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Author for correspondence:
*Celia M de Araujo,
Email: celia.fit@gmail.com

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Are serum brain-derived neurotrophic factor concentrations related to brain structure and psychopathology in late childhood and early adolescence?

Celia Maria de Araujo[1,2*], Walter Swardfager[3,4], Andre Zugman[1,2], Hugo Cogo-Moreira[1], Sintia I. Belangero[1,2,5], Vanessa K. Ota[2,5], Leticia M. Spindola[2,5], Hakon Hakonarson[6], Renata Pellegrino[6], Ary Gadelha[1,2], Giovanni A. Salum[1,7], Pedro M. Pan[1,2], Rodrigo B. Mansur[8,9], Marcelo Hoexter[1,10], Felipe Picon[1,7], João R. Sato[1,11], Elisa Brietzke[2,12], Rodrigo Grassi-Oliveira[13], Luis A. P. Rohde[1,7], Euripedes C. Miguel[1,9], Rodrigo A. Bressan[1] and Andrea P. Jackowski[1,2]

[1]National Institute of Developmental Psychiatry for Children and Adolescents (INCTCNPq), São Paulo, Brazil, [2]Department of Psychiatry, Queen's University School of Medicine, Kingston ON, Canada, [3]Department of Pharmacology & Toxicology, University of Toronto, Toronto, Canada, [4]Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, Canada, [5]Department of Morphology and Genetics, Universidade Federal de São Paulo, São Paulo, Brazil, [6]Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, [7]Department of Psychiatry, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [8]Mood Disorders Psychopharmacology Unit, University of Toronto, Toronto, ON Canada, [9]Department of Psychiatry, University of Toronto, Toronto, ON Canada, [10]Department & Institute of Psychiatry, Universidade de São Paulo, São Paulo, Brazil, [11]Mathematics & Statistics Institute, Universidade Federal do ABC, Santo André, Brazil, [12]Department of Psychiatry, Queen's University School of Medicine, Kingston ON, Canada, and [13]Developmental Cognitive Neuroscience Laboratory (DCNL), Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil

Abstract

Objective. Mental disorders can have a major impact on brain development. Peripheral blood concentrations of brain-derived neurotrophic factor (BDNF) are lower in adult psychiatric disorders. Serum BDNF concentrations and BDNF genotype have been associated with cortical maturation in children and adolescents. In 2 large independent samples, this study tests associations between serum BDNF concentrations, brain structure, and psychopathology, and the effects of BDNF genotype on BDNF serum concentrations in late childhood and early adolescence.
Methods. Children and adolescents (7-14 years old) from 2 cities (n = 267 in Porto Alegre; n = 273 in São Paulo) were evaluated as part of the Brazilian high-risk cohort (HRC) study. Serum BDNF concentrations were quantified by sandwich ELISA. Genotyping was conducted from blood or saliva samples using the SNParray Infinium HumanCore Array BeadChip. Subcortical volumes and cortical thickness were quantified using FreeSurfer. The Development and Well-Being Behavior Assessment was used to identify the presence of a psychiatric disorder.
Results. Serum BDNF concentrations were not associated with subcortical volumes or with cortical thickness. Serum BDNF concentration did not differ between participants with and without mental disorders, or between *Val* homozygotes and *Met* carriers.
Conclusions. No evidence was found to support serum BDNF concentrations as a useful marker of developmental differences in brain and behavior in early life. Negative findings were replicated in 2 of the largest independent samples investigated to date.

Introduction

Brain-derived neurotrophic factor (BDNF) is involved in brain morphological plasticity.[1–4] In depression, meta-analytic results have shown low serum[5–8] and plasma concentrations[5] of BDNF in drug-naive patients compared to healthy controls, and increased BDNF concentrations after treatment with antidepressants.[5–8] Other meta-analyses found reduced peripheral blood levels of BDNF in bipolar disorder[9] and in drug-naive and medicated individuals with schizophrenia,[10] suggesting that BDNF may be a useful marker of psychiatric disorders in adult populations.

Studies in children and adolescents have shown conflicting results. Although some studies showed alterations in BDNF concentrations in children with obsessive–compulsive disorder (OCD),[11] attention deficit-hyperactivity disorder (ADHD),[12] and depression,[13] other studies did not show differences in BDNF concentrations between patients and controls with OCD,[14]

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bipolar disorder,[15] or ADHD.[16] In a younger population, concentrations of serum BDNF were found to be higher among those at ultra-high risk for psychosis compared to a healthy control group.[17] Further studies of serum BDNF as a marker of psychopathology in children and adolescents are needed.

A growing literature reports structural brain changes related to serum BDNF concentrations, and psychiatric illnesses,[18–21] with conflicting results. In individuals with schizophrenia, higher peripheral blood concentrations of BDNF have been correlated with thinner prefrontal cortical thickness[20] and increased hippocampal volume.[21] However, other studies of individuals with bipolar disorder showed no correlation between BDNF concentrations and hippocampal volumes in children,[22] and no association between BDNF and gray matter volumes in adults.[23] In 1 study, peripheral BDNF concentrations and brain volumes (including cortical areas) were correlated negatively in bipolar offspring but positively in healthy controls[19]; suggesting the need for larger studies investigating interactive effects between psychopathology and serum BDNF in predicting brain volumes.

A likely interactive effect on brain development has been supported in genetic studies. We identified thicker parietal and occipital lobes and prefrontal cortices in typically developing (TD) *Met* carriers compared to *Val* homozygotes, but also an interaction between the *Val66Met* genotype and a psychiatric diagnosis (PD), such that *Met* carriers with a PD showed thicker medial and lateral temporal cortices, and thinner bilateral prefrontal cortices.[24] Studies have also found effects of genotype on cortical and subcortical volumes in TD children[24–26] and in children at risk for depression[27] and other psychiatric disorders.[24] However, reports of relationships between BDNF genotype and serum concentrations have been conflicting. Although a meta-analysis found no significant association between serum BDNF concentrations and the BDNF *Val66Met* polymorphism,[28] higher concentrations of serum BDNF in *Met* allele carriers were associated with male sex,[29] depression,[30] and anxiety,[31] and some studies showed lower serum BDNF concentrations related to the *Met* allele.[32,33] These findings suggest the need to determine if serum BDNF concentrations are related to a PD and to brain structure in childhood and early adolescence, and to examine sex-specific associations.

The main objectives of this study were to determine, in 2 large samples, if there are replicable differences between BDNF serum concentrations between TD children and adolescents and those with a PD, and to identify relationships between serum BDNF concentrations and neuroanatomical markers (cortical thickness, and volumes of the hippocampus and amygdala). Given effects of the BDNF genotype on these outcomes observed previously, BDNF serum concentrations were also examined in relation to the BDNF genotype. Based on an interaction between sex and genotype on BDNF concentrations in 548 older subjects (age range 50-72 years old, mean age 62.8 ± 5.4 years, 267 males),[29] gender interactions were also considered.

Methods

Participants

All data were acquired with the approval of the Ethical Committee of the School of Medicine, University of São Paulo. Written consent was obtained from all parents or their legal guardians, and all children provided verbal assent. The Ethical Committee of the Federal University of São Paulo approved the study.

Participants were drawn from the Brazilian school-based high-risk cohort (HRC) study for the Development of Childhood Psychiatric Disorders. For a detailed description of HRC sampling, see Salum et al.[34] Fifty-seven schools from 2 Brazilian cities, São Paulo and Porto Alegre, participated. In Brazil, parents are required to register their children in a local school. On school registry day, we invited biological parents of 6- to 12-year-old children at these schools to participate in the study. Biological parents (87.3% mothers) answered the family history screening[35] for 8012 families, representing 9937 children. From this pool, the HRC was created by combining 2 strata (n = 2511). The first stratum included a sample of randomly selected subjects, the "random group" (n = 958). The second stratum, the "high-risk group" (n = 1553), included youth at risk for psychopathology, selected using a validated prioritization algorithm.[34] Only 1 child per family was included. The baseline evaluation included a household lay interview with a biological parent (94.5% mothers), including extensive risk factor and psychopathology evaluations.

Clinical assessment

We used a structured psychiatric interview, the Brazilian Portuguese version[36] of the Development and Well-Being Assessment (DAWBA,[37] see http://www.dawba.info), to ascertain psychiatric diagnoses according to DSM-IV criteria. The wide range of psychiatric diagnoses observed by the DAWBA questionnaire was categorized by a variable named "any disorder" indicating the presence or absence of any psychiatric illness. We used a categorical approach to psychiatric disorders to facilitate comparisons to previous studies, given that the majority used case–control designs. The multivariate analyses were conducted with this variable as a covariate.

The estimated intelligence quotient (IQ) was evaluated using 2 tests from the Wechsler Intelligence Scale for Children,[38] the vocabulary and block subtests, and computed scores using the Tellegen and Briggs[39] method, according to the correspondent Brazilian norms.[40]

Magnetic resonance imaging acquisition, biological samples, and BDNF genotyping

The HRC study involved magnetic resonance imaging (MRI) scans performed in a subsample of the subject population. Subjects who completed household and school evaluations were eligible for participation, following the same procedure employed during the screening phase. From the pool of 2511 subjects, a subsample of 750 children and adolescents underwent MRI; 540 (267 in Porto Alegre and 273 in São Paulo) of these also agreed to have their blood collected. This phase occurred approximately 6 to 8 months after the clinical household interview.

We used 1.5 T MRI systems (GE Signa HDX and GE Signa HD, G.E., USA) at 2 sites, with the same protocols and the following T1-weighted image parameters: TR = 10.916 ms, TE = 4.2 ms, thickness = 1.2 mm, flip angle = 15°, NEX = 1, matrix size = 256 × 192, FOV = 245 mm, bandwidth = 122.109, yielding 156 axial slices.

Blood samples were obtained after MRI acquisition. After blood processing, serum was stored at −80 °C, and BDNF levels were quantified by sandwich ELISA following the manufacturer's instructions (cat. no. CYT306; Millipore, Billerica, MA). Briefly, after blood was withdrawn, the samples were centrifuged at 2000*g* for 10 minutes and the serum was frozen (−80 °C) until placed on

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microtiter plates and diluted 1:75 in sample diluents. The standard curve ranged from 7.8 to 500 ng/ml BDNF. After that, the plates were washed 4 times with wash buffer and incubated for 3 hours at room temperature (after adding the biotinylated mouse antihuman BNDF monoclonal antibody diluted 1:1000 with sample diluents). A fifth washing took place and then a second incubation with streptavidin-horseradish conjugated solution of peroxidase (diluted 1:1000) for 1 hour at room temperature was performed. Finally, BDNF concentrations were determined with absorbance set at 450 nm, and the standard curve resulted in a graph that showed a direct relationship between BDNF concentrations and the corresponding ODs (absorbances).

The genotyping procedure was conducted in blood or saliva (for children that refused to have their blood collected) using the SNParray Infinium HumanCore Array BeadChip (Illumina, San Diego, CA) at the Center for Applied Genomics at the Children's Hospital of Philadelphia (USA) according to the manufacturer's instructions. The *Val66Met* genotypes were extracted using a PLINK 1.9 script (open-source toolset at http://pngu.mgh.harvard.edu/purcell/plink/).[41] BDNF genotyping for this sample has been described elsewhere in more detail.[24]

MRI processing and statistical analyses

Image processing and analyses were performed using an automated, nonbiased, atlas-based Bayesian segmentation method, applied in FreeSurfer v.5.1 (http://surfer.nmr.mgh.harvard.edu/).[42] Volumes of subcortical structures (ie, amygdala and hippocampus) were also extracted from FreeSurfer.

The graphical Query Design Estimate Contrast interface of FreeSurfer was used to model and test the parameters of a general linear model (GLM) at each vertex across the cortical surface. The correlation between serum BDNF levels and cortical thickness was considered the response variable, while sex, age, IQ, and site were considered nuisance variables. Results were corrected for multiple comparisons using the false discovery rate (pFDR < .05).

For purposes of replicability, GLM analyses were conducted separately by site. The first sample comprised a group of 273 individuals from 1 city (São Paulo) and the replication sample comprised a group of 267 participants from the other city (Porto Alegre). These sample sizes provide at least 90% power to detect small effect sizes ($f^2 \geq .04$) at a 2-sided alpha = .05.

A GLM was used to test the correlations between BDNF concentrations and the selected brain structures. The amygdala and the hippocampus were chosen due to the key role that BDNF seems to play in the neurobiological mechanisms involved in anxiety disorders[1,43–45]; in addition, the action of BDNF in these regions may be directly implicated in the synaptic regulation of affective disorders.[1] These volumes were entered as outcome variables, with serum BDNF levels (main predictor of interest), and other measures (age, the presence of any psychiatric disorder, intracranial volume, IQ, and sex) as covariates. Statistical significance was set at $p < .05$ and, to control for multiple comparison testing, we used Bonferroni corrections (p-value = .0125, .05/4). To assess our second objective, we conducted an interaction analysis between sex and *Val66Met* polymorphism in a univariate GLM, corrected for the same covariates used in the main analysis, with serum BDNF levels as the dependent variable.

Analyses were performed with SPSS for Windows (version 21.0; SPSS, Chicago, IL).

Results

Five hundred and forty individuals enrolled in the HRC, aged 7 to 14 years, participated in the BDNF and neuroimaging substudies. To establish replicability, Sao Paulo was considered the discovery sample ($n = 273$) and Porto Alegre the replication sample ($n = 267$) a priori. Demographics and clinical, biomarker, and imaging data are presented in Table 1.

Mean serum BDNF concentration was 24.25 (*SD* 12.39) ng/ml for the discovery sample and 30.79 (*SD* 8.37) ng/ml for the replication sample. There was a significant difference in BDNF serum concentrations between males and females in the discovery sample (22.07 [*SD* 10.16] and 27.10 [*SD* 14.38] ng/ml, respectively; $p = .001$) but not in the replication sample ($p = .231$).

There was no difference between PD and TD groups in serum BDNF concentrations in the discovery sample (t test = −.428; $p = .669$) or in the replication sample (t test = −1.813; $p = .071$).

There was no association between serum BDNF concentration and subcortical volumes (Table 2) or overall cortical thickness in the discovery sample or in the replication sample ($p > .05$).

For comparisons between BDNF genotype and BDNF serum concentrations, 6 participants from the replication center were excluded due to genotyping failure. No significant differences in serum BDNF concentrations were found between *Met* carriers (22.92 [*SD* 10.66] ng/ml) and *Val* homozygote carriers (24.68 [*SD* 12.9] ng/ml, $p = .315$) in the discovery sample ($n = 273$; *Met* carriers = 67, *Val* homozygotes = 206), or between *Met* carriers (30.47 [*SD* 9.32] ng/ml) and *Val/Val* carriers (30.89 [*SD* 8.07] ng/ml, $p = .730$) in the replication sample ($n = 261$; *Met* carriers = 63, *Val* homozygotes = 198; see Table 3 for details).

Variance in BDNF concentrations was not explained by interaction effects between *Val66Met* and sex, or between *Val66Met* and a PD, in the discovery sample (genotype × sex $F = .125$, $p = .724$, partial eta squared < .001; genotype × PD $F = 2.466$, $p = .118$, partial eta squared = .009) or in the replication sample (genotype × sex $F = .112$, $p = .739$, partial eta squared < .001; genotype × PD $F = .278$, $p = .599$, partial eta squared = .001).

Discussion

This study found a lack of evidence to support any association between serum BDNF concentrations and the diagnosis of a mental disorder in children and adolescents. There were no associations between serum BDNF concentrations and volumes of cortical or subcortical brain structures, and no correlations between serum BDNF concentrations and cortical thickness. Findings were negative in the TD and PD subgroups, and in subgroups of boys and girls. In addition, we found no differences in serum BDNF concentrations between *Met* carriers and *Val* homozygote carriers at both sites, and no interactions between *Val66Met*, sex, and psychiatric diagnoses in predicting serum BDNF concentrations.

Although in adults with schizophrenia, BDNF has been associated with cortical thickness[20,46] and hippocampal volume,[21] the literature investigating the relationship between peripheral concentrations of BDNF and brain structures in children and adolescents remains scant. Although an association between peripheral BDNF concentrations and brain volumes and cortical areas was observed in a study of bipolar offspring and healthy controls,[19] another study did not find differences between BDNF serum concentrations and hippocampal volume in children and adolescents diagnosed with bipolar disorder.[22]

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Table 1. Demographics and clinical characteristics of the sample; *p* value refers to the differences between male and female in each city.

	São Paulo (discovery sample)						Porto Alegre (replication sample)				
	All	Male	Female				All	Male	Female		
	(TD/PD)	(TD/PD)	(TD/PD)				(TD/PD)	(TD/PD)	(TD/PD)		
	n = 273 (215/58)	*n* = 155 (119/36)	*n* = 132 (78/54)	*t* test	*p* value*	Effect size Cohen's *d*	*n* = 267 (154/113)	*n* = 135 (76/59)	(TD/PD)	*p* value*	Effect size Cohen's *d*
BDNF ng/ml (*SD*)	24.25 (12.39)	22.07 (10.16)	27.1 (14.38)	−3.234	.001*	.404	30.59 (8.45)	29.97 (7.47)	31.21 (9.33)	.231	.146
Age (mean/*SD*)	10.39 (1.74)	10.42 (1.76)	10.35 (1.72)	.311	.756	.040	10.75 (2.01)	10.46 (2.0)	11.05 (1.98)	.017	.296
IQ (mean/*SD*)	102.97 (16.91)	103.43 (17.39)	102.36 (16.3)	.516	.606	.063	101.35 (16.3)	102.37 (16.76)	100.3 (15.81)	.299	.127

Abbreviations: IQ, intelligence quotient; PD, psychiatric diagnosis; *SD*, standard deviation; TD, typically developing.
*$p < .05$.

Table 2. BDNF effect on brain structures (amygdala and hippocampus).

Brain structures*	São Paulo (discovery sample)				Porto Alegre (replication sample)			
	n = 273	*F*	*p* value	Partial eta squared	*n* = 267	*F*	*p* value	Partial eta squared
Left amygdala Mean (*SD*)	1518.22 (213.6)	.510	.476	.002	1482.46 (192.04)	.334	.564	.001
Right amygdala Mean (*SD*)	1622.13 (253.67)	.008	.930	<.001	1555.37 (211.9)	1.05	.306	.004
Left hippocampus Mean (*SD*)	3924.11 (562.39)	.262	.609	.001	4023.28 (463.22)	.022	.882	<.001
Right hippocampus Mean (*SD*)	4012.80 (511.1)	2.715	.101	.010	4007.03 (453.98)	1.932	.166	.007

The analyses were conducted controlling sex, age, IQ, intracranial volume, and any psychiatric disorder; *p* value refers to BDNF effects on brain structures.
Abbreviation: *SD*, standard deviation.
*vol in mm^3.

Table 3. BDNF serum concentrations (ng/ml) and *Val66Met* genotype.

	São Paulo (discovery sample)						Porto Alegre (replication sample)					
	Val/Val	*Met* carriers	All genotypes	Statistics			*Val/Val*	*Met* carriers	All genotypes	Statistics		
	N; BDNF mean (*SD*)	*N*; BDNF mean (*SD*)	*N*; BDNF mean (*SD*)	*t* test	*p* value	Cohen's *d*	*N*; BDNF mean (*SD*)	*N*; BDNF mean (*SD*)	*N*; BDNF mean (*SD*)	*t* test	*p* value	Cohen's *d*
Male	114; 22.62 (10.57)	41; 20.55 (8.87)	155; 22.07 (10.16)	1.211	.264	.212	96; 30.31 (7.97)	36; 29.53 (5.57)	132; 30.1 (7.38)	.633	.528	.113
Female	92; 27.23 (14.98)	26; 26.66 (12.26)	118; 27.1 (14.38)	.176	.861	.041	102; 31.43 (8.16)	27; 31.72 (12.75)	129; 31.49 (9.25)	−.113	.911	.027

p value refers to differences in BDNF between genotypes of males and females.
Abbreviation: *SD*, standard deviation.

Other studies have observed *Val66Met* effects on cortical and subcortical brain regions in TD children[24–26] and children diagnosed with psychiatric disorders.[24,27] In previous analyses from the present cohort, we identified an association between the *Val66Met* genotype and brain cortical maturation in children and adolescents with TD *Met* carriers showing thicker parietal, occipital, and prefrontal cortices compared to *Val* homozygotes, and PD *Met* carriers presenting thicker right temporal cortex.[27] Moreover, this previous study showed a significant genotype × PD interaction, with PD *Met* carriers presenting thinner bilateral prefrontal cortices than *Val* homozygote carriers and TD *Met* carriers. The present findings suggest that those relationships are not related to peripheral BDNF concentrations.

Jasinska et al[26] found larger right hippocampal volume and greater cortical thickness in lateral occipital/parietal regions, and Hashimoto et al[25] observed greater regional gray matter volume related to the BDNF *Val66Met* polymorphism (*Met* allele carriers) in TD children. Although those studies did not investigate associations between the genotypes and serum BDNF concentrations, studies conducted in adult populations have suggested correlations between peripheral BDNF and *Val66Met* polymorphisms, with higher serum concentrations of BDNF in *Met* allele carriers associated with male sex,[29] depression,[30] and anxiety.[31]

Previously, a clinical study[29] found significant interactions between sex and *Val66Met* genotype on serum BDNF levels, with *Met* carriers showing higher BDNF than *Val* homozygotes only in males. In this present study, with the purpose of replicating this finding, we tested the interaction between sex and *Val66Met* and the interaction between psychiatric diagnoses and BDNF genotype on serum BDNF concentrations. Although 1 sample showed differences between boys and girls in serum BDNF concentrations (higher levels in girls), this was not associated with genotypes. Our results are in contrast with the results of Bus et al,[29] and some methodological differences between samples may explain the divergent results. For example, while in the study of Bus and colleagues the age of the subjects ranged from 50 to 72 years, our study was conducted in a population of children and adolescents.

The lack of evidence to support an association between cortical thickness and serum BDNF levels does not preclude a role of BDNF in cortical maturation (evidence of absence, see Altman and Bland[47]); however, given the small effect sizes observed, the present findings suggest that serum BDNF offers little as a relevant biomarker in this context. Lower concentrations of the mature BDNF peptide have been observed in major depressive disorder,[48] but higher serum concentrations have been observed in bipolar disorder in comparison with healthy controls.[19,23] Future studies might reassess cortical and subcortical features in relation to the mature BDNF peptide.

This study is one of the first to investigate the relationships between serum BDNF concentrations and brain development in healthy and psychiatrically diagnosed children and adolescents. The findings are strengthened by a large sample size obtained from a community-based cohort, and by a replication sample. Several limitations should be considered. The cross-sectional design does not permit causal inference; future studies might explore longitudinal associations. The operational definition of a PD group encompassed multiple diagnoses, which may have obscured relationships with individual psychiatric diagnoses. Although BDNF concentrations can differ between serum and plasma, only serum concentrations were available. As another potential limitation, inflammatory biomarkers that have been

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related to psychiatric disorders were not considered, but they could influence serum BDNF. These interactions might be explored in future studies.

Conclusion

In conclusion, serum BDNF concentrations were not related to cortical or subcortical volumes, or to psychopathology, in the 2 largest samples of children and adolescents investigated to date. Furthermore, analyses testing interactions between *Val66Met* and sex or psychiatric diagnoses did not detect effects on serum BDNF concentrations, suggesting that serum concentrations are unrelated to the effects of the BDNF system on anatomical and behavioral neurodevelopment. Serum BDNF did not seem to be a useful marker for tracking developmental changes in brain and behavior in early life.

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Conflicts of Interest: None.

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