Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

BDNF as a marker of response to cognitive remediation in patients with schizophrenia: A randomized and controlled trial

Rafael Penadés [a,b,c,d,*], Irene López-Vílchez [b,e], Rosa Catalán [a,b,d], Bárbara Arias [c,f], Alexandre González-Rodríguez [d], Clemente García-Rizo [c,d], Guillem Masana [c,d], Victoria Ruíz [d], Gisela Mezquida [d], Miquel Bernardo [a,b,c,d]

[a] Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Spain
[b] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[c] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain
[d] Barcelona Clinic Schizophrenia Unit (BCSU), Institut Clínic de Neurociències (ICN), Hospital Clinic, Barcelona, Spain
[e] Department of Hemotherapy and Hemostasis, Centre for Biomedical Diagnosis (CDB), Hospital Clínic, Barcelona, Spain
[f] Department of Anthropology, Faculty of Biology and Biomedicine Institute, University of Barcelona, Spain

ARTICLE INFO

Article history:
Received 1 July 2017
Received in revised form 1 December 2017
Accepted 10 December 2017
Available online xxxx

Keywords:
BDNF
Neuroplasticity
Cognitive remediation
Genotype
Biomarker
Schizophrenia

ABSTRACT

Background: Brain-derived neurotrophic factor (BDNF) is considered to be a putative biomarker for cognitive recovery in schizophrenia. However, current evidence is still scarce for pharmacological treatments, and the use of BDNF as a biomarker has only been tested once with cognitive remediation treatment (CRT).
Methods: A randomized and controlled trial (NCT02341131) with 70 schizophrenia outpatients and 15 healthy volunteers was conducted. The participants with schizophrenia were randomly assigned to either CRT or the control group. All the participants were assessed in terms of cognition, quality of life, and their serum BDNF levels at both baseline and after the intervention. Additionally, comparisons of the effects of the different genotypes of the Val66Met polymorphism at the *BDNF* gene on the outcome variables were also performed.
Results: The patients in the CRT group presented with improvements in both cognition and quality of life. However, no significant changes were detected in the serum levels of BDNF. Interestingly, we found a significant positive interaction effect between the serum BDNF levels and the different *BDNF* genotypes. The Val/Val group showed significantly higher serum levels after the CRT treatment. However, the interaction among the serum BDNF levels, the *BDNF* genotypes and the treatment condition was not statistically significant.
Conclusions: The replication of the previous finding of increased serum BDNF levels after cognitive remediation in clinically stable individuals with schizophrenia was not achieved. However, our data indicated that genetic variability may be mediating serum BDNF activity in the context of CRT.

1. Introduction

Brain-derived neurotrophic factor (BDNF) has been proposed as a putative candidate biomarker for schizophrenia and particularly for the process of cognitive recovery (Penadés et al., 2015). BDNF and cognition have been found to be slightly associated in schizophrenia (Ahmed et al., 2015; Carlino et al., 2011). Even though there is substantial heterogeneity across studies (Skilleter et al., 2015), a recent study investigated the relation between BDNF and cognition and found that BDNF levels were associated with cognitive domain areas (Hori et al., 2017). Moreover, *BDNF* genetic variants, such as the Val66Met polymorphism, seem to play a role in cognitive performance among both patients and healthy controls (Zhang et al., 2016).

In terms of treatment, one meta-analysis showed that peripheral BDNF levels increased after antipsychotic treatment (Fernandes et al., 2015). Nonetheless, this incremental change was not related to the response to the medication, and thus, the meaning of these BDNF changes remains unclear. Currently, only one study has directly tested the role of BDNF as a marker of response to cognitive remediation therapy CRT. Vinogradov et al. (2009) found a significant increase in serum BDNF levels after cognitive training, relative to participants in a control condition. Interestingly, the BDNF levels in the participants after CRT were found to be similar to the levels in the group of the healthy controls, but the incremental change in the BDNF levels was not correlated with cognitive improvements. Finally, by enlarging the initial sample and using an intent-to-treat analysis, the authors confirmed the results

* Corresponding author at: Clinical Institute of Neurosciences (ICN), Hospital Clinic, C/ Villarroel 170, 08036 Barcelona, Spain.
E-mail address: rpenades@clinic.ub.es (R. Penadés).

https://doi.org/10.1016/j.schres.2017.12.002
0920-9964/

(Fisher et al., 2016). Nevertheless, no other replication of this trial has been accomplished yet.

The main objective of this study was to replicate the previous finding of increased serum BDNF levels after cognitive remediation in clinically stable individuals with schizophrenia. In addition, we tried to test whether changes in cognition, symptoms, or quality of life were associated with changes in the levels of serum BDNF. Finally, and for the first time in the literature, we investigated the role of the Val66Met polymorphism (rs6265) in the *BDNF* gene in relation to the outcome variables.

2. Materials and methods

2.1. Participants

The whole sample (n = 70) was recruited from the Hospital Clinic of Barcelona. The sample size was initially chosen to guarantee good statistical power in the analysis of the BDNF serum levels. However, we assume that the sample size was too small for the analysis of the genotype polymorphisms, and thus, this should only be considered an exploratory analysis. The inclusion criteria were as follows: 1) fulfilment of the required criteria for schizophrenia in the DSM-IV-TR using the semi-structured interview (SCID) for axis 1 disorders; 2) evidence of cognitive impairment established by means of a neuropsychological battery; and 3) no significant changes in symptomatology that required modifications of the pharmacological antipsychotic treatment, at least during the prior six months. The exclusion criteria were as follows: 1) neurological or traumatic conditions causing cerebral affectation; 2) abuse of psychotropic substances and 3) other comorbid psychiatric syndromes. A comparison control group of healthy participants (n = 15) was also recruited. The occurrence of lifetime psychiatric symptoms, as assessed with the structured clinical interview for the DSM-IV (non-patient version), was an exclusion criterion for the healthy participants. All the participants gave written informed consent after considering the characteristics of the study.

2.2. Study procedure

The randomization was set by a free, web-based programme (www.randomizer.org) that generated lots. The lots were drawn as sealed envelopes whereby the patients were assigned to either the experimental (CRT) or the control group (Social Skills Training, SST), with each group having 35 patients. The CONSORT flowchart is provided in Fig. 1. The participants were assessed approximately 3 days before the first treatment session and no >3 days after the last session. The blood draw collection time was established between 9 and 10 am, always preceding a complete neuropsychological assessment. The MATRICS Consensus Cognitive Battery (MCCB) was not yet available in a Spanish translation when the study was designed, but we tried to use the recommended measures and domains. Regarding the blinding aspects of the data collectors, the measurement of the serum BDNF levels and the *BDNF* genotyping were performed in completely blinded conditions by authors IL and BA. All the symptom ratings were carried out by a psychiatrist, the author AG, who was totally blinded to the group assignment.

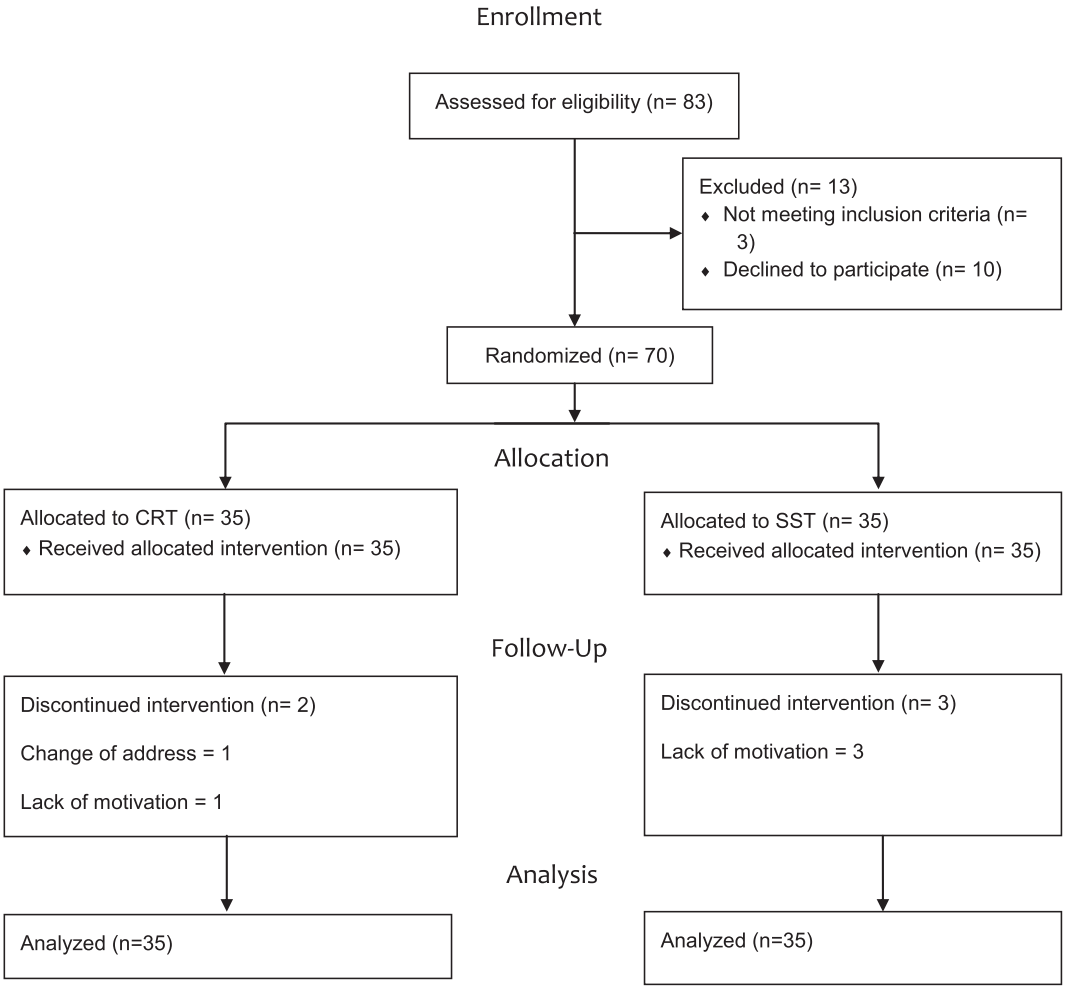

Fig. 1. CONSORT flow diagram.

Please cite this article as: Penadés, R., et al., BDNF as a marker of response to cognitive remediation in patients with schizophrenia: A randomized and controlled trial, Schizophr. Res. (2017), https://doi.org/10.1016/j.schres.2017.12.002