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Research Article

Do Long-Acting Injectable Antipsychotics Influence Serum Levels of Brain-Derived Neurotrophic Factor in People With Schizophrenia and Schizoaffective Disorder?

Mirko Manchia,[1,2,3] **Ulker Isayeva**,[1,4] **Roberto Collu**,[4] **Diego Primavera**,[1] **Luca Deriu**,[1] **Edoardo Caboni**,[1] **Maria Novella Iaselli**,[1] **Davide Sundas**,[1] **Massimo Tusconi**,[1] **Clement C. Zai**,[5,6] **Maria Scherma**,[4] **Alessio Squassina**,[4] **Donatella Congiu**,[4] **Pasquale Paribello**,[1,2] **Federica Pinna**,[1,2] **Claudia Pisanu**,[4] **Anna Meloni**,[4] **Walter Fratta**,[4,7] **Paola Fadda**,[4,7] **and Bernardo Carpiniello**[1,2]

[1]*Section of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy*
[2]*Unit of Clinical Psychiatry, University Hospital Agency of Cagliari, Cagliari, Italy*
[3]*Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada*
[4]*Division of Neuroscience and Clinical Pharmacology, Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy*
[5]*Tanenbaum Centre for Pharmacogenetics, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada*
[6]*Department of Psychiatry, Institute of Medical Science, Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada*
[7]*Centre of Excellence "Neurobiology of Dependence", University of Cagliari, Cagliari, Italy*

Correspondence should be addressed to Mirko Manchia; mirko.manchia@dal.ca

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Schizophrenia (SCZ) and schizoaffective disorder (SAD) are severe and complex psychiatric disorders whose liability threshold is modulated by the interplay of biological, mainly genetic, and environmental factors. Consistent evidence has pointed to the role of serum brain-derived neurotrophic factor (BDNF) as a plausible illness biomarker in SCZ spectrum disorders. There is no consensus, however, on the temporal trajectory of this decline. Here, we present a secondary analysis of the Longitudinal Assessment of BDNF in Sardinian Psychotic patients (LABSP) study, focusing on the impact of antipsychotic therapy, particularly long-acting injectable (LAI), on the longitudinal trajectory of serum BDNF levels and analyzing the effect of *BDNF* genetic variants. LABSP patients were assessed every 6 months for a series of measures, including the assessment of BDNF serum levels over 24 months. Blood samples for each patient were taken at the same time of the day (between 8:00 and 10:00 a.m.). BDNF serum levels were determined using the BDNF ELISA Kit. Four tag single nucleotide polymorphisms (SNPs) within the *BDNF* gene (rs1519480, rs11030104, rs6265 [Val66Met], and rs7934165) were selected using standard parameters and analyzed with polymerase chain reaction (PCR). Mixed-effects linear regression models (MLRMs) were used to analyze longitudinal data. Twenty-four patients out of 105 LABSP (22.9%) patients received therapy with LAI. Analysis with MLRM showed a significant effect of LAI treatment associated with increasing serum BDNF levels ($Z = 2.2$, $p = 0.02$). However, oral antipsychotics did not significantly impact the longitudinal trajectory of serum BDNF levels ($Z = 0.15$, $p = 0.9$). There was no moderating effect of variants within the BDNF gene on the identified association. We identified a significant longitudinal increase in serum BDNF in SCZ and SAD patients treated with LAI antipsychotic therapy. The significant impact of this preparation of antipsychotic treatment on serum BDNF, despite the limited sample size, points to a moderate to large magnitude of effect that should be investigated in future prospective studies.

1. Introduction

Schizophrenia (SCZ) is a severe, chronic mental disorder causing substantial clinical and functional impairment in people living with the disorder [1]. Typically, delusions and hallucinations (positive symptoms), impaired motivation and social withdrawal (negative symptoms), and cognitive impairment represent the core symptoms of SCZ. Schizoaffective disorder (SAD) is described by the concomitance of these clinical manifestations with major mood disruption, either depressive or manic [2]. These disorders appear to be close nosologically [3] and share a complex diathesis. Indeed, risk liability for SCZ and SAD is likely modulated by the interplay of biological, including genetic, and environmental factors [4–6]. Family, twin, and adoption studies have demonstrated the presence of a substantial genetic contribution to the risk of SCZ and SAD [7, 8]. This has prompted molecular genetic studies, particularly genome-wide analyses, which have identified hundreds of genetic loci significantly associated with the risk of SCZ in a large meta-analysis of samples, including SAD [9].

Predicting illness status and the course of the disorder is a key aim of precision psychiatry approaches [10], which are often based on the application of algorithms that can estimate the risk of developing a trait/disorder based on multimodal data [11]. Measurements informing these predictive algorithms are biomarkers, either based on neuroimaging or detectable in peripheral tissues such as serum, plasma, or cerebrospinal fluid (CSF). Brain-derived neurotrophic factor (BDNF) is extensively studied as a candidate biomarker for the pathogenesis of complex psychiatric disorders due to its role in neurogenesis, synaptic plasticity, and the activity of dopaminergic neurons [12, 13]. Dysregulation of BDNF signaling pathways has been implicated in the pathogenesis of a myriad of neuropsychiatric disorders, including SCZ [14], depression [15], anxiety [16], and bipolar disorder [17]. BDNF is able to cross the blood–brain barrier bidirectionally [18], and positive correlations between central and peripheral BDNF concentrations have been previously found [19, 20]. Indeed, substantial evidence has highlighted serum BDNF as a plausible illness biomarker in SCZ spectrum disorders, with consensus on the presence of decreased levels in patients compared to healthy controls [21, 22]. There is no consensus, however, on the temporal trajectory of this decline. The decrease of peripheral BDNF could be constant, with premorbid levels roughly similar to those detected in unaffected individuals, linearly declining during the course of the illness. Alternatively, BDNF peripheral levels might fluctuate in association with the acute psychopathological phases of the disorder. Indeed, meta-analytical estimates have shown that BDNF decreases significantly in relation to illness activity [22]. Importantly, a critical factor modulating peripheral BDNF levels in SCZ spectrum disorders is pharmacological treatment. BDNF is known to promote the survival of dopaminergic neurons [23] and modulate major neurotransmitter systems implicated in SCZ, including dopamine, serotonin, GABA, and glutamate systems [24]. Quantitative data synthesis shows small but significant increases in serum BDNF levels under antipsychotic treatment [21], although existing studies have a length of follow-up not longer than 1 year. Of particular interest is the impact long-acting injectable (LAI) antipsychotics could exert on BDNF. These pharmacological preparations are key in decreasing the likelihood of poor adherence to treatment [25] and, importantly, appear to be significantly protective against all-cause mortality in patients with SCZ [26]. LAI treatment has also been previously associated with a decrease in symptom severity and a reduction in hospitalization rates in patients with SCZ spectrum disorders [27]. Surprisingly, there is a lack of data on BDNF in relation to the use of LAI in SCZ and SAD.

In a series of studies [28–30], we have sought to investigate the longitudinal variation of serum BDNF levels over 24 months in the Longitudinal Assessment of BDNF in Sardinian Psychotic patients (LABSP) study cohort of Sardinian patients. Briefly, LABSP patients were assessed every 6 months for a series of measures, including the assessment of BDNF serum levels [31]. Here, we present a secondary analysis of LABSP data, focusing on the impact of antipsychotic therapy, particularly LAI, on the longitudinal trajectory of serum BDNF levels. Further, we tested whether genetic variation within the gene encoding for BDNF could moderate the relationship between BDNF serum levels and treatment with LAI.

2. Materials and Methods

2.1. Sample. The LABSP sample of SCZ and SAD patients was recruited at the community mental health center of the Unit of Psychiatry of the Department of Medical Science and Public Health, University of Cagliari and University of Cagliari Health Agency, Cagliari, Italy. The study received approval from the Ethics Committee of the University of Cagliari Health Agency and adhered to the principles outlined in the Declaration of Helsinki. All participants provided their written informed consent. The diagnosis of SCZ or SAD was confirmed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (SCID-I/P) [32] administered by trained mental health professionals. Patients were recruited into LABSP if they fulfilled the following inclusion criteria: (1) age between 18 and 65 years, (2) diagnosis of SCZ or SAD according to DSM-IV-TR, and (3) stability during the 6 months before recruitment. Exclusion criteria were (1) refusal to provide consent, (2) presence of acute psychopathological symptoms, (3) presence of illness-related cognitive impairment of such severity that affects their ability to cooperate, (4) presence of major unstable medical illness, (5) severe mental retardation, (6) major neurological disorder or previous head injury, and (7) current drug and alcohol dependence. Given the characteristics of the patient population followed up at our community mental health center, our sample was not comprised of drug-naïve patients and was on a pharmacological treatment regimen mainly based on antipsychotics.

2.2. Assessment Procedures. Details of the assessment procedures have been previously published [30, 31]. Briefly, blood samples were taken at baseline (T_0), and at four consecutive time points: 6 months (T_1), 12 months (T_2), 18 months (T_3),

and 24 months (T_4). Detailed information on the ongoing pharmacological treatment regimen was collected through a direct assessment of the proband and an accurate review of available medical records. Further details have been illustrated in [30, 33].

2.3. Sampling and Assessment of BDNF Serum Levels. As detailed in Manchia et al. [30], blood samples for each patient were taken at the same time of the day (between 8:00 and 10:00 a.m.). BDNF serum levels were determined using the BDNF ELISA Kit (Booster Immunoleader, Cat. No. EK0307) for the quantitative detection of human BDNF in cell culture supernatants, serum, and plasma. This kit is based on a standard sandwich enzyme-linked immune-sorbent assay technology for specific quantifications of natural and recombinant human BDNF with high sensitivity (<2 pg/mL) and with no detectable cross-reactivity with other relevant proteins. After blood sampling, serum was allowed to clot in a serum separator tube for about 4 h at room temperature (25°C). After that, it was centrifuged at approximately 1000 × g for 15 min. Supernatant serum samples were collected in small aliquots and stored immediately at −20°C for future analysis. Then, samples were processed according to the kit protocol and instructions. The optical density absorbance of each sample was read with a 450-nm filter in a microplate reader (Thermo Scientific Multiskan FC) within 30 min after the final step of the kit procedure. The data obtained were analyzed using the Thermo Scientific SkanIt Software 3.0 for Multiskan FC.

2.4. Genetic Analysis. Standard analytical approaches were performed with the selection of tag single nucleotide polymorphisms (SNPs) using the Tagger tool in Haploview (v4.2) based on linkage disequilibrium (LD) by including SNPs with $r2 \geq 0.8$ and a minor allele frequency threshold of 0.01. Genotyping of the following *BDNF* SNPs: rs1519480, rs11030104, rs6265 (Val66Met), and rs7934165 was carried out using the TaqMan probe on demand (C_11592757_20, C_1751792_10, C_11592758_10, and C_1197567_10, Thermo Fisher) on a StepOne Plus instrument (Thermo Fisher). Primers were marked with VIC and FAM to discriminate between alleles. The reaction was carried out in a 10 μL final volume, containing 5 μL of MasterMix (2×), 0.5 μL of probe assay (20×), 1 μL of cDNA, and 3.5 μL of RNA-free water. Polymerase chain reaction (PCR) settings were as follows: 30 s at 60°C, 10 min at 90°C, and 40 cycles at 95°C for 15 s and 60°C for 1 min.

2.5. Data Analysis. As previously described [30], mixed-effects linear regression models (MLRMs) were used to analyze longitudinal data [34, 35]. Specifically, we regressed independent variables (both categorical and continuous) on BDNF serum levels (dependent variable). We used MLRM because this approach allows for modeling individual changes over time and appears to be more flexible in terms of repeated measures, particularly when the number of observations per subject is not the same at each time point. Further, these models allow the generalization of non-normally distributed data for independent variables. We used MLRM to analyze the impact of oral antipsychotic and/or LAI therapy on the longitudinal variation of BDNF levels. Specifically, these independent variables were regressed on BDNF serum levels while correcting for age and sex. In addition, each *BDNF* SNP was added to MLRM as a covariate while correcting for age and sex to check for a possible moderating effect. Furthermore, an ANOVA was conducted to compare BDNF levels among different LAI molecule groups. All data were analyzed using the "lme4" package implemented in R. Missing data for independent variables was dealt with by the "na.action" function implemented in R that omits missing data. The statistical significance of the identified MLRM was calculated using the "multcomp" R package. Finally, a graphical representation of MLRM was obtained with the R packages "sJPlot" and "sjmisc."

3. Results

3.1. Sample Characteristics. The sample included 105 patients, 64 with a diagnosis of SCZ and 41 with SAD. The main clinical and demographic characteristics of the sample are detailed in Table 1. Relevant to this secondary analysis is the number of subjects who were treated with oral antipsychotic therapy at the time of recruitment (T_0) ($N = 103$, 98%) and those who received therapy with LAI over the course of the study ($N = 24$, 22.9%). Importantly, a proportion of patients treated with LAI had concomitant oral antipsychotic therapy. Practiced antipsychotics vary in line with the real-world setting, frequently featuring combinations of medications. The most frequently employed medications in these treatment regimens are the oral formulations of haloperidol (19.3%), amisulpride (6.4%), aripiprazole (12.9%), chlorpromazine (3.2%), clozapine (25.8%), olanzapine (20.4%), paliperidone (1.0%), quetiapine (6.4%), and risperidone (4.3%). As for LAI medications, the relative frequencies are haloperidol (47.3%), paliperidone (26.3%), risperidone (10.4%), aripiprazole (10.5%), and zuclopenthixol (5.2%). During the study period, no changes were recorded for concomitant psychotherapies or other nonpharmacological interventions.

3.2. Use of Oral Antipsychotics and LAI Antipsychotics and Longitudinal Trajectory of Serum BDNF Levels. Analysis with MLRM did not show a significant influence of treatment with oral antipsychotics on the longitudinal trajectory of serum BDNF levels (Model 1: $Z = 0.15$, $p = 0.9$) (Table 2). This was confirmed when we added sex and age as covariates (Model 2: $Z = -0.04$, $p = 0.9$). We then tested the effect of LAI therapy, observing a trend towards elevated serum BDNF levels over 24 months. Specifically, the subgroup of patients treated with LAI had an increase in serum BDNF levels ($Z = 1.9$, $p = 0.053$). The significance and magnitude of this association increased when the above covariates were included in the model ($Z = 2.2$, $p = 0.02$).

Furthermore, to examine the differences in BDNF levels between different LAI molecule groups, an ANOVA was conducted. The ANOVA was not statistically significant ($F = 0.703$, $p = 0.6$), indicating that there were no significant differences in BDNF levels across the groups.

Table 1: Main demographic and clinical characteristics of the LABSP sample.

	SCZ			SAD		
Variable (continuous)	*N*	Mean	SD	*N*	Mean	SD
Age (years)	64	49.2	10.45	41	48.2	10.26
Education (years)	64	8.80	3.17	41	9.98	3.22
Offspring (*N*)	64	0.23	0.68	41	0.51	1.25
Age of onset (years)	64	21	9.45	41	22.9	9.06
Duration of illness (months)	64	324	127	41	284.34	143.2
Age at first treatment (years)	64	23.8	9.57	41	24.9	7.96
Duration of untreated illness (months)	64	33.8	60.74	41	21.7	43
Antipsychotics, chlorpromazine equivalents (mg/day)	63	394.6	290.3	40	365.16	220.5
Variable (categorical)	*N*	%		*N*	%	
Sex (male)	46	71.9		28	68.3	
Age class						
18–20	1	1.6		1	2.4	
21–25	21	32.8		17	41.5	
26–44	38	59.4		20	48.8	
45–65	4	6.3		3	7.3	
Marital status						
Single	55	85.9		28	68.3	
Married/cohabiting	4	6.3		4	9.8	
Separated/divorced	4	6.3		6	14.6	
Widowed	1	1.6		1	2.4	
NA	0	0		2	4.9	
Presence of offspring	9	14.1		10	24.4	
Employment						
Employed	2	3.1		5	12.2	
Student	1	1.6		0	0	
Registered disabled civilian	61	95.3		34	82.9	
Unemployed	0	0		2	4.9	
Presence of smoking	35	60.3		18	50	
History of substance abuse	23	39		6	16.2	
Current use of substances	5	8.5		0	0	
Presence of family history of mental disorders	42	65.6		22	53.7	
Long-acting antipsychotic therapy	15	23.8		13	32.5	

Abbreviations: NA: not available, SAD: schizoaffective disorder, SCZ: schizophrenia, SD: standard deviation.

3.3. Moderating Effect of BDNF Genetic Variation. Considering these results, we tested whether the four polymorphisms within the *BDNF* gene might influence the impact of LAI therapy on the longitudinal trajectory of serum BDNF levels. The moderating effects of the SNPs within the *BDNF* gene were examined using genotypic and allelic effect models, including additive, dominant, and recessive models. No SNP significantly moderated the identified association (Table 3).

4. Discussion

This secondary analysis of LABSP data found that treatment with LAI antipsychotics, but not with oral antipsychotics, significantly impacted the longitudinal trajectory of serum BDNF levels over the time of follow-up. Specifically, the 24 patients treated with LAI presented a longitudinal increase in serum BDNF levels. This finding is consistent with a number of preclinical [36–38] and clinical [21] studies. Regarding preclinical evidence, Park et al. [37] showed that chronic (21 days) treatment with quetiapine attenuated the hippocampal decrease of BDNF induced in rats through immobilization stress. These authors subsequently suggested that this effect of antipsychotics on BDNF might be class-specific, with second-generation antipsychotics (aripiprazole and olanzapine) but not first-generation antipsychotics (haloperidol) effective in restoring the loss of BDNF induced by immobilization stress [38]. This finding is partly concordant with the work of Pillai, Terry, and Mahadik [36], showing that striatal and hippocampal levels of BDNF in rats decreased after 90 days of treatment with haloperidol but were significantly restored after switching to a subsequent 90-day treatment with either olanzapine or risperidone.

Table 2: Results of mixed-effects linear regression models.

Model	Independent variable	Estimated coefficient	Standard error	*Z*	*p*
Model 1	Time	−0.008	0.002	−5.0	6.3×10^{-7}
	Oral antipsychotic	0.00001	0.00009	0.15	0.9
Model 2	Time	−0.008	0.002	−4.9	1.0×10^{-6}
	Oral antipsychotic	-3×10^{-7}	0.00009	−0.04	0.9
	Age	−0.002	0.003	−0.75	0.4
Model 3	Time	−0.08	0.02	−5.1	3.9×10^{-7}
	LAI	0.11	0.06	1.9	0.053
Model 4	Time	−0.08	0.02	−5.0	6.7×10^{-7}
	LAI	0.14	0.06	2.2	**0.02**
Model 5	Age	−0.003	0.003	−1.07	0.3
	Time	−0.0128	0.003	−4.56	5.31×10^{-6}
	LAI	0.148	0.069	−2.15	**0.032**
	Gender	0.008	0.066	0.117	0.907
	Age	−0.002	0.003	−0.615	0.539
	Smoking	0.114	0.061	1.879	0.06

Note: Model 4 (LAI [0.02]) and Model 5 (LAI [0.032]) set in bold are significant.

Table 3: Interaction of *BDNF* genetic variants with long-acting injectables in modulating longitudinal serum BDNF levels.

Genetic model	Interaction effect	Estimated coefficient	*Z* value	*p* value
Genotypic effect	LAI ∗ rs7934165AG	−0.00052	−0.003	0.998
	LAI ∗ rs7934165GG	0.29835	1.505	0.132
	LAI ∗ rs6265_Val66MetCT	0.13183	0.878	0.379
	LAI ∗ rs6265_Val66MetTT	0.05883	0.222	0.824
	LAI ∗ rs1519480CT	−0.04744	−0.340	0.734
	LAI ∗ rs11030104AG	0.08415	0.573	0.567
	LAI ∗ rs11030104GG	0.30318	1.288	0.198
Allelic effect				
Additive model	LAI ∗ rs7934165_add	−0.16211	−1.624	0.104
	LAI ∗ rs6265_Val66Met_add	−0.07164	−0.662	0.508
	LAI ∗ rs1519480_add	0.03583	0.267	0.790
	LAI ∗ rs11030104_add	−0.12929	−1.268	0.205
Dominant model	LAI ∗ rs7934165_dom	−0.28116	−1.833	0.067
	LAI ∗ rs6265_Val66Met_dom	−0.01080	−0.042	0.967
	LAI ∗ rs11030104_dom	−0.26619	−1.175	0.240
Recessive model	LAI ∗ rs7934165_rec	0.09628	0.581	0.562
	LAI ∗ rs6265_Val66Met_rec	0.11532	0.823	0.410
	LAI ∗ rs1519480_rec	−0.03871	−0.280	0.780
	LAI ∗ rs11030104_rec	0.13186	0.961	0.336

Other authors have suggested that first- (haloperidol) or second-generation (risperidone) antipsychotics can reduce BDNF levels in the rat brain (cortex and hippocampus) [39, 40]. This discrepancy might be reconciled by taking into account antipsychotic dosage [41]. Indeed, Chlan-Fourney et al. [41] observed that intermediate doses of risperidone had no effect on BDNF hippocampal levels in rats, suggesting that higher chronic doses of antipsychotics might determine long-term downregulation of BDNF in the brain. Concerning clinical evidence, our results are consistent with the meta-analysis by Fernandes et al. [21], which included 14 longitudinal studies (total $N = 463$) showing that the use of antipsychotics was associated with a small but significant increase in serum and plasma BDNF levels. Of importance,

this increase in BDNF serum and plasma levels was independent of treatment response (defined as at least 40% reduction in the Positive and Negative Symptoms Scale [PANSS] total score), but, differently from our work, was mainly led by studies showing an increase in plasma levels of BDNF rather than in serum [21]. Prior research has demonstrated that the decrease in peripheral BDNF levels has been associated with more severe depressive symptomatology and cognitive impairments [28, 29, 42] in patients with SCZ spectrum disorders. Depressive symptoms and cognitive impairments are prevalent among patients with SCZ [43, 44], indicating that reduced peripheral BDNF levels may serve as a biomarker for disease activity.

Another finding of our secondary analysis is the discrepant effect of oral and LAI antipsychotic therapy on serum BDNF levels. This might be explained by at least two factors: (1) the increased adherence among patients treated with LAI intrinsic to the nature of this therapy and (2) the specific pharmacokinetics of LAI formulation. LAI preparations have many advantages over oral therapy, such as not having to remember to take drugs daily, reducing the risk of unintentional or deliberate overdose, and transparency of adherence. Secondly, LAI antipsychotics have a more consistent bioavailability [45] and reduced peak-trough plasma levels [46], ensuring a more effective action of the drug centrally. These factors can explain the presence of an increase in BDNF serum levels specific to the subgroup of patients receiving LAI treatment in our study. Indeed, preclinical studies show that serum BDNF increases significantly in rats administered continuously (4–6 weeks, which equals >3 years in humans), but not intermittently, with risperidone [47].

A final remark concerns the absence of a moderating effect of genetic variants within the *BDNF* gene on the significant impact of LAI therapy on the serum levels of this neurotrophin. This is consistent with the quantitative data synthesis of 13 studies performed by Terracciano et al. [48] showing that the Val66Met genetic polymorphism was not associated with BDNF serum levels, a finding corroborated by the GWAS analysis in a large cohort of Sardinian individuals ($N = 2054$). Consistent with the high pattern of LD among the SNPs investigated in this study, no *BDNF* genetic variant significantly moderated the identified patterns of association. However, it is possible that the genetic effects of *BDNF* polymorphisms on serum levels are of such small magnitude that only studies with a very large sample size will be able to detect a significant effect.

Our results should be interpreted in the context of several limitations. First, the subgroup of patients treated with LAI antipsychotics has a limited sample size, a factor that hindered further secondary analysis (for instance, testing an antipsychotic class-specific effect). However, it should be noted that the identification of a significant pattern of association between LAI and serum BDNF in such a small subgroup of patients points to the presence of an effect size of moderate to large magnitude that should be investigated in future prospective studies. Secondly, given the limited sample size of the subgroup treated with LAI, MLRM was run with a limited number of covariates to avoid saturation of models. Nevertheless, all tested models converged flawlessly, suggesting their relative stability. Finally, it is possible that changes in a serum biomarker may not accurately represent the alterations at the brain level. However, the identification of a peripheral marker, such as serum BDNF, associated with a specific trait or phenotype, such as treatment with LAI antipsychotics, might not necessarily offer mechanistic insights into the pathophysiology of the disorder being studied but might rather be of prognostic utility in clinical settings.

5. Conclusions

In summary, our study identified a significant longitudinal increase in serum BDNF in SCZ and SAD patients treated with LAI antipsychotic therapy. The identification of a significant impact of this preparation of antipsychotic treatment on serum BDNF, despite the limited sample size, points to a moderate to large magnitude of effect that should be investigated in future prospective studies.

Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

The authors acknowledge that an earlier version of this work was presented as an abstract submission. The abstract is available at the following source: https://iris.unica.it/handle/11584/250948.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

M.M. 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. U.I. performed data analysis, contributed to the assessment protocol and to the design of the study, and codrafted the manuscript. P.P. and F.P. contributed to statistical analysis and data interpretation. L.D., M.T., E.C., N.I., and D.S. contributed to assessments. M.S. and R.C. contributed to brain-derived neurotrophic factor (BDNF) serum level assessments and laboratory procedures. A.S., D.C., A.M., C.P., and 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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