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Research article

Reduced serum concentrations of brain-derived neurotrophic factor (BDNF) in transsexual Brazilian men

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HIGHLIGHTS

- Serum BDNF levels were significantly lower in transsexual men than in *cis*-sexual men and women.
- There are many factors that may explain the variation observed in BDNF serum levels, such as cross-sex hormone treatment and chronic social stress.

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ABSTRACT

Serum BDNF levels are significantly decreased in transsexual Brazilian women when compared to *cis*-sexual men. Since transsexual men are also exposed to chronic social stress and have a high prevalence of associated psychopathologies, it is plausible to inquire if BDNF serum levels are altered in transsexual men as well. Therefore, our objective was to evaluate differences in BDNF serum level of transsexual men when compared to *cis*-sexual men and women. Our sample comprises 27 transsexual men, 31 *cis*-sexual women and 30 *cis*-sexual men recruited between 2011 and 2015. We observed that BDNF serum concentration is decreased in transsexual men comparing to *cis*-sexual men and women. Cross-sex hormone treatment, chronic social stress or long-term gender dysphoria (GD) could explain the variation found in BDNF serum levels.

Gender dysphoria (GD) is a marked incongruence between one's experienced gender and one's assigned gender, resulting in a strong and persistent desire to belong to the other gender by hormone therapy (HT) or surgical procedures. Its prevalence varies according to the diagnosed criteria employed, to the country analyzed and to the period studied [1,38]. Even considering these variations, transsexual women are more prevalent than transsexual men [38]. It is not surprising that transsexual men are less frequently studied than transsexual women.

Brain-derived neurotrophic factor (BDNF) is a member of the growth factor family and is involved in synaptic plasticity, neurogenesis and neuronal survival [15,21]. BDNF has an extensively reported relation with the corticosteroids that appear to play a key role in the environmentally mediated vulnerability to psychopathology [21]. BDNF has also been widely associated with child maltreatment outcomes [11] and with mental disorders [3] such

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as bulimic eating syndromes [36], substance dependence [22] and bipolar disorder [21]. Decreased serum BDNF levels have also been associated with traumatic childhood events in patients with bipolar disorder (BD) [25]. Furthermore, Kapczinsky and colleagues, reviewing the importance of BDNF in BD, reported that their previous results position BDNF as an essential factor in the transduction of the psychosocial stress experienced by their patients [23].

Comparing a group of transsexual women (n = 45) with a control group of *cis*-sexual men (n = 66), our previous study observed that the serum BDNF levels were significantly decreased in individuals diagnosed with GD [16]. Because prejudice against gender nonconformity is a common phenomenon occurring across many contexts in Brazil [13], we proposed that the decreased BDNF serum concentration in transsexual persons may be a result of those environmentally mediated vulnerabilities, suggesting that BDNF could be considered an indicator of the health effect of a social factor such as prejudice [12]. Nevertheless, according to Fuss et al., variations in BDNF among transsexual persons may be justified, not only by exposure to traumatic events or by association with psychiatric disorders but also by HT [18]. Because treatment with estradiol affects subcutaneous and visceral fat depots [14] and because body weight can influence plasma BDNF levels [31], it is reasonable to question the effect of HT on BDNF serum concentration. In our ambulatory clinic, transsexual women use estradiol and spironolactone whereas transsexual men utilize testosterone. Each sex hormone interacts differently with BDNF [30]; however, a recently published study by Auer et al. showed in a longitudinal setting that BDNF levels in transsexual men are not influenced by a 12-month course of testosterone treatment [4]. Finding that use of testosterone by transsexual men does not change BDNF serum levels is intriguing: testosterone supplementation may improve cognitive function in men [10] and androgen deprivation, during treatment for prostate cancer, may impair memory performance [6]. BDNF has been studied as an important contributor to the effects of circulating androgens on the brain [33]. Furthermore, testosterone induces platelet activation [2], which was associated with BDNF release [17,24]. Auer and collaborators hypothesized that other mechanisms interfering with peripheral BDNF release might be masking the effects of testosterone on BDNF in transsexual men [4].

Expanding on our report on BDNF serum levels of transsexual women [16], this study seeks to elucidate whether BDNF concentration follows the same pattern in transsexual men as in *cis*-sexual men and women. In addition, because in the majority of social contexts, most transsexual men are exposed to similar traumatic events as transsexual women but utilize a different HT, it is plausible to inquire whether BDNF serum levels are altered in transsexual men in the same manner that BDNF levels are altered in transsexual women.

1. Methods

The Ethical Committee of Hospital de Clínicas de Porto Alegre (HCPA) approved this study. All participants were informed regarding the procedure and signed the informed consent prior to participating in the research. The sample comprised 27 transsexual men, 31 *cis*-sexual women and 30 *cis*-sexual men recruited between 2011 and 2015.

1.1. Mental health, demographic, psychosocial and family history assessment in transsexual sample

All transsexual persons fulfilled the criteria for GID (gender identity disorder according to the DSM-IV criteria) and were diagnosed by a specialized physician. The diagnostic criteria, from DSM-IV to DSM-5, changed during our data collection; however, we chose to complete this research using the DSM-IV criteria. The individuals diagnosed with GID attended both group and individual medical appointments on a biweekly basis in a GD outpatient clinic at HCPA, a university hospital situated in southern Brazil. HCPA is the only public hospital currently performing sex reassignment surgery (SRS) in the country, the only reference for specialized care for GD in southern Brazil and one of the primary Latin American centers for GD studies. Since its creation in 1998, the program for GD care has been conducting multidisciplinary outpatient treatment, which includes psychology, hormonal therapy and surgical options to individuals diagnosed with GD.

In the transsexual sample, after a well-established diagnosis, a protocol covering demographic, psychosocial and family history variables was applied. Current psychiatric diseases were evaluated by a psychiatrist using Mini International Neuropsychiatric Interview – Brazilian Version, 5.0.0 (MINI). The lifetime presence or absence of childhood maltreatment was investigated by asking three questions regarding sexual abuse, sexual violence and negligence. Those questions were similar to specific questions related to sexual abuse and negligence included in the Traumatic Events Screening Inventory – Self Report Revised [34,35]. Transsexual persons who had current psychiatric diseases, HIV, are obese (BMI of 30 or greater), have performed SRS or have used a different HT (in our ambulatory, transsexual women are treated with estradiol and spironolactone whereas transsexual men utilize testosterone) were not included in our study. Those transsexual men who disclosed childhood maltreatment were not included in the data analysis.

1.2. Mental health, demographic, psychosocial and family history assessment in cis*-sexual sample*

Cis-sexual men and women were invited from a pool of blood donors and companions of HCPA patients. We applied a summarized protocol on *cis*-sexual men and women in which we evaluated psychological morbidity by directly asking whether these volunteers had any psychiatric diagnosis or had used psychiatric medication. The lifetime presence or absence of childhood maltreatment was investigated by asking the same three questions involving sexual abuse, sexual violence and negligence that were asked of the transsexual sample. None of the controls reported being diagnosed with HIV. Those volunteers who disclosed childhood maltreatment, psychiatric diagnosis, psychiatric medication or were obese (BMI of 30 or greater) were not included in the data collection.

1.3. Measurement of BDNF levels

The BDNF assay was performed as described in a previous study [16]. Briefly, five milliliters of blood were drawn from each subject by venipuncture and placed in a free-anticoagulant vacuum tube. The samples were centrifuged at 4000RPM for 10 min, and the serum was kept frozen at −80° C until assayed. BDNF serum levels, from plasma, were measured with sandwich-ELISA, using ChemiKine™ Brain Derived Neurotrophic Factor (BDNF) Sandwich Elise Kit Cat No CYT306. There were enough reagents included in this kit for two 96-well immuno-assay plates; therefore, all participants were evaluated using the same kit. With the ChemiKine BDNF assay system, mouse monoclonal antibodies generated against human BDNF were coated onto a microplate and were used to capture BDNF from a sample. The standard curve demonstrated a direct relationship between Optical Density and BDNF concentration. The reaction presents a sensitivity of 15 pg/mL, a range of detection from 15 pg/mL to 1000 pg/mL, an intra-assay variation of + 3.7% (250 pg/mL) and an inter-assay variation of + 8.5% (250 pg/mL). No significant cross reactivity with NGF, NT4/5 or NT3 was reported.

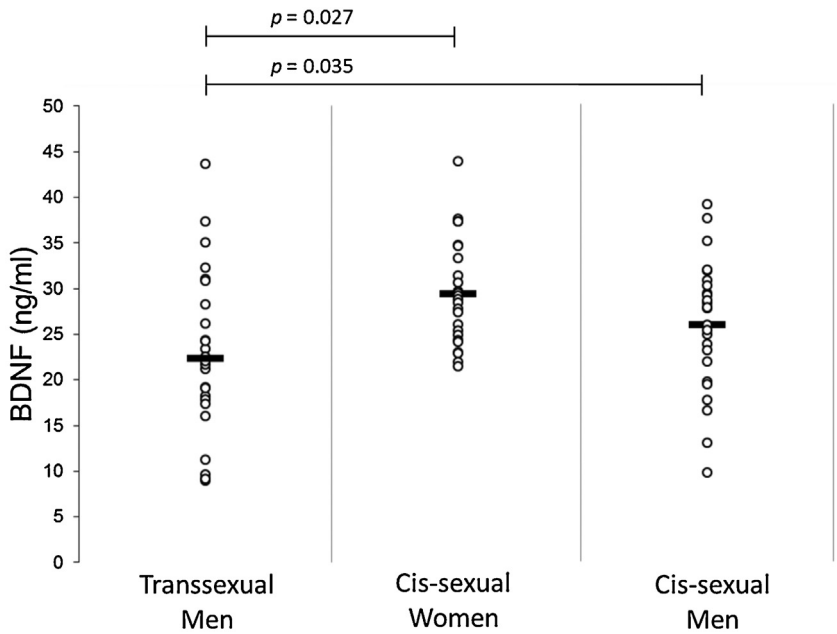

Fig. 1. BDNF levels in transsexual men and in *cis*-sexual women and men. BDNF serum concentration was significantly different among transsexual men, *cis*-sexual men and *cis*-sexual women determined by one-way ANOVA ($F(2,87) = 3.15$, $p = 0.048$). A LSD post-hoc test revealed that BDNF concentrations was statistically significantly lower in transsexual men when compared to *cis*-sexual men (-4.99 ± 2.09, $p = 0.035$) and women (-4.67 ± 2.08, $p = 0.027$).

1.4. Statistical analysis

Statistical analysis was conducted using Statistical Product and Service Solutions 18.0 Version (SPSS). Shapiro–Wilk test was applied to verify normality (among groups $p = 0.435$; whereas, considering each group individually, transsexual men $p = 0.799$, *cis*-sexual men $p = 0.985$ and *cis*-sexual women $p = 0.835$). After establishing normality distribution in the three groups (transsexual men, *cis*-sexual men and *cis*-sexual women), ANOVA followed by LSD's test was performed comparing BDNF measures, ages and schooling among transsexual men and *cis*-sexual men and women. Data were presented as the mean ± Standard Deviation (S.D.), and *p*-values <0.05 were considered significant.

2. Results

BDNF serum concentration was significantly different among transsexual men, *cis*-sexual men and *cis*-sexual women determined by one-way ANOVA ($F(2,87) = 3.15$, $p = 0.048$). A LSD post-hoc test revealed that BDNF concentrations was statistically significantly lower in transsexual men when compared to *cis*-sexual men (-4.99 ± 2.09, $p = 0.035$) and women (-4.67 ± 2.08, $p = 0.027$). These data are illustrated in Fig. 1. Sociodemographic characteristics are listed in Table 1.

3. Discussion

To date, this is the only study evaluating the differences in serum BDNF levels in transsexual men and *cis*-sexual women and men. In addition, this study is a pioneer in establishing comparisons between transsexual persons and *cis*-sexual persons with not only the correspondent sex assigned at birth but also the desired gender. We observed a significant reduction in BDNF serum level concentration when comparing transsexual men with *cis*-sexuals, both men and women.

Cross-sex hormone treatment and chronic social stress may explain the variation observed in BDNF serum levels. Anti-androgen and estrogen therapy decreased brain volumes in transsexual women whereas androgen treatment increased total brain and hypothalamus volume in transsexual men [32]. Hormone-treated transsexual persons report less social distress, anxiety and depression [20]. In this context, it is possible that the influence of HT was mediated by BDNF [18]. Fuss et al. verified that 12 months of cross-sex hormone treatment reduces serum BDNF levels in transsexual women [18]. These results supported a possible relation between sexual hormones and BDNF levels, which has been widely reported in the literature [7,18,28]. However, because Fuss et al. did not compare transsexual and *cis*-sexual persons, it is possible that the variation identified before and after HT occurs even with the BDNF serum level remaining decreased in transsexual persons when compared with *cis*-sexual persons. Furthermore, Auer and collaborators have verified that BDNF levels in transsexual men are not influenced by 12 months of testosterone treatment [4].

Further exploring the influence of hormone therapy on BDNF serum levels, one controversial issue highlights. It was established that androgen treatment increases total brain and hypothalamus volume in transsexual men [32]. Enhancing the brain volume is

Table 1
Sociodemographic characteristics and BDNF serum level.

	Transsexual Men (n = 27)	Cis-sexual Men (n = 30)	Cis-sexual Women (n = 31)	p*	
				Transsexual Men versus *cis*-sexual Men	Transsexual Men versus *cis*-sexual Women
Age (years)	33.04 (10.17)	32.63 (11.51)	34.58 (13.31)	0.898	0.621
Schooling (years)	9.37 (4.01)	12.37 (2.77)[c]	13.00 (3.89)	**0.002**	**0.000**
BDNF (ng/ml)	22.28 (8.94)	26.77 (7.32)[e]	26.94 (7.42)	**0.035**	**0.027**

*ANOVA followed LSD's test was performed to compare BDNF measures, ages and schooling among transsexual men, *cis*-sexual men and *cis*-sexual women.

expected to elevate BDNF concentration. In parallel, using HT attenuates social distress, anxiety and depression of transsexual men [20]. Depression is widely associated with BDNF levels [27] and it was speculated that increasing BDNF could relieve depression symptomatology [29]. Thus, what could be reducing the levels of BDNF in the present study, knowing that these two observations in other patient cohorts have rather been associated with an increase in BDNF levels?

Gass and Hellweg argue that the reduced levels of serum BDNF found in many neuropsychiatric disorders are occasioned by various kinds of stress, which can reduce BDNF levels [19]. Thus, humoral and peripheral BDNF levels should not be considered a disease-specific diagnostic marker [19]. Buchmann et al. evaluated the impact of early psychosocial adversity on BDNF and depressive symptoms moderated by BDNF Val66Met and 5-HTTLPR genotype. After analyzing 259 individuals at 3 months of age and at 19 years old, they verified participants homozygous for both the BDNF Val and the 5-HTTLPR L allele showed significantly reduced BDNF levels following exposure to high adversity when compared to volunteries with BDNF Met or the 5-HTTLPR S allele [9]. Considering the influence of childhood maltreatment in BDNF serum concentration [11], the role of BDNF in resilience [21,25], and the chronic social stress transsexual persons are exposed to [5,12,26], it is possible that the BDNF reduction are occasioned by social stress, specifically minority stress [12]. Previous studies highlight BDNF as a possible indicator of social vulnerability in individuals diagnosed with GD [12,16]. Unfortunately, the present study, due to its cross-section nature and limited sample, can only speculate and provide basis for further researches to analyze this hypothesis.

Our sample comprised a subgroup of transsexual men who were interested in specialized medical care and were able to reach our public hospital, overcoming common difficulties of access identified in our health care system; our volunteers, *cis*-sexual men and women, were predominantly blood donors. A diverse socioeconomic background may explain the variations observed in schooling: our transsexual sample has fewer years of education than our *cis*-sexual group. In addition, a higher rate of school dropouts among transgender people may explain this observation [8].

This study presents some limitations. BDNF is complex and susceptible to a number of factors. Platelets are the major peripheral source of BDNF and a significant correlation of BDNF with platelet count has been reported [37]; however, the present study measured BDNF plasma concentration and, therefore, did not assessed platelet count. Although none of our participants were diagnosed with associated psychiatric diseases or childhood maltreatment history, we have not applied scales to identify psychiatric symptoms in the controls and specific patterns of childhood maltreatment in both groups. Furthermore, given the small sample size, we chose not to include volunteers who presented known factors associated with serum BDNF concentrations such as exposure to traumatic events, neuropsychiatric condition, obesity and HIV. A more appropriate methodology should consider such factors in the statistical analysis.

4. Conclusion

In conclusion, our data suggest that BDNF levels are decreased in transsexual men compared with *cis*-sexual men and women. This study is innovative in that we compare transsexual men with *cis*-sexual men and women. In addition, this study is pioneering the investigation of serum BDNF levels in this specific population. Based on the data confirming the relation between BDNF and transsexuality, subsequent studies should further explore the causal relation between BDNF, GD and minority stress in different cultural contexts.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Conflict of interest statements

The authors declare no competing interests.

Authors' contributions

All authors contributed significantly and are in agreement with the content of this manuscript. Anna Fontanari and Angelo Costa designed the study, wrote the protocol, were responsible for the analysis, and participated in data interpretation, drafting the article and giving final approval to this version. Raffael Massuda participated in data analysis and interpretation, drafted the article and engaged in the final approval of this version. Tahiana Andreazza, Bianca Soll, Karine Schwarz, Maiko Schneider, Dhiordan da Silva, André Borba and Andressa Mueller participated in study design and gave final approval to this version. Bianca Aguiar and Eduarda Rosa conducted laboratory tests. Cintia Tusset gave final approval to this version. Maria Lobato was responsible for the study design and interpretation of data, drafting the article and giving final approval to this version.

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