42.66 (10.52)	0.12	46.87 (13.78)	44.27 (13.26)	0.45	44.97 (11.8)	38.85 (6.63)	0.04
Positive symptom scores	10.56 (4.13)	10.21 (4.73)	0.65	10.40 (4.02)	10.95 (4.44)	0.59	10.67 (5.25)	9.45 (3.72)	0.37
Negative symptom scores	12.65 (5.62)	10.23 (4.10)	0.01	13.16 (5.96)	11.36 (4.57)	0.20	11.33 (4.65)	8.40 (1.98)	0.01
General symptom scores	22.92 (6.48)	22.23 (4.46)	0.50	23.31 (6.90)	21.95 (5.34)	0.41	22.97 (4.81)	21 (3.627)	0.12

Group differences were investigated using ANOVA. SD: standard deviation; FEP: first-episode psychosis; NA: not applicable; VAL: valine; MET: methionine.

Also, even though previous studies have suggested genetic influences on cognitive performance in FEP,[32,33] it was found no interaction between BDNF genotype and general cognitive performance in FEP. These results are in contrast with our previous findings of cognitive impairment and interrelated structural brain abnormalities in a FEP sample that very substantially overlapped with the FEP group studied herein.[18,21] Taken together, the findings from our companion studies argue against a view that structural brain abnormalities and associated cognitive deficits would be substantially influenced by BDNF gene polymorphisms.

It is important to note that, due to the need to devise a neuropsychological battery easily applicable in the context of a large epidemiological study, it was only tested a limited number of cognitive functions in the current study. Perhaps the inclusion of other cognitive tests could reveal a

significant influence of BDNF genotype on cognition in FEP. Consistent with this possibility, previous investigations of patients with schizophrenia have suggested that BDNF polymorphisms may exert a significant influence specifically on their visuospatial[13] and attentional performance,[34] but not on other cognitive abilities. Also, regardless of diagnostic status, such investigations[13] have suggested that the BDNF Met variant significantly influences medial temporal-related verbal episodic memory performance, which was not evaluated in the current study. Finally, one has also to consider that other genes may exert a greater influence on the cognitive indices evaluated in our FEP sample than the BDNF gene evaluated in the current study.

In contrast with the above non-significant findings, our analyses revealed a significant association between decreased severity of negative symptoms and the presence of the M*et a*llele in subjects with FEP subjects. Previous studies have demonstrated a similar relationship specifically for subjects with schizophrenia.[17] When we carried out separate analyses for diagnostic subgroups in the present study, the severity of negative symptoms was reduced in Met carriers with schizophrenia, but this finding did not attain statistical significance. Conversely, the relationship between the Met66 variant and negative symptom scores in the sample of affective psychoses subjects did reach statistical significance. Negative symptoms in affective psychoses may not remain stable over time, and do not persist during the post-acute phase of such disorders.[35,36] However, negative symptoms do occur in the acute phase of affective psychoses, and our results suggest that BDNF expression may play an important role on the emergence and severity of these symptoms in such patients. The presence of the Met66 variant is known to decrease BDNF expression,[3] and this could lead to a decrement in negative symptom severity by reducing the expression of the D3R.[37,38] This dopamine receptor subtype has been found to be reduced in patients presenting psychotic episodes, but it is conversely over-expressed in the presence of negative symptoms.[39] The presence of a M*et a*llele might modify the synaptic strength of pathways implicated in the emergence of negative symptoms in affective FEP.

One other significant finding in the present study is the higher prevalence of Met carriers among healthy women. Gender differences in genotype distribution have been reported before.[40] However, in our study, separate analyses stratified by gender demonstrated no influence of this parameter on cognitive and clinical ratings in any of the groups.

A number of limitations must be taken into account when interpreting our results. First and foremost, the size of our sample is relatively modest, thus increasing the risk of both type I and II errors. Second, even though statistical analyses showed that the M*et a*llele was independently related to a decreased severity of negative symptoms, the majority of our patients received antipsychotics, which may lead to motor side effects that mimic negative symptoms. Third, we have evaluated psychopathology and cognitive performance at a single point in time. Therefore, the effect of BDNF genotype on clinical symptoms may be transient. Fourth, we were not able to collect data on serum BDNF levels,[11,34] and this prevented us from investigating correlations between plasma BDNF levels and cognitive symptom; this would have added relevant information on the interplay between activity-dependent BDNF secretion, genotype and clinical features of psychosis.

In summary, our findings suggest that in FEP, the BDNF gene Val66Met polymorphism does not have a pervasive influence on cognitive functioning but may modulate the severity of negative symptoms. Further longitudinal studies of FEP involving more comprehensive cognitive batteries and serial evaluations of clinical symptoms in larger samples are warranted, as well as studies using probes to evaluate the interplay between BDNF expression and BDNF-regulated neurotransmitter systems that are relevant to the emergence of psychosis symptoms, such as the dopaminergic system.

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Disclosures

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** Modest*
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