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Symptomatic remission and recovery in major psychosis: is there a role for BDNF? A secondary analysis of the LABSP cohort data

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Abstract:	Remission, relapse prevention, and clinical recovery are crucial areas of interest in schizophrenia (SCZ) research. Although SCZ is a chronic disorder with poor overall outcomes, years of research demonstrated that recovery is possible. There are considerable data linking brain-derived neurotrophic factor (BDNF) to SCZ, however, evidence on the role of BDNF in remission in SCZ is scarce. This study aimed to investigate the relationship between serum BDNF levels and symptomatic remission, simultaneous clinical and functional remission, and recovery in patients with SCZ. A total of 105 patients with SCZ or schizoaffective disorder were recruited for a longitudinal assessment of BDNF levels over 24 months. Longitudinal data were analyzed using mixed-effects linear regression models. The study found significant associations between use of long acting injectables ($\chi 2 = 7.075$, df = 1, p= 0.008), baseline serum BDNF levels (U = 701, z = -2.543, p = 0.011), and “childhood” (U = 475, z = -2.124, p = .034) and “general” (U = 55, z= -2.014, p=0.044) subscales of the Premorbid Adjustment Scale (PAS) with patients maintaining remission and recovery.

	The diagnosis of SCZ was significantly associated with lower BDNF levels for patients with simultaneous clinical and functional remission (Z = 2.035, p = 0.0419) and recovery (Z = 2.009, p = 0.0445) compared to those without. There were no significant associations between remission in the entire sample and longitudinal serum BDNF levels or genetic variants within the BDNF gene. These findings provide further insight into the complex relationship between BDNF and SCZ.
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Editor-in-Chief

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Dear Editor,

Thank you for considering our manuscript for publication and for forwarding the reviewers comments. We have now submitted the revision of our research article extensively modified according to the reviewers' comments. We would like to highlight that the title and the text have been modified to clarify that this paper presents the results of a secondary analysis of the Longitudinal assessment of brain-derived neurotrophic factor in Sardinian psychotic patients (LAPSB) data. As detailed in the method section the protocol was approved by the local ethics committee and published in 2017 (Primavera et al. BMJ Open. 2017 May 25;7(5):e014938). This manuscript represents original work. We believe that the content of our correspondence could be of interest to the readership of *Schizophrenia Research*. The authors of this paper do not have any competing interest in connection with this manuscript.

Yours sincerely,

Prof. Mirko Manchia, on behalf of the co-authors

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Reviewer #1:

Q) The authors have mostly responded to the reviewers' comments. However, they notably did not respond to the following comment: "The longitudinal nature of the study is a strength, but, despite what the authors report, there are other longitudinal studies examining the relationship between BDNF levels and outcome in schizophrenia (e.g., Martinez-Pinteno, 2022)." This reviewer recommends that the authors respond to this comment as they are suggesting that their study is the first of its kind, when this does not seem to be the case.

R) We appreciate the opportunity to clarify the distinct focus and contributions of our study. In our manuscript, we have stated that, to the best of our knowledge, our study is the first to examine the relationship between the longitudinal variation of BDNF and both remission and recovery in SCZ. This was specifically pointed out as most existing studies on remission in SCZ do not incorporate the time criterion, while in our study we assessed patients at five different time points and employed three distinct criteria to operationalize remission and recovery.
Indeed, there are several other longitudinal studies examining the relationship between BDNF and outcomes in schizophrenia, such as the study by Martinez-Pinteno et al. (2022). Their research, which includes two main analyses in two cohorts of first-episode psychosis (FEP) patients, focuses on BDNF levels in relation to relapse after three years and the association with symptom severity. In contrast, our study specifically investigates the association between serum BDNF levels and remission in individuals with SCZ or SAD, tracked over several time points. The key distinctions of our study include the patient population and the clinical outcome focus, which in our case is clinical and functional remission and recovery, as opposed to the focus on relapse and symptom severity in the Martinez-Pinteno et al. study.
To ensure clarity and completeness, we have included a discussion of the Martinez-Pinteno study in the introduction section of our manuscript where we mention that there is a scarcity of studies studying the relationship of BDNF and remission in SCZ : “A recent study examined the BDNF plasma levels in a cohort of first episode SCZ patients that were in remission and did not find difference between BDNF levels of those who did and did not experience a relapse after the three-year follow-up (Martínez-Pinteño et al., 2022)”

Reviewer #3:

Q) The authors have addressed most of the reviewers’ comments. Yet, I could not find the study pre-registration on the European or US registry as required. This in turn raises concerns regarding the distinction between the a-priory study hypothesis and post-hoc analysis and findings. This issue should be fully clarified in the published manuscript.

We would like to clarify that our study, being a secondary analysis of the LABSP data, did not fall under the category of clinical trials that typically require pre-registration in European or US clinical trial registries. As such, our study protocol was not registered in these databases. However, the protocol was approved by the local ethics committee and was published in 2017 (Primavera et al., BMJ Open, 2017 May 25;7(5):e014938), as mentioned in the Methods section of our manuscript.

Symptomatic remission and recovery in major psychosis: is there a role for BDNF? A secondary analysis of the LABSP cohort data ~~tA secondary analysis of the LABSP cohort~~

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Abstract: Remission, relapse prevention, and clinical recovery are crucial areas of interest in schizophrenia (SCZ) research. Although SCZ is a chronic disorder with poor overall outcomes, years of research demonstrated that recovery is possible. There are considerable data linking brain-derived neurotrophic factor (BDNF) to SCZ, however, evidence on the role of BDNF in remission in SCZ is scarce. This ~~study~~ secondary analysis of the Longitudinal Assessment of BDNF in Sardinian patients (LABSP) data aimed to investigate the relationship between serum BDNF levels and symptomatic remission, simultaneous clinical and functional remission, and recovery in patients with SCZ. A total of 105 patients with SCZ or schizoaffective disorder were recruited for a longitudinal assessment of BDNF levels over 24 months. Longitudinal data were analyzed using mixed-effects linear regression models. The study found significant associations between use of long acting injectables ($\chi2 = 7.075$, df = 1, p= 0.008), baseline serum BDNF levels (U = 701, z = -2.543, p = 0.011), and "childhood" (U = 475, z = -2.124, p = .034) and "general" (U = 55, z= -2.014, p=0.044) subscales of the Premorbid Adjustment Scale (PAS) with patients maintaining remission and recovery. The diagnosis of SCZ was significantly associated with lower BDNF levels for patients with simultaneous clinical and functional remission (Z = 2.035, p = 0.0419) and recovery (Z = 2.009, p = 0.0445) compared to those without. There were no significant associations between remission in the entire sample and longitudinal serum BDNF levels or genetic variants within the *BDNF* gene. These findings provide further insight into the complex relationship between BDNF and SCZ.

Keywords: schizophrenia spectrum disorder; remission; BDNF; recovery; longitudinal data; complex psychiatric disorders

1. Introduction

Schizophrenia (SCZ) is a chronic and severe psychiatric disorder with heterogeneous outcomes. Currently, the outcomes of SCZ range from cases requiring repeated hospitalizations to those in which first-episode is followed by complete remission of symptoms **(Vita and Barlati, 2018)**. Marked impairments in social and occupational functioning are frequent, with unemployment rates being extremely high **(Bouwmans et al., 2015; Crespo-Facorro**

et al., 2021), and life expectancy being 10-20 years shorter than the general population **(Chang et al., 2011)**. Nevertheless, it has been demonstrated that some patients affected by SCZ can display a substantial degree of symptomatic and functional improvements over time **(Zipursky et al., 2013)**.

In 2005, in the absence of a univocal method for assessing recovery and remission, the Remission in Schizophrenia Working Group (RSWG) developed a definition of symptomatic remission in SCZ and proposed consensus-based operational criteria for its assessment **(Andreasen et al., 2005)**. According to RSWG, symptomatic remission is evaluated in relation to two criteria: symptom-based and time-based. To meet remission criteria, patients are required to achieve a symptom severity score of mild or less in seven core symptoms of SCZ according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), sustained for a minimum period of 6 months. Since they were first proposed, numerous studies have utilized RSWG criteria to assess clinical remission in diverse patient samples and have proven to be conceptually valid and easy to use both in clinical trials and in clinical practice **(Lambert et al., 2010; Van Os et al., 2006)**, despite possibly failing to capture additional dimensions such as cognitive functioning, depressive symptoms, quality of life, and functional improvements SCZ **(Giordano et al., 2022)**.

In recent years there has been a growing interest in the role of neurotrophins in the pathophysiology of serious psychiatric disorders, including SCZ spectrum disorders **(Angelucci et al., 2005; Fernandes, 2015; Green et al., 2011)**. Brain-derived neurotrophic factor (BDNF) is the most prevalent neurotrophin in the central nervous system (CNS) **(BINDER and SCHARFMAN, 2004)** and plays a crucial role in neuronal differentiation, neurogenesis, synaptogenesis, and neuronal plasticity **(Bramham and Messaoudi, 2005; Huang et al., 1999; Kowiański, 2018)**. Clinical evidence related to the relationship between BDNF levels and schizophrenia has been inconsistent. Despite some studies failing to identify substantial variations between ~~the~~ BDNF levels of ~~SCZ~~ patients with SCZ and those of healthy controls **(Huang and Lee, 2006; Shimizu et al., 2003)**~~, nevertheless~~, several meta-analyses have shown that SCZ patients display reduced levels of BDNF ~~when compared to healthy controls~~ **(Fernandes, 2015; Green et al., 2011; Rodrigues-Amorim et al., 2018)**. BDNF levels have been associated with symptom severity in SCZ, with several studies indicating an association between lower BDNF levels and higher severity of depressive and negative symptoms**(Fang et al., 2019; Isayeva et al., 2022; Manchia et al., 2022; Wysokiński, 2016)**, as well as impaired cognitive function **(Ahmed et al., 2015; Carlino et al., 2011; Green et al., 2004; Isayeva et al., 2022; Zhang et al., 2012)**. The Val66Met (rs6265) polymorphism within the *BDNF* gene, produces valine (Val) to methionine (Met) substitution at codon 66, and is the most commonly studied polymorphism within the BDNF gene. It has been well established that Val66Met polymorphism has been associated with intracellular trafficking **(Chiaruttini et al., 2009)** and affects activity-dependent secretion of BDNF and hippocampal activity **(Egan et al., 2003)**.The presence of Met allele has been previously associated with incidence and clinical features of SCZ **(Rosa et al., 2006; Sun et al., 2013)**, specifically cognitive symptoms of SCZ **(Ahmed et al., 2015; Lu et al., 2012; Rybakowski et al., 2006; Zhai et al., 2013)**. However, large number of previous studies report no evidence that Val66Met poly-morphism is directly associated with the risk of developing SCZ (**Chang et al., 2009; Skibinska et al., 2004; Tochigi et al., 2006; Zhou et al., 2010)**.

The findings of the studies examining the relationship between BDNF levels with clinical and treatment factors associated with SCZ are quite mixed and inconclusive. Although there are considerable data linking BDNF to schizophrenia, there is a scarcity of evidence in the literature examining the role of BDNF in remission or recovery in SCZ. A recent study examined the BDNF plasma levels in a cohort of first episode SCZ patients that were in remission and did not find difference between BDNF levels of those who did and did not experience a relapse after the three-year follow-up **(Martínez-Pinteño et al., 2022)** ~~One study~~ Another study that ~~examined the relationship~~investigated the association between BDNF levels and remission status in a sample of 64 Chinese patients with SCZ, did not find any difference in se-rum BDNF between remitters and non-remitters **(Renjan et al., 2014)**. To our knowledge, there are no other studies that looked at the correlation between BDNF and remission or recovery. Thus we used data of the longitudinal assessment of BDNF in Sardinian psychotic patients (LABSP) study e ~~main aim of this study wats t~~o examine the association of serum BDNF levels with symptomatic remission, simultaneous presence of clinical and functional remission, and recovery in patients with SCZ. Additional aims of this secondary analysis were: i) to evaluate eventual differences between SCZ and schizoaffective disorder (SAD) in longitudinal BDNF levels and various remission criteria; ii) probe the possible association of genetic variants in the *BDNF* gene with remission and recovery; iii) to identify ~~examine the~~ possible predictors of remission in SCZ.~~.~~

2. Materials and Methods

2.1. Study design

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This study is a secondary post-hoc analysis of the LABSP data focusing on the relationship between serum BDNF levels and clinical outcomes in SCZ. ~~(Primavera et al., 2017)~~A total of 105 patients with SCZ spectrum disorders were recruited for ~~a longitudinal assessment of BDNF in Sardinian psychotic patients (~~the LABSP~~)~~ study over the course of 24 months. Repeated Measures and Sample Size (RMASS) software was used to calculate sample size for mixed-effects linear regression models for the analysis of longitudinal data. The sample comprised SCZ or SAD patients recruited in the community mental health center of the Unit of Psychiatry of the University of Cagliari, Italy. The inclusion criteria were: age between 18 and 65 years; diagnosis of SCZ or SAD according to DSM-IV-TR; clinical stability during the past six months before recruitment. The latter was ascertained through direct assessment of the patients and review of clinical charts. Patients with severe medical conditions, mental retardation, neurological disease or previous head injury, and current alcohol and drug dependence were excluded from the study. Only those patients who were able to provide written informed consent were recruited for the study. LABSP study protocol including detailed design and methodology have been published previously (Primavera et al., 2017). Ethics approval was obtained from the University of Cagliari Health Agency Ethics Committee, and the study was carried out according to national laws and the principles of the Declaration of Helsinki.

2.2. Measures and assessments

Initial diagnosis of SCZ or SAD was confirmed through the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (SCID-I/P) **(FIRST, 1997)**. The patients were assessed for various measures at baseline (T0), 6 months (T1), 12 months (T2), 18 months (T3), and 24 months (T4). Temporal variations in psychopathology, functioning, and subjective well-being, along with other parameters, were evaluated at each time point. The study sample is the same as the one described in previous publications from our group **(Isayeva et al., 2022; Manchia et al., 2022, 2018; Primavera et al., 2017)**, where more detailed information regarding the assessment and evaluation process and preliminary findings are presented. Socio-demographic data were collected using the Association for Methodology and Documentation in Psychiatry (AMDP) **(Conti et al., 1988)** assessment tool. We also evaluated premorbid dysfunction, a well-established prognostic marker in schizophrenia patients, using the Premorbid Adjustment Scale (PAS) **(Cannon-Spoor et al., 1982)**. This scale measures four age periods which are childhood, early adolescence, late adolescence, and adulthood, using five psychosocial domains: sociability and withdrawal, peer relations, school performance, school adjustment and socio-sexual adjustment.

2.3. Classification of types of remission

The criteria defined by RSWG **(Andreasen et al., 2005)** were applied to assess the clinical remission status of the patients. The assessment of acute psychopathological symptoms and clinical status of the patients was evaluated using the 30-item Positive and Negative Syndrome Scale (PANSS) **(Kay et al., 1987)**. Symptom-based criteria considered eight focal items of the PANSS scale, specifically, P1-Delusions, P2-Conceptual disorganization, P3-Hallucinatory behavior, N1-Blunted affect, N4-Passive-apathetic social withdrawal, N6-Lack of spontaneity and flow of conversation, G5-Mannerisms and posturing and G9- Unusual thought content. Time-based criteria were not applied at the baseline (T_0), however, it was applied during all subsequent evaluations which are 6 months(T_1), 12 months (T_2), 18 months (T_3), and 24 months (T_4). Patients were in clinical remission when the scores obtained for each of those items were less than or equal to 3 for a period of at least six months. The evaluation of functional remission was carried out using the Personal and Social Performance (PSP) scale **(Goldman et al., 1992)**, which analyzes the social functioning of patients with schizophrenia across four dimensions: social activities, personal and social relationships, self-care, and disturbing and aggressive behaviors. We considered patients to reach functional remission when a total score was more than or equal to 70 since this score is associated with overall good functioning. Subjective well-being, which was considered a personal recovery measure, was assessed using the Subjective Well-being Under Neuroleptic Scale–short version SWN-K scale **(Naber, 1995)**; a total score of 80 and above was considered a good overall level of personal well-being. For the purposes of this study, we applied two additional classifications of remission: an intermediate group was comprised of patients who simultaneously maintained clinical and functional remission for at least six months and a recovery group included patients who simultaneously maintained clinical, functional remission and good subjective well-being for at least six months.

2.3. Assessment of serum BDNF levels and genetic analysis

The peripheral blood sample was drawn from each patient at the same time of the day (between 8 am and 10 am) at each visit. After being kept in serum separator tubes at room temperature (25°C) for about 4 hours to coagulate, the blood samples were centrifuged at approximately 1,000 x g for 15 min. Following that, the supernatant serum samples were instantaneously stored in small aliquots at −20 °C for future analysis. Serum BDNF was assessed using a commercial human enzyme-linked immunoassay (ELISA) kit (Booster Immunoleader, Cat. N° EK0307) following the manufacturer's protocol and kit instructions. The optical absorbance density of each sample was read with a 450 nm filter in a microplate reader (Thermo Scientific Multiskan FC) within 30 minutes after the final stage of the kit procedure. The obtained data was analyzed using Thermo Scientific software SkanIt 3.0 for Multiskan FC.

Tag single nucleotide polymorphisms (SNPs), with $r2 \geq 0.8$ and with a minor allele frequency threshold of 0.01, were selected using the Tagger program implemented in the Haploview v4.2 based on linkage disequilibrium (LD). Genotyping of the BDNF SNPs rs1519480, rs11030104, rs6265 (Val66Met), and rs7934165 was performed using TaqMan genotyping assays on demand (C_11592757_20, C_1751792_10, C_11592758_10, C_1197567_10, ThermoFisher Scientific) on a StepOne Plus instrument (ThermoFisher Scientific). Primers were marked in VIC and FAM to discriminate between alleles. The reaction was carried out in 10 µL final volume, containing 5 µL of MasterMix (2X), 0.5 ul of probe assay (20X), 1 µL of cDNA and 3.5 µL of RNA-free water. Polymerase Chain Reaction (PCR) conditions were the following: 30 sec. 60°C, 10 min 90°C, and 40 cycles of 95°C for 15 sec, and 60°C for 1 min.

2.4. Statistical analysis

Continuous variables were evaluated and expressed through the median, while for categorical variables, the percentage frequency and odds ratio (OR) was used. Comparisons of demographic and clinical data were carried out between different groups (clinical remission/ clinical non-remission, clinical-functional remission/ clinical-functional non-remission, recovery/non-recovery) using the Mann-Whitney rank test for continuous variables and the Pearson Chi-square or the exact Fisher test for categorical variables. We used linear mixed-effects regression models (MLRM) to analyze longitudinal data. Mixed-effects linear models flexibly describe relationships between the response variable and multiple covariates while taking into account repeated measures across participants particularly when the number of observations for the subject is not the same across time **(Hedeker et al., 2009; Pinheiro and Bates, 2000)**. We first performed a visual inspection of mean serum BDNF levels at each time-point using boxplots. This allowed us to assess the normality of the distribution of serum levels and to identify outliers. Then we log-transformed our BDNF data to reduce the skewness in our original data. After evaluating the normal distribution of the log-transformed variable, we regressed our independent variables and covariates (age and sex) on serum BDNF levels over time. Missing data for independent variables were treated with the "na.action" function implemented in R **(Bates et al., 2015)**. The MLRM analysis was performed using "lme4" package **(Bates et al., 2015)** in R. The calculation of the significance of the identified MLRM models was carried out with the "multcomp" package. Finally, the graphical representations of the regression models were derived using the "sJPlot" and "sjmisc " packages.

3. Results

3.1. Characteristics of the sample

Our sample included 105 patients, 64 diagnosed with SCZ and 41 with SAD. The mean age of the sample at baseline was 48.85±10.45 years.

The main demographic and clinical characteristics of the study sample can be found in Table 1. More details about the characteristics of the sample can be found in the Supplementary Table 1.

Table 1. Main Demographic and Clinical Characteristics of LABSP Sample.

Variable (continuous)	N	Mean	SD
BDNF serum levels, ng/ml	105	25.45	13.67
Age, years	105	48.85	10.45
Age of onset, years	105	21.77	9.30
Duration of illness, months	105	308.51	134.33
Age at first treatment, years	105	24.23	8.95
Duration of untreated illness, months	105	29.07	54.60
Antipsychotics, chlorpromazine equivalents, mg/day	103	378.92	272.03

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Variable (categorical)	N	%
Sex (male)	74	70.5
Presence of family history of mental disorders	64	61.0
Presence of family history of schizophrenia	31	29.5
Presence of family history of bipolar disorder	8	7.6
Presence of family history of major depressive disorder	19	18.1
Presence of family history of anxiety disorders	10	9.5
Diagnosis of schizophrenia (SCID-I)	64	61.0
Diagnosis of schizoaffective disorder (SCID-I)	41	39.0
Diagnosis of obsessive-compulsive disorder (SCID-I)	5	4.8
Diagnosis of cluster A personality disorders (SCID-II)	2	1.9
Diagnosis of cluster B personality disorders (SCID-II)	2	1.9
Diagnosis of cluster C personality disorders (SCID-II)	2	1.9
Diagnosis of personality disorder NOS (SCID-II)	1	1.0

Abbreviations: LABSP, longitudinal assessment of BDNF in Sardinian psychotic patients; BDNF, brain-derived neurotrophic factor; SD, standard deviation; SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I); SCID-II, Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II).

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3.2. Clinical remission and recovery

According to the RSWG criteria, 28.6% of the subjects maintained clinical remission at T1. The percentage of the subjects who maintained clinical remission at T2, T3, and T4 months were 19.0%, 11.4% and 1.9%, respectively. Those who maintained functional remission only for at least 6 months were 12.4%, while those who reported good subjective well-being for at least 6 months were 52.4%. The subjects who were able to maintain both clinical and functional remission simultaneously at 6 months were 6.7%, at 12 months 1.9%, and there were none at 18 months and further. As for recovery (clinical, functional remission, and subjective well-being together), the percentages at 6 and 12 months were respectively 3.8% and 1.0%. No ~~patient maintained~~patient maintained recovery at 18 months and further. Table 2 indicates the percentages of the patients who maintained different categories of remission at different timepoints and those who dropped out.

Table 2. Percentage of patients maintaining different categories of remission and dropping out.

Variables (categorical)	N (%)	Missing N (%)
Clinical Remission		
6 months	30 (28.6)	6 (5.0)
12 months	20 (19.0)	14 (13.3)
18 months	12 (11.4)	29 (27.6)
24 months	2 (1.9)	37 (35.2)
Clinical Remission + Functional Remission		
6 months	7 (6.7)	6 (5.7)
12 months	2 (1.9)	13 (12.4)
18 months	0 (0.0)	28 (26.7)
24 months	0 (0.0)	39 (37.1)
Clinical Remission + Functional Remission + Subjective Well-Being (Recovery)		
6 months	4 (3.8)	11 (10.5)
12 months	1 (1.0)	20 (19.0)

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18 months	0 (0.0)	32 (30.0)
24 months	0 (0.0)	49 (46.7)

We then compared subjects in clinical remission at T1 with those who did not maintain clinical remission by sex, age, diagnosis (SCZ or SAD), comorbidity with medical conditions, previous or current use of substances, long-acting injectable (LAI) therapy, education, duration of illness, duration of untreated disease (DUP), various subscales of the PAS scale and serum levels of BDNF at baseline (Table 3).

Table 3. Comparison of categorical and continuous variables between clinical remission and non-remission group

Variables (categorical)	**Clinical Remission 6 months N = 30 (%)**	**Clinical Non-remission 6 months N = 69 (%)**	**P value**
Gender (M)	21 (70.0)	50 (72.5)	0.812
Diagnosis SCZ	17 (56.7)	44 (63.8)	0.653
Diagnosis SAD	13 (43.3)	24 (34.8)	0.499
Comorbid Medical Diagnosis	13 (43.3)	33 (47.8)	0.847
Substance use (previous)	10 (33.3)	18 (26.1)	0.457
Substance use (current)	1 (3.3)	4 (5.8)	1
LAI therapy	2 (6.67)	22 (31.9)	**0.008**
Variables (continuous)	**Clinical Remission 6 months N = 30 Median**	**Clinical Non-remission 6 months N = 69 Median**	**P Value**
Age	50	49	0.792
Education (years)	9.96	8	0.338
Duration of Illness (months)	306	288	0.393
DUP	7	6	0.842
PAS (childhood)	0.7	1.8	**0.034**
PAS (early adolescence)	1.8	2	0.35
PAS (late adolescence)	2.6	2.6	0.522
PAS (adulthood)	2.3	3.7	0.063
PAS (general)	2.9	3.6	0.073
PAS (4 periods)	2	2.7	0.063
PAS (4 periods + general)	2.2	3	0.068
PANSS (total score)	56	78.5	**0.001**
Serum BDNF levels (baseline)	26.0	16.1	**0.011**

Abbreviations: SCZ, schizophrenia; SAD, schizoaffective disorder; LAI, long acting injectable; DUP, duration of untreated psychosis; PAS, Premorbid Adjustment Scale; BDNF, brain-derived neurotrophic factor.

The same parameters were also compared in subjects with clinical and functional remission at 6 months (Table 4) and recovery at 6 months (Table 5). The statistically significant associations were with LAI ($\chi 2 = 7.075$, df = 1, p= 0.008), the "childhood" subscale of the PAS scale (U = 475, z = -2.124, p = .034), and baseline serum BDNF levels (U = 701, z = -2.543, p = 0.011) for subjects in clinical remission (Figure 1), the "general" subscale of PAS (U = 55, z= -2.014, p=0.044) for subjects in recovery. Furthermore, the PANSS total score was significantly associated with

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participants in clinical remission (U = 271, z = -5.818, p < 0.001), those in clinical and functional remission (U = 48, z = -3.741, p = 0.0002), as well as participants in the recovery group (U = 53.5, z = -2.370, p = 0.018).

No significant associations were found for subjects in simultaneous clinical and functional remission. We also compared the parameters of functional remission and subjective well-being with the baseline BDNF levels, finding no correlations respectively. It was therefore decided to examine the longitudinal trend of serum BDNF in relation to various criteria for remission.

Table 4. Comparison of categorical and continuous variables between clinical and functional remission and non-remission group

Variables (categorical)	**Clinical + Functional Remission 6 months N = 7 (%)**	**No Remission 6 months N = 92 (%)**	**P value**
Gender (M)	6 (85.7)	65 (70.6)	0.669
Diagnosis SCZ	4 (57.1)	57 (62.0)	1
Diagnosis SAD	3 (42.9)	34 (40.0)	1
Comorbid Medical Diagnosis	2 (28.6)	44 (47.8)	0.445
Substance use (previous)	4 (57.1)	24 (26.1)	0.194
Substance use (current)	0 (0.0)	5 (5.4)	1
LAI therapy	1 (14.3)	23 (25.0)	0.677
Variables (continuous)	**Clinical + Functional Remission 6 months N= 730 Median**	**No Remission 6 months N= 9269 Median**	**P value**
Age	44	49	0.44
Education (years)	12	8	0.12
Duration of Illness (months)	336	312	0.99
DUP	6	6	0.88
PAS (childhood)	1	1.5	0.46
PAS (early adolescence)	1.6	2	0.11
PAS (late adolescence)	2	2.9	0.1
PAS (adulthood)	1.7	3.5	0.053
PAS (general)	2.6	3.56	0.06
PAS (4 periods)	1.8	2.45	0.074
PAS (4 periods + general)	2.2	2.87	0.128
PANSS (total score)	47	75	**0.0002**
Serum BDNF levels baseline	28.5	21.15	0.181

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Table 5. Comparison of categorical and continuous variables between recovery and non-recovery group

Variables (categorical)	**Recovery 6 months N = 4 (%)**	**No Recovery 6 months N = 90 (%)**	**P value**
Gender (M)	3 (75.0)	63 (70.0)	1
Diagnosis SCZ	3 (75.0)	55 (61.1)	0.659
Diagnosis SAD	1 (25.0)	34 (37.8)	1
Comorbid Medical Diagnosis	1 (25.0)	43 (47.8)	0.62

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Substance use (previous)	2 (50.0)	26 (28.9)	0.589
Substance use (current)	0 (0.0)	5 (5.5)	1
LAI therapy	0 (0.0)	23 (25.6)	0.569
Variables (continuous)	**Recovery 6 months N= 4 Median**	**No Recovery 6 months N= 90 Median**	**P value**
Age	57	49	0.68
Education (years)	12	8	0.5
Duration of Illness (months)	396	276	0.189
DUP	6	6	0.445
PAS (childhood)	0.75	1.5	0.669
PAS (early adolescence)	1.6	1.8	0.19
PAS (late adolescence)	1.6	2.8	0.102
PAS (adulthood)	2	3.33	0.226
PAS (general)	2	3.44	**0.044**
PAS (4 periods)	2	2.4	0.324
PAS (4 periods + general)	2.33	2.76	0.331
PANSS (total score)	52	75	**0.018**
Serum BDNF levels baseline	31.9	21.3	0.330

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3.3. Role of remission and recovery variables and diagnosis of schizophrenia

We evaluated the role of clinical remission measures (6, 12, 18, and 24 months), clinical and functional measures simultaneously, and recovery measures (6 and 12 months) with respect to BDNF levels over time and did not detect any statically significant associations (Table 6). We further evaluated BDNF levels across subjects who sustained remission and recovery according to specified criteria at each time point, compared to those who did not maintain remission or recovery. Our analysis revealed no significant differences in BDNF levels between these groups at any time point (see Supplementary Table 2). We also looked at the difference between the patients with SCZ and SAD regarding longitudinal BDNF levels and various remission criteria. We found that the diagnosis of SCZ was significantly associated with BDNF levels for patients maintaining simultaneous clinical and functional remission at 12 months ($Z = 2.035$, $p = 0.0419$) and recovery at 6 months ($Z = 2.009$, $p = 0.0445$). In addition, despite not finding statistically significant associations with other remission variables, we observed trends for the analysis of SCZ diagnosis with BDNF levels and remission at 6 months ($p = 0.0818$), remission at 12 months ($p = 0.0545$), remission at 18 months ($p = 0.0727$), and recovery at 12 months ($p = 0.0632$).

Table 6. Longitudinal association between serum BDNF levels and clinical remission (at 6, 12 ,18, and 24 months) and recovery (at 6 and 12 months): mixed-effect regression models.

Variables (categorical)	Estimated Coefficient	Z value	P value
Clinical Remission (6 months)	0.037286	0.623	0.533
Diagnosis of SCZ	-0.099666	-1.741	0.0817
Clinical Remission (12 months)	-0.037986	-0.526	0.599
Diagnosis of SCZ	-0.112151	-1.923	0.0544
Clinical Remission (18 months)	0.007438	0.073	0.942
Diagnosis of SCZ	-0.112180	-1.795	0.0727
Clinical Remission (24 months)	0.062762	0.399	0.689807
Diagnosis of SCZ	-0.105038	-1.509	0.131307

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Clinical+Functional Remission (6 months)	0.049713	0.585	0.558
Diagnosis of SCZ	-0.095889	-1.688	0.0914
Clinical+Functional Remission (12 months)	0.043872	0.142	0.887
Diagnosis of SCZ	-0.118707	-2.031	**0.0422**
Recovery (6 months)	0.061492	0.474	0.635
Diagnosis of SCZ	-0.117490	-2.011	**0.0443**
Recovery (12 months)	-0.273496	-0.521	0.603
Diagnosis of SCZ	-0.115452	-1.859	0.063

3.4. Changes in the BDNF levels over time among subjects who subsequently relapsed

We evaluated the changes in BDNF levels among subjects who had experienced clinical remission at T1 but subsequently relapsed at T2, T3, or T4. The results showed that there was a significant decrease in BDNF levels of these subjects over time (Z = -4.79, p =1.67e-06).

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3.5. Association between remission and genetic variance within BDNF gene

Finally, we did not identify any statistically significant association between different remission criteria and genetic variants within the *BDNF* gene (Supplementary Table 1).

4. Discussion

This ~~study~~ secondary post-hoc analysis of LABSP data investigated whether the longitudinal variation of BDNF could correlate with levels of remission in patients with SCZ and SAD defined according to diverse criteria. We did not find a statistically significant relationship between different criteria for remission and longitudinal serum BDNF levels in the whole sample. Similarly, a cross-sectional study in a Chinese patient sample of SCZ patients did not find a significant relationship between remission and BDNF **(Renjan et al., 2014)**.

We compared the different demographic and clinical characteristics of the subjects in symptomatic remission at T1 with those of non-remitters. Interestingly, our results indicated that LAI therapy and the "childhood" subscale of the PAS scale were significantly correlated with not being able to maintain remission. LAIs have been considered extremely beneficial for patients with a history of poor treatment adherence **(Correll et al., 2016)**, and have been associated with improved patient outcomes **(Peuskens et al., 2010)** and lower relapse rates **(Gaebel et al., 2010; Kane et al., 2010)**. LAIs have been shown to improve medication adherence in patients who lack insight or comply poorly with oral medication **(Park et al., 2013)**. The attitude of healthcare professionals in prescribing LAI to patients may influence the choice of treatment offered to the patients, and therefore offer a plausible explanation for our results **(Geerts et al., 2013)**. In fact, a recent survey of 891 European psychiatrists and nurses found that while 96% of them preferred LAI medications over oral treatment for patients with chronic SCZ, only 40% of them favored LAI medications for first-episode patients **(Geerts et al., 2013)**. Thus, the correlation we found between LAIs, and non-remitted patients may be due to the tendency to prescribe LAIs to severe patients rather than to functioning patients with fewer symptoms.

As we expected, our analysis revealed a significant association between symptom severity, assessed using the PANSS total score, and established criteria for remission and recovery. We have also observed a significant relationship between worse functioning during childhood according to PAS and not being able to maintain clinical remission at T1, as well as the "general" subscale of PAS and recovery. Our results are in accordance with previous research that has shown that poor premorbid adjustment is associated with symptom severity **(MacBeth and Gumley, 2008; Mezquida et al., 2017; Stefanatou et al., 2018)**, functionality, and subjective recovery **(Caqueo-Urízar et al., 2022)**. Specifically, lower premorbid adjustment during childhood and adolescence predicted which patients were less likely to reach symptomatic and functional recovery after three years **(Treen Calvo et al., 2018)**.

Even though we did not find a significant association between the longitudinal variation of BDNF and remission, one significant relationship that we observed in this study was the association between baseline (T0) serum BDNF levels and clinical remission at 6 months where patients in remission had higher levels of BDNF compared to those who did not maintain remission. In previous analyses of current data, we found that BDNF levels were significantly lower in patients displaying more severe depressive and negative symptomology and cognitive impairment **(Isayeva et al., 2022; Manchia et al., 2022)** which are consistent with the findings of several previous studies where BDNF levels were associated with symptom severity in SCZ **(Chen et al., 2009; Pillai et al., 2010; Rizos et al., 2010)**. Here, we observed a general decline in the trajectory of BDNF levels over time for both remitters and non-remitters. This might explain why we were able to find a significant association between baseline BDNF and remission, but not between a longitudinal variation of BDNF and remission. Another plausible explanation could be the insufficient sample size, which was significantly reduced by attrition during the course of the study.

Moreover, we found that the diagnosis of SCZ was significantly associated with lower BDNF levels for the patients maintaining simultaneous clinical and functional remission at T2 and recovery at T1. The diagnosis of SCZ seemed to also show a trend for the negative association between remission at T1, T2, and T3, recovery at T2, and BDNF levels. There is an ongoing controversy in the literature regarding the diagnostic reliability and validity of SAD and the necessity of considering it a separate nosological entity **(Florentin et al., 2023)**. These findings may suggest the possibility that SAD may appear more clinically stable and display better outcomes. However, further research with larger cohorts is needed to clarify the differences between the groups.

We examined if there was a relationship between genetic variants within the *BDNF* gene and remission, using allelic and genotypic (additive, dominant, and recessive) models. The *BDNF* gene Val66Met polymorphism has been previously associated with various clinical aspects of SCZ **(Karacetin et al., 2021; Xiu and Zhang, 2010; Zhang et al., 2012)**. In addition, the rs11030104, rs10501087, and rs6265 (Val66Met) SNPs within the *BDNF* gene have been significantly associated with treatment resistance in SCZ **(Zhang et al., 2013)**. Therefore, we hypothesized that there might be a significant relationship between Val66Met polymorphism and remission in SCZ. However, we found no significant association between them.

Several limitations should be considered in interpreting these results. Firstly, our sample size, especially when considering several events in each remission criteria, was considerably small, which may have restricted our capacity to include more variables in the analyses. Another important limitation of our study is a patient drop-out at each timepoint. Furthermore, our sample included patients only from outpatient settings which might limit the generalizability of our results to other settings. In addition, although we used RSWG criteria for clinical remission **(Andreasen et al., 2005)** which have proven to be a clinically valid construct to measure symptomatic remission **(Van Os et al., 2006)**, there is still a lack of operationalized definition for recovery. Nevertheless, in this study, we attempted to evaluate recovery by incorporating its dimensional view **(Resnick et al., 2004)**, which comprises objective clinical recovery defined by symptom severity and level of functioning, together with subjective personal recovery. Finally, in light of the high attrition rate observed for remission and recovery over the duration of the study we would like to highlight the exploratory nature of our results that await confirmation in larger prospective cohorts.

Notwithstanding these limitations, the main strength of this study is the longitudinal follow-up assessments. Most of the existing studies on remission do not include the time criterion of remission **(AlAqeel and Margolese, 2013)**, while in this study we were able to assess patients at five different time points and use three different criteria to operationalize remission and recovery. To our knowledge, this is the first study that examined the relationship of the longitudinal variation of BDNF with remission and recovery in SCZ.

5. Conclusions

In summary, ~~we~~ our secondary post-hoc analysis found a significant correlation between baseline serum BDNF levels and clinical remission for at least 6 months according to the criteria proposed by the RSWG, while we found no significant correlations with other psychopathological remission measures. This result, if confirmed by other studies, could suggest peripheral dosing of BDNF as a biomarker of clinical remission in patients with SCZ and SAD. The findings of this study provide further insight into the complex relationship between BDNF and SCZ, highlighting the need for further research in this area.

Author Contributions: U.I. performed data analysis and drafted the first version of the manuscript; D.P. contributed to the design of the study. B.C. conceived the study, led the study team, and critically revised the manuscript. M.M. performed data analysis, contributed to the assessment protocol, to the design of the study and co-drafted the manuscript. P.P. and F.P. contributed to statistical analysis and data interpretation. L.D., M.T., E.C., N.I., D.S., contributed to assessments. M.S. and R.C. contributed to brain-derived neurotrophic factor (BDNF) serum levels assessments and laboratory procedures. A.S., D.C., A.M., C.P., C.C.Z. performed genetic analyses. P.F. and W.F. designed the experimental procedures for BDNF assessment and critically revised the manuscript. All authors read and approved the final version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Study data are available upon request to the corresponding author.

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Declaration of Interest statement

The authors of this study declare that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Contributors

U.I. performed data analysis and drafted the first version of the manuscript; D.P. contributed to the design of the study. B.C. conceived the study, led the study team, and critically revised the manuscript. M.M. performed data analysis, contributed to the assessment protocol, to the design of the study and co-drafted the manuscript. P.P. and F.P. contributed to statistical analysis and data interpretation. L.D., M.T., E.C., N.I., D.S., contributed to assessments. M.S. and R.C. contributed to brain-derived neurotrophic factor (BDNF) serum levels assessments and laboratory procedures. A.S., D.C., A.M., C.P., C.C.Z. performed genetic analyses. P.F. and W.F. designed the experimental procedures for BDNF assessment and critically revised the manuscript. All authors read and approved the final version of the manuscript.

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