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Preliminary Communication

Does BDNF genotype influence creative output in bipolar I manic patients?

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ABSTRACT

Introduction: Creativity is a complex human ability influenced by affective and cognitive components but little is known about its underlying neurobiology. Bipolar Disorder (BD) is highly prevalent among creative individuals. Brain-derived neurotrophic factor (BDNF) is the most widely distributed neurotrophic factor, and has been implicated in the pathophysiology of BD. In contrast to the better functioning of the BDNF polymorphism (Val^{66}Met) Val *allele*, the Met *allele* decreases BDNF transport and has been associated with worsened performance on several cognitive domains in euthymic BD subjects and controls. We hypothesized that the Val *allele* is associated with increased creativity in bipolar disorder.
Materials and methods: Sixty-six subjects with BD (41 in manic and 25 in depressive episodes) and 78 healthy volunteers were genotyped for BDNF Val^{66}Met and tested for creativity using the Barrow Welsh Art Scale (BWAS) and neuropsychological tests.
Results: Manic patients with the Val *allele* (Met−) had higher BWAS scores than Met+ carriers. This relationship was not observed among patients in depressive episodes or among control subjects. BDNF Met *allele* status showed no association with cognitive function in any of the groups.
Conclusion: As postulated, these findings suggest that the better functioning *allele* of BDNF may selectively facilitate creative thinking in subjects with manic episodes, but not in controls or depressives. Further studies exploring the role of BDNF in the neurobiology of creativity in BD and in euthymic phases are warranted.

1. Introduction

Previous studies have suggested an increased prevalence of bipolar disorder (BD) among creative individuals (Akiskal et al., 2005; Andreasen and Glick, 1988; Jamison, 1994). In this sense, creativity has been studied as both a trait (Akiskal et al., 2005) and recently, as a state variable in BD (Soeiro de Souza et al., 2011). The neurobiological of creativity remains unknown. Furthermore subtle cognitive alterations associated with BD episodes can co-occur with alterations in creativity (Soeiro de Souza et al., 2011).

Neurotrophic factors mediate neuronal differentiation, proliferation, synaptogenesis, learning, memory and cell survival (Poo, 2001). Over the last decade, neurotrophins have been associated with cognitive function (Egan et al., 2003; Hariri et al., 2003; Woo and Lu, 2006) and potentially linked to the pathophysiology of depression and BD (Post, 2007). Brain-derived neurotrophic factor (BDNF) is one of the most abundant neurotrophic factors (Zigova et al., 1998) and expressed throughout the brain, particularly in the hippocampus and prefrontal cortex (PFC) (Pezawas et al., 2004), exerting long-term effects on neuronal survival, migration, and growth (Pang and Lu, 2004).

Importantly, a single nucleotide polymorphism (SNP) in the BDNF gene (rs6265) produces a Val to Met amino acid

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substitution at codon 66 (Val^{66}Met) in the pro-BDNF sequence, affecting the activity-dependent secretion of BDNF (Egan et al., 2003). Regarding functional effects, depolarization-dependent secretion of BDNF is impaired by the presence of Met *allele* (Met+) (Egan et al., 2003). The Met *allele* is also associated with deficient intracellular transport of BDNF to dendrites and reduced magnitude of long term potentiation (LTP) (Kleim et al., 2006). This *allele* has also been associated with cognitive deficits in patients with BD (Rybakowski et al., 2003; Savitz et al., 2006) and schizophrenia (Rybakowski et al., 2006), as well as in healthy controls (Hariri et al., 2003; Pezawas et al., 2004).

Previous studies have shown that BDNF Met+ carriers have impaired performance in memory (Egan et al., 2003; Hariri et al., 2003), executive function (Rybakowski et al., 2003) and intelligence (Tsai et al., 2004). Few studies have evaluated the potential role of BDNF in regulating cognition in BD. Some studies have reported better executive function among BD euthymic medicated BDNF Met− patients (Rybakowski et al., 2003), which was subsequently not confirmed (Rybakowski et al., 2006; Tramontina et al., 2009). Serum BDNF levels are lower in both mania (Machado-Vieira et al., 2007) and depression (Cunha et al., 2006) and tend to be associated with episode severity. Recent meta-analyses support these observations and suggest that levels return to normal in euthymia, but not in all instances (Monteleone et al., 2008). Also, BDNF levels have been shown to increase after lithium treatment in mania (de Sousa et al., 2011). To the best of our knowledge there are no studies evaluating the effects of BDNF SNPs on cognitive function during mood episodes in BD patients or medication-free subjects.

High levels of creativity are observed in mania along with one of its cardinal features namely, increases in word production and associativity (loose associations) (Goodwin and Jamison, 2007). Based on the link of BD to increased creativity, we postulated that the better functioning Val *allele* of BDNF (Met−), and its related increases in the magnitude of LTP, is associated with greater in creativity in patients with BD compared to those with the less well functioning Met+ *allele*. In addition this study sought to further explore the previously reported associations of the Met+ *allele* to poorer cognitive functioning in a variety of medication-free patients and normal controls. This approach would allow the discrimination of the possible contributions of cognitive functioning to the putative relationship of BDNF with creativity.

2. Material and methods

The patients sample included sixty-six medication-free individuals with BD I (44 females), aged between 18 and 35 years old and currently in manic (n = 41) or depressive (n = 25) episodes according to DSM-IV TR criteria (DSM-IV, 2000). All patients were participants in the *LICAVAL* (*lithium plus carbamazepine versus lithium plus valproate*) clinical trial (Campos et al., 2010) and were evaluated immediately after a four week wash-out period for antidepressants, mood stabilizers or antipsychotics, and after eight weeks for *depot* medications. Diagnosis was determined by trained psychiatrists using the Structured Clinical Interview (SCID-I) (First et al., 1997) for DSM-IV TR (DSM-IV, 2000). The Young Mania Rating Scale (YMRS) (Young et al., 1978), and the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) were used to evaluate the severity of symptoms. The cut-off point for mania was YMRS ≥ 12 and for depression was MARDS ≥ 15. Mean YMRS was 17.41 (±6.39) in mania, while MADRS mean score was 24.28 (±7.17) for depression. Subjects with neurological disorders, previous head trauma, any illness requiring medical intervention, current substance abuse, or that had undergone electroconvulsive therapy in the preceding six months, were excluded.

The control group comprised of healthy subjects (n = 78), age 18–35 years, recruited at the University of São Paulo (mostly medical students). Inclusion criteria for controls included absence of any psychiatric diagnosis (present or past) according to the evaluation by trained psychiatrists using The Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Also, subjects with a positive family history of mood or psychotic disorders in first degree relatives, use of any psychopharmacological agent, and/or substance abuse over the last three months, were excluded.

Neurocognitive and creativity tests were carried out under standard conditions and scored by two trained neuropsychologists. Given the known high correlation between intelligence and creativity (Cropley and Field, 1969), it was necessary to exclude a potential association between creativity and SNPs that could merely reflect a relationship to intelligence. The neurocognitive battery was designed to assess the following domains: *Attention*: Wechsler Adult Intelligence Scale III (WAIS-III) subtest Digit Span (WAIS-DS), Trail Making Test-part A (TMT-A), Stroop Color-Word Test (SCWT); *Verbal Memory*: Wechsler Memory Scale subtest-Logical Memory (WMS-LM) immediate (1) and delayed (2); Visual Memory: Rey-Osterrieth Complex Figure Test (RCFT) delayed recall; *Visuospatial Function*: Wechsler Abbreviated Scale of Intelligence (WASI)-Block Design (WASI-BD), RCFTcopy; *Language*: Controlled Oral Word Association Test (FAS), WASI-Vocabulary subtest (WASI-V); *Psychomotor Speed*: Trail Making Test-part A (TMT-A); *Executive Function*: Letter-Number Sequence (WAIS-LNS), WAIS-DS, SCWT, TMT-B, WASI Similarities (WASI-S), WASI Matrix Reasoning (WASI-MR), RCFT copy, WCST (Wisconsin Card Sorting Test)-Conceptual level responses (WCST-CONC), Perseverative Responses (WCST-PR), Failure to Maintain Set (WCST-FMS), Corrected Categories (WCST-CC), Errors (WCST-E), Non-Perseverative Errors (WCST-NP), Perseverative Errors (WCST-P); *Intelligence*: WASI: Total Intelligence Quotient (IQ), Estimated IQ (EIQ), Execution IQ (EXIQ), Verbal IQ (VIQ).These are well-established and validated tests (Lezak, 2004; Strauss et al., 2006; Wechsler, 1981, 1999). Higher scores indicate better performance, with the exception of the SCWT, TMT, WCST-PR, WCST-E, WCST-NP and WCST-P.

Creativity was assessed using the Barrow Welsh Art Scale (BWAS). The BWAS (Barron, 1963) is an empirically-derived metric consisting of 86 black and white images that individuals rate as “like” or “dislike”, with higher scores reflecting preference for more asymmetrical and complex figures over more symmetrical and simple figures. Preference for more asymmetrical and complex figures is higher among artists than non-artists according to BWAS scores (Gough and Hall, 1996). The BWAS scale may also reflect cognitive/affective contributions to creativity, as it involves not only visual

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processing, but also affective processing (like or dislike). Indeed, BWAS scores have been linked not only to creativity as measured by other means but also to emotionality (King and Curtis, 1991).

The research ethics board of the *Hospital das Clínicas of the University of São Paulo* approved this study. Written informed consent was obtained from all subjects.

2.1. Genotyping

DNA was extracted from peripheral blood according to the salting-out protocol (Laitinen et al., 1994) and then genotyped for BDNF rs6265 (Val^{66}Met) using real-time PCR allelic discrimination. PCR amplification for rs6265 was performed in 5 μl reactions with 5 ng of template DNA, 1× TaqMan Universal Master Mix (Applied Biosystems, Foster City, CA), 1× each primer and probe assay, and H_2O. Thermal cycling consisted of initial denaturation for10 min at 95 °C, followed by 40 cycles of denaturation at 95 °C for 15 s and annealing at 60 °C for 1 min. The *allele*-detection process and allelic discrimination were performed for 1 min at 60 °C on a 7500 Real-Time System (Applied Biosystems, Foster City, CA).

2.2. Statistical analyses

Subjects were grouped according to BDNF genotype into Met carriers (Met+) {Val^{66}Met and Met^{66}Met} and non-carriers (Met−) {Val^{66}Val} and compared using the Chi-square test for categorical data (*e.g.* gender), and Student's *t*-test for continuous data (*e.g.* BWAS, age, IQ). BWAS mean scores (total, like, dislike) were compared according to BDNF *allele* Met status using the *t*-test. Scores in mania, depression and control groups were compared for BDNF Met+ and Met−. The influence of IQ, age, education, gender, YMRS and MADRS on the results was assessed by backward regression analysis. All statistical analyses were carried out using version 18.0 of the PASW statistics software (SPSS Inc., Chicago, Illinois).

3. Results

BDNF rs6265 genotype distribution in the experimental samples of men and women were in accordance with the Hardy–Weinberg equilibrium ($p=0.65$) indicating that the samples were representative. Allelic frequency was 72.7% Met− and 27.3% Met+ in the patient groups *versus* 52.56% Met− and 47.44% Met+ in the control group. Thus, Met carrier prevalence was higher in the control group (n=37) compared to the BD group (n=18) ($p=0.01$).

No significant differences in sociodemographics were observed between genotypes or *allele* Met in terms of age, gender or years of schooling in the patient or control groups (Table 1).

In agreement with previous findings (Soeiro de Souza et al., 2011), subjects in mania had higher BWAS total scores than depressives (t=3.67 $p=0.001$). Manic patients had a mean BWAS total score of 27.02 (±11.38) while depressed patients' mean score was 16.76 (±10.97).

The BD group (mania+depression) subjects had worse cognitive performance than controls across all tests from the battery, with the exception of the WCST-FMS ($p=0.35$) in which no difference was observed. The manic patient group had lower scores on the WCST-CONC ($p=0.014$) and higher scores on the WCST-PR ($p=0.011$), WCST-ERRORS ($p=0.006$) and WCST-P ($p=0.007$) when compared to the depressed group, indicating worse executive function.

3.1. Manic (but not depressive or control) BDNF Met− carriers had higher BWAS scores than Met+ carriers

As hypothesized, BDNF Val^{66}Val (Met−) was associated with high creativity scores on the BWAS. However, this relationship was not observed among patients in the depressive phase or among controls.

Analysis of all subjects with BD (mania+depression) continued to show that BDNF Met− subjects (mean 25.14±12.59) had higher BWAS total scores (t=2.45; $p=0.019$) compared to Met+ carriers (mean 17.88±9.89) (Table 2). In controls, no difference in BWAS scores was found between Met+ (mean 27±13.57) and Met− carriers (mean 24.88±12.75) (t=0.69; $p=0.48$) (Table 2).

BDNF Met− carriers in manic episodes had higher BWAS total scores (30.03±10.72), then Met+ carriers (18.81±9.15), (t=3.31; $p=0.003$) (Fig. 1). Moreover, BWAS dislike scores were higher in BDNF Met− carriers (15.41±9.89) in manic episode (t=2.55; $p=0.024$) compared to Met+ carriers (7.33±5.95). No differences in BWAS scores (total, like, dislike) were observed between Met+ and Met− in patients with depressive episodes (Table 3). Backward linear

Table 1
Sociodemographic variables and symptoms scales in patients and controls according to BDNF rs6265 genotype.

	Bipolar disorder (N=66)				Between-groups differences[a]	Healthy controls (N=78)				Between-groups differences[a]
	Met+ (N=18)		Met− (N=48)			Met+ (N=37)		Met− (N=41)		
	Mean	SD	Mean	SD	*Sig. (2-tailed)*	Mean	SD	Mean	SD	*Sig. (2-tailed)*
Age (years)	29	5.70	27.60	4.90	0.36	23.81	3.93	23.34	3.20	0.56
Gender (men/women)[b]	8/10		14/34		0.25[b]	23/14		16/25		0.07[b]
Years of education	11.72	3.06	12.63	3.18	0.30	14.29	2.36	14.13	2.39	0.76
YMRS	12.72	7.04	13.64	6.82	0.63	–	–	–	–	–
MADRS	21.83	9.81	19.57	8.48	0.39	–	–	–	–	–

YMRS: Young Mania rating Scale; MADRS: Montgomery–Asberg Depression rating Scale.
[a] *t*-test, significance level $p<0.05$.
[b] Chi square test $p<0.05$.

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Table 2
Comparison of intelligence and creativity according to BDNF rs6265 genotype in patients and controls.

	Bipolar disorder (N = 66)						Controls (N = 78)					
	Met+ (N = 18)		Met− (N = 48)		*t*-test		Met+ (N = 37)		Met− (N = 41)		*t*-test	
	Mean	SD	Mean	SD	t	*p*	Mean	SD	Mean	SD	t	*p*
IQ	94.44	11.50	96.27	14.17	0.53	0.59	115.81	14.20	113.73	11.16	−0.71	0.47
BWAS like	8.77	4.69	10.94	8.20	0.99	0.99	12.50	6.54	11.39	6.22	−0.74	0.45
BWAS dislike	8.55	7.40	14.11	9.26	1.89	0.07	14.50	9.69	13.56	9.49	−0.42	0.67
BWAS total	17.88	9.89	25.14	12.59	2.45	0.019	27	13.57	24.88	12.75	−0.69	0.48

BWAS: Barrow Welsh Art Scale; IQ: Intelligence Quotient (Wechsler Abbreviated Scale of Intelligence). Significance level $p<0.05$.

regression analysis using age, IQ, education, the YMRS, and MADRS as predictors revealed no influence on BWAS scores in manic Met− subjects.

No differences in BWAS scores (total, "like", "dislike") were observed between Met+ and Met− patients in depressive episode (Table 3).

3.2. Met allele did not influence cognitive function in manic, depressive or control subjects

The presence of the Met *allele* was found not to influence cognitive function (attention, verbal memory, visuospatial function, language, psychomotor speed, executive functions and intelligence) in manic subjects or controls. In depressive episodes, only executive function (WCST-NP) showed better performance for Met+ ($t=-3.18$; $p=0.004$).

3.3. BWAS score was correlated with cognitive function in depression and control groups but not in mania group

In the manic group, creativity scores were not correlated with any of the cognitive tests. In depressives, BWAS total score was weakly correlated with performance on the SCWT-2 ($r=0.45$; $p=0.02$). In the control group, BWAS total score was correlated with performance on both the WAIS-DS ($r=0.23$; $p=0.05$), and WAIS-LNS ($r=0.28$; $p=0.014$).

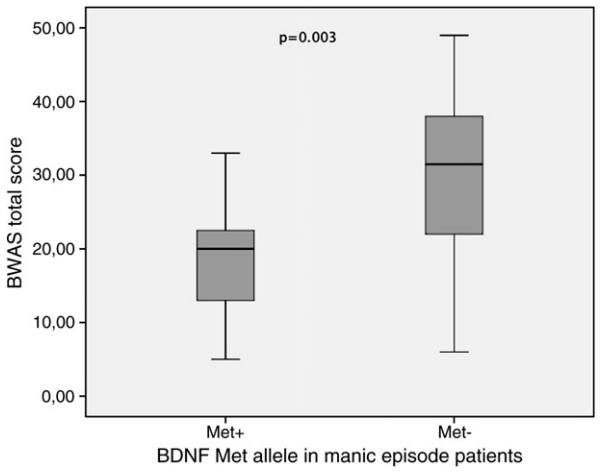

Fig. 1. Comparison of BWAS total score between manic patients with and without Met *allele*.

4. Discussion

To the best of our knowledge, this is the first study investigating the relationship of common BDNF *alleles* to creativity in BD. As hypothesized, the better functioning Val *allele* of proBDNF (Met−) was associated with greater creativity in BP patents. However, this association was selective for patients in manic phases whose BWAS scores were higher but was not seen among patients in the depressed phase or in normal controls.

Carriers of the Met *allele* Met (Met+) of the BDNF functional SNP rs6265 are known to have lower activity-dependent secretion of BDNF as well as a lesser magnitude of long-term potentiation (LTP) (Egan et al., 2003). In contrast, Met− subjects have higher BDNF levels and better executive function in euthymia (Rybakowski et al., 2003). Nonetheless, the Met *allele* has been associated with decreased cortex and hippocampal volume in bipolar patients (Chepenik et al., 2009; Matsuo et al., 2009) as well as normal controls (Hajek et al., 2011). BD Met+ patients exhibit poorer executive function in euthymia (Rybakowski et al., 2003). Similarly, Met+ normal controls and patients with schizophrenia had lower scores on measures of prefrontal cortical memory functioning (Dempster et al., 2005; Egan et al., 2003; Hariri et al., 2003). The lack of relationship of Met+ to cognition in manics and controls is puzzling, but supports the view that higher BWAS scores in mania are not simply secondary to cognitive functioning.

BD subjects with BDNF rs6265 Met− had higher creativity scores during manic episodes. This higher creativity score probably indicates that creativity has different underlying neurobiology when compared to cognition *per se*. This indicates that the potentially higher BDNF levels of Met− might be involved in the modulation of creative thinking. The explanation for the specificity in mania may involve higher dopamine (DA) levels postulated to occur in mania, a phenomenon previously associated with creativity (Burch et al., 2006; Folley and Park, 2005; Richards et al., 1988). Also, the ability to generate many different ideas about a topic in a short period of time (divergent thinking), a key aspect of creativity (Gundlach and Gesell, 1979), is influenced by dopaminergic function (Reuter et al., 2006). We speculate that higher DA function associated with the better functioning BDNF (Met−) *allele* in mania may lead to higher creativity scores. Given cognitive functioning was, if anything, lower in manic individuals than controls, coupled with the fact that creativity was not correlated with cognitive measures,

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Table 3
Comparison intelligence and creativity in Bipolar Disorder manic and depressive episodes according to BDNF rs6265 genotype.

	Mania (N = 41)						Depression (N = 25)						Controls (N = 78)					
	Met+ (N = 11)		Met− (N = 30)		*t*-test		Met+ (N = 7)		Met− (N = 18)		*t*-test		Met+ (N = 37)		Met− (N = 41)		*t*-test	
	Mean	SD	Mean	SD	t	*p*	Mean	SD	Mean	SD	t	*p*	Mean	SD	Mean	SD	t	*p*
IQ	94.09	12.46	94.87	14.82	0.16	0.86	95	10.73	98.61	13.10	0.70	0.49	115.81	14.20	113.73	11.16	−0.71	0.47
BWAS like	9.16	5.81	12.95	7.23	1.35	0.20	8	3.60	6.10	8.71	−0.55	0.59	12.50	6.54	11.39	6.22	−0.74	0.45
BWAS dislike	7.33	5.95	15.41	9.89	2.55	0.024	11	10.81	11	7.03	0	1	14.50	9.69	13.56	9.49	−0.42	0.67
BWAS total	18.81	9.15	30.03	10.72	3.31	0.003	16.42	11.55	17	11.39	0.76	0.91	27	13.57	24.88	12.75	−0.69	0.48

BWAS: Barrow Welsh Art Scale; IQ: Intelligence Quotient (Wechsler Abbreviated Scale of Intelligence). Significance level $P<0.05$.

the higher BWAS scores observed in BDNF (Met−) do not appear to stem from superior cognitive abilities.

Regarding healthy subjects, few studies have addressed the genetics of creativity. A recent study described an association between divergent thinking and DA receptor SNPs. Higher creativity scores were observed in the A1 *allele* of DA receptor D2 (rs1800497) (Reuter et al., 2006), which has a 30–40% reduction in DA-D2 receptor density (Ritchie and Noble, 2003). Similar findings were observed for the A *allele* carriers of the serotonin SNP TPH1 A779C (Reuter et al., 2006). In another study, Kéri (2009) found that the T *allele* in the promoter region of neuregulin 1 was associated with higher creativity scores in healthy volunteers (Kéri, 2009). Neuregulin 1 affects neuronal development, synaptic plasticity, glutamatergic neurotransmission, and glial functioning (Harrison and Law, 2006) in actions which have many parallels to BDNF.

Meta-analyses have shown lower peripheral BDNF levels in patients with depression and mania compared to controls (Lin, 2009). The mechanism of interaction of these alterations in brain or peripheral levels has yet t to be fully explored. One study reported that excellent lithium responders have higher BDNF levels as well as better working memory and attention (Rybakowski and Suwalska, 2010), while another reported negative results (Dias et al., 2009). However, the relationship to BDNF rs 6265 SNP was not studied.

While this is the first report describing a positive association between creativity and the better functioning *allele* of BDNF (Val), whether this association is also seen in euthymia (and thus, if it might help account for the general link between increased creativity and BD) remains a topic for future investigations. Clearly, further studies are required to assess the relationships of Val and BD vulnerability and creativity.

A limitation of this study is that the state-trait relationship of BDNF (Met−) cannot be dissected and larger samples including euthymic patients need to be studied. It would also be valuable to utilize other measures of creativity that do not depend on a measure of increased (loose) association which is so closely linked to manic symptomatology. On the other hand, the strength of this study was that it included unmedicated subjects, which allowed a clear observation of the phenotypic boundaries in mania and depression. Moreover, the inclusion of comprehensive measures of cognition allowed the inference that the observed relationships to creativity were not dependent on superior cognitive abilities.

5. Conclusion

Creativity scores were selectively influenced by the functional BDNFrs6265 SNP in manic BD (but not depressive or control) subjects. The effect of BDNF rs6265 Met− in improving creativity during mania may involve neuroprotective mechanisms. No evidence that this *allele* modulates cognitive function during mood episodes was found. The known alterations in the monoaminergic system associated with mood episodes in BD may also contribute to these effects on creativity. Future studies exploring the neurobiology of creativity in BD are warranted.

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Conflict of interest

The authors do not have any conflict of interest to report.

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