P.132. Clinical and genetic determinants of serum brain-derived neurotrophic factor (BDNF) levels in psychotic patients: a longitudinal 24-month prospective study

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Abstract

Background: There is evidence indicating that serum brain-derived neurotrophic factor (BDNF) levels are lower in schizophrenic (SCZ) patients, irrespective of the stage of illness, compared to unaffected subjects [1]. This decrease could be constant, with pre-morbid levels roughly similar to those found in unaffected individuals, linearly declining during the course of SCZ. Alternatively, BDNF peripheral levels might fluctuate in association with acute psychopathological phases of the disorder. Further, pharmacological treatment, such as antipsychotics, might influence BDNF levels. Here, we tested whether: 1) longitudinal changes in BDNF serum levels were associated with psychopathological, cognitive, and treatment variables, and 2) genetic variation within BDNF gene had a role in modulating the longitudinal trajectory of serum BDNF levels. To this end, we followed-up a cohort of SCZ and schizoaffective disorder (SAD) patients over a period of 24 months, measuring serum BDNF levels, as well as clinical and treatment variables, every 6 months.

Methods: Inclusion criteria were 1) age between 18 and 65 years, 2) diagnosis of SCZ or SAD according to DSM-IV-TR criteria, and 3) stability of symptoms during the six months before recruitment. Psychopathological measures included the Positive and Negative Symptom Scale for Schizophrenia (PANSS), and the Clinical Global Impression Scale for Schizophrenia (CGI-SCH), while cognitive function was assessed with the Brief Assessment of Cognition in Schizophrenia (BACS) scale [2]. BDNF serum levels were evaluated using human BDNF ELISA Kit. DNA was extracted from peripheral blood leukocytes by NaCl precipitation and genotyping of rs1519480, rs11030104, rs6265 (Val66Met), and rs7934165 of the BDNF gene was performed using the TaqMan 5'exonuclease method. Mixed-effects linear regression models (MLRM) were used to analyze longitudinal data. In all analyses, performed in R, we regressed independent variables (both categorical and continuous) on BDNF serum levels (dependent variable).

Results: Seventy-four patients (70.5%) out of 105 were male. The MLRM analysis correcting for sex and age showed a statistically significant decrease of BDNF levels over time (Z=-4.09, p=7.4 x 10-7). Concerning psychopathological measures, the severity of negative and depressive symptoms assessed with the CGI-SCH was associated with a longitudinal decrease of serum BDNF levels, correcting for age and sex (Z=-2.1, p=0.04 and Z=-2.8, p=0.004). This result remained significant even when correcting for presence of oral or depot/long-acting injectable (LAI) antipsychotic treatment (Z=-2.65, p=0.008). In addition, higher BDNF serum levels were associated with higher scores in verbal fluency (controlled oral word association test) of the BACS (Z=3.1, p=0.002). Again, this result remained significant after correcting for presence of oral or depot/long-acting injectable (LAI) antipsychotic treatment (Z=2.6, p=0.01). There was no effect of BDNF gene polymorphisms on the longitudinal trajectory of serum BDNF (Z=-1.1, p = 0.26).

Conclusions: In our prospective study we found a decline of BDNF serum levels over 24-month. Further, BDNF serum levels decreased over time in relation to the severity of depressive symptoms and increased with higher scores of cognitive performance. Although awaiting replication, these results point to distinct trends in the longitudinal variation of BDNF levels, which may help setting up predictive clinical models in major psychoses.

Methods

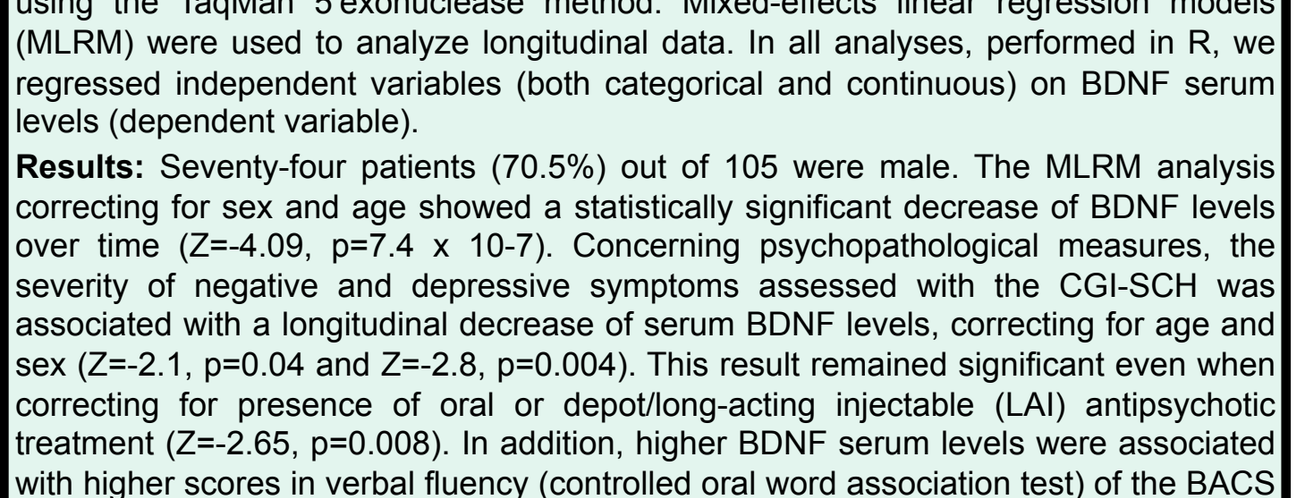

Figure 1. Flowchart of recruitment and assessment procedures for the Longitudinal assessment of BDNF in Sardinian psychotic patients study.

References

[1] Fernandes, B.S. et al., 2015. Mol Psychiatry 20, 1108-19.
[2] Keefe, R.S., et al., 2004. Schizophr Res 68, 283-297.
[3] Zai, C.C. et al., 2010. Prog Neuropsychopharmacol Biol Psychiatry 34, 1412-8.

Methods

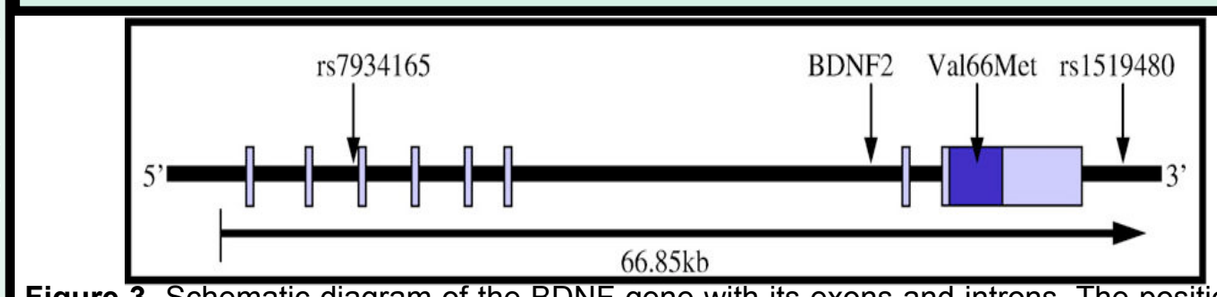

Figure 3. Schematic diagram of the BDNF gene with its exons and introns. The positions of the four polymorphisms used for the present study are indicated within the gene [3]).

Results

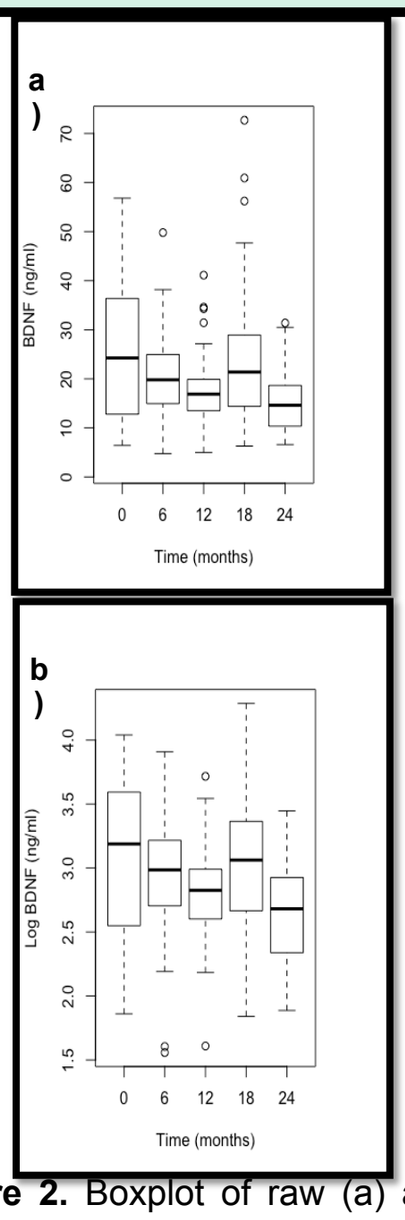

Figure 2. Boxplot of raw (a) and log-normalized (b) serum BDNF levels over 24 months.

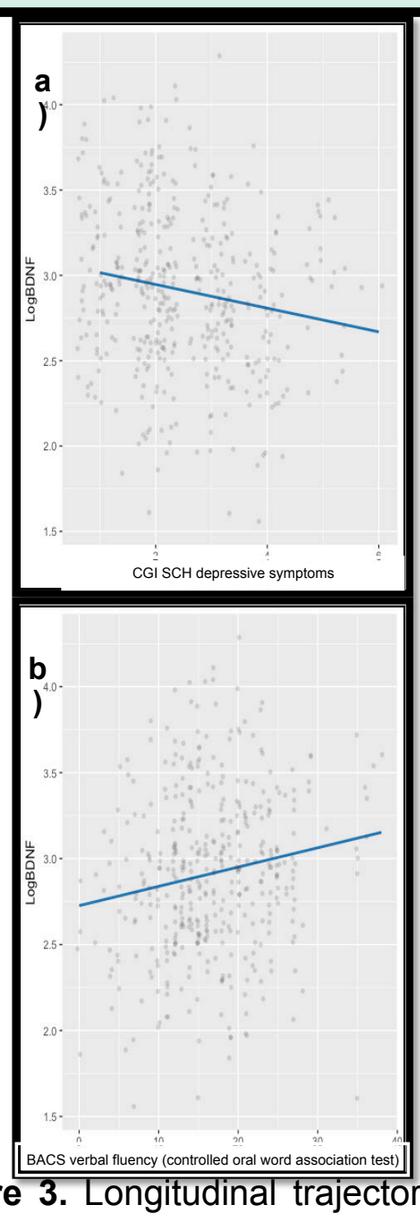

Figure 3. Longitudinal trajectory of serum BDNF levels and depressive (a) and cognitive (b) symptoms.

Model	Independent variable	Coefficient	Standard Error	Z	*p*
1	Time	-1.34	0.55	-2.42	**0.015**
	CGI-SCH depressive symptoms	-1.39	0.52	-2.8	**0.004**
	Age	0.03	0.07	0.47	0.64
2	Time	-1.38	0.56	-2.46	**0.01**
	BACS, verbal fluency (controlled oral word association test)	0.17	0.08	3.1	**0.002**
	Age	0.08	0.07	1.21	0.22
3	Time	-1.33	0.57	-2.35	**0.02**
	CGI-SCH depressive symptoms	-1.39	0.53	-2.65	**0.008**
	Oral antipsychotics	0.0006	0.002	0.27	0.78
	Depot/LAI	0.84	1.46	0.58	0.56
4	Time	-1.36	0.57	-2.37	**0.02**
	BACS verbal fluency (controlled oral word association test)	0.19	0.09	2.6	**0.01**
	Oral antipsychotics	0.0002	0.002	0.11	0.91
	Depot/LAI	1.86	1.56	1.20	0.23

Table 1. Results of MLRM models.

Conclusions

1. BDNF serum levels declined significantly over 24 months.
2. Lower BDNF serum levels correlated with higher severity of depressive symptoms, while the opposite was found for cognitive performance
3. We did not detect an effect of genetic polymorphisms within BDNF gene