frontiers | Research Topics

Negative symptoms and cognitive impairment in schizophrenia-spectrum disorders

Edited by
Armida Mucci, Ingrid Melle, Gabriele Sachs and Joseph Ventura

Published in
Frontiers in Psychiatry

ISSN 1664-8714
ISBN 978-2-83251-132-9
DOI 10.3389/978-2-83251-132-9

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Negative symptoms and cognitive impairment in schizophrenia-spectrum disorders

Topic editors

Armida Mucci — University of Campania Luigi Vanvitelli, Italy
Ingrid Melle — University of Oslo, Norway
Gabriele Sachs — Medical University of Vienna, Austria
Joseph Ventura — UCLA Department of Psychiatry, United States

Citation

Mucci, A., Melle, I., Sachs, G., Ventura, J., eds. (2023). *Negative symptoms and cognitive impairment in schizophrenia-spectrum disorders*.
Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83251-132-9

Table of contents

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 22 July 2021
doi: 10.3389/fpsyt.2021.707291

The Cognitive Model of Negative Symptoms in Schizophrenia: A Hierarchical Component Model With PLS-SEM

Ali Ebrahimi[1], *Hamid Poursharifi*[1]*, *Behrooz Dolatshahi*[1], *Omid Rezaee*[2], *Hamid Reza Hassanabadi*[3] and *Farooq Naeem*[4]

[1] Department of Clinical Psychology, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran, [2] Department of Psychiatry, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran, [3] Department of Clinical Psychology, Faculty of Psychology and Educational Sciences, Kharazmi University, Tehran, Iran, [4] Department of Psychiatry, University of Toronto & Centre for Addiction and Mental Health, Toronto, ON, Canada

The cognitive model of negative symptoms suggests that some dysfunctional beliefs mediate the relationship between neurocognitive deficits and negative symptoms and disability. This study tested the hypothesis that dysfunctional performance beliefs mediate neurocognitive deficits, negative symptoms, and disability. We used a hierarchal component model with 85 men patients diagnosed with chronic schizophrenia. Results showed a moderate to strong correlation between dysfunctional performance beliefs, neurocognitive deficits, negative symptoms, and disability. These results support the Hierarchal component model (HCM) of the cognitive model of negative symptoms. Our results indicated that the disability in schizophrenia is mediated through dysfunctional performance beliefs, neurocognitive deficits, and negative symptoms pathway. Further, dysfunctional performance beliefs have a crucial role in this pathway. Therefore, targeting this vicious cycle of dysfunctional beliefs can improve disability in patients with schizophrenia.

Keywords: negative symptom, schizophenia, cognitive model, structural equating modeling, hierarachical model

OPEN ACCESS

Edited by:
Armida Mucci, University of Campania Luigi Vanvitelli, Italy

Reviewed by:
Chao Zhou, Nanjing Brain Hospital Affiliated to Nanjing Medical University, China
Mette Ødegaard Nielsen, Center for Neuropsychiatric Schizophrenia Research (CNSR), Denmark

***Correspondence:**
Hamid Poursharifi
poursharifih@gmail.com

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *09 May 2021*
Accepted: *24 June 2021*
Published: *22 July 2021*

Citation:
Ebrahimi A, Poursharifi H, Dolatshahi B, Rezaee O, Hassanabadi HR and Naeem F (2021) The Cognitive Model of Negative Symptoms in Schizophrenia: A Hierarchical Component Model With PLS-SEM. Front. Psychiatry 12:707291. doi: 10.3389/fpsyt.2021.707291

INTRODUCTION

Negative symptoms such as diminished emotional expression, avolition, alogia, anhedonia, and asociality account for significant disability in persons diagnosed with schizophrenia (1). Approximately 60% of people with schizophrenia suffer from negative symptoms that persist despite treatment (2, 3). The negative symptoms can be disabling and can significantly burden psychosocial health, occupational functioning, and quality of life in people with schizophrenia (4, 5). Psychotropic medications have limited efficacy on negative symptoms (6–8). Evidence indicates that psychotropic medications have little efficacy on the real-world functioning of people with schizophrenia in general (9, 10). Similarly, side effects of antipsychotic drugs might lead to secondary negative symptoms or at least exacerbate negative symptoms (3, 11, 12).

In addition to negative symptoms, cognitive deficits can be troubling features of schizophrenia, adding to their real-world functioning, with almost 98% of the persons with schizophrenia suffering from cognitive deficits (13, 14). Cognitive deficits such as processing speed, attention, vigilance, working memory, verbal learning, visual learning, reasoning, problem-solving, and social cognition are common cognitive deficits in persons with schizophrenia (15, 16).

The cognitive model of negative symptoms suggests that the dysfunctional beliefs such as pessimistic beliefs about performance (e.g., *"If I fail at my work, then I am a failure as a person")* and need for approval (e.g., *"If someone disagrees with me, it probably indicates he does not like me")* mediate the relationship between neurocognitive deficits, negative symptoms, and disability (17–20). Grant and Beck (20) suggest that the psychological aspects of negative symptoms have been less acknowledged. They suggested that the psychological reaction of patients to their neurocognitive deficits (e.g., dysfunctional beliefs) exacerbates negative symptoms and disability (20, 21).

Several studies have examined the cognitive model of negative symptoms. For example, Horan et al. (4) reported the association between dysfunctional beliefs and negative symptoms with quality of life in schizophrenia. However, this study has been criticized for not conducting an in-depth analysis of dysfunctional beliefs. In another study, Green (22) tested functional impairment in schizophrenia through a single-path model from early visual perception, social cognition, defeatist beliefs, and negative symptoms to functional outcomes. They found that defeatist beliefs and negative symptoms mediate the relationship between perception and functional outcomes. Quinlan et al. (23) examined the mediating role of dysfunctional beliefs in the relationship between neurocognitive deficits, negative symptoms, and functional outcomes in patients diagnosed with schizophrenia and schizoaffective disorders. Their result supported the mediating role of dysfunctional beliefs in the relationship between neurocognitive deficits and functional outcomes.

In a recent study, Luther et al. (24) tested the cognitive model of negative symptoms in a community sample. Their results showed a significant path from self-efficacy to negative symptoms and the mediating role of defeatist beliefs. Further, they found a direct relationship between defeatist beliefs and the negative symptoms.

Reviewing the literature of the cognitive model of negative symptoms [e.g., (4, 20, 24)] indicated that the previously proposed models consisted of simple path analysis. Conceptually, it is often better to use hierarchical component models rather than standard one-dimensional structures because their use often reduces the number of structural model relationships, making the PLS path model more parsimonious and easier to understand (25). For example, in most of the currently proposed models [e.g., (4, 20, 22–24)], it has not been well-explained that what type of dysfunctional beliefs is specific and more strongly related to negative symptoms (e.g., performance evaluation, need for approval subscale). Also, while measurement model (outer model) misspecifications is a threat to the validity of SEM results, earlier models seem to have ignored it (26). Therefore, a separate study is needed to examine the cognitive model of negative symptoms using the hierarchical component model (HCM).

Toward this end, the present study is the first one designed to examine the cognitive model of negative symptoms using the hierarchical component model (HCM). In the current study, we utilized the hierarchal component method (HCM) using the Partial Least Squares-Structural Equation Modeling (PLS-SEM). This method is a composite-based approach for modeling complicated interrelationships between observed and latent variables, which has become popular in recent years (27). In addition, PLS-SEM has several advantages over other methods such as first-generation and covariance-based SEM. For example, PLS-SEM is an exploratory method based on an ordinary least squares regression method that predicts the path relationships in complex models. Additionally, PLS-SEM does not require assumptions about the normal distribution of the data and works well with small sample sizes and complex models (25).

Furthermore, the present study implemented a comprehensive assessment battery, that is, neuropsychological tests based on the MATRICS Consensus Cognitive Battery (MCCB), an agreed-upon battery for assessing negative symptoms in schizophrenia (28). MCCB is a performance-based measurement method, and previous studies (4, 23) have recommended using such performance-based assessment tools instead of merely relying on self-report and clinician-rated measures, which improves the accuracy of the measurement that enhances the fitness of a model.

In the current study, we hypothesizeed that dysfunctional performance beliefs significantly mediate the relationship between neurocognitive deficits, negative symptoms, and disability hierarchically in a patient with schizophrenia. We also expected to find significant associations between neurocognitive deficits, dysfunctional performance beliefs, negative symptoms, and disability in patient with schizophrenia.

MATERIALS AND METHODS

Participants

Participants included 100 male patients diagnosed with a schizophrenia spectrum disorder in Tehran Razi Psychiatric Center and were recruited through the purposive sampling method. Data from 15 patients were excluded from the study because of the patients' lack of cooperation and their incomplete data. Thus, we analyzed data from the remaining 85 participants using a structured form; information on the patients' primary demographic data, diagnosis, duration of illness, and psychotropic use, were recorded. Patients have been prescribed Second-generation antipsychotics, Antidepressants, Mood stabilizers, Concomitant medications, and did no patients receive first-generation antipsychotics (For demographics information, see **Table 1**). While the determination of appropriate sample size is a critical issue in SEM, there is no consensus in the literature regarding the appropriate method for estimating sample size for SEM. Notwithstanding, some evidence suggests that simple SEM models could be meaningfully tested even if the sample size is quite small (29, 30). Also, we used PLS-SEM for data analysis, which is not sensitive to small sample sizes (25). In the current study, inclusion criteria were: (a) being 20–60-year-old (b) at least 2 years duration of illness since the onset of schizophrenia spectrum disorder, (c) presence of significant negative symptoms with SANS scores above the cut-off point of 24, and (d) being able to read and write in the Persian language. Exclusion criteria included: (a) a brain injury, learning disability or physical disability, and neurological disease (e.g., Epilepsy, Alzheimer disease, Dementia, Parkinson disease,

TABLE 1 | Demographic characteristic.

	Patients ($N = 85$)			
	Mean	**SD**	***t***	**Sig.**
Age (year)	45.63	8.97	0.005	0.99
Education (year)	10.0	1.94	−122.88	0.00**
Length of condition (year)	13.0	1.68	−140.35	0.00**
Diagnosis	***N***	**%**		
Schizophrenia				
Multiple episodes in partial remission	14	16.5		
Multiple episodes in full remission	64	75.3		
Schizoaffective				
Multiple episodes in full remission	5	5.9		
Multiple episodes in partial remission	2	2.4		
Medication	***N***	**%**		
Second-generation antipsychotics	55	65		
Antidepressants	15	18		
Mood stabilizers	7	8		
Concomitant medications	8	9		

$^{**}p < 0.001$.

Multiple sclerosis) that interfere with the assessment process, (b) side effects of psychiatric medications that interfere with the assessment process (c) presence of acute psychotic symptoms (delusions and hallucinations) that were assessed by SCID-5 in the pre-assessment stage, and (d) being severely disturbed by substance use.

Assessments

Structured Clinical Interview for DSM-5 (SCID-5)

SCID-5 is a semi-structured clinical interview used to diagnose psychiatric disorders based on DSM-5 diagnostic criteria. This interview is designed to reduce interview-related problems, clinical errors, and clinical judgment. The Persian translation of SCID-5 has been found to have acceptable reliability and validity for various categorical diagnoses in different clinical settings (31, 32).

The Scale for the Assessment of Negative Symptoms (SANS)

The Scale for the Assessment of Negative Symptoms (SANS) includes 24 items and categorizes negative symptoms into five dimensions, including Blunted Affect, Alogia, Avolition and Apathy, Asociality, and Attention (33). The Persian version of SANS has an excellent internal consistency ($\alpha = 0.94$), and test-retest reliability ($r = 0.92$) (34). In the current study, the internal consistency of SANS was in a good range ($\alpha = 0.82$).

Dysfunctional Attitude Scale [DAS; Weissman and Beck (17)]

DAS consists of 40 items designed to measure underlying beliefs about depressive symptoms. Fifteen items of DAS assess dysfunctional beliefs about performance, and 10 items measure the need for approval subscale. The measure is completed based on a 7-point Likert scale from 1 = *strongly agree* to 7 = *strongly disagree*. The Persian version of DAS showed good test-retest reliability ($r = 0.76$) (35). In the present study, the internal consistency of DAS was in the excellent range ($\alpha = 0.82$).

MATRICS Consensus Cognitive Battery (MCCB)

Measurement and treatment research to improve cognition in schizophrenia consensus cognitive battery (MCCB) is a standard cognitive assessment method in Schizophrenia. The MCCB measures Processing Speed, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning/Problem Solving, and Social Cognition. It has a high test-retest reliability (28). In the current study, the internal consistency of 0.75 was reported for MCCB.

World Health Organization Disability Assessment Schedule (WHODAS 2.0)

This 36-item self-administered questionnaire assesses disability in general areas of life. WHODAS 2.0 subscales include Cognition, Mobility, Getting Along, Life Activities, Participation, and Self-Care. The total Cronbach's alpha of 0.98 has been reported for the Persian version of WHODAS 2.0 total score, and scores of 0.97, 0.98, 0.98, 0.98, and 0.97 has been found for the general population, substance abusers, alcohol abuser sample, patients with mental disorders, and patients with the physical illness, respectively (36, 37). The internal consistency of WHODAS 2.0 was 0.80 in the current study.

Procedure

The study received ethical approval from the Research Ethics Committee of the University of Social Welfare and Rehabilitation Sciences (IR.USWR.REC.1399.103). All participants were informed about the aims of the study and the confidentiality of the data. Those who provided written informed consent were invited to participate. Each assessment lasted between 3 and 5 h. Diagnostic assessments to confirm diagnosis criteria of schizophrenia spectrum disorder were carried out by a psychiatrist and a clinical psychologist using the Persian Version of Structured Clinical Interview for DSM-5, SANS, MCCB, DAS, and WHODAS 2.0. These assessments were carried out between July 2020 and November 2020.

Analyses

Descriptive statistics and correlational analysis were performed using SPSS 22.0. To deal with outliers and missing data, the Boxplot method and the Series mean method was used. Finally, 85 valid data were found eligible for analyses. We first conducted the descriptive analyses for the study sample and the measures (see **Tables 1**, **2**).

Structural equation modeling (SEM) was conducted by Smart PLS 2.0.M3 (38). We performed a partial least squares—structural equation modeling method because PLS-SEM predicts path relationships in complex models more effectively. Also, data distribution criteria are not among PLS-SEM assumptions, and it applies efficiently with small sample sizes and more complex models (25). It is noteworthy that in comparison or other SEM approaches, the model fit indices in PLS-SEM are determined by R^2 (explained variance), T-values, and beta paths (β) (25).

TABLE 2 | Descriptive statistic of Variables ($n = 85$).

Variables	Domains	Min	Max	Mean	SD	Kurtosis	Skewness	*t*	*Sig.*
NCD	Speed of processing	104	211	14.14	42.2	0.077	−0.141	50.90	0.00**
	Attention/Vigilance	29	143	98.59	14.55	0.655	1.000	−42.40	0.00**
	Working memory	71	19	7.41	3.01	1.596	2.416	55.32	0.00**
	Verbal learning	37	74	49.74	10.21	0.332	−0.719	0.003	0.99
	Visual learning	31	79	49.09	9.58	0.551	0.657	0.006	0.99
	Reasoning/Problem solving	32	74	49.44	9.98	0.565	−0.432	0.001	0.99
	Social cognition	18	69	49.64	9.98	−0.481	0.353	0.006	0.99
	Total composite score	360	615	495.14	57.86	−0.314	−0.419	0.00	1.00
DAS	Performance evaluation	36	95	61.97	12.36	0.394	−0.009	0.003	0.99
	Need for approval	7	34	21.32	5.35	0.280	0.761	0.001	0.99
	Total	51	123	83.29	15.07	0.180	−0.208	0.003	0.99
NS	Blunted affect	0	35	10.97	8.19	1.218	0.723	0.005	0.99
	Alogia	0	25	8.57	6.51	0.983	−0.104	0.009	0.99
	Avolition and apathy	0	19	8.35	5.62	0.346	−1.365	0.014	0.98
	Asociality	0	23	7.06	5.05	0.874	0.404	0.871	0.387
	Attention	0	12	4.98	3.26	0.535	−0.532	0.019	0.98
	Total	0	95	40.50	25.69	0.649	−0.672	0.00	1.00
Dis	Cognition	6	27	14.79	6.28	0.266	−0.999	0.007	0.99
	Mobility	5	25	16.75	6.55	−0.349	−1.099	0.009	0.99
	Getting along	5	21	12.11	4.31	0.164	−0.548	14.48	0.00**
	Life activities	8	40	20.97	9.84	0.396	−1.192	3.72	0.00**
	Participation	8	37	19.61	9.12	0.173	−1.389	0.005	0.99
	Self–care	4	20	16.82	2.87	−1.252	3.631	0.002	0.99
	Total	36	156	101.07	34.51	0.107	−1.382	0.002	0.99

***p < 0.00; NCD, Neurocognitive deficits; DPBs, Dysfunctional Performance Beliefs; NS, Negative Symptoms; Dis, Disability.*

To execute PLS-SEM following steps were performed. First, we addressed preliminary considerations, such as data distribution assumption and multicollinearity. Second, we estimated the loadings, Cronbach's alpha, composite reliability (CR), average variance extracted (AVE), and R^2 (explained variance) value for all variables (see **Table 3**). The visual learning subscale of neurocognitive deficits was removed because of the low loading factor (<3). We considered a factor loading of <3 representing a weak relationship, CR >0.7, and AVE >0.5 as was deemed to be desirable (39). Discriminant validity was also calculated to evaluate the measurement model. Discriminant validity indicates how the observed indicators are related to their constructs (25). Cross-loading estimation revealed that the correlation values for selected observed indicators were higher than other constructs. Therefore, each indicator showed the highest correlation with its construct and had the lowest correlation with other constructs.

We also examined the discriminant validity of the latent variables using the Pearson correlation coefficient (see **Table 4**). Furthermore, to evaluate the overall measurement model fitness, we obtained the goodness-of-fit-index (GOF) measure, which was 0.54, indicating a strong model fit. Tenenhaus et al. (40) considered values of 0.01, 0.25, and 0.36 as weak, medium to high, and robust values for GOF. Then, after examining the measurement model, we performed PLS-SEM (see **Figure 1**), and the Sobel test was performed to assess indirect effects (41).

RESULTS

The Pearson correlation results indicated a significant positive association between neurocognitive deficits, dysfunctional performance beliefs, negative symptoms, and disability. All correlations were positively significant at the range of ($0.15 \leq r \leq 0.84$; $p < 0.01$, $p < 0.05$). The results showed that neurocognitive deficits are significantly correlated with dysfunctional performance beliefs ($r = 0.150$, $p = 0.05$), negative symptoms ($r = 0.510$, $p = 0.01$), and disability ($r = 0.410$, $p = 0.01$) (For full information, see **Table 4**).

Structural Model

We started with a theoretical model based on our hypothesis that dysfunctional performance beliefs would mediate the association between neurocognitive deficits and negative symptoms with disability hierarchically. The results showed non-significant direct paths from neurocognitive deficits and dysfunctional performance beliefs to disability ($T = 1.17$, $\beta = 0.10$; $T = 0.86$ and $\beta = 0.05$ respectively). By removing non-significant paths, our hypothesized model yielded a proper fit. As **Figure 1** shows, neurocognitive deficits, as an exogenous construct,

TABLE 3 | Assessment of measurement model of latent Variables ($n = 85$).

Variables	Domains	Loading	CR	AVE	Cronbach's Alpha	R^2
NCD	Speed of processing	0.71				
	Attention/Vigilance	0.55				
	Working memory	0.30				
	Verbal learning	0.68				
	Reasoning/Problem solving	0.77				
	Social cognition	0.65				
	Total composite score		0.79	0.40	0.75	
DPBs	Performance evaluation	0.66				
	Need for approval	0.92				
	Total		0.77	0.64	0.82	0.07
NS	Blunted affect	0.84				
	Alogia	0.84				
	Avolition and apathy	0.92				
	Asociality	0.89				
	Attention	0.91				
	Total		0.94	0.78	0.82	0.56
Dis	Cognition	0.92				
	Mobility	0.87				
	Getting along	0.82				
	Life activities	0.92				
	Participation	0.90				
	Self–care	0.67				
	Total	0.92	0.94	0.73	0.80	0.74

NCD, Neurocognitive deficits; DPBs, Dysfunctional Performance Beliefs; NS, Negative Symptoms; Dis, Disability; CR, Composite Reliability; AVE, Average variance extracted.

TABLE 4 | Pearson correlations between neurocognitive deficits, dysfunctional performance believe, negative symptoms, and disability ($n = 85$).

	Variables	1	2	3	4
1	NCD	1			
2	DPBs	0.150*	1		
3	NS	0.510**	0.418**	1	
4	Dis	0.410**	0.403**	0.845**	1

***p < 0.01; *p < 0.05; NCD, Neurocognitive deficits; DPBs, Dysfunctional Performance Beliefs; NS, Negative Symptoms; Dis, Disability.*

affect dysfunctional performance beliefs and negative symptoms significantly ($T = 2.78$, $\beta = 0.27$, $R^2 = 0.076$, $p < 0.01$). Furthermore, neurocognitive deficits significantly affect negative symptoms as the dependent variable ($T = 12.06$ $\beta = 0.64$, $p < 0.01$). On the other hand, dysfunctional performance beliefs significantly mediated the association between neurocognitive deficits and negative symptoms ($T = 3.48$, $\beta = 0.23$ $R^2 = 0.562$, $p < 0.01$). Finally, negative symptoms affected disability significantly ($T = 9.54$, $\beta = 0.85$, $R^2 = 0.734$, $p < 0.01$). We assumed T-values above 1.96 as significant (25).

Assessing the Indirect Effect in the Structural Model

Due to its parametric nature and reliance on unstandardized path coefficients, the indirect is not applicable in a PLS-SEM context (25). Therefore, the Sobel test was performed to assess the significance of the model's indirect effects. As **Table 5** shows, the path from neurocognitive deficits to negative symptoms is mediated significantly by dysfunctional performance beliefs ($T = 2.007$, $p = 0.044$). Similarly, the path from neurocognitive deficits to disability was mediated considerably by negative symptoms ($T = 7.873$, $p = 0.001$). Also, a path from dysfunctional performance beliefs to disability was mediated significantly by negative symptoms ($T = 2.856$, $p = 0.004$). Finally, dysfunctional performance beliefs did not significantly mediate the path from neurocognitive deficits to disability ($T = 0.677$, $p = 0.49$).

DISCUSSION

To the best of our knowledge, this study is the first study that utilized the hierarchal component method (HCM) with a partial least squares—structural equation modeling (PLS-SEM) to examine that dysfunctional performance beliefs would mediate the association between neurocognitive deficits and negative symptoms with disability hierarchically in a patient with schizophrenia. Our results indicated that dysfunctional performance beliefs significantly mediated the association between neurocognitive deficits, negative symptoms, and disability hierarchically. In addition, a moderate to strong correlation was found between dysfunctional performance beliefs, neurocognitive deficits, negative symptoms, and disability. More specifically, dysfunctional performance beliefs had a moderate correlation with neurocognitive deficits and a strong correlation with negative symptoms and disability. Also, the highest correlation was found between disability and neurocognitive deficits. These findings are consistent with previous studies [e.g., (4, 20, 22–24, 42)].

Our results supported the hierarchal component model (HCM) of the cognitive model of negative symptoms. A growing body of studies proposed the dual-path (20), simple (4, 24), and structural (22, 23) models of the cognitive model of negative symptoms. The closest model to our suggested model proposed by Quinlan et al. (23) is a dual-path model with two mediational paths between neurocognition and real-world functioning, including one well-replicated pathway from neurocognition to functional skill capacity to real-world functioning, and the second from neurocognition to defeatist attitudes to negative symptoms to real-world functioning. However, our research differs from Quinlan et al.'s (23) study in several areas. First, the main difference between the current study and Quinlan et al.'s (23) is that we used the hierarchal component method (HCM) with PLS-SEM. This method offers a detailed and more accurate indicator. For example, in Quinlan et al.'s (23) suggested model, defeatist attitudes and functional capacity each affected the real-world functioning in one pathway, and it doesn't appear to be well-integrated and parsimonious. While in the original cognitive model of negative symptoms (20), the

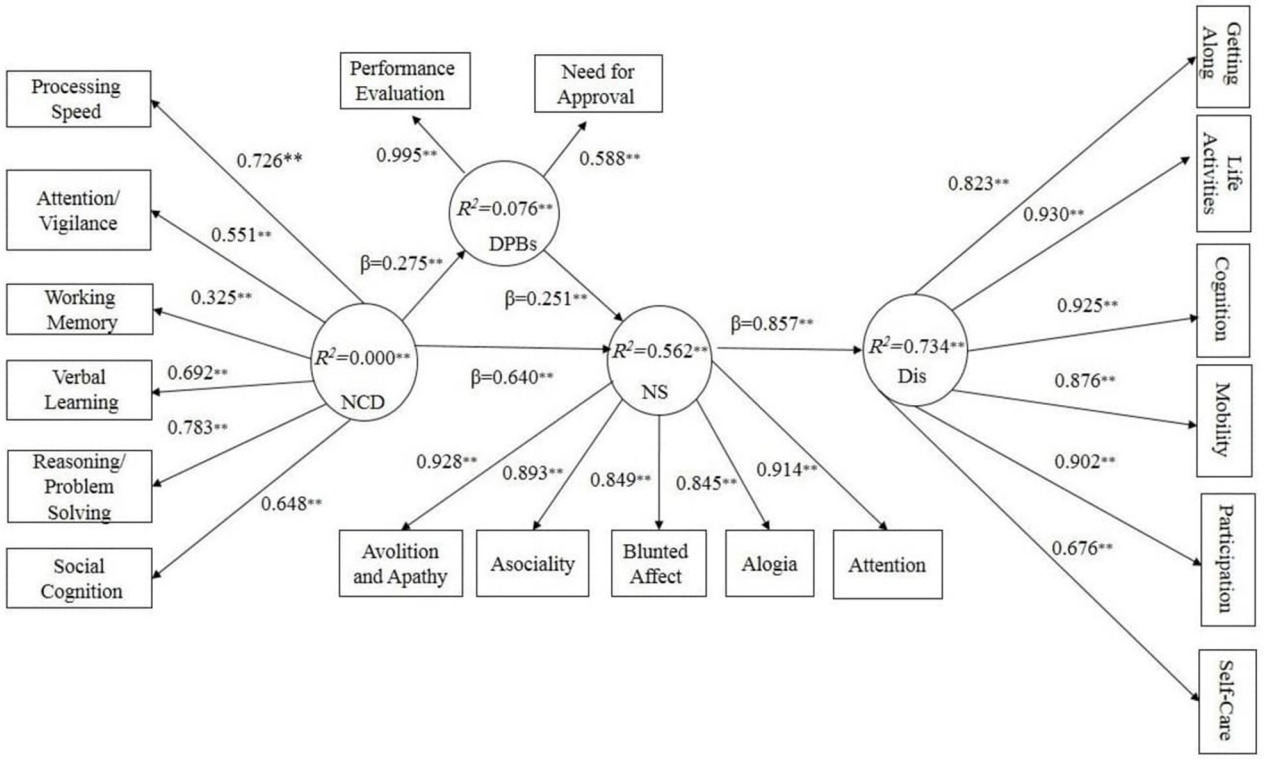


FIGURE 1 | Structural model results show Dysfunctional Performance Beliefs mediate Neurocognitive deficits Negative Symptoms and disability. *NCD*, Neurocognitive deficits; *DPBs*, Dysfunctional Performance Beliefs; *NS*, Negative Symptoms; *Dis*, Disability. β, path coefficients; R^2, explained variance; $^{**}p < 0.01$.

main emphasis is on dysfunctional beliefs and how they can lead to negative symptoms and disability, Quinlan et al. (23) introduced two pathways in which the role of defeatist attitude was not considered appropriately. Also, the subscales of defeatist attitudes, negative symptoms, and real-world functioning were not assessed. However, in our hierarchal component method (HCM), we assessed neurocognitive deficits, dysfunctional performance beliefs, negative symptoms, disability subscales; in addition, paths from neurocognitive deficits to dysfunctional performance beliefs to negative symptoms explained 73 percent of disability in Schizophrenia, making our model more detailed. However, it should be emphasized that because of different analysis approaches used in our research and Quinlan et al. (23), different indices were considered for examining model fitness. For example, we relied on R^2 (explained variance), T-values, and beta paths (β) to examine model fitness, while Quinlan et al., (23) considered χ^2, CFI, and RMSEA as model fit indices, which makes it difficult to compare the two models. Our findings (based on theoretical reasoning) revealed a more precise and detailed model of the cognitive model of negative symptoms. It means that, conceptually, disability in schizophrenia is affected by neurocognitive deficits, dysfunctional performance beliefs, and negative symptoms. Further, while each of these paths provides a weak and incomplete prediction of disability separately and directly, the indirect paths from neurocognitive deficits → dysfunctional performance beliefs → and negative symptoms better explain the disability in schizophrenia (see **Figure 1**, **Table 5**).

TABLE 5 | Sobel test results for indirect effects of neurocognitive deficits, dysfunctional performance beliefs, negative symptoms, and disability ($n = 85$).

Independent variables	Mediating variables	Dependent variables	*T-values*	*Std. error*	*p-value*
NCD	DPBs	NS	2.00	0.03	0.04**
NCD	DPBs	Dis	0.67	0.02	0.49
NCD	NS	Dis	7.87	0.06	0.001**
DPBs	NS	Dis	2.85	0.06	0.004**

NCD, Neurocognitive deficits; DPBs, Dysfunctional Performance Beliefs; NS, Negative Symptoms; Dis, Disability; Std. Error, Standard Error. $^{**}p < 0.01$.

To conceptualize psychosocial mechanism underlying negative symptoms and disability in schizophrenia, our findings provide some evidence that neurocognitive deficits in schizophrenia can lead to failure experiences or failure expectations, which affect persons daily life functioning, leading to dysfunctional, and asocial attitudes and negative evaluation of their self and potentials (e.g., *"If I do not do well all the time, people will not respect me*" or *"If I fail partly, it is as bad as being a complete failure*") (17). Dysfunctional and asocial attitudes could lead to negative symptoms (e.g.,

apathy, indifference, withdrawing social relationships, a lack of engagement in purposeful actions) and interfere with their most social competencies. As a result, patients develop a dysfunctional attitude as defective mechanisms, which lead to repeated failure experiences, underestimating themselves, and low expectation of pleasurable experiences. Usually, this vicious cycle continues and is repeated constantly.

Our model supports the idea that negative symptoms serve as a maladaptive mechanism that protects individuals from the anticipated pain and rejection associated with engagement in constructive activity. Furthermore, beliefs induced by the stigma of mental illness (e.g., "*I won't be able to achieve anything or have meaningful relationships because I have schizophrenia*") exacerbate the situation. Further, neurocognitive deficits can put the patient in a recurring cycle of frustration and failure, such as inaccurate goal setting and reduced ability to learn from errors (18, 43, 44).

The therapeutic implication of our results is that if patients with schizophrenia receive effective therapy to modify and disconfirm their dysfunctional beliefs, their daily life performance could significantly improve. In this context, different evidence-based versions of cognitive-behavioral therapy and cognitive remediation have emerged to target these issues s (9, 45–56).

There are several limitations to this study that need to be explained. First, despite using accurate assessment measures, we used a self-report tool (e.g., DAS), so it is recommended that future studies use more precise assessment tools, especially in measuring dysfunctional beliefs. Furthermore, our research design was a cross-sectional study, which does not confirm causal relationships; therefore, future research should focus on longitudinal studies. Similarly, this model can be tested with persons at different stages of the illness; in our study, we conducted on patients with chronic illness and predominantly negative symptoms. Also, Participants were prescribed second-generation antipsychotics, antidepressants, mood stabilizers, and Concomitant medications. Negative symptoms can be primary expressions of illness or secondary to other factors (e.g., depression, medication). To what degree the negative symptoms were primary or secondary cannot be estimated. In addition, side effects were not assessed systematically using a validated scale, only the classification of psychotropic drugs was recorded, and no information related to dosage was recorded.

Further, in the current study, we assessed positive symptoms using SCID-5 criteria; we recommend that future studies use valid measures such as the Scale for the Assessment of Positive Symptoms (SAPS) and other valid and reliable tools for assessing positive symptoms. Also, we did not measure the level of depressive symptoms, which is an essential source for secondary negative symptoms and should be included and controlled. Finally, the present study's sample included only men, so one should be careful not to generalize the results from this sample to other groups. Therefore, It is recommended that future studies include and study women and adolescents samples with schizophrenia spectrum disorder.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study received ethical approval from the Research Ethics Committee of the University of Social Welfare and Rehabilitation Sciences (IR.USWR.REC.1399.103). The patients/participants provided their written informed consent to participate in this study.

AUTHOR'S NOTE

The manuscript was extracted from a Ph.D. dissertation of the first author of the study conducted in the Department of Clinical Psychology, University of Social Welfare and Rehabilitation Sciences of Tehran, Iran.

AUTHOR CONTRIBUTIONS

AE designed the study and investigation and prepared the manuscript. HP, BD, OR, and HH supervised and reviewed the manuscript. FN review and editing the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was financially supported by the University of Social Welfare and Rehabilitation Sciences, Tehran, Iran (grant number 2698).

ACKNOWLEDGMENTS

The authors appreciate all participants who participated in this study.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association (2013).
2. Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. *Lancet Psychiatry.* (2018) 5:664–77. doi: 10.1016/S2215-0366(18)30050-6
3. Correll CU, Schooler NR. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatr Dis Treat.* (2020) 16:519. doi: 10.2147/NDT.S225643
4. Horan WP, Rassovsky Y, Kern RS, Lee J, Wynn JK, Green MF. Further support for the role of dysfunctional attitudes in models of real-world functioning in schizophrenia. *J Psychiatr Res.* (2010) 44:499–505. doi: 10.1016/j.jpsychires.2009.11.001

5. Sadock BJ, Sadock VA, Ruiz P. *Kaplan & Sadock's Synopsis of Psychiatry*. 11th ed. New York, NY: Wolters Kluwer (2014).
6. Kane JM, Correll CU. Past and present progress in the pharmacologic treatment of schizophrenia. *J Clin Psychiatry*. (2010) 71:1115. doi: 10.4088/JCP.10r06264yel
7. Koblan KS, Kent J, Hopkins SC, Krystal JH, Cheng H, Goldman R, et al. A non–D2-receptor-binding drug for the treatment of schizophrenia. *N Eng J Med*. (2020) 382:1497–506. doi: 10.1056/NEJMoa1911772
8. Goff DC. The pharmacologic treatment of schizophrenia-−2021. *JAMA*. (2021) 325:175–6. doi: 10.1001/jama.2020.19048
9. Grant PM, Huh GA, Perivoliotis D, Stolar NM, Beck AT. Randomized trial to evaluate the efficacy of cognitive therapy for low-functioning patients with schizophrenia. *Arch Gen Psychiatry*. (2012) 69:121–7. doi: 10.1001/archgenpsychiatry.2011.129
10. Foussias G, Agid O, Fervaha G, Remington G. Negative symptoms of schizophrenia: clinical features, relevance to real world functioning and specificity versus other CNS disorders. *Europ Neuropsychopharmacol*. (2014) 24:693–709. doi: 10.1016/j.euroneuro.2013.10.017
11. Kingdon D, Hansen L. Cognitive therapy for psychosis. *Psychiatry*. (2007) 6:362–6. doi: 10.1016/j.mppsy.2007.06.007
12. Kirschner M, Aleman A, Kaiser S. Secondary negative symptoms - a review of mechanisms, assessment and treatment. *Schizophr Res*. (2017) 186:29–38. doi: 10.1016/j.schres.2016.05.003
13. Tripathi A, Kar SK, Shukla R. Cognitive deficits in schizophrenia: understanding the biological correlates and remediation strategies. *Clin Psychopharmacol Neurosci*. (2018) 16:7–17. doi: 10.9758/cpn.2018.16.1.7
14. Halder S, Mahato A. Cognitive remediation therapy in chronic schizophrenia. In: *Research Anthology on Rehabilitation Practices and Therapy*. IGI Global (2021). p. 1337–53. doi: 10.4018/978-1-7998-3432-8.ch067
15. Harvey PD, Strassnig M. Predicting the severity of everyday functional disability in people with schizophrenia: cognitive deficits, functional capacity, symptoms, health status. *World Psychiatry*. (2012) 11:73–9. doi: 10.1016/j.wpsyc.2012.05.004
16. Malaspina D, Walsh-Messinger J, Gaebel W, Smith LM, Gorun A, Prudent V, et al. Negative symptoms, past and present: a historical perspective and moving to DSM-5. *Europ Neuropsychopharmacol*. (2014) 24:710–24. doi: 10.1016/j.euroneuro.2013.10.018
17. Weissman AN, Beck AT. *Development and validation of the Dysfunctional Attitude* Scale: *A Preliminary Investigation* (1978).
18. Rector NA, Beck AT, Stolar N. The negative symptoms of schizophrenia: a cognitive perspective. *Canad J Psychiatry*. (2005) 50:247–57. doi: 10.1177/070674370505000503
19. Beck A, Rector N, Stolar N, Grant P. *A Cognitive Conceptualization of Negative Symptoms*. New York, NY: Guilford Press (2009).
20. Grant PM, Beck AT. Defeatist beliefs as a mediator of cognitive impairment, negative symptoms, and functioning in schizophrenia. *Schizophr Bull*. (2009) 35:798–806. doi: 10.1093/schbul/sbn008
21. Perivoliotis D, Cather C. Cognitive behavioral therapy of negative symptoms. *J Clin Psychol*. (2009) 65:815–30. doi: 10.1002/jclp.20614
22. Green MF, Hellemann G, Horan WP, Lee J, Wynn JK. From perception to functional outcome in schizophrenia: modeling the role of ability and motivation. *Arch Gen Psychiatry*. (2012) 69:1216–24. doi: 10.1001/archgenpsychiatry.2012.652
23. Quinlan T, Roesch S, Granholm E. The role of dysfunctional attitudes in models of negative symptoms and functioning in schizophrenia. *Schizophr Res*. (2014) 157:182–9. doi: 10.1016/j.schres.2014.05.025
24. Luther L, Coffin GM, Firmin RL, Bonfils KA, Minor KS, Salyers MP. A test of the cognitive model of negative symptoms: Associations between defeatist performance beliefs, self-efficacy beliefs, and negative symptoms in a non-clinical sample. *Psychiatry Res*. (2018) 269:278–85. doi: 10.1016/j.psychres.2018.08.016
25. Hair JF Jr, Hult GTM, Ringle C, Sarstedt M. *A Primer on Partial Least Squares Structural Equation Modeling (PLS-SEM)*. Thousand Oaks, CA: Sage publications (2016). doi: 10.15358/9783800653614
26. Jarvis CB, MacKenzie SB, Podsakoff PM. A critical review of construct indicators and measurement model misspecification in marketing and consumer research. *J Consumer Res*. (2003) 30:199–218. doi: 10.1086/376806
27. Hwang H, Takane Y. *Generalized Structured Component Analysis: A Component-Based Approach to Structural Equation Modeling*. New York, NY: CRC Press (2014). doi: 10.1201/b17872
28. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. (2008) 165:203–13. doi: 10.1176/appi.ajp.2007.07010042
29. Hoyle RH, editor. *Statistical Strategies for Small Sample Research*. Thousand Oaks, CA: Sage (1999).
30. Hoyle RH, Kenny DA. Sample size, reliability, and tests of statistical mediation. *Statist Strateg Small Sample Res*. (1999) 1:195–222.
31. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders: Patient Edition*. New York, NY: Biometrics Research Department, Columbia University (2002).
32. Mohammadkhani P, Forouzan AS, Hooshyari Z, Abasi I. Psychometric properties of persian version of structured clinical interview for DSM-5-Research Version (SCID-5-RV): a diagnostic accuracy study. *Iranian J Psychiatry Behav Sci*. (2020) 14:3–4. doi: 10.5812/ijpbs.100930
33. Andreasen NC. Negative symptoms in schizophrenia: definition and reliability. *Arch Gen Psychiatry*. (1982) 39:784–8. doi: 10.1001/archpsyc.1982.04290070020005
34. Yasrebi K, Jazayeri AR, Pourshahbaz A, Dolatshahi B. The effectiveness of psychosocial rehabilitation in reducing negative symptoms and improving social skills of chronic schizophrenia patients. *Iranian J Psychiatry Clin Psychol*. (2009) 14:363–70.
35. Kaviani H, Javaheri F, Bahiray H. Efficacy of mindfulness-based cognitive therapy in reducing automatic thoughts, dysfunctional attitude, depression and anxiety: a sixty day follow-up. *Adv Cogn Sci*. (2005) 7:49–59.
36. McKibbin C, Patterson TL, Jeste DV. Assessing disability in older patients with schizophrenia: results from the WHODAS-II. *J Nerv Ment Dis*. (2004) 192:405–13. doi: 10.1097/01.nmd.0000130133.32276.83
37. Rajeziesfahani S, Federici S, Bacci S, Meloni F, Bartolucci F, Zahiroddin A, et al. Validity of the 36-item Persian (Farsi) version of the world health organization disability assessment schedule (WHODAS) 2.0. *Int J Ment Health*. (2019) 48:14–39. doi: 10.1080/00207411.2019.1568172
38. Ringle CM. *SmartPLS 2.0 (M3)*. (2005). Available online at: https://www.smartpls.com (accessed November 03, 2020).
39. Fornell C, Larcker DF. Evaluating structural equation models with unobservable variables and measurement error. *J Market Res*. (1981) 18:39–50. doi: 10.1177/002224378101800104
40. Tenenhaus M, Amato S, Esposito Vinzi V. A global goodness-of-fit index for PLS structural equation modelling. In: *Proceedings of the XLII SIS Scientific Meeting*. (2004). p. 739–42.
41. Preacher KJ, Leonardelli GJ. *Calculation for the Sobel Test: An Interactive Calculation Tool for Mediation Tests*. (2021). Available online at: http://quantpsy.org/sobel/sobel.htm (accessed November 03, 2020).
42. Ventura J, Subotnik KL, Ered A, Gretchen-Doorly D, Hellemann GS, Vaskinn A, et al. The relationship of attitudinal beliefs to negative symptoms, neurocognition, and daily functioning in recent-onset schizophrenia. *Schizophr Bull*. (2014) 40:1308–18. doi: 10.1093/schbul/sbu002
43. Perivoliotis D, Morrison AP, Grant PM, French P, Beck AT. Negative performance beliefs and negative symptoms in individuals at ultra-high risk of psychosis: a preliminary study. *Psychopathology*. (2009) 42:375–9. doi: 10.1159/000236909
44. Beck AT, Rector NA, Stolar N, Grant P. *Schizophrenia: Cognitive Theory, Research, and Therapy*. New York, NY: Guilford Press (2011).
45. Beck AT, Grant PM, Huh GA, Perivoliotis D, Chang NA. Dysfunctional attitudes and expectancies in deficit syndrome schizophrenia. *Schizophr Bull*. (2013) 39:43–51. doi: 10.1093/schbul/sbr040
46. Eack SM, Mesholam-Gately RI, Greenwald DP, Hogarty SS, Keshavan MS. Negative symptom improvement during cognitive rehabilitation: results from a 2-year trial of Cognitive Enhancement Therapy. *Psychiatry Res*. (2013) 209:21–6. doi: 10.1016/j.psychres.2013.03.020
47. Granholm E, Holden J, Link PC, McQuaid JR, Jeste DV. Randomized controlled trial of cognitive behavioral social skills training for older consumers with schizophrenia: defeatist performance attitudes and functional outcome. *Am J Geriatric Psychiatry*. (2013) 21:251–62. doi: 10.1016/j.jagp.2012.10.014

48. Granholm E, Holden J, Link PC, McQuaid JR. Randomized clinical trial of cognitive behavioral social skills training for schizophrenia: improvement in functioning and experiential negative symptoms. *J Consult Clin Psychol.* (2014) 82:1173. doi: 10.1037/a0037098
49. Granholm EL, McQuaid JR, Holden JL. *Cognitive-Behavioral Social Skills Training for Schizophrenia: A Practical Treatment Guide*. New York, NY: Guilford Publications (2016).
50. Grant P, Bredemeier K, Beck A. (2017) *A Longitudinal Study of Defeatist Beliefs, Neurocognition, & Functional Outcomes*. Philadelphia, PA: U. r. data).
51. Grant P, Bredemeier K, Beck A. *Mechanisms of Change in Clinical Trial of Recovery-Oriented Cognitive Therapy: Change in Beliefs (but not neurocognition) correlate With Change In Outcome*. Philadelphia, PA: Manuscript in preparation (2017).
52. Grant PM, Bredemeier K, Beck AT. Six-month follow-up of recovery-oriented cognitive therapy for low-functioning individuals with schizophrenia. *Psychiatric Serv.* (2017) 68:997–1002. doi: 10.1176/appi.ps.201600413
53. Beck AT, Himelstein R, Bredemeier K, Silverstein SM, Grant P. What accounts for poor functioning in people with schizophrenia: a re-evaluation of the contributions of neurocognitive v. attitudinal and motivational factors. *Psychol Med.* (2018) 48:2776–85. doi: 10.1017/S0033291718000442
54. Grant P, Perivoliotis D, Luther L, Bredemeier K, Beck A. Rapid improvement in beliefs, mood, and performance following an experimental success experience in an analogue test of recovery-oriented cognitive therapy. *Psychol Med.* (2018) 48:261–8. doi: 10.1017/S003329171700160X
55. Mahmood Z, Clark JM, Twamley EW. Compensatory cognitive training for psychosis: effects on negative symptom subdomains. *Schizophr Res.* (2019) 204:397–400. doi: 10.1016/j.schres.2018.09.024
56. Ventura J, Subotnik KL, Gretchen-Doorly D, Casaus L, Boucher M, Medalia A, et al. Cognitive remediation can improve negative symptoms and social functioning in first-episode schizophrenia: a randomized controlled trial. *Schizophr Res.* (2019) 203:24–31. doi: 10.1016/j.schres.2017.10.005

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 26 July 2021
doi: 10.3389/fpsyt.2021.648108

The Impact of Negative Symptoms and Neurocognition on Functioning in MDD and Schizophrenia

Yue Feng Quek[1], *Zixu Yang*[1], *Justin Dauwels*[2] *and Jimmy Lee*[1,3,4]*

[1] *Research Division, Institute of Mental Health, Singapore, Singapore,* [2] *School of Electrical and Electronic Engineering, Nanyang Technological University, Singapore, Singapore,* [3] *North Region & Department of Psychosis, Institute of Mental Health, Singapore, Singapore,* [4] *Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore*

Introduction: Negative symptoms, neurocognitive deficits and functional impairment are prevalent in individuals with major depressive disorder (MDD) and schizophrenia (SCZ). However, unlike neurocognitive deficits, little is known about the role of negative symptoms toward functioning in individuals with MDD. On the other hand, both factors are well-studied in individuals with SCZ. Thus, this study aimed to examine the contributions of negative symptoms and neurocognitive impairments in functioning in individuals with MDD, compared to individuals with SCZ.

Methods: Participants included 50 individuals with MDD, 49 individuals with SCZ and 49 healthy controls. The following measures were administered—Negative Symptom Assessment (NSA-16), Brief Assessment of Cognition in Schizophrenia (BACS), Patient Health Questionnaire (PHQ-9), and MIRECC-Global Assessment of Functioning (MIRECC-GAF) to evaluate negative symptoms, neurocognition, depressive symptoms, and functioning respectively.

Results: Both MDD and SCZ groups had significantly more severe negative symptoms, depressive symptoms, and poorer functioning than healthy controls. Individuals with SCZ performed significantly poorer on the BACS than the other two groups. Both negative symptoms and neurocognition were significantly correlated with social and occupational functioning in SCZ. Motivation subdomain of the negative symptoms was significantly correlated with occupational functioning, while depressive symptoms correlated with functioning in MDD.

Conclusion: Both negative symptoms and neurocognitive deficits appear to play differential roles on individual domains of functioning between MDD and SCZ. Future longitudinal studies with larger sample sizes should be done for a better understanding about the associations between the factors and functioning.

Keywords: major depressive disorder, schizophrenia, negative symptoms, neurocognition, functioning

OPEN ACCESS

Edited by:
Ingrid Melle,
University of Oslo, Norway

Reviewed by:
Li Hui,
Suzhou Guangji Hospital, China
Michael W. Best,
University of Toronto Scarborough, Canada

***Correspondence:**
Jimmy Lee
jimmy_lee@imh.com.sg

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *04 February 2021*
Accepted: *25 June 2021*
Published: *26 July 2021*

Citation:
Quek YF, Yang Z, Dauwels J and Lee J (2021) The Impact of Negative Symptoms and Neurocognition on Functioning in MDD and Schizophrenia. Front. Psychiatry 12:648108. doi: 10.3389/fpsyt.2021.648108

INTRODUCTION

According to the World Health Organisation (WHO) (1), MDD is a leading cause for non-fatal health loss and has prevailed as one for nearly three decades. With varying degrees of severity and scope, most individuals with major depressive disorder (MDD) face some forms of impairment in their daily functioning, such as work or interpersonal relationships (2). Studies have reported that only 20% of individuals with MDD manage to attain complete functional recovery (3, 4). The persistence of functional disruption, even in symptomatic remission, highlights the insufficiency of symptom reduction as an end goal for individuals with MDD. A return to premorbid level of functioning remains a key treatment goal (5). As such, it is important to understand factors that influence functioning in order to provide the right treatment to people with MDD and aid them in their functional recovery.

In the literature, two factors—neurocognitive deficits and negative symptoms often stand out in relation to their strong association with functioning. Specifically in MDD, neurocognitive deficits are prevalent in the individuals and have been reported to be one of the core features of the condition (6, 7). These deficits often involve multiple subdomains of cognitive functions and are heterogeneous between individuals (8, 9). Strong and consistent associations have been demonstrated linking neurocognitive deficits to functional impairment in individuals with MDD (7, 10). Another study (11) also found that baseline cognitive deficits was significantly associated with functional disability measured 6 months later. In addition, the authors found that improvements in neurocognition was associated with greater functional recovery over the course of follow up. These results support the role of neurocognitive deficits in functional recovery for individuals with MDD.

Negative symptoms, i.e., asociality, amotivation, affect blunting and alogia, commonly described in schizophrenia are less studied in MDD population (12). While studies (13–15) have provided substantial evidence about the presence of negative symptoms in this population, the relationship between negative symptoms and functioning in MDD is however sparely addressed. Two studies (16, 17) have found motivation-related deficits to be significantly related to functioning. Another study (18) also found that loss of interest was associated with work and family life impairment. However, the authors had classified loss of interest as part of *residual depressive symptoms* alongside sleeping and concentration difficulties, rather than as a construct of negative symptoms. While depressive symptoms have a considerable amount of overlap with negative symptoms (12, 19), both concepts are often suggested to be separable and independent concepts (12, 14). On the other hand, there were contrary old findings (20) where no significant associations between negative symptoms and role functioning were observed. In that study, the authors had studied negative symptoms in three specific domains—flat affect, alogia, and motor retardation. This incongruence might suggest that specific negative symptoms domains have differential effects on functioning in MDD. Therefore, the role of negative symptoms in functional impairment in individuals with MDD remains unclear and require further examinations.

On the other hand, both neurocognitive deficits and negative symptoms have been widely studied and can be considered the most significant correlates of impaired functioning in individuals with schizophrenia (SCZ) (21–24). Few studies have compared the predictive abilities of both factors; some studies reported neurocognitive deficits to be superior (25, 26) while some found otherwise (27). However, they support the contribution of both factors toward functional impairment in SCZ.

Therefore, the aim of the current study is to better understand negative symptoms and neurocognitive deficits in MDD in their individual contribution toward functioning, alongside individuals with SCZ and healthy individuals.

METHODS

Participants

Fifty individuals with MDD and 49 individuals with SCZ were recruited from the Institute of Mental Health, Singapore. Forty-nine healthy controls (HC) were recruited from the community. The data collection was completed between September 2017 and April 2019.

The inclusion criteria for the patient groups were as follows: diagnosis of SCZ or MDD, aged 21–65 years, English-speaking and has capacity to provide informed consent. The inclusion criteria for the HC group includes aged 21–65, English-speaking, has capacity to provide informed consent and no history of any mental disorder. Individuals with intellectual disability, neurological disorders, and history of cerebrovascular accidents or traumatic brain injuries were excluded.

The diagnoses of SCZ and MDD were ascertained on the Structured Clinical Interview for DSM-IV (SCID-I/P) (28); HCs were screened using the non-patient version (SCID-I/NP) (29).

Procedure

All the assessments were conducted by trained research psychologists in a single visit. In order to reduce bias in rating negative symptoms, the assessments for negative symptoms were conducted by a research psychologist who was not involved in the SCID interview and blinded to the participant's condition. This study was reviewed and approved by the National Healthcare Group Domain Specific Review Board (DSRB), Singapore. Written informed consent was obtained from all participants.

Measures

Negative Symptoms

The 16-item Negative Symptom Assessment (NSA-16) (30, 31) was used to assess the negative symptoms in all participants. The NSA-16 is a semi-structured interview which assesses negative symptomology in the past 7 days. There are 16 items in the scale, each scored on a 6-point scale. A 7-point global negative symptom rating is also scored, assessed based on the interviewer's overall gestalt of the severity of the individual's negative symptoms. Higher scores in the scale reflect higher severity of negative symptoms. Five symptom factors—Emotion/affect, communication, social involvement, motivation, and retardation

were derived from factor analysis (31) and used in the analysis. The NSA-16 has a high Cronbach's alpha of 0.92 (31).

Neurocognition

The Brief Assessment of Cognition in Schizophrenia (BACS) (32) was used to assess the cognitive abilities of the participants. The BACS consists of six tasks that evaluate the cognitive domains that are persistently impaired and strongly associated with functional outcomes in individuals with SCZ—Verbal memory, working memory, motor speed, attention, executive functioning, and verbal fluency. The BACS has been shown to have high test-retest reliability in individuals with SCZ and controls (32). *Z*-scores of each subtest were computed based on the results from the original developers and a composite score was then obtained by averaging the z-scores of the six subtests (32). BACS has also been used in other studies to assess cognitive abilities in MDD (33–35) and has shown its ability to differentiate cognitive abilities between individuals with MDD from HC (8).

Depressive Symptoms

The Patient Health Questionnaire-9 (PHQ-9) (36, 37) was used to assess severity of depressive symptoms in the participants. PHQ-9 is a patient-reported questionnaire which used the criteria from the DSM-IV symptoms for MDE. The scale consists of 9 items that are each scored on a frequency scale from 0 to 3, 0 being not at all and 3 being nearly every day. It also consists of a tenth item that rates the patient's difficulty in functioning, which is not used for scoring. PHQ-9 has been found to have good psychometric properties (36).

Functioning

The MIRECC-Global Assessment of Functioning (MIRECC-GAF) (38) was used to assess the real-world functioning of the participants. This clinician-rater scale measures the participants' occupational functioning, social functioning and symptom severity on three individual subscales. The range of the scores on each subscale is from 0 to 100, with higher scores reflecting better functioning or lower symptom severity. The developers have reported that MIRECC-GAF has high reliability (ICCs >0.98), predictive abilities, and superior concurrent validity than the conventional GAF scores (38).

Statistical Analysis

Normality assumptions and homogeneity of variance were tested using Shapiro-Wilk and Levene's tests respectively. Transformation was performed on those variables that were not normally distributed. The NSA-16 subdomains—social involvement in SCZ and motivation in MDD groups were normally distributed after applying square root transformation. All three MIRECC-GAF domains in MDD and SCZ groups were normally distributed after applying Blom's transformation. However, for the three MIRECC-GAF domains in HC, departure from normality was severe and none of the transformation method could yield a normal distribution. Parametric tests were used for normally-distributed variables while non-parametric tests were used when non-normally distributed variables were involved. For comparisons between the three diagnostic groups, the Chi-squared tests were used for categorical variables; the Univariate Analysis of Variance (ANOVA) was used for continuous variables if normality assumption was met, while the Kruskal-Wallis H test was used if the normality assumption was violated. Correlation analysis was used to measure the association between NSA-16, BACS, PHQ-9, and MIRECC-GAF. The NSA-16 total scores were used in this study. The analyses with NSA-16 global scores are available in the **Supplementary Table 1**. The data was analyzed using IBM SPSS version 23 (39).

RESULTS

Demographics and Clinical Characteristics

The demographics and clinical characteristics of the participants are shown in **Table 1**. There were no statistical differences between the groups in terms of gender, employment status, age and total years of education. Significantly more HCs (57.1%) are married as compared to the MDD (24%) and SCZ (14.3%) groups. The SCZ group ($M = 14.30$, $SD = 10.22$) has significantly longer duration of illness than the MDD group ($M = 4.80$, $SD = 4.94$).

Within the MDD group, males ($M = 62.77$, $SD = 24.16$) were found to have significantly higher MIRECC-GAF occupational functioning scores than females ($M = 48.08$, $SD = 20.00$), $T_{(47)} = 2.17$, $p = 0.035$. None of the other socio-demographic factors were found to be significantly associated with the three MIRECC-GAF domains.

With regards to the clinical characteristics between groups, the SCZ group performed significantly poorer on BACS composite score than the other two groups. Both the SCZ and MDD groups had significantly poorer MIRECC-GAF ratings, higher NSA-16 total, subdomains, global scores, and PHQ-9 total than the HCs.

Associations Between Cognition, Negative Symptoms, Depressive Symptoms, and Functioning Across Groups

Univariate analyses were performed to test whether socio-demographic factors including age, gender, duration of illness and total years of education were associated with functioning in each diagnostic group. Only gender was significantly associated with occupational functioning in MDD.

The results of correlational analyses between cognition, negative symptoms, depressive symptoms, and functioning across groups are presented in **Tables 2**, **3** and **Supplementary Table 3**. For individuals with MDD, NSA-16 total was significantly associated with the MIRECC-GAF symptomatic ($r = -0.39$, $p = 0.005$). Within the subdomains of NSA-16, motivation was significantly correlated with the MIRECC-GAF occupational functioning ($r = -0.48$, $p < 0.001$) and symptomatic functioning ($r = -0.42$, $p = 0.003$). Another subdomain, motor retardation was significantly associated with the MIRECC-GAF symptomatic subscale ($r = -0.38$, $p = 0.007$). No significant association was observed between BACS composite score and MIRECC-GAF subscales. The 6 individual BACS domains were also not significantly

TABLE 1 | Demographic and clinical characteristics.

Variable	MDD	SCZ	HC	Statistic value	*p*
	(*n* = 50)	**(*n* = 49)**	**(*n* = 49)**		
Male	26 (52.0)	25 (51.0)	26 (53.1)	$\chi^2_{(2)} = 0.04$	0.980
Married	12 (24.0)	7 (14.3)	28 (57.1)	$\chi^2_{(2)} = 22.04$	<0.001
Employed	33 (66.0)	30 (61.2)	34 (69.4)	$\chi^2_{(2)} = 0.73$	0.694
Ethnicity				$\chi^2_{(2)} = 15.56$	0.016
Chinese	36 (72.0)	41 (83.7)	32 (65.3)		
Malay	5 (10.0)	2 (4.1)	13 (26.5)		
Indian	6 (12.0)	6 (12.2)	3 (6.1)		
Other	3 (6.0)	0 (0.0)	1 (2.0)		
Age in years	36.66 ± 13.01	40.53 ± 10.42	39.98 ± 12.41	$H_{(2)} = 4.16$	0.125
Total years of education	14.20 ± 2.60	13.50 ± 2.86	13.54 ± 2.90	$F_{(2,145)} = 0.97$	0.382
Duration of illness (in years)	4.80 ± 4.94	14.30 ± 10.22	NA	$U = 459.50$	<0.001
MIRECC-GAF					
Symptomatic	50.02 ± 17.43	55.16 ± 16.20	90.90 ± 7.62	$H_{(2)} = 64.94$	<0.001
Social	63.56 ± 10.41	62.94 ± 11.99	81.94 ± 8.17	$H_{(2)} = 65.76$	<0.001
Occupational	55.72 ± 23.25	53.16 ± 23.14	87.39 ± 7.47	$H_{(2)} = 94.48$	<0.001
BACS Z-score					
Verbal memory	−0.01 ± 1.11	−0.76 ± 1.25	−0.11 ± 1.02	$F_{(2,145)} = 6.39$	0.002
Digit sequencing	−0.03 ± 1.11	−0.61 ± 1.23	−0.10 ± 1.10	$H_{(2)} = 6.83$	0.033
Token motor task	−0.56 ± 1.02	−1.41 ± 1.19	−0.30 ± 1.00	$H_{(2)} = 21.92$	<0.001
Semantic fluency (Total)	0.36 ± 1.19	−0.84 ± 0.87	0.21 ± 1.19	$H_{(2)} = 29.47$	<0.001
Symbol coding	−0.40 ± 1.23	−1.55 ± 1.23	−0.29 ± 1.13	$H_{(2)} = 21.91$	<0.001
Tower of London	0.17 ± 0.77	−0.56 ± 1.62	−0.03 ± 1.05	$H_{(2)} = 5.80$	0.055
Composite	0.13 ± 1.19	−1.60 ± 1.59	−0.17 ± 1.21	$F_{(2,145)} = 19.30$	<0.001
NSA-16					
Communication	7.02 ± 2.33	8.00 ± 3.27	6.14 ± 2.39	$H_{(2)} = 11.76$	0.003
Emotion/Affect	8.46 ± 2.29	8.96 ± 2.39	7.86 ± 1.98	$H_{(2)} = 6.03$	0.049
Social involvement	8.30 ± 2.64	8.82 ± 2.72	7.04 ± 2.27	$H_{(2)} = 11.26$	0.004
Motivation	12.14 ± 2.70	11.61 ± 2.63	7.78 ± 2.47	$H_{(2)} = 54.48$	<0.001
Motor retardation	4.46 ± 1.89	4.59 ± 2.06	3.08 ± 1.24	$H_{(2)} = 19.00$	<0.001
Total	40.38 ± 7.79	41.98 ± 9.87	31.90 ± 7.07	$H_{(2)} = 37.52$	<0.001
Global impression score*	3.50 (4)	3 (3)	2 (3)	$H_{(2)} = 62.47$	<0.001
PHQ-9	14.02 (7.00)	6.84 (5.92)	2.55 (2.99)	$H_{(2)} = 63.23$	<0.001

Data are expressed as mean ± SD or n (%).

**Global impression score is reported as median (range).*

MIRECC-GAF, MIRECC-Global Assessment of Functioning; BACS, Brief Assessment of Cognition in Schizophrenia; NSA-16, Negative Symptom Assessment. PHQ-9, Patient Health Questionnaire.

associated with the MIRECC-GAF subscales (details were presented in **Supplementary Table 2**). PHQ-9 score was found to be significantly correlated with MIRECC-GAF social ($r = -0.54$, $p < 0.001$) and symptomatic ($r = -0.50$, $p < 0.001$) domains. In view of the significant relationship of gender on occupational functioning in MDD, a multiple regression for occupational functioning was performed using gender and NSA-16 motivation as predictors ($F = 11.35$, $p < 0.001$); this revealed a significant effect of NSA-16 motivation ($\beta = -0.18$, $p < 0.001$) on occupational functioning in MDD.

For individuals with SCZ, both the NSA-16 total and BACS composite score were significantly correlated with most MIRECC-GAF subscale scores. Within the NSA-16 subdomains, motivation was significantly correlated with the MIRECC-GAF occupational functioning ($r = -0.49$ $p < 0.001$), while social involvement was associated with MIRECC-GAF social functioning ($r = -0.32$, $p = 0.24$). Communication was significantly correlated with two MIRECC-GAF subscales—Social ($r = -0.42$, $p = 0.002$) and Symptomatic ($r = -0.33$, $p = 0.002$). PHQ-9 score was significantly correlated with only MIRECC-GAF symptomatic domain (Spearman's rho = −0.32, $p = 0.026$).

In HC, neither the BACS nor NSA-16 total scores were significantly correlated with the MIRECC-GAF score.

TABLE 2 | Association between MIRECC-GAF, BACS composite, NSA-16 total and PHQ-9 total across groups.

Measure	MDD			SCZ			HC		
	Occ	Soc	Symp	Occ	Soc	Symp	Occ	Soc	Symp
BACS	0.22[a]	0.12[a]	0.001[a]	0.41**[a]	0.25[a]	0.39**[a]	0.14	0.17	0.08
NSA-16	−0.19[a]	−0.19[a]	−0.39**[a]	−0.32*[a]	−0.36*[a]	−0.20[a]	0.08	−0.17	−0.07
PHQ-9	−0.07[a]	−0.54** [a]	−0.50**[a]	−0.18	−0.11	−0.32*	−0.10	−0.21	−0.15

*$p < 0.05$, **$p < 0.01$.
[a]*Pearson's correlation.*
BACS, Brief Assessment of Cognition in Schizophrenia; NSA-16, Negative Symptom Assessment; PHQ-9, Patient Health Questionnaire; Occ, MIRECC-GAF Occupational functioning; Soc, MIRECC-GAF Social functioning; Symp, MIRECC-GAF Symptomatic functioning.

TABLE 3 | Correlations between MIRECC-GAF and NSA-16 domains between groups.

NSA-16 domains	MDD			SCZ			HC		
	Occ	Soc	Symp	Occ	Soc	Symp	Occ	Soc	Symp
Communication	−0.001[a]	−0.19[a]	−0.24[a]	−0.26[a]	−0.42**[a]	−0.33**[a]	−0.04	−0.05	−0.11
Emotion/Affect	0.002[a]	−0.003[a]	−0.21[a]	−0.18[a]	−0.17[a]	−0.11[a]	0.38**	−0.03	0.12
Social involvement	−0.07[a]	−0.12[a]	−0.08[a]	−0.09[a]	−0.32*[a]	−0.03[a]	0.01	−0.26	0.06
Motivation	−0.48** [a]	−0.23[a]	−0.42**[a]	−0.49**[a]	−0.28[a]	−0.18[a]	0.11	−0.29*	−0.03
Motor retardation	−0.05[a]	−0.11[a]	−0.38**[a]	−0.18[a]	−0.05[a]	−0.06[a]	0.06	0.09	−0.14

*$p < 0.05$, **$p < 0.01$.
[a]*Pearson's correlation.*
NSA-16, Negative Symptom Assessment; Occ, MIRECC-GAF Occupational functioning; Soc, MIRECC-GAF Social functioning; Symp, MIRECC-GAF Symptomatic functioning.

However, two of the NSA-16 subdomains—emotion/affect and motivation were significantly associated with the MIRECC-GAF occupational (Spearman's rho = −0.38, $p = 0.007$) and social (Spearman's rho = −0.29, $p = 0.045$) subscales respectively. PHQ-9 score was not significantly correlated with MIRECC-GAF.

DISCUSSION

This study examined the association of negative symptoms, neurocognitive deficits, and depressive symptoms with functioning in individuals with MDD, individuals with SCZ and HC. The results revealed differences across the three groups in terms of severity of neurocognitive deficits, negative symptoms, depressive symptoms and functioning. The MDD and SCZ groups had more severe depressive ratings than the HC, while the SCZ group had greater impairments in neurocognition compared to the two other groups, consistent with existing studies (28, 29, 40). Both the MDD and SCZ groups had significantly greater negative symptom severity and poorer functioning than HC, which is consistent with the current literature (2, 13, 40, 41). The relationships between the NSA-16 subdomains differed across the three groups. In MDD, the NSA-16 motivation subdomain was significantly associated with occupational functioning. On the other hand, depressive symptoms were associated with social functioning, which is consistent with existing literature (42, 43). Both motivation subdomain and depressive symptoms were also associated with symptomatic functioning. On the other hand, in SCZ, neurocognition was associated with occupational and symptomatic functioning while overall negative symptoms and some of the subdomains were associated with all three domains of functioning. As for the HC, negative symptom subdomains, specifically emotion/affect and motivation, were significantly associated with occupational and social functioning. Neurocognition was not significantly associated with functioning in MDD and HC.

The results have implications on the presence and nature of negative symptoms in individuals with MDD. Negative symptoms are present in MDD, almost to the same degree of severity as individuals with SCZ, as seen in the lack of significant difference in the negative symptom subdomains and total severity rating between both groups. This is consistent with existing studies (44, 45), which have shown comparable severity between both groups. This further highlights the importance of assessing and treating negative symptoms in MDD in clinical treatment.

This study found that the overall negative symptoms severity was not significantly associated with functioning in MDD; only the motivation subdomain was associated with occupational functioning in MDD. Though the impairments in negative symptoms are present across multiple subdomains, the subdomains are however, not equal in terms of their impact on functioning. This further suggests that treatments that target functional recovery in MDD should focus on motivation in order to ensure optimal results. Furthermore, the differential associations between SCZ and MDD suggest that specific subdomains of negative symptoms are related to different domains of functioning in the two diagnostic groups.

Only motivation appears to be consistently associated with occupational functioning in both groups. This finding has also been seen in other studies that examined both groups individually (16, 46). A possible explanation for the link between motivation and occupational functioning could be the individuals having aberrant cost-benefit calculations as a result of neural abnormalities in reward-processing circuit (47), which leads them to choose passive tasks that mostly require lesser effort e.g., laying on bed instead of performing active tasks like going out to work or doing housework when at home. There had been some focus in explicitly targeting rewards in psychosocial treatments in individuals with MDD, with a goal of providing the individuals with more exposure to rewarding elements and personal experience of reward (48). A review (49) has found that such explicit behavioral exposure has benefits on clinical outcomes in the individuals. A more recent study has also found that reward exposure therapy through behavioral activation helped reduce depressive symptoms in a group of older adults with MDD (50). With this positive finding, it might be worth studying if such benefits could also be broadened onto the individuals' functioning abilities.

Unexpectedly, this study did not find a significant association between neurocognitive deficits and functioning in MDD, which is inconsistent with the current literature (6, 10, 11). A potential explanation would be relevant to the relatively younger ages of the MDD participants in the study, where almost half the group (46%) is aged 30 years old and below. It is also evident in the significantly shorter duration of illness in the MDD group. Neurocognitive abilities tend to deteriorate with age (51), and studies have found that neurocognitive impairments are typically less pronounced in younger adults with MDD (52). As such, this suggests that the neurocognitive impairments in this current sample of MDD might have been minimal, as backed by the lack of significant difference in BACS performance between them and the HC. Hence, the seemingly absent neurocognitive deficits faced by the younger MDD group might have been the reason for the minimal association with functioning seen in this study. On the other hand, neurocognitive impairments were significantly associated with occupational functioning in the SCZ group. This difference between both groups can thus be attributed to the younger MDD group, and the relationship between neurocognitive impairments and functioning being age-dependent in MDD, unlike that in SCZ (53).

This study provided more information on the effects of negative symptoms on functioning in MDD, an area that has not been studied widely (54, 55). One strength of this study is that the raters who performed NSA-16 were blinded to the diagnosis of the participants. This would reduce rating bias related to rater's preconceived notions of negative symptoms in MDD or SCZ. However, there are also limitations worthy of mention. First, this is a cross-sectional study, and findings reported are only associational in nature. As such, we were not able to examine the trajectories of negative symptoms and cognitive impairments in MDD and its relationship to functioning. Second, NSA-16 is a measure that is validated in SCZ and its validity in MDD might not have been previously reported. Also, NSA-16 does not directly address anhedonia, one of the negative symptom subdomains (56). A past study (57) has found that anhedonia is a strong predictor of psychosocial functioning in depressed patients. That said, the objective of the study requires a common scale to be used across all groups so that comparisons can be made. Future studies might seek to address these issues related to the properties of the measures. Third, medication use might have effects on the variables of interest, e.g., benzodiazepine and antidepressants use were found to affect different cognitive domains (8). However, due to the small sample size in this study, the effects of medications were not studied. Lastly, the short duration of illness for the MDD group might affect the generalizability of the study results. The relationship between negative symptom and neurocognition with functioning may vary as a function of illness duration. Future studies may seek to examine the relationship between factors with a sample of a larger range of illness duration for better generalizability.

CONCLUSION

In this study, we reported the presence of negative symptoms in individuals with MDD. Also, specific negative symptoms subdomains and neurocognitive deficits were found to play different roles in individual domains of functioning between MDD and SCZ. Having validation studies on transdiagnostic measures might be useful for interpreting results of future MDD studies. Additionally, future longitudinal studies with larger sample sizes would improve our understanding about the relationship between the factors and functioning in MDD and SCZ.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by NHG Domain Specific Review Board (DSRB). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YQ has been involved in the data entry, data analysis, drafting and revision of the manuscript, and the final approval of the final submission. ZY has been involved in the conception and design of research study, writing the protocol, data collection, data entry, data analysis, revision of the manuscript, and final approval of the final submission. JD has been involved in the conception and design of research study, and final approval of the final submission. JL has been involved in the conception and design of research study, data collection, data analysis, revision of the manuscript and final approval of the final submission. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by Rehabilitation Research Institute of Singapore (RRIS) (Psychosocial Rehabilitation & Quality of Life (QoL)/RRG2-16009).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.648108/full#supplementary-material

REFERENCES

1. World Health Organisation. *International Statistical Classification of Diseases and Related Health Problems (11th Revision)*. (2018). Availability online at: https://icd.who.int/browse11/l-m/en
2. Lam RW, Malhi GS, McIntyre RS, Demyttenaere K, Gorwood P, Michalak EE, et al. Fatigue and occupational functioning in major depressive disorder. *Aust N Z J Psychiatry.* (2013) 47:989–91. doi: 10.1177/0004867413488222
3. Andrews G. Should depression be managed as a chronic disease? *Br Med J.* (2001) 322:419–21. doi: 10.1136/bmj.322.7283.419
4. Judd LL. The clinical course of unipolar major depressive disorders. *Arch Gen Psychiatry.* (1997) 54:989–91. doi: 10.1001/archpsyc.1997.01830230015002
5. Zimmerman M, McGlinchey JB, Posternak MA, Friedman M, Boerescu D, Attiullah N. Discordance between self-reported symptom severity and psychosocial functioning ratings in depressed outpatients: implications for how remission from depression should be defined. *Psychiatry Res.* (2006) 141:185–91. doi: 10.1016/j.psychres.2005.05.016
6. Perini G, Cotta Ramusino M, Sinforiani E, Bernini S, Petrachi R, Costa A. Cognitive impairment in depression: recent advances and novel treatments. *Neuropsychiatr Dis Treat.* (2019) 15:1249–58. doi: 10.2147/NDT.S199746
7. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med.* (2014) 44:2029–40. doi: 10.1017/S0033291713002535
8. Chen RA, Lee CY, Lee Y, Hung CF, Huang YC, Lin PY, et al. Defining cognitive profiles of depressive patients using the brief assessment of cognition in affective disorders. *PeerJ.* (2019) 7:e7432. doi: 10.7717/peerj.7432
9. Mohn C, Rund BR. Neurocognitive profile in major depressive disorders: Relationship to symptom level and subjective memory complaints. *BMC Psychiatry.* (2016) 16:108. doi: 10.1186/s12888-016-0815-8
10. Naismith SL, Longley WA, Scott EM, Hickie IB. Disability in major depression related to self-rated and objectively-measured cognitive deficits: a preliminary study. *BMC Psychiatry.* (2007) 7:32. doi: 10.1186/1471-244X-7-32
11. Jaeger J, Berns S, Uzelac S, Davis-Conway S. Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Res.* (2006) 145:39–48. doi: 10.1016/j.psychres.2005.11.011
12. Richter J, Hölz L, Hesse K, Wildgruber D, Klingberg S. Measurement of negative and depressive symptoms: discriminatory relevance of affect and expression. *Eur Psychiatry.* (2019) 55:23–8. doi: 10.1016/j.eurpsy.2018.09.008
13. Chuang JY, Murray GK, Metastasio A, Segarra N, Tait R, Spencer J, et al. Brain structural signatures of negative symptoms in depression and schizophrenia. *Front Psychiatry.* (2014) 5:116. doi: 10.3389/fpsyt.2014.00116
14. Galynker II, Cohen LJ, Cai J. Negative symptoms in patients with major depressive disorder: a preliminary report. *Neuropsychiatry Neuropsychol Behav Neurol.* (2000) 13:171–6.
15. Chaturvedi SK, Sarmukaddam S. Negative symptoms in depression. *Indian J. Psychiatr.* (1985) 27:139–44.
16. Fervaha G, Foussias G, Takeuchi H, Agid O, Remington G. Motivational deficits in major depressive disorder: cross-sectional and longitudinal relationships with functional impairment and subjective well-being. *Compr Psychiatry.* (2016) 66:31–8. doi: 10.1016/j.comppsych.2015.12.004
17. Rothschild AJ, Raskin J, Wang CN, Marangell LB, Fava M. The relationship between change in apathy and changes in cognition and functional outcomes in currently non-depressed SSRI-treated patients with major depressive disorder. *Compr Psychiatry.* (2014) 55:1–10. doi: 10.1016/j.comppsych.2013.08.008
18. Xiao L, Feng L, Zhu X, Feng Y, Wu W, Ungvari GS, et al. Comparison of residual depressive symptoms and functional impairment between fully and partially remitted patients with major depressive disorder: a multicenter study. *Psychiatry Res.* (2018) 261:547–53. doi: 10.1016/j.psychres.2018.01.020
19. Edwards CJ, Garety P, Hardy A. The relationship between depressive symptoms and negative symptoms in people with non-affective psychosis: a meta-analysis. *Psychol Med.* (2019) 49:2486–98. doi: 10.1017/S0033291719002381
20. Pogue-Geile MF, Harrow M. Negative and positive symptoms in schizophrenia and depression: a followup. *Schizophr Bull.* (1984) 10:371–87. doi: 10.1093/schbul/10.3.371
21. Iosifescu DV. The relation between mood, cognition and psychosocial functioning in psychiatric disorders. *Eur Neuropsychopharmacol.* (2012) 22:S499–504. doi: 10.1016/j.euroneuro.2012.08.002
22. Robertson BR, Prestia D, Twamley EW, Patterson TL, Bowie CR, Harvey PD. Social competence versus negative symptoms as predictors of real world social functioning in schizophrenia. *Schizophr Res.* (2014) 160:136–41. doi: 10.1016/j.schres.2014.10.037
23. van Winkel R, Myin-Germeys I, De Hert M, Delespaul P, Peuskens J, van Os J. The association between cognition and functional outcome in first-episode patients with schizophrenia: mystery resolved? *Acta Psychiatr Scand.* (2007) 116:119–24. doi: 10.1111/j.1600-0447.2007.01014.x
24. Ventura J, Subotnik KL, Gitlin MJ, Gretchen-Doorly D, Ered A, Villa KF, et al. Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later. *Schizophr Res.* (2015) 161:407–13. doi: 10.1016/j.schres.2014.10.043
25. Kurtz MM, Moberg PJ, Ragland JD, Gur RC, Gur RE. Symptoms versus neurocognitive test performance as predictors of psychosocial status in schizophrenia: a 1- and 4-year prospective study. *Schizophr Bull.* (2005) 31:167–74. doi: 10.1093/schbul/sbi004
26. Penadés R, Gastó C, Boget T, Catalán R, Salamero M. Deficit in schizophrenia: the relationship between negative symptoms and neurocognition. *Compr Psychiatry.* (2001) 42:64–9. doi: 10.1053/comp.2001.19745
27. Mohamed S, Rosenheck R, Swartz M, Stroup S, Lieberman JA, Keefe RSE. Relationship of cognition and psychopathology to functional impairment in schizophrenia. *Am J Psychiatry.* (2008) 165:978–87. doi: 10.1176/appi.ajp.2008.07111713
28. First MB, Spitzer RL, Gibson M, Williams JBW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P).* Biometric Research, New York State Psychiatric Institute, New York (2002).
29. First MB, Spitzer RL, Gibson M, Williams JBW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient Edition* (SCID-I/NP). Biometrics Research, New York State Psychiatric Institute, New York (2002).
30. Alphs LD, Summerfelt A, Lann H, Muller RJ. The negative symptom assessment: a new instrument to assess negative symptoms of schizophrenia. *Psychopharmacol Bull.* (1989) 25:159–63.
31. Axelrod BN, Goldman RS, Alphs LD. Validation of the 16-item negative symptom assessment. *J Psychiatr Res.* (1993) 27:253–8. doi: 10.1016/0022-3956(93)90036-2
32. Keefe RSE, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The brief assessment of cognition in schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res.* (2004) 68:283–97. doi: 10.1016/j.schres.2003.09.011
33. Huang YC, Lee Y, Lee CY, Lin Y, Hung CF, Lee SY, et al. Defining cognitive and functional profiles in schizophrenia and affective disorders. *BMC Psychiatry.* (2020) 20:39. doi: 10.1186/s12888-020-2459-y
34. Pu S, Setoyama S, Noda T. Association between cognitive deficits and suicidal ideation in patients with major depressive disorder. *Sci Rep.* (2017) 7:11637. doi: 10.1038/s41598-017-12142-8

35. Terachi S, Yamada T, Pu S, Yokoyama K, Matsumura H, Kaneko K. Comparison of neurocognitive function in major depressive disorder, bipolar disorder, and schizophrenia in later life: a cross-sectional study of euthymic or remitted, non-demented patients using the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J). *Psychiatry Res.* (2017) 254:205–10. doi: 10.1016/j.psychres.2017.04.058
36. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* (2001) 16:606–13. doi: 10.1046/j.1525-1497.2001.016009606.x
37. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. primary care evaluation of mental disorders. patient health questionnaire. *JAMA.* (1999) 282:1737–44. doi: 10.1001/jama.282.18.1737
38. Niv N, Cohen AN, Sullivan G, Young AS. The MIRECC version of the Global Assessment of Functioning scale: reliability and validity. *Psychiatr Serv.* (2007) 58:529–35. doi: 10.1176/ps.2007.58.4.529
39. IBM Corp. *IBM SPSS Statistics for Windows, Version 23.0.* (23.0) [Computer software] (2015).
40. Zhu Y, Womer FY, Leng H, Chang M, Yin Z, Wei Y, et al. The relationship between cognitive dysfunction and symptom dimensions across schizophrenia, bipolar disorder, and major depressive disorder. *Front Psychiatry.* (2019) 10:253. doi: 10.3389/fpsyt.2019.00253
41. Kline ER, Seidman LJ, Cornblatt BA, Woodberry KA, Bryant C, Bearden CE, et al. Depression and clinical high-risk states: baseline presentation of depressed vs. non-depressed participants in the NAPLS-2 cohort. *Schizophr Res.* (2018) 192:357–63. doi: 10.1016/j.schres.2017.05.032
42. Saris IMJ, Aghajani M, van der Werff SJA, van der Wee NJA, Penninx BWJH. Social functioning in patients with depressive and anxiety disorders. *Acta Psychiatr Scand.* (2017) 136:352–61. doi: 10.1111/acps.12774
43. Denninger JW, van Nieuwenhuizen AO, Wisniewski SR, Luther JF, Trivedi MH, Rush AJ, et al. Changes in depressive symptoms and social functioning in the sequenced treatment alternatives to relieve depression study. *J Nerv Ment Dis.* (2011) 199:807–10. doi: 10.1097/NMD.0b013e31822fcbe2
44. Herbener ES, Harrow M. Longitudinal assessment of negative symptoms in schizophrenia/schizoaffective patients, other psychotic patients, depressed patients. *Schizophr Bull.* (2001) 27:527–37. doi: 10.1093/oxfordjournals.schbul.a006893
45. Jeste DV, Heaton SC, Paulsen JS, Ercoli L, Harris J, Heaton RK. Clinical and neuropsychological comparison of psychotic depression with nonpsychotic depression and schizophrenia. *Am J Psychiatry.* (1996) 153:490–6. doi: 10.1176/ajp.153.4.490
46. Fulford D, Piskulic D, Addington J, Kane JM, Schooler NR, Mueser KT. Prospective relationships between motivation and functioning in recovery after a first episode of schizophrenia. *Schizophr Bull.* (2018) 44:369–77. doi: 10.1093/schbul/sbx096
47. Ng TH, Alloy LB, Smith DV. Meta-analysis of reward processing in major depressive disorder reveals distinct abnormalities within the reward circuit. *Transl Psychiatry.* (2019) 9:293. doi: 10.1038/s41398-019-0644-x
48. Forbes EE. Where's the fun in that? Broadening the focus on reward function in depression. *Biol Psychiatry.* (2009) 66:199–200. doi: 10.1016/j.biopsych.2009.05.001
49. Ekers D, Richards D, Gilbody S. A meta-analysis of randomized trials of behavioural treatment of depression. *Psychol Med.* (2008) 38:611–23. doi: 10.1017/S0033291707001614
50. Alexopoulos GS, Raue PJ, Gunning F, Kiosses DN, Kanellopoulos D, Pollari C, et al. "Engage" therapy: behavioral activation and improvement of late-life major depression. *Am J Geriatr Psychiatry.* (2016) 24:320–6. doi: 10.1016/j.jagp.2015.11.006
51. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med.* (2013) 29:737–52. doi: 10.1016/j.cger.2013.07.002
52. Grant MM, Thase ME, Sweeney JA. Cognitive disturbance in outpatient depressed younger adults: evidence of modest impairment. *Biol Psychiatry.* (2001) 50:35–43. doi: 10.1016/S0006-3223(00)01072-6
53. Kalache SM, Mulsant BH, Davies SJC, Liu AY, Voineskos AN, Butters MA, et al. The impact of aging, cognition, and symptoms on functional competence in individuals with schizophrenia across the lifespan. *Schizophr Bull.* (2015) 41:374–81. doi: 10.1093/schbul/sbu114
54. Gupta M, Holshausen K, Best MW, Jokic R, Milev R, Bernard T, et al. Relationships among neurocognition, symptoms, and functioning in treatment-resistant depression. *Arch Clin Neuropsychol.* (2013) 28:272–81. doi: 10.1093/arclin/act002
55. Herbener ES, Harrow M. Are negative symptoms associated with functioning deficits in both schizophrenia and nonschizophrenia patients? A 10-year longitudinal analysis. *Schizophr Bull.* (2004) 30:813–25. doi: 10.1093/oxfordjournals.schbul.a007134
56. Daniel DG. Issues in selection of instruments to measure negative symptoms. *Special Section.* (2013) 150:343–5. doi: 10.1016/j.schres.2013.07.005
57. Vinckier F, Gourion D, Mouchabac S. Anhedonia predicts poor psychosocial functioning: results from a large cohort of patients treated for major depressive disorder by general practitioners. *Eur Psychiatry.* (2017) 44:1–8. doi: 10.1016/j.eurpsy.2017.02.485

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 09 August 2021
doi: 10.3389/fpsyt.2021.700747

Real-World Functioning in Patients With Schizophrenia: Beyond Negative and Cognitive Symptoms

María Paz García-Portilla[1,2,3,4,5], *Leticia García-Álvarez*[2,3,4,5,6], *Leticia González-Blanco*[1,2,3,4,5]*, *Francesco Dal Santo*[1,2,4,5], *Teresa Bobes-Bascarán*[1,3,4,5,6], *Clara Martínez-Cao*[2,4,5], *Ainoa García-Fernández*[2,4,5], *Pilar A. Sáiz*[1,2,3,4,5] and *Julio Bobes*[1,2,3,4,5]

[1] Servicio de Salud del Principado de Asturias (SESPA), Oviedo, Spain, [2] Department of Psychiatry, Universidad de Oviedo, Oviedo, Spain, [3] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain, [4] Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain, [5] Instituto Universitario de Neurociencias del Principado de Asturias (INEUROPA), Oviedo, Spain, [6] Department of Psychology, Universidad de Oviedo, Oviedo, Spain

OPEN ACCESS

Edited by:
Armida Mucci, University of Campania Luigi Vanvitelli, Italy

Reviewed by:
Janusz K. Rybakowski, Poznan University of Medical Sciences, Poland
Krzysztof Krysta, Medical University of Silesia, Poland
Cristiana Montemagni, University of Turin, Italy

***Correspondence:**
Leticia González-Blanco
leticiagonzalezblanco@gmail.com

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *26 April 2021*
Accepted: *15 July 2021*
Published: *09 August 2021*

Citation:
García-Portilla MP, García-Álvarez L, González-Blanco L, Dal Santo F, Bobes-Bascarán T, Martínez-Cao C, García-Fernández A, Sáiz PA and Bobes J (2021) Real-World Functioning in Patients With Schizophrenia: Beyond Negative and Cognitive Symptoms. Front. Psychiatry 12:700747. doi: 10.3389/fpsyt.2021.700747

Introduction: Interest in the idea of recovery for certain patients with schizophrenia has been growing over the last decade. Improving symptomatology and functioning is crucial for achieving this. Our study aims to identify those factors that substantially contribute to real-world functioning in these patients.

Methods: We carried out a cross-sectional study in stable outpatients with schizophrenia on maintenance antipsychotic monotherapy. *Patients*: We studied 144 outpatients with schizophrenia (DSM-IV-TR criteria) meeting the following criteria: (1) 18–65 years of age; (2) being clinically stable for at least the previous three months; (3) on maintenance antipsychotic monotherapy (prescriptions $\leq$ 10 mg olanzapine, $\leq$200 mg quetiapine, or $\leq$100 mg levomepromazine as hypnotics were also allowed); and (4) written informed consent. *Assessment*: We collected information on demographic and clinical variables by using an *ad hoc* questionnaire. For psychopathology, we employed the Spanish versions of the following psychometric instruments: the Positive and Negative Syndrome Scale (PANSS), the Brief Negative Symptom Scale (BNSS-Sp), and the Calgary Depression Scale (CDS). In addition, cognitive domains were assessed using the Verbal Fluency Test (VFT), the Digit Symbol Substitution Test (DSST), and the Trail Making Test, parts A and B (TMT-A and TMT-B). Finally, we employed the Spanish versions of the University of California San Diego Performance-based Skills Assessment (Sp-UPSA) and the Personal and Social Performance (PSP) for assessing functional capacity and real-world functioning, respectively. *Statistical analysis*: A forward stepwise regression was conducted by entering those variables significantly associated with PSP total score into the univariate analyses (Student's *t*-test, ANOVA with Duncan's *post-hoc* test, or bivariate Pearson correlation).

Results: A total of 144 patients; mean age 40 years, 64% males, mean length of illness 12.4 years, PSP total score 54.3. The final model was a significant predictor of real-world functioning [$F_{(7,\ 131)} = 36.371$, $p < 0.001$] and explained 66.0% of the variance. Variables

retained in the model: BNSS-Sp abulia, asociality, and blunted affect, PANSS general psychopathology, Sp-UPSA transportation, TMT-B, and heart rate.

Conclusion: Our model will contribute to a more efficient and personalized daily clinical practice by assigning specific interventions to each patient based on specific impaired factors in order to improve functioning.

Keywords: functioning, recovery, schizophrenia, monotherapy, antipsychotic

INTRODUCTION

Although schizophrenia has traditionally been linked to severe functional deficits, interest in the idea of recovery as a possibility for particular patients has been growing in recent years. This concept of recovery is relatively new and still under construction in schizophrenia. It is complex, encompasses multiple aspects of the patient's life, and can be operationalized in two domains that are distinct, but to some extent interdependent, i.e., the objective or clinical and the subjective or personal (1–3).

The objective clinical recovery domain includes symptomatology and functioning, and it is well known that there is no direct relationship between the two (4). Furthermore, numerous studies have focused on functioning predictors, but their results are rarely replicated. Among the most consistently reported predictors are negative symptoms and cognitive performance (2, 5–15). Recently, a systematic review and evidence synthesis on the relationship between functional capacity, as measured by the University of California San Diego Performance-based Skills Assessment (UPSA), and different measurements of real-world functioning reported a connection between these two constructs that merits further investigation (16). In this sense, Menendez-Miranda et al. (9) quantified the relationship between the UPSA and the Personal and Social Performance scale (PSP), one of the most widely used real-world functioning measures, reporting that each one explained 17% of the variance of the other. Depressive symptoms have also been associated with worse functioning (10, 17), although the strength of this relationship was very weak (17). Gonzalez-Blanco et al. (15) found IL-2, a peripheral inflammatory biomarker, to be associated with worse functioning and negative and general psychopathology symptoms. Other predictors of functional remission or recovery in patients with schizophrenia identified by Vita and Barlati (3) in their review were education level, employment status, family economic status, age at onset, hospitalizations, relapses, adherence to treatment, and disorganization symptoms. Except for age at onset, all of these were reported by a single study.

Concerning treatment, Tandon et al. (18) concluded that side effects associated with second-generation antipsychotics substantially impact patient functioning and quality of life. However, they acknowledged that this is a convoluted, under-researched area. To better understand the relationship between different treatment options and outcomes measures, we need studies in naïve patients, but the difficulty enrolling them severely hampers the research (19).

With the above in mind, it can be hypothesized that different factors would have a small but significant effect on the real-world functioning of patients with schizophrenia. Therefore, identifying this plethora of factors would help to manage this disorder with greater precision and reduce its associated functional impairments through specific interventions aimed at their modification. Thus, this study aims to model the relationship between the real-world functioning of patients with schizophrenia on maintenance antipsychotic monotherapy and an extensive range of independent variables. We hypothesize that, in addition to negative symptoms and cognitive performance, depressive symptoms, somatic comorbidities, and functional capacity will be found to substantially contribute to patient functioning.

METHODS

Design

This is a naturalistic, cross-sectional study carried out in outpatients with schizophrenia consecutively seen at either of the two mental health centers participating in the study. Both centers are in Oviedo, Northern Spain, and each has a catchment area population of about 80,000 inhabitants.

The study was conducted according to the Declaration of Helsinki (20). The Clinical Research Ethics Committee of Hospital Universitario Central de Asturias in Oviedo approved the study protocol (Ref. 127/15), and written informed consent was obtained from all participants before enrolment.

Patients

A total of 144 outpatients with schizophrenia (DSM-IV-TR criteria) were included in the study. Inclusion criteria were: (1) 18–65 years of age; (2) being clinically stable for at least the previous 3 months (without hospitalizations, symptom exacerbation, or any significant change in the type/dose of antipsychotic treatment); (3) on maintenance antipsychotic monotherapy (prescriptions $\leq$ 10 mg olanzapine, $\leq$ 200 mg quetiapine, or $\leq$ 100 mg levomepromazine as hypnotics were also allowed); and (4) written informed consent. Having an intellectual disability disorder or acquired brain injury was the sole exclusion criteria.

The sample was collected between July 2017 and December 2019. Therefore, we consecutively offered the study to the patients meeting all the inclusion criteria and none of the exclusion criteria at the clinic.

Assessment

Information on sociodemographic and clinical characteristics, including weight, heart rate, and blood pressure, was collected using an *ad hoc* questionnaire. To evaluate different psychopathological domains, we used the Spanish versions of the following psychometric instruments: Positive and Negative Syndrome Scale (PANSS) (21), Brief Negative Symptoms Scale (BNSS-Sp) (22), and Calgary Depression Scale for Schizophrenia (CDSS) (23). In all cases, higher scores indicate greater severity of the symptomatology.

Cognition was evaluated using phonemic (F-A-S) and semantic (animals) Verbal Fluency (VF) tests (24, 25), Digit Symbol Substitution Test (DSST) (26), and Trail Making Test parts A and B (TMT-A and TMT-B) (27). These tests measure the following cognitive domains:

- VF tests: attention, memory, verbal fluency, and executive functions (28)
- DSST: motor speed, attention, and visuoperceptual functions, but probably also associative learning and working memory (29) and
- TMT: Part A measures psychomotor speed, attention, and spatial organization, while Part B measures attention switching, mental flexibility, and recall (30).

For VF and DSST, lower scores indicate lower cognitive performance, while for TMT-A and -B, higher scores reflect lower cognitive performance.

We employed the Spanish version of the University of California San Diego Performance-based Skills Assessment (Sp-UPSA) to measure functional capacity (31). It assesses everyday adaptive skills, including finance management, communication, planning recreational activities, and transportation, under optimal conditions. The Sp-UPSA provides four domain scores (from 0 to 25 points) and a total score, potentially ranging from 0 to 100 points. In all cases, higher scores indicate better functional capacity.

Finally, real-world functioning was assessed using the Personal and Social Performance scale (PSP) (32). The PSP is a clinician-rated instrument that evaluates patient functioning in four areas of their lives: self-care, socially useful activities including work and study, personal and social relationships, and disturbing and aggressive behaviors. It provides scores in each of the four areas ranging from 0 to 6, where higher scores indicate worse functioning. It also provides a single total score ranging from 0 to 100, where higher scores reflect better personal and social functioning.

Statistical Analysis

To estimate the proportion of patients with a PSP total score $\geq$70, starting from a population size of 250 patients on maintenance antipsychotic monotherapy at our clinics, a sample of 144 subjects is required. This sample size was determined for a 95% confidence interval, with a precision of $\pm$5%, and taking into account that the true estimated proportion will be 33%.

The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 24.0. For all tests, the significance level was set at $p < 0.05$. To explore the potential relationships between PSP total score and sociodemographic, clinical, and psychometric variables, we used Student's *t*-test, ANOVA with Duncan's *post-hoc* test, or bivariate Pearson correlation. Finally, to model the relationship between the PSP total score and all variables found to be significantly associated with it in the univariate analysis, we performed a multiple linear regression (forward stepwise regression). To avoid collinearity, for those psychometric instruments that provide subscale scores (i.e., PANSS total score, UPSA total score), we do not include the total score in the analysis, nor do we include redundant measures (i.e., PANSS negative subscale or Marder negative factor).

RESULTS

Sociodemographic and Clinical Characteristics

Patient mean age was 39.67 (11.93), 63.6% were males, and 58.3% had a secondary school degree. Most of the patients were never married (72.2%), were living with their family of origin (64.6%), and were not working (70.1%), and almost half were receiving a mental disability benefit (43.8%).

Their mean length of illness was 12.36 (10.91) years. Most had had at least one previous hospitalization (70.8%), and 19.4% had a history of suicide attempts. In addition, 45.8% had psychiatric comorbidities (substance use disorders, especially tobacco), and 63.9% had physical comorbidities (see **Table 1**).

Concerning psychopharmacotherapy, all patients were on maintenance antipsychotic monotherapy (paliperidone 46.5%, aripiprazole 19.5%, olanzapine 13.9%, clozapine 4.9%, and only 3.5% of patients received typical antipsychotics). Almost half were on long-acting intramuscular antipsychotics (paliperidone LAI-3 months 20.1%, paliperidone LAI-1 month 13.9%, aripiprazole LAI 1-month 6.3%, fluphenazine decanoate 2.1%, and Risperdal Consta LAI 1.4%). Furthermore, 15% of patients were taking low doses of olanzapine (7.6%) or quetiapine (7.6%) as hypnotics, 19.4% were taking antidepressants and 43.8% at least one benzodiazepine (see **Table 2**).

On the whole, patients included in the study had predominantly negative symptoms [PANSS Negative = 18.68 (5.57), PANSS Positive = 12.31 (5.30)], almost no depressive symptomatology [CDSS = 2.96 (3.62)] and performed relatively poorly on the cognitive tests [Verbal Fluency phonemic total = 26.03 (10.18), semantic animals = 16.70 (5.33), Digit Symbol Substitution = 41.73 (17.02), and TMT-A = 50.02 (25.89) and -B = 124.96 (67.19)]. Their functional capacity was mildly impaired [Sp-UPSA total score = 70.90 (14.56)], with communication being the domain most impaired [15.87 (4.75)] while transportation was the least [18.87 (4.72); see **Table 1**].

Real-World Functioning and Its Predictors

Patients showed manifest impairment in real-world functioning [PSP total score = 54.33 (18.43)], and only 18.1% of the patients showed a reasonable level of functioning (PSP total score > 70). Useful activities and relationships were the areas most impaired [2.32 (1.29) and 2.31 (1.29), respectively].

As shown in **Tables 3**, **4**, several independent variables were significantly associated with patient real-world functioning. All

TABLE 1 | Sociodemographic and clinical characteristics of the sample.

Sociodemographic	*n* (%)	Clinical	*n* (%)
Age [mean (sd)]	39.67 (11.93)	Length of illness (years) [mean (sd)]	12.36 (10.91)
Sex, males	92 (63.9)	Hospitalizations, yes	102 (70.8)
Marital status		No. of hospitalizations [mean (sd)]	2.04 (1.64)
Never married	104 (72.2)	Age at first hospitalization [mean (sd)]	28.15 (8.82)
Married[$]	40 (27.8)	Suicide attempts, yes	28 (19.4)
Living arrangement		No. of suicide attempts [mean (sd)]	1.82 (3.59)
Alone	16 (11.1)	Psychiatric comorbidities, yes	66 (45.8)
Family of origin	93 (64.6)	One disorder	57 (39.6)
Own family	30 (20.8)	Two disorders	7 (4.9)
Institutionalized	2 (1.4)	Three disorders	2 (1.4)
Other	3 (2.1)	SUD tobacco	65 (45.1)
Educational level		SUD cannabis	9 (6.3)
Primary school	38 (26.4)	SUD alcohol	3 (2.1)
Secondary school	84 (58.3)	SUD cocaine	1 (0.7)
University	22 (15.3)	Somatic comorbidities, yes	92 (63.9)
Years of education [mean (sd)]	14.09 (4.42)	One disease	47 (32.6)
Work status		Two diseases	28 (19.4)
Working	18 (12.5)	Three diseases	13 (9.0)
Not working*	101 (70.1)	Four diseases	2 (1.4)
Homemaker or student	25 (17.4)	Five diseases	2 (1.4)
Mental disability benefit, yes	63 (43.8)	Ophthalmological problems	45 (31.3)
Anthropometry and vital signs		Hypercholesterolemia	15 (10.4)
BMI [mean (sd)]	27.69 (5.28)	Hypertension	13 (9.0)
Low weight (<18.5)	3 (2.1)	Hypertriglycerides	10 (6.9)
Normal weight (18.5–24.9)	46 (31.9)	Constipation	8 (5.6)
Overweight (25–29.9)	50 (34.7)	Diabetes II	8 (5.6)
Obesity (≥30)	43 (29.9)	Respiratory disease	8 (5.6)
SBP [mean (sd)]	117.68 (14.68)	Hearing impairment	5 (3.5)
DBP [mean (sd)]	78.34 (10.74)	Migraine	5 (3.5)
Heart rate [mean (sd)]	80.79 (14.55)	Cardiovascular disease	3 (2.1)
		Hyperthyroidism	3 (2.1)

*sd, standard deviation; [$]Married includes married, living as married, widow, and divorced. *Not working includes permanently disabled due to health conditions other than a mental disorder, temporarily disabled, retired, and unemployed. AP, abdominal perimeter; DBP, diastolic blood pressure; SBP: systolic blood pressure; SUD: substance use disorder.*

variables involving negative symptoms showed the strongest correlations, followed by general psychopathology and functional capacity. On the contrary, the cognitive domains showed the weakest correlation with functioning, with attention switching, mental flexibility, and recall being the most strongly related. Also, being female, having some higher education, working or a homemaker/student, not receiving a mental disability benefit, having no history of suicide attempts, and no alcohol or benzodiazepine use were associated with better real-world functioning.

Results of the multiple linear regression are shown in **Table 5**. The final model explained 66.0% of the variance ($R^2 = 0.660$, standard error of the estimate = 10.928), and the model was a significant predictor of real-world functioning [$F_{(7,\ 131)} = 36.371$, $p < 0.001$]. As shown in **Table 2**, the seven variables retained in the model contributed significantly to it. The final predictive model was:

$$\begin{aligned} PSP\ total\ score\ =\ & 78.189 + (-1.626 * BNSS\ Abulia) \\ & + (-0.391 * PANSS\ General\ Psychopathology) \\ & + (-1.448 * BNSS\ Asociality) \\ & + (0.968 * UPSA\ Transportation\ ) \\ & + (-846 * BNSS\ Blunted\ Affect) \\ & + (0.041 * TMT - B) + (-0.161\ Heart\ Rate) \end{aligned}$$

Abulia and asociality were the independent variables that had the highest multicollinearity with other variables, but their variance inflation factor (VIF) values were very far from 5 (2.410 and 2.166, respectively, see **Table 2**).

TABLE 2 | Prescribed pharmacological treatment in descending order of frequency.

Monotherapy antipsychotic	***n* (%)**
Paliperidone LAI-3 months	29 (20.1)
mg [mean (sd)]/DE-OLZ1 mg	456.38 (142.4)/7.04
Paliperidone LAI-1 month	20 (13.9)
mg [mean (sd)]/DE-OLZ1 mg	121.25 (48.8)/16.84
Olanzapine	20 (13.9)
mg [mean (sd)]/DE-OLZ1 mg	10.25 (8.6)/10.25
Aripiprazole oral	19 (13.2)
mg [mean (sd)]/DE-OLZ1 mg	11.71 (7.1)/8.30
Paliperidone oral	18 (12.5)
mg [mean (sd)]/DE-OLZ1 mg	5.66 (3.1)/14.18
Risperidone	10 (6.9)
mg [mean (sd)]/DE-OLZ1 mg	3.2 (1.8)/8.42
Aripiprazole LAI-1 month	9 (6.3)
mg [mean (sd)]/DE-OLZ1 mg	255.56 (88.2)/8.97
Clozapine	7 (4.9)
mg [mean (sd)]/DE-OLZ1 mg	264.29 (143.5)/8.63
Amisulpride	3 (2.1)
mg [mean (sd)]/DE-OLZ1 mg	233.33 (152.7)/6.09
Fluphenazine decanoate	3 (2.1)
mg [mean (sd)]/DE-OLZ1 mg	29.17 (7.2)/58.34
Quetiapine	2 (1.4)
mg [mean (sd)]/DE-OLZ1 mg	712.50 (689.4)/22.08
Risperdal consta LAI	2 (1.4)
mg [mean (sd)]/DE-OLZ1 mg	150.00 (70.7)/89.29
Haloperidol	1 (0.7)
mg [mean (sd)]/DE-OLZ1 mg	60.00 (0.0)/81.08
Ziprasidone	1 (0.7)
mg [mean (sd)]/DE-OLZ1 mg	120.00 (0.0)/15.15
Antipsychotic as hypnotic	***n* (%)**
None	121 (84.0)
Olanzapine	11 (7.6)
mg [mean (sd)]	9.55 (1.5)
Quetiapine	11 (7.6)
mg [mean (sd)]	122.50 (58.3)
Levomepromazine	1 (0.7)
mg [mean (sd)]	25.00 (0.0)

Antidepressant	***n* (%)**
None	116 (80.6)
Escitalopram	11 (7.6)
Sertraline	6 (4.2)
Desvenlafaxine	3 (2.1)
Mirtazapine	2 (1.4)
Venlafaxine	2 (1.4)
Bupropion	1 (0.7)
Clomipramine	1 (0.7)
Maprotiline	1 (0.7)
Vortioxetine	1 (0.7)
Benzodiazepines	***n* (%)**
None	81 (56.3)
One	58 (40.3)
Two	5 (3.5)
Lorazepam	29 (21.2)
Clonazepam	10 (7.0)
Clorazepate dipotassium	9 (6.3)
Diazepam	7 (4.9)
Bromazepam	2 (1.4)
Ketazolam	2 (1.4)
Alprazolam	1 (0.7)
Flurazepam	1 (0.7)
Lormetazepam	5 (3.5)
Zoplicone	2 (1.4)
Other treatments	***n* (%)**
None	118 (82.0)
Biperiden	19 (13.2)
Gabapentin	4 (2.8)
Folic acid	1 (0.7)
Oxcarbazepine	1 (0.7)

DE-OLZ1 mg, Dose equivalent to Olanzapine 1 mg/day; LAI, long-acting injectable; mg, milligrams; sd, standard deviation.

DISCUSSION

In line with our objective, we were able to model the relationship between the real-world functioning of patients with schizophrenia on maintenance antipsychotic monotherapy and several independent variables. Our hypothesis identified seven factors with a small but significant effect on patient real-world functioning. Negative symptomatology (BNSS abulia, asociality, and blunted affect subscales), general psychopathology (PANSS subscale), functional capacity (UPSA transportation domain), cognitive performance (Trail Making Test, part B), and heart rate were found to significantly contribute to predicting real-world functioning.

Unsurprisingly, negative symptomatology was found to be the most robust predictor of real-world functioning, as reported by other authors (8, 9, 11–15, 33). It is worth highlighting the advantage of using the BNSS over the PANSS negative subscale or the Marder negative factor. It allowed us to determine the relationships between these two domains more accurately. We found that three out of the five dimensions that constitute the negative syndrome (34)—abulia, asociality, and blunted affect—were retained in the model. In this respect, we previously found identical results in patients during their first 10 years

TABLE 3 | Statistically significant associations between PSP total score and independent (categorical) variables.

Variables	Categories	PSP total score Mean (S.D.)	Statistical test, *p*
Sex	Males	50.73 (18.22)	−3.217[a], 0.002
	Females	60.69 (17.19)	
Education level	Primary school	51.16 (17.15)	4.328[b], 0.015 Higher ≠ (primary = secondary school)[c]
	Secondary school	53.08 (18.61)	
	Higher	64.55 (17.07)	
Work status	Working	66.39 (14.76)	10.988[b], <0.001 Not working ≠ (working = homemaker or student)[c]
	Not working[@]	49.96 (18.15)	
	Homemaker or student	63.28 (14.95)	
Mental disability benefit	No	58.53 (18.04)	3.203[a], 0.002
	Yes	48.92 (17.62)	
History of suicide attempts	No	56.30 (17.69)	2.674[a], 0.008
	Yes	46.14 (19.49)	
Alcohol use	No	51.08 (18.75)	−2.585[a], 0.011
	Yes	59.00 (17.05)	
Benzodiazepine use	No	59.15 (18.06)	3.607[a], <0.001
	Yes	48.46 (17.26)	

[a]*Student's t-test.*
[b]*ANOVA.*
[c]*Duncan's post-hoc test.*
S.D., standard deviation.
[@]*Not working includes permanently disabled due to a health condition other than a mental disorder, temporarily disabled, retired, and unemployed.*

TABLE 4 | Statistically significant associations between PSP total score and independent (continuous) variables.

Variables	Statistical test[#], *p**
Years of education	0.253[4]**
Length of illness (months)	−0.190[4]*
Weight (kg)	−0.195[4]*
Heart rate	−0.303[4]**
PANSS positive	−0.367[4]**
PANSS negative	−0.683[4]**
PANSS marder negative factor	−0.728[4]**
PANSS general psychopathology	−0.567[4]**
BNSS-Sp anhedonia	−0.648[4]**
BNSS-Sp distress	−0.428[4]**
BNSS-Sp asociality	−0.653[4]**
BNSS-Sp abulia	−0.705[4]**
BNSS-Sp blunted affect	−0.602[4]**
BNSS-Sp alogia	−0.375[4]**
CDSS	−0.347[4]**
VF Semantic (animals)	0.194[4]*
DSST	0.215[4]**
TMT-A	−0.290[4]**
TMT-B	−0.254[4]**
Sp-UPSA finance management	0.407**
Sp-UPSA communication	0.425**
Sp-UPSA planning recreational activities	0.296[4]**
Sp-UPSA transportation	0.463[4]**

[#]*Bivariate Pearson correlation. *p = 0.05 **p = 0.01.*
BNSS-Sp, brief negative symptoms scale, Spanish version; CDSS, calgary depression scale for schizophrenia; DSST, digit symbol substitution test; Kg, kilograms; PANSS, positive and negative syndrome scale; PSP, personal and social performance scale; TMT-A, trail making test, part A; TMT-B, trail making test, part B; Sp-UPSA, University of California San Diego performance-based skills assessment, Spanish version; VF, verbal fluency.

of the disorder (mean age 31.7, mean length of illness 4.6 years) (15), although other authors (11, 13, 35) did not find any relationship between the so-called expressive dimension of the negative symptomatology (blunted affect and alogia) and functioning. However, as early as 2000; Jablensky et al. (36) had linked the deficit in language and communication with difficulties in daily life, interpersonal relationships, and social functioning. We find our result regarding the relevance of affective expression to real-world functioning of great interest since non-verbal language constitutes more than 90% of the oral communication between human beings, and communication is a crucial ability for appropriate functioning in our society. Thus, psychosocial interventions intended to improve language and communication difficulties in these patients could also help enhance their psychosocial functioning.

Although Szabo et al. (16), in their systematic review and evidence synthesis, did not find a significant impact of functional capacity, measured using the UPSA, on different measurements of real-world functioning [Specific Level of Functioning (SLOF), Global Assessment of Functioning (GAF), and Multidimensional Scale of Independent Functioning (MSIF)] some studies have demonstrated the opposite. For example, Menendez-Miranda et al. (9) and Galderisi et al. (11) reported a positive and significant influence of functional capacity on real-world functioning (PSP and SLOF, respectively), as we did in this study. Specifically, we found that out of the four domains included in the functional capacity construct, the use of public transportation was retained in the model. Like the other tasks included in the UPSA, this specific task reflects general abilities essential to independent living, such as planning and organizing (37), and would mediate the potential functional impact of cognitive performance (11, 38).

TABLE 5 | Multiple linear regression model predicting real-world functioning (PSP total score).

Variables	B	S.E.	Beta	*t*	*P*	VIF
Constant	78.189	8.766		8.919	<0.001	
BNSS-Sp Abulia	−1.626	0.493	−0.261	−3.296	0.001	2.410
PANSS general psychopathology	−0.391	0.145	−0.172	−2.698	0.008	1.571
BNSS-Sp asociality	−1.448	0.527	−0.206	−2.746	0.007	2.166
Sp-UPSA transportation	0.968	0.232	0.251	4.170	<0.001	1.394
BNSS-Sp blunted affect	−0.846	0.267	−0.217	−3.172	0.002	1.808
TMT-B	0.041	0.017	0.144	2.442	0.016	1.349
Heart rate	−0.161	0.068	−0.128	−2.379	0.019	1.123

S.E., standard error; VIF, variable inflation factors. BNSS-Sp, brief negative symptoms scale, Spanish version; PANSS, positive and negative syndrome scale; PSP, personal and social performance scale; TMT-B, trail making test, part B; Sp-UPSA, University of California San Diego performance-based skills assessment, Spanish version.

The impact of cognitive performance on functioning was also demonstrated in patients with schizophrenia (5–7, 11), but the majority of the studies proving their relationship were carried out more than 10 years ago. Recently, Galderisi et al. (11) reported an indirect neurocognitive effect on patient work skills and interpersonal relationships. Social cognition was the mediator in both areas of real-world functioning, while functional capacity acted as a mediator only for work skills. However, Gonzalez-Blanco et al. (15) did not find any effect. These contradictory results could be explained by the fact that in the first study, the performance in the different neurocognitive areas was considered a single factor, while in the second, each cognitive domain was considered separately. Our study found that attention switching, mental flexibility, and recall were the only cognitive domains retained in the model. But, to further cloud the issue they were associated with functioning in the unexpected direction (partial correlation coefficient = 0.041); that is, if the rest of the variables in the equation remain constant, an increase of 1 second in performing the TMT-B will result in an increase of 0.041 points in the PSP total score. The magnitude of the coefficient is indeed minimal, but its contribution to the model is significant. This unexpected result could have been due to multicollinearity between TMT-B and other independent variables in the model, but this is not the case, as shown in **Table 2**. The TMT-B is a multifactorial test that measures processing speed, complex attention, cognitive flexibility, inhibitory control, and for some authors working memory as well. It is known that it is influenced by several factors such as age, motor speed (related to the former), and years of education, among others. Although neither age nor educational level was included in the model, both significantly affected the results of the univariate analysis in the expected direction (results not shown).

Furthermore, some prospective studies reported the effect of cognition on functioning to be mediated by negative and general symptomatology (39, 40), and Gonzalez-Blanco et al. (15) also found a significant effect of general psychopathology on PSP total score, as we did. Thus, further research is required to elucidate the real contribution of the TMT-B on real-world functioning. Unfortunately, there are no TMT-B normative data for Spanish patients with schizophrenia, and our sample size does not allow us to conduct the analysis stratifying for these factors.

Increased heart rate has been described in patients with schizophrenia since Kraepelin and also demonstrated in untreated first-episode patients and healthy first-degree relatives (41). This autonomic dysfunction has been related to the excess cardiovascular and metabolic morbidity and mortality seen in these patients (41, 42), as well as those with positive symptomatology (43, 44) and impairment in psychosocial functioning (45), even in first-episode patients (46). Our results add more support to the negative impact of autonomic dysfunction on real-world functioning, providing a specific line of intervention to improve it. This relationship may be mediated by the cognitive impairment often present in these patients. In this sense, a recent meta-analysis confirmed a significant association between the presence of several cardiovascular risk factors and cognitive impairment in patients with schizophrenia (47); thus, cognitive impairment is a plausible mediating factor between autonomic dysfunction and poor real-world functioning.

Contrary to our hypothesis, our model did not include depressive symptoms. However, in the bivariate analysis, total score on the CDSS was significantly related to PSP total score. Therefore, we think our result is mainly connected to the sample characteristics and their effect on the statistical analyses. On the one hand, our patients had almost no depressive symptomatology when they were evaluated. On the other, negative symptomatology, which showed the most robust relationship to patient functioning, displaced depressive symptoms in the multivariate analysis.

It is beyond the scope of this study to detect differences in the level of functioning according to the pharmacological treatment patients were prescribed. Still, we would like to highlight that only benzodiazepine use was related to real-world functioning in the univariate analysis. Although this is highly speculative, the lack of relationship to the antipsychotic treatment could be associated with the inclusion criterion of a monotherapy regimen.

The main limitation of our study is its cross-sectional design. Long-term longitudinal studies could describe changes in real-world functioning and search for predictor variables of these changes. It would also be of great interest to conduct this research in first-episode schizophrenia patients before starting pharmacological treatment. Thus, we could more accurately delineate the influence of the different factors from the beginning of the disorder and design phase-specific interventions to modify their impact. As for our study's strengths, the extensive range of variables and domains included and the use of the BNSS to assess

the negative syndrome of schizophrenia instead of the PANSS negative subscale are the two main ones. Finally, the condition of being on antipsychotic monotherapy is a novelty in this field.

In conclusion, we have provided clinicians with a simple formula that identifies the factors most substantially associated with patient real-world functioning. This formula will contribute to a more efficient and personalized daily clinical practice by assigning specific interventions to each patient based on specific impaired factors to improve functioning.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Clinical Research Ethics Committee of Hospital Universitario Central de Asturias in Oviedo (Ref. 127/15). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG-P, PS, and JB designed the study and wrote the protocol. LG-Á, LG-B, and FD managed the literature searches and analyses. LG-Á undertook the statistical analysis. MG-P wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

FUNDING

This work was partly supported by the Instituto de Salud Carlos III (grant ref. PI16/01761), the Government of the Principality of Asturias PCTI-2018-2022 IDI/2018/235, and Fondos Europeos de Desarrollo Regional (FEDER). This study received funding from an unrestrictive grant from Janssen (ref. CIB-APS-2015-01). This funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

ACKNOWLEDGMENTS

The authors wish to thank Sharon Grevet for her English assistance.

REFERENCES

1. Van Eck RM, Burger TJ, Velling A, Schirmbeck F, de Haan L. The relationship between clinical and personal recovery patients with schizophrenia spectrum disorders: a systematic review and meta-analysis. *Schizophr Bull.* (2018) 44:631–42. doi: 10.1093/schbul/sbx088
2. Lahera G, Gálvez JL, Sánchez P, Martínez-Roig M, Pérez-Fuster JV, García-Portilla P, et al. Functional recovery in patients with schizophrenia: recommendations from a panel of experts. *BMC Psychiatry.* (2018) 18:176. doi: 10.1186/s12888-018-1755-2
3. Vita A, Barlati S. Recovery from schizophrenia: is it possible? *Curr Opin Psychiatry.* (2018) 32:246–55. doi: 10.1097/YCO.0000000000000407
4. Bobes J, Ciudad A, Alvarez E, San L, Polavieja P, Gilaberte I. Recovery from schizophrenia: results from 1-year follow-up observational study of patients in symptomatic remission. *Schizophr Res.* (2009) 115:58–66. doi: 10.1016/j.schres.2009.07.003
5. Bowie CR, Harvey PD. Cognitive deficits and functional outcome in schizophrenia. *Neuropsychiatr Dis Treat.* (2006) 2:531–6. doi: 10.2147/nedt.2006.2.4.531
6. Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J Clin Psychiatry.* (2006) 67:3–8. doi: 10.4088/JCP.1006e12
7. Bowie CR, Leung WW, Reichenberg A, McClure MM, Patterson TL, Heaton RK, et al. Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. *Biol Psychiatry.* (2008) 63:505–11. doi: 10.1016/j.biopsych.2007.05.022
8. Harvey PD. Disability in schizophrenia: contributing factors and validated assessments. *J Clin Psychiatry.* (2014) 75:15–20. doi: 10.4088/JCP.13049su1c.03
9. Menendez-Miranda I, Garcia-Portilla MP, Garcia-Alvarez L, Arrojo M, Sanchez P, Sarramea F, et al. Predictive factors of functional capacity and real-world functioning in patients with schizophrenia. *Eur Psychiatry.* (2015) 30:622–7. doi: 10.1016/j.eurpsy.2014.12.011
10. Strassnig MT, Raykov T, O'Gorman C, Bowie CR, Sabbag S, Durand D, et al. Determinants of different aspects of everyday outcome in schizophrenia: the roles of negative symptoms, cognition, and functional capacity. *Schizophr Res.* (2015) 165:76–82. doi: 10.1016/j.schres.2015.03.033
11. Galderisi S, Rossi A, Rocca P, Bertolino A, Mucci A, Bucci P, et al. Italian network for research on psychoses. Pathways to functional outcome in subjects with schizophrenia living in the community and their unaffected first-degree relatives. *Schizophr Res.* (2016) 175:154–60. doi: 10.1016/j.schres.2016.04.043
12. Immonen J, Jääskeläinen E, Korpela H, Miettunen J. Age at onset and the outcomes of schizophrenia: a systematic review and meta-analysis. *Early Interv Psychiatry.* (2017) 11:453–60. doi: 10.1111/eip.12412
13. Bucci P, Galderisi S, Mucci A, Rossi A, Rocca P, Bertolino A, et al. Italian network for research on psychoses. Premorbid academic and social functioning in patients with schizophrenia and its association with negative symptoms and cognition. *Acta Psychiatr Scand.* (2018) 138:253–66. doi: 10.1111/acps.12938
14. Strassnig M, Bowie C, Pinkham AE, Penn D, Twamley EW, Patterson TL, et al. Which levels of cognitive impairments and negative symptoms are related to functional deficits in schizophrenia? *J. Psychiatr Res.* (2008) 104:124–9. doi: 10.1016/j.jpsychires.2018.06.018
15. Gonzalez-Blanco L, Garcia-Portilla MP, Dal Santo F, Garcia-Alvarez L, de la Fuente-Tomas L, Menendez-Miranda I, et al. Predicting real-world functioning in outpatients with schizophrenia: role of inflammation and psychopathology. *Psychiatry Res.* (2019) 280:112509. doi: 10.1016/j.psychres.2019.112509
16. Szabo S, Merikle E, Lozano-Ortega G, Powell L, Macek T, Cline S. Assessing the relationship between performance on the University of California performance skills assessment (UPSA) and outcomes in schizophrenia: a systematic review and evidence synthesis. *Schizophr Res Treat.* (2018) 2018:9075174. doi: 10.1155/2018/9075174
17. Galderisi S, Rossi A, Rocca P, Bertolino A, Mucci A, Bucci P, et al. Italian network for research on psychoses. The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. *World Psychiatry.* (2014) 13:275–87. doi: 10.1002/wps.20167
18. Tandon R, Lenderking WR, Weiss C, Shalhoub H, Barbosa CD, Chen J, et al. The impact on functioning of second-generation antipsychotic medication side effects for patients with schizophrenia: a worldwide, cross-sectional, web-based survey. *Ann Gen Psychiatry.* (2020) 19:42. doi: 10.1186/s12991-020-00292-5
19. Martinuzzi E, Barbosa S, Daoudlarian D, Bel Haj Ali W, Gilet C, Fillatre L, et al. Stratification and prediction of remission in first-episode psychosis patients: the OPTiMiSE cohort study. *Transl Psychiatry.* (2019) 9:20. doi: 10.1038/s41398-018-0366-5

20. World Medical Association General Assembly. *Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects*. Fortaleza: World Medical Association (2013).
21. Peralta V, Cuesta MJ. Validación de la Escala de los Síndromes Positivo y Negativo (PANSS) en una muestra de esquizofrénicos españoles. *Actas Luso-Esp Neurol Psiquiatr.* (1994) 4:44–50.
22. Mané A, García-Rizo C, Garcia-Portilla MP, Bergé D, Sugranyes G, Garcia-Alvarez L, et al. Spanish adaptation and validation of the brief negative symptoms scale. *Compr Psychiatry.* (2014). 55:1726–9. doi: 10.1016/j.comppsych.2014.05.024
23. Sarró S, Dueñas RM, Ramírez N, Arranz B, Martínez R, Sánchez JM, et al. Cross-cultural adaptation and validation of the Spanish version of the calgary depression scale for schizophrenia. *Schizophr Res.* (2004) 68:349–56. doi: 10.1016/S0920-9964(02)00490-5
24. Benton AL, Hamsher K. *Multilingual Aphasia Examination Manual - Revised*. Iowa City, IA: University of Iowa (1978).
25. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests. Administration, Norms, and Commentary*. New York, NY: Oxford University Press (1998).
26. Wechsler D. *Wechsler Adult Intelligence Scale-Third Edition (WAIS-III)*. San Antonio, TX: The Psychological Corporation (1997). doi: 10.1037/t49755-000
27. Reitan RM. *Trail Making Test: Manual for Administration and Scoring*. Tucson, AZ: Reitan Neuropsychology Laboratory (1992).
28. Crowe SF. Decrease in performance on the verbal fluency test as a function of time: evaluation in a young healthy sample. *J Clin Exp Neuropsychol.* (1998) 20:391–401. doi: 10.1076/jcen.20.3.391.810
29. Jaeger J. Digit symbol substitution test. The case for sensitivity over specificity in neuropsychological testing. *J Clin Psychopharmacol.* (2018) 38:513–9. doi: 10.1097/JCP.0000000000000941
30. Corrigan JD, Hinkeldey NS. Relationships between parts A and B of the trail making test. *J Clin Psychol.* (1987) 43:402–9. doi: 10.1002/1097-4679(198707)43:4<402::AID-JCLP2270430411>3.0.CO;2-E
31. Garcia-Portilla MP, Gomar JJ, Bobes-Bascaran MT, Menendez-Miranda I, Saiz PA, Muñiz J, et al. Validation of a European Spanish-version of the University of California performance Skills Assessment (Sp-UPSA) in patients with schizophrenia and bipolar disorder. *Schizophr Res.* (2013) 150:421–6. doi: 10.1016/j.schres.2013.07.049
32. Garcia-Portilla MP, Saiz PA, Bousoño M, Bascaran MT, Guzmán-Quilo C, Bobes J, et al. Validation of the Spanish Personal and Social Performance scale (PSP) in outpatients with stable and unstable schizophrenia. *Rev Psiquiatr Salud Ment*. (2011) 4:9–18. doi: 10.1016/S2173-5050(11)70003-6
33. Lahera G, Ruiz A, Brañas A, Vicens M, Orozco A. Reaction time, processing speed and sustained attention in schizophrenia: impact on social functioning. *Rev Psiquiatr Salud Ment.* (2017) 10:197–205. doi: 10.1016/j.rpsm.2017.04.001
34. Ahmed AO, Kirkpatrick B, Galderisi S, Mucci A, Rossi A, Bertolino A, et al. Cross-cultural validation of the 5-Factor structure of negative symptoms in schizophrenia. *Schizophr Bull.* (2019) 45:305–14. doi: 10.1093/schbul/sby050
35. Rocca P, Montemagni C, Zappia S, Piterà R, Sigaudo M, Bogetto F. Negative symptoms and everyday functioning in schizophrenia: a cross-sectional study in a real world-setting. *Psychiatry Res*. (2014) 218:284–9. doi: 10.1016/j.psychres.2014.04.018
36. Jablensky A, McGrath J, Herrman H, Castle D, Gureje O, Evans M, et al. Psychotic disorders in urban areas: an overview of the study on low prevalence disorders. *Aust NZ J Psychiatry.* (2000) 34:221–36. doi: 10.1080/j.1440-1614.2000.00728.x
37. Patterson TL, Goldman S, McKibbin CL, Hughs T, Jeste DV. UCSD performance-based skills assessment: development of a new measure of everyday functioning for severely mentally ill adults. *Schizophr Bull.* (2001) 27:235–45. doi: 10.1093/oxfordjournals.schbul.a006870
38. Green MF, Nuechterlein KH, Kern RS, Baade LE, Fenton WS, Gold JM, et al. Functional co-primary measures for clinical trials in schizophrenia: results from the MATRICS Psychometric and Standardization Study. *Am J Psychiatry.* (2008) 165:221–8. doi: 10.1176/appi.ajp.2007.07010089
39. Simons CJ, Bartels-Velthuis AA, Pijnenborg GH, Genetic Risk and Outcome of Psychosis (GROUP) Investigators. Cognitive performance and long-term social functioning in psychotic disorder: a three-year follow-up study. *PLoS ONE.* (2016) 11:e0151299. doi: 10.1371/journal.pone.0151299
40. Lee EHM, Hui CLM, Chan KPK, Chan PY, Law EYL, Chong CSY, et al. The role of symptoms and insight in mediating cognition and functioning in first-episode psychosis. *Schizophr Res.* (2019) 206:251–6. doi: 10.1016/j.schres.2018.11.009
41. Bär KJ. Cardiac autonomic dysfunction in patients with schizophrenia and their healthy relatives - a small review. *Front Neurol.* (2015) 24:139. doi: 10.3389/fneur.2015.00139
42. De Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, et al. Physical illness in patients with severe mental disorders. I Prevalence, impact of medications and disparities in health care. *World Psychiatry.* (2011) 10:52–77. doi: 10.1002/j.2051-5545.2011.tb00014.x
43. Bär KJ, Letzsch A, Jochum T, Wagner G, Greiner W, Sauer HJ. Loss of efferent vagal activity in acute schizophrenia. *Psychiatr Res.* (2005) 39:519–27. doi: 10.1016/j.jpsychires.2004.12.007
44. Bär KJ, Boettger MK, Koschke M, Schulz S, Chokka P, Yeragani VK, et al. Non-linear complexity measures of heart rate variability in acute schizophrenia. *Clin Neurophysiol.* (2007) 118:2009–15. doi: 10.1016/j.clinph.2007.06.012
45. Fujibayashi M, Matsumoto T, Kishida I, Kimura T, Ishii C, Ishii N, et al. Autonomic nervous system activity and psychiatric severity in schizophrenia. *Psychiatry Clin Neurosci.* (2009) 63:538–45. doi: 10.1111/j.1440-1819.2009.01983.x
46. Reed AC, Lee J, Green MF, Hamilton HK, Miller GA, Subotnik KL, et al. Associations between physiological responses to social-evaluative stress and daily functioning in first-episode schizophrenia. *Schizophr Res.* (2020) 218:233–9. doi: 10.1016/j.schres.2019.12.040
47. Hagi K, Nosaka T, Dickinson D, Lindenmayer JP, Lee J, Friedman J, et al. Association between cardiovascular risk factors and cognitive impairment in people with schizophrenia: a systematic review and meta-analysis. *JAMA Psychiatry*. (2021) 78:510–8. doi: 10.1001/jamapsychiatry.2021.0015

Conflict of Interest: MG-P has been a consultant to and/or has received honoraria/grants from Angelini, Alianza OtsukaLundbeck, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, and Pfizer. LG-Á has received honoraria from the 7th Framework Program European Union. LG-B has received honoraria/grants from the Spanish Foundation of Psychiatry and Mental Health, European Psychiatric Association, Otsuka, Lundbeck, Angelini, Janssen-Cilag and Pfizer. FS has received grants from the Spanish Foundation of Psychiatry and Mental Health. PS has been a consultant to and/or has received honoraria or grants from Adamed, CIBERSAM, European Comission, GlaxoSmithKline, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Plan Nacional Sobre Drogas and Servier. JB has received research grants and served as consultant, advisor, or speaker within the last 5 years for: AB-Biotics, Acadia Pharmaceuticals, Angelini, Casen Recordati, D&A Pharma, Exeltis, Gilead, GSK, Ferrer, Indivior, Janssen-Cilag, Lundbeck, Mundipharma, Otsuka, Pfizer, Reckitt-Benckiser, Roche, Sage Therapeutics, Servier, Shire, Schwabe Farma Ibérica, research funding from the Spanish Ministry of Economy and Competiveness–Centro de Investigación Biomedica en Red area de Salud Mental (CIBERSAM) and Instituto de Salud Carlos III-, Spanish Ministry of Health, Social Services and Equality—Plan Nacional sobre Drogas—and the 7th Framework Program of the European Union.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 03 September 2021
doi: 10.3389/fpsyt.2021.736094

Effects of High-Frequency rTMS on Negative Symptoms and Cognitive Function in Hospitalized Patients With Chronic Schizophrenia: A Double-Blind, Sham-Controlled Pilot Trial

Na Wen[1,2†], Lei Chen[2†], Xuemeng Miao[2], Min Zhang[2], Yaoyao Zhang[2], Jie Liu[2], Yao Xu[2], Siyu Tong[2], Wei Tang[1], Mengpu Wang[2], Jiahong Liu[1], Siyao Zhou[2], Xinyu Fang[3*] and Ke Zhao[2,4*]*

[1] The Affiliated Kangning Hospital of Wenzhou Medical University, Wenzhou Medical University, Wenzhou, China, [2] School of Mental Health, Wenzhou Medical University, Wenzhou, China, [3] Affiliated Nanjing Brain Hospital, Nanjing Medical University, Nanjing, China, [4] Department of Psychiatry, The Affiliated Kangning Hospital of Wenzhou Medical University, Wenzhou, China

This study aimed to evaluate the efficacy of high-frequency repetitive transcranial magnetic stimulation (rTMS) over left dorsolateral pre-frontal cortex (DLPFC) in ameliorating negative symptoms and cognitive impairments in patients with chronic schizophrenia. Fifty-two patients with chronic schizophrenia were randomly assigned to two groups: active rTMS group and sham rTMS group, with existing antipsychotic drugs combined 20 sessions of 10 Hz active/sham rTMS over DLPFC (20 min/session, 5 times/week). The PANSS, RBANS, and SCWT were used to evaluate the clinical symptoms and cognitive functions of the patients. Our results indicated significant improvements in clinical symptoms (PANSS total and subscale scores) and cognitive functions (RBANS total and subscale scores, card 1 and card 3 of the SCWT test) (All $p < 0.05$) after 4-week intervention both in active and sham rTMS group. Moreover, the active rTMS group showed more effective on ameliorating negative symptoms ($p = 0.002$), immediate memory ($p = 0.016$) and delayed memory ($p = 0.047$) compared to the sham group. Interestingly, PANSS negative symptom scores was negatively correlated with RBANS language scores in the real stimulation group ($p = 0.046$). The study found that the high frequency rTMS stimulation over left DLPFC as a supplement to antipsychotics may have potential benefits in improving clinical symptoms and cognitive functions in patients with chronic schizophrenia.

Keywords: schizophrenia, negative symptoms (schizophrenia), cognitive impairment, repetitive transcranial magnetic stimulation, treatment

OPEN ACCESS

Edited by:
Armida Mucci, University of Campania Luigi Vanvitelli, Italy

Reviewed by:
Massimo Tusconi, University of Cagliari, Italy
Michel Sabe, Geneva University Hospitals (HUG), Switzerland

***Correspondence:**
Ke Zhao
cocozk1986@163.com
Xinyu Fang
fxywilbur@163.com
Siyao Zhou
zsy950823@163.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *04 July 2021*
Accepted: *11 August 2021*
Published: *03 September 2021*

Citation:
Wen N, Chen L, Miao X, Zhang M, Zhang Y, Liu J, Xu Y, Tong S, Tang W, Wang M, Liu J, Zhou S, Fang X and Zhao K (2021) Effects of High-Frequency rTMS on Negative Symptoms and Cognitive Function in Hospitalized Patients With Chronic Schizophrenia: A Double-Blind, Sham-Controlled Pilot Trial. Front. Psychiatry 12:736094. doi: 10.3389/fpsyt.2021.736094

INTRODUCTION

Schizophrenia is a severe and chronic mental disorder that affects ∼1.0% of the global population (1). Patients with schizophrenia usually suffer from positive symptoms (i.e., delusions, hallucinations, experiences of being controlled, or Confusion of thoughts) and negative symptoms (i.e., apathy, diminished expression) (2), and may experience other symptoms such as cognitive impairments (3, 4). Compared to the general population, patients with schizophrenia have a two to three times increased risk of death. Generally, the prognosis of patients with schizophrenia is poor, with about one in seven people achieve complete remission (5). Further, according to the 2016 Global Burden of Disease Study, about 1.7% of the total global years lived with disability (YLDs) is caused by schizophrenia (6).

At present, the main treatment for schizophrenia relies on antipsychotic drugs. Antipsychotic drugs have been widely used to treat schizophrenia patients since chlorpromazine was found to uniformly alleviate positive symptoms in the 1950s. Since then, antipsychotics have been the primary treatment for schizophrenia (7–9). However, these drugs have limited effect, especially on negative symptoms and cognitive deficits (9). For example, for some schizophrenia patients, even though when the positive symptoms are controlled with effective antipsychotic drugs, the negative symptoms can persist (10). Moreover, negative symptoms and cognitive deficits are common in patients with chronic schizophrenia. Psychosocial therapy may be effective for the positive and negative symptoms or cognitive symptoms of early schizophrenia, but its therapeutic efficacy may be reduced when the course of schizophrenia is prolonged (11). Therefore, it is necessary to find other treatment options, such as other non-pharmaco-therapies, to better treat schizophrenia and meet the unmet needs of patients (12, 13).

In recent years, repetitive transcranial magnetic stimulation (rTMS), a non-invasive and safe brain stimulation technology, has been widely used in the clinical treatment of mental disorders, such as schizophrenia, major depressive disorder, anxiety and insomnia (14). rTMS is based on the principle that rapidly changing magnetic field can induce electric currents in localized areas of the cerebral cortex, thereby including changes in neuronal activity in the cerebral cortex. Generally speaking, high-frequency rTMS increases cortical excitability, while low-frequency rTMS can suppress cortical excitability (15–17). In addition, rTMS can alter the metabolic activity of the brain, neuronal plasticity, local brain function, and the functional connections between different brain regions (18). rTMS may be a useful treatment for some of the symptoms of schizophrenia, such as persistent auditory hallucinations, negative symptoms (19), and cognitive impairments. The current study focused on the refractory symptoms that cannot be effectively controlled by antipsychotic drugs, including negative symptoms and cognitive function deficits. Evidences from recent studies suggest that high-frequency rTMS is an effective treatment option for improving the prognosis of schizophrenia (20), but there are mixed reports in the literature. Some studies have confirmed that high-frequency rTMS has a significant effect on negative symptoms and cognitive impairments (20–22) in schizophrenia patients. For instance, Gan et al. found that high-frequency rTMS relieved the negative symptoms (especially affective flattening and anhedonia) of schizophrenia to a certain degree and the improvement in negative symptoms lasted for at least 2 months (12). Li et al. found that an improvement in negative symptoms occurred in 8 weeks after rTMS treatment, suggesting a delayed effect of 10 Hz rTMS on negative symptoms (21). Moreover, several rTMS studies using different methods have reported beneficial effects of rTMS on single cognitive domains (i.e., working memory, facial emotion recognition, or short-term language memory) (22–24). However, other studies have reported no effect of high-frequency rTMS on clinical symptoms and cognitive impairments. For example, Wobrock et al. found that the application of active 10 Hz rTMS to the left dorsolateral pre-frontal cortex (DLPFC) was not superior to false rTMS in ameliorating the negative symptoms of schizophrenia (25). Further, Hasan et al. found that a 3-week intervention (10 Hz rTMS, 15 sessions) with active or sham rTMS produce no significant differences in negative or cognitive symptoms compared to the pre-interaction period (26). Several factors may account for the discrepancies in these studies, including the disease status of the patients (acute or stable phase) and the characteristics of the rTMS stimulation (including frequency, intensity of stimulation, and electrical placement). It should be noted that several meta-analyses with larger sample sizes have demonstrated a therapeutic effect of rTMS on negative symptoms and cognitive impairment in schizophrenia patients (27–32). These meta-analyses concluded that the best rTMS parameter for the treatment of clinical symptoms in schizophrenia is a 4-week (20 times) intervention on the left DLPFC. However, it should be noted that these previous meta-analyses did not specify the status of patients the time of study selection. Thus, effectiveness of high-frequency rTMS in patients with chronic schizophrenia remains controversial.

To this end, the aim of the present study was to determine whether high-frequency rTMS over the DLPFC (20 min/session, 5 times/week) ameliorates negative symptoms and cognitive impairments in chronic schizophrenia patients. Based on the available literature, we hypothesized that patients who received the recommended rTMS protocol may improve negative symptoms and cognitive function in patients with chronic schizophrenia.

METHODS

Participants

Fifty-two patients were consecutively recruited into the study between December 2018 and December 2019 at the Affiliated Kangning Hospital of Wenzhou Medical University. All participants provided written informed consent and had the ability to comply with the rTMS therapy protocol and cognitive assessment. And participant's rTMS treatment fee was waived. The clinical trial protocol was approved by the institutional review committee of the Affiliated Kangning Hospital of Wenzhou Medical University.

The patients were diagnosed with schizophrenia based on the Structured Clinical Interview for DSM-IV Axis I disorders

(SCID). The study inclusion criteria were as follows: (1) Han Chinese, (2) aged 18–70 years, (3) with a disease course of more than 1 year, and (4) on a stable dose of antipsychotic medication for at least 1 month before study enrollment. The exclusion criteria were: (1) any major physical diseases (e.g., cardiovascular, liver, kidney, gastrointestinal diseases, etc.), (2) the presence of a cardiac pacemaker, intracranial metal, or prior history of epilepsy or head injury, (3) female patients who were pregnant, planning to become pregnant, or breastfeeding during the study period, (4) patient had received rTMS or modified electroconvulsive therapy (MECT) in the previous month, and (5) patient had a history of alcohol or other substance abuse or dependence.

All experimental procedures in this study were carried out in strict accordance with the Declaration of Helsinki and other relevant regulations.

Study Design

The recruited patients were assigned a sequential number. If the patient chooses to quit the study between the randomization and the rTMS intervention, this patient will be excluded from the final analyses. And then we randomly divided the patients into two groups by using default random number generator of SPSS version 25.0 (SPSS Inc., Chicago, IL). The groups were as follows: the active rTMS group ($n = 26$, with existing antipsychotic drugs + 20 sessions of 10 Hz active rTMS over the DLPFC, lasting for 20 min/session, 5 times/week) and the sham rTMS group ($n = 26$, with existing antipsychotic drugs + 20 sessions of sham rTMS over the DLPFC, lasting for 20 min/session, 5 times/week). Before the intervention, the patients didn't take any psychotherapeutic treatment. And the clinical symptoms of the two groups were basically the same at baseline. The most common antipsychotic drug taken by the patients was clozapine, followed by risperidone and olanzapine. Clinical data was collected at baseline and after rTMS treatment, including the Positive and Negative Syndrome Scale (PANSS), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and the Stroop Color and Word Test (SCWT). The study was a double-blind randomized control trial. The scale raters and patients were blind to the study grouping. The study was registered in the clinicaltrials.gov database (NCT04055181).

Intervention

rTMS was administered using a YRDCCY-I stimulator (Yiruide Medical Equipment New Technology Co., Ltd., Wuhan, China) with a figure-eight-shaped coil. The patient was awake and maintained a comfortable seated position when receiving rTMS. The loop coil provides stimulation tangentially to the plane of the skull; the middle position of the loop coil is aligned with the stimulation point. Participants all received 20 treatment sessions on consecutive weekdays and were randomly assigned to receive either 10 Hz rTMS applied to the DLPFC with the YRDCCY-I stimulator or the sham condition. The rTMS was presented at 110% of the motor threshold (MT) and stimulation lasted for 4 s with 26 s intervals, with a total of 1,600 pulses per session for a total time of 20 min per day. The left DLPFC stimulation site was determined on a para-sagittal plane 5.5 cm anterior to the area of the optimal site. The sham condition involved tilting of the magnetic coil on one wing at a 45-degree angle, resulting in a similar skin sensation, but the biological activity was significantly reduced (33). Thus, in the sham group, all procedures were identical to the 10 Hz group except that in the sham rTMS, the probe of the apparatus was held perpendicular to the patient's skull plane.

Clinical Assessments

The PANSS (34) was used to evaluate patients' psychotic symptoms. It consists of 30 items that are scored from 1 to 7, with higher scores indicating greater symptom burden. In this study, the positive (PANSS-P), negative (PANSS-N), and general psychopathology (PANSS-G) subscales as well as the total score (PANSS-T) pre- and post-rTMS treatment were analyzed.

The RBANS and the SCWT were used to assess the cognitive function in all participants. The 12-item RBANS consists of five subsets, corresponding to the following five neuropsychological processes: immediate memory, visuospatial function, language, attention, and delayed memory (35). The RBANS has good validity and reliability in Chinese people and is suitable for the cognitive evaluation of patients with schizophrenia (36). Generally, a higher RBANS score reflects a better cognitive function. The SCWT consists of three white cards containing a matrix of stimulus materials, which are words or color patches (37). The reaction time and the number of errors a participant makes when responding to the stimuli are recorded. In general, the shorter the answering time and the higher the correct rate indicate that the patient's executive function is better.

The Udvalg for Kliniske Under-sogelser (UKU) side effect rating scale was also used to evaluate side effects 4 weeks after the rTMS intervention. The scale comprises 48 items, measuring psychic, neurologic, autonomic, and other adverse effects. All scales exhibited test-retest correlations of up to 0.8 in repeated assessments (38).

All assessments were performed by at least two professionally trained psychiatrists at baseline and at 4 weeks after rTMS intervention.

Data Analysis

Comparison of the baseline demographics and clinical features between the active and sham rTMS groups was carried out using the chi-square test for categorical variables and analysis of variance (ANOVA) for metric variables. The post-intervention data were all analyzed using repeated measures. The time course and treatment differences in relation to changes in clinical symptoms and cognitive functions were evaluated by means of a mixed-effects model for repeated measures analysis with the main effects of treatment and time and a treatment × time interaction adjusted for age, sex, education level, duration of illness, and daily antipsychotic dose. Finally, correlation analysis was carried out between the reduction in PANSS scores and improvement in RBANS in the two groups, with age, gender, education level, duration of illness, and daily antipsychotic dose as covariates. For all models, a two-sided P-value of <0.05 was considered statistically significant. The statistical analyses were carried out using SPSS 26.0 (SPSS Inc., Chicago, IL, USA).

RESULT

Demographic and Clinical Characteristics at Baseline

In total, 52 patients were recruited into the study and randomly assigned to either the active rTMS ($N = 26$) or sham rTMS ($N = 26$) groups. All patients received a stable dose of antipsychotics during the treatment period. **Table 1** shows that aside from the duration of illness and the negative symptoms as measured by the PANSS (both $p < 0.05$), there were no significant differences between the two groups in terms of demographic characteristics, the PANSS-T, PANSS-P, and PANSS-G, the RBANS total and subscale scores, as well as Stroop reaction time (all $p > 0.05$) at the baseline assessment.

Four patients dropped out of the active rTMS group and three from the sham rTMS group during the study, leaving a final experimental sample of 22 patients in the active rTMS group and 23 patients in the sham rTMS group.

TABLE 1 | Baseline socio-demographics and clinical characteristics between groups of active rTMS and sham rTMS.

	Active rTMS ($n = 26$)	Sham rTMS ($n = 26$)	X^2/F	P
Age (years)	41.4 ± 7.5	38.8 ± 9.1	1.27	0.26
Gender (M/F)	15/11	14/12	0.08	0.78
Education (years)	9.3 ± 3.1	8.8 ± 2.8	0.37	0.55
Age of onset (years)	23.0 ± 5.6	24.4 ± 8.5	0.48	0.49
Duration of illness (years)	18.4 ± 7.3	14.4 ± 6.5	4.37	0.04*
Antipsychotics type				
Clozapine	17	15	–	–
Risperidone	4	6	–	–
Olanzapine	5	5	–	–
DAD (mg)	435.8 ± 302.6	467.1 ± 267.6	0.16	0.69
PANSS total score	102.0 ± 11.2	98.7 ± 9.9	1.27	0.27
P-subscore	20.1 ± 3.7	20.5 ± 4.0	0.13	0.72
N-subscore	28.9 ± 3.9	26.7 ± 3.2	5.00	0.03*
G-subscore	52.6 ± 8.2	51.6 ± 7.8	0.22	0.64
RBANS total score	60.2 ± 12.1	59.3 ± 11.2	0.08	0.77
Immediate memory	51.0 ± 11.9	53.3 ± 14.2	0.40	0.53
Attention	73.4 ± 15.6	71.5 ± 16.9	0.17	0.68
Visuospatial	74.8 ± 19.7	74.9 ± 12.4	0.00	0.97
Delayed memory	63.1 ± 19.0	58.7 ± 16.4	0.79	0.38
Language	71.3 ± 15.1	68.8 ± 14.4	0.37	0.54
SCWT				
Card 1 word (s)	29.1 ± 11.4	28.2 ± 10.9	0.08	0.78
Card 2 color (s)	33.1 ± 11.8	37.0 ± 12.0	1.36	0.25
Card 3 word (s)	35.5 ± 13.3	36.5 ± 13.9	0.07	0.79
Card 3 color (s)	51.5 ± 10.0	53.7 ± 7.3	0.79	0.38

*DAD, Daily Antipsychotic Dose (chlorpromazine equivalent); PANSS, Positive and Negative Syndrome Scale; P, positive symptom; N, negative symptom; G, general psychopathology; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SCWT, Stroop Color-Word test. *p < 0.05.*

Psychotic Symptoms and Cognitive Function After 4-week rTMS Treatment

The PANSS total and subscale scores stratified by group (active rTMS group and sham rTMS group) and time (baseline and post-treatment) are presented in **Figure 1** and **Table 2**. The repeated-measures ANOVA showed a significant time effect ($F = 34.9$, df $= 1, 43$, $p < 0.001$) and an interaction effect (group × time: $F = 10.3$, df $= 1, 43$, $p < 0.01$), but no significant group effect ($F = 0.21$, df $= 1, 43$, $p = 0.648$) on negative symptoms, while there was only a significant time effect on the PANSS total score ($F = 119.5$, df $= 1, 43$, $p < 0.001$), positive symptoms subscore ($F = 56.9$, df $= 1, 43$, $p < 0.001$), and general psychopathology subscore ($F = 29.7$, df $= 1, 43$, $p < 0.001$). Further, ANOVA revealed that the average PANSS negative symptom score at week 4 in the active rTMS group was significantly lower than that in the sham group ($F = 9.088$, df $= 1, 43$, $p < 0.01$; ES $= 0.327$), after controlling for age, education level, duration of illness, and dose of antipsychotic drugs (chlorpromazine equivalent). However, there were no significant differences in the PANSS positive symptoms and general psychopathology scores at week 4 between the active and sham rTMS groups (both $P > 0.05$).

In terms of changes in cognitive function, the repeated-measures ANOVA showed a significant time effect ($F = 62.1$, df $= 1, 43$, $p < 0.001$) and a marginally significant group effect ($F = 3.0$, df $= 1, 43$, $p = 0.089$) on RBANS total scores; however, there was no significant interaction effect ($F = 2.4$, df $= 1, 43$, $p = 0.127$). Further, the RBANS subscales were analyzed with repeated-measures ANOVA and the results showed a significant time effect ($F = 33.2$, df $= 1, 43$, $p < 0.001$) and interaction effect (group × time: $F = 6.3$, df $= 1, 43$, $p < 0.05$), as well as a marginally significant group effect ($F = 3.1$, df $= 1, 43$, $p = 0.085$) on immediate memory, a significant time effect ($F = 26.4$, df $= 1, 43$, $p < 0.001$) and group effect on delayed memory, and significant time effects on attention ($F = 15.6$, df $= 1, 43$, $p < 0.001$) and visuospatial/constructional function ($F = 6.4$, df $= 1, 43$, $p < 0.05$) (see **Table 2** and **Figure 1**). The ANOVA further indicated that immediate memory was significantly better in the active rTMS group than in the sham group at week 4 ($F = 6.713$, df $= 1, 43$, $p = 0.013$; ES $= 0.161$), after controlling for age, duration of illness, dose of antipsychotics, and PANSS negative symptoms subscore.

Associations Between the Reduction of Negative Symptoms of Schizophrenia and the Improvement of Cognitive Function

The correlation analysis showed that the change in RBANS language subscore was negatively correlated with the change in the PANSS negative subscore when age, education level, duration of illness and DAD ($\beta = 0.446$, $t = 2.15$, $p < 0.05$) were all controlled (see **Figure 2**).

Safety Assessment

After 4 weeks of treatment, four patients in the active rTMS group reported mild adverse reactions (one reported a reduced duration of sleep, one reported emotional indifference, two reported tension headaches) and three patients in the sham rTMS

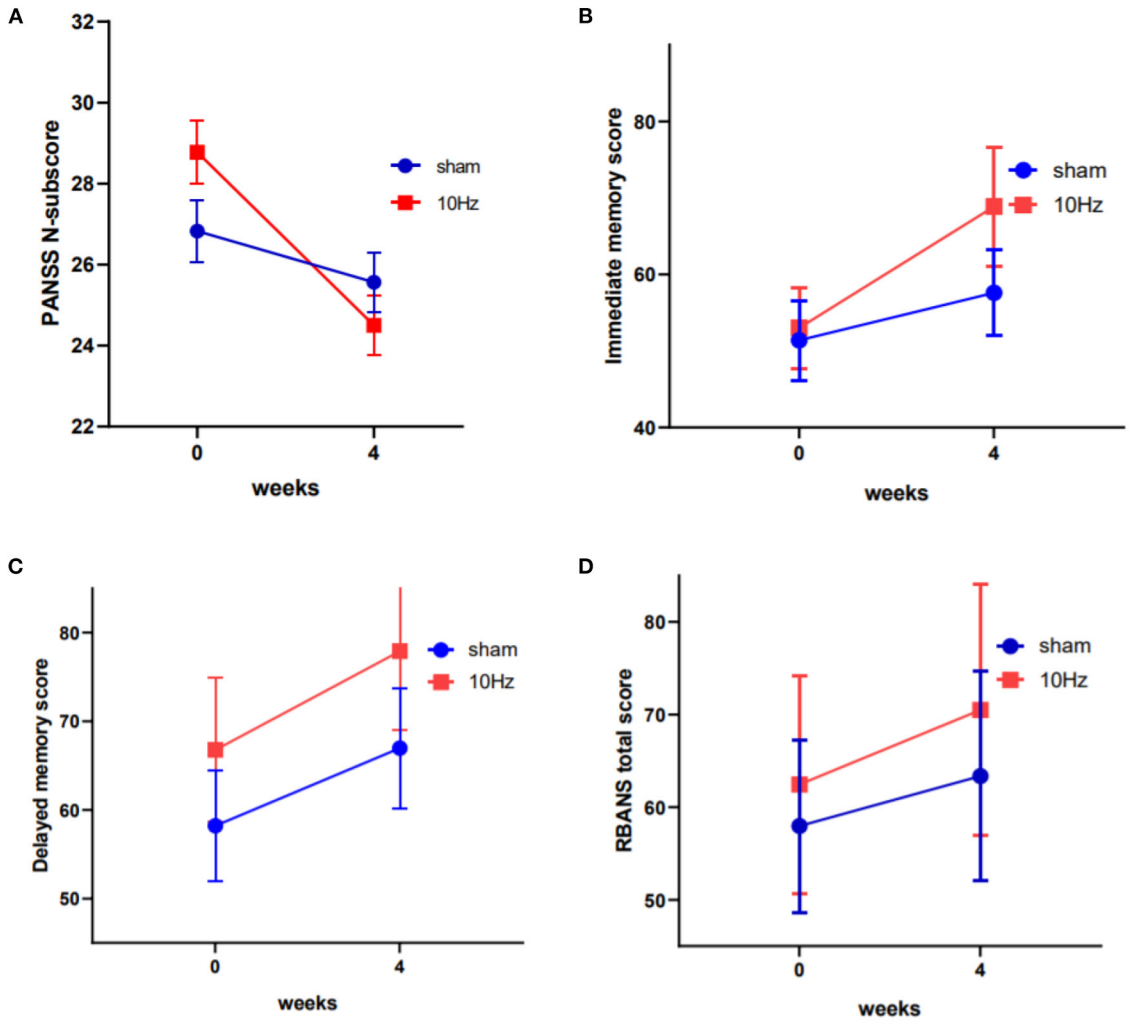


FIGURE 1 | Changes in the PANSS negative symptom scores, the RBANS immediate memory scores and the RBANS delayed memory scores between active rTMS and sham group at baseline and endpoint (4th week) **(A–C)**. Changes in the total score of RBANS between the two groups was of marginal significant **(D)**.

group reported mild adverse reactions (one reported a reduced duration of sleep and two reported tension headaches). There was no significant difference in the incidence of adverse events between the two groups ($p > 0.05$).

DISCUSSION

As a non-pharmacological treatment strategy, rTMS has great application prospect for the treatment or cure of schizophrenia. Research has shown that rTMS may reduce positive and negative symptoms in patients with schizophrenia who take antipsychotic drugs, but there has been significant heterogeneity in the reported effects in different trials (39). In contrast to previous studies, the current study focused on exploring the role of high-frequency rTMS on both negative symptoms and cognitive deficits in chronic schizophrenia patients. The efficacy of high-frequency (10 Hz) rTMS over left DLPFC in ameliorating psychotic symptoms and cognitive impairments in chronic schizophrenia patients was evaluated. After the 4-week intervention, active rTMS was found to improve negative symptoms and immediate and delayed memory in schizophrenia patients. Further, our study found that the improvement in cognitive function in the active rTMS group was positively correlated with the decrease in negative symptoms score in hospitalized patients with chronic schizophrenia, which is consistent with the previous study (40).

Other studies had reported similar benefits of rTMS on negative symptoms in patients with schizophrenia. For example, Prikryl et al. found that high-frequency (10 Hz) rTMS stimulation of the left DLPFC with high stimulation intensity effectively reduced the negative symptoms of schizophrenia (41). Kumar et al. verified that the rTMS intervention with a frequency of 10 Hz may lead to better improvement of negative symptoms (42). Research suggests that the efficacy of rTMS on negative symptoms is best with a 10 Hz stimulating frequency and a longer

TABLE 2 | Primary and secondary outcome measures at the beginning and the end of 4 weeks of rTMS treatment.

	Baseline ($n = 52$)		After treatment ($n = 45$)		Group	Time	Group × Time
	Sham rTMS ($n = 26$)	Active rTMS ($n = 26$)	Sham rTMS ($n = 22$)	Active rTMS ($n = 23$)	*F* (*p*-value)	*F* (*p*-value)	*F* (*p*-value)
PANSS total score	102.0 ± 11.2	98.7 ± 9.9	86.0 ± 12.4	86.9 ± 8.8	0.78 (0.382)	119.5 (0.000)	2.2 (0.148)
P-subscore	20.1 ± 3.7	20.5 ± 4.0	16.9 ± 4.2	16.7 ± 2.8	0.03 (0.859)	56.9 (0.000)	0.64 (0.429)
N-subscore	28.9 ± 3.9	26.7 ± 3.2	25.6 ± 3.1	24.5 ± 3.9	0.21 (0.648)	34.9 (0.000)	10.3 (0.002**)
G-subscore	52.6 ± 8.2	51.6 ± 7.8	45.3 ± 9.6	45.6 ± 5.8	0.16 (0.690)	29.7 (0.000)	0.27 (0.607)
RBANS total score	60.2 ± 12.1	59.3 ± 11.2	63.3 ± 11.3	70.5 ± 13.5	3.0 (0.089)	62.1 (0.000)	2.4 (0.127)
Immediate memory	51.0 ± 11.9	53.3 ± 14.2	57.6 ± 13.0	68.9 ± 17.6	3.1 (0.085)	33.2 (0.000)	6.3 (0.016*)
Attention	73.4 ± 15.6	71.5 ± 16.9	74.7 ± 14.9	81.4 ± 13.5	1.8 (0.183)	15.6 (0.000)	0.57 (0.454)
Visuospatial	74.8 ± 19.7	74.9 ± 12.4	81.2 ± 15.2	80.4 ± 18.9	0.14 (0.707)	6.4 (0.015)	2.1 (0.155)
Delayed memory	63.1 ± 19.0	58.7 ± 16.4	67.0 ± 15.7	77.9 ± 20.1	4.2 (0.047*)	26.4 (0.000)	0.39 (0.538)
Language	71.3 ± 15.1	68.8 ± 14.4	70.2 ± 14.9	74.8 ± 13.0	2.0 (0.166)	3.2 (0.080)	0.41 (0.525)
SCWT							
Card 1 word (s)	29.1 ± 11.4	28.2 ± 10.9	25.1 ± 10.5	24.1 ± 10.1	0.19 (0.667)	21.8 (0.000)	0.24 (0.629)
Card 2 color (s)	33.1 ± 11.8	37.0 ± 12.0	36.2 ± 12.5	30.0 ± 9.3	3.8 (0.057)	2.0 (0.169)	0.002 (0.967)
Card 3 word (s)	35.5 ± 13.3	36.5 ± 13.9	36.6 ± 14.3	36.7 ± 10.8	0.32 (0.575)	0.50 (0.485)	1.3 (0.265)
Card 3 color (s)	51.5 ± 10.0	53.7 ± 7.3	55.5 ± 8.1	54.4 ± 7.8	0.99 (0.327)	4.9 (0.031)	1.4 (0.249)

*PANSS, Positive and Negative Syndrome Scale; P, positive symptom; N, negative symptom; G, general psychopathology; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SCWT, Stroop Color-Word test. *p < 0.05, **p < 0.01.*

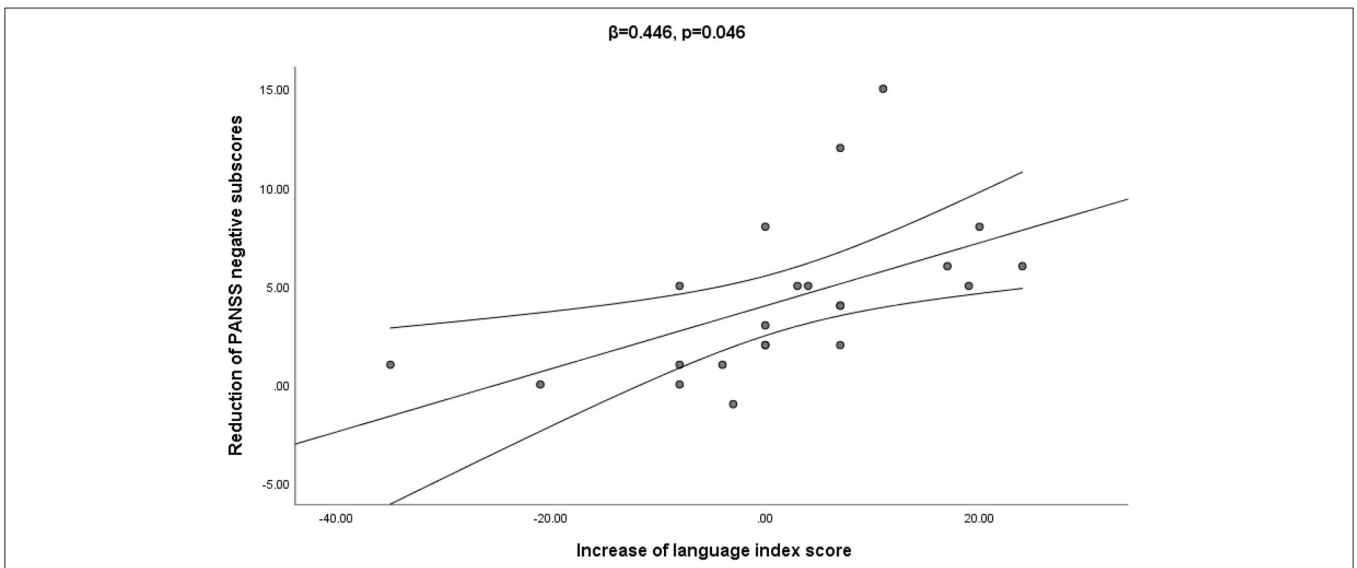


FIGURE 2 | The multiple regression analysis confirmed that the increase in language index score was significantly associated with the decrease of the PANSS negative score from baseline to week 4 ($\beta = 0.446$, $p = 0.046$).

stimulation period, ideally 4–6 weeks (29). Further, a recent study not only showed negative symptom improvement after 4 weeks of 10 Hz rTMS over the DLPFC, but this effect was maintained at the 24-week follow up (43). Most previous studies that treated schizophrenia patients with 20 Hz rTMS over the left DLPFC also showed significant improvements in negative symptoms (44–46). What we know is that higher frequencies of rTMS (frequencies of 5 Hz and greater) have been shown to have excitatory effects on neurons in the stimulated cortex (47). Earlier research found that schizophrenic patients exhibited hypoactivity of the prefrontal cortex (48), which is related to the negative symptoms. By stimulating the cerebral cortex, the activity of the cortex increases, and the negative symptoms improve. Furthermore, recent research reported that disruption of the cerebellar-prefrontal network functional connection was the basis for the negative symptoms in schizophrenia (49). The disrupted network connectivity may be restored with rTMS, resulting in a reduction in negative symptoms. Interestingly, previous human and animal

studies have also indicated that rTMS induces dopamine release in the pre-frontal cortex (50, 51). Therefore, the release of endogenous dopamine in subcortical structures may be the most likely mechanism underlying the improvement in negative symptoms by rTMS. In addition, Kirschner et al. suggested that the improvement of depression would reduce negative symptoms with the reduction of secondary negative symptoms (52). We only asked the individuals whether they had depressive symptoms verbally, while we didn't conduct a scale assessment. Even though, we also speculated that rTMS may improve negative symptoms by affecting depressive symptoms. We will further verify this in future studies.

However, other studies have failed to find any benefit of 10 Hz rTMS on negative symptoms in patients with schizophrenia. Holi et al. found no significant difference in negative symptoms of schizophrenia between the group who received 10 Hz rTMS and the sham treatment group, though both groups showed improvement in negative symptoms (53). Wobrock and colleagues performed a sham-controlled, randomized multicenter trial with 76 schizophrenia patients treated with 10 Hz rTMS to the left DLPFC. The results revealed no statistically significant difference in improvement in negative symptoms between the active and sham rTMS groups at day 21 or subsequently through today 105 (25). The discrepancy in the treatment effect of 10 Hz rTMS over the DLPFC on negative symptoms among different studies may be due to complex confounding factors, such as heterogeneity in the sample, the assessment tool used for negative symptoms (54), total stimulation number or duration, number of treatment sessions, concomitant medication, sample size, and the setting of the clinical trial (25). Hence, more research should be performed to identify the optimal mode at a frequency of 10 Hz over DLPFC to achieve the best improvement effects on negative symptoms.

The current study showed a beneficial effect of 10 Hz rTMS on cognitive function, including immediate memory and delayed memory. An early study found that both 10 and 20 Hz rTMS improved memory in patients with schizophrenia, while another study found that both 10 and 20 Hz rTMS had delayed effects on cognitive function at the 6-month follow-up (55). Guan et al. also found the effectiveness of high-frequency rTMS stimulation in improving the cognitive function of patients with schizophrenia (56). A recent meta-analysis also found that 10 Hz rTMS over the DLPFC significantly improved all indicators of working memory performance, including reaction time and accuracy (57). It has been well-documented that abnormalities in beta and gamma-band activity are implicated in the cognitive deficits in schizophrenia (58). High-frequency rTMS may be a possible approach for cognitive improvement in schizophrenia patients via the modulation of gamma oscillatory activity in the brain. Interestingly, we found a significant correlation between the decrease in PANSS negative scores and the increase in RBANS language scores. Previous studies have shown that negative symptoms aggravate cognitive impairment in schizophrenia, and the current findings further highlight the significance of focusing on improving negative symptoms, which will, in turn, promote cognitive rehabilitation to a certain extent (59). The exact mechanism underlying the effect of rTMS on cognitive impairment and negative symptoms in schizophrenia remains unclear. Many studies have demonstrated that cognitive impairment and negative symptoms in schizophrenia share a common pathological mechanism, which may be associated with structural and functional abnormalities in the frontal lobe of the brain (19, 60). The improvement in immediate memory and delayed memory by active rTMS treatment over the DLPFC in chronic schizophrenia patients may be explained by the enhanced cortical excitability and metabolic activity of target neurons in the pre-frontal cortex, which is the brain area responsible for memory function. Nonetheless, this association and the mechanisms behind it deserve more research.

In the present study, there was no significant difference in the improvement in positive symptoms between the active rTMS and sham groups, which is in agreement with most previous studies (39, 61–63). The most important reasons underlying the lack of improvement in positive symptoms may be the frequencies and sites of stimulation. Evidence suggests that low-frequency ($\leq$1 Hz) rTMS over the temporal-parietal cortex (TPC) could significantly ameliorate positive symptoms, especially in relation to auditory hallucinations (28, 62). Therefore, the improvement of positive symptoms by 10 Hz rTMS over DLPFC may not be significant. Future studies should verify this hypothesis.

The current research has several limitations: (1) the relatively small sample size meant that there was limited statistical power to detect differences between the groups; (2) the relatively short intervention period made it impossible to compare whether there was a difference between the short- and long-term effects of rTMS treatment;(3) the rTMS stimulation site was not guided by MRI;(4) there are no assessment and follow-up of depressive symptoms;(5) our study excluded patients who had received rTMS treatment more than a month before the beginning of this study, but some researchers believed that the benefits of rTMS on negative symptoms can be maintained for several months (43), so patients who had previously received rTMS treatment may have an impact on the results. We will pay attention to these issues in our future studies.

CONCLUSIONS

The current study sheds light on the effect of high-frequency (10 Hz) rTMS over the left DLPFC on negative symptoms, immediate memory, and delayed memory in chronic schizophrenia patients. As a non-pharmacological strategy, rTMS has broad application prospects. Our study provides some practical significance to the clinic that when curing some treatment-resistant symptoms of schizophrenia, especially negative symptoms and cognitive deficit, 10 Hz rTMS maybe a good treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary files, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Affiliated Kangning Hospital of Wenzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KZ, XF, and SZ conceptualized and designed the study. NW, LC, MZ, YZ, XM, MW, and WT recruited the participants and completed the screening assessments. JL, YX, ST, and XF performed the rTMS manipulation. NW, LC, MZ, JL, and KZ analyzed the data and performed the statistical analysis. NW, LC, and SZ wrote the first draft of the manuscript. All authors revised the manuscript and approved the final manuscript.

FUNDING

This work was supported by the Science and Technology Program of Wenzhou (S20190026, Y20190478, Y20180115), the traditional Chinese Medicine Program of Zhejiang (2020KY926), and the Science and Technology Development Program of Nanjing Medical University (NMUB2019107).

ACKNOWLEDGMENTS

We are deeply grateful to all participants who made contributions to our study for their generous participation, and psychiatrists for their help in the recruitment and diagnosis of schizophrenia patients.

REFERENCES

1. Mueser KT, McGurk SR. Schizophrenia. *Lancet.* (2004) 363:2063–72. doi: 10.1016/S0140-6736(04)16458-1
2. Kaiser S, Lyne J, Agartz I, Clarke M, Mørch-Johnsen L, Faerden A. Individual negative symptoms and domains - relevance for assessment, pathomechanisms and treatment. *Schizophr Res.* (2017) 186:39–45. doi: 10.1016/j.schres.2016.07.013
3. Castelnovo A, Ferrarelli F, D'Agostino A. Schizophrenia: from neurophysiological abnormalities to clinical symptoms. *Front Psychol.* (2015) 6:478. doi: 10.3389/fpsyg.2015.00478
4. Keeley JW, Gaebel W. Symptom rating scales for schizophrenia and other primary psychotic disorders in ICD-11. *Epidemiol Psychiatr Sci.* (2018) 27:219–24. doi: 10.1017/S2045796017000270
5. Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, et al. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull.* (2013) 39:1296–306. doi: 10.1093/schbul/sbs130
6. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, et al. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. *Schizophr Bull.* (2018) 44:1195–203. doi: 10.1093/schbul/sby058
7. Tandon R. Antipsychotics in the treatment of schizophrenia: an overview. *J Clin Psychiatry.* (2011) 72(Suppl. 1):4–8. doi: 10.4088/JCP.10075su1.01
8. Luft B, Taylor D. A review of atypical antipsychotic drugs versus conventional medication in schizophrenia. *Expert Opin Pharmacother.* (2006) 7:1739–48. doi: 10.1517/14656566.7.13.1739
9. Yu L, Fang X, Chen Y, Wang Y, Wang D, Zhang C. Efficacy of transcranial direct current stimulation in ameliorating negative symptoms and cognitive impairments in schizophrenia: a systematic review and meta-analysis. *Schizophr Res.* (2020) 224:2–10. doi: 10.1016/j.schres.2020.10.006
10. Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Möller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, Part 1: acute treatment of schizophrenia. *World J Biol Psychiatry.* (2005) 6:132–91. doi: 10.1080/15622970510030090
11. Howells FM, Kingdon DG, Baldwin DS. Current and potential pharmacological and psychosocial interventions for anxiety symptoms and disorders in patients with schizophrenia: structured review. *Hum Psychopharmacol.* (2017) 32:e2628. doi: 10.1002/hup.2628
12. Gan H, Zhu J, Zhuo K, Zhang J, Tang Y, Qian Z, et al. High frequency repetitive transcranial magnetic stimulation of dorsomedial prefrontal cortex for negative symptoms in patients with schizophrenia: a double-blind, randomized controlled trial. *Psychiatry Res.* (2021) 299:113876. doi: 10.1016/j.psychres.2021.113876
13. Sciortino D, Pigoni A, Delvecchio G, Maggioni E, Schiena G, Brambilla P. Role of rTMS in the treatment of cognitive impairments in Bipolar Disorder and Schizophrenia: a review of Randomized Controlled Trials. *J Affect Disord.* (2021) 280(Pt A):148–55. doi: 10.1016/j.jad.2020.11.001
14. Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol.* (2014) 125:2150–206. doi: 10.1016/j.clinph.2014.05.021
15. Muellbacher W, Ziemann U, Boroojerdi B, Hallett M. Effects of low-frequency transcranial magnetic stimulation on motor excitability and basic motor behavior. *Clin Neurophysiol.* (2000) 111:1002–7. doi: 10.1016/S1388-2457(00)00284-4
16. Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. *Annu Rev Neurosci.* (2005) 28:377–401. doi: 10.1146/annurev.neuro.27.070203.144216
17. Peinemann A, Reimer B, Löer C, Quartarone A, Münchau A, Conrad B, et al. Long-lasting increase in corticospinal excitability after 1800 pulses of subthreshold 5 Hz repetitive TMS to the primary motor cortex. *Clin Neurophysiol.* (2004) 115:1519–26. doi: 10.1016/j.clinph.2004.02.005
18. Cordes J, Thünker J, Agelink MW, Arends M, Mobascher A, Wobrock T, et al. Effects of 10 Hz repetitive transcranial magnetic stimulation (rTMS) on clinical global impression in chronic schizophrenia. *Psychiatry Res.* (2010) 177:32–6. doi: 10.1016/j.psychres.2009.01.014
19. Aleman A, Enriquez-Geppert S, Knegtering H, Dlabac-de Lange JJ. Moderate effects of non-invasive brain stimulation of the frontal cortex for improving negative symptoms in schizophrenia: meta-analysis of controlled trials. *Neurosci Biobehav Rev.* (2018) 89:111–8. doi: 10.1016/j.neubiorev.2018.02.009
20. Galderisi S, Kaiser S, Bitter I, Nordentoft M, Mucci A, Sabé M, et al. EPA guidance on treatment of negative symptoms in schizophrenia. *Eur Psychiatry.* (2021) 64:e21. doi: 10.1192/j.eurpsy.2021.13
21. Li Z, Yin M, Lyu XL, Zhang LL, Du XD, Hung GC. Delayed effect of repetitive transcranial magnetic stimulation (rTMS) on negative symptoms of schizophrenia: findings from a randomized controlled trial. *Psychiatry Res.* (2016) 240:333–5. doi: 10.1016/j.psychres.2016.04.046
22. Barr MS, Farzan F, Rajji TK, Voineskos AN, Blumberger DM, Arenovich T, et al. Can repetitive magnetic stimulation improve cognition in schizophrenia? Pilot data from a randomized controlled trial. *Biol Psychiatry.* (2013) 73:510–7. doi: 10.1016/j.biopsych.2012.08.020
23. Oh SY, Kim YK. Adjunctive treatment of bimodal repetitive transcranial magnetic stimulation (rTMS) in pharmacologically non-responsive patients with schizophrenia: a preliminary study. *Prog Neuropsychopharmacol Biol Psychiatry.* (2011) 35:1938–43. doi: 10.1016/j.pnpbp.2011.07.015
24. Wölwer W, Lowe A, Brinkmeyer J, Streit M, Habakuck M, Agelink MW, et al. Repetitive transcranial magnetic stimulation (rTMS) improves facial affect recognition in schizophrenia. *Brain Stimul.* (2014) 7:559–63. doi: 10.1016/j.brs.2014.04.011
25. Wobrock T, Guse B, Cordes J, Wölwer W, Winterer G, Gaebel W, et al. Left prefrontal high-frequency repetitive transcranial magnetic stimulation

for the treatment of schizophrenia with predominant negative symptoms: a sham-controlled, randomized multicenter trial. *Biol Psychiatry*. (2015) 77:979–88. doi: 10.1016/j.biopsych.2014.10.009

26. Hasan A, Guse B, Cordes J, Wölwer W, Winterer G, Gaebel W, et al. Cognitive effects of high-frequency rTMS in schizophrenia patients with predominant negative symptoms: results from a multicenter randomized sham-controlled trial. *Schizophr Bull.* (2016) 42:608–18. doi: 10.1093/schbul/sbv142
27. Jiang Y, Guo Z, Xing G, He L, Peng H, Du F, et al. Effects of high-frequency transcranial magnetic stimulation for cognitive deficit in schizophrenia: a meta-analysis. *Front Psychiatry*. (2019) 10:135. doi: 10.3389/fpsyt.2019.00135
28. Stanford AD, Sharif Z, Corcoran C, Urban N, Malaspina D, Lisanby SH. rTMS strategies for the study and treatment of schizophrenia: a review. *Int J Neuropsychopharmacol.* (2008) 11:563–76. doi: 10.1017/S1461145707008309
29. Shi C, Yu X, Cheung EF, Shum DH, Chan RC. Revisiting the therapeutic effect of rTMS on negative symptoms in schizophrenia: a meta-analysis. *Psychiatry Res.* (2014) 215:505–13. doi: 10.1016/j.psychres.2013.12.019
30. Veerman SRT, Schulte PFJ, de Haan L. Treatment for negative symptoms in schizophrenia: a comprehensive review. *Drugs*. (2017) 77:1423–59. doi: 10.1007/s40265-017-0789-y
31. Chou YH, Ton That V, Sundman M. A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging.* (2020) 86:1–10. doi: 10.1016/j.neurobiolaging.2019.08.020
32. Beynel L, Appelbaum LG, Luber B, Crowell CA, Hilbig SA, Lim W, et al. Effects of online repetitive transcranial magnetic stimulation (rTMS) on cognitive processing: a meta-analysis and recommendations for future studies. *Neurosci Biobehav Rev.* (2019) 107:47–58. doi: 10.1016/j.neubiorev.2019.08.018
33. Lisanby SH, Gutman D, Luber B, Schroeder C, Sackeim HA. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biol Psychiatry*. (2001) 49:460–3. doi: 10.1016/S0006-3223(00)01110-0
34. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* (1987) 13:261–76. doi: 10.1093/schbul/13.2.261
35. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol.* (1998) 20:310–9. doi: 10.1076/jcen.20.3.310.823
36. Fang X, Chen Y, Wang Y, Ren J, Zhang C. Depressive symptoms in schizophrenia patients: a possible relationship between SIRT1 and BDNF. *Progr Neuro Psychopharmacol Biol Psychiatry*. (2019) 95:109673. doi: 10.1016/j.pnpbp.2019.109673
37. Scarpina F, Tagini S. The stroop color and word test. *Front Psychol.* (2017) 8:557. doi: 10.3389/fpsyg.2017.00557
38. Chen KP, Lung FW. Reliability and validity of the short version of Udvalg for Kliniske Undersogelser in antipsychotic treatment. *Psychiatr Q.* (2017) 88:787–96. doi: 10.1007/s11126-017-9494-y
39. Kennedy NI, Lee WH, Frangou S. Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: a meta-analysis of randomized controlled trials. *Eur Psychiatry*. (2018) 49:69–77. doi: 10.1016/j.eurpsy.2017.12.025
40. Zhang C, Fang X, Yao P, Mao Y, Cai J, Zhang Y, et al. Metabolic adverse effects of olanzapine on cognitive dysfunction: a possible relationship between BDNF and TNF-alpha. *Psychoneuroendocrinology*. (2017) 81:138–43. doi: 10.1016/j.psyneuen.2017.04.014
41. Prikryl R, Ustohal L, Prikrylova Kucerova H, Kasparek T, Venclikova S, Vrzalova M, et al. A detailed analysis of the effect of repetitive transcranial magnetic stimulation on negative symptoms of schizophrenia: a double-blind trial. *Schizophr Res.* (2013) 149:167–73. doi: 10.1016/j.schres.2013.06.015
42. Kumar N, Vishnubhatla S, Wadhawan AN, Minhas S, Gupta P. A randomized, double blind, sham-controlled trial of repetitive transcranial magnetic stimulation (rTMS) in the treatment of negative symptoms in schizophrenia. *Brain Stimul.* (2020) 13:840–9. doi: 10.1016/j.brs.2020.02.016
43. Quan WX, Zhu XL, Qiao H, Zhang WF, Tan SP, Zhou DF, et al. The effects of high-frequency repetitive transcranial magnetic stimulation (rTMS) on negative symptoms of schizophrenia and the follow-up study. *Neurosci Lett.* (2015) 584:197–201. doi: 10.1016/j.neulet.2014.10.029
44. Zhuo K, Tang Y, Song Z, Wang Y, Wang J, Qian Z, et al. Repetitive transcranial magnetic stimulation as an adjunctive treatment for negative symptoms and cognitive impairment in patients with schizophrenia: a randomized, double-blind, sham-controlled trial. *Neuropsychiatr Dis Treat.* (2019) 15:1141–50. doi: 10.2147/NDT.S196086
45. Barr MS, Farzan F, Tran LC, Fitzgerald PB, Daskalakis ZJ. A randomized controlled trial of sequentially bilateral prefrontal cortex repetitive transcranial magnetic stimulation in the treatment of negative symptoms in schizophrenia. *Brain Stimul.* (2012) 5:337–46. doi: 10.1016/j.brs.2011.06.003
46. Rabany L, Deutsch L, Levkovitz Y. Double-blind, randomized sham controlled study of deep-TMS add-on treatment for negative symptoms and cognitive deficits in schizophrenia. *J Psychopharmacol.* (2014) 28:686–90. doi: 10.1177/0269881114533600
47. Esslinger C, Schuler N, Sauer C, Gass D, Mier D, Braun U, et al. Induction and quantification of prefrontal cortical network plasticity using 5 Hz rTMS and fMRI. *Hum Brain Mapp.* (2014) 35:140–51. doi: 10.1002/hbm.22165
48. Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M, et al. Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. *Nat Neurosci.* (2002) 5:267–71. doi: 10.1038/nn804
49. Brady RO Jr, Gonsalvez I, Lee I, Öngür D, Seidman LJ, Schmahmann JD, et al. Cerebellar-prefrontal network connectivity and negative symptoms in schizophrenia. *Am J Psychiatry*. (2019) 176:512–20. doi: 10.1176/appi.ajp.2018.18040429
50. Keck ME, Welt T, Muller MB, Erhardt A, Ohl F, Toschi N, et al. Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. *Neuropharmacology*. (2002) 43:101–9. doi: 10.1016/S0028-3908(02)00069-2
51. Keck ME, Sillaber I, Ebner K, Welt T, Toschi N, Kaehler ST, et al. Acute transcranial magnetic stimulation of frontal brain regions selectively modulates the release of vasopressin, biogenic amines and amino acids in the rat brain. *Eur J Neurosci.* (2000) 12:3713–20. doi: 10.1046/j.1460-9568.2000.00243.x
52. Conforto AB, Amaro E Jr, Gonçalves AL, Mercante JP, Guendler VZ, Ferreira JR, et al. Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. *Cephalalgia.* (2014) 34:464–72. doi: 10.1177/0333102413515340
53. Holi MM, Eronen M, Toivonen K, Toivonen P, Marttunen M, Naukkarinen H. Left prefrontal repetitive transcranial magnetic stimulation in schizophrenia. *Schizophr Bull.* (2004) 30:429–34. doi: 10.1093/oxfordjournals.schbul.a007089
54. Dlabac-de Lange JJ, Bais L, van Es FD, Visser BG, Reinink E, Bakker B, et al. Efficacy of bilateral repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: results of a multicenter double-blind randomized controlled trial. *Psychol Med.* (2015) 45:1263–75. doi: 10.1017/S0033291714002360
55. Xiu MH, Guan HY, Zhao JM, Wang KQ, Pan YF, Su XR, et al. Cognitive enhancing effect of high-frequency neuronavigated rtms in chronic schizophrenia patients with predominant negative symptoms: a double-blind controlled 32-week follow-up study. *Schizophr Bull.* (2020) 46:1219–30. doi: 10.1093/schbul/sbaa035
56. Guan HY, Zhao JM, Wang KQ, Su XR, Pan YF, Guo JM, et al. High-frequency neuronavigated rTMS effect on clinical symptoms and cognitive dysfunction: a pilot double-blind, randomized controlled study in Veterans with schizophrenia. *Transl Psychiatry.* (2020) 10:79. doi: 10.1038/s41398-020-0745-6
57. Brunoni AR, Vanderhasselt MA. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. *Brain Cogn.* (2014) 86:1–9. doi: 10.1016/j.bandc.2014.01.008
58. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci.* (2010) 11:100–13. doi: 10.1038/nrn2774

59. Kaneko K. Negative symptoms and cognitive impairments in schizophrenia: two key symptoms negatively influencing social functioning. *Yonago Acta Med.* (2018) 61:91–102. doi: 10.33160/yam.2018.06.001
60. Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship? *Schizophr Bull.* (2006) 32:250–8. doi: 10.1093/schbul/sbj011
61. Limongi R, Mackinley M, Dempster K, Khan AR, Gati JS, Palaniyappan L. Frontal-striatal connectivity and positive symptoms of schizophrenia: implications for the mechanistic basis of prefrontal rTMS. *Eur Arch Psychiatry Clin Neurosci.* (2021) 271:3–15. doi: 10.1007/s00406-020-01163-6
62. Freitas C, Fregni F, Pascual-Leone A. Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia. *Schizophr Res.* (2009) 108:11–24. doi: 10.1016/j.schres.2008.11.027
63. Goyal N, Nizamie SH, Desarkar P. Efficacy of adjuvant high frequency repetitive transcranial magnetic stimulation on negative and positive symptoms of schizophrenia: preliminary results of a double-blind sham-controlled study. *J Neuropsychiatry Clin Neurosci.* (2007) 19:464–7. doi: 10.1176/jnp.2007.19.4.464

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

REVIEW
published: 14 December 2021
doi: 10.3389/fpsyt.2021.791117

Improving Knowledge on Pathways to Functional Outcome in Schizophrenia: Main Results From the Italian Network for Research on Psychoses

*Luigi Giuliani, Giulia Maria Giordano, Paola Bucci, Pasquale Pezzella, Francesco Brando and Silvana Galderisi**

Department of Psychiatry, University of Campania "Luigi Vanvitelli", Naples, Italy

OPEN ACCESS

Edited by:
Joseph Ventura, UCLA Department of Psychiatry, United States

Reviewed by:
Paola Rocca, University of Turin, Italy
Giacomo Deste, Civil Hospital of Brescia, Italy

***Correspondence:**
Silvana Galderisi
silvana.galderisi@gmail.com

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *07 October 2021*
Accepted: *15 November 2021*
Published: *14 December 2021*

Citation:
Giuliani L, Giordano GM, Bucci P, Pezzella P, Brando F and Galderisi S (2021) Improving Knowledge on Pathways to Functional Outcome in Schizophrenia: Main Results From the Italian Network for Research on Psychoses. Front. Psychiatry 12:791117. doi: 10.3389/fpsyt.2021.791117

The identification of factors associated with functional outcome of subjects with schizophrenia is a great challenge in current research oriented to the personalization of care. The Italian Network for Research on Psychoses (NIRP) is a network of 26 university psychiatric clinics and/or mental health departments aimed to carry out multicenter research projects to improve the standards of prevention, diagnosis, and treatments of schizophrenia. The network has promoted 2 main studies, a cross-sectional one and a longitudinal one and seven "add-on" studies. The cross-sectional study of the network included 921 subjects with schizophrenia, 379 unaffected first-degree relatives of these patients, and 780 healthy controls. Results from this study documented that social and non-social cognition, functional capacity, negative symptoms, resilience, and family or social incentives strongly influence a measure of global functioning. The follow-up study included 618 patients from the original sample and has produced evidence of the key role of cognition, functional capacity, the experiential domain of negative symptoms, and everyday life skills in predicting functional outcome. The longitudinal study demonstrated that social cognition and the experiential domain of negative symptoms had an impact on interpersonal functioning, while non-social cognition had an impact on everyday life skills. Both non-social cognition and social cognition predicted work skills. The research question concerning the relationships of cognitive impairment and negative symptoms has been investigated with an innovative approach, using a structural equation model (SEM) and a network analysis. Both analyses demonstrated that only the experiential domain of negative symptoms had a distinct direct effect on functioning. The network analysis showed that expressive deficit was connected to functional capacity, as were social and non-social cognitive variables, and to disorganization. These findings were confirmed by the follow-up study. The add-on studies showed distinct electrophysiological correlates of the two negative symptom domains and the partial overlap between disorganization and neurocognitive impairment. Moreover, they identified and characterized a specific subgroup of patients suffering from

schizophrenia with autism spectrum symptoms. The NIRP studies have implications for personalized management of patients with schizophrenia and highlight the need for a careful assessment of several domains rarely evaluated in clinical settings.

Keywords: schizophrenia, real-life functioning, recovery, neurocognition, social cognition, negative symptoms

INTRODUCTION

Schizophrenia is a severe mental disorder that presents a high heterogeneity in terms of risk factors, clinical manifestations, comorbidities, treatment response, and outcomes (1–19).

About 75% of people suffering from this disorder shows a clinical course characterized by relapses and remissions (20–23), and <1 in 7 people meets the criteria for recovery (24, 25). Two aspects are fundamental to achieve clinical recovery in schizophrenia: the remission of symptoms and the improvement in functioning (26–29). However, despite the introduction of innovative pharmacological and psychosocial treatments that facilitate symptomatic remission (3, 6–8, 10), the impairment in different areas of real-life functioning still represents an unmet need in the care of people suffering from schizophrenia, thus causing a huge burden on patients, their families, and health care systems (30–41).

A variety of factors, some related to the illness, some to personal resources, and others to the social context, seem to influence functional outcome, through direct or indirect relationships (18, 41–50). The identification of these factors, as well as their relative impact on the outcome through complex pathways, represents, to date, a main goal of current psychiatric research, in order to develop integrated and individualized treatments aiming at ameliorating functioning and thus at achieving recovery (51, 52).

Within this frame, a national multicenter project, promoted by the Italian Network for Research on Psychoses, has been developed. This is a network of 26 university psychiatric clinics and/or mental health departments, coordinated by the Department of Psychiatry of the University of Campania "Luigi Vanvitelli" (**Table 1**). By promoting and enhancing the collaboration among the involved centers, this network is intended to carry out research projects in order to improve the standards of prevention, diagnosis, and treatments for people suffering from primary psychotic disorders. So far, the network promoted two main studies, a cross-sectional one and a longitudinal 4-year follow-up one. In addition, seven "add-on" studies have been promoted by the network (**Table 2**).

The cross-sectional study had been carried out between 2011 and 2013 (32, 33). The primary objective of the study was to identify factors affecting real-life functioning of subjects with schizophrenia and to define their relative contribution. The longitudinal study was conducted after 4 years. This study investigated whether factors identified as predictors and mediators of real-life functioning in the cross-sectional study were confirmed as such as follow-up (34, 37). As compared to previous studies on the topic, both studies analyzed a greater number of variables, some of which have never been examined before. Moreover, these studies used state-of-the-art instruments for the assessment of each variable included and appropriate data analysis methods in order to explore the complex relationships between possible predictors, mediators, and outcome measures.

The implementation of the longitudinal assessment allowed us to overcome the limitations of the cross-sectional design, which prevented inferences about the direction of causality. In fact, the majority of studies investigating factors associated with functional outcome in schizophrenia have had a cross-sectional design, while only few and inconsistent findings have been reported by investigations with a longitudinal design (44, 53–63). The inconsistency of results might be due to different factors, such as the small sample sizes included in the studies, the use of different measures of functional outcome, and the use of assessment instruments, especially for cognitive impairment and negative symptoms, that were often not in line with their current conceptualization (32, 64–67). Indeed, although negative symptoms and cognitive impairment are stable dimensions of schizophrenia, are often present since the early phases of the illness, persist into clinical remission, and predict outcomes (41, 56, 57), uncertainties still remain about the correct evaluation and management of these dimensions (4, 68–70).

In the present article, we report the main findings of the two studies conducted by the network, which have contributed to the advancement of knowledge on the complex pathways involved in functional outcomes in people with schizophrenia.

CROSS-SECTIONAL STUDY

Participants

Within the cross-sectional study, 921 patients with a diagnosis of schizophrenia, aged between 18 and 66 years; 379 unaffected first-degree relatives of these patients; and 780 healthy controls were recruited (32, 33). For the patient group, inclusion criteria were a diagnosis of schizophrenia according to DSM-IV, confirmed with the Structured Clinical Interview for DSM-IV–patient version (SCID-I-P), and an age between 18 and 66 years. Exclusion criteria were a history of head trauma with loss of consciousness; a history of moderate to severe mental retardation or of neurological diseases; a history of alcohol and/or substance abuse in the last 6 months; current pregnancy or lactation; inability to provide an informed consent; and treatment modifications and/or hospitalization due to symptom exacerbation in the last 3 months. For each recruited patient who agreed to involve relatives, two first-degree relatives were recruited, when available. They were preferably the two parents, or one parent and one sibling, or two siblings. These relatives were included in the study if criteria for a current or lifetime psychiatric diagnosis were not met when they were interviewed with the SCID-I–non-patient version and the SCID-II. Exclusion criteria were (a) a history of head trauma with loss of consciousness; (b) a history of moderate

TABLE 1 | Centers involved in the Italian Network for Research on Psychoses and their coordinators.

Center	Coordinator
Department of Psychiatry, University of Campania "Luigi Vanvitelli"	Silvana Galderisi
Department of Neuroscience, Section of Psychiatry, University of Turin	Filippo Bogetto/Paola Rocca
Department of Translational Medicine, Psychiatric Unit, University of Eastern Piedmont	Patrizia Zeppegno
Department of Psychiatry, State University of Milan	Carlo Altamura
Psychiatric Unit, School of Medicine, University of Brescia, Brescia	Emilio Sacchetti/Antonio Vita
Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health, Section of Psychiatry, University of Genoa	Mario Amore
Department of Neurosciences, Psychiatric Clinic, University of Padua	Paolo Santonastaso/Angela Favaro
Department of Biomedical and Neuromotor Sciences, University of Bologna	Diana De Ronchi
Department of Neuroscience, Psychiatry Unit, University of Parma	Carlo Marchesi
Department of Neurosciences, Psychology, Drug Research and Child Health, University of Florence	Stefano Pallanti
Department of Health Sciences, Psychiatry Unit, University of Florence	Valdo Ricca
Department of Clinical and Experimental Medicine, Section of Psychiatry, University of Pisa	Liliana Dell'Osso
Department of Molecular Medicine and Clinical Department of Mental Health, University of Siena	Andrea Fagiolini
Department of Life, Health and Environmental Sciences, Unit of Psychiatry, University of L'Aquila	Massimo Casacchia/Rita Roncone
Department of Biotechnological and Applied Clinical Sciences, Section of Psychiatry, University of L'Aquila	Alessandro Rossi
Department of Neuroscience and Imaging, G. D'Annunzio University of Chieti	Massimo di Giannantonio
Department of Neurology and Psychiatry, Sapienza University of Rome	Massimo Biondi
Department of Neurosciences, Mental Health and Sensory Organs, S. Andrea Hospital, Sapienza University of Rome	Paolo Girardi/Maurizio Pompili
Department of Systems Medicine, Psychiatry and Clinical Psychology Unit, Tor Vergata University of Rome, Rome	Alberto Siracusano
Department of Neuroscience, Reproductive Science, and Odontostomatology, Section of Psychiatry, Federico II University of Naples	Andrea De Bartolomeis
Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana," Section of Neuroscience, University of Salerno	Palmiero Monteleone
Department of Neurological and Psychiatric Sciences, University of Bari	Alessandro Bertolino
Department of Clinical and Molecular Biomedicine, Psychiatry Unit, University of Catania	Eugenio Aguglia
Department of Public Health, Clinical and Molecular Medicine, Section of Psychiatry, University of Cagliari	Bernardo Carpiniello
Psychiatry Unit, Department of Medical Sciences, University of Foggia	Antonello Bellomo
Department of Psychiatry, Neurobiology, Pharmacology and Biotechnologies, UNIPI	Mauro Mauri

TABLE 2 | Add-on studies of the Italian Network for Research on Psychoses.

Add-on studies
Investigation of electrophysiological correlates of schizophrenia and their association with psychopathology, social and non-social cognition, and real-life functioning
Investigation of structural–functional magnetic resonance imaging features associated with diagnosis and real-world functioning in patients with schizophrenia
Investigation of autistic spectrum symptoms and their impact on real-life functioning in subjects with schizophrenia
Investigation of sexual functioning in subjects with schizophrenia and its association with psychopathology and social functioning
Investigation of obsessive symptoms and their impact on real-life functioning in subjects with schizophrenia
Investigation of resources and global burden of patients' families and their impact on psychopathology and real-life functioning of subjects with schizophrenia
Investigation of post-traumatic spectrum symptoms and their impact on real-life functioning in subjects with schizophrenia

to severe mental retardation or of neurological diseases; (c) a history of alcohol and/or substance abuse in the last 6 months; (d) inability to provide an informed consent. Healthy subjects matched with patients for gender and geographical area of origin were recruited from the community at the same sites as the patient sample. Inclusion and exclusion criteria were the same as those listed for first-degree relatives.

Assessment Instruments

The study evaluated the impact on real-life functioning of a larger number of variables compared to previous investigations, some of which had never been investigated before. The assessed variables were grouped into three categories: (a) illness-related variables (positive, negative, disorganized, depressive, and extrapyramidal symptoms; neurocognition; social cognition; and functional capacity); (b) personal resources (resilience and engagement with mental health services); and (c) context-related factors (socio-demographic variables; socioeconomic status; availability of a disability pension; access to family and social incentives; and social network). The variables included

TABLE 3 | Investigated variables in the cross-sectional and follow-up studies of the network.

Factors	Variables	References
Illness-related variables	Neurocognitive deficit	(71–73)
	Social cognition deficit	(74, 75)
	Negative symptoms	(66, 70, 76–81)
	Depressive symptoms	(78, 82, 83)
	Positive symptoms	(42, 50, 84)
	Disorganization	(50, 85)
Personal resources	Resilience	(49, 86)
	Service engagement	(87)
Context-related variables	Social network	(45, 46)
	Job or housing opportunities and residential support	(45, 46)
	Disability compensation	(45, 46)
	Internalized stigma	(48, 88)

in each category are reported in **Table 3**. Real-life functioning was chosen as any index of clinical recovery. State-of-the-art instruments were used to assess variables of each category and real-life functioning. The adopted instruments were chosen on the basis of the literature and the researchers' experience, to overcome limitations of previous studies. When it was necessary, assessment instruments were translated, adapted, and validated for the Italian context.

All the instruments have been used to evaluate subjects with schizophrenia, their first-degree relatives, and healthy controls.

Illness-Related Variables

A clinical form was filled in with data on age of disease onset, course of the disease, and treatments received, using all available sources of information (patient, family, medical records, and mental health workers).

The severity of positive and disorganized symptoms was evaluated using the Positive and Negative Syndrome Scale (PANSS) (89).

Negative symptoms were assessed with the Brief Negative Symptom Scale (BNSS), a second-generation rating scale which is in line with the current conceptualization of negative symptoms (64, 90). As compared to first-generation rating scales, the BNSS shows several advantages. It does not include aspects that are related to cognitive or depressive dimensions; it provides a separate assessment of behavior and inner experience for items referring to experiential deficits such as avolition, thus enabling a better differentiation from social functioning and other subjective experiences such as decreased interest or energy; it provides a separate assessment of consummatory and anticipatory anhedonia; it generates a total score as well as separate scores for the five negative symptom domains (avolition, anhedonia, asociality, blunted affect, and alogia). The two-factor structure, consisting of the experiential domain (avolition, anhedonia, and asociality) and the expressive deficit domain (blunted affect and alogia), is supported by the use of this instrument (64, 66, 90–92). Depressive symptoms were evaluated using the Calgary Depression Scale for Schizophrenia (CDSS) (93); extrapyramidal symptoms, with the St. Hans Rating Scale (SHRS) (94). The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) was adopted to evaluate cognitive impairment (65, 67). This instrument was built up within the MATRICS initiative, aiming to develop a cognitive battery for subjects with schizophrenia designed for use in clinical trials (65, 67). MCCB assesses seven cognitive domains that are reported to be compromised in subjects with schizophrenia: speed of processing, attention and vigilance, working memory, verbal learning and memory, visuospatial learning and memory, reasoning and problem solving, and social cognition (44). The MCCB Mayer-Salovey-Caruso Emotional Intelligent Test (MSCEIT), the Facial Emotion Identification Test (FEIT) (95), and the Awareness of Social Inference Test (TASIT) (96) were used to measure different aspects of social cognition, such as emotional intelligence, emotion recognition, and theory of mind.

Personal Resources

The Resilience Scale for Adults (RSA) (97) was used to assess resilience; the Service Engagement Scale (SES) (87), to evaluate the access of subjects with schizophrenia to mental health services.

Context-Related Factors

A socio-demographic questionnaire was developed *ad hoc* to collect data on gender, age, marital status, schooling, housing, eating habits, substance use, socioeconomic status, availability of a disability pension, and access to family and social incentives (32). The Internalized Stigma of Mental Illness (ISMI) (98) was used to assess stigma in subjects with schizophrenia.

Functional Capacity and Real-Life Functioning

The functional capacity was assessed through the brief version of the University of California, San Diego (UCDS) Performance-Based Skills Assessment–brief version (UPSA-B), a performance-based instrument that assesses "financial skills" and "communication skills" (99).

Real-life functioning was evaluated with the Specific Level of Functioning Scale (SLOF) (100, 101), a hybrid scale endorsed by the panel of experts involved in the Validation of Every-day Real-World Outcomes (VALERO) (100–103), which evaluates different areas of functioning and is based on the key caregiver's judgment on behavior and functioning of patients. The use of the SLOF allowed us to overcome limitations of previous studies investigating real-life functioning, which examined only a single or fewer domain(s) of functioning and collected only information from patients that could be influenced by many factors (e.g., delusions, hallucinations, lack of insight, disorganized thinking, cognitive deficits, or depression). The SLOF includes 43 items grouped into six domains: physical functioning, personal care skills, interpersonal relationships, social acceptability, everyday life skills, and work skills.

For each category of variables, at least one researcher per site was trained. In order to avoid halo effects, the same researcher could not be trained for more than one category. A

good to excellent agreement among raters was observed for the instruments included in the study (32).

Translation and Validation of Assessment Instruments

The BNSS was translated in Italian and validated within the cross-sectional study (92, 104). The validation study showed an excellent inter-rater reliability and a good convergent and discriminant validity, confirming that BNSS is a reliable tool for the assessment of negative symptoms in multicenter studies.

The validation study of the Italian version of the SLOF showed a good construct validity and internal consistency and a well-delineated factor structure of the instrument (100, 105).

The MCCB was translated in Italian (106), and this version was validated in a large sample, composed by subjects with schizophrenia, their unaffected first-degree relatives, and healthy controls (107). Furthermore, in collaboration with the MCCB developers, the standardization of raw scores through the computation of T scores was performed, using the scores of the normative Italian sample (107).

The TASIT manual was translated and the related video clips were dubbed in Italian, at the Fono Roma Studio (www.fonoroma.com) (108). In addition, the Italian version of the FEIT was developed (108).

Statistical Analysis

In order to investigate the simultaneous impact on functional outcome of multiple factors interacting with each other, two main statistical approaches were used: the structural equation model (SEM) and the network analysis. The SEM consists in a set of simultaneous multiple regression models for estimating and testing a pathway of relationships among variables (measured variables and latent constructs) (109). This approach allows researchers to infer causal relationship among predictors and outcome and to identify possible mediation and moderation factors, with the estimation of direct, indirect and total effects. It requires *a priori* assumptions of the possible associations among variables and of possible predictors, mediators, and outcomes, which is not always possible, especially because of the non-unidirectionality of some relationships (e.g., illness-related variables may influence real-life functioning and vice versa). In order to overcome these limits, a second approach, the network analysis, was used (110, 111). This type of analysis is a data-driven approach which does not require an *a priori* modeling of relationship among variables but generates a spatial ordered network where strongly related variables are at the center of the network and the weakly related ones at the periphery. Furthermore, estimating the number and the strength of variable connections and their closeness, this approach allows us to investigate which variables belong to the same construct and how different constructs are mutually interacting and reinforcing each other (111).

Results From SEM and Network Analyses

SEM analysis (32) showed that disorganization, the experiential domain of negative symptoms (including avolition, asociality, and anhedonia), positive symptoms, deficits in neurocognition, social cognition and functional capacity, internalized stigma, low resilience, and poor access to familial and social incentives had a significant direct and/or indirect impact on real-life functioning, explaining 53.8% of the variance. Neurocognition showed the strongest association with real-life functioning. The impact of neurocognition on the outcome turned out to be mainly indirect, mediated by functional capacity, social cognition, engagement with services, and internalized stigma. Social cognition also had a direct influence on real-life functioning, independently from neurocognition and negative symptoms. Service engagement was directly associated with the functional outcome, while internalized stigma showed an indirect impact on real-life functioning, mediated by resilience. Psychopathology, in particular positive and disorganized symptoms, and the experiential domain of negative symptoms were found to be directly and indirectly correlated with real-life functioning. The impact of positive symptoms was mediated by service engagement; the effect of disorganization, by functional capacity; and the impact of the experiential domain, by services engagement, internalized stigma, and resilience (see **Figure 1**).

The network analysis (33) confirmed that neurocognition, social cognition, resilience, and real-life functioning are well-defined independent constructs.

With respect to psychopathologic aspects, the experiential and expressive deficit domains of negative symptoms were highly interconnected but showed different associations. In particular, the experiential domain was associated with depression, social competence, "interpersonal relationships," and "work skills," while the expressive deficit was associated with disorganization, functional capacity, and "everyday life skills." Depression did not show any connection with real-life functioning. Positive and disorganized symptoms had few connections to the other nodes and were peripheral nodes in the network.

The most central and interconnected nodes of the obtained network were functional capacity and everyday life skills.

Functional capacity was shown to be the bridge between cognition (neurocognition and social cognition) and real-life functioning, in particular with the "everyday life skills." The neurocognition and social cognition constructs were adjacent and densely connected and interconnected. Both constructs had a high impact on functional capacity, and through this, on real-life functioning. In the social cognition domain, the TASIT-1, which measures the ability to identify basic emotions, showed the highest connection with functional capacity. This finding might suggest that a good comprehension of social and emotional stimuli may lead to a better acquisition of interpersonal skills required for some of the tasks incorporated in the functional capacity assessment (e.g., communication skills).

Furthermore, also the SLOF domain "everyday life skills" had a central position within the network and connected other real-life functioning domains with psychopathology, internalized stigma, functional capacity, and through this, neurocognition and social cognition.

Other Results of the Cross-Sectional Study

In first-degree relatives of subjects with schizophrenia, similar direct or indirect interactions among predictors, mediators, and functional outcome were observed (112). These findings confirm

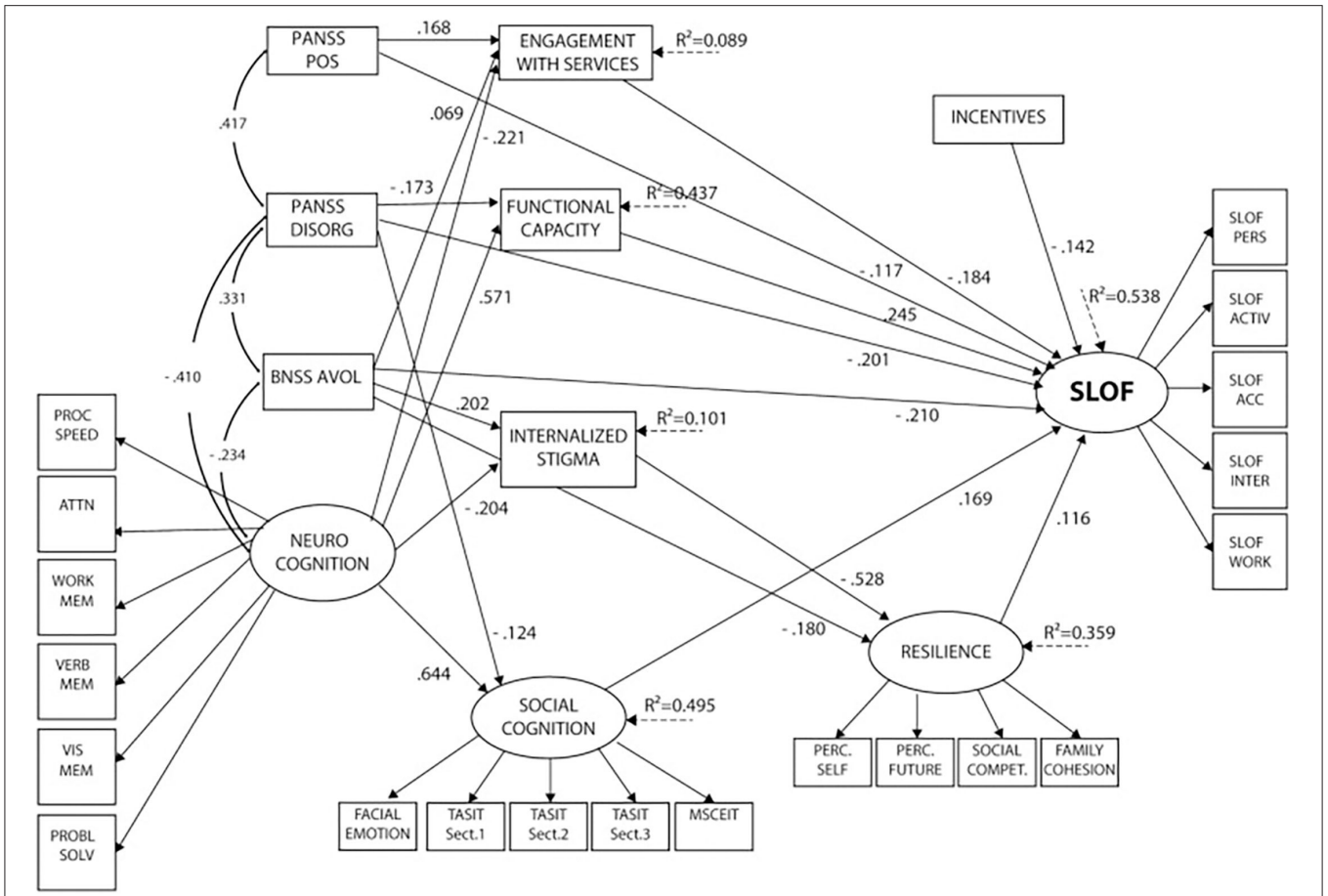


FIGURE 1 | Final structural equation model after trimming of non-significant paths. Neurocognition, social cognition, resilience, and SLOF are latent variables (with arrows pointing to their respective indicators). PANSS POS, PANSS DISORG, BNSS avolition, neurocognition, and incentives are independent predictors. Social cognition, functional capacity, internalized stigma, resilience, and service engagement are mediators, and SLOF is the dependent variable. PANSS, Positive and Negative Syndrome Scale; POS, positive; DISORG, disorganization; BNSS, Brief Negative Symptom Scale; EE, poor emotional expression; AVOL, avolition; PROC SPEED, processing speed; ATTN, attention; WORK MEM, working memory; VERB MEM, verbal memory; VIS MEM, visuospatial memory; PROBL SOLV, problem solving; TASIT, The Awareness of Social Inference Test; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test; PERC. SELF, perception of self; PERC. FUTURE, perception of the future; SOCIAL COMPET, social competence; SLOF, Specific Level of Functioning; PERS, skills in self-care; ACTIV, community activities; ACC, social acceptability; INTER, interpersonal relationships; WORK, working abilities.

the results of the main cross-sectional study, in the absence of confounding factors, such as residual psychotic symptoms and pharmacological treatment. In addition, the presence of impairment in the "interpersonal relationships" and "work skills" also in the group of unaffected relatives suggests the possible involvement of schizophrenia vulnerability factors.

The specific impact of personal resources on functional outcome has been investigated in three different network studies (113–115). A greater resilience and a higher degree of education were associated with a better social functioning, while worse problem solving and higher internalized stigma, along with male gender and depression, were associated with more severe symptoms (114). Furthermore, lower resilience, more severe negative symptoms, and female gender were associated with depressive symptoms, while internalized stigma represented a mediator between negative symptoms and resilience, suggesting a complex relationship between personal resources, negative symptoms, and depression in schizophrenia (115). The third study investigated the relationship between self-reported personal recovery and functional recovery, identifying three different clusters of patients: (a) patients with good personal recovery and good functional outcome; (b) patients with poor personal recovery and poor functional outcome; and (c) patients with intermediate personal recovery (between the other two clusters), with good insight and high levels of depression (113). These studies underline the importance and need of an accurate characterization of personal resources in subjects with schizophrenia, in order to implement individualized treatment plans aimed at improving different aspects of these resources, which have a different impact on functioning.

The role of social cognition and its impact on functioning were investigated in a study conducted by Rocca et al. (108). The authors identified three groups of patients: (a) patients without impairment in social cognition; (b) patients with a

moderate impairment in social cognition; and (c) patients with a strong impairment in social cognition. This study revealed a linear relationship between social cognition, neurocognition, disorganization, and real-life functioning across the three groups. Positive symptoms were lower in patients without social cognition impairment, as compared to those with a moderate and a strong impairment in social cognition. Furthermore, negative symptoms were highest in subjects with moderate social cognition deficits, compared to subjects with absent or severe impairment in social cognition (108).

The relationship between disorganization and real-life functioning has emerged in one study that demonstrated that conceptual disorganization, among other disorganized symptoms, was the most relevant one impacting, through direct or indirect associations, "everyday life skills" (116).

Mucci et al. (107) reported impairment of all MCCB domains in subjects with schizophrenia. First-degree relatives showed a pattern of neurocognitive impairment, with intermediate scores between those of patients and healthy controls. In addition, patients' MCCB scores were able to predict the first-degree relatives scores on all domains except for visual learning.

One study investigated the role of premorbid academic and social functioning impairment on real-life functioning, cognition, and psychopathology. Subjects with schizophrenia showed an impairment in premorbid academic and social functioning compared to healthy controls, while first-degree relatives had only impairment in academic aspects (117). In patients, impairment of premorbid functioning predicted severity of negative symptoms, working memory deficits, social cognition deficits, and real-life functioning. These data suggest that a poor premorbid functioning might represent a vulnerability marker of schizophrenia and highlight the need to implement early psychosocial and cognitive remediation interventions (118).

One study explored the association between insight and depressive symptoms and reported greater self-depreciation, pathological guilt, morning depression, and suicidal ideation in patients with high levels of insight (119).

Another explored aspect was the prevalence of extrapyramidal symptoms in subjects with schizophrenia and its association with neurocognition, social cognition, and psychopathology. The network analysis showed that parkinsonism was directly connected to both psychopathological and neurocognitive indices, whereas no direct connection emerged between extrapyramidal symptoms and social cognition (120).

Two studies investigated also genetic aspects in this population (121, 122). In particular, one study investigated *de novo* copy number variations (CNVs) in the whole-genomic DNA obtained from 46 family trios of schizophrenia probands. The authors reported the presence of *de novo* CNVs in genes involved in brain and neural development, suggesting that these alterations could contribute to the genetic vulnerability to the disorder (122). The study by Gennarelli et al. (121) aimed to explore the genetic basis of social cognition, using a genome-wide study approach. The authors found significant associations between the patients' ability in social inference and the *TMEM7M4* gene.

LONGITUDINAL STUDY

Participants

After 4 years, 618 subjects, out of the 921 subjects with schizophrenia enrolled in the cross-sectional study, agreed to participate in the longitudinal study (34, 37). These subjects did not differ from the rest of the baseline sample with respect to socio-demographic characteristics, illness-related factors, personal resources, context-related factors, and real-life functioning (34, 37). First-degree relatives and healthy controls were not recruited for the longitudinal study.

Assessment Instruments

In order to evaluate illness-related variables, personal resources, context-related factors, and real-life functioning in subjects with schizophrenia after 4 years from the cross-sectional study, the same assessment instruments used at baseline were adopted.

In addition, in the longitudinal study, the patients' insight on their real-life functioning impairment, as well as the awareness of their own cognitive impairment in several domains, was also investigated. Therefore, the SLOF was administered to both patients and their caregivers, in order to explore their accuracy in self-reporting functioning. Moreover, the Cognitive Assessment Interview (CAI) was introduced in the longitudinal study (123). This is a second-generation co-primary measure and consists of 10 items that investigate six of the seven impaired domains in subjects with schizophrenia (concerning the visuospatial memory domain, no interview question was deemed appropriate). This instrument was administered to the patient and his or her caregiver to measure the perceived severity of the impairment in several cognitive domains. The impact of cognitive impairment on the patients' daily functioning, the patients' awareness of their own cognitive deficits, and the possible discrepancy between the patients' and caregivers' interviews were evaluated. The CAI was translated and adapted for the Italian context and showed a good to excellent reliability and excellent internal consistency (124).

Statistical Analysis

In order to test whether variables affecting real-life functioning in the cross-sectional study confirmed their influence at follow-up and which variables were related to changes in real-life functioning at follow-up, SEM and latent change score (LCS) modeling were conducted, respectively. Moreover, a network analysis was used to investigate whether the pattern of relationships among variables involved in the cross-sectional study was similar at follow-up and to compare the network structure of recovered and non-recovered patients at follow-up. For the classification of recovered and non-recovered patients at the 4-year follow-up, we used two criteria: (1) the presence or absence of symptomatic remission according to the Andreasen criteria and (2) the presence or absence of functional recovery, defined as a weighted score of at least 76.2 on SLOF "interpersonal relationships," "work skills," and "everyday life skills" scales (34).

Results From SEM and Network Analyses in the Longitudinal Study

In the longitudinal study, SEM and LCS analyses (37) showed that baseline measures of neurocognition, social cognition, the experiential domain of negative symptoms, everyday life skills, and to a lesser degree, positive symptoms predicted functional outcome after a 4-year follow-up.

The SEM model confirmed that neurocognition, social cognition, positive symptoms, the experiential domain, and available incentives had a significant direct or indirect impact on at least one real-life functioning domain at the 4-year follow-up assessment. Higher baseline neurocognitive functioning predicted better everyday life skills and work skills; better social cognition predicted better work skills and interpersonal relationships; more severe positive symptoms predicted lower work skills; more severe experiential domain symptoms predicted worse interpersonal relationships; and more social incentives predicted better everyday life skills. The LCS model showed that the same baseline variables, except incentives, predicted changes in functioning at the 4-year follow-up. In particular, better baseline neurocognition predicted improvement in everyday life skills, work skills, social cognition, and functional capacity after 4 years. Less severe experiential domain symptoms and better social cognition at baseline predicted improvement in interpersonal relationships at follow-up, while less severe positive symptoms at baseline predicted improvement in work skills. Finally, better baseline everyday life skills predicted improvement in work skills and in functional capacity at follow-up.

The network analysis in the longitudinal study (34) confirmed the results of the cross-sectional one (33). The network structure remained substantially unchanged: neurocognition, social cognition, resilience, and real-life functioning were spatially contiguous and highly interconnected; everyday life skills and functional capacity were the most central and interconnected nodes of the network, while psychopathological domains were more peripheral. The number and the strengths of network connections in non-recovered patients were significantly different compared to those of the recovered ones. In fact, the network of non-recovered patients had more connections, whose strengths were higher than those found in recovered patients. The SLOF domain everyday life skills and disorganization had a higher strength among non-recovered patients, as compared to recovered ones.

Other Results of the Longitudinal Study

The network longitudinal study also contributed to the investigation of the accuracy of subjects with schizophrenia in self-evaluation of functioning. The study, conducted by Rocca et al. (125), aimed to investigate the concordance of patients' reported impairment in real-life functioning with the caregivers' reported one. Furthermore, it aimed to identify which factors are associated with discrepancies between patients' and caregivers' reports. Results indicated that patients systematically reported a higher functional level than their relatives; however, the patient–caregiver discrepancy was significant only in 17.6% of the cases. The strongest predictors of patient–caregiver discrepancies were caregivers' ratings in each SLOF domain. These findings underline the possibility to use in clinical practice patients' self-evaluation of functioning in order to design tailored rehabilitative programs.

ELECTROPHYSIOLOGICAL AND OTHER ADD-ON STUDIES

Two investigations were carried out within the electrophysiological add-on study (126, 127). The first study aimed to investigate neurophysiological correlates of negative symptom domains. This study showed that the brain electrical microstate A (microstate associated with the visual network) was related to the experiential domain and not to the expressive one. Within the experiential domain, avolition, asociality, and anticipatory anhedonia, but not consummatory anhedonia, showed a similar pattern of correlation. These data suggest the existence of distinct electrophysiological correlates of the two negative symptom domains and lend support to the hypothesis that only the anticipatory component of anhedonia shares the same pathophysiological underpinnings of the experiential domain (126). The second study aimed to investigate electrophysiological and neurocognitive correlates of the PANSS disorganization dimension, in order to evaluate the heterogeneity of this dimension and its possible overlap with neurocognitive deficits. The authors reported that the slow alpha activity was negatively correlated with disorganization in subjects with schizophrenia. At item level, only the PANSS item "Difficulty in abstract thinking" showed the same correlation. The MCCB neurocognitive composite score was associated with disorganization dimension as well as PANSS items "Conceptual disorganization" and "Difficulty in abstract thinking". These findings support a partial overlap between disorganization and neurocognitive impairment. In addition, they suggest that some aspects of disorganization could be related to the impairment of basic neurobiological functions that are only partially evaluated using MCCB (127).

Finally, the network longitudinal study contributed also to the characterization of a subgroup of subjects with schizophrenia defined by the presence of autistic spectrum symptoms. Patients with autistic traits represent a specific population of subject with schizophrenia, characterized by specific patterns of functioning, resilience, and coping abilities (128). Moreover, autistic symptoms may have a relevant impact on different aspects of the disease, in particular neurocognitive and social cognition domains, functional capacity, real-world interpersonal relationships, and participation in everyday life activities (129).

The other add-on studies are still ongoing, and their results have yet to be published.

DISCUSSION

So far, the network has published more than 20 scientific papers and contributed to the validation of state-of-the-art assessment tools and to the training of many researchers from all the involved centers. Furthermore, in the last decade, the network

contributions have led to an improvement in knowledge about main determinants of functioning and, therefore, of clinical recovery in subjects with schizophrenia. Despite the introduction of innovative pharmacological and psychosocial treatments that facilitate symptomatic remission, the impairment in different areas of real-life functioning still represent an unmet need in the care of people suffering from schizophrenia, thus causing a huge burden on patients, their families, and health care systems (31–35, 37, 39–41). The strengths of the two main network studies, with respect to previous studies, include the analysis of a greater number of variables, some of which had never been examined before; the use of state-of-the-art instruments for the assessment of each variable included; and appropriate data analysis methods, in order to explore the complex relationship between possible predictors, mediators, and functional outcome measures. Finally, the implementation of the longitudinal study allowed us to overcome the limitations of the cross-sectional design that prevented inferences about the direction of causality.

The findings from the network studies (32–34, 37) suggest that different factors–some related to the illness, some to personal resources, and others to the social context–contribute to functional outcome, through direct or indirect associations.

The network findings strongly support the implementation of integrated treatments, combining pharmacological, psychosocial, and rehabilitative interventions. In fact, pharmacotherapy is mainly used in order to achieve the remission of positive symptoms, which had a small impact on real-life functioning of subjects with schizophrenia. Functional capacity and everyday life skills were the most central and interconnected nodes of the schizophrenia network, suggesting that they should be the main target of rehabilitative recovery-oriented programs. Moreover, since impairment in neurocognition and social cognition was the most important predictors of real-life functioning, cognitive remediation interventions should be integrated into routine clinical practice. Negative symptoms, in particular those belonging to the experiential domain, i.e., avolition, asociality, and anhedonia, have a direct impact on interpersonal functioning and predict follow-up levels of functioning in the same domain. These negative symptoms do not show any connections with functional capacity or social and non-social cognitive abilities. Their treatment remains an unmet need of schizophrenia care. Further research is needed in order to disentangle the complexity of this negative symptom domain, looking also at behavioral and neurobiological correlates in order to search for effective treatments (130).

The research question concerning the relationships of cognitive impairment and negative symptoms has been investigated with an innovative approach in the two network studies. In the cross-sectional study, SEM analysis demonstrated that only the experiential domain of negative symptoms had a distinct direct effect on functioning, while the expressive domain was not retained in the model when including cognitive impairment. The network analysis findings added further insight to the issue, showing that expressive deficit had no direct connection to real-life functioning nodes and was connected to functional capacity, as were social and non-social cognitive variables, and to disorganization. The experiential domain was directly connected to the interpersonal relationships and work skills domains of real-life functioning, while having no direct or indirect connections with the cognitive nodes, functional capacity, and disorganization. These findings were confirmed by the network analysis carried out on the follow-up data and have implications for the personalized management of patients with negative symptoms. The implementation of psychosocial interventions focused on motivation and pleasure, which targeted the experiential domain of negative symptoms, is very recent and awaits further testing. Effective treatments such as social skills training and cognitive remediation interventions should be made available to subjects with negative symptoms, in particular to those with expressive deficit, such as alogia and blunted affect. Clinical research on the effectiveness of these interventions for negative symptoms should always include at least as a secondary outcome the differential efficacy on the two domains of the negative symptoms.

The network studies document that many other factors have an impact on functional outcome, such as other aspects of psychopathology, personal resources, or context-related factors. This suggests the importance of personalized treatments based on a detailed characterization of each patient, as recently suggested by a group of experts in the field (51).

Moreover, the electrophysiological add-on studies of the network contributed to improve the knowledge of neurophysiological correlates of psychopathology. In fact, although several papers reported resting-state electrophysiological alterations in subjects with schizophrenia (131–133) and their association with psychopathology and cognitive impairment (134, 135), no study investigated the neurophysiological mechanisms underlying distinct negative symptom domains and the disorganization dimension. The network studies showed the existence of distinct electrophysiological correlates of the two negative symptom domains. Furthermore, they suggested the partial overlap between disorganization and neurocognitive impairment and the relationship of some aspects of disorganization with basic electrophysiological alterations which might represent biomarkers of this dimension.

Finally, moving from the evidence of significant levels of autistic traits in a substantial proportion of patients with schizophrenia (136, 137), the network add-on studies on this topic showed that patients with autistic traits represent a population of subject with schizophrenia, characterized by peculiar patterns of social and non-social cognitive impairment and deficits in real-life functioning, thus suggesting that these patients might benefit from specific and targeted interventions.

The network will continue to promote research in this field in order to improve the functional outcome of people suffering from schizophrenia, thus reducing the burden on patients, their families, and health care systems.

AUTHOR CONTRIBUTIONS

The project idea was initiated by SG, involving a collaboration with LG and GG. LG wrote the first draft of the manuscript.

All authors were responsible for the interpretation of the results, contributed to critically revising the content, and approved the final manuscript for submission to *Frontiers in Psychiatry*.

FUNDING

The study was funded by the Italian Ministry of Education (Grant Number: 2010XP2XR4), the Italian Society of Psychopathology (SOPSI), the Italian Society of Biological Psychiatry (SIPB), Roche, Switzerland Lilly, United States AstraZeneca, United Kingdom Lundbeck foundation, Denmark, and Bristol-Myers Squibb, United Kingdom. These entities had no role in the study design, in the collection, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

REFERENCES

1. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. *Schizophr Res.* (2009) 110:1–23. doi: 10.1016/j.schres.2009.03.005
2. Guloksuz S, Pries LK, Delespaul P, Kenis G, Luykx JJ, Lin BD, et al. Examining the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia: results from the EUGEI study. *World Psychiatry.* (2019) 18:173–82. doi: 10.1002/wps.20629
3. Bond GR, Drake RE, Becker DR. An update on individual placement and support. *World Psychiatry.* (2020) 19:390–1. doi: 10.1002/wps.20784
4. Reichenberg A, Velthorst E, Davidson M. Cognitive impairment and psychosis in schizophrenia: independent or linked conditions? *World Psychiatry.* (2019) 18:162–3. doi: 10.1002/wps.20644
5. Reininghaus U, Bohnke JR, Chavez-Baldini U, Gibbons R, Ivleva E, Clementz BA, et al. Transdiagnostic dimensions of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *World Psychiatry.* (2019) 18:67–76. doi: 10.1002/wps.20607
6. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet.* (2019) 394:939–51. doi: 10.1016/S0140-6736(19)31135-3
7. Kishimoto T, Hagi K, Nitta M, Kane JM, Correll CU. Long-term effectiveness of oral second-generation antipsychotics in patients with schizophrenia and related disorders: a systematic review and meta-analysis of direct head-to-head comparisons. *World Psychiatry.* (2019) 18:208–24. doi: 10.1002/wps.20632
8. McKenna P, Leucht S, Jauhar S, Laws K, Bighelli I. The controversy about cognitive behavioural therapy for schizophrenia. *World Psychiatry.* (2019) 18:235–6. doi: 10.1002/wps.20636
9. Reed GM, First MB, Kogan CS, Hyman SE, Gureje O, Gaebel W, et al. Innovations and changes in the ICD-11 classification of mental, behavioural and neurodevelopmental disorders. *World Psychiatry.* (2019) 18:3–19. doi: 10.1002/wps.20611
10. Gaebel W, Falkai P, Hasan A. The revised German evidence- and consensus-based schizophrenia guideline. *World Psychiatry.* (2020) 19:117–9. doi: 10.1002/wps.20706
11. Guloksuz S, Pries LK, Ten Have M, de Graaf R, van Dorsselaer S, Klingenberg B, et al. Association of preceding psychosis risk states and non-psychotic mental disorders with incidence of clinical psychosis in the general population: a prospective study in the NEMESIS-2 cohort. *World Psychiatry.* (2020) 19:199–205. doi: 10.1002/wps.20755
12. Kotov R, Jonas KG, Carpenter WT, Dretsch MN, Eaton NR, Forbes MK, et al. Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): I. Psychosis superspectrum. *World Psychiatry.* (2020) 19:151–72. doi: 10.1002/wps.20730
13. McCutcheon RA, Krystal JH, Howes OD. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. *World Psychiatry.* (2020) 19:15–33. doi: 10.1002/wps.20693
14. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia-an overview. *JAMA Psychiatry.* (2020) 77:201–10. doi: 10.1001/jamapsychiatry.2019.3360
15. Moritz S, Silverstein SM, Dietrichkeit M, Gallinat J. Neurocognitive deficits in schizophrenia are likely to be less severe and less related to the disorder than previously thought. *World Psychiatry.* (2020) 19:254–5. doi: 10.1002/wps.20759
16. Singh SP, Javed A. Psychosis WPAEIAPfEIi. Early intervention in psychosis in low- and middle-income countries: a WPA initiative. *World Psychiatry.* (2020) 19:122. doi: 10.1002/wps.20708
17. Smeland OB, Frei O, Dale AM, Andreassen OA. The polygenic architecture of schizophrenia - rethinking pathogenesis and nosology. *Nat Rev Neurol.* (2020) 16:366–79. doi: 10.1038/s41582-020-0364-0
18. Taipale H, Tanskanen A, Mehtala J, Vattulainen P, Correll CU, Tiihonen J. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). *World Psychiatry.* (2020) 19:61–8. doi: 10.1002/wps.20699
19. Zandersen M, Parnas J. Borderline personality disorder or a disorder within the schizophrenia spectrum? A psychopathological study. *World Psychiatry.* (2019) 18:109–10. doi: 10.1002/wps.20598
20. Andreasen NC, Carpenter WT Jr., Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry.* (2005) 162:441–9. doi: 10.1176/appi.ajp.162.3.441
21. Bebbington PE, Craig T, Garety P, Fowler D, Dunn G, Colbert S, et al. Remission and relapse in psychosis: operational definitions based on case-note data. *Psychol Med.* (2006) 36:1551–62. doi: 10.1017/S0033291706008579
22. Haro JM, Novick D, Suarez D, Alonso J, Lepine JP, Ratcliffe M, et al. Remission and relapse in the outpatient care of schizophrenia: three-year results from the Schizophrenia Outpatient Health Outcomes study. *J Clin Psychopharmacol.* (2006) 26:571–8. doi: 10.1097/01.jcp.0000246215.49271.b8
23. Vita A, Barlati S. Recovery from schizophrenia: is it possible? *Curr Opin Psychiatry.* (2018) 31:246–55. doi: 10.1097/YCO.0000000000000407
24. Jaaskelainen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, et al. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull.* (2013) 39:1296–306. doi: 10.1093/schbul/sbs130
25. Liberman RP, Kopelowicz A. Recovery from schizophrenia: a concept in search of research. *Psychiatr Serv.* (2005) 56:735–42. doi: 10.1176/appi.ps.56.6.735
26. Davidson M. Cognitive impairment as a diagnostic criterion and treatment target in schizophrenia. *World Psychiatry.* (2019) 18:171–2. doi: 10.1002/wps.20651
27. Harvey PD, Bellack AS. Toward a terminology for functional recovery in schizophrenia: is functional remission a viable concept? *Schizophr Bull.* (2009) 35:300–6. doi: 10.1093/schbul/sbn171
28. Harvey PD, Strassnig MT. Cognition and disability in schizophrenia: cognition-related skills deficits and decision-making challenges add to morbidity. *World Psychiatry.* (2019) 18:165–7. doi: 10.1002/wps.20647
29. Shrivastava A, Johnston M, Shah N, Bureau Y. Redefining outcome measures in schizophrenia: integrating social and clinical parameters. *Curr Opin Psychiatry.* (2010) 23:120–6. doi: 10.1097/YCO.0b013e328336662e
30. Falkai P, Schmitt A. The need to develop personalized interventions to improve cognition in schizophrenia. *World Psychiatry.* (2019) 18:170. doi: 10.1002/wps.20650
31. Fleischhacker WW, Arango C, Arteel P, Barnes TR, Carpenter W, Duckworth K, et al. Schizophrenia–time to commit to policy change. *Schizophr Bull.* (2014) 40 Suppl 3:S165–94. doi: 10.1093/schbul/sbu006

32. Galderisi S, Rossi A, Rocca P, Bertolino A, Mucci A, Bucci P, et al. The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. *World Psychiatry.* (2014) 13:275–87. doi: 10.1002/wps.20167
33. Galderisi S, Rucci P, Kirkpatrick B, Mucci A, Gibertoni D, Rocca P, et al. Interplay among psychopathologic variables, personal resources, context-related factors, and real-life functioning in individuals with schizophrenia: a network analysis. *JAMA Psychiatry.* (2018) 75:396–404. doi: 10.1001/jamapsychiatry.2017.4607
34. Galderisi S, Rucci P, Mucci A, Rossi A, Rocca P, Bertolino A, et al. The interplay among psychopathology, personal resources, context-related factors and real-life functioning in schizophrenia: stability in relationships after 4 years and differences in network structure between recovered and non-recovered patients. *World Psychiatry.* (2020) 19:81–91. doi: 10.1002/wps.20700
35. Green MF, Hellemann G, Horan WP, Lee J, Wynn JK. From perception to functional outcome in schizophrenia: modeling the role of ability and motivation. *Arch Gen Psychiatry.* (2012) 69:1216–24. doi: 10.1001/archgenpsychiatry.2012.652
36. Keefe RSE. Why are there no approved treatments for cognitive impairment in schizophrenia? *World Psychiatry.* (2019) 18:167–8. doi: 10.1002/wps.20648
37. Mucci A, Galderisi S, Gibertoni D, Rossi A, Rocca P, Bertolino A, et al. Factors associated with real-life functioning in persons with schizophrenia in a 4-year follow-up study of the Italian Network for Research on Psychoses. *JAMA Psychiatry.* (2021) 78:550–9.
38. Sahakian BJ, Savulich G. Innovative methods for improving cognition, motivation and wellbeing in schizophrenia. *World Psychiatry.* (2019) 18:168–70. doi: 10.1002/wps.20649
39. Strassnig MT, Raykov T, O'Gorman C, Bowie CR, Sabbag S, Durand D, et al. Determinants of different aspects of everyday outcome in schizophrenia: the roles of negative symptoms, cognition, and functional capacity. *Schizophr Res.* (2015) 165:76–82. doi: 10.1016/j.schres.2015.03.033
40. Ventura J, Subotnik KL, Gitlin MJ, Gretchen-Doorly D, Ered A, Villa KF, et al. Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later. *Schizophr Res.* (2015) 161:407–13. doi: 10.1016/j.schres.2014.10.043
41. Leifker FR, Bowie CR, Harvey PD. Determinants of everyday outcomes in schizophrenia: the influences of cognitive impairment, functional capacity, and symptoms. *Schizophr Res.* (2009) 115:82–7. doi: 10.1016/j.schres.2009.09.004
42. Bowie CR, Reichenberg A, Patterson TL, Heaton RK, Harvey PD. Determinants of real-world functional performance in schizophrenia subjects: correlations with cognition, functional capacity, and symptoms. *Am J Psychiatry.* (2006) 163:418–25. doi: 10.1176/appi.ajp.163.3.418
43. Drake RE, Xie H, McHugo GJ, A. 16-year follow-up of patients with serious mental illness and co-occurring substance use disorder. *World Psychiatry.* (2020) 19:397–8. doi: 10.1002/wps.20793
44. Green MF, Horan WP, Lee J. Nonsocial and social cognition in schizophrenia: current evidence and future directions. *World Psychiatry.* (2019) 18:146–61. doi: 10.1002/wps.20624
45. Harvey PD. Functional recovery in schizophrenia: raising the bar for outcomes in people with schizophrenia. *Schizophr Bull.* (2009) 35:299. doi: 10.1093/schbul/sbn186
46. Ho BC, Nopoulos P, Flaum M, Arndt S, Andreasen NC. Two-year outcome in first-episode schizophrenia: predictive value of symptoms for quality of life. *Am J Psychiatry.* (1998) 155:1196–201. doi: 10.1176/ajp.155.9.1196
47. Hultman CM, Wieselgren IM, Ohman A. Relationships between social support, social coping and life events in the relapse of schizophrenic patients. *Scand J Psychol.* (1997) 38:3–13. doi: 10.1111/1467-9450.00002
48. Livingston JD, Boyd JE. Correlates and consequences of internalized stigma for people living with mental illness: a systematic review and meta-analysis. *Soc Sci Med.* (2010) 71:2150–61. doi: 10.1016/j.socscimed.2010.09.030
49. Torgalsboen AK. Sustaining full recovery in schizophrenia after 15 years: does resilience matter? *Clin Schizophr Relat Psychoses.* (2012) 5:193–200. doi: 10.3371/CSRP.5.4.3
50. Ventura J, Hellemann GS, Thames AD, Koellner V, Nuechterlein KH. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. *Schizophr Res.* (2009) 113:189–99. doi: 10.1016/j.schres.2009.03.035
51. Maj M, van Os J, De Hert M, Gaebel W, Galderisi S, Green MF, et al. The clinical characterization of the patient with primary psychosis aimed at personalization of management. *World Psychiatry.* (2021) 20:4–33. doi: 10.1002/wps.20809
52. Vancampfort D, Firth J, Correll CU, Solmi M, Siskind D, De Hert M, et al. The impact of pharmacological and non-pharmacological interventions to improve physical health outcomes in people with schizophrenia: a meta-review of meta-analyses of randomized controlled trials. *World Psychiatry.* (2019) 18:53–66. doi: 10.1002/wps.20614
53. Ahmed AO, Murphy CF, Latoussakis V, McGovern KE, English J, Bloch A, et al. An examination of neurocognition and symptoms as predictors of post-hospital community tenure in treatment resistant schizophrenia. *Psychiatry Res.* (2016) 236:47–52. doi: 10.1016/j.psychres.2016.01.001
54. Chang WC, Hui CL, Chan SK, Lee EH, Chen EY. Impact of avolition and cognitive impairment on functional outcome in first-episode schizophrenia-spectrum disorder: a prospective one-year follow-up study. *Schizophr Res.* (2016) 170:318–21. doi: 10.1016/j.schres.2016.01.004
55. Fu S, Czajkowski N, Rund BR, Torgalsboen AK. The relationship between level of cognitive impairments and functional outcome trajectories in first-episode schizophrenia. *Schizophr Res.* (2017) 190:144–9. doi: 10.1016/j.schres.2017.03.002
56. Galderisi S, Bucci P, Mucci A, Kirkpatrick B, Pini S, Rossi A, et al. Categorical and dimensional approaches to negative symptoms of schizophrenia: focus on long-term stability and functional outcome. *Schizophr Res.* (2013) 147:157–62. doi: 10.1016/j.schres.2013.03.020
57. Galderisi S, Mucci A, Bitter I, Libiger J, Bucci P, Fleischhacker WW, et al. Persistent negative symptoms in first episode patients with schizophrenia: results from the European First Episode Schizophrenia Trial. *Eur Neuropsychopharmacol.* (2013) 23:196–204. doi: 10.1016/j.euroneuro.2012.04.019
58. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res.* (2004) 72:41–51. doi: 10.1016/j.schres.2004.09.009
59. Horan WP, Green MF, DeGroot M, Fiske A, Hellemann G, Kee K, et al. Social cognition in schizophrenia, Part 2: 12-month stability and prediction of functional outcome in first-episode patients. *Schizophr Bull.* (2012) 38:865–72. doi: 10.1093/schbul/sbr001
60. McCleery A, Lee J, Fiske AP, Ghermezi L, Hayata JN, Hellemann GS, et al. Longitudinal stability of social cognition in schizophrenia: a 5-year follow-up of social perception and emotion processing. *Schizophr Res.* (2016) 176:467–72. doi: 10.1016/j.schres.2016.07.008
61. Reichenberg A, Feo C, Prestia D, Bowie CR, Patterson TL, Harvey PD. The course and correlates of everyday functioning in schizophrenia. *Schizophr Res Cogn.* (2014) 1:e47–52. doi: 10.1016/j.scog.2014.03.001
62. Robinson DG, Woerner MG, McMeniman M, Mendelowitz A, Bilder RM. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry.* (2004) 161:473–9. doi: 10.1176/appi.ajp.161.3.473
63. Stirling J, White C, Lewis S, Hopkins R, Tantam D, Huddy A, et al. Neurocognitive function and outcome in first-episode schizophrenia: a 10-year follow-up of an epidemiological cohort. *Schizophr Res.* (2003) 65:75–86. doi: 10.1016/S0920-9964(03)00014-8
64. Daniel DG. Issues in selection of instruments to measure negative symptoms. *Schizophr Res.* (2013) 150:343–5. doi: 10.1016/j.schres.2013.07.005
65. Kern RS, Nuechterlein KH, Green MF, Baade LE, Fenton WS, Gold JM, et al. The MATRICS consensus cognitive battery, part 2: co-norming and standardization. *Am J Psychiatry.* (2008) 165:214–20. doi: 10.1176/appi.ajp.2007.07010043
66. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The brief negative symptom scale: psychometric properties. *Schizophr Bull.* (2011) 37:300–5. doi: 10.1093/schbul/sbq059
67. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. *Am J Psychiatry.* (2008) 165:203–13. doi: 10.1176/appi.ajp.2007.07010042

68. Grant PM, Best MW, Beck AT. The meaning of group differences in cognitive test performance. *World Psychiatry.* (2019) 18:163–4. doi: 10.1002/wps.20645
69. Melle I. Cognition in schizophrenia: a marker of underlying neurodevelopmental problems? *World Psychiatry.* (2019) 18:164–5. doi: 10.1002/wps.20646
70. Mucci A, Vignapiano A, Bitter I, Austin SF, Delouche C, Dollfus S, et al. A large European, multicenter, multinational validation study of the Brief Negative Symptom Scale. *Eur Neuropsychopharm.* (2019) 29:947–59. doi: 10.1016/j.euroneuro.2019.05.006
71. Couture SM, Penn DL, Roberts DL. The functional significance of social cognition in schizophrenia: a review. *Schizophr Bull.* (2006) 32(Suppl 1):S44–63. doi: 10.1093/schbul/sbl029
72. Green MF, Leitman DI. Social cognition in schizophrenia. *Schizophr Bull.* (2008) 34:670–2. doi: 10.1093/schbul/sbn045
73. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry.* (1996) 153:321–30. doi: 10.1176/ajp.153.3.321
74. Fett AK, Viechtbauer W, Dominguez MD, Penn DL, van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci Biobehav Rev.* (2011) 35:573–88. doi: 10.1016/j.neubiorev.2010.07.001
75. Kee KS, Green MF, Mintz J, Brekke JS. Is emotion processing a predictor of functional outcome in schizophrenia? *Schizophr Bull.* (2003) 29:487–97. doi: 10.1093/oxfordjournals.schbul.a007021
76. Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. *Lancet Psychiatry.* (2018) 5:664–77. doi: 10.1016/S2215-0366(18)30050-6
77. Couture SM, Granholm EL, Fish SC, A. path model investigation of neurocognition, theory of mind, social competence, negative symptoms and real-world functioning in schizophrenia. *Schizophr Res.* (2011) 125:152–60. doi: 10.1016/j.schres.2010.09.020
78. Bowie CR, Leung WW, Reichenberg A, McClure MM, Patterson TL, Heaton RK, et al. Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. *Biol Psychiatry.* (2008) 63:505–11. doi: 10.1016/j.biopsych.2007.05.022
79. Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. *Schizophr Bull.* (2006) 32:238–45. doi: 10.1093/schbul/sbj013
80. Kirkpatrick B, Fischer B. Subdomains within the negative symptoms of schizophrenia: commentary. *Schizophr Bull.* (2006) 32:246–9. doi: 10.1093/schbul/sbj054
81. Strauss GP, Esfahlani FZ, Galderisi S, Mucci A, Rossi A, Bucci P, et al. Network analysis reveals the latent structure of negative symptoms in schizophrenia. *Schizophr Bull.* (2019) 45:1033–41. doi: 10.1093/schbul/sby133
82. Rieckmann N, Reichenberg A, Bowie CR, Parrella M, White L, Friedman JI, et al. Depressed mood and its functional correlates in institutionalized schizophrenia patients. *Schizophr Res.* (2005) 77:179–87. doi: 10.1016/j.schres.2005.04.007
83. Best MW, Gupta M, Bowie CR, Harvey PD. A longitudinal examination of the moderating effects of symptoms on the relationship between functional competence and real world functional performance in schizophrenia. *Schizophr Res Cogn.* (2014) 1:90–5. doi: 10.1016/j.scog.2014.03.002
84. Pogue-Geile MF, Harrow M. Negative and positive symptoms in schizophrenia and depression: a followup. *Schizophr Bull.* (1984) 10:371–87. doi: 10.1093/schbul/10.3.371
85. Norman RM, Malla AK, Cortese L, Cheng S, Diaz K, McIntosh E, et al. Symptoms and cognition as predictors of community functioning: a prospective analysis. *Am J Psychiatry.* (1999) 156:400–5.
86. Tait L, Birchwood M, Trower P. Adapting to the challenge of psychosis: personal resilience and the use of sealing-over (avoidant) coping strategies. *Br J Psychiatry.* (2004) 185:410–5. doi: 10.1192/bjp.185.5.410
87. Tait L, Birchwood M, Trower P, A. new scale (SES) to measure engagement with community mental health services. *J Ment Health.* (2002) 11:191–8. doi: 10.1080/09638230020023570-2
88. Gerlinger G, Hauser M, De Hert M, Lacluyse K, Wampers M, Correll CU. Personal stigma in schizophrenia spectrum disorders: a systematic review of prevalence rates, correlates, impact and interventions. *World Psychiatry.* (2013) 12:155–64. doi: 10.1002/wps.20040
89. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* (1987) 13:261–76. doi: 10.1093/schbul/13.2.261
90. Galderisi S, Mucci A, Dollfus S, Nordentoft M, Falkai P, Kaiser S, et al. EPA guidance on assessment of negative symptoms in schizophrenia. *Eur Psychiatry.* (2021) 64:e23. doi: 10.1192/j.eurpsy.2021.11
91. Garcia-Portilla MP, Garcia-Alvarez L, Saiz PA, Al-Halabi S, Bobes-Bascaran MT, Bascaran MT, et al. Psychometric evaluation of the negative syndrome of schizophrenia. *Eur Arch Psychiatry Clin Neurosci.* (2015) 265:559–66. doi: 10.1007/s00406-015-0595-z
92. Mucci A, Galderisi S, Merlotti E, Rossi A, Rocca P, Bucci P, et al. The Brief Negative Symptom Scale (BNSS): Independent validation in a large sample of Italian patients with schizophrenia. *Eur Psychiatry.* (2015) 30:641–7. doi: 10.1016/j.eurpsy.2015.01.014
93. Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. *Br J Psychiatry Suppl.* (1993) 22:39–44. doi: 10.1192/S0007125000292581
94. Gerlach J, Korsgaard S, Clemmesen P, Lauersen AM, Magelund G, Noring U, et al. The St. Hans Rating Scale for extrapyramidal syndromes: reliability and validity. *Acta Psychiatr Scand.* (1993) 87:244–52. doi: 10.1111/j.1600-0447.1993.tb03366.x
95. Kerr SL, Neale JM. Emotion perception in schizophrenia: specific deficit or further evidence of generalized poor performance? *J Abnorm Psychol.* (1993) 102:312–8. doi: 10.1037/0021-843X.102.2.312
96. McDonald S, Bornhofen C, Shum D, Long E, Saunders C, Neulinger K. Reliability and validity of The Awareness of Social Inference Test (TASIT): a clinical test of social perception. *Disabil Rehabil.* (2006) 28:1529–42. doi: 10.1080/09638280600646185
97. Friborg O, Hjemdal O, Rosenvinge JH, Martinussen M, A. new rating scale for adult resilience: what are the central protective resources behind healthy adjustment? *Int J Methods Psychiatr Res.* (2003) 12:65–76. doi: 10.1002/mpr.143
98. Ritsher JB, Otilingam PG, Grajales M. Internalized stigma of mental illness: psychometric properties of a new measure. *Psychiatry Res.* (2003) 121:31–49. doi: 10.1016/j.psychres.2003.08.008
99. Mausbach BT, Harvey PD, Goldman SR, Jeste DV, Patterson TL. Development of a brief scale of everyday functioning in persons with serious mental illness. *Schizophr Bull.* (2007) 33:1364–72. doi: 10.1093/schbul/sbm014
100. Mucci A, Rucci P, Rocca P, Bucci P, Gibertoni D, Merlotti E, et al. The specific level of functioning scale: construct validity, internal consistency and factor structure in a large Italian sample of people with schizophrenia living in the community. *Schizophr Res.* (2014) 159:144–50. doi: 10.1016/j.schres.2014.07.044
101. Schneider LC, Struening EL, SLOF. a behavioral rating scale for assessing the mentally ill. *Soc Work Res Abstr.* (1983) 19:9–21. doi: 10.1093/swra/19.3.9
102. Harvey PD, Raykov T, Twamley EW, Vella L, Heaton RK, Patterson TL. Validating the measurement of real-world functional outcomes: phase I results of the VALERO study. *Am J Psychiatry.* (2011) 168:1195–201. doi: 10.1176/appi.ajp.2011.10121723
103. Leifker FR, Patterson TL, Heaton RK, Harvey PD. Validating measures of real-world outcome: the results of the VALERO expert survey and RAND panel. *Schizophr Bull.* (2011) 37:334–43. doi: 10.1093/schbul/sbp044
104. Merlotti E, Mucci A, Bucci P, Nardi A, Galderisi S. Italian version of the "Brief Negative Symptom Scale". *J Psychopathol.* (2015) 20:199–215.
105. Montemagni C, Rocca P, Mucci A, Galderisi S, Maj M. Italian version of the "Specific Level of Functioning". *J Psychopathol.* (2015) 21:287–96.
106. Mancuso F, Mucci A, Galderisi S. MATRICS consensus cognitive battery: storia e sviluppo della batteria cognitiva. *Nòos - Aggiornamenti Psichiatria.* (2013) 19:83–98. doi: 10.1722/3349.33203
107. Mucci A, Galderisi S, Green MF, Nuechterlein K, Rucci P, Gibertoni D, et al. Familial aggregation of MATRICS Consensus Cognitive Battery scores in a large sample of outpatients with schizophrenia and their unaffected relatives. *Psychol Med.* (2018) 48:1359–66. doi: 10.1017/S0033291717002902

108. Rocca P, Galderisi S, Rossi A, Bertolino A, Rucci P, Gibertoni D, et al. Social cognition in people with schizophrenia: a cluster-analytic approach. *Psychol Med.* (2016) 46:2717–29. doi: 10.1017/S0033291716001100
109. Beran TN, Violato C. Structural equation modeling in medical research: a primer. *BMC Res Notes.* (2010) 3:267. doi: 10.1186/1756-0500-3-267
110. Forbes MK, Wright AGC, Markon KE, Krueger RF. The network approach to psychopathology: promise versus reality. *World Psychiatry.* (2019) 18:272–3. doi: 10.1002/wps.20659
111. Hevey D. Network analysis: a brief overview and tutorial. *Health Psychol Behav Med.* (2018) 6:301–28. doi: 10.1080/21642850.2018.1521283
112. Galderisi S, Rossi A, Rocca P, Bertolino A, Mucci A, Bucci P, et al. Pathways to functional outcome in subjects with schizophrenia living in the community and their unaffected first-degree relatives. *Schizophr Res.* (2016) 175:154–60. doi: 10.1016/j.schres.2016.04.043
113. Rossi A, Amore M, Galderisi S, Rocca P, Bertolino A, Aguglia E, et al. The complex relationship between self-reported 'personal recovery' and clinical recovery in schizophrenia. *Schizophr Res.* (2018) 192:108–12. doi: 10.1016/j.schres.2017.04.040
114. Rossi A, Galderisi S, Rocca P, Bertolino A, Mucci A, Rucci P, et al. The relationships of personal resources with symptom severity and psychosocial functioning in persons with schizophrenia: results from the Italian Network for Research on Psychoses study. *Eur Arch Psychiatry Clin Neurosci.* (2017) 267:285–94. doi: 10.1007/s00406-016-0710-9
115. Rossi A, Galderisi S, Rocca P, Bertolino A, Rucci P, Gibertoni D, et al. Personal resources and depression in schizophrenia: the role of self-esteem, resilience and internalized stigma. *Psychiatry Res.* (2017) 256:359–64. doi: 10.1016/j.psychres.2017.06.079
116. Rocca P, Galderisi S, Rossi A, Bertolino A, Rucci P, Gibertoni D, et al. Disorganization and real-world functioning in schizophrenia: results from the multicenter study of the Italian Network for Research on Psychoses. *Schizophr Res.* (2018) 201:105–12. doi: 10.1016/j.schres.2018.06.003
117. Bucci P, Galderisi S, Mucci A, Rossi A, Rocca P, Bertolino A, et al. Premorbid academic and social functioning in patients with schizophrenia and its associations with negative symptoms and cognition. *Acta Psychiatr Scand.* (2018) 138:253–66. doi: 10.1111/acps.12938
118. Bowie CR. Cognitive remediation for severe mental illness: state of the field and future directions. *World Psychiatry.* (2019) 18:274–5. doi: 10.1002/wps.20660
119. Amore M, Murri MB, Calcagno P, Rocca P, Rossi A, Aguglia E, et al. The association between insight and depressive symptoms in schizophrenia: Undirected and Bayesian network analyses. *Eur Psychiatry.* (2020) 63:1–21. doi: 10.1192/j.eurpsy.2020.45
120. Monteleone P, Cascino G, Monteleone AM, Rocca P, Rossi A, Bertolino A, et al. Prevalence of antipsychotic-induced extrapyramidal symptoms and their association with neurocognition and social cognition in outpatients with schizophrenia in the "real-life". *Prog Neuropsychopharmacol Biol Psychiatry.* (2021) 109:110250. doi: 10.1016/j.pnpbp.2021.110250
121. Gennarelli M, Monteleone P, Minelli A, Monteleone AM, Rossi A, Rocca P, et al. Genome-wide association study detected novel susceptibility genes for social cognition impairment in people with schizophrenia. *World J Biol Psychiatry.* (2021) 1–9. doi: 10.1080/15622975.2021.1907722. [Epub ahead of print].
122. Piluso G, Monteleone P, Galderisi S, Giugliano T, Bertolino A, Rocca P, et al. Assessment of *de novo* copy-number variations in Italian patients with schizophrenia: detection of putative mutations involving regulatory enhancer elements. *World J Biol Psychiatry.* (2019) 20:126–36. doi: 10.1080/15622975.2017.1395072
123. Ventura J, Reise SP, Keefe RS, Baade LE, Gold JM, Green MF, et al. The Cognitive Assessment Interview (CAI): development and validation of an empirically derived, brief interview-based measure of cognition. *Schizophr Res.* (2010) 121:24–31. doi: 10.1016/j.schres.2010.04.016
124. Palumbo D, Bucci P, Mucci A, Pietrafesa D, Giordano GM, Vignapiano A, et al. Inter-rater reliability and psychometric characteristics of the Italian version of the Cognitive Assessment Interview (CAI). *J Psychopathol.* (2019) 25:85–114.
125. Rocca P, Brasso C, Montemagni C, Bellino S, Rossi A, Bertolino A, et al. Accuracy of self-assessment of real-life functioning in schizophrenia. *NPJ Schizophr.* (2021) 7:11. doi: 10.1038/s41537-021-00140-9
126. Giordano GM, Koenig T, Mucci A, Vignapiano A, Amodio A, Di Lorenzo G, et al. Neurophysiological correlates of Avolition-apathy in schizophrenia: A resting-EEG microstates study. *Neuroimage Clin.* (2018) 20:627–36. doi: 10.1016/j.nicl.2018.08.031
127. Vignapiano A, Mucci A, Giordano GM, Di Lorenzo G, Ferrentino F, Altamura M, et al. Neurophysiological correlates of negative symptom domains: an auditory oddball study in schizophrenia. *Eur Psychiat.* (2019) 56:S287–S8. doi: 10.1016/S0924-977X(16)31527-9
128. Dell'Osso L, Carpita B, Cremone IM, Gesi C, D'Ermo A, De Iorio G, et al. Autism spectrum in patients with schizophrenia: correlations with real-life functioning, resilience, and coping styles. *CNS Spectr.* (2021) 1–11. doi: 10.1017/S1092852921000353. [Epub ahead of print].
129. Vita A, Barlati S, Deste G, Rocca P, Rossi A, Bertolino A, et al. The influence of autistic symptoms on social and non-social cognition and on real-life functioning in people with schizophrenia: Evidence from the Italian Network for Research on Psychoses multicenter study. *Eur Psychiatry.* (2020) 63:e98. doi: 10.1192/j.eurpsy.2020.99
130. Cohen AS, Schwartz E, Le TP, Fedechko T, Kirkpatrick B, Strauss GP. Using biobehavioral technologies to effectively advance research on negative symptoms. *World Psychiatry.* (2019) 18:103–4. doi: 10.1002/wps.20593
131. Newson JJ, Thiagarajan TC, EEG. Frequency Bands in Psychiatric Disorders: A Review of Resting State Studies. *Front Hum Neurosci.* (2018) 12:521. doi: 10.3389/fnhum.2018.00521
132. da Cruz JR, Favrod O, Roinishvili M, Chkonia E, Brand A, Mohr C, et al. EEG microstates are a candidate endophenotype for schizophrenia. *Nat Commun.* (2020) 11:3089. doi: 10.1038/s41467-020-16914-1
133. Galderisi S, Mucci A, Volpe U, Boutros N. Evidence-based medicine and electrophysiology in schizophrenia. *Clin EEG Neurosci.* (2009) 40:62–77. doi: 10.1177/155005940904000206
134. Grohn C, Norgren E, Eriksson L, A. systematic review of the neural correlates of multisensory integration in schizophrenia. *Schizophr Res Cogn.* (2022) 27:100219. doi: 10.1016/j.scog.2021.100219
135. Li X, Honda S, Nakajima S, Wada M, Yoshida K, Daskalakis ZJ, et al. TMS-EEG research to elucidate the pathophysiological neural bases in patients with schizophrenia: a systematic review. *J Pers Med.* (2021) 11:388. doi: 10.3390/jpm11050388
136. Zheng Z, Zheng P, Zou X. Association between schizophrenia and autism spectrum disorder: A systematic review and meta-analysis. *Autism Res.* (2018) 11:1110–9. doi: 10.1002/aur.1977
137. Kastner A, Begemann M, Michel TM, Everts S, Stepniak B, Bach C, et al. Autism beyond diagnostic categories: characterization of autistic phenotypes in schizophrenia. *BMC Psychiatry.* (2015) 15:115. doi: 10.1186/s12888-015-0494-x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 20 December 2021
doi: 10.3389/fpsyt.2021.790745

Tracing Links Between Early Auditory Information Processing and Negative Symptoms in Schizophrenia: An ERP Study

Giulia M. Giordano[1], Francesco Brando[1], Andrea Perrottelli[1], Giorgio Di Lorenzo[2], Alberto Siracusano[2], Luigi Giuliani[1], Pasquale Pezzella[1], Mario Altamura[3], Antonello Bellomo[3], Giammarco Cascino[4], Antonio Del Casale[5], Palmiero Monteleone[4], Maurizio Pompili[5], Silvana Galderisi[1], Mario Maj[1] and the Italian Network for Research on Psychoses*

[1] Department of Psychiatry, University of Campania "Luigi Vanvitelli", Naples, Italy, [2] Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy, [3] Department of Clinical and Experimental Medicine, Psychiatry Unit, University of Foggia, Foggia, Italy, [4] Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", Section of Neurosciences, University of Salerno, Salerno, Italy, [5] Department of Neurosciences, Mental Health and Sensory Organs, S. Andrea Hospital, University of Rome "La Sapienza", Rome, Italy

OPEN ACCESS

Edited by:
Ingrid Melle,
University of Oslo, Norway

Reviewed by:
Joshua T. Kantrowitz,
Columbia University, United States
Stefano Barlati,
University of Brescia, Italy

***Correspondence:**
Silvana Galderisi
silvana.galderisi@gmail.com

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: 07 October 2021
Accepted: 19 November 2021
Published: 20 December 2021

Citation:
Giordano GM, Brando F, Perrottelli A, Di Lorenzo G, Siracusano A, Giuliani L, Pezzella P, Altamura M, Bellomo A, Cascino G, Del Casale A, Monteleone P, Pompili M, Galderisi S, Maj M and the Italian Network for Research on Psychoses (2021) Tracing Links Between Early Auditory Information Processing and Negative Symptoms in Schizophrenia: An ERP Study. Front. Psychiatry 12:790745. doi: 10.3389/fpsyt.2021.790745

Background: Negative symptoms represent a heterogeneous dimension with a strong impact on functioning of subjects with schizophrenia (SCZ). Five constructs are included in this dimension: anhedonia, asociality, avolition, blunted affect, and alogia. Factor analyses revealed that these symptoms cluster in two domains: experiential domain (avolition, asociality, and anhedonia) and the expressive deficit (alogia and blunted affect), that might be linked to different neurobiological alterations. Few studies investigated associations between N100, an electrophysiological index of early sensory processing, and negative symptoms, reporting controversial results. However, none of these studies investigated electrophysiological correlates of the two negative symptom domains.

Objectives: The aim of our study was to evaluate, within the multicenter study of the Italian Network for Research on Psychoses, the relationships between N100 and negative symptom domains in SCZ.

Methods: Auditory N100 was analyzed in 114 chronic stabilized SCZ and 63 healthy controls (HCs). Negative symptoms were assessed with the Brief Negative Symptom Scale (BNSS). Repeated measures ANOVA and correlation analyses were performed to evaluate differences between SCZ and HCs and association of N100 features with negative symptoms.

Results: Our findings demonstrated a significant N100 amplitude reduction in SCZ compared with HCs. In SCZ, N100 amplitude for standard stimuli was associated with negative symptoms, in particular with the expressive deficit domain. Within the expressive deficit, blunted affect and alogia had the same pattern of correlation with N100.

Conclusion: Our findings revealed an association between expressive deficit and N100, suggesting that these negative symptoms might be related to deficits in early auditory processing in SCZ.

Keywords: schizophrenia, negative symptoms, EEG, ERP, N100

INTRODUCTION

Negative symptoms represent an unmet therapeutic need in the care of subjects with schizophrenia (SCZ) (1, 2). Indeed, these symptoms do not respond satisfactorily to current available treatments and are regarded as one of the main determinants of the poor outcome of SCZ (1–6). According to the present conceptualization, negative symptoms are described as five individual symptoms: avolition (reduced interest and motivation for goal-directed activities), asociality (diminished social drive or interest and desire for affiliation), anhedonia (reduced ability to experience or anticipate pleasure), blunted affect (reduced intensity and range of emotional expression), and alogia (reduced spontaneous speech and loss of conversational fluency) (2, 7–10). Different factor analytic studies demonstrated the existence of two negative symptom domains, which are named as experiential domain, including anhedonia, avolition, and asociality, and the expressive deficit domain, including blunted affect and alogia (2, 8, 10–14). Clustering into two domains is also supported by studies that showed how these domains are associated with different behavioral and neurobiological alterations (8, 10, 15, 16). The experiential domain is associated with abnormalities in different aspects of the motivational processes, which might be related to the motivational value system (research domain criteria-RDoC-positive valence system) (17, 18) or to the salience system (8, 19). The former refers to motivational aspects such as reward prediction, value encoding, action outcome contingency learning, and the integration of goal-directed behavior and experienced value (8, 10, 16, 20–45). On the other side, the salience system refers to motivational aspects related to orientation toward salient stimuli (aversive or rewarding stimuli), cognitive activation, and general motivation (8, 46–48). Another hypothesis, which has not been entirely supported by previous studies (8), poses at the bases of the experiential domain deficits in the executive control of behavior (16, 49–53).

The pathophysiology of the expressive deficit domain has been less investigated, in comparison to the experiential domain (8). Symptoms that belong to the expressive deficit have been found to relate to deficits in neurocognitive and social cognition abilities and to neurological soft signs, suggesting that these symptoms are probably subtended by a diffuse neurodevelopmental disconnectivity (8, 54, 55). In particular, it is possible that the expressive deficit domain is related to limited availability of cognitive resources. According to this hypothesis, alogia might depend on deficits in semantic memory organization and verbal fluency. Furthermore, it has been suggested that in "high-load" situations (e.g., social situations) subjects might allocate less cognitive resources to speech production due to the high cognitive demands required from the surrounding environment (15). Another hypothesis has indicated emotion expression and emotion perception deficits as possible candidate mechanisms that subtend this domain and in particular blunted affect (15, 56, 57).

Electrophysiology (EEG), which is a non-invasive and inexpensive technique with a high temporal resolution, represents a valid method to identify abnormalities of cortical brain functions and to investigate the neurophysiological bases of different psychopathological aspects, such as negative symptoms (58–61). Specifically, the analysis of event-related potentials (ERPs) represents an objective tool to study mental processes, due to its high temporal resolution in capturing responses to internal and external events (62, 63). However, so far, findings regarding associations between ERPs and negative symptoms are scattered/scarce and often inconsistent. Three studies investigated abnormalities of reward anticipation and evaluation processes (assessed using the stimulus preceding negativity-SPN, P300, and N200) and their eventual association with negative symptoms (64–66). Wynn et al. (66) found that the SPN was associated with trait anhedonia and with the total negative symptoms score. P300 (64) and N200 (65) amplitude did not correlate with the two negative symptom domains, while the P300 amplitude was found to be associated with social anhedonia (64). However, other studies found that these ERP indices correlated also with other psychopathological aspects, for instance P300 was associated also to positive and disorganized dimensions. The inconsistence about previous findings might be due to different factors, such as the heterogeneity of negative symptoms, the improper conceptualization of these symptoms, the use of assessment instruments often not in line with the current conceptualization of negative symptoms and the small sample sizes of the studies.

Another ERP that has been extensively studied in SCZ is the N100, which is thought to measure early perceptual processing. N100 is one of the largest auditory and visually evoked ERP and can be visualized as a negative deflection peaking between 80 and 120 ms after the stimulus onset (67). The N100 has gained attention due to the fact that its alterations (a reduction in N100 amplitude and delayed latency of its peak) represent well-replicated findings in SCZ, since the early phases of the disorder (67–78). Furthermore, aberrations of N100 in schizophrenia include also deficits in N100 gating ratio probably due to decreased N100 amplitude to initial stimulus, whereas the N100 amplitudes to the repeated stimulus did not systematically vary between patients and controls (79). Previous findings demonstrated that abnormalities in sensory gating and decreased N100 amplitude might be associated with deficits in processing of auditory salience, auditory verbal hallucinations (80–82), antipsychotic intake (67), and attention deficits (83, 84). Subjects

with primary and persistent negative symptoms demonstrated a reduction of N100 but not of other ERP components such as P300 (69, 85), suggesting a link between early information processing and primary negative symptoms.

Alterations in N100, reflecting deficits in gating and early sensory processing, are consistently found in SCZ, and contribute to poor outcome (86–88). Indeed, some "cascade" models have hypothesized that impairment in early visual and auditory processing might contribute to deterioration of higher-level processing, such as social cognition. These deficits might be related to negative symptoms and might contribute to impairment in functioning (86–88).

Therefore, it seems to be of great interest the investigation of eventual associations between N100 impairment and negative symptoms. However, also in this case findings are inconsistent. In particular, two studies investigated abnormalities in ERPs in subjects with deficit schizophrenia (subjects with primary and persistent negative symptoms) as compared to subjects with non-deficit schizophrenia and healthy controls (HCs) (69, 89). One study (69) reported an association between N100 and primary and persistent negative symptoms. The authors of this study found that subjects with deficit schizophrenia, as compared to subjects with non-deficit schizophrenia and HCs, had a reduction in N100 amplitude for target tones and also topographic abnormalities for standard tones in brain areas involved in the evaluation of motivational relevance of events, auditory discrimination, and memory retrieval (69).

In contrast, the study conducted by Li et al. failed to find any specific associations between primary and persistent negative symptoms and N100, since both subjects with deficit and those with non-deficit schizophrenia presented the same alterations in N100 (reduced amplitude and delayed latency) as compared to HCs (89). Other two studies did not find a significant correlation between N100 and negative symptom severity (90, 91). While in a small sample of men with recent-onset psychosis, a correlation was found between N100 and negative symptom severity (85). In particular, the authors reported that men with recent onset psychosis had lower right-anterior N100, as compared to HCs, and that this abnormality correlated with the severity of negative symptoms, measured with the positive and negative syndrome scale (PANSS) (92). Starting from the assumption that the main generator of the anterior N100 is the anterior cingulate cortex, these results suggested that negative symptoms might be due to abnormalities in anterior cingulate cortex in modulating signal to noise ratio (85).

However, the majority of the above-mentioned studies (85, 89–91) used first generation rating scales, such as the PANSS (92) and the scale for the assessment of negative symptoms (SANS) (93) to assess negative symptoms. These assessment instruments present some limitations, as they include aspects that actually are not conceptualized as negative symptoms, but are mostly related to cognitive functions and disorganization (2). Furthermore, the study of Li et al. (89) used a proxy from the PANSS for categorizing subjects with deficit and non-deficit schizophrenia. However, it has been demonstrated that the proxy for categorizing DS and NDS patients has some problems in terms of face validity and temporal stability (2). The association between N100 abnormalities with the two negative symptom domains in SCZ has never been investigated.

Therefore, in the light of above observations, our study aims to fill the gap investigating in SCZ the relationships between N100 and the two negative symptom domains, evaluated with state-of-the-art instruments, in a large sample of SCZ.

To achieve this aim, the study investigated: (1) the differences in N100 parameters between subjects with SCZ and HCs; (2) the associations between N100 parameters with negative symptom domains in SCZ.

METHODS

Study Participants

The study has been conducted as part of the add-on EEG study of the Italian Network for Research on Psychoses (3). One hundred and forty-eight SCZ and 70 HCs were recruited for the study, at five research sites in Naples, Foggia, Rome "Tor Vergata", Rome "Sapienza", and Salerno. The SCZ sample included individuals seen at the outpatient units of the five mentioned Italian university psychiatric clinics. All patients had a diagnosis of schizophrenia according to DSM-IV, confirmed with the Structured Clinical Interview for DSM IV-Patient version (SCID-I-P), and an age between 18 and 65 years.

The HCs sample was recruited from the community at the same sites mentioned above. Inclusion criteria for HCs were the absence of a current or lifetime Axis I or II psychiatric diagnosis. Exclusion criteria for both groups were: (a) a history of head trauma with loss of consciousness; (b) a history of moderate to severe mental retardation or of neurological diseases; (c) a history of alcohol and/or substance abuse in the last six months; (d) current pregnancy or lactation; and (e) inability to provide an informed consent. Schizophrenia with treatment modifications and/or hospitalization due to symptom exacerbation in the last three months were excluded.

The Ethics Committee of the involved institutions approved the electrophysiological add-on study. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All participants signed a written informed consent to participate after receiving a detailed explanation of the study procedures and goals.

Clinical and Neurocognitive Assessments

All subjects recruited were evaluated for sociodemographic variables such as age, education, and gender, through a clinical form filled using every available source of information.

For SCZ, a semi-structured interview, the Brief Negative Symptom Scale (BNSS) was used to assess negative symptoms (94, 95). The scale includes 13 items, organized into six subscales (blunted affect, alogia, avolition, anhedonia, asociality, and a control subscale named distress). All the items are rated on a 7-point (0–6) scale, thus ranging from absent (0) to moderate (3) to extremely severe (6) symptoms (except distress for which the severity rating is reversed: 0 normal distress and 6 absent).

With regard to the two domains, the experiential domain was computed by summing the scores on the subscales anhedonia, avolition, and asociality; the expressive deficit was computed

by summing the scores on the subscales blunted affect and alogia (94).

The PANSS was used to rate the severity of positive symptoms and disorganization (92). All items are rated on a 7-point scale from 1 to 7, ranging from absent (1) to moderate (4) to extremely severe (7). We also assessed depressive symptoms using the Calgary Depression Scale for Schizophrenia (CDSS) (96) and extrapyramidal symptoms using the St. Hans rating scale (SHRS) (97).

EEG Recording Procedure

EEGs were recorded using two highly comparable EEG recording systems: EASYS2 (Brainscope, Prague) and Galileo MIZAR-sirius (EBNeuro, Florence). Before starting the study, a harmonization of the amplifier settings and recording procedure was carried out to ensure the same settings in all the centers. All EEGs were recorded using a cap electrode system with 29 unipolar leads (Fpz, Fz, Cz, Pz, Oz, F3, F4, C3, C4, FC5, FC6, P3, P4, O1, O2, Fp1, Fp2, F7, F8, T3, T4, T5, T6, AF3, AF4, PO7, PO8, right mastoid, and left mastoid), which were placed following the 10–20 system. All the leads were referenced to the linked earlobes (a resistor of 10 kΩ was interposed between the earlobe leads). A ground electrode was placed on the forehead.

For artifact monitoring, a horizontal electro-oculogram (hEOG) was recorded from the epicanthus of each eye, and a vertical EOG (vEOG) from the leads beneath and above the right eye. All impedances of the leads were kept below 5 kΩ. The EEG data were filtered with a band-pass of 0.15–70 Hz and recorded with a sampling rate of 512 Hz.

A calibration was performed for all channels, using a 50 μV sine wave, before each recording session. Subjects were seated in a reclining chair, in a sound attenuated room, minimizing eye movement or muscle tension. Subjects performed an auditory "odd-ball" task during which 320 standard stimuli (1,500 Hz, 80 dB) and 80 target stimuli, deviant for their frequency (1,000 Hz, 80 dB), were played. Patient were asked to press the button as fast as possible upon the appearance of every target stimulus. Participants who scored <60% on the behavioral target detection task were excluded from the analysis.

Participants were instructed not to drink coffee or tea and to abstain from smoking cigarettes in the 2 h before the beginning of the recording session and did not take psychotropic medications in the morning. Information on the quality of sleep during the night prior to the recording was collected and the EEG session was postponed if the subject reported a non-restoring sleep.

EEG Data Preprocessing

One expert from the coordinating center (Naples) using Brain Vision Analyzer software (Brain Products, Munich, Germany) performed all the pre-processing analyses on data collected by the different recording sites. Data were parsed into epochs of 1,000 ms duration, which were time-locked to the onset of the cue and spanned from a 100 ms pre-stimulus period up to 900 ms post-stimulus. The recorded EEG was digitally filtered offline using a band-pass filter of 0.01–30 Hz. N100 waves were extracted in each subject by the averaging method in order to improve the signal/noise ratio, ruling out baseline activity not related to the stimulus. The N100 components for standard and target tones were analyzed separately. Trials with drifts larger than ±100 μV in any scalp electrode were rejected. If following artifacts and noisy trials removal, <40 usable target trials (50% of target trials) remained, the subject was excluded from the analysis. Data were baseline-corrected using the 100 ms time window preceding stimuli. N100 peaks were automatically marked using the "peak finder" function of Brain Analyzer, as the most negative peak point ranging from 80 to 120 ms post-stimulus. We analyzed amplitude and latency of N100 from the Fz, Cz, and Pz electrodes. Target stimuli also elicited a later auditory ERP known as the P3b, which is related to the allocation of attentive resources toward task relevant tones. Although the current study aimed to characterize the very early processing stages of auditory perception rather than higher-order processing phases, a control analysis was carried out to verify whether the later component was associated with negative symptoms. Findings concerning the difference between patients and controls for this component are reported elsewhere (Giordano et al., unpublished).

Statistical Analysis

All statistical analyses were computed using SPSS Version 22.0 (IBM Corporation, 2014). Normality tests were performed on demographic, clinical, and electrophysiological variables to test distribution of data in order to set up parametric or non-parametric tests.

Mann-Whitney U-Tests and χ^2-tests were used to compare SCZ and HCs on demographic characteristics. N100 amplitude and latency were entered separately into a two-factor repeated measures ANOVA design, incorporating electrode × stimulus type × group, with electrode and stimulus type as within subjects' variables and group as between subjects' factors. The Huynh-Feldt correction was applied. Significant main and interaction effects were further analyzed by *post-hoc* comparisons with Bonferroni adjusted alpha level using independent samples *t*-test and Mann-Whitney U-test.

Pearson or Spearman rank correlations, based on normality test results, were performed to test the relationships between N100 amplitude and latency for standard and target stimuli separately at the three midline electrodes (Fz, Cz, and Pz) with negative symptom severity (BNSS total score) in SCZ. For all the correlations considered, Bonferroni-Holm correction was applied in order to control for type-I error inflation, accordingly to the number of tests (three tests for each stimulus type, $p < 0.016$). Only when a significant correlation of BNSS total score with N100 measures was observed, correlations of the same measures with the two negative symptom domains (experiential domain and expressive deficit), and their component symptoms were further assessed (*p*-value threshold corrected accordingly to the number of symptom domains). Furthermore, if correlations with negative symptoms were statistically significant, we performed partial correlations to exclude the influence of positive and extrapyramidal symptoms, disorganization, and depression.

TABLE 1 | Demographic characteristics and illness related variables.

	SCZ ($n = 114$)	**HCs ($n = 63$)**	**Statistics**	
Gender	81 M–33 W	32 M–31 W	$\chi^2 = 7.214$; **$p = 0.007$**	
	Mean ± SD	**Mean ± SD**	***t/U***	***p***
Age	36.86 ± 9.39	34.44 ± 12.48	$U = 2982.00$	0.062
Educational level (years)	12.35 ± 3.02	13.98 ± 4.04	$U = 2759.00$	**0.0083**
BNSS total score	34.75 ± 16.31			
BNSS expressive deficit domain	11.35 ± 7.27	–	–	–
BNSS experiential domain	21.11 ± 9.25	–	–	–
PANSS total	70.50 ± 19.41	–	–	–
PANSS negative factor	15.82 ± 5.84	–	–	–
PANSS positive factor	8.33 ± 4.74	–	–	–
PANSS disorganization Factor	8.60 ± 3.49	–	–	–
CDSS total score	3.24 ± 3.92	–	–	–
SHRS global Parkinsonism	0.86 ± 1.15	–	–	–

BNSS, brief negative symptom scale; CDSS, the Calgary depression scale for schizophrenia; HCs, healthy controls; PANSS, positive and negative syndrome scale; SCZ, subjects with schizophrenia; SD, standard deviation; SHRS, the St. Hans rating scale for extrapyramidal syndrome. p-Values in bold indicate statistical significance.

TABLE 2 | Comparisons of N100 mean amplitude for standard and target stimuli between subjects with schizophrenia and healthy controls.

N100 amplitude	**SCZ ($n = 114$)**	**HCs ($n = 63$)**	**Statistics**	
	Mean ± SD	**Mean ± SD**	***t/U***	***p***
Standard–Fz	−5.71 ± 2.94	−7.78 ± 3.22	$t = 4.315$	**<0.001**
Standard–Cz	−5.34 ± 2.79	−7.06 ± 2.91	$t = 3.869$	**<0.001**
Standard–Pz	−2.58 ± 2.01	−3.74 ± 1.87	$t = 3.752$	**<0.001**
Target–Fz	−6.56 ± 3.18	−8.91 ± 3.68	$U = 2165.00$	**<0.001**
Target–Cz	−5.94 ± 3.34	−7.69 ± 3.45	$t = 3.292$	**<0.01**
Target–Pz	−2.55 ± 2.42	−4.04 ± 2.22	$U = 2280.00$	**<0.001**

HCs, healthy controls; SCZ, subjects with schizophrenia; SD, standard deviation. p-Values in bold indicate statistical significance.

RESULTS

Participants

One hundred and forty-eight SCZ and 70 HCs were originally enrolled as part of the add-on EEG study. However, 23 SCZ and 4 HCs did not complete the paradigm for the electrophysiological recording. Furthermore, 11 SCZ and 3 HCs were excluded either for the presence of artifacts in the ERP recordings or for poor behavioral performance on the active target recognition task. Thus, the final study sample consisted of 114 SCZ and 63 HCs.

Demographic and Clinical Characteristics

Data on relevant demographic and clinic characteristics are provided in **Table 1**. The gender ratio was significantly different between the two groups ($\chi^2 = 7.214$; $p < 0.01$) since in the SCZ group the number of male subjects was higher, as compared to HCs; the mean age was not significantly different between the two sample groups ($U = 2982.00$; $p > 0.05$). Furthermore, as expected, SCZ had significantly lower education as compared to HCs ($U = 2759.00$; $p < 0.01$). Schizophrenia were characterized by mild to moderate severity of the negative symptoms (BNSS total score of 34.75) and absent to mild severity of both positive and disorganization dimensions (PANSS mean dimension score < 9 for both). They had a low mean level of depression (CDSS total score < 4) and of Parkinsonism (SHRS Parkinsonism score < 1).

Group Comparison on N100 Amplitude and Latency

Mean values of N100 amplitude (**Table 2**) and latency (**Table 3**) were calculated for SCZ and HCs.

No significant electrode × stimulus × group interaction [$F_{(1.724,\ 301.67)} = 0.906$; $p > 0.05$] on N100 amplitude was detected. A significant main effect of the electrode was recorded [$F_{(1.772,\ 310.18)} = 354.03$; $p < 0.001$; highest peaks amplitude recorded on Fz and Cz electrodes], while no significant electrode × group interaction was detected ($p > 0.05$). A significant main effect of the stimulus type was observed [$F_{(1,\ 175)} = 27.658$; $p < 0.001$; higher peak amplitude on target trials], but this was not influenced by group ($p > 0.05$). Finally, a main effect of group

TABLE 3 | N100 mean latency for standard and target stimuli in subjects with schizophrenia and healthy controls.

N100 latency	SCZ ($n = 114$) Mean ± SD	HCs ($n = 63$) Mean ± SD
Standard–Fz	88.55 ± 10.54	88.97 ± 9.46
Standard–Cz	87.90 ± 10.04	90.27 ± 11.29
Standard–Pz	88.38 ± 11.31	89.75 ± 12.84
Target–Fz	92.53 ± 12.23	92.26 ± 11.34
Target–Cz	90.66 ± 11.47	93.84 ± 11.93
Target–Pz	90.25 ± 11.95	90.37 ± 12.48

HCs, healthy controls; SCZ, subjects with schizophrenia; SD, standard deviation. No comparisons between the two groups were made since the main effect of group was not significant (please refer to the text).

was found [$F_{(1,\ 175)} = 20.272$; $p < 0.001$]. Given the above group main effect and influence of stimulus type and electrode, the difference between the two groups were further investigated at each electrode level, separately for standard and target stimuli. *Post-hoc* analysis showed that remarkable reductions ($p < 0.001$) in N100 amplitude could be observed both in standard and target stimuli (lower N100 absolute value in SCZ; **Figure 1**; **Table 2**).

No significant interaction group × electrodes × stimulus type was detected for N100 latency [$F_{(1.757,\ 307.55)} = 0.550$; $p > 0.05$]. No significant electrode × group interaction or main effect of electrode was found ($p > 0.05$). A significant main effect was detected for stimulus type [$F_{(1,\ 175)} = 15.976$; $p < 0.001$; longer latency for target stimuli], which was not affected by the group variable ($p > 0.05$).

Finally, no significant main effect of group was detected [$F_{(1,\ 175)} = 0.\ 542$; $p > 0.05$]. Given the absence of a main effect of group, no *post-hoc* analysis for N100 latency was implemented (**Table 3**).

Correlation Analysis Between N100 Characteristics and Negative Symptoms

Correlations between N100 features and severity of negative symptoms, assessed through the BNSS total score, were initially performed. Correlations between BNSS total score and N100 amplitude and latency are reported in **Tables 4**, **5**, respectively. We found that N100 amplitude recorded at Fz elicited by standard stimuli correlated with the BNSS total score ($r_s = 0.241$; $p = 0.011$) (**Figure 2**; **Table 4**). No significant associations between N100 latency and BNSS total score were observed (**Table 5**).

Furthermore, when we considered the two domains of negative symptoms, we found a different pattern of correlations between these domains and N100 amplitude. In particular, while a correlation was observed between N100 amplitude (standard stimuli–Fz electrode) and the expressive deficit domain ($r_s = 0.296$; $p = 0.002$) (**Figure 2**; **Table 6**), no significant correlation was found for the experiential domain ($r_s = 0.188$; $p = 0.051$) (**Table 6**). Since the *p*-value of this last correlation was close to the threshold value, we performed an exploratory analysis focusing on the correlations between N100 amplitude and all the symptoms constituting the experiential domain (avolition, anhedonia, and asociality). The correlations between the N100 amplitude and avolition ($r_s = 0.075$; $p = 0.445$) and asociality ($r_s = 0.040$; $p = 0.686$) were not statistically significant, while the correlation with anhedonia did not survive correction for multiple tests ($r_s = 0.205$; $p = 0.035$).

Finally, within the expressive deficit, both blunted affect ($r_s = 0.240$; $p = 0.011$) and alogia ($r_s = 0.253$ $p = 0.007$) had the same pattern of correlation with N100 (**Table 6**). All correlations remained significant after controlling for the possible confounding effects of positive symptoms, extrapyramidal side effects, depression, and disorganization.

Control Analysis of Correlations of P3b With Negative Symptoms

No association of P3b with negative symptoms was observed in the study. In particular, no significant correlations were found between P3b amplitude and the BNSS total ($r_s = -0.054$; $p = 0.575$) or the experiential ($r_s = -0.053$; $p = 0.577$) and the expressive deficit ($r_s = -0.060$; $p = 0.533$) domains. Finally, no significant correlations were found between P3b latency and the BNSS total ($r_s = -0.046$; $p = 0.635$) and the experiential ($r_s = -0.037$; $p = 0.701$) and the expressive deficit ($r_s = -0.083$; $p = 0.387$) domains.

DISCUSSION

The current study aimed to investigate auditory-elicited N100 in SCZ and its association with negative symptom domains. The two main aims were: (1) to identify differences in N100 amplitude between SCZ and HCs; (2) to investigate the presence of associations between N100 and negative symptom domains (experiential and expressive deficit) in SCZ. The main results of our study included: (1) N100 amplitude was reduced in SCZ, compared to HCs, while no significant differences were detected in N100 latency between the two groups; (2) negative symptoms, assessed by BNSS scale, showed an association with N100 amplitude for standard stimuli; (3) expressive deficit, but not the experiential domain, was associated with N100 amplitude; and (4) both blunted affect and alogia were associated with N100 amplitude.

N100 amplitude was reduced in SCZ compared to HCs, for both standard and target stimuli. These results are in line with previous literature findings, which robustly documented diminished N100 amplitude in SCZ (67–71, 73, 76, 77). Abnormalities of N100 are already detectable in early stages of the disease and in high-risk individuals (74, 75) and, therefore, have been proposed as indicators of brain functional changes related to schizophrenia vulnerability (98). In line with this hypothesis, N100 amplitude deficit has also been recorded in unaffected first-degree relatives of subjects with SCZ (72). Using topographic analysis, such as low-resolution electromagnetic tomography analysis (LORETA), it is possible to detect the main brain areas involved in N100 generation: the primary auditory cortex, the dorsolateral prefrontal cortex, and the anterior cingulate (69, 99). Abnormalities in these areas, along with widespread connectivity

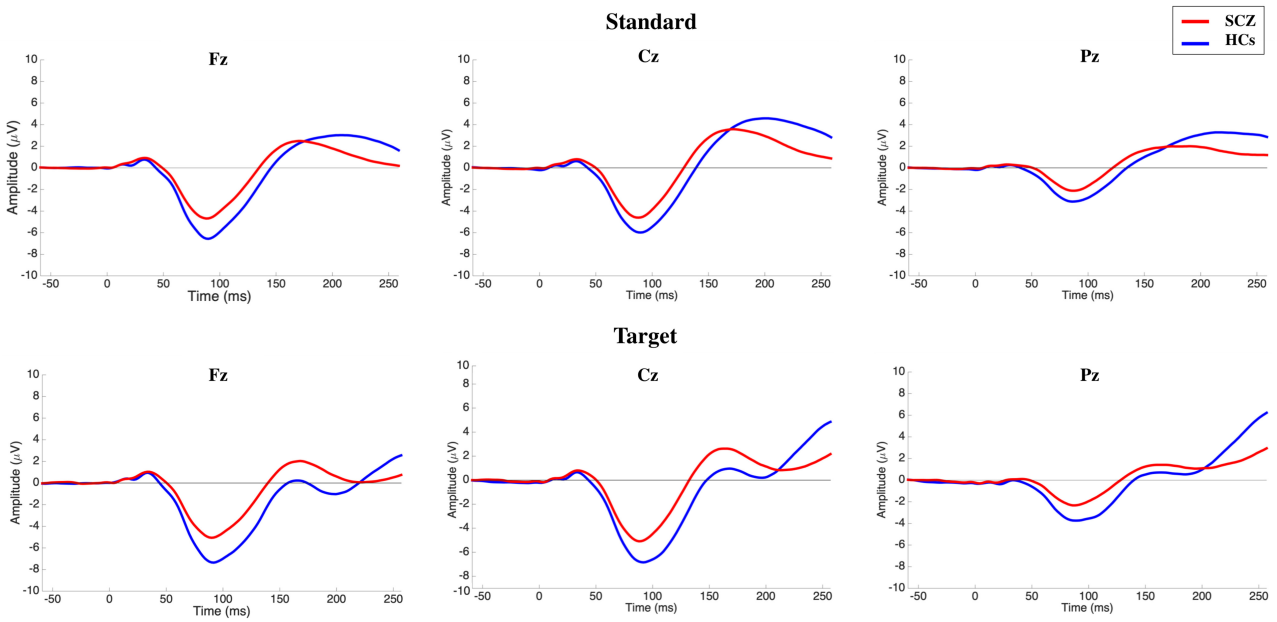


FIGURE 1 | Grand-average N100 waves elicited by standard (top) and target (bottom) stimuli on the three midlines electrodes for subjects with schizophrenia (SCZ) and healthy controls (HCs). Following stimulus onset, the N100 component was measured in a time window within 80–120 ms. The potential was filtered between 0.01 and 30 Hz to optimize scoring of the N100 component.

alterations are consistently reported in neuroimaging studies conducted in SCZ (8, 100, 101).

The N100 is regarded as an index of early visual and auditory processing, which is also influenced by selective attention and unpredictability of the stimuli. Therefore, the reduction in N100 amplitude in SCZ is interpreted as a deficit in early sensory processing of the stimulus, an aspect well documented in schizophrenia both through behavioral and neurophysiology studies, since the earliest stages of the disease (67, 70, 75, 79, 85). Deficits in early visual and auditory processing, along with aberrations in the integration of simultaneous and multisensory stimulation, might lead to impairment also in higher-level functions (86, 102–105).

The second part of our study aimed to evaluate the relationship between N100 and negative symptoms. Previous studies have found an association between dysfunctions in N100 elicitation in SCZ and auditory hallucinations (80–82), antipsychotic intake (67), attention deficits (83, 84), and negative symptoms (69, 85).

As reported in the Introduction, the association between N100 abnormalities and negative symptoms remains unclear since results reported by different studies are inconsistent (69, 85, 89–91). However, the majority of the above-mentioned studies (85, 89–91) used first generation rating scales, such as the PANSS (92) and the SANS (93) to assess negative symptoms. These assessment instruments present some limitations, as they include aspects that actually are not conceptualized as negative symptoms, but are mostly related to cognitive functions and disorganization (2). In addition, previous studies did not investigate associations between N100 and the two negative symptom domains.

TABLE 4 | Correlations between N100 amplitude for standard and target stimuli and BNSS total score in SCZ.

N100 amplitude	BNSS total score	
	Spearman's correlation coefficient	*p*-values
Fz–Standard	0.241	**0.011**
Cz–Standard	0.089	0.351
Pz–Standard	0.132	0.167
Fz–Target	0.123	0.197
Cz–Target	0.030	0.754
Pz–Target	0.076	0.428

BNSS, brief negative symptom scale. Significant p-value thresholds for the three correlations ran for each stimulus type ($p < 0.016$). p-values in bold indicate statistical significance.

In a large sample of stabilized subjects with chronic schizophrenia, our study demonstrated a relationship between N100 abnormalities with negative symptoms. The strength of this finding stem from fact that negative symptoms were evaluated with the BNSS, a second-generation rating scale in line with the current conceptualization of negative symptoms, and that as documented by partial correlation analysis, this outcome was not mediated by positive symptoms, extrapyramidal side effects, disorganization, or depression, frequently causing secondary negative symptoms within negative symptoms, the expressive deficit domain was strongly correlated with N100 amplitude, as compared to the experiential domain. In particular, although the

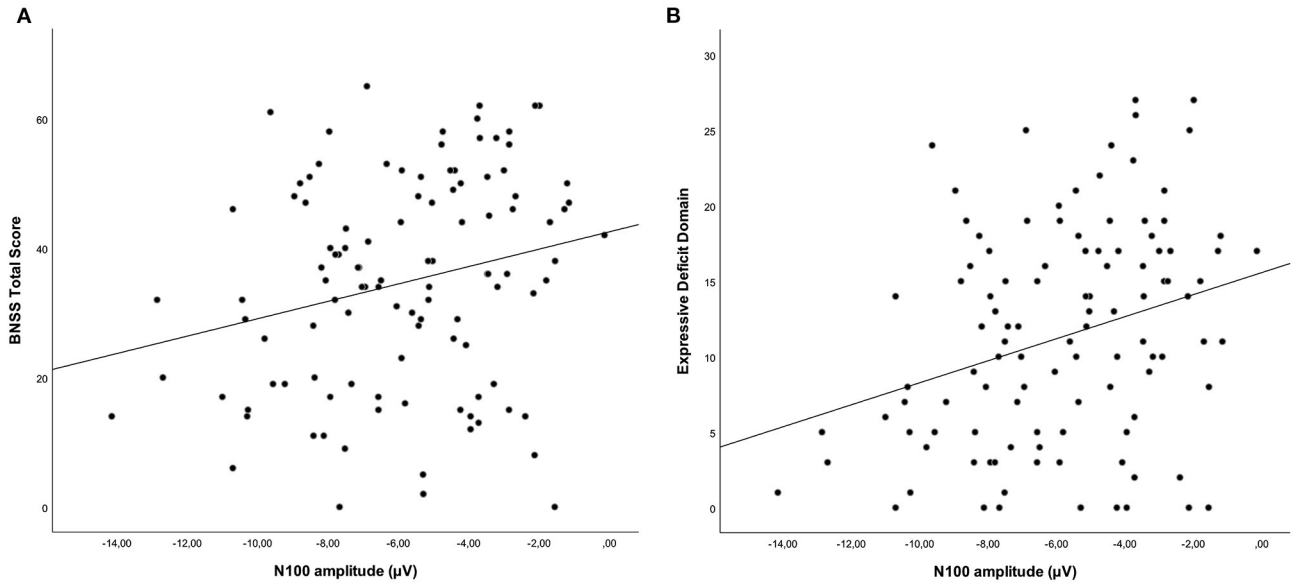


FIGURE 2 | Correlations between standard-stimuli N100 amplitude (Fz electrode) with the BNSS total score **(A)** ($r_s = 0.241$; $p = 0.011$) and the expressive deficit domain **(B)** ($r_s = 0.296$; $p = 0.002$) in subjects with schizophrenia. Both correlations remained significant after controlling for the possible confounding effects of positive symptoms, extrapyramidal side effects, depression, and disorganization.

TABLE 5 | Correlations between N100 latency for standard and target stimuli and BNSS total score in SCZ.

N100 latency	BNSS total score	
	Spearman's correlation coefficient	*p*-values
Fz–Standard	0.052	0.586
Cz–Standard	0.094	0.328
Pz–Standard	0.113	0.236
Fz–Target	− 0.006	0.946
Cz–Target	−0.040	0.674
Pz–Target	− 0.015	0.878

BNSS, brief negative symptom scale; Significant p-value thresholds for the three correlations ran for each stimulus type (p < 0.016).

TABLE 6 | Correlations between N100 amplitude (standard stimuli–Fz electrode) and negative symptom domains.

BNSS	N100 amplitude (standard stimuli–Fz electrode)	
	Spearman's correlation coefficient	*p*-values
Experiential domain	0.188	0.051
Expressive deficit	0.296	**0.002***
Blunted affect	0.240	**0.011***
Alogia	0.253	**0.007***

BNSS, brief negative symptom scale. Significant p-value thresholds for the three correlations ran for each stimulus type (p < 0.025). p-values in bold indicate statistical significance.

**The correlation remained significant when controlling for positive and extrapyramidal symptoms, disorganization and depression.*

p-value of association between the experiential domain and the N100 was close to threshold, none of the symptoms belonging to this domain was significantly correlated with N100 amplitude, while the expressive deficit domain and its subcomponent symptoms were correlated with N100.

The presence of an association of N100 amplitude with only one of the two negative symptom domains is in agreement with previous results that suggest the existence of separate neurobiological mechanisms at the core of the experiential domain and expressive deficit (8, 10, 15, 16, 37, 58).

Indeed, neuroimaging studies have provided a rich evidence of the possible faulty neuronal circuits underlying the two domains of negative symptoms. The experiential domain seems to be related to abnormalities in brain networks regulating different aspects of motivation, and probably to impairment in executive functions. On the other side, the pathophysiological mechanisms at the basis of the expressive deficit domain remain less understood (8, 10, 15, 16). This domain of negative symptoms has been related to deficit in neurocognitive skills, social cognition abilities, and neurological soft signs, which comprise also subtle deficits in sensory integration, along with motor coordination, and sequencing of complex motor acts (8). These associations seem to pinpoint that this domain is related to a diffuse neurodevelopmental disconnectivity.

According to the hypothesis of the limited cognitive resource, expressive deficit symptoms, in particular alogia, might depend

on deficits in different cognitive functions, such as semantic memory organization and verbal fluency. Starting from limited cognitive resources, in "high-load" situations (e.g., social situations) subjects are exposed to high cognitive demands and might allocate less cognitive resources to speech production (15). As we have reported above, reduced N100 amplitude is an index of deficits in sensory processing and sensory gating, a well-replicated finding in SCZ. It has been proposed that alterations in sensory gating of N100 cause sensory flooding and defective processing of information to the brain, contributing to the symptoms of SCZ (91). Given the relationship between N100 and sensory processing deficits, our study demonstrated a connection between deficits in sensory processing with negative symptom severity, in particular those belonging to the expressive deficit. A possible interpretation of this connection is based on some "cascade" models that have hypothesized that impairment in early sensory processing might contribute to deficits in higher-level processing which are related to negative symptoms, leading to poor functioning (86–88, 106).

Certain limitations of this study should be taken into account. For instance, age and pharmacological treatment might have had an impact on our results. In our study, we used a sample in which subjects were matched for age: therefore, we could exclude the effect of age on the differences between HCs and SCZ. With regard to medication, we excluded the confounding effect of medication on correlation between N100 and negative symptoms, using partial correlation analysis in which we controlled for extrapyramidal symptoms that might cause secondary negative symptoms. However, further studies including drug-naïve subjects at their first episode, as well as subjects at high risk for psychosis, using a proper characterization of negative symptoms, are needed in order to disentangle different neurobiological underpinnings of negative symptom domains.

CONCLUSIONS

In conclusion, in line with previous studies, our results suggested that chronic individuals with schizophrenia are affected by neurophysiological abnormalities in early stages of auditory processing, as indexed by reduced N100 amplitude. In addition, we reported a correlation between reductions of N100 amplitude and severity of the expressive deficit domain, while no correlation was found with the experiential domain. These results reinforce the hypothesis of separate neurophysiological correlates of the two negative symptom domains. Furthermore, previous models have hypothesized a concatenation of pathological features starting from impairment in early sensory processing up to deficits in higher-level processing that could lead to negative symptoms, and finally might contribute to poor functioning in real life. Further studies, including large sample sizes, a proper characterization of negative symptoms, and an analysis of pathways to functional outcome, are needed.

Improving knowledge in the pathophysiology of different aspects of negative symptoms and their relative contribution to poor functioning is one of the main goals of the research, since it could help in the design and implementation of effective treatments for negative symptoms, which unfortunately still represent an unmet need in the care of SCZ.

ITALIAN NETWORK FOR RESEARCH ON PSYCHOSES

Members of the Italian Network for Research on Psychoses participating in the add-on EEG study include: Eleonora Merlotti and Giuseppe Piegari, University of Campania "Luigi Vanvitelli"; Girolamo Francavilla and Flavia A. Padalino, University of Foggia; Cinzia Niolu and Michele Ribolsi, University of Rome Tor Vergata; Roberto Brugnoli and Paolo Girardi, University of Rome "La Sapienza"; Giulio Corrivetti and Francesca Marciello, University of Salerno.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Università degli Studi della Campania Luigi Vanvitelli—A.O.U. Luigi Vanvitelli and A.O.R.N. Ospedali dei Colli. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The project idea was initiated by SG, involving a collaboration with GMG, FB, AP, GDL, and MM. SG and GMG planned the experimental procedures. GMG, FB, and AP performed the analyzes of the data and wrote the first draft of the manuscript. All authors were responsible for the interpretation of the analyzes, contributed to critically revising the content, and approved the final manuscript for submission to Frontiers in Psychiatry.

FUNDING

This study was funded by the Italian Ministry of Education (grant number: 2010XP2XR4), the Italian Society of Psychopathology (SOPSI), the Italian Society of Biological Psychiatry (SIPB), Roche, Switzerland; Lilly, United States; AstraZeneca, United Kingdom; Lundbeck Foundation, Denmark; and Bristol-Myers Squibb, United Kingdom. These entities had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report and in the decision to submit the paper for publication.

REFERENCES

1. Galderisi S, Kaiser S, Bitter I, Nordentoft M, Mucci A, Sabé M, et al. EPA guidance on treatment of negative symptoms in schizophrenia. *Eur. Psychiatry.* (2021) 64:e21. doi: 10.1192/j.eurpsy.2021.13
2. Galderisi S, Mucci A, Dollfus S, Nordentoft M, Falkai P, Kaiser S, et al. EPA guidance on assessment of negative symptoms in schizophrenia. *Eur Psychiatry.* (2021) 64:e23. doi: 10.1192/j.eurpsy.2021.11
3. Galderisi S, Rossi A, Rocca P, Bertolino A, Mucci A, Bucci P, et al. The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. *World Psychiatry.* (2014) 13:275–87. doi: 10.1002/wps.20167
4. Galderisi S, Rucci P, Kirkpatrick B, Mucci A, Gibertoni D, Rocca P, et al. Interplay among psychopathologic variables, personal resources, context-related factors, and real-life functioning in individuals with schizophrenia: a network analysis. *JAMA Psychiatry.* (2018) 75:396–404. doi: 10.1001/jamapsychiatry.2017.4607
5. Galderisi S, Rucci P, Mucci A, Rossi A, Rocca P, Bertolino A, et al. The interplay among psychopathology, personal resources, context-related factors and real-life functioning in schizophrenia: stability in relationships after 4 years and differences in network structure between recovered and non-recovered patients. *World Psychiatry.* (2020) 19:81–91. doi: 10.1002/wps.20700
6. Mucci A, Galderisi S, Gibertoni D, Rossi A, Rocca P, Bertolino A, et al. Factors associated with real-life functioning in persons with schizophrenia in a 4-year follow-up study of the Italian Network for Research on Psychoses. *JAMA Psychiatry.* (2021) 78:550–9. doi: 10.1001/jamapsychiatry.2020.4614
7. Galderisi S, Färden A, Kaiser S. Dissecting negative symptoms of schizophrenia: history, assessment, pathophysiological mechanisms and treatment. *Schizophr Res.* (2017) 186:1–2. doi: 10.1016/j.schres.2016.04.046
8. Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. *Lancet Psychiatry.* (2018) 5:664–77. doi: 10.1016/s2215-0366(18)30050-6
9. Kirkpatrick B, Fenton WS, Carpenter WT Jr., Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull.* (2006) 32:214–9. doi: 10.1093/schbul/sbj053
10. Marder SR, Galderisi S. The current conceptualization of negative symptoms in schizophrenia. *World Psychiatry.* (2017) 16:14–24. doi: 10.1002/wps.20385
11. Correll CU, Schooler NR. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatr Dis Treat.* (2020) 16:519–34. doi: 10.2147/ndt.s225643
12. Gaebel W, Falkai P, Hasan A. The revised German evidence- and consensus-based schizophrenia guideline. *World Psychiatry.* (2020) 19:117–9. doi: 10.1002/wps.20706
13. Kirkpatrick B, Fischer B. Subdomains within the negative symptoms of schizophrenia: commentary. *Schizophr Bull.* (2006) 32:246–9. doi: 10.1093/schbul/sbj054
14. Reed GM, First MB, Kogan CS, Hyman SE, Gureje O, Gaebel W, et al. Innovations and changes in the ICD-11 classification of mental, behavioural and neurodevelopmental disorders. *World Psychiatry.* (2019) 18:3–19. doi: 10.1002/wps.20611
15. Begue I, Kaiser S, Kirschner M. Pathophysiology of negative symptom dimensions of schizophrenia - current developments and implications for treatment. *Neurosci Biobehav Rev.* (2020) 116:74–88. doi: 10.1016/j.neubiorev.2020.06.004
16. Kaiser S, Lyne J, Agartz I, Clarke M, Mørch-Johnsen L, Faerden A. Individual negative symptoms and domains - relevance for assessment, pathomechanisms and treatment. *Schizophr Res.* (2017) 186:39–45. doi: 10.1016/j.schres.2016.07.013
17. Cuthbert BN, Morris SE. Evolving concepts of the schizophrenia spectrum: a research domain criteria perspective. *Front Psychiatry.* (2021) 12:641319. doi: 10.3389/fpsyt.2021.641319
18. Sanislow CA. RDoC at 10: changing the discourse for psychopathology. *World Psychiatry.* (2020) 19:311–2. doi: 10.1002/wps.20800
19. Menon V. Brain networks and cognitive impairment in psychiatric disorders. *World Psychiatry.* (2020) 19:309–10. doi: 10.1002/wps.20799
20. Barch DM, Dowd EC. Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. *Schizophr Bull.* (2010) 36:919–34. doi: 10.1093/schbul/sbq068
21. Cohen AS, Minor KS. Emotional experience in patients with schizophrenia revisited: meta-analysis of laboratory studies. *Schizophr Bull.* (2010) 36:143–50. doi: 10.1093/schbul/sbn061
22. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. *Schizophr Res.* (2007) 93:253–60. doi: 10.1016/j.schres.2007.03.008
23. Heerey EA, Gold JM. Patients with schizophrenia demonstrate dissociation between affective experience and motivated behavior. *J Abnorm Psychol.* (2007) 116:268–78. doi: 10.1037/0021-843x.116.2.268
24. Heerey EA, Robinson BM, McMahon RP, Gold JM. Delay discounting in schizophrenia. *Cogn Neuropsychiatry.* (2007) 12:213–21. doi: 10.1080/13546800601005900
25. Kring AM, Moran EK. Emotional response deficits in schizophrenia: insights from affective science. *Schizophr Bull.* (2008) 34:819–34. doi: 10.1093/schbul/sbn071
26. Waltz JA, Frank MJ, Robinson BM, Gold JM. Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. *Biol Psychiatry.* (2007) 62:756–64. doi: 10.1016/j.biopsych.2006.09.042
27. Dowd EC, Barch DM. Anhedonia and emotional experience in schizophrenia: neural and behavioral indicators. *Biol Psychiatry.* (2010) 67:902–11. doi: 10.1016/j.biopsych.2009.10.020
28. Foussias G, Remington G. Negative symptoms in schizophrenia: avolition and Occam's razor. *Schizophr Bull.* (2010) 36:359–69. doi: 10.1093/schbul/sbn094
29. Mann CL, Footer O, Chung YS, Driscoll LL, Barch DM. Spared and impaired aspects of motivated cognitive control in schizophrenia. *J Abnorm Psychol.* (2013) 122:745–55. doi: 10.1037/a0033069
30. Pizzagalli DA. The "anhedonia paradox" in schizophrenia: insights from affective neuroscience. *Biol Psychiatry.* (2010) 67:899–901. doi: 10.1016/j.biopsych.2010.02.022
31. Simpson EH, Waltz JA, Kellendonk C, Balsam PD. Schizophrenia in translation: dissecting motivation in schizophrenia and rodents. *Schizophr Bull.* (2012) 38:1111–7. doi: 10.1093/schbul/sbs114
32. Morris RW, Quail S, Griffiths KR, Green MJ, Balleine BW. Corticostriatal control of goal-directed action is impaired in schizophrenia. *Biol Psychiatry.* (2015) 77:187–95. doi: 10.1016/j.biopsych.2014.06.005
33. Strauss GP, Waltz JA, Gold JM, A. review of reward processing and motivational impairment in schizophrenia. *Schizophr Bull.* (2014) 40(Suppl 2):S107–16. doi: 10.1093/schbul/sbt197
34. Strauss J. Reconceptualizing schizophrenia. *Schizophr Bull.* (2014) 40(Suppl 2):S97–100. doi: 10.1093/schbul/sbt156
35. Mucci A, Dima D, Soricelli A, Volpe U, Bucci P, Frangou S, et al. Is avolition in schizophrenia associated with a deficit of dorsal caudate activity? A functional magnetic resonance imaging study during reward anticipation and feedback. *Psychol Med.* (2015) 45:1765–78. doi: 10.1017/s0033291714002943
36. Amodio A, Quarantelli M, Mucci A, Prinster A, Soricelli A, Vignapiano A, et al. Avolition-apathy and white matter connectivity in schizophrenia: reduced fractional anisotropy between amygdala and insular cortex. *Clin EEG Neurosci.* (2018) 49:55–65. doi: 10.1177/1550059417745934
37. Giordano GM, Stanziano M, Papa M, Mucci A, Prinster A, Soricelli A, et al. Functional connectivity of the ventral tegmental area and avolition in subjects with schizophrenia: a resting state functional MRI study. *Eur Neuropsychopharmacol.* (2018) 28:589–602. doi: 10.1016/j.euroneuro.2018.03.013
38. Grant PM, Best MW, Beck AT. The meaning of group differences in cognitive test performance. *World Psychiatry.* (2019) 18:163–4. doi: 10.1002/wps.20645
39. Harvey PD, Strassnig MT. Cognition and disability in schizophrenia: cognition-related skills deficits and decision-making challenges add to morbidity. *World Psychiatry.* (2019) 18:165–7. doi: 10.1002/wps.20647
40. Culbreth AJ, Moran EK, Kandala S, Westbrook A, Barch DM. Effort, avolition and motivational experience in schizophrenia: analysis of behavioral and neuroimaging data with relationships

to daily motivational experience. *Clin Psychol Sci.* (2020) 8:555–68. doi: 10.1177/2167702620901558
41. Davidson M. Cognitive impairment as a diagnostic criterion and treatment target in schizophrenia. *World Psychiatry.* (2019) 18:171–2. doi: 10.1002/wps.20651
42. Falkai P, Schmitt A. The need to develop personalized interventions to improve cognition in schizophrenia. *World Psychiatry.* (2019) 18:170. doi: 10.1002/wps.20650
43. Moritz S, Silverstein SM, Dietrichkeit M, Gallinat J. Neurocognitive deficits in schizophrenia are likely to be less severe and less related to the disorder than previously thought. *World Psychiatry.* (2020) 19:254–5. doi: 10.1002/wps.20759
44. Reichenberg A, Velthorst E, Davidson M. Cognitive impairment and psychosis in schizophrenia: independent or linked conditions? *World Psychiatry.* (2019) 18:162–3. doi: 10.1002/wps.20644
45. Sahakian BJ, Savulich G. Innovative methods for improving cognition, motivation and wellbeing in schizophrenia. *World Psychiatry.* (2019) 18:168–70. doi: 10.1002/wps.20649
46. Bissonette GB, Roesch MR. Development and function of the midbrain dopamine system: what we know and what we need to. *Genes Brain Behav.* (2016) 15:62–73. doi: 10.1111/gbb.12257
47. Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron.* (2010) 68:815–34. doi: 10.1016/j.neuron.2010.11.022
48. Bowie CR. Cognitive remediation for severe mental illness: state of the field and future directions. *World Psychiatry.* (2019) 18:274–5. doi: 10.1002/wps.20660
49. Faerden A, Vaskinn A, Finset A, Agartz I, Ann Barrett E, Friis S, et al. Apathy is associated with executive functioning in first episode psychosis. *BMC Psychiatry.* (2009) 9:1. doi: 10.1186/1471-244x-9-1
50. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex.* (2006) 16:916–28. doi: 10.1093/cercor/bhj043
51. Kring AM, Elis O. Emotion deficits in people with schizophrenia. *Annu Rev Clin Psychol.* (2013) 9:409–33. doi: 10.1146/annurev-clinpsy-050212-185538
52. Hartmann-Riemer MN, Hager OM, Kirschner M, Bischof M, Kluge A, Seifritz E, et al. The association of neurocognitive impairment with diminished expression and apathy in schizophrenia. *Schizophr Res.* (2015) 169:427–32. doi: 10.1016/j.schres.2015.10.032
53. Cohen AS, Schwartz E, Le TP, Fedechko T, Kirkpatrick B, Strauss GP. Using biobehavioral technologies to effectively advance research on negative symptoms. *World Psychiatry.* (2019) 18:103–4. doi: 10.1002/wps.20593
54. Melle I. Cognition in schizophrenia: a marker of underlying neurodevelopmental problems? *World Psychiatry.* (2019) 18:164–5. doi: 10.1002/wps.20646
55. Galderisi S, Caputo F, Giordano G, Mucci A. Aetiopathological mechanisms of negative symptoms in schizophrenia. *Die Psychiatrie.* (2016) 13:121–9. doi: 10.1055/s-0038-1669683
56. Barch DM. Nonsocial and social cognitive function in psychosis: interrelationships, specificity and innovative approaches. *World Psychiatry.* (2019) 18:117–8. doi: 10.1002/wps.20653
57. Green MF, Horan WP, Lee J. Nonsocial and social cognition in schizophrenia: current evidence and future directions. *World Psychiatry.* (2019) 18:146–61. doi: 10.1002/wps.20624
58. Giordano GM, Koenig T, Mucci A, Vignapiano A, Amodio A, Di Lorenzo G, et al. Neurophysiological correlates of Avolition-apathy in schizophrenia: a resting-EEG microstates study. *Neuroimage Clin.* (2018) 20:627–36. doi: 10.1016/j.nicl.2018.08.031
59. Kotov R, Jonas KG, Carpenter WT, Dretsch MN, Eaton NR, Forbes MK, et al. Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): I. Psychosis superspectrum. *World Psychiatry.* (2020) 19:151–72. doi: 10.1002/wps.20730
60. Hasey GM, Kiang M, A. review of recent literature employing electroencephalographic techniques to study the pathophysiology, phenomenology, and treatment response of schizophrenia. *Curr Psychiatry Rep.* (2013) 15:388. doi: 10.1007/s11920-013-0388-x
61. Ince E, Üçok A. Relationship between persistent negative symptoms and findings of neurocognition and neuroimaging in schizophrenia. *Clin EEG Neurosci.* (2017) 49:27–35. doi: 10.1177/1550059417746213
62. Phillips JM, Maxwell CR, Ehrlichman RS, Siegel SJ. Event-related potentials (ERPs) in the study of schizophrenia: how preclinical ERP studies have contributed to our understanding of schizophrenia. In: Lajtha A, Javitt D, Kantrowitz J, editors. *Handbook of Neurochemistry and Molecular Neurobiology: Schizophrenia.* Springer (2009) p. 525–43.
63. Qiu Y-Q, Tang Y-X, Chan RCK, Sun X-Y, He J. P300 aberration in first-episode schizophrenia patients: a meta-analysis. *PLoS ONE.* (2014) 9:e97794-e. doi: 10.1371/journal.pone.0097794
64. Vignapiano A, Mucci A, Ford J, Montefusco V, Plescia GM, Bucci P, et al. Reward anticipation and trait anhedonia: an electrophysiological investigation in subjects with schizophrenia. *Clin Neurophysiol.* (2016) 127:2149–60. doi: 10.1016/j.clinph.2016.01.006
65. Vignapiano A, Mucci A, Merlotti E, Giordano GM, Amodio A, Palumbo D, et al. Impact of reward and loss anticipation on cognitive control: an event-related potential study in subjects with schizophrenia and healthy controls. *Clin EEG Neurosci.* (2018) 49:46–54. doi: 10.1177/1550059417745935
66. Wynn JK, Horan WP, Kring AM, Simons RF, Green MF. Impaired anticipatory event-related potentials in schizophrenia. *Int J Psychophysiol.* (2010) 77:141–9. doi: 10.1016/j.ijpsycho.2010.05.009
67. Rosburg T, Boutros NN, Ford JM. Reduced auditory evoked potential component N100 in schizophrenia – a critical review. *Psychiatry Res.* (2008) 161:259–74. doi: 10.1016/j.psychres.2008.03.017
68. Bruder G, Kayser J, Tenke C, Rabinowicz E, Friedman M, Amador X, et al. The time course of visuospatial processing deficits in schizophrenia: an event-related brain potential study. *J Abnorm Psychol.* (1998) 107:399–411. doi: 10.1037//0021-843x.107.3.399
69. Mucci A, Galderisi S, Kirkpatrick B, Bucci P, Volpe U, Merlotti E, et al. Double dissociation of N1 and P3 abnormalities in deficit and nondeficit schizophrenia. *Schizophr Res.* (2007) 92:252–61. doi: 10.1016/j.schres.2007.01.026
70. Sumich A, Kumari V, Dodd P, Ettinger U, Hughes C, Zachariah E, et al. N100 and P300 amplitude to Go and No-Go variants of the auditory oddball in siblings discordant for schizophrenia. *Schizophr Res.* (2008) 98:265–77. doi: 10.1016/j.schres.2007.09.018
71. Turetsky BI, Bilker WB, Siegel SJ, Kohler CG, Gur RE. Profile of auditory information-processing deficits in schizophrenia. *Psychiatry Res.* (2009) 165:27–37. doi: 10.1016/j.psychres.2008.04.013
72. Turetsky BI, Greenwood TA, Olincy A, Radant AD, Braff DL, Cadenhead KS, et al. Abnormal auditory N100 amplitude: a heritable endophenotype in first-degree relatives of schizophrenia probands. *Biol Psychiatry.* (2008) 64:1051–9. doi: 10.1016/j.biopsych.2008.06.018
73. Dias EC, Butler PD, Hoptman MJ, Javitt DC. Early sensory contributions to contextual encoding deficits in schizophrenia. *Arch Gen Psychiatry.* (2011) 68:654–64. doi: 10.1001/archgenpsychiatry.2011.17
74. Del Re E, Spencer K, Oribe N, Mesholam-Gately R, Goldstein J, Shenton M, et al. Clinical high risk and first episode schizophrenia: auditory event-related potentials. *Psychiatry Res.* (2014) 231:126–33. doi: 10.1016/j.pscychresns.2014.11.012
75. Hsieh MH, Lin Y-T, Chien Y-L, Hwang T-J, Hwu H-G, Liu C-M, et al. Auditory event-related potentials in antipsychotic-free subjects with ultra-high-risk state and first-episode psychosis. *Front Psychiatry.* (2019) 10:223. doi: 10.3389/fpsyt.2019.00223
76. Perrottelli A, Giordano GM, Brando F, Giuliani L, Mucci A. EEG-based measures in at-risk mental state and early stages of schizophrenia: a systematic review. *Front Psychiatry.* (2021) 12:653642. doi: 10.3389/fpsyt.2021.653642
77. Boutros NN, Brockhaus-Dumke A, Gjini K, Vedeniapin A, Elfakhani M, Burroughs S, et al. Sensory-gating deficit of the N100 mid-latency auditory evoked potential in medicated schizophrenia patients. *Schizophr Res.* (2009) 113:339–46. doi: 10.1016/j.schres.2009.05.019
78. Oribe N, Hirano Y, Kanba S. del Re EC, Seidman LJ, Mesholam-Gately R, et al. Early and late stages of visual processing in individuals in prodromal state and first episode schizophrenia: an ERP study. *Schizophr Res.* (2013) 146:95–102. doi: 10.1016/j.schres.2013.01.015

79. Rosburg T. Auditory N100 gating in patients with schizophrenia: a systematic meta-analysis. *Clin Neurophysiol.* (2018) 129:2099–111. doi: 10.1016/j.clinph.2018.07.012
80. Heinks-Maldonado TH, Mathalon DH, Houde JF, Gray M, Faustman WO, Ford JM. Relationship of imprecise corollary discharge in schizophrenia to auditory hallucinations. *Arch Gen Psychiatry.* (2007) 64:286–96. doi: 10.1001/archpsyc.64.3.286
81. Ford JM, Dierks T, Fisher DJ, Herrmann CS, Hubl D, Kindler J, et al. Neurophysiological studies of auditory verbal hallucinations. *Schizophr Bull.* (2012) 38:715–23. doi: 10.1093/schbul/sbs009
82. Thoma RJ, Meier A, Houck J, Clark VP, Lewine JD, Turner J, et al. Diminished auditory sensory gating during active auditory verbal hallucinations. *Schizophr Res.* (2017) 188:125–31. doi: 10.1016/j.schres.2017.01.023
83. Lijffijt M, Moeller FG, Boutros NN, Steinberg JL, Meier SL, Lane SD, et al. Diminished P50, N100 and P200 auditory sensory gating in bipolar I disorder. *Psychiatry Res.* (2009) 167:191–201. doi: 10.1016/j.psychres.2008.04.001
84. Smith AK, Edgar JC, Huang M, Lu BY, Thoma RJ, Hanlon FM, et al. Cognitive abilities and 50- and 100-msec paired-click processes in schizophrenia. *Am J Psychiatry.* (2010) 167:1264–75. doi: 10.1176/appi.ajp.2010.09071059
85. Sumich A, Harris A, Flynn G, Whitford T, Tunstall N, Kumari V, et al. Event-related potential correlates of depression, insight and negative symptoms in males with recent-onset psychosis. *Clin Neurophysiol.* (2006) 117:1715–27. doi: 10.1016/j.clinph.2006.04.017
86. de Jong JJ, de Gelder B, Hodiamont PP. Sensory processing, neurocognition, and social cognition in schizophrenia: towards a cohesive cognitive model. *Schizophr Res.* (2013) 146:209–16. doi: 10.1016/j.schres.2013.02.034
87. Javitt DC. When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. *Annu Rev Clin Psychol.* (2009) 5:249–75. doi: 10.1146/annurev.clinpsy.032408.153502
88. Sergi MJ, Rassovsky Y, Nuechterlein KH, Green MF. Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. *Am J Psychiatry.* (2006) 163:448–54. doi: 10.1176/appi.ajp.163.3.448
89. Li Z, Zheng B, Deng W, Liu X, Zheng Z, Li T. Multi-components of evoked-brain potentials in deficit and nondeficit schizophrenia. *Asia Pac Psychiatry.* (2013) 5:69–79. doi: 10.1111/appy.12030
90. Pinheiro AP, Del Re E, Mezin J, Nestor PG, Rauber A, McCarley RW, et al. Sensory-based and higher-order operations contribute to abnormal emotional prosody processing in schizophrenia: an electrophysiological investigation. *Psychol Med.* (2013) 43:603–18. doi: 10.1017/S003329171200133X
91. Shen CL, Chou TL, Lai WS, Hsieh MH, Liu CC, Liu CM, et al. P50, N100, and P200 auditory sensory gating deficits in schizophrenia patients. *Front Psychiatry.* (2020) 11:868. doi: 10.3389/fpsyt.2020.00868
92. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* (1987) 13:261–76. doi: 10.1093/schbul/13.2.261
93. Andreasen NC. Scale for the assessment of negative symptoms (SANS). *Brit J Psychiatry.* (1989) 155:53–8.
94. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The brief negative symptom scale: psychometric properties. *Schizophr Bull.* (2010) 37:300–5. doi: 10.1093/schbul/sbq059
95. Mucci A, Galderisi S, Merlotti E, Rossi A, Rocca P, Bucci P, et al. The Brief Negative Symptom Scale (BNSS): independent validation in a large sample of Italian patients with schizophrenia. *Eur Psychiatry.* (2015) 30:641–7. doi: 10.1016/j.eurpsy.2015.01.014
96. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. *Schizophr Res.* (1990) 3:247–51. doi: 10.1016/0920-9964(90)90005-r
97. Gerlach J, Korsgaard S, Clemmesen P, Lauersen AM, Magelund G, Noring U, et al. The St. Hans Rating Scale for extrapyramidal syndromes: reliability and validity. *Acta Psychiatr Scand.* (1993) 87:244–52. doi: 10.1111/j.1600-0447.1993.tb03366.x
98. Ahveninen J, Jaaskelainen IP, Raij T, Bonmassar G, Devore S, Hamalainen M, et al. Task-modulated "what" and "where" pathways in human auditory cortex. *Proc Natl Acad Sci USA.* (2006) 103:14608–13. doi: 10.1073/pnas.0510480103
99. Gallinat J, Mulert C, Bajbouj M, Herrmann WM, Schunter J, Senkowski D, et al. Frontal and temporal dysfunction of auditory stimulus processing in schizophrenia. *Neuroimage.* (2002) 17:110–27. doi: 10.1006/nimg.2002.1213
100. Goghari VM, Sponheim SR, MacDonald AW III. The functional neuroanatomy of symptom dimensions in schizophrenia: a qualitative and quantitative review of a persistent question. *Neurosci Biobehav Rev.* (2010) 34:468–86. doi: 10.1016/j.neubiorev.2009.09.004
101. Millan MJ, Fone K, Steckler T, Horan WP. Negative symptoms of schizophrenia: clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. *Eur Neuropsychopharmacol.* (2014) 24:645–92. doi: 10.1016/j.euroneuro.2014.03.008
102. de Jong JJ, Hodiamont PP, de Gelder B. Modality-specific attention and multisensory integration of emotions in schizophrenia: reduced regulatory effects. *Schizophr Res.* (2010) 122:136–43. doi: 10.1016/j.schres.2010.04.010
103. Van den Stock J, de Jong SJ, Hodiamont PP, de Gelder B. Perceiving emotions from bodily expressions and multisensory integration of emotion cues in schizophrenia. *Soc Neurosci.* (2011) 6:537–47. doi: 10.1080/17470919.2011.568790
104. Williams LE, Light GA, Braff DL, Ramachandran VS. Reduced multisensory integration in patients with schizophrenia on a target detection task. *Neuropsychologia.* (2010) 48:3128–36. doi: 10.1016/j.neuropsychologia.2010.06.028
105. Stein BE, Stanford TR, Rowland BA. Multisensory integration and the society for neuroscience: then and now. *J Neurosci.* (2020) 40:3–11. doi: 10.1523/JNEUROSCI.0737-19.2019
106. Green MF, Hellemann G, Horan WP, Lee J, Wynn JK. From perception to functional outcome in schizophrenia: modeling the role of ability and motivation. *Arch Gen Psychiatry.* (2012) 69:1216–24. doi: 10.1001/archgenpsychiatry.2012.652

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 24 December 2021
doi: 10.3389/fpsyt.2021.797386

Association of Negative Symptoms of Schizophrenia Assessed by the BNSS and SNS Scales With Neuropsychological Performance: A Gender Effect

Paweł Wójciak[1], *Klaudia Domowicz*[1], *Marta Zabłocka*[1], *Michał Michalak*[2] *and Janusz K. Rybakowski*[1]*

[1] Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland, [2] Department of Computer Science and Statistics, Poznan University of Medical Sciences, Poznan, Poland

OPEN ACCESS

Edited by:
Armida Mucci, University of Campania Luigi Vanvitelli, Italy

Reviewed by:
Stefano Barlati, University of Brescia, Italy
Ernest Marek Tyburski, Pomeranian Medical University in Szczecin, Poland

***Correspondence:**
Janusz K. Rybakowski
janusz.rybakowski@gmail.com

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *18 October 2021*
Accepted: *08 December 2021*
Published: *24 December 2021*

Citation:
Wójciak P, Domowicz K, Zabłocka M, Michalak M and Rybakowski JK (2021) Association of Negative Symptoms of Schizophrenia Assessed by the BNSS and SNS Scales With Neuropsychological Performance: A Gender Effect. Front. Psychiatry 12:797386. doi: 10.3389/fpsyt.2021.797386

Objective: The relationship between negative symptoms and neurocognitive performance in schizophrenia is well documented, but the mechanism of these connections remains unclear. The study aims to measure the relationship between the results on the new scales for the assessment of negative symptoms such as Brief Negative Symptom Scale (BNSS) and Self-evaluation of Negative Symptoms (SNS), and the results of some neurocognition tests. The second aim is to assess a possible gender effect on these associations.

Methods: The study included 80 patients (40 men, 40 women) with schizophrenia, aged 19–63 (mean 38 years), during the improvement period (total PANSS score <80, unchanged pharmacological treatment in the last 3 weeks). They were assessed using the BNSS, SNS, Personal and Social Performance (PSP) scales, and the tests for neuropsychological performance such as the Trail Making Test (TMT-A, TMT-B), Stroop Color-Word Interference Test, Verbal fluency tests (VFT), Category fluency test (CFT), and Digit Symbol Substitution Test (DSST).

Results: Male patients obtained higher scores than females on some PANSS and BNSS items. No gender differences were observed for the SNS scale. Female patients scored better in the PSP and CFT. In male patients, a significant positive correlation between the intensity of negative symptoms measured by the BNSS and the results of PSP with the Trail Making Test was observed. In female patients, we found a positive correlation between the results of BNSS and PSP with the Stroop Color-Word Interference Test.

Conclusion: The obtained results confirm the relationship between negative symptoms and neurocognition in schizophrenia patients. However, in male and female patients such association was observed for different cognitive domains. Further research is needed to explain the nature of these differences.

Keywords: self-evaluation of negative symptoms, negative symptoms, neurocognition, brief negative symptom scale, schizophrenia

INTRODUCTION

Schizophrenia is a multidimensional disorder, the disease syndrome consists of positive, negative, disorganized, and affective symptoms with varying degrees of intensity, accompanied by disorders of neurocognition and social cognition. Many studies focus on assessing the mutual relations between these domains. The relationship between negative symptoms and cognitive impairment is well documented (1), it seems to be stronger (2) than for positive (3) and affective symptoms (4). The mechanism of these connections, however, remains unclear (5), the obtained results are heterogeneous, and there are also methodological controversies.

Negative symptoms and cognitive impairment share many things in common. Their frequency, course, prognostic significance, and correlation with many aspects of daily functioning are similar (6). In most studies, the severity of both disorders negatively correlates with each other (7, 8). It should be noted, however, that there are also studies in which no correlation between negative symptoms and neurocognition was found (9, 10).

To explain these discrepancies, Harvey et al. (6) suggest the possibility of the occurrence of as many as four different models of the relationship between negative symptoms and cognitive impairment. Both disorders are a common dimension of the disease, both disorders are a separate dimension but with a similar etiology, each disorder has a separate etiology but with some common elements, and finally both disorders are a separate dimension and have a separate etiology. Summing up, the authors support the conclusion that both symptoms are separate, a similar position is taken by Yolland et al. (11). In their work, they did not observe the relationship between the severity of negative symptoms and cognitive impairment, which led them to suggest that negative symptoms and neurocognition are separate constructs and require separate therapeutic strategies.

Despite the above reservations, it seems that the mutual relationship between these two symptoms is more complex and multidimensional. Harvey et al. (6) indicate that cognitive disorders appear even before the clinical onset of psychosis and, similarly to negative symptoms, can be referred to as "early symptoms," which allows treating them as a neurodevelopmental component of schizophrenia. Ventura et al. (7) point out that negative symptoms may mediate between cognitive impairment and functional outcome, for Velligan et al. (12) negative symptoms are a behavioral consequence of cognitive impairment.

Harvey et al. (6) also indicate that the relationship between negative symptoms and cognitive impairment depends on the definition of negative symptoms while emphasizing that negative symptoms are defined based on the clinical picture, and cognitive disorders based on the tests performed. Additionally, the definition of negative symptoms differs depending on whether we are dealing with primary or secondary negative symptoms. Thus, patients with stable negative symptoms forming the deficit syndrome are characterized by a significant intensification of cognitive disorders (13).

As indicated by Milev et al. (2), the type of research tool used has a significant impact on the obtained results. In the research so far, the most frequently used scale is the Positive and Negative Syndrome Scale (PANSS). Some symptoms of cognitive nature (deficits in abstract thinking, stereotyped thinking, poor attention) are defined as negative or as general symptoms of schizophrenia by the PANSS. SANS also describes behavioral disorders such as deficits in social, occupational, and educational activity as negative symptoms, the same problem applies to attention disorders treated as negative symptoms (6). In a large systematic review of studies assessing the relationship of schizophrenia symptoms, including negative ones, with cognitive impairment, the authors cited the results of 18 studies from 2008-2019, none of the research protocols included the so-called 2nd generation scales for the assessment of negative symptoms, taking into account the NIMH- MATRICS consensus statement on negative symptoms (14, 15).

The nature and structure of the scales used so far lead, as noted by Alpert et al. (16) to evaluate individual items of negative symptoms through the prism of the global assessment of the clinical picture, which significantly affects the obtained results.

It also seems important to consider sex differences in research protocols that affect the age of onset of the disease, premorbid adjustment, course, and expression of clinical symptoms, which is particularly important in the context of the assessment of cognitive disorders and their relationship with negative symptoms (17).

Significant gender effects have been observed in schizophrenia for both negative symptoms and neurocognition. Moriarty et al. (18) suggested that negative symptom severity is greater in male patients. This was confirmed in subsequent research of Galderisi et al. (19) as well as our recent study as to the assessment on the BNSS scale (20).

The results of studies assessing the relationship between gender and cognitive processes in patients with schizophrenia are inconclusive. Some studies have reported superior cognitive function in women, others found the opposite or no gender difference, while some observed a reversal of normal sexual dimorphism (21). In numerous studies, men with schizophrenia performed worse in terms of cognitive functions, both in comparison with the control group (22) and female patients (23, 24). Only a few studies have shown better neurocognitive performance in men compared to women with schizophrenia (25, 26). There are also studies showing no difference in terms of neurocognition between men and women with schizophrenia (27, 28). As a factor assisting better cognitive performance in women with schizophrenia, estrogen and its neuroprotective role in the body are most often indicated (17, 29).

It seems that the endocrine system and its influence on the central nervous system are more closely related to the development of schizophrenia and sexual differences in the course of this disease than previously thought (30). Recent studies show that structural plasticity of the brain is regulated by hormones (31), not only in the systemic aspect, but also in the local–the brain is also capable of locally generating estrogens, either from androgens and possibly also directly from cholesterol (32, 33). The estrogen hypothesis is supported by late-onset age and second incidence peak around menopausal age in women. Indeed, estrogen deficiency is highly related

to the severity of psychiatric symptoms in women during menopause (34). For example, female schizophrenia patients often have more severe symptoms in the low estrogen phase of their menstrual cycle (35). Interestingly, the negative correlation between plasma estrogen levels and schizophrenia symptoms was also reported in male patients (36). The biochemical nature of the neuroprotective effects of estrogens has not been fully identified yet, but a number of studies points to a direct implication of the dopaminergic system, in addition to glutamate and GABA (37). When it comes to testosterone, studies found that low levels of testosterone appear to be associated with more severe symptoms, although results are less consistent than for estrogens (38). For instance, studies found that schizophrenia patients with low levels of testosterone often have predominantly negative symptoms, and serum testosterone levels are associated with greater severity of negative symptoms (39). Another important hormone associated with the pathogenesis of schizophrenia appears to be oxytocin. Several studies suggest that schizophrenia patients with higher levels of plasma oxytocin develop fewer psychotic symptoms (40), and have better cognition (41). Oxytocin is thought to regulate central dopamine, and might therefore exhibit antipsychotic effects (42).

The study aims to evaluate the relationship between negative symptoms assessed by the so-called 2nd generation scales such as the Brief Negative Symptoms Scale (BNSS) (43), and the Self-evaluation of Negative Symptoms (SNS) (44), with neuropsychological performance, in patients with chronic schizophrenia. The hypothesis was put forward postulating that such a relationship can be connected with gender.

METHODS

Study Design and Participants

This is a cross-sectional study. The study participants were recruited among subjects attending the outpatient and inpatient unit of the Department of Adult Psychiatry, Poznan University of Medical Sciences. The recruitment was carried out from October 31, 2016, to July 15, 2017.

Eighty patients (40 male, 40 female), aged 19–63 (mean 38 ± 11) years, with a diagnosis of schizophrenia, according to ICD-10 and DSM-5 were included. Their onset of illness was 26 ± 8 years, the duration of illness was 12 ± 9 years, and the number of hospitalization was 6 ± 6. They were either inpatients (60 subjects) or were under the care of the outpatient clinic (20 subjects), at the Department of Adult Psychiatry, Poznan University of Medical Sciences. All patients remained in the phase of symptomatic stabilization defined as achieving a total PANSS score of the maximum of 80 points. They received unchanged pharmacological treatment in the last 3 weeks (inpatients) or 3 months (outpatients). Four male and four female patients were treated with haloperidol. The remaining subjects received atypical antipsychotics (olanzapine, clozapine, aripiprazole, risperidone, quetiapine, amisulpride, and ziprasidone) the proportion of which was comparable in male and female patients.

Participants with significant physical, visual, verbal impairments, neurological disorders, and substance abuse or dependence, were excluded.

The local Ethics Committee approved the study (Agreement no 1122/16), and it was performed in accordance with the ethical standards of the Declaration of Helsinki (45). All participants signed a written informed consent to participate in the study, after receiving a detailed explanation of the study's procedures and goals.

Neuropsychological and Clinical Assessment

General Psychopathological Assessment

The Positive and Negative Syndrome Scale (PANSS) PANSS was developed by Kay et al. (46). It is a 30-item rating scale developed specifically to assess patients with schizophrenia. It is divided into three subscales, a positive scale with seven positive symptoms (P1-P7), a negative scale with seven negative symptoms (N1-N7), and a general psychopathology scale with 16 items (G1G16). Psychopathology severity is defined as 1 = absent; 2 = minimal; 3 = mild; 4 =moderate; 5 = moderate-severe; 6 = severe; 7 = extreme.

Assessment of Negative Symptoms

The Brief Negative Symptoms Scale

The BNSS was developed by Kirkpatrick et al. (43). The scale defines negative symptoms as the absence or decrease in behaviors and subjective experiences that are normally present in a person from the same culture and age group. The scale has 13 items organized into six subscales: anhedonia (intensity and frequency of pleasure, the intensity of expected pleasure), distress (subject's experience of unpleasant or distressing emotion of any kind, such as sadness, depression, anxiety, grief, anger), asociality (reported as reduced social activity accompanied by decreased interest in forming close relationships with others–behavior, internal experience), avolition (reported as a reduction in the initiation of and persistence in activity–behavior, internal experience), blunted affect (which refers to a decrease in the outward expression of emotion–facial expression, vocal expression, gestures), and alogia (reported as poverty of speech–the quantity of speech, spontaneous elaboration of speech). The examination is of an interview nature, based on a manual including, among other things, prompts and suggested questions. All items are rated on a 7-point scale (0–6), with anchor points ranging from a symptom being absent (0) to severe (6). The time frame for the ratings is 1 week. The basis for the interview is provided by the patient–participant observation also constitutes an important element–or, if needed, data obtained from external sources. The Polish version of BNSS was used in the study (47).

The Self-Evaluation of Negative Symptoms

The SNS was developed by Dollfus et al. (44). The scale evaluates all five groups of negative symptoms, i.e., social withdrawal, blunted affect, avolition, anhedonia, and alogia. Social withdrawal (asociality) assesses social relationships as well as the patient's propensity to establish new relationships; diminished emotional range (blunted affect) reflects a presence

of happiness or sadness in situations in which they are usually felt; avolition relates to motivation, energy level and the ability to achieve goals; anhedonia describes the experienced and expected pleasure; alogia (poverty of speech) is evaluated by the subjective assessment of the examined person. The scale contains 20 items, four items for each negative symptom, and the evaluation pertains to the previous week. For maximal simplification, the number of responses was limited to 3: "strongly agree" scoring 2, "somewhat agree" scoring 1, and "strongly disagree" scoring 0. The total score is the sum of the 20 items, ranging from 0 (no negative symptoms) to 40 (severe negative symptoms). The Polish version of SNS was used in the study (48).

Assessment of Social Functioning

The Personal and Social Performance scale (PSP) evolved based on the social functioning component of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) as an effort to assess social functioning in schizophrenia. It is being proposed as an improvement over the Global Assessment of Functioning (GAF) scale and SOFAS. PSP is a 100-item scale, divided into 10 similar intervals. The score is based on the assessment of patient's performance in four categories: socially useful activities, personal and social relationships, self-care, disturbing and aggressive behavior. PSP provides a score between 1 and 100, divided into 10 equal intervals to rate the degree of difficulty. Higher scores represent better personal and social functioning (49).

Assessment of Neurocognition

Trail Making Test (TMT-A, TMT-B)

Trail Making Test is used to assess working memory and as an indicator of visual scanning, graphomotor speed, and executive function. In part A, the subject is asked to connect the circles marked with numbers from 1 to 25 as quickly as possible, which allows the measurement of psychomotor speed. In part B, the subject's task is to as quickly as possible connect the circles marked with numbers 1–13 and letters A-L in the order 1-A-2-B-3-C, etc. This operation requires keeping two different sequences of numbers and letters in working memory. The result of the test is the time and correctness of parts A and B of the test (50). We also calculated the TMT B-A difference as proposed in recent studies (51).

Stroop Color–Word Interference

Test Stroop Color–Word Interference Test is used to evaluate verbal working memory. The test consists of two parts. In the first one (Reading Color Names in Black, RCNb, Stroop A), the respondent is asked to read the words (color names) written in black on a white sheet as soon as possible. In the second part (Naming Color of Word different, NCWd, Stroop B), the respondent's task is to name the font color of individual words, whereby the font color of the word is different from the color indicated by him. This activity requires a change in the form of reaction (switching from content to color). The result of the test is the time needed to complete the first and second parts and the number of incorrect answers (52). The difference between Stroop B-A was also calculated (53).

Verbal Fluency Tests and Category Fluency Test

Verbal fluency tests and Category fluency test are used to evaluate speech functions, and semantic memory access and executive functions. The tests assess the ability to pronounce words fluently in accordance with a specific criterion in a given time (for 60 seconds). This criterion is a given letter (in VFT) or category (in CFT). In the Polish version used in the study, in the part assessing verbal fluency, the respondent's task is to list for 1 min as many words starting with the letters of the alphabet as possible: K, O, S, and in the part assessing categorical fluency, the greatest number of words from three categories: animals, vegetables, fruits (54, 55).

Digit Symbol Substitution Test

Digit Symbol Substitution Test is a wordless test on the Wechsler Adult Intelligence Scale (WAIS-R). It is used to evaluate motor speed, attention, and visuoperceptual functions. The task of the examined person is to assign symbols to digits according to a given key within a specified time (90 s). The result of the test is the number of correctly assigned symbols (56, 57).

Statistics

Continuous data is presented as means and standard deviations. Except of the descriptive statistics the effect size was denoted (d Cohen). The Shapiro-Wilk test was applied to check if data follow the normal distribution. Because the data of BNSS, SNS, and PSP were consistent with a normal distribution, the gender differences were assessed by the two-tailed *t*-test. The data of neurocognitive tests was not normally distributed which is why the Box-Cox transformation of non-normal dependent variables was performed in order to assess a normal shape. Additionally, the Benjamini–Hochberg adjusted *p*-value for multiple comparisons was calculated. Statistical relationships between BNSS, SNS, PSP and the results of neurocognitive tests were calculated using Pearson correlation coefficient. The statistical analysis was performed with the use of TIBCO Software Inc. (2017). Statistica (data analysis software system), version 13. http://statistica.io. All test were considered significant at $p < 0.05$.

RESULTS

The mean age of women with schizophrenia was higher than men (41 vs. 35, $p = 0.048$), the mean number of years of education was greater in the group of women than in men (13 vs 12, $p = 0.046$). There was no gender difference in disease duration and number of hospitalizations (see **Table 1**).

The comparison of the results of psychometric tests in male and female schizophrenia patients is shown in **Table 2**.

Among the PANSS scores, there was a significantly higher score on negative symptoms and total score in male patients (both $p < 0.05$, d Cohen 0.6, medium effect size). On the BNSS scale, there was a significantly higher score of male patients in subscales of distress ($p = 0.01$, d Cohen 0.7) and asociality ($p = 0.05$, d Cohen 0.6). There was also a tendency ($p < 0.1$, d Cohen 0.5) for the higher total BNSS score. No gender differences were found as to the assessment on the SNS scale.

Female patients scored significantly better on the PSP scale (68.1 vs. 60.7, $p = 0.021$, d Cohen 0.5)

The comparison of the results of neurocognition tests in male and female schizophrenia patients is shown in **Table 3**.

No significant gender differences were observed except that female patients performed significantly better on the Category Fluency Test ($p < 0.001$, d Cohen 1.0).

The relationships between the results of women and men on the BNSS, SNS, and PSP scales and the results of neurocognitive tests are shown in **Table 4**.

In male patients, we found a significant positive correlation between BNSS total and subscales and a significant negative correlation between the results on PSP with the Trail Making Test (TMT-A, TMT-B).

In female patients, a significant positive correlation between the intensity of negative symptoms measured by the BNSS total and most subscales, and the results of Stroop B was found. The BNSS asociality correlated with the results of Stroop A. The intensity of negative symptoms measured by the SNS sum, social withdrawal, and anhedonia subscale correlated with the results of Stroop A. A significant negative correlation between the results of PSP with the results of both Stroop A and B was observed.

TABLE 1 | Demographic characteristics of the study group.

Category	Total $n = 80$	Women $n = 40$	Men $n = 40$	p
Age Mean ± SD (years)	38 ± 10	40 ± 12	35 ± 8	**0.048***
Years of education Mean ± SD	12 ± 2	13 ± 2	12 ± 2	**0.046***
Illness duration Mean ± SD (years)	12 ± 9	13 ± 9	10 ± 9	0.090
Number of hospitalizations Mean ± SD	6 ± 6	6 ± 6	6 ± 6	0.785

*Difference between men and women significant $p < 0.05$.

DISCUSSION

The results obtained may indicate gender differences in schizophrenia patients in the assessment of negative symptoms and personal and social performance as well as in the correlations between negative symptoms and the results of neurocognitive tests. In male patients, the higher score on BNSS and worse results on PSP make a corroboration of our previous work (58). Also, the better results in schizophrenic women on PSP were recently confirmed by Spanish investigators (59).

The main aim of our study was to investigate the correlation between negative symptoms and neurocognitive functions. Such correlation of negative symptoms with various indexes of neurocognition has been described in many papers (5, 6, 60). In all these studies, the negative symptoms were assessed by the PANSS. However, in a recent validation of the BNSS in Korean patients with schizophrenia, a correlation of negative symptoms assessed by this scale with neurocognitive tests of verbal memory, processing speed, and attention was found (61).

TABLE 2 | The comparison of the results of clinical and psychometric tests in female and male schizophrenia patients.

Parameter	Total		Women		Men		Effect size	p-value	Adjusted p-value*
	Mean	SD	Mean	SD	Mean	SD	d Cohen		
PANSS positive	13.6	3.1	12.8	3.1	14.3	3	−0.5	0.041	0.082
PANSS negative	16.6	5	15.1	4.9	18.2	4.8	−0.6	0.006	**0.022***
PANSS general	29	5.3	28.2	6.2	29.7	4.3	−0.3	0.221	0.221
PANSS sum	59.2	10.8	56.2	11.7	62.2	8.8	−0.6	0.012	**0.035***
BNSS anhedonia	6.2	3.4	5.6	3.7	6.6	3.1	−0.3	0.156	0.156
BNSS distress	1.3	1	1	1	1.7	1	−0.7	0.001	**0.010***
BNSS asociality	3.9	2	3.3	2	4.5	1.9	−0.6	0.009	**0.050***
BNSS avolition	4.1	2.1	3.7	2.1	4.6	2	−0.4	0.086	0.156
BNSS blunted affect	4.9	3.2	4.2	3.2	5.7	3	−0.5	0.038	0.153
BNSS alogia	2.6	2.2	2.1	2	3	2.4	−0.4	0.086	0.156
BNSS sum	23.3	11.5	20.2	11.7	26.4	11.6	−0.5	0.020	0.099
SNS social withdrawal	2.9	2	2.5	2.1	3.3	1.8	−0.4	0.076	0.455
SNS diminished emotion	3.4	2.1	3	2.1	3.7	2	−0.3	0.144	0.499
SNS alogia	3.8	2.4	3.6	2.6	4	2.3	−0.2	0.499	0.499
SNS avolition	3.8	2.3	3.5	2.5	4	2	−0.2	0.388	0.499
SNS anhedonia	2.8	2.4	2.5	2.5	3.1	2.4	−0.2	0.301	0.499
SNS sum	16.7	8.8	15.2	9.9	18.2	7.4	−0.3	0.144	0.499
PSP	60.4	14.5	68.1	14.1	60.7	14.1	0.5	0.021	**0.021***

*Difference between men and women significant $p \leq 0.05$. Significant differences are marked in bold.

TABLE 3 | The comparison of the results of neurocognition tests in female and male schizophrenia patients.

Parameter	Total		Women		Men		Effect size	*p*-value	Adjusted *p*-value*
	Mean	SD	Mean	SD	Mean	SD	d Cohen		
TMT-A	44.7	23.1	42.7	17.8	46.6	27.4	−0.2	0.457	1.000
TMT-B	113.2	73.1	108.8	51.8	117.6	89.9	−0.1	0.593	1.000
TMT B-A	68.5	60.5	66.1	45.6	71	72.3	−0.1	0.718	1.000
Stroop A time	28.6	12.6	28.6	12.1	28.6	13.1	0.0	1.000	1.000
Stroop B time	81.7	39.1	77.6	35.6	85.7	42.2	−0.2	0.360	1.000
Stroop B-A time	53.1	34.0	49.1	33.2	57.1	34.7	−0.2	0.293	1.000
Stroop B incorrect answers	4.6	12.6	4.6	16.4	4.4	7.2	0.0	0.937	1.000
Category fluency test	36.6	13.4	42.7	12.2	30.4	11.6	1.0	<0.001	**<0.001**
Verbal fluency tests	32.4	14.7	34.8	15.2	30	13.8	0.3	0.138	1.000
Digit Symbol	34.6	14.8	36.7	15.9	32.5	13.5	0.3	0.213	1.000

**Difference between men and women significant $p < 0.001$. Significant differences are marked in bold.*

TABLE 4 | Relationships between the results of men and women on the BNSS, SNS, and PSP scale and the results of neurocognition tests.

Parameter	Male				Female			
	TMT-A	TMT-B	Stroop A	Stroop B	TMT-A	TMT-B	Stroop A	Stroop B
BNSS anhedonia	0.399 $p = 0.011$	0.328 $p = 0.039$	0.127	0.179	0.027	−0.203	0.306	0.368 $p = 0.019$
BNSS asociality	0.343 $p = 0.03$	0.359 $p = 0.023$	0.209	0.207	−0.099	−0.250	0.380 $p = 0.015$	0.3
BNSS avolition	0.459 $p = 0.003$	0.356 $p = 0.024$	0.18	0.257	−0.053	−0.284	0.308	0.405 $p = 0.009$
BNSS blunted affect	0.524 $p = 0.001$	0.398 $p = 0.011$	−0.026	0.225	0.07	−0.255	0.24	0.509 $p = 0.001$
BNSS alogia	0.523 $p = 0.001$	0.414 $p = 0.008$	0.284	0.266	0.079	−0.216	0.24	0.585 $p = 0.001$
BNSS sum	0.502 $p = 0.001$	0.406 $p = 0.009$	0.158	0.254	0.009	−0.272	0.311	0.487 $p = 0.001$
SNS social withdrawal	0.165	0.263	0.007	0.011	−0.114	−0.113	0.432 $p = 0.005$	0.148
SNS diminished emotion	0.285	0.225	0.003	0.099	0.013	−0.166	0.33	0.35
SNS alogia	0.142	0.069	0.216	0.005	0.038	−0.153	0.337	0.129
SNS avolition	−0.715	0.208	0.067	−0.037	0.004	−0.013	0.166	0.21
SNS anhedonia	0.215	0.209	−0.175	0.001	0.026	−0.055	0.388 $p = 0.013$	0.126
SNS sum	0.218	0.275	0.029	0.019	−0.001	−0.097	0.391 $p = 0.012$	0.23
PSP sum	−0.439 $p = 0.005$	−0.343 $p = 0.03$	−0.163	−0.245	−0.001	0.124	−0.315 $p = 0.047$	−0.367 $p = 0.02$

Pearson correlation coefficient and "p" of significant correlations were given.

Recently, Eack and Keshavan (62) suggested three potential underpinnings of such correlation. First, that cognitive and negative symptoms share similar underlying pathophysiology giving rise to their overlap and impact on functioning. Second, that cognitive impairment leads to greater negative symptoms and reduced functional performance, and third, that negative symptoms lead to impaired cognitive abilities that drive poor functional outcomes. In this respect, is of importance the paper of Luther et al. (63) in which in the 20-year longitudinal study, it was found that greater negative symptoms predicted reduced neurocognition and indirectly–impaired work functioning.

In our research, the results of the neurocognitive tests were numerically worse in males, however, the only significant difference was in the category fluency. Whereas, significant correlations between negative symptoms and the results on some neurocognitive tests were obtained. However, in male and female

patients they were observed for different cognitive tests. In males, a significant positive correlation between the intensity of negative symptoms measured by the BNSS and the Trail Making Test was observed. In female patients, we found positive correlations between the results of the BNSS and Stroop Color-Word Interference Test. Interestingly, similar correlations in male and female schizophrenia patients were obtained between these neurocognitive tests and the results of the PSP scale.

Therefore, the most intriguing result of our study is a relationship obtained in male and female schizophrenia patients between negative symptoms and social functioning, with different cognitive domains. In men, increased negative symptoms and worse functioning were correlated with inferior results of TMT test measuring visual attention and task switching, while in female patients such correlations were obtained with a worse outcome of the Stroop test, assessing the ability to inhibit cognitive interference. Probably, it can be speculated that these clinical and functioning disturbances are mostly underpinned by different cognitive factors depending on gender.

Why impaired cognitive abilities involved in the Trail Making Test are related to the intensity of negative symptoms and social performance in men but not in women? It can be speculated that in men, impaired psychomotor speed, attention, and mental flexibility are more important than in women for a generation of negative symptoms and social functioning. A similar question can be asked, why impaired performance on the Stroop test is related to the intensity of negative symptoms and social performance in women but not in men? Probably, in women, impaired ability to inhibit cognitive interference is more important than in men for a generation of negative symptoms and social functioning.

Regardless of the neurophysiological mechanisms of these differences, the results may point to distinctive features of negative symptoms in male and female schizophrenia patients. This was also shown in our recent study in which in female patients, a significant positive correlation between the intensity of negative symptoms measured by the BNSS scale and the concentration of high-density lipoprotein (HDL) cholesterol, and a trend for negative correlation with BMI was observed. Whereas, such correlations were not found in male patients (58).

The study suffers from four major limitations. First, the experimental sample consisted of chronic and clinically stable subjects with schizophrenia and did not include a control group (e.g., healthy controls). Second, we did not include the measure of IQ, which is important for cognitive functioning in schizophrenia and potential differences between groups. Third, the study took place in a controlled environment, which resulted in a low ecological validity of the used neuropsychological assessment, consequently, it is more difficult to generalize the study's findings. Last, but not least, the chlorpromazine equivalents of drugs that were administered to patients and which may have an important role for cognitive functioning in schizophrenia were not recorded in the study. Given the importance of the above limitations, future research should take them into account.

In conclusion, the results obtained confirm the relationship between negative symptoms and neurocognition in schizophrenia patients, although for different cognitive domains, depending on gender. Considering the above aspects together seems to be important from a clinical point of view, as suggested by Li et al. (34). Consideration of gender differences in schizophrenia provides an important insight for understanding the sex-specific characteristics of the disease's onset, symptoms, and the opportunity to deliver sex-specific treatments and care for schizophrenia. The above observations have already been reflected in previous studies in which an integrated therapeutic approach with the combination of neurocognition and social cognition might be a more effective approach to treating the symptomatology of people with schizophrenia (1, 64).

Further research is needed to confirm these findings and to explain the nature of these differences. It seems particularly important to correctly define negative symptoms, to standardize tools for the assessment of neurocognition, and in the aspect of gender differences-to take into account such differentiating factors as the endocrine system or molecular-genetic findings. Study design should also take into account ecological validity in subsequent studies, to predict better behaviors in real-world settings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Bioethics Committee, Poznan University of Medical Sciences, Poznan, Poland. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PW took part in the design of the study and wrote the first draft of the manuscript. KD performed psychometric assessments. MZ performed neurocognitive assessments. MM performed statistical calculation. JR elaborated the design of the study and wrote the final version of the manuscript. All authors accepted the final version of the manuscript.

FUNDING

The paper was helped by own funds of the Department of Adult Psychiatry, Poznan University of Medical Sciences.

REFERENCES

1. Lam BYH, Raine A, Lee TMC. The relationship between neurocognition and symptomatology in people with schizophrenia: social cognition as the mediator. *BMC Psychiatry*. (2014) 14:138. doi: 10.1186/1471-244X-14-138
2. Milev P, Ho BC, Arndt S, Andreasen NC. (2005). Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am J Psychiatry*. (2005) 162:495–506. doi: 10.1176/appi.ajp.162.3.495
3. Ventura J, Wood RC, Hellemann GS. Symptom Romains and neurocognitive functioning can help differentiate social cognitive process in schizophrenia: a meta-analysis. *Schizophr Bull*. (2011) 39:102–11. doi: 10.1093/schbul/sbr067
4. Smith TE, Hull JW, Goodman M, Hedayat-Harris A, Willson DF, Israel LM, et al. The relative influences of symptoms, insight, and neurocognition on social adjustment in schizophrenia and schizoaffective disorder. *J Nerv Ment Dis*. (1999) 187:102–8. doi: 10.1097/00005053-199902000-00006
5. Lin CH, Huang CL, Chang YC, Chen PW, Lin CY, Tsai GE. Clinical symptoms, mainly negative symptoms, mediate the influence of neurocognition and social cognition on functional outcome of schizophrenia. *Schizophr Res*. (2013) 146:231–7. doi: 10.1016/j.schres.2013.02.009
6. Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship? *Schizophrenia Bulletin*. (2006) 32:250–8. doi: 10.1093/schbul/sbj011
7. Ventura J, Hellemann GS, Thames AD, Koellner V, Nuechterlein KH. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. *Schizophrenia Research*. (2009) 111:189–99. doi: 10.1016/j.schres.2009.03.035
8. Dominguez Md G, Viechtbauer W, Simons,CJ, van Os J, Krabbendam L. Are psychotic psychopathology and neurocognition orthogonal? a systematic review of their associations. *Psychological Bulletin*. (2009) 135:157–71. doi: 10.1037/a0014415
9. Altamura AC, Caletti E, Paoli RA, Cigliobianco M, Zugno E, Grillo P. Correlation between neuropsychological and social cognition measures and symptom dimensions in schizophrenic patients. *Psychiatry Research*. (2015) 230:172–80. doi: 10.1016/j.psychres.2015.08.034
10. Bismark AW, Thomas ML, Tarasenko M, Shiluk AL, Rackelmann SY, Young JW. Relationship between effortful motivation and neurocognition in schizophrenia. *Schizophr Res*. (2018) 193:69–76. doi: 10.1016/j.schres.2017.06.042
11. Yolland COB, Carruthers SP, Toh WL, Neill E, Sumner PF, Thomas EHX. The relationship between negative symptoms and both emotion management and non-social cognition in schizophrenia. Spectrum disorders. *J Int Neuropsychol Soc*. (2020) 1–13. doi: 10.1017/S1355617720001290
12. Velligan DI, Mahurin RK, Diamond PL, Hazleton BC, Eckert SL, Miller AL. The functional significance of symptomatology and cognitive function in schizophrenia. *Schizophr Res*. (1997) 25:21–31. doi: 10.1016/S0920-9964(97)00010-8
13. Lysaker PH, Bell MD, Bioty SM, Zito WS. Cognitive impairment and substance abuse history as predictors of the temporal stability of negative symptoms. *J Nerv Ment Dis*. (1997) 185:21–6. doi: 10.1097/00005053-199701000-00004
14. Habtewold TD, Rodijk LH, Liemburg EJ, Sidorenkov G, Boezen HM, Bruggeman R. A systematic review and narrative synthesis of data-driven studies in schizophrenia symptoms and cognitive deficits. *Transl Psychiatry*. (2020) 10:244. doi: 10.1038/s41398-020-00919-x
15. Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull*. (2006) 32:214–9. doi: 10.1093/schbul/sbj053
16. Alpert M, Shaw RJ, Pouget ER, Lim KO. A comparison of clinical ratings with vocal acoustic measures of flat affect and alogia. *J Psychiatr Res*. (2002) 36:347–53. doi: 10.1016/S0022-3956(02)00016-X
17. Ko YH, Joe SK, Cho W, Park JH, Lee JJ, Jung IK, et al. Estrogen, cognitive function and negative symptoms in female schizophrenia. *Neuropsychobiology*. (2006) 53:169–75. doi: 10.1159/000093780
18. Moriarty PJ, Lieber D, Bennet A, White L, Parrella M, Harvey PD. Gender differences in poor outcome patients with lifelong schizophrenia. *Schizophr Bull*. (2001) 27:103–13. doi: 10.1093/oxfordjournals.schbul.a006850
19. Galderisi S, Bucci P, Üçok A, Peuskens J. No gender differences in social outcome in patients suffering from schizophrenia. *Eur Psychiatry*. (2012) 27:406–8. doi: 10.1016/j.eurpsy.2011.01.011
20. Wójciak P, Domowicz K, Andrzejewska M, Rybakowski JK. Negative symptoms in schizophrenia, assessed by the brief negative symptom scale, self-evaluation of negative symptom scale, and social cognition: a gender effect. *Int J Psychiatry Clin Pract*. (2021) 25:252–7. doi: 10.1080/13651501.2020.1810278
21. Mendrek A, Mancini-Marië A. Sex/gender differences in the brain and cognition in schizophrenia. *Neurosci Biobehav Rev*. (2016) 67:57–78. doi: 10.1016/j.neubiorev.2015.10.013
22. Goldstein JM, Seidman LJ, Goodman JM, Koren D, Lee H, Weintraub S. Are there sex differences in neuropsychological function among patients with schizophrenia? *Am J Psychiatry*. (1998) 155:1358–64. doi: 10.1176/ajp.155.10.1358
23. Vaskinn A, Sundet K, Simonsen C, Hellvin T, Melle I, Andreassen OA. Sex differences in neuropsychological performance and social functioning in schizophrenia and bipolar disorder. *Neuropsychology*. (2011) 25:499–510. doi: 10.1037/a0022677
24. Han M, Huang XF, Chen da C, Xiu MH, Hui L, Liu H, et al. Gender differences in cognitive function of patients with chronic schizophrenia. *Neuropsychopharmacol Biol Psychiatry*. (2012) 39:358–63. doi: 10.1016/j.pnpbp.2012.07.010
25. Perlick D, Mattis S, Stastny P, Teresi J. Gender differences in cognition in schizophrenia. *Schizophr Res*. (1992) 8:69–73. doi: 10.1016/0920-9964(92)90062-A
26. Lewine RR, Walker EF, Shurett R, Caudle J, Haden C. Sex differences in neuropsychological functioning among schizophrenic patients. *Am J Psychiatry*. (1996) 153:1178–80. doi: 10.1176/ajp.153.9.1178
27. Andia AM, Zisook S, Heaton RK, Hesselink J, Jernigan T, Kuck J, et al. Gender differences in schizophrenia. *J Nerv Ment Dis*. (1995) 183:522–8. doi: 10.1097/00005053-199508000-00005
28. Kao YC, Liu YP, Lien YJ, Lin SJ, Lu CW, Wang TS, et al. The influence of sex cognitive insight and neurocognitive functioning in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. (2013) 1:193–200. doi: 10.1016/j.pnpbp.2013.02.006
29. Hoff AL, Kremen WS, Wieneke MH, Lauriello J, Blankfeld HM, Faustman WO. Association of estrogen levels with neuropsychological performance in women with schizophrenia. *Am J Psychiatry*. (2001) 158:1134–9. doi: 10.1176/appi.ajp.158.7.1134
30. Morgan VA, Castle DJ, Jablensky AV. Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders. *Aust N Z J Psychiatry*. (2008) 42:74–82. doi: 10.1080/00048670701732699
31. McEwen BS, Milner TA. Understanding the Broad Influence of Sex Hormones and Sex Differences in the Brain. *J Neurosci Res*. (2017) 95:24–39. doi: 10.1002/jnr.23809
32. Hajszan T, Milner TA, Leranth C. Sex steroids and the dentate gyrus. *Prog Brain Res*. (2007) 163:399–415. doi: 10.1016/S0079-6123(07)63023-4
33. Hojo Y. Hattori T-a, Enami T, Furukawa A, Suzuki K, Ishii K, et al. Adult Male rat hippocampus synthesizes estradiol from pregnenolone by cytochromes P45017α and P450 aromatase localized in neurons. *Proc Natl Acad Sci USA*. (2004) 101:865–70. doi: 10.1073/pnas.2630225100
34. Li R, Ma X, Wang G, Yang J, Wang Ch. Why sex differences in schizophrenia? *J Transl Neurosci*. (2016) 1:37–42.
35. Grigoriadis S, Seeman MV. The role of estrogen in schizophrenia: implications for schizophrenia practice guidelines for women. *Can J Psychiatry*. (2002) 47:437–42. doi: 10.1177/070674370204700504
36. Kaneda Y, Ohmori T. Relation between estradiol and negative symptoms in men with schizophrenia. *J Neuropsychiatry Clin Neurosci*. (2005) 17:238–42. doi: 10.1176/jnp.17.2.239
37. Fink G, Sumner BE. McQueen JK, Wilson H, Rosie R. Sex steroid control of mood, mental state and memory. *Clin Exp Pharmacol Physiol*. (1998) 25:764–75. doi: 10.1111/j.1440-1681.1998.tb02151.x
38. Ko YH, Jung SW, Joe SH, Lee HCH, Jung HG, Jung IK. Association between serum testosterone levels and severity of negative symptoms in male patients with chronic schizophrenia. *Psychoneuroendocrinology*. (2007) 32:385–91. doi: 10.1016/j.psyneuen.2007.02.002

39. Sisek-Sprem M, Krizaj A, Jukic V, Milosevic M, Petrovic Z, Herceg M. (2015). Testosterone levels and clinical features of schizophrenia with emphasis on negative symptoms and aggression. *Nord J Psychiatry*. (2015) 69:102–9. doi: 10.3109/08039488.2014.947320
40. Sasayama D, Hattori K, Teraishi T, Hori H, Ota M, Yoshida S. Negative correlation between cerebrospinal fluid oxytocin levels and negative symptoms of male patients with schizophrenia. *Schizophr Res*. (2012) 139:201–6. doi: 10.1016/j.schres.2012.06.016
41. Frost KH, Keller WR, Buchanan RW, Gold JM, Koenig JI, Ossenfort KL. Plasma Oxytocin Levels are Associated with Impaired Social Cognition and Neurocognition in Schizophrenia. *Archives of Clinical Neuropsycholog.* (2014) 29:577–8. doi: 10.1093/arclin/acu038.195
42. Feitel D. Is oxytocin a promising treatment for schizophrenia? *Expert Rev Neurother.* (2011) 11:157–9. doi: 10.1586/ern.10.199
43. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A. The brief negative symptom scale: psychometric properties. *Schizophr Bull*. (2011) 37:300–5. doi: 10.1093/schbul/sbq059
44. Dollfus S, Mach C, Morello R. Self-evaluation of negative symptoms: a novel tool to assess negative symptoms. *Schizophr Bull*. (2016) 42:571–8. doi: 10.1093/schbul/sbv161
45. World Medical Association General Assembly. *Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects*. Fortaleza: World medical Association (2013).
46. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* (1987) 13:261–76. doi: 10.1093/schbul/13.2.261
47. Wójciak P, Górna K, Domowicz K, Jaracz K, Gołebiewska K, Michalak M. Polish version of the Brief Negative Symptom Scale (BNSS). *Psychiatr Pol.* (2019) 53:541–9. doi: 10.12740/PP/OnlineFirst/91490
48. Wójciak P, Górna K, Domowicz K, Jaracz K, Szpalik R, Michalak M. Polish version of the Self-evaluation of Negative Symptoms (SNS). *Psychiatr Pol.* (2019) 53:551–9. doi: 10.12740/PP/OnlineFirst/97352
49. Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand.* (2000) 101:323–9. doi: 10.1111/j.1600-0447.2000.tb10933.x
50. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills.* (1958) 8:271–6. doi: 10.2466/pms.1958.8.3.271
51. Periáñez JA, Ríos-Lago M, Rodríguez-Sánchez JM, Adrover-Roig D, Sánchez-Cubillo I, Crespo-Facorro B. Trail Making Test in traumatic brain injury, schizophrenia, and normal ageing: Sample comparisons and normative data. *Arch Clin Neuropsychol.* (2007) 22:433–47. doi: 10.1016/j.acn.2007.01.022
52. Stroop JR. Studies of interference in serial verbal reaction. *J Exp Psychology*. (1935) 18:643–62. doi: 10.1037/h0054651
53. Tyburski E, Karabanowicz E, Mak M, Lebiecka Z, Samochowiec A, Pełka-Wysiecka J. Color trails test: a new set of data on cognitive flexibility and processing speed in schizophrenia. *Front Psychiatry*. (2020) 11:521. doi: 10.3389/fpsyt.2020.00521
54. Thurstone LL. *Primary Mental Abilities*. Chicago: University of Chicago Press (1938).
55. Piskunowicz M, Bieliński M, Zgliński A, Borkowska A. Verbal fluency tests–application in neuropsychological assessment. *Psychiatria Polska*. (2013) 47: 475–85.
56. Wechsler D. *Manual for the Wechsler Adult Intelligence Scale*. New York: The Psychological Corporation (1955).
57. Brzeziński J, Gaul M, Hornowska E, Machowski A, Zakrzewska MS. *Wechslera dla dorosłych Wersja zrewidowana WAIS-R (PL).* Warszawa: Pracownia Testów Psychologicznych PTP (1996).
58. Wójciak P, Domowicz K, Rybakowski JK. Metabolic indices in schizophrenia: association of negative symptoms with higher HDL cholesterol in female patients. *World J Biol Psychiatry.* (2021) 22:552–6. doi: 10.1080/15622975.2020.1849796
59. García-Portilla MP, García-Álvarez L, González-Blanco L, Dal Santo F, Bobes-Bascarán T, Martínez-Cao C, et al. Real-world functioning in patients with schizophrenia: beyond negative and cognitive symptoms. *Front Psychiatry*. (2021) 12:700747. doi: 10.3389/fpsyt.2021.700747
60. Priyamvada R, Ranjan R, Jha GK, Chaudhury S. Correlation of neurocognitive deficits with positive and negative symptoms in schizophrenia. *Ind Psychiatry J.* (2021) 30:249–54. doi: 10.4103/ipj.ipj_44_20
61. Jeakal E, Park K, Lee E, Strauss GP, Choi KH. Validation of the Brief Negative Symptom Scale in Korean patients with schizophrenia. *Asia Pac Psychiatry*. (2020) 12:e12382. doi: 10.1111/appy.12382
62. Eack SM, Keshavan MS. Cognition, negative symptoms, and functional outcome in psychosis. *Schizophr Res.* (2020) 224:22–3. doi: 10.1016/j.schres.2020.06.029
63. Luther L, Suor JH, Rosen C, Jobe TH, Faull RN, Harrow M. Clarifying the direction of impact of negative symptoms and neurocognition on prospective work functioning in psychosis: a 20-year longitudinal study. *Schizophr Res.* (2020) 220:232–9. doi: 10.1016/j.schres.2020.03.012
64. Bartholomeusz CF, Allott K. Neurocognitive and social cognitive approaches for improving functional outcome in early psychosis: theoretical consideration and current state of evidence. *Schizophrenia Res Treatment*. (2012) 2012:815315. doi: 10.1155/2012/815315

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 07 January 2022
doi: 10.3389/fpsyt.2021.825681

Negative Symptom Domains Are Associated With Verbal Learning in Adolescents With Early Onset Psychosis

Lynn Mørch-Johnsen[1,2], Runar Elle Smelror[1,3], Dimitrios Andreou[1,3,4], Claudia Barth[1,3], Cecilie Johannessen[5], Kirsten Wedervang-Resell[1], Laura A. Wortinger[1,3], Ricardo Díaz[6], Gamaliel Victoria[7], Torill Ueland[8,9], Ole A. Andreassen[1,8], Anne M. Myhre[8,10], Bjørn Rishovd Rund[9,11], Rosa Elena Ulloa[12] and Ingrid Agartz[1,3,4,13]*

[1] Norwegian Centre for Mental Disorders Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [2] Department of Psychiatry and Department of Clinical Research, Østfold Hospital, Grålum, Norway, [3] Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway, [4] Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet and Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden, [5] Department of Neurohabilitation, Oslo University Hospital Ullevål, Oslo, Norway, [6] Research Department, Arete Proyectos y Administración, Mexico City, Mexico, [7] Planning of Prevention Programs in the Directorate of Integral Attention to Girls, Boys and Adolescents, System for the Integral Development of the Family, Mexico City, Mexico, [8] Division of Mental Health and Addiction, Norwegian Centre for Mental Disorders Research, Oslo University Hospital, Oslo, Norway, [9] Department of Psychology, University of Oslo, Oslo, Norway, [10] Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [11] Research Department, Vestre Viken Hospital Trust, Drammen, Norway, [12] Developmental Psychopharmacology at the Research Division, Child Psychiatric Hospital, Mexico City, Mexico, [13] Institute of Clinical Medicine, K.G. Jebsen Centre for Neurodevelopmental Disorders, University of Oslo, Oslo, Norway

OPEN ACCESS

Edited by:
Armida Mucci, University of Campania Luigi Vanvitelli, Italy

Reviewed by:
Giulia Maria Giordano, University of Campania Luigi Vanvitelli, Italy
Oleg Papsuev, Moscow Research Institute of Psychiatry, Russia

***Correspondence:**
Lynn Mørch-Johnsen
lynn.morch-johnsen@medisin.uio.no

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *30 November 2021*
Accepted: *16 December 2021*
Published: *07 January 2022*

Citation:
Mørch-Johnsen L, Smelror RE, Andreou D, Barth C, Johannessen C, Wedervang-Resell K, Wortinger LA, Díaz R, Victoria G, Ueland T, Andreassen OA, Myhre AM, Rund BR, Ulloa RE and Agartz I (2022) Negative Symptom Domains Are Associated With Verbal Learning in Adolescents With Early Onset Psychosis. Front. Psychiatry 12:825681. doi: 10.3389/fpsyt.2021.825681

Background: Early-onset psychosis (EOP) is among the leading causes of disease burden in adolescents. Negative symptoms and cognitive deficits predicts poorer functional outcome. A better understanding of the association between negative symptoms and cognitive impairment may inform theories on underlying mechanisms and elucidate targets for development of new treatments. Two domains of negative symptoms have been described in adult patients with schizophrenia: *apathy* and *diminished expression*, however, the factorial structure of negative symptoms has not been investigated in EOP. We aimed to explore the factorial structure of negative symptoms and investigate associations between cognitive performance and negative symptom domains in adolescents with EOP. We hypothesized that (1) two negative symptom factors would be identifiable, and that (2) diminished expression would be more strongly associated with cognitive performance, similar to adult psychosis patients.

Methods: Adolescent patients with non-affective EOP ($n = 169$) were included from three cohorts: Youth-TOP, Norway ($n = 45$), Early-Onset Study, Norway ($n = 27$) and Adolescent Schizophrenia Study, Mexico ($n = 97$). An exploratory factor analysis was performed to investigate the underlying structure of negative symptoms (measured with the Positive and Negative Syndrome Scale (PANSS)). Factor-models were further assessed using confirmatory factor analyses. Associations between negative symptom domains and six cognitive domains were assessed using multiple linear regression models controlling for age, sex and cohort. The neurocognitive domains from the MATRICS Consensus Cognitive Battery included: speed of processing, attention, working memory, verbal learning, visual learning, and reasoning and problem solving.

Results: The exploratory factor analysis of PANSS negative symptoms suggested retaining only a single factor, but a forced two factor solution corroborated previously described factors of apathy and diminished expression in adult-onset schizophrenia. Results from confirmatory factor analysis indicated a better fit for the two-factor model than for the one-factor model. For both negative symptom domains, negative symptom scores were inversely associated with verbal learning scores.

Conclusion: The results support the presence of two domains of negative symptoms in EOP; apathy and diminished expression. Future studies on negative symptoms in EOP should examine putative differential effects of these symptom domains. For both domains, negative symptom scores were significantly inversely associated with verbal learning.

Keywords: apathy, diminished expression, early-onset schizophrenia, MATRICS, MCCB, factor analysis

INTRODUCTION

Early-onset psychosis (EOP) is defined as the onset of a psychotic disorder before 18 years of age (1). Although EOP is rare [affecting about 0.05–0.5% of the general population (2–4)], it is among the leading causes of disease burden in adolescents (5). Negative symptoms are present in 37–50% of EOP at illness onset (6, 7), and offer a particular challenge concerning outcome and quality of life as they are associated with poor functional outcome (8), cognitive impairments (9), and multiple treatment failures (6).

Negative symptoms commonly refer to symptoms reflecting diminished normal functions and behaviors, including alogia, blunted affect, anhedonia, asociality, and avolition (10). Studies investigating the factorial structure of different negative symptom rating scales in adult-onset schizophrenia, suggest that negative symptoms consist of two or more factors (11, 12). Most consistently reported and investigated are the two domains: *apathy,* including avolition, asociality and anhedonia, and *diminished expression*, including blunted affect and alogia (11, 13–16). Previous studies examining the factorial structure of negative symptoms in the widely used Positive and Negative Syndrome Scale [PANSS; (17)] have confirmed the two domains, and the models have been largely convergent (13, 14, 18). The reported two-factor structure comprise of: (1) an *apathy* domain, including emotional withdrawal, passive social withdrawal, and active social avoidance and (2) a *diminished expression* domain, including blunted affect, poor rapport, lack of spontaneity, and motor retardation (13, 14). This structure has been supported by a confirmatory factor analysis in an adult schizophrenia sample (19), and validated against corresponding subdomains of the Brief Negative Symptom Assessment Scale (20). Investigations of the two negative symptom domains, separately, have reported differential associations with other clinical aspects of psychotic disorders and neurobiology, including functional outcome (21), cognitive impairments (22, 23), neuronal task activation (24), and white matter connectivity (25). Although the exact mechanisms still need to be elucidated, these results may indicate different underlying pathophysiology (26), which may require different treatment approaches. Current conceptualizations of negative symptoms advocate the importance of deconstructing this symptom construct into separate symptoms and dimensions to achieve a better understanding of the phenomenology, and the functional and biological correlates (15, 27).

In adult-onset schizophrenia, associations with cognitive deficits have been shown for both apathy and diminished expression when the domains have been investigated separately (26). Specific problems with executive functioning and working memory may be associated with motivational deficits and reduced goal directed behavior in the apathy domain (26). More general cognitive impairments, according to the "cognitive resource limitation model", have been proposed to contribute to diminished expression symptoms (26, 28, 29). Some studies exploring the putative associations between cognition and the two negative symptom domains, have suggested a stronger association to cognitive impairments for diminished expression, than for apathy (22, 23, 30).

Adolescence is a sensitive developmental period associated with rapid neuro-maturational changes (31). Negative symptoms and cognitive difficulties are particularly challenging as currently available treatment is not adequately effective (32, 33). Studies of children and adolescents with EOP have demonstrated higher genetic heritability, poorer premorbid adjustment, longer duration of untreated psychosis (DUP), more severe illness course and outcome, and higher suicide rate, relative to patients with adult-onset psychosis (7, 34–36). These findings illustrate a crucial need for increased knowledge of pathological mechanisms associated with EOP. In a previous study from our group including an overlapping EOP sample with the present study, negative and disorganized symptoms were found to mediate the relationship between verbal learning and global functioning (37). However, to the best of our knowledge, the factorial structure of negative symptoms and how specific subdomains of negative symptoms relate with cognition, have not yet been investigated in adolescent patients with EOP. A better understanding of the phenomenology of negative symptoms, and how these symptoms relate to cognitive domains may improve early detection and inform theories on underlying mechanisms.

Thus, we aimed to (1) explore the factorial structure of the negative symptom construct and (2) investigate associations between cognitive impairments and negative symptom domains in EOP. We hypothesized that two factors of negative symptoms will be identifiable; an apathy factor and a diminished expression factor, and that diminished expression is more strongly associated with cognitive impairments, in accordance with studies of adult patients [e.g., (22, 23)].

MATERIALS AND METHODS

Participants

The subject sample included 169 adolescents with non-affective EOP with the following diagnoses: schizophrenia ($n = 101$), schizophreniform disorder ($n = 33$), schizoaffective disorder ($n = 4$), brief psychotic disorder ($n = 2$) and psychosis not otherwise specified ($n = 29$). Participants were recruited from three different cohorts: (1) the Thematically Organized Psychosis Study for Youth (Youth-TOP), Norway ($n = 45$, recruited from 2013 to 2019), (2) the Early-Onset Study, Norway ($n = 27$, recruited from 2005 to 2007) and (3) the Adolescent Schizophrenia Study, Mexico ($n = 97$, recruited from 2011 to 2020). The Norwegian cohorts were recruited from adolescent inpatient units and outpatient clinics in the south-east area of Norway (mainly the Oslo area). The Mexican cohort was recruited from an inpatient unit at the Child and Adolescent Psychiatric Hospital in Mexico City.

Inclusion criteria for the current study were: (1) A non-affective psychotic disorder, verified according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (38), (2) age 12–18 years, and (3) adequate language abilities to complete the interviews and self-rating questionnaires. Patients were excluded if they had a substance-induced psychotic disorder, organic brain disease, previous moderate/severe head injury, or IQ outside of the normal range. IQ was formally tested in the participants from the Youth-TOP and Early-Onset Study using the Wechsler Abbreviated Scale of Intelligence (39), and participants with IQ below 70 were excluded. In the Adolescent Schizophrenia Study, IQ was considered within the normal range if the patient did not have significant developmental delays and was attending regular school without any formal educational support.

All participants (and/or legal guardians if age <16 years) were thoroughly informed about the study and signed a written consent form. The Youth-TOP and Early-Onset Study were approved by the Norwegian South-East Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. The Adolescent Schizophrenia Study was approved by the Child Psychiatric Hospital Ethics Committee. All studies were conducted in accordance with the Helsinki declaration.

Clinical Assessments

Diagnosis and Global Functioning

Diagnoses were established according to the DSM-IV, using the following structured interviews: (1) Youth-TOP study: the Schedule for Affective Disorders and Schizophrenia for School Aged Children – Present and Lifetime Version (K-SADS-PL) (40), (2) Early-Onset Study: the Structural Clinical Instrument of Diagnosis for DSM-IV Axis I disorders (SCID-I), module A-D (41), and (3) Adolescent Schizophrenia Study: the Mini International Neuropsychiatric Interview (MINI-KID) (42).

Global functioning was assessed using three different scales: the Youth-TOP study: the Children's Global Assessment Scale (CGAS) (43), (2) Early-Onset Study: the Global Assessment of Functioning Scale, split version (GAF-F) (44), (3) Adolescent Schizophrenia Study: the Personal and Social Performance Scale (PSP) (45).

Negative Symptoms

Characteristic symptoms of psychosis, including negative symptoms were assessed using the PANSS (17). Although the PANSS was originally developed for adults, it has been used in several studies in adolescent patients (46, 47). In line with previous work in adult patients with schizophrenia (13, 14), negative symptom items from the negative symptom factor scores published by Marder and colleagues (48) were included for the exploratory factor analysis. The PANSS items included: n1 (blunted affect), n2 (emotional withdrawal), n3 (poor rapport), n4 (passive/apathetic social withdrawal), n6 (reduced spontaneity and flow of conversation), g7 (motor retardation), g16 (active social avoidance).

Cognitive Measures

Six cognitive domains were investigated based on nine tests from the MATRICS Consensus Cognitive Battery (MCCB) (49): (1) *Speed of processing* [combining BACS Symbol coding (50), Trail making test, part A (51), and Category fluency (52)], (2) *Attention/vigilance* (Continuous performance test, identical pairs) (53), (3) *Working memory* [combining WMS-III Spatial span (54) and Letter-number span (55)], (4) *Verbal learning* (Hopkins verbal learning test, revised) (56), (5) *Visual learning* (Brief visuospatial memory test, revised) (57), and (6) *Reasoning and problem solving* (NAB Mazes) (58). Although the MCCB was developed for adult patients with schizophrenia, the cognitive tests have been successfully used in adolescent EOP patients (59–62) and healthy adolescents (63, 64). The social cognition test (MSCEIT: Managing emotions) (65) included in the MCCB has been shown to be less suitable for adolescents (61) and was therefore excluded from the analyses in the current study. A global composite cognition score was calculated based on the nine included tests.

Medication

Information on current use of psychotropic medication was assessed, and chlorpromazine (CPZ) equivalents (66) were calculated for antipsychotic medication.

Statistical Analyses

Statistical analyses were performed with SPSS (version 27), except for the confirmatory factor analysis which was performed using R (version 4.0.5).

Clinical and Demographic Data

Demographic and clinical data were compared between cohorts using analysis of variance (ANOVA) and chi-square statistics. All tests were two-tailed.

Factor Analysis

The exploratory factor analysis (EFA, Principal Axis Factoring, SPSS) was performed to investigate the underlying structure of negative symptoms. The Kaiser-Meyer-Oklin (KMO) and Bartlett's test of sphericity were calculated to assess sampling adequacy. Number of factors to retain was determined based on Kaiser's criterion of an eigenvalue >1, and visual inspection of the scree plot. As two factors have been demonstrated in adult schizophrenia populations (13, 14, 18) we also explored setting the number of factors to be retained to two. The Promax oblique rotation was applied as we expected factors to be correlated, and items with loadings >0.3 were used for factor interpretation.

To further assess the models derived from the exploratory factor analysis, confirmatory factor analysis was conducted using the Lavaan package in R (67). Because of non-normality of data, the maximum likelihood estimation with robust standard errors and Satorra-Bentler scaled test statistics was used (68). Two models were assessed: (1) a one-factor model (n1, n2, n3, n4, n6, g7 and g16), and (2) the two-factor model of diminished expression (n1, n3, n6 and g7) and apathy (n2, n4 and g16) (13, 14). Goodness-of-fit was evaluated using different indices: chi-square, comparative fit index (CFI >0.95), Tucker-Lewis index (TLI >0.95), root mean square error of approximation (RMSEA <0.06), and standardized root mean square residual (SRMR <0.08) (69). As chi-square may be affected by sample size, a normed chi-square was calculated by dividing the chi-square by degrees of freedom, and a value below 5.0 was considered acceptable (70).

Associations of Negative Symptom Domains and Cognition

Based on previously published negative symptom factor models in adult-onset schizophrenia using PANSS (13, 14), scores for avolition-apathy (n1 + n3 + n6 + g7) and diminished expression (n2 + n4 + n6) were calculated by summing the scores of items included in each factor. Putative associations between cognitive domains and negative symptom factors were investigated using separate multiple linear regression models, controlling for age, sex, and cohort. Sex-specific associations were assessed by exploring models including sex-by-negative domain interactions. The linear regression models were investigated for influential cases. Standardized residuals >3 were identified for the models in speed of processing (3 cases), working memory (1 case) and global cognition (2 cases). However, Cook's distances did not exceed a value of 1 and all cases were retained in the analyses. The cognitive raw tests scores from the MCCB were transformed to standard scores (Z scores) using the standardization function in SPSS. For composite scores such as speed of processing, working memory and global cognition, Z scores from the individual tests were summated and transformed into a composite Z score, in line with the recommended procedure from the MCCB standardization study (71). The TMT-A score included in the speed of processing domain was reversed as high scores on this test indicate lower performance.

As the cognitive domains are not independent, a modified Bonferroni correction that accounts for correlations between outcome variables was used (72). Applying this method resulted in a p-value threshold of $p < 0.018$ (accounting for 7 domains and an intra-class correlation coefficient of 0.714).

Significant associations between cognition and negative symptom domains were investigated for the influence of PANSS positive and depressive symptom factors (73) and antipsychotic medication (antipsychotic medication use, and among patient using antipsychotics; CPZ equivalents).

RESULTS

Clinical and Demographic Data

Demographic and clinical data for the patients are presented in **Table 1**, and comparisons on mean scores on cognitive domains in **Table 2**. The Adolescent Schizophrenia Study consisted of significantly more males, with greater symptom severity, and lower cognitive performance compared to the Youth-TOP and the Early-Onset study. Patients in the Youth-TOP study had more PANSS negative and disorganized symptoms compared to the Early-Onset study. Use of antipsychotic medication was more prevalent in the Adolescent Schizophrenia Study, but there were no significant differences in medication dose (CPZ-equivalents) between the cohorts.

Factor Analysis

The exploratory factor analysis showed excellent Kaiser-Meyer-Oklin value of 0.886, and a significant Bartlett's test ($p < 0.001$), indicating adequate sample size and correlation matrix for factor analysis. When considering both criteria of eigenvalue >1 and visual inspection of the scree plot, one factor was retained (eigenvalue of 4.758, explaining 68% of the variance). As shown in **Table 3**, when the model was forced to extract two factors, items n2, n4 and g16 loaded highly on factor 1 (corresponding to the avolition-apathy domain) and n1, n3, n6 and g7 loaded highly on factor 2 (corresponding to the diminished expression domain. Factors 1 and 2 were highly correlated 0.798. The two domains showed good internal consistency as demonstrated by a Cronbach's alpha of 0.852 for the apathy domain, and 0.890 for the diminished expression domain.

Results from the confirmatory factor analysis for the one- and two-factor models are presented in **Table 4**. Overall, goodness-of-fit statistics were better for a two-factor model than for a one-factor model, with a smaller chi-square as compared to the one-factor model, and values for normed chi-square (2.84), CFI (0.964), and SRMR (0.033) indicating a good fit.

Associations of Negative Symptom Domains and Cognition

Negative symptom scores for both apathy ($\beta = -0.257$, $p = 0.002$) and diminished expression ($\beta = -0.259$, $p = 0.001$) were inversely associated with verbal learning scores. An association was also seen between diminished expression and speed of processing ($\beta = -0.173$, $p = 0.024$), but this result was not

TABLE 1 | Demographic and clinical data.

	All $n = 169$		1. Youth-TOP $n = 45$		2.Early-Onset Study n = 27		3.Adolescent Schizophrenia Study $n = 97$			
	Mean/n	SD/%	Mean/n	SD/%	Mean/n	SD/%	Mean/n	SD/%	Test statistics	*Post-hoc*
Diagnoses									$\chi^2 = 51.30$, $p < 0.001$	
Schizophrenia spectrum	138	81.7%	25	55.6%	16	59.3%	97	100%		
Other psychosis[a]	31	18.2%	20	44.4%	11	40.7%	0	0		
Age	15.5	1.5	15.6	1.3	15.9	1.8	15.4	1.6	$F = 1.42$, $p = 0.24$	
Sex, male	100	59.2%	16	35.6%	13	48.1%	71	73.2%	$\chi^2 = 19.64$, $p < 0.001$	3>1, 3>2
Hand dominance, right	156	92.3%	42	93.3%	23	85.2%	91	93.8%	$\chi^2 = 2.30$, $p = 0.316$	
Ethnicity									$\chi^2 = 163.14$, $p < 0.001$	
Caucasian	59	34.7%	38	84.4%	21	77.8%	0	0		
Hispanic	97	57.6%	1	2.2%	0	0	96	99.0%		
Other	13	7.6%	6	13.3%	6	22.6%	1	1.0%		
Age of onset	14.0	1.9	14.2	1.7	14.1	2.0	13.9	1.9	$F = 0.42$, $p = 0.659$	
Global functioning[b]			45.2	11.7	48.0	15.2	34.6	13.1		
PANSS positive[c]	14.3	5.1	11.3	3.6	9.8	3.3	16.9	4.4	$F = 49.78$, $p < 0.001$	3>1, 3>2
PANSS negative[c]	18.5	7.6	16.6	6.3	11.6	4.5	21.2	7.4	$F = 23.84$, $p < 001$	1>2, 3>1, 3>2
PANSS disorganized[c]	9.0	4.1	6.7	2.6	4.8	1.9	11.2	3.5	F=63.16, p<0.001	1>2, 3>1, 3>2
PANSS depression[c]	7.6	3.3	8.4	2.9	7.8	3.4	7.2	3.4	$F = 1.85$, $p = 0.161$	
PANSS excited[c]	9.1	4.4	6.6	2.0	6.7	2.5	11.0	4.7	$F = 26.71$, $p < 0.001$	3>1, 3>2
PANSS total	85.9	25.7	71.6	15.2	57.5	12.9	100.5	21.5	$F = 72.53$, $p < 0.001$	1>2, 3>1, 3>2
Apathy	3.3	1.3	3.0	1.1	2.0	0.8	3.8	1.2	$F = 32.08$, $p < 0.001$	1>2, 3>1, 3>2
Diminished expression	2.9	1.3	2.6	1.1	1.9	0.9	3.3	1.3	$F = 15.79$, $p < 0.001$	1>2, 3>1, 3>2
Antipsychotic use	144	85.2%	28	62.2%	19	70%	97	100%	$\chi^2 = 40.41$, $p < 0.001$	3>1, 3>2
Antipsychotic dose (CPZ[d])	245.0	128.4	236.3	137.0	263.5	181.0	243.9	116.6	$F = 0.26$, $p = 0.772$	

[a] *Other psychosis: Brief psychotic disorder (n = 2), psychosis not otherwise specified (NOS, n = 29).*
[b] *Global functioning: Children's Global Assessment Scale (Youth-TOP), Global Assessment of Functioning Scale (Early-Onset Study), and the Personal and Social Performance Scale (Adolescent Schizophrenia Study).*
[c] *Positive and Negative Syndrome Scale Wallwork 5-factor model.*
[d] *Chlorpromazine equivalents.*

TABLE 2 | Cognition across cohorts.

	All		1. Youth-TOP		2.Early-Onset Study		3.Adolescent Schizophrenia Study		F	p	*Post-hoc*, $p < 0.05$
Domain	Mean Z score	SD	Mean Z score	SD	Mean Z score	SD	Mean Z score	SD			
Speed of processing	−0.11	1.00	0.55	0.63	0.34	0.59	−0.50	1.03	23.8	<0.001	3>1, 3>2
Attention/vigilance	−0.08	0.96	0.47	0.91	0.28	0.92	−0.43	0.84	18.0	<0.001	3>1, 3>2
Working memory	−0.09	0.97	0.58	0.77	0.25	0.61	−0.51	0.93	28.4	<0.001	3>1, 3>2
Verbal learning	−0.05	1.00	0.51	0.82	0.21	0.84	−0.38	0.99	15.4	<0.001	3>1, 3>2
Visual learning	−0.05	1.02	0.52	0.81	0.26	1.05	−0.41	0.95	17.1	<0.001	3>1, 3>2
Reasoning and problem solving	−0.11	0.98	0.64	0.76	0.41	0.80	−0.60	0.82	44.3	<0.001	3>1, 3>2
Global cognition	−0.10	0.96	0.71	0.67	0.35	0.58	−0.55	0.92	35.2	<0.001	3>1, 3>2

significant after correction for multiple comparisons. No other significant associations were observed between the negative symptom domains and cognitive performance (**Table 5**). There were no significant sex-by-negative domain interactions.

The association between verbal learning and the two negative symptom domains remained significant after controlling for positive psychotic symptoms, depressive symptoms and antipsychotic medication use and dose.

DISCUSSION

In the present study, we explored the factorial structure of negative symptoms in patients with EOP and investigated how domains of negative symptoms were related to cognition. Overall, our results indicated a factorial structure of two domains similar to what has been shown for PANSS negative symptoms in adults (13, 14). However, the two factors were highly correlated. Both negative symptom domains were significantly associated with verbal learning.

We performed an exploratory factor analysis to investigate the factorial structure of negative symptoms in EOP as to our knowledge, this has not been investigated in EOP before. When considering standard criteria for factor retention, such as retaining only factors with an eigenvalue above 1 or by investigating the scree plot, the results suggested that only one factor should be retained. However, because of the theoretically supported model of two factors from adult schizophrenia, we explored forcing the extraction of two factors. Interestingly, the pattern of item loadings that emerged were identical to the two-factor model described from factor analytic studies in adult patients with schizophrenia (13, 14). PANSS items addressing blunted affect, poor rapport, lack of spontaneity, and motor retardation loaded the highest on a factor corresponding to a *diminished expression* domain, and emotional withdrawal, passive social withdrawal, and active social avoidance loaded highest on a second factor corresponding to an *apathy* domain. We further assessed both a one-factor model and a two-factor model (13, 14) using confirmatory factor analysis. Goodness-of-fit indices were better for the two-factor model, supporting this latent structure of two domains of negative symptoms in EOP. Discrepancies in the results from the exploratory and confirmatory factor analyses may reflect the different methodology and rationale for the two methods. In the exploratory factor analysis, the number of factors are explored in a data-driven approach, while the confirmatory factor analysis tests a predefined factor-model. Our sample size, although large with respect to EOP studies, did not allow for splitting the sample to perform exploratory and confirmatory factor analyses in separate samples. As such, replications of the confirmatory factor analysis should be performed in independent samples for generalizability.

An important implication of investigating subdomains of negative symptoms is that if such subdomains exist, they may have different biological and clinical correlates and may require different treatment strategies (15, 26). For instance, for the apathy domain, behavioral and neural dysfunctions related to motivation and goal-directed behavior have been shown, which

TABLE 3 | Factor structure.

PANSS item	Factor 1 Apathy	Factor 2 Diminished expression
N1 Blunted affect		**0.595**
N2 Emotional withdrawal	**0.902**	
N3 Poor rapport	0.418	**0.498**
N4 Passive/apathetic social withdrawal	**0.891**	
N6 Lack of spontaneity		**0.795**
G7 Motor retardation		**0.794**
G16 Active social avoidance	**0.569**	

Pattern coefficients from exploratory factor analysis on PANSS items N1, N2, N3, N4, N6, G7, G16, forced two factor solution, after Promax rotation. For simplicity, only item loadings >0.3 are shown. Bolded values indicate the factor with the strongest loading.

TABLE 4 | Results from confirmatory factor analysis.

	One-factor model	Two-factor model
Chi-square	62.210 ($p < 0.001$)	36.938 ($p < 0.001$)
Normed chi-square	**4.44**	**2.84**
CFI	0.928	**0.964**
TLI	0.892	0.942
RMSEA	0.160	0.117
SRMR	**0.045**	**0.033**

CFI, comparative fit index (CFI > 0.95); TLI, Tucker-Lewis index (TLI > 0.95); RMSEA root mean square error of approximation (RMSEA < 0.06). SRMR, standardized root mean square residual (SRMR < 0.08). Values within the considered thresholds for adequate fit are bolded.

TABLE 5 | Associations between negative symptom domains and cognition.

	Apathy					Diminished expression				
	B	SE	β	*t*	*p*	B	SE	β	*t*	*p*
Speed of processing, $n = 164$	−0.122	0.063	−0.159	−1.932	0.055	−0.136	0.060	−0.173	−2.279	0.024*
Attention/vigilance, $n = 157$	0.029	0.065	0.038	0.440	0.660	−0.008	0.063	−0.011	−0.133	0.894
Working memory, $n = 165$	0.029	0.061	0.037	0.472	0.637	−0.018	0.059	−0.023	−0.307	0.759
Verbal learning, $n = 168$	−0.197	0.064	−0.257	−3.090	0.002**	−0.204	0.061	−0.259	−3.368	0.001**
Visual learning, $n = 169$	−0.010	0.067	−0.012	−0.146	0.884	−0.056	0.063	−0.070	−0.889	0.375
Reasoning and problem solving, $n = 170$	−0.018	0.056	−0.024	−0.323	0.747	−0.036	0.054	−0.047	−0.673	0.502
Global cognition, $n = 148$	−0.006	0.063	−0.008	−0.099	0.921	−0.081	0.061	−0.101	−1.324	0.188

Results from the separate linear regression models controlled for age, sex and cohort.
**Significant at $p < 0.05$ **Significant after correction for multiple comparisons.*

have inspired the emerging research on targeted treatment options (26). Generally, models for underlying mechanisms of diminished expression are less clear (15, 26). One line of research points to cognitive deficits underlying symptoms of this domain (26, 28, 29). In support of this theory, a stronger association to cognitive deficits for diminished expression than apathy has been shown in some studies of adult patients with schizophrenia, although the overall differences are not large, and not consistent regarding the cognitive domains involved (22, 23, 30). In the present study of adolescents with EOP, apathy and diminished expression were similarly associated with lower verbal learning performance.

Overall, our results show that, although the factor analysis supports two domains of negative symptoms, these two domains could not be as clearly discriminated in our sample of patients with EOP as has been shown in previous studies of adult patients with schizophrenia (13, 14, 18). This may reflect differences between patients with adult- and early-onset schizophrenia. EOP has been associated with higher genetic heritability, poorer premorbid adjustment, longer duration of untreated psychosis (DUP), more severe illness course and outcome, and higher suicide rate, relative to patients with adult-onset psychosis (7, 34–36). Furthermore, the clinical presentation of underlying pathology may be different in adolescents who are in a period of life where the brain is rapidly changing, and cognitive abilities are developing.

Verbal learning deficits have been associated with earlier age of onset (74), and shown to be one of the earliest predictors of psychosis development in at-risk individuals (75, 76). Thus, verbal learning deficits and negative symptoms may be early markers for psychosis development and functional decline in youth. As cognitive assessment is better at predicting psychosis development in adolescents than in adults (77), our results indicate that clinicians working with young people need to be attentive to both verbal learning difficulties and negative symptoms. The patients presenting with these symptoms may represent a subgroup who may require closer follow-up and quick access to alternative treatment strategies in addition to antipsychotic medication, such as cognitive remediation. Furthermore, the results encourage future studies on how verbal learning and negative symptoms are associated and whether they relate to common underlying neurobiology.

Strengths of the study include a large and well-characterized sample of patients with early onset psychosis, which allowed for performing a factor analysis. Furthermore, a complete and standardized battery (MCCB) for cognitive testing was used. Nevertheless, some limitations should be mentioned. First, as a manifest diagnosis of a psychotic disorder is relatively rare in adolescents, combining samples from geographically different cohorts was necessary to obtain a sufficient sample size, however this may introduce unwanted variation related to cohort. There were significant cohort differences in sex, symptom severity and cognitive scores between cohorts. To address this concern all our multivariate analyses were controlled for cohort. Second, there are limitations to the PANSS as an assessment of negative symptoms (12). The ratings of negative symptoms in PANSS are based only on observation of behaviors, and not the subjective experience of the patients. For symptoms within the domain of apathy, this means that the patient's own experience of pleasure and motivation is not assessed. Newer scales for assessment of negative symptoms have been developed, so called "second-generation rating scales" (12), for instance the Brief Negative Symptom Scale (BNSS) (78) and the Clinical Assessment Interview for Negative Symptoms (CAINS) (79)) have been developed that include assessment of the subjective experience of symptoms within the apathy domain. However, these scales are currently not widely used in adolescents. Third, we included PANSS items for motor retardation (G7) and active social avoidance (G16) in the factor analysis, in line with previous factor analytic studies on negative symptoms in adult patients with schizophrenia. However, it should be noted, that recent guidelines from the European Psychiatric Association (12) on the assessment of negative symptoms advise against including these items as negative symptoms due to their inconsistent loading on the negative symptom factor. Fourth, high total PANSS scores indicate that some patients were in an acute or subacute phase of illness, which may have influenced their cognitive performance. Furthermore, positive symptoms, psychotropic medication, and depression may contribute to secondary negative symptoms. In our multivariate models on cognitive measures, we controlled for such possible secondary sources of negative symptoms (positive symptoms, depression and antipsychotic medication), but this did not change any results. Further, given the young age of the patients, we would expect them to be less influenced by chronicity and medication.

In conclusion, the results support the presence of two domains of negative symptoms in EOP, but the domains were highly correlated, and should be confirmed in independent samples. Contrary to our hypothesis of a stronger association between diminished expression and cognition, we found that for both domains, the negative symptom scores were similarly significantly associated with lower verbal learning scores. Based on the results, we recommend that future studies of negative symptoms in adolescents should examine differential effects of the two negative symptom domains. Furthermore, the association between negative symptoms and verbal learning warrants more studies on how these features are related and whether they for instance share common biological mechanisms that could be targeted for treatment.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of legal and privacy restrictions. Requests to access the datasets should be directed to lynn.morch-johnsen@medisin.uio.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and The Youth-TOP and Early-Onset Study were approved by the Norwegian South-East Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. The

Adolescent Schizophrenia Study was approved by the Child Psychiatric Hospital Ethics Committee, Mexico. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LM-J, RS, and IA took part in designing the analyses for present study. LM-J carried out the statistical analysis. LM-J and RS managed the literature search and wrote the first draft of the manuscript. RS, CJ, KW-R, RD, GV, AM, BR, RU, and IA were involved in data collection. All authors, LM-J, RS, DA, CB, CJ, KW-R, RD, GV, LW, TU, OA, AM, BR, RU, and IA have contributed to and approved the manuscript.

FUNDING

This work was supported by the South-Eastern Norway Regional Health Authority (2019-108, 2019-099, 2004-259, 2006-186, 2020-020) and the Research Council of Norway (223273, 213700, 250358).

ACKNOWLEDGMENTS

We would like to thank the study participants and the clinicians involved in recruitment and assessments in the studies. Furthermore, we would like to thank the University Center for Information Technology (USIT) at University of Oslo for statistical guidance.

REFERENCES

1. Werry JS, McClellan JM, Chard L. Childhood and adolescent schizophrenic, bipolar, and schizoaffective disorders: a clinical and outcome study. *J Am Acad Child Adolesc Psychiatry.* (1991) 30:457–65. doi: 10.1097/00004583-199105000-00017
2. Gillberg C, Wahlström J, Forsman A, Hellgren L, Gillberg IC. Teenage psychoses—epidemiology, classification and reduced optimality in the pre-, peri-and neonatal periods. *J Child Psychol Psychiatry.* (1986) 27:87–98. doi: 10.1111/j.1469-7610.1986.tb00624.x
3. Boeing L, Murray V, Pelosi A, McCabe R, Blackwood D, Wrate R. Adolescent-onset psychosis: prevalence, needs and service provision. *Br J Psychiatry.* (2007) 190:18–26. doi: 10.1192/bjp.190.1.18
4. Sikich L. Diagnosis and evaluation of hallucinations and other psychotic symptoms in children and adolescents. *Child Adolesc Psychiatric Clin.* (2013) 22:655–73. doi: 10.1016/j.chc.2013.06.005
5. Gore FM, Bloem PJ, Patton GC, Ferguson J, Joseph V, Coffey C, et al. Global burden of disease in young people aged 10-24 years: a systematic analysis. *Lancet.* (2011) 377:2093–102. doi: 10.1016/S0140-6736(11)60512-6
6. Downs J, Dean H, Lechler S, Sears N, Patel R, Shetty H, et al. Negative symptoms in early-onset psychosis and their association with antipsychotic treatment failure. *Schizophr Bull.* (2018) 45:69–79. doi: 10.1093/schbul/sbx197
7. Stentebjerg-Olesen M, Pagsberg AK, Fink-Jensen A, Correll CU, Jeppesen P. Clinical characteristics and predictors of outcome of schizophrenia-spectrum psychosis in children and adolescents: a systematic review. *J Child Adolesc Psychopharmacol.* (2016) 26:410–27. doi: 10.1089/cap.2015.0097
8. Diaz-Caneja CM, Pina-Camacho L, Rodriguez-Quiroga A, Fraguas D, Parellada M, Arango C. Predictors of outcome in early-onset psychosis: a systematic review. *NPJ Schizophr.* (2015) 1:14005. doi: 10.1038/npjschz.2014.5
9. Nieto RG, Castellanos FX. A meta-analysis of neuropsychological functioning in patients with early onset schizophrenia and pediatric bipolar disorder. *J Clin Child Adolesc Psychol.* (2011) 40:266–80. doi: 10.1080/15374416.2011.546049
10. Kirkpatrick B, Fenton WS, Carpenter WT Jr, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull.* (2006) 32:214–9. doi: 10.1093/schbul/sbj053
11. Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. *Schizophr Bull.* (2006) 32:238–45. doi: 10.1093/schbul/sbj013
12. Galderisi S, Mucci A, Dollfus S, Nordentoft M, Falkai P, Kaiser S, et al. EPA guidance on assessment of negative symptoms in schizophrenia. *Eur Psychiatry.* (2021) 64:e23. doi: 10.1192/j.eurpsy.2021.11
13. Fervaha G, Foussias G, Agid O, Remington G. Motivational and neurocognitive deficits are central to the prediction of longitudinal functional outcome in schizophrenia. *Acta Psychiatr Scand.* (2014) 130:290–9. doi: 10.1111/acps.12289
14. Khan A, Liharska L, Harvey PD, Atkins A, Ulshen D, Keefe RSE. Negative symptom dimensions of the positive and negative syndrome scale across geographical regions: implications for social, linguistic, and cultural consistency. *Innov Clin Neurosci.* (2017) 14:30–40. Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5788249/
15. Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. *Lancet Psychiatry.* (2018) 5:664–77. doi: 10.1016/S2215-0366(18)30050-6
16. Foussias G, Remington G. Negative symptoms in schizophrenia: avolition and Occam's razor. *Schizophr Bull.* (2010) 36:359–69. doi: 10.1093/schbul/sbn094
17. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophr Bull.* (1987) 13:261–76. doi: 10.1093/schbul/13.2.261
18. Liemburg E, Castelein S, Stewart R, van der Gaag M, Aleman A, Knegtering H, et al. Two subdomains of negative symptoms in psychotic disorders: established and confirmed in two large cohorts. *J Psychiatr Res.* (2013) 47:718–25. doi: 10.1016/j.jpsychires.2013.01.024
19. Jang SK, Choi HI, Park S, Jaekal E, Lee GY, Cho YI, et al. A two-factor model better explains heterogeneity in negative symptoms: evidence from the positive and negative syndrome scale. *Front Psychol.* (2016) 7:707. doi: 10.3389/fpsyg.2016.00707
20. Kaliuzhna M, Kirschner M, Carruzzo F, Hartmann-Riemer MN, Bischof M, Seifritz E, et al. Clinical, behavioural and neural validation of the PANSS amotivation factor. *Schizophr Res.* (2020) 220:38–45. doi: 10.1016/j.schres.2020.04.018
21. Galderisi S, Rossi A, Rocca P, Bertolino A, Mucci A, Bucci P, et al. The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. *World Psychiatry.* (2014) 13:275–87. doi: 10.1002/wps.20167
22. Hartmann-Riemer MN, Hager OM, Kirschner M, Bischof M, Kluge A, Seifritz E, et al. The association of neurocognitive impairment with diminished expression and apathy in schizophrenia. *Schizophr Res.* (2015) 169:427–32. doi: 10.1016/j.schres.2015.10.032
23. Sevy S, Lindenmayer JP, Khan A, Ljuri I, Kulsa MKC, Jones O. Differential improvement of negative-symptom subfactors after cognitive remediation in low-functioning individuals with schizophrenia. *Schizophr Res Cogn.* (2020) 19:100145. doi: 10.1016/j.scog.2019.100145
24. Kirschner M, Hager OM, Bischof M, Hartmann MN, Kluge A, Seifritz E, et al. Ventral striatal hypoactivation is associated with apathy but not diminished expression in patients with schizophrenia. *J Psychiatry Neurosci.* (2016) 41:152–61. doi: 10.1503/jpn.140383
25. Amodio A, Quarantelli M, Mucci A, Prinster A, Soricelli A, Vignapiano A, et al. Avolition-apathy and white matter connectivity in schizophrenia: reduced fractional anisotropy between amygdala and insular cortex. *Clin EEG Neurosci.* (2018) 49:55–65. doi: 10.1177/1550059417745934
26. Begue I, Kaiser S, Kirschner M. Pathophysiology of negative symptom dimensions of schizophrenia - Current developments and implications for treatment. *Neurosci Biobehav Rev.* (2020) 116:74–88. doi: 10.1016/j.neubiorev.2020.06.004
27. Kaiser S, Lyne J, Agartz I, Clarke M, Morch-Johnsen L, Faerden A. Individual negative symptoms and domains - Relevance for assessment,

pathomechanisms and treatment. *Schizophr Res.* (2017) 186:39–45. doi: 10.1016/j.schres.2016.07.013
28. Cohen AS, McGovern JE, Dinzeo TJ, Covington MA. Speech deficits in serious mental illness: a cognitive resource issue? *Schizophr Res.* (2014) 160:173–9. doi: 10.1016/j.schres.2014.10.032
29. Cohen AS, Morrison SC, Brown LA, Minor KS. Towards a cognitive resource limitations model of diminished expression in schizotypy. *J Abnorm Psychol.* (2012) 121:109–18. doi: 10.1037/a0023599
30. Garcia-Mieres H, Lundin NB, Minor KS, Dimaggio G, Popolo R, Cheli S, et al. A cognitive model of diminished expression in schizophrenia: the interface of metacognition, cognitive symptoms and language disturbances. *J Psychiatr Res.* (2020) 131:169–76. doi: 10.1016/j.jpsychires.2020.09.008
31. Dahl RE, Allen NB, Wilbrecht L, Suleiman AB. Importance of investing in adolescence from a developmental science perspective. *Nature.* (2018) 554:441–50. doi: 10.1038/nature25770
32. Fusar-Poli P, Papanastasiou E, Stahl D, Rocchetti M, Carpenter W, Shergill S, et al. Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. *Schizophr Bull.* (2015) 41:892–9. doi: 10.1093/schbul/sbu170
33. Galderisi S, Kaiser S, Bitter I, Nordentoft M, Mucci A, Sabe M, et al. EPA guidance on treatment of negative symptoms in schizophrenia. *Eur Psychiatry.* (2021) 64:e21. doi: 10.1192/j.eurpsy.2021.13
34. Hoffmann A, Ziller M, Spengler D. Childhood-onset schizophrenia: insights from induced pluripotent stem cells. *Int J Mol Sci.* (2018) 19:3829. doi: 10.3390/ijms19123829
35. Ahn K, An S, Shugart YY, Rapoport J. Common polygenic variation and risk for childhood-onset schizophrenia. *Mol Psychiatry.* (2016) 21:94–6. doi: 10.1038/mp.2014.158
36. Remschmidt H, Martin M, Fleischhaker C, Theisen FM, Hennighausen K, Gutenbrunner C, et al. Forty-two-years later: the outcome of childhood-onset schizophrenia. *J Neural Transm.* (2007) 114:505–12. doi: 10.1007/s00702-006-0553-z
37. Smelror RE, Rund BR, Lonning V, Jorgensen KN, Wedervang-Resell K, Andreassen OA, et al. Negative and disorganized symptoms mediate the relationship between verbal learning and global functioning in adolescents with early-onset psychosis. *Eur Child Adolesc Psychiatry.* (2020) 29:1693–703. doi: 10.1007/s00787-020-01479-7
38. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed text rev. Washington, DC: American Psychiatric Association (2000).
39. Wechsler D. *Wechsler Abbreviated Scale of Intelligence WASI: Manual*. San Antonio, SA: Pearson/PsychCorp (1999).
40. Kaufman J, Birmaher B, Brent D, Rao UMA, Flynn C, Moreci P, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry.* (1997) 36:980–8. doi: 10.1097/00004583-199707000-00021
41. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured clinical interview for DSM-IV-TR axis I disorders, research version*. New York, NY: Biometrics Research, New York State Psychiatric Institute (2002).
42. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* (1998) 59 (Suppl 20):22—33;quiz 4–57. Available online at: https://www.psychiatrist.com/jcp/neurologic/neurology/mini-international-neuropsychiatric-interview-mini/
43. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry.* (1983) 40:1228–31. doi: 10.1001/archpsyc.1983.01790100074010
44. Pedersen G, Hagtvet KA, Karterud S. Generalizability studies of the global assessment of functioning–split version. *Compr Psychiatry.* (2007) 48:88–94. doi: 10.1016/j.comppsych.2006.03.008
45. Morosini PL, Magliano L. Brambilla La, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatrica Scandinavica.* (2000) 101:323–9. doi: 10.1111/j.1600-0447.2000.tb10933.x
46. Ropcke B, Eggers C. Early-onset schizophrenia: a 15-year follow-up. *Eur Child Adolesc Psychiatry.* (2005) 14:341–50. doi: 10.1007/s00787-005-0483-6
47. Savitz AJ, Lane R, Nuamah I, Gopal S, Hough D. Efficacy and safety of paliperidone extended release in adolescents with schizophrenia: a randomized, double-blind study. *J Am Acad Child Adolesc Psychiatry.* (2015) 54:126–37.e1. doi: 10.1016/j.jaac.2014.11.009
48. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry.* (1997) 58:538–46. doi: 10.4088/JCP.v58n1205
49. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. *Am J Psychiatry.* (2008) 165:203–13. doi: 10.1176/appi.ajp.2007.07010042
50. Keefe RSE, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The brief assessment of cognition in schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res.* (2004) 68:283–97. doi: 10.1016/j.schres.2003.09.011
51. Army Individual Test Battery. *Manual of Directions and Scoring*. Washington, DC: War Department (1944).
52. Spreen O, Strauss E, A. *Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. 2nd edition. New York, NY: Oxford University Press (1998).
53. Cornblatt BA, Risch NJ, Faris G, Friedman D, Erlenmeyer-Kimling L. The continuous performance test, identical pairs version (CPT-IP): I. new findings about sustained attention in normal families. *Psychiatry Res.* (1988) 26:223–38. doi: 10.1016/0165-1781(88)90076-5
54. Wechsler D. *WMS-III: Wechsler Memory Scale Administration and Scoring Manual*. London, UK: The Psychological Corporation (1997).
55. Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR. Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Arch Gen Psychiatry.* (1997) 54:159–65. doi: 10.1001/archpsyc.1997.01830140071013
56. Brandt J, Benedict RHB. *Hopkins Verbal Learning Test-Revised: Professional Manual. Lutz, FL: Psychological Assessment Resources* (2001).
57. Benedict RHB. *Brief Visuospatial Memory Test—Revised*. Odessa, FL: Psychological Assessment Resources (1997).
58. Stern RA, White T. *Neuropsychological Assessment Battery (NAB)*. Lutz, FL: Psychological Assessment Resources (2003).
59. Smelror RE, Johannessen C, Wedervang-Resell K, Jørgensen KN, Barth C, Andreou D, et al. Cognitive impairment profile in adolescent early-onset psychosis using the MATRICS Battery: age and sex effects. *Neuropsychology.* (2021) 35:300–9. doi: 10.1037/neu0000723
60. Victoria G, Apiquian R, Rosetti MF, Ulloa RE. Cognitive impairment and its improvement after six months in adolescents with schizophrenia. *Schizophr Res Cogn.* (2019) 17:100135. doi: 10.1016/j.scog.2019.100135
61. Holmen A, Juuhl-Langseth M, Thormodsen R, Melle I, Rund BR. Neuropsychological profile in early-onset schizophrenia-spectrum disorders: measured with the MATRICS battery. *Schizophr Bull.* (2010) 36:852–9. doi: 10.1093/schbul/sbn174
62. Nitzburg GC, Derosse P, Burdick KE, Peters BD, Gopin CB, Malhotra AK, et al. cognitive consensus battery (MCCB) performance in children, adolescents, and young adults. *Schizophr Res.* (2014) 152:223–8. doi: 10.1016/j.schres.2013.11.023
63. Smelror RE, Jørgensen KN, Lonning V, Kelleher I, Cannon M, DeRosse P, et al. Healthy adolescent performance with standardized scoring tables for the MATRICS consensus cognitive battery: a multisite study. *Schizophr Bull.* (2019) 45:773–83. doi: 10.1093/schbul/sby131
64. Stone WS, Mesholam-Gately RI, Giuliano AJ, Woodberry KA, Addington J, Bearden CE, et al. Healthy adolescent performance on the MATRICS Consensus Cognitive Battery (MCCB): Developmental data from two samples of volunteers. *Schizophr Res.* (2016) 172:106–13. doi: 10.1016/j.schres.2016.02.003
65. Mayer JD, Salovey P, Caruso D. *Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT© V2.0)*. Toronto, ON: Multi-Health Systems (2002).
66. Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho BC. Antipsychotic dose equivalents and dose-years: a standardized method for comparing

exposure to different drugs. *Biol Psychiatry.* (2010) 67:255–62. doi: 10.1016/j.biopsych.2009.08.040
67. Rosseel Y. lavaan: an R Package for Structural Equation Modeling. *J Stat Softw.* (2012) 48:1–36. doi: 10.18637/jss.v048.i02
68. Satorra A, Bentler PM. Corrections to test statistics and standard errors in covariance structure analysis. In: von Eye A, Clogg CC, editor. *Latent Variables Analysis: Applications for Developmental Research Thousand Oaks*. CA: Sage Publications, Inc. p. 399–419.
69. Hu LT, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Struct Equ Modeling.* (1999) 6:1–55. doi: 10.1080/10705519909540118
70. Wheaton B, Muthén B, Alwin DF, Summers GF. Assessing reliability and stability in panel models. *Sociol Methodol.* (1977) 8:84–136. doi: 10.2307/270754
71. Kern RS, Nuechterlein KH, Green MF, Baade LE, Fenton WS, Gold JM, et al. The MATRICS consensus cognitive battery, part 2: co-norming and standardization. *Am J Psychiatry.* (2008) 165:214–20. doi: 10.1176/appi.ajp.2007.07010043
72. Shi Q, Pavey ES, Carter RE. Bonferroni-based correction factor for multiple, correlated endpoints. *Pharm Stat.* (2012) 11:300–9. doi: 10.1002/pst.1514
73. Wallwork RS, Fortgang R, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of the positive and negative syndrome scale for schizophrenia. *Schizophr Res.* (2012) 137:246–50. doi: 10.1016/j.schres.2012.01.031
74. Tuulio-Henriksson A, Partonen T, Suvisaari J, Haukka J, Lönnqvist J. Age at onset and cognitive functioning in schizophrenia. *Br J Psychiatry.* (2004) 185:215–9. doi: 10.1192/bjp.185.3.215
75. Carrión RE, Walder DJ, Auther AM, McLaughlin D, Zyla HO, Adelsheim S, et al. From the psychosis prodrome to the first-episode of psychosis: no evidence of a cognitive decline. *J Psychiatr Res.* (2018) 96:231–8. doi: 10.1016/j.jpsychires.2017.10.014
76. Seidman LJ, Shapiro DI, Stone WS, Woodberry KA, Ronzio A, Cornblatt BA, et al. Association of neurocognition with transition to psychosis: baseline functioning in the second phase of the North American prodrome longitudinal study. *JAMA Psychiatry.* (2016) 73:1239–48. doi: 10.1001/jamapsychiatry.2016.2479
77. Zhang T, Cui H, Wei Y, Tang X, Xu L, Hu Y, et al. Neurocognitive assessments are more important among adolescents than adults for predicting psychosis in clinical high risk. *Biolo Psychiatry Cogn Neurosci Neuroimaging.* (2021). S2451-9022(21)00195-6. [Epub ahead of print]. doi: 10.1016/j.bpsc.2021.06.015
78. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The brief negative symptom scale: psychometric properties. *Schizophr Bull.* (2011) 37:300–5. doi: 10.1093/schbul/sbq059
79. Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. *Am J Psychiatry.* (2013) 170:165–72. doi: 10.1176/appi.ajp.2012.12010109

Conflict of Interest: OA has received speaker's honorarium from Lundbeck and Sunovion and is a consultant for HealthLytix.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Psychiatry

REVIEW
published: 04 February 2022
doi: 10.3389/fpsyt.2021.820801

Assessment and Treatment of Negative Symptoms in Schizophrenia—A Regional Perspective

Istvan Bitter[1], Pavel Mohr[2,3], Natalia Raspopova[4], Agata Szulc[5], Jerzy Samochowiec[6], Ioana Valentina Micluia[7], Oleg Skugarevsky[8], Róbert Herold[9], Alma Mihaljevic-Peles[10], Nino Okribelashvili[11], Jozef Dragašek[12], Virginija Adomaitiene[13], Elmars Rancans[14], Jana Chihai[15], Natalia Maruta[16], Nadja P. Marić[17], Vihra Milanova[18], Rok Tavčar[19] and Sergey Mosolov[20,21]*

[1] Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary, [2] Clinical Center, National Institute of Mental Health, Klecany, Czechia, [3] Third Faculty of Medicine, Charles University in Prague, Prague, Czechia, [4] Department of Psychiatry, Narcology and Neurology of Kazakh-Russian Medical University, Almaty, Kazakhstan, [5] Department of Psychiatry, Medical University of Warsaw, Warsaw, Poland, [6] Department of Psychiatry, Pomeranian Medical University in Szczecin, Szczecin, Poland, [7] Discipline of Psychiatry, Department of Neurosciences, University of Medicine and Pharmacy, Iuliu Haieganu, Cluj-Napoca, Romania, [8] Department of Psychiatry & Medical Psychology, Belarusian State Medical University, Minsk, Belarus, [9] Department of Psychiatry and Psychotherapy, Medical School, University of Pécs, Pécs, Hungary, [10] Clinical Hospital Centre Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia, [11] Department of Psychiatry and Medical Psychology, Tbilisi State University, Tbilisi, Georgia, [12] First Department of Psychiatry, University of P. J. Safarik, Medical Faculty and University Hospital of L. Pasteur, Kosice, Slovakia, [13] Department of Psychiatry, Lithuanian University of Health Sciences, Kaunas, Lithuania, [14] Department of Psychiatry and Narcology, Riga Stradins University, Riga, Latvia, [15] Medical Psychology and Narcology Department, State Medical and Pharmaceutical University Nicolae Testemitanu, Chisinau, Moldova, [16] Department of Borderline Psychiatry, Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Science of Ukraine, Kharkiv, Ukraine, [17] Faculty of Medicine University of Belgrade & Institute of Mental Health, Belgrade, Serbia, [18] Psychiatric Clinic, University Hospital "Alexandrovska", Sofia, Bulgaria, [19] University Psychiatric Clinic Ljubljana and School of Medicine, University of Ljubljana, Ljubljana, Slovenia, [20] Department for Therapy of Mental Disorders, Moscow Research Institute of Psychiatry, Moscow, Russia, [21] Department of Psychiatry, Russian Medical Academy of Continuous Professional Education, Moscow, Russia*

OPEN ACCESS

Edited by:
Gabriele Sachs,
Medical University of Vienna, Austria

Reviewed by:
Armida Mucci,
University of Campania Luigi Vanvitelli, Italy
Uma Suryadevara,
University of Florida, United States

***Correspondence:**
Istvan Bitter
bitter.istvan@med.semmelweis-univ.hu

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *23 November 2021*
Accepted: *17 December 2021*
Published: *04 February 2022*

Citation:
Bitter I, Mohr P, Raspopova N, Szulc A, Samochowiec J, Micluia IV, Skugarevsky O, Herold R, Mihaljevic-Peles A, Okribelashvili N, Dragašek J, Adomaitiene V, Rancans E, Chihai J, Maruta N, Marić NP, Milanova V, Tavčar R and Mosolov S (2022) Assessment and Treatment of Negative Symptoms in Schizophrenia—A Regional Perspective. Front. Psychiatry 12:820801. doi: 10.3389/fpsyt.2021.820801

Clinicians and researchers consider that there are a variety of symptoms that constitute negative symptoms in schizophrenia, and they may use different definitions for the same symptoms. These differences are also reflected in a variety of negative symptom rating scales. Both research and clinical work are negatively affected by the lack of consensus regarding the symptoms that constitute negative symptoms in schizophrenia. Leading research groups have investigated ways to reduce heterogeneity in the domain of negative symptoms in schizophrenia; however, little attention has been paid to regional differences in the concepts of negative symptoms in schizophrenia. The objective of this review was to collect and summarize information about the assessment and treatment of negative symptoms of schizophrenia in Central and Eastern Europe (CEE). Nineteen experts from 17 countries in CEE participated in this project. The participants collected information about their countries, including the following: (1) the most important publications about negative symptoms in schizophrenia (irrespective of the time of their publication); (2) the most frequently used negative symptom of schizophrenia in clinical practice; (3) definitions of frequently used negative symptoms; and (4) treatment of

negative symptoms in schizophrenia. The participating experts/countries most frequently reported the following five negative symptoms: avolition, blunted affect, alogia, asociality, and anhedonia. Several experts also considered other symptoms as belonging to the negative symptom domain, such as a decrease in energy level and changes in personality. The importance of evaluating the long-term course and the relationship between negative symptoms and other symptom domains was also noted. No noticeable differences were reported in the treatment of negative symptoms compared to currently published guidelines and algorithms. The most frequently reported negative symptoms included those defined by the NIMH-MATRICS consensus statement on negative symptoms and recently endorsed in a guidance paper of the European Psychiatric Association. The main differences in the concepts, names, and definitions of primary negative symptoms, especially those related to personality changes, and to the evaluation of the long-term course and relationship between different symptom domains in CEE compared to the current English language literature deserve the attention of psychiatrists and other professionals in this field.

Keywords: negative symptoms, schizophrenia, assessment, treatment, review, personality, Central and Eastern Europe

INTRODUCTION

Clinicians and researchers consider a variety of symptoms as negative symptoms of schizophrenia and may use different definitions for the same symptom (1). This ambiguity is also reflected by a variety of negative symptom rating scales, which include a range of different negative symptoms, sometimes with the same name but with different definitions (2). Both research and clinical work are negatively affected by the lack of consensus regarding negative symptoms. Expert groups addressed ways to improve the definitions of negative symptoms in schizophrenia in order to improve their assessment and treatment (2–4); however, little attention has been paid to regional—including cultural—differences in the clinical approaches of different schools of psychiatry.

Examples of geographical/regional differences in psychiatry that have been previously addressed include the following: in the context of large regional variability in the time to all-cause discontinuation of antipsychotic treatment of schizophrenia (5, 6); or "the lack of uniformity in the definition of treatment resistant depression (TRD) within the Asia-Pacific (APAC) region," which "may have implications for patient management" (7). A review on mental health care for people with severe mental illnesses in Central and Eastern Europe (CEE) resulted in a large "review on mental health systems in the former Eastern Bloc"; however, the focus of this work was on the structure and functioning of mental health care in post-communist countries rather than research, medical education, and training (8). The authors of a literature review on the "Epidemiology and Treatment Guidelines of Negative Symptoms in Schizophrenia in Central and Eastern Europe…" (9) concluded the following: "Despite the extensive search, we were unable to find relevant data in all areas of interest." A similar conclusion was made by the authors of a previously published paper about psychiatry in nine CEE countries: "There is a great tradition of psychiatry in the region; however, the scientific output and number of psychiatric publications in international peer-reviewed journals is considerably low." (10). However, in another study focusing on patients with a diagnosis of schizophrenia in CEE, the authors reported that the information provided by selected experts was useful (11), which is similar to the conclusion in the paper by Winkler et al. (8).

The discussion of the history of psychiatry and the heterogeneity of higher education and research systems in CEE countries is far beyond the scope of this paper; however, it is important to emphasize that these countries are rather heterogeneous. Indeed, CEE countries are even more heterogeneous than countries in Western Europe. Some CEE countries were part of the Habsburg Empire; for example, Czechia, Croatia, Hungary, Slovakia, Slovenia, parts of Poland, Ukraine, and Romania, and others have been in close contact with Russia and were included in the Soviet Union. Most countries in the region were significantly influenced by German psychiatry until the 1980s, while other countries (especially the former republics of the Soviet Union) had ties to Russian psychiatry. Considering the representation of psychiatry as a medical discipline in each respective country, we find substantial differences in the history of psychiatry. For example, Tbilisi State University was founded in 1918 (https://en.wikipedia.org/wiki/Tbilisi_State_University), which contributed to the development of the discipline of psychiatry in the native language in Georgia (12). In contrast, Kraepelin was the Professor of Psychiatry at the University of Tartu (earlier: Dorpat) in Estonia between 1886 and 1891. Meanwhile, the Charles University in Prague was founded in 1348. "As a date of the very beginning of the Psychiatric Clinic of the Czech University, the November 19th, 1886, is considered." Before this date, the language of teaching in Prague was German and the same applied to Dorpat.

The University in Vilnius (Lithuania) was founded in 1579 and has been a leading university in Europe. The names of the two founding fathers of Russian psychiatry, Korsakoff (1854-1900) from Moscow (https://link.springer.com/referenceworkentry/10.1007%2F978-0-387-79948-3_631) and Bekhterev (1857-1927) from St. Petersburg (https://en.wikipedia.org/wiki/Vladimir_Bekhterev), are well-known worldwide. After the major political changes in the CEE region in the 1990s, English language publications and US psychiatry had an overwhelming influence on psychiatry. Several countries from the CEE region became EU member states, and psychiatrists also participated in EU-funded research and educational projects.

There is a detectable increase in interest in the negative symptoms of schizophrenia. Based on data from Google Scholar, 44% of papers on schizophrenia published in 2000 and 73% published in 2020 (38,900/53,200 hits) refer to negative symptoms (12,100/27,600 hits) (the search was performed on October 16, 2021, and the search terms were "schizophrenia negative symptoms" and "schizophrenia," respectively). During professional meetings, the authors of this paper had the opportunity to discuss the development of research on negative symptoms in schizophrenia and concluded that some current issues in this field could be more efficiently addressed with contributions from experts working in CEE. These contributions may pose some challenges, since some contributions do not simply increase the amount of current information about negative symptoms in schizophrenia, but also raise questions about the usefulness of current phenotyping in schizophrenia for much needed basic research, including drug discovery and development for the treatment of this disease. Examples include long-term evaluation of negative symptoms and personality changes during the course of schizophrenia.

The objective of this scoping review was to summarize the selected literature and expert opinions on negative symptoms in schizophrenia from CEE countries.

METHODS

Nineteen experts (the authors of this paper) from 17 countries participated in this project. We used the World Health Organization's definition of Europe, which includes some Asian countries. The selection of countries also reflects the availability of interested experts in the region. The 17 countries are Belarus, Bulgaria, Croatia, Czech Republic, Georgia, Hungary, Kazakhstan, Latvia, Lithuania, Moldova, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, and Ukraine.

The coordinator of the project (IB) distributed a questionnaire and collected additional information from the project participants, mainly via email communication. The questionnaire included the following questions and requests with additional instructions.

- Request for the identification of the most important publications on negative symptoms of schizophrenia in the participating countries, irrespective of the time of their publication.
- Request for a list of the negative symptoms of schizophrenia used in clinical practice in the participating countries ranked by their "popularity" and endorsed by academia (e.g., textbooks). We collected all symptoms that were considered negative symptoms in the participating countries, irrespective of the current views on negative symptoms.
- Request for the description of the definitions of the listed negative symptoms (e.g., "How are they defined in well-accepted textbooks in your language/country?").
- The following questions were included in the questionnaire: "Are there recommendations in the participating country for the treatment of negative symptoms in schizophrenia? If yes, please refer to (short summary)." If no recommendation existed, participants were asked to summarize the clinical practice for the treatment of negative symptoms in their countries. Based on the participants' responses regarding lack of or limited availability of psychosocial interventions for negative symptoms in schizophrenia, the question was changed and included only pharmacological treatment.

RESULTS

Evaluation

Online Supplementary 1 includes a list of selected references provided by participating experts. The literature provided by the experts addressed the assessment more than the treatment of negative symptoms. Many important contributions are available only in the local languages. Russian is also used in some countries that were republics of the Soviet Union. A few of the provided references were from outside the country of the responding expert, which illustrates the importance of some authors and/or schools of psychiatry in a specific country; they are either translated into the language used in the country or published in English or Russian.

The literature collected by the participants of this regional project shows that negative symptoms are considered important, and the selected literature and expert opinions reflect high-level interest in the negative symptoms of schizophrenia in CEE countries. In the majority of CEE, the terminology of negative symptoms is dominated by English, as summarized in the currently published European guidance paper on the evaluation of negative symptoms in schizophrenia (2) however, traditional German psychopathology [e.g., the work of Huber (13, 14)] has a significant influence in the region, and Russian schools have a strong influence not only in Russia, but also in some other countries, especially in former republics of the Soviet Union (15, 16). **Table 1** includes the names and frequencies of negative symptoms listed by experts from 17 countries.

The following symptoms were collected by Raspopova from Kazakhstan: "emotional decline, socially withdrawn and passive, gross personality changes, narrowing of the range of interests, increasing autism, slowly increasing autism, slight decrease in energy potential, violation of logical harmony and of the purposefulness of thinking; disorganization of psychic activity; a significant decrease in interests and activity characteristic for a given person; emotional impoverishment; increasing social withdrawal (autism); various disorders of

TABLE 1 | List of the negative symptoms used in 17 countries across CEE.

Symptom	Times mentioned	Country/countries endorsed
Avolition Reduction of volitive action, Abulia Abulia Abulia-apathy* Reduced volitional activity	16	Croatia, Czech Republic, Georgia, Hungary, Latvia, Lithuania, Moldova, Poland, Romania, Russia, Serbia Slovakia Kazakhstan Belarus Ukraine Bulgaria
Blunted affect, flat affect, Affective flattening / blunting Impoverishment of emotional reactions and blunted affect, Affective blunting, and poverty of emotional expression Lack of emotional expression Flattening of affect (apathy) Blunted or inappropriate affect	16	Croatia, Czech Republic, Hungary, Kazakhstan, Latvia, Lithuania, Moldova, Poland, Romania, Slovakia, Ukraine, Russia Serbia Belarus Bulgaria Slovenia
Asociality Lack of social interest Social withdrawal Social withdrawal Limitation of social contacts Anhedonia-asociality Social withdrawal	14	Czech Republic, Georgia, Hungary, Kazakhstan, Lithuania, Poland, Serbia, Ukraine Croatia Romania Russia Slovakia Bulgaria Slovenia
Alogia Poverty of quantity or content of speech No spontaneity/fluency in discussion (alogy) Poverty of verbal expression	14	Czech Republic, Georgia, Hungary, Kazakhstan, Russia, Lithuania, Moldova, Romania, Serbia, Ukraine, Slovenia Latvia Poland Slovakia, Russia
Anhedonia Anhedonia-asociality	11	Croatia, Czech Republic, Georgia, Hungary, Kazakhstan, Lithuania, Moldova, Romania, Serbia, Ukraine, Bulgaria
Apathy Abulia-apathy* Flattening of affect (apathy) Apathy, Abulia, Hypobulia	6	Georgia, Russia, Slovakia Ukraine Bulgaria Slovenia
Autism	4	Croatia, Moldova, Kazakhstan, Russia
Personality changes	3	Kazakhstan, Russia, Ukraine
Emotional withdrawal	2	Croatia Poland
Psychomotor slowing Motor retardation	2	Latvia Poland
Passivity, Indifference	2	Latvia, Belarus
Lack of initiative	2	Latvia, Belarus
Reduction of energy capacity/reduced mental activity, Asthenia	2	Russia, Kazakhstan
Poor rapport, poor contact with others	2	Croatia, Poland
Poor social performance Poor social functioning	2	Latvia, Slovenia
Underactivity	1	Latvia
Poor self-care	1	Latvia
Deficit syndrome	1	Lithuania
Poor non-verbal communication	1	Latvia
Deterioration/reduction of intellectual activity	1	Russia
Indecisiveness	1	Slovakia
Narrowing of the circle of interests	1	Belarus

The item "abulia-apathy" appears both as "abulia" associated with the item "avolition" and as "apathy" associated with the item "apathy".

thinking and behavior." Raspopova et al. published a study guide in Russian focusing on negative symptoms and provided a detailed review on cariprazine (17). The following terms were included in a 1968 dissertation by Chiladze (1968; see **Online Supplementary 1**): (1) the "loosening up" of concepts; (2) poverty of imagination/fantasy; (3) the flatness of spiritual feelings; (4) emotional alienation; (5) indifferent/"indisciplined." These two examples uncover the results of old research in the field and show the wealth of terms used to describe the devastating effects of schizophrenia.

The most noticeable difference in the current descriptions of negative symptoms in the English language literature is the inclusion of "personality changes ("personality shift")" in the negative symptom domain in some countries (e.g., Russia, Ukraine, and Kazakhstan) and the proposed analysis of the long-term course and relationship of negative symptoms to positive and other symptom domains during the course of schizophrenia (16, 18).

Based on the selected publications from the region and on the written reports from the authors of this review, we found that in routine clinical practice, negative symptoms are not stratified by the doctors in most countries into "primary" and "secondary" symptoms. Cognitive symptoms are often not differentiated; however, Capatina and Miclutia (19) published a study demonstrating the absence of a relationship between cognitive and negative factors when using the Positive and Negative Syndrome Scale (PANSS) scale. Nevertheless, when investigating the relationship of the PANSS cognitive factor with the negative symptoms evaluated using the Negative Symptom Assessment (NSA-16) scale, it was shown that there was a

significant association between cognition and motor retardation. They concluded that negative symptoms represent a separate treatment target. The same group identified studies on the stability of negative symptoms over 1 year (20), as well as secondary negative symptoms. In their review, they reported the following. "Factorial analyses showed that secondary negative symptoms encompass the same domains as primary negative symptoms: avolition/apathy and diminished expression, but it is not yet clear, and evidence are sparse regarding how specific causes of secondary negative symptoms are related which negative symptom domain. Although recent research has defined the main causes of secondary negative symptoms, evidence-based treatment recommendations remain scattered."

Based on a survey of the Russian Association of Psychiatry, including 807 psychiatrists representing 78 regions of Russia, 35% of the respondents supported the proposal that negative symptoms should be defined and considered obligatory for the diagnosis of schizophrenia in the diagnostic systems, and the respondents estimated that the specificity of "emotional-volitional reduction" for schizophrenia was 72.1% (SD = 19.6; $n = 685$) (21).

None of the participants in this study reported ethnic or transcultural diversities in the description of negative symptoms in patients with schizophrenia, either in scientific research or in clinical practice.

Pharmacological Treatment

All experts reported that the current literature on the treatment of negative symptoms is available in their countries. Approaches to the treatment of negative symptoms in schizophrenia in the CEE [e.g., (22–24)] are in line with the current literature, including suggested algorithms, guidelines, and reviews about the treatment of negative symptoms (3, 25, 26). In some countries (e.g., Georgia and Romania), cariprazine was unavailable at the time of writing this manuscript. A number of countries (e.g., Czechia, Kazakhstan, Russia, and Slovakia) incorporated the treatment algorithm for negative symptoms in schizophrenia suggested by Cerveri et al. (2, 24) in their new guidelines or in other publications, which reflects the current progress and limitations in the field. The authors emphasize the need for further research on the treatment of primary or predominant and persistent negative symptoms. Their recommendation is to use cariprazine as a first-line drug for the treatment of negative symptoms in schizophrenia; amisulpride is a second-generation antipsychotic with a partial agonist effect on D2/D3 dopamine receptors and with variable levels of evidence (3). The third-line options include other second-generation antipsychotics (SGAs), specifically olanzapine and quetiapine, and the fourth option is the addition of antidepressants. The Czech guidelines also cautiously suggest high-frequency, repetitive transcranial magnetic stimulation (rTMS) administered over the left dorsolateral prefrontal cortex (DLPFC Czechia, Croatia, and Russia have reported the use of rTMS for negative symptoms in patients with schizophrenia with variable outcomes (27–30).

DISCUSSION

Evaluation

The majority of the participating experts/countries endorsed the five main symptoms as conceptualized by the NIMH-MATRICS consensus statement on negative symptoms: avolition, blunted affect, alogia, asociality, and anhedonia (4). Avolition and blunted affect were the most frequently endorsed symptoms in the CEE study. Research of the psychopathology of "will" has long been a tradition both in Germany and Russia, which has been addressed by Mosolov and Yaltonskaya (in press) (12). The severity (from mild inhibition of will to lack of will), components (drive, imagination, decision making, etc.), and temporal phases of the disturbances of will are present in different works about negative symptoms from CEE; however, those details [see for example (31)] are not included in currently used rating scales for negative symptoms (2). A current treatment study suggests that decoupling the influence of motivational processes from other negative symptom domains is essential for producing global improvements. The search for pathophysiological mechanisms and targeted treatment development should focus on avolition, with the expectation of improvement in the entire constellation of negative symptoms if avolition is effectively treated (32). Considering this finding and the accumulated knowledge about the disturbances of "will" (31), a detailed analysis of the components of avolition and their relationship to constructs, such as drive, motivation, decision making, asthenia, ambivalence, etc., may help make significant advances in this field. For example, we have witnessed how the distinction between anticipatory and consummatory pleasure changed our thinking about anhedonia in schizophrenia (33). Additional symptoms were also named in CEE; for example, negative symptoms from Russia, Kazakhstan, and Ukraine included "decrease in energy potential" and "personality changes," where "decrease in energy potential" was defined as the initial core symptom in the hierarchy of negative symptoms.

The complex relationship between schizophrenia and personality disorders has been an important topic in psychopathology, with a focus on personality disorders during the premorbid and prodromal phases of schizophrenia and in the differential diagnosis of schizophrenia (34). The Russian School of Psychopathology includes personality changes in the hierarchy of negative symptoms associated with poor outcomes in patients with schizophrenia. Personality changes as negative symptoms have also been reported by Ukrainian and Kazakh experts. They refer to a hierarchy of negative symptoms by the level of their severity and report 10 levels, which include several personality-related negative symptoms.

The Russian school also emphasizes the "long-term course of negative symptoms and their relationship" between symptom domains in the course of schizophrenia; for example, it differentiates between a "synchronized" and "desynchronized" course of positive and negative symptoms (18). In the case of a "synchronized" relationship between positive and negative symptoms, the secondary nature of the increase in severity of negative symptoms can be hypothesized, while in the case of a "desynchronized" course, the increase in the severity

of negative symptoms is not associated with an increase in positive symptoms. The 11th edition of the International Statistical Classification of Diseases and Related Health Problems (35) includes the following "Symptom Specifiers" for the cross-sectional characterization of the symptomatology in schizophrenia: "Positive symptoms," "Negative symptoms," "Depressive symptoms," "Manic symptoms," "Psychomotor symptoms," and "Cognitive impairments." These specifiers should characterize the symptom status of a patient only for 1 week and not over longer periods of time; thus, the length of time of the presence or absence of a specifier is a major difference between the approach of ICD-11 and of the representatives of Russian psychopathology (18). The requirement of predominant negative symptoms for a long period by the European Medicines Agency results in the exclusion of a group of patients with primary negative symptoms, which is one of the reasons that the concept of predominant negative symptoms as an inclusion criterion in clinical trials has been challenged (1, 2). There is a well-defined need for more research into the primary symptoms of schizophrenia (36).

Pharmacological Treatment

In contrast to the evaluation of negative symptoms in schizophrenia, we found no differences between the current evidence-based literature (3, 26, 37) and the opinions of experts and papers published on this topic by experts from CEE countries. This finding is not surprising, considering that very few drugs are available worldwide that have any evidence of efficacy for the treatment of negative symptoms of schizophrenia. The third and fourth switches of medication indicate treatment resistance. The concept of treatment-resistant schizophrenia is broader than resistance to the treatment of negative symptoms; however, it also includes negative symptoms. In addition, the evidence base is quite low at the 3rd or 4th step of the proposed treatment algorithms for primary negative symptoms; for example, the recommendation of quetiapine is based on a small study with 44 patients comparing quetiapine to risperidone (23).

Our study highlights the need for more intensive collaborative research and dialogue between researchers in different parts of the world.

LIMITATIONS

The 17 countries included in the study cover a large proportion of, but not all, countries in CEE. Data collection was based on the opinion of participating experts; however, the selected experts had a demonstrable track record (oral presentations during national and international meetings, and published books, papers, and abstracts about or closely related to the topic of negative symptoms in schizophrenia).

CONCLUSIONS

Our review reports the most important information regarding the evaluation and treatment of negative symptoms in a large geographic region. The region has rich diversity in the form of different languages, traditions, and current trends in psychiatry. The main differences in the concepts, names, and definitions of primary negative symptoms in CEE compared to the current English language literature deserve the attention of psychiatrists and other interested professionals, such as the inclusion of personality changes in the negative symptom domain or the importance of considering the long-term course of negative symptoms in schizophrenia.

AUTHOR CONTRIBUTIONS

IB: concept, coordination of the project that resulted in this manuscript, and drafting the manuscript of this review. All authors reviewed and approved the concept, collected data on negative symptoms in their countries (on the use, definition, evaluation, and pharmacological treatment of negative symptoms and country-specific references to these topics), contributed with their summaries to the draft manuscript, reviewed the draft manuscript, reviewed, and approved the final manuscript.

FUNDING

The fee for language editing and the open access publication fee were covered by unrestricted support from Gedeon Richter. IB's work was partly supported by the Hungarian Brain Research Program (2017-1.2.1-NKP-2017-0002). RH's work was supported by the National Brain Research Program [Grant No. NAP KTIA NAP-A-II/12(2017-2021)] and The National Excellence programme (2019-2021, FIKP II.).

ACKNOWLEDGMENTS

The authors thank Ms. Zsüliet Kristóf, Ph.D. student of Semmelweis University, Budapest, for her technical support.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.820801/full#supplementary-material

REFERENCES

1. Bitter I. Definitions and measurement of negative symptoms in schizophrenia. In: Bitter I, editor. *Managing Negative Symptoms of Schizophrenia*. Oxford: Oxford University Press (2020). p. 1–18. doi: 10.1093/med/9780198840121.003.0001
2. Galderisi S, Mucci A, Dollfus S, Nordentoft M, Falkai P, Kaiser S, et al. EPA guidance on assessment of negative symptoms in schizophrenia. *Eur Psychiatry*. (2021) 64:e23. doi: 10.1192/j.eurpsy.2021.11
3. Galderisi S, Kaiser S, Bitter I, Nordentoft M, Mucci A, Sabé M, et al. EPA guidance on treatment of negative symptoms in schizophrenia. *Eur Psychiatry*. (2021) 64:e21. doi: 10.1192/j.eurpsy.2021.13
4. Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull*. (2006) 32:214–9. doi: 10.1093/schbul/sbj053
5. Su CC, Chia-Cheng Lai E, Kao Yang YH, Man KKC, Kubota K, Stang P, et al. Incidence, prevalence and prescription patterns of antipsychotic medications use in Asia and US: a cross-nation comparison with common data model. *J Psychiatr Res*. (2020) 131:77–84. doi: 10.1016/j.jpsychires.2020.08.025
6. Bitter I, Treuer T, Dyachkova Y, Martenyi F, McBride M, Ungvari GS. Antipsychotic prescription patterns in outpatient settings: 24-month results from the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study. *Eur Neuropsychopharmacol*. (2008) 18:170–80. doi: 10.1016/j.euroneuro.2007.08.001
7. Ng CH, Kato T, Han C, Wang G, Trivedi M, Ramesh V, et al. Definition of treatment-resistant depression - Asia Pacific perspectives. *J Affect Disord*. (2019) 245:626–36. doi: 10.1016/j.jad.2018.11.038
8. Winkler P, Krupchanka D, Roberts T, Kondratova L, Machu V, Höschl C, et al. A blind spot on the global mental health map: a scoping review of 25 years' development of mental health care for people with severe mental illnesses in central and eastern Europe. *Lancet Psychiatry*. (2017) 4:634–42. doi: 10.1016/S2215-0366(17)30135-9
9. Szkultecka-Debek M, Walczak J, Augustyńska J, Miernik K, Stelmachowski J, Pieniazek I, et al. Epidemiology and treatment guidelines of negative symptoms in schizophrenia in Central and Eastern Europe: a literature review. *Clin Pract Epidemiol Ment Health*. (2015) 11:158–65. doi: 10.2174/1745017901511010158
10. Furedi J, Mohr P, Swingler D, Bitter I, Gheorghe MD, Hotujac L, et al. Psychiatry in selected countries of Central and Eastern Europe: an overview of the current situation. *Acta Psychiatr Scand*. (2006) 114:223–31. doi: 10.1111/j.1600-0447.2006.00804.x
11. Szkultecka-Debek M, Miernik K, Stelmachowski J, Jakovljević M, Jukić V, Aadamsoo K, et al. Schizophrenia causes significant burden to patients' and caregivers' lives. *Psychiatr Danub*. (2016) 28:104–10
12. Kentchadze V, Okribelashvili N, Naneishvili G. History of psychiatry in georgia: hidden pages (dedicated to our teachers). *Georgian Med News*. (2017) 265:130–8.
13. Huber, Huber G, Huber G. Defektsyndrome und basisstadien endogener psychosen. *Fortsch Neurol Psychiatr*. (1966) 34:409–4015.
14. Ebel H, Gross G, Klosterkötter J, Huber G. Basic symptoms in schizophrenic and affective psychoses. *Psychopathology*. (1989) 22:224–32. doi: 10.1159/000284602
15. Mosolov SN, Yaltonskaya PA. Primary and secondary negative symptoms in schizophrenia. *Front Psychiatry*. (2021) 12:766692. doi: 10.3389/fpsyt.2021.766692
16. Mosolov SN, Yaltonskaya PA. Concept, classification and clinical differentiation of negative symptoms inschizophrenia. *Sovrem Psih Rasstrojstv*. (2020) 1:2–14. doi: 10.21265/PSYPH.2020.15.30.001
17. Raspopova NI, Bastasova UA, Eshimbetova SZ. *Negative Disorders in the Clinical Picture of Schizophrenia. Study Guide*. Almaty: Lambert Academic Publishing (2021). p. 60.
18. Smulevich A, Romanov D. Long-term course of negative symptoms in schizophrenia. In: Bitter I, editor. *Managing Negative Symptoms of Schizophrenia*. Oxford: Oxford University Press (2020). p. 39–50. doi: 10.1093/med/9780198840121.003.0003
19. Capatina OO, Miclutia IV. Are negative symptoms in schizophrenia a distinct therapeutic target? *Clujul Med*. (2018) 91:58–64. doi: 10.15386/cjmed-864
20. Capaţina OO, Miclutia I. Course of negative symptoms sudomanins in schizophrenia: a one year follow-up study. In: *26th European Congress of Psychiatry*. Issy-les-Moulineaux: European Psychiatry (2018). p. S348-S. PW0859. doi: 10.26226/morressier.5a7070e5d462b80290b571f4
21. Neznanov N, Martynikhin I, Mosolov S. Diagnosis of schizophrenia in Russia: the results of a web-based survey of psychiatrists. *Sovrem Psih Rasstrojstv*. (2019) 1:2–13. doi: 10.21265/PSYPH.2019.24.24.001
22. Capatina OO, Miclutia IV, Fadgyas-Stanculete M. Current perspectives in treating negative symptoms of schizophrenia: a narrative review (Review). *Exp Ther Med*. (2021) 21:276. doi: 10.3892/etm.2021.9707
23. Masopust J, Mohr P, Kopeček M. Antipsychotics in treatment of predominant negative symptoms in schizophrenia: an update of guidelines. *Psychiatrie*. (2020) 24:40–3.
24. Mosolov SN, Yaltonskaya PA. An algorithm for the treatment of primary negative symptoms in schizophrenia. *Sovrem Psih Rasstrojstv*. (2020) 2:2–10. doi: 10.21265/PSYPH.2020.26.17.001
25. Cerveri G, Gesi C, Mencacci C. Pharmacological treatment of negative symptoms in schizophrenia: update and proposal of a clinical algorithm. *Neuropsychiatr Dis Treat*. (2019) 15:1525–35. doi: 10.2147/NDT.S201726
26. Czobor P, Bitter I. Pharmacologic treatment of negative symptoms: focus on efficacy. In: Bitter I, editor. *Managing Negative Symptoms of Schizophrenia*. Oxford: Oxford University Press (2020). p. 67–86. doi: 10.1093/med/9780198840121.003.0005
27. Novak T, Horacek J, Mohr P, Kopecek M, Skrdlantova L, Klirova M, et al. The double-blind sham-controlled study of high-frequency rTMS (20 Hz) for negative symptoms in schizophrenia: negative results. *Neuro Endocrinol Lett*. (2006) 27:209–13.
28. Prikryl R, Kasparek T, Skotakova S, Ustohal L, Kucerova H, Ceskova E. Treatment of negative symptoms of schizophrenia using repetitive transcranial magnetic stimulation in a double-blind, randomized controlled study. *Schizophr Res*. (2007) 95:151–7. doi: 10.1016/j.schres.2007.06.019
29. Prikryl R, Ustohal L, Prikrylova Kucerova H, Kasparek T, Venclikova S, Vrzalova M, et al. A detailed analysis of the effect of repetitive transcranial magnetic stimulation on negative symptoms of schizophrenia: a double-blind trial. *Schizophr Res*. (2013) 149:167–73. doi: 10.1016/j.schres.2013.06.015
30. Maslenikov NV, Mosolov SN, Smirnov NA, Tsukarzi EE. Repetitive transcranial magnetic stimulation (rTMS) effects on depression, negative symptoms and cognition in schizophrenia. *Brain Stimul*. (2015) 8:333 doi: 10.1016/j.brs.2015.01.078
31. Fuchs T, Broschmann D. [Disorders of the will in psychopathology]. *Nervenarzt*. (2017) 88:1252–8. doi: 10.1007/s00115-017-0323-1
32. Strauss GP, Zamani Esfahlani F, Sayama H, Kirkpatrick B, Opler MG, Saoud JB, et al. Network analysis indicates that avolition is the most central domain for the successful treatment of negative symptoms: evidence from the roluperidone randomized clinical trial. *Schizophr Bull*. (2020) 46:964–70. doi: 10.1093/schbul/sbz141
33. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. *Schizophr Res*. (2007) 93:253–60. doi: 10.1016/j.schres.2007.03.008
34. Erkwoh R, Herpertz S, Sass H. [Personality disorders and schizophrenic psychoses]. *Nervenarzt*. (2003) 74:740–7. doi: 10.1007/s00115-003-1474-9
35. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems*. 11th ed. (2019). Avaialble online at: https://icd.who.int/ (accessed November 20, 2021).
36. Kirkpatrick B, Cohen A, Bitter I, Strauss GP. Primary negative symptoms: refining the research target. *Schizophr Bull*. (2021) 47:1207–10. doi: 10.1093/schbul/sbab069
37. Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Nikolakopoulou A, et al. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*. (2018) 268:625–39. doi: 10.1007/s00406-018-0869-3

Conflict of Interest: In the past 5 years, IB received honoraria or consultation fees outside of this work from Angelini, Eli Lilly, Gedeon Richter, Hikma Pharmaceuticals, Janssen/Janssen Cilag, Lundbeck, Medichem Pharmaceuticals, Inc. by Unilab, Philippines, Mitsubishi Tanabe Pharma Singapore, and Sun Pharma. He received royalties from the Oxford University Press. In the past 5

years, VA received honoraria or consultation fees from Janssen/Janssen Cilag. JS received honoraria as a member of the Speaker Bureau of Gedeon Richter. In the past 5 years, RT received speaker's honoraria from Angelini, Gedeon Richter, Janssen, Krka, Lek, Lundbeck, Mylan, Promed, Servier, Teva. In the past 5 years, AM-P received honoraria as speaker from Gedeon Richter, Janssen, Lundbeck, Pliva-Teva. PM has been a consultant and received honoraria and/or speaker fees from Angelini Pharma. Janssen-Cilag, Gedeon Richter, Lundbeck, and Viatris Mylan. In the past 5 years, NM received honoraria or consultation fees from Gedeon Richter, Maylan, Actavis-Teva and Pfizer. AS received honoraria or consultation fees from Gedeon Richter, Janssen Poland, and Angelini, Bausch Poland. In the past 5 years, RH received honoraria or consultation fees from Egis, Eli Lilly, Gedeon Richter, Janssen, Krka, Lundbeck, Mylan-Viatris, Servier, and Teva. In the past 5 years, ER received research grants from Gedeon Richter and Lundbeck, speaker honoraria, and is a member of advisory panels for Abbvie, Gedeon Richter, Grindex, Janssen Cilag, Lundbeck, Servier, and Zentiva. He has been the principal investigator in clinical trials for Lundbeck, Janssen Cilag, and Sunovion. In the past 5 years, SM received honoraria or consultation fees from Angelini, Gedeon Richter, Janssen, Lundbeck, Abbott, Grindex, and Servier. In the past 5 years, IM received honoraria as speaker from Angelini, Gedeon Richter, Janssen J&J, Lundbeck, Plantextract, and Terapia. NM has received in the past 5 years honoraria or consultation fees from Gedeon Richter, Sanofi, Acino, OlainFarm, Ever-pharma, Dileo Farma. NO, as a speaker, has received honoraria from Abbott, Abdi Ibrahim, Acino, Angelini, Egis, Gedeon Richter, Grindex, Novartis, Sanofi Aventis, Servier in the past 5 years. JD has received in the past 5 years honoraria or consultation fees from Angelini, Eli Lilly, Gedeon Richter, Janssen, Krka, Lundbeck, Sandoz. VM has received in the past 5 years honoraria or consultation fees from Angelini, Gedeon Richter, Janssen/Janssen Cilag, Medochemie, Lundbeck.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past co-authorship with one of the authors IB.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 21 February 2022
doi: 10.3389/fpsyt.2022.829363

Characteristics of Facial Muscle Activity Intensity in Patients With Schizophrenia and Its Relationship to Negative Symptoms

*Xia Du, Hong Zhen Fan, Yun Hui Wang, Jie Zhang, Xiao Lin Zhu, Yan Li Zhao and Shu Ping Tan**

Beijing HuiLongGuan Hospital, Beijing, China

OPEN ACCESS

Edited by:
Gabriele Sachs,
Medical University of Vienna, Austria

Reviewed by:
Marcel Riehle,
University of Hamburg, Germany
Mary V. Seeman,
University of Toronto, Canada

***Correspondence:**
Shu Ping Tan
shupingtan@126.com

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *05 December 2021*
Accepted: *17 January 2022*
Published: *21 February 2022*

Citation:
Du X, Fan HZ, Wang YH, Zhang J, Zhu XL, Zhao YL and Tan SP (2022) Characteristics of Facial Muscle Activity Intensity in Patients With Schizophrenia and Its Relationship to Negative Symptoms. Front. Psychiatry 13:829363. doi: 10.3389/fpsyt.2022.829363

Introduction: Previous studies have shown that in addition to having impairments in facial emotion recognition, patients with schizophrenia also show a lack of facial expression. Although negative symptoms such as decreased facial activity are common symptoms of schizophrenia, the related factors remain inconclusive. Therefore, this study compared healthy controls to explore the characteristics of facial muscle activity intensity in patients with schizophrenia and its relationship with negative symptoms.

Methods: This observational and cross-sectional study conducted in a psychiatric hospital in China included a total of 135 patients with schizophrenia and 134 healthy controls. The negative symptoms of schizophrenia were evaluated using the Brief Negative Symptom Scale. The intensity of facial muscle activity under positive, neutral, and negative emotional stimuli conditions was automatically collected by a computer, including 17 values (F01-F17) that represent different facial muscle activities. Statistical tests were performed to analyze facial muscle activity indexes, to explore an objective and quantitative method to evaluate the negative symptoms of schizophrenia.

Results: The facial muscle activity intensity of the schizophrenia group at F02 (outer eyebrow), F04 (upper eyelid), F07 (nose), F10 (dimple), F12 (lower jaw 1), F14 (lip 2), and F17 (blink) was lower than that of the healthy controls ($p < 0.05$). Under positive, neutral, and negative emotional stimuli conditions, the facial muscle activity intensity of F16 (lower jaw 2) was positively correlated with negative symptoms ($p < 0.05$).

Conclusion: Our study indicated that patients with schizophrenia show defects in facial muscle activity and that is associated with negative symptoms.

Keywords: schizophrenia, facial muscles, activity intensity, negative symptoms, emotional stimuli

INTRODUCTION

Schizophrenia is a serious mental disorder. According to an epidemiological survey in China in 2019, the lifetime prevalence of schizophrenia is 0.6%, second only to depressive and anxiety disorders (1). Moreover, surveys in some cities in China show that schizophrenia accounts for 70.8% of psychiatric diseases and 46.7% of hospitalized patients and that these figures trend upward annually (2, 3). Therefore, schizophrenia has placed a serious burden on Chinese patients' families and society. The common symptoms of schizophrenia include positive and negative symptoms; negative symptoms such as decreased facial activity and indifference are the most common initial symptoms of schizophrenia (4). Negative symptoms exist even in the early stages of the disease, but they are easily masked by strong positive symptoms, so they may be delayed and even gradually aggravated, which is also an important reason for the high disability rate in relation to schizophrenia. At present, the primary methods of evaluation for negative symptoms either are various scales or rely on the subjective judgment of doctors' clinical experience, and there is a lack of objective and quantitative evaluation methods.

The existence of negative symptoms may also lead to cognitive impairment (5, 6), especially social cognitive impairment with emotional expression as the core. A study on the autonomous facial emotion expression of patients with schizophrenia (that is, in the absence of stimulation materials, subjects spontaneously express facial emotions such as sadness, anger, and happiness) suggests that the emotional expression ability of such patients is significantly weaker than that of healthy controls; moreover, the impairment of emotional expression is related to the score of negative symptoms (7). In another study, in daily life, patients with schizophrenia talked with their families about numerous practical problems. The study found that the number of facial expression changes in patients with schizophrenia per unit time was significantly lower than that in healthy controls, and the correlation between facial expression changes and conversation content decreased (8). It is suggested that there are obvious defects in both intentional emotional expression and autonomous emotional expression in patients with schizophrenia. These defects are not caused by clinical symptoms and drug side effects, but rather by a group of independent symptoms (9). Although the above studies suggest that there is a correlation between facial emotional expression and the negative symptoms of schizophrenia, these studies either only focus on a designated emotional expression or only study the indicators of the number of changes in facial expression and cannot completely quantitatively evaluate negative symptoms.

Therefore, we assume that the facial muscle activity of patients with schizophrenia under the same emotional stimuli is different from that of healthy controls, which may reflect the severity of negative symptoms. We preliminarily explore negative symptoms using an objective and quantitative evaluation method to provide reference for the symptom evaluation of auxiliary diseases. This will assist clinicians in noticing negative symptoms earlier, assessing the severity of negative symptoms more accurately, and formulating intervention plans for negative symptoms earlier so as to reduce the social function defects caused by negative symptoms as well as to reduce the burden on patients' families and society.

MATERIALS AND METHODS

Subjects

Based on the previous literature on the changes of facial emotion in relation to the negative symptoms of schizophrenia, the reported effect value is 0.80 (10), calculated by G-Power software using a two-tailed test and setting $\alpha = 0.05$ and $1\text{-}\beta = 0.85$; the ratio between the case group and the control group is set to 1:1, and the sample size of each group is 30 cases. The subjects were outpatients and inpatients with schizophrenia at Beijing HuiLongGuan Hospital between October 2017 and July 2019. Healthy controls were recruited through the community and media advertising during the same period. The inclusion criteria for patients with schizophrenia were as follows: meeting the diagnostic criteria for schizophrenia in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) (11), being aged 18–60 years old, and having a junior high school level of education or above. Exclusion criteria were having an intellectual disability, having a serious physical diseases or adverse drug reactions, substance dependence or abuse, having excited, impulsive behavior or, during the decline associated with schizophrenia, being unable to cooperate with the test, and lactation or pregnancy. Inclusion criteria for healthy controls were as follows: having no abnormal mental state in the fixed interview with psychiatrists, having no family history of mental disorders, being aged 18–60 years old, and having a junior high school level of education or above. Exclusion criteria were having an intellectual disability, suffering from serious physical diseases, substance dependence or abuse, and lactation or pregnancy. Following the application of the inclusion and exclusion criteria, a total of 160 patients with schizophrenia and 143 healthy controls were included. Because some subjects failed to complete the experimental task, 135 patients with schizophrenia and 134 healthy controls were ultimately included in the study. The task comprised measurements of facial muscle strength under three different emotional states as well as evaluation of the scale to determine whether there is a difference in the intensity of facial muscle activity between the two groups and whether the difference correlates with negative symptoms of schizophrenia.

This study was approved by the ethics committee of Beijing HuiLongGuan Hospital. After the subjects were fully informed of the study plan, we obtained their written informed consent to participate in the study.

Basic Information and Clinical Symptom Evaluation

The gender, age, and years of education of the subjects were collected using a self-made basic information questionnaire. The Brief Negative Symptom Scale (BNSS) (12) was used to evaluate the severity of negative symptoms in patients with schizophrenia. There are 13 items on the scale, including six subscales: anhedonia subscale, depression subscale, blunted affect subscale and so on. Each of the 13 items is rated

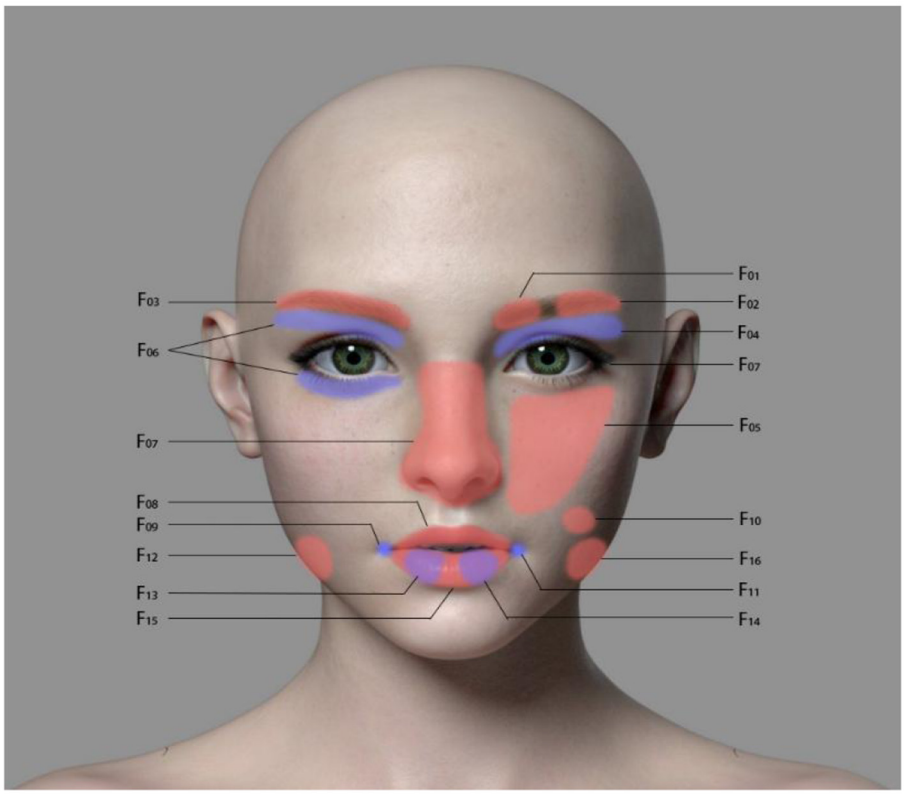


FIGURE 1 | The 17 sites of facial muscle activity intensity measurement in this study.

TABLE 1 | Demographic and clinical data for the schizophrenia group and the healthy control group ($N = 269$).

	SZ ($n = 135$)	HC ($n = 134$)	t/χ^2	p
Gender, *n* (%)			3.57	0.059
Male	76 (56.30)	60 (44.78)		
Female	59 (43.70)	74 (55.22)		
Age (years) (Mean ± SD)	43.28 ± 11.54	41.32 ± 11.13	−1.42	0.157
Education (years) (Mean ± SD)	13.07 ± 2.57	14.21 ± 2.95	3.36	0.001**
Course of disease (years) (Mean ± SD)	11.69 ± 9.32			
BNSS total score (Mean ± SD)	23.79 ± 13.49			

$^{**}p < 0.01$.
SZ, schizophrenia group; HC, healthy control.

on a 7-point scale (0–6). The total score ranges from 0–78, with a higher score indicating more serious symptoms. The reliability of the scale was evaluated by psychiatrists who had received unified training, and the consistency among raters was good (intra-class correlation coefficient, *ICC* > 0.8).

Evaluation of Facial Muscle Activity Intensity (FMAI)

The subjects sat in front of a computer with a camera (full HD camera, model Logitech C920 Pro) facing them about 80cm from their face, such that they subject could watch (as well as hear the corresponding audio) three videos including positive, neutral, and negative emotions, respectively. The name of the positive-emotion video is "Funny insects"; this video depicts interesting things that happen to three insects together, and the plot is humorous. The neutral-emotion video is called "The millennium of the universe" and is a documentary about astronauts exploring the universe. Finally, the negative-emotion video is called "Besieged city in October" and describes an old father's grief-stricken scene after seeing his son killed. The computer automatically collected the facial muscle activity state of the subjects throughout the entire experiment under the projection of the three emotional stimuli. The program E-face was used to process the data related to facial muscle activity. The duration of the positive, neutral, and negative videos was 83 s, 82 s, and 95 s, respectively. The corresponding facial muscle activity data were intercepted according to the time start and

TABLE 2 | Comparison of facial muscle activity intensity between the schizophrenia group and the healthy control group under three different emotional stimuli conditions.

Face Muscle	SZ (Mean ± SD)			HC (Mean ± SD)			Group		Emotion		Group × Emotion	
	PSE	NUE	NGE	PSE	NUE	NGE	F	p	F	p	F	p
F01	1.79 ± 1.45	1.79 ± 1.44	1.87 ± 1.45	1.34 ± 1.41	1.61 ± 1.30	1.65 ± 1.39	3.42	0.065	5.15	0.007	2.75	0.069
F02	1.72 ± 1.35	1.71 ± 1.38	1.78 ± 1.39	1.45 ± 1.21	1.64 ± 1.11	1.75 ± 1.16	0.78	0.377	4.88	0.009	2.60	0.078
F03	1.00 ± 0.76	1.03 ± 0.81	1.12 ± 0.81	0.88 ± 0.79	0.89 ± 0.77	0.99 ± 0.79	2.12	0.147	8.44	0.000*	0.16	0.843
F04	1.18 ± 0.75	1.16 ± 0.75	1.19 ± 0.82	1.07 ± 0.74	1.21 ± 0.75	1.28 ± 0.83	0.02	0.902	5.98	0.004	5.91	0.004
F05	0.74 ± 0.61	0.75 ± 0.61	0.76 ± 0.59	0.82 ± 0.58	0.62 ± 0.52	0.59 ± 0.55	1.17	0.280	13.96	0.000*	20.19	0.000*
F06	1.24 ± 0.87	1.26 ± 0.89	1.28 ± 0.95	1.17 ± 0.84	1.01 ± 0.82	0.97 ± 0.85	4.31	0.039	4.35	0.014	8.47	0.000*
F07	0.90 ± 0.66	0.95 ± 0.73	0.96 ± 0.74	0.84 ± 0.66	0.69 ± 0.62	0.71 ± 0.70	6.12	0.014	1.19	0.304	5.97	0.004
F08	0.92 ± 0.62	0.96 ± 0.61	0.98 ± 0.67	0.96 ± 0.63	0.77 ± 0.60	0.85 ± 0.65	1.72	0.191	3.91	0.023	9.88	0.000*
F09	0.65 ± 0.50	0.63 ± 0.49	0.61 ± 0.48	0.71 ± 0.45	0.53 ± 0.38	0.51 ± 0.41	0.84	0.360	21.13	0.000*	9.65	0.000*
F10	0.88 ± 0.63	0.96 ± 0.60	0.92 ± 0.63	1.04 ± 0.71	0.87 ± 0.75	0.86 ± 0.69	0.00	0.987	2.64	0.075	10.15	0.000*
F11	1.81 ± 1.28	1.93 ± 1.17	2.01 ± 1.23	1.18 ± 0.88	1.50 ± 1.01	1.45 ± 0.95	18.72	0.000*	19.10	0.000*	2.52	0.081
F12	1.26 ± 0.93	1.41 ± 0.91	1.48 ± 0.93	1.43 ± 0.95	1.64 ± 0.89	1.66 ± 0.94	3.56	0.060	20.21	0.000*	0.39	0.663
F13	1.18 ± 0.79	1.21 ± 0.74	1.24 ± 0.79	0.86 ± 0.54	0.84 ± 0.52	0.89 ± 0.52	23.58	0.000*	1.19	0.303	0.51	0.593
F14	1.15 ± 0.82	1.31 ± 0.81	1.32 ± 0.85	1.14 ± 0.68	1.15 ± 0.70	1.24 ± 0.73	1.07	0.302	5.95	0.003	1.67	0.190
F15	1.10 ± 0.78	1.02 ± 0.81	1.06 ± 0.79	1.19 ± 0.95	0.96 ± 0.79	0.93 ± 0.80	0.13	0.723	9.49	0.000*	3.82	0.026
F16	1.32 ± 0.99	1.35 ± 1.00	1.33 ± 1.08	1.37 ± 1.00	1.26 ± 1.02	1.33 ± 1.06	0.01	0.910	0.34	0.706	1.49	0.228
F17	1.18 ± 0.88	1.31 ± 0.80	1.34 ± 0.84	0.88 ± 0.72	0.96 ± 0.71	0.95 ± 0.76	15.47	0.000*	7.83	0.001*	1.04	0.353

*$p < 0.003$.

SZ, schizophrenia group; HC, healthy controls; PSE, positive emotion; NUE, neutral emotion; NGE, negative emotion.

end points with a sampling rate was 20 frames per second. For each subject, the total sampling rate of positive, neutral, and negative stimuli was approximately 1,660, 1,620, and 1,900 frames, respectively. Each frame collects 17 values (F01-F17), representing the intensity of 17 facial muscle activities. The data collection range was divided according to Ekman's facial action coding system (FACS) (13), which included the following, as shown in **Figure 1**: F01, inner eyebrow; F02, outer eyebrow; F03, eyebrow; F04, upper eyelid; F05, cheek; F06, eyelid; F07, nose; F08, upper lip; F09, lip angle 1; F10, dimple; F11, lip angle 2; F12, lower jaw 1; F13, lip 1; F14, lip 2; F15, lip 3; F16, lower jaw 2; and F17, blink.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM, USA) was used for data analysis. The chi-square test was used for comparison between continuous data groups. Repeated measurement analysis of variance (ANOVA) was used to test the intensity of the facial muscle activity of the two groups (schizophrenia group, SZ; healthy control group, HC) under three different emotional stimuli conditions, used Bonferroni correction (statistical significance set at $p < 0.003$). Taking the patient group and the healthy control group as dependent variables and the facial muscle activity intensity of different parts as independent variables, F01-F17 facial muscle activity intensity was included in the logistic regression model for logistic regression analysis. Taking the total BNSS score as the dependent variable and the intensity of facial muscle activity under three emotional stimuli conditions as the independent variable, the relationship between facial muscle activity intensity and negative symptoms was analysed by multiple linear regression. Statistical significance was set at $p < 0.05$.

RESULTS

Demographic and Clinical Characteristics

There was no significant difference in sex and age between the schizophrenia group ($n = 135$) and healthy control group ($n = 134$) ($p > 0.05$), but there was a significant difference in the years of education between the two groups ($p < 0.05$) in that the schizophrenia group had fewer years of education than the healthy control group (**Table 1**).

Facial Muscle Activity Intensity Under Different Emotional Stimuli Conditions

A comparison of facial muscle activity intensity between the schizophrenia group and the healthy control group under three different emotional stimuli conditions is outlined in **Table 2**. Repeated measurement ANOVA showed that the grouping main effect of F11, F13, and F17 facial muscle activity intensity was statistically significant ($p < 0.003$), while the emotional main effect of F03, F05, F09, F11, F12, F15, and F17 facial muscle activity intensity was statistical significance ($p < 0.003$). The interaction effect of grouping and emotion of F05, F06, F08, F09, and F10 was statistically significant ($p < 0.003$).

The facial muscle activity intensity of the schizophrenia group in F11, F13, and F17 was higher than that of the healthy control group. The intensity of facial muscle activity for positive emotion was higher than that of neutral and negative emotion at F05, F09 and F15, and lower at F11 and F17; the facial muscle activity intensity of negative emotion was higher than that of positive

TABLE 3 | Results of the logistic regression model of facial muscle activity intensity in the schizophrenia group and the healthy control group.

Independent variable	*β*	*SE*	*Wals*	*df*	*p*	*Exp (B)*	*95%CI*
F01	0.23	0.18	0.02	1	0.902	1.02	1.48–1.80
F02	0.42	0.13	10.07	1	0.002**	1.52	1.50–1.77
F03	−0.25	0.25	0.97	1	0.325	0.78	0.79–0.95
F04	0.55	0.21	7.14	1	0.008**	1.73	1.12–1.30
F05	−0.55	0.41	1.86	1	0.172	0.58	0.69–0.82
F06	0.31	0.24	1.58	1	0.208	1.36	1.10–1.29
F07	0.79	0.25	10.04	1	0.002**	2.20	0.75–0.90
F08	0.18	0.37	0.24	1	0.627	1.20	0.76–0.88
F09	−0.41	0.44	0.85	1	0.358	0.67	0.59–0.68
F10	−0.58	0.25	5.44	1	0.020*	0.56	0.93–1.07
F11	0.14	0.19	0.60	1	0.437	1.16	1.30–1.53
F12	−0.64	0.19	11.19	1	0.001**	0.53	1.34–1.55
F13	0.44	0.32	1.86	1	0.172	1.55	0.91–1.04
F14	0.62	0.24	6.48	1	0.011*	1.85	1.10–1.26
F15	0.04	0.29	0.21	1	0.885	1.04	1.04–1.20
F16	−0.17	0.22	0.62	1	0.433	0.84	1.31–1.55
F17	0.63	0.21	9.26	1	0.002**	1.88	0.92–1.10

*$p < 0.05$; **$p < 0.01$.

and neutral emotion at F03. Further simple effect analysis of the inteaction showed that, the intensity of facial muscle activity for positive emotion was higher than that of neutral and negative emotion at F05, F06, F08, F09 and F10 in healthy control group, and was not significant in patient group ($p < 0.05$).

Facial Muscle Activity Intensity in the Schizophrenia and Healthy Control Groups

Taking the grouping of the schizophrenia group and healthy control group as dependent variables and the intensity of facial muscle activity in different parts of the face as independent variables, all intensities of facial muscle activity for F01-F17 were simultaneously included in the logistic regression model. The results of the logistic regression analysis showed that facial muscle activity for F02, F04, F07, F10, F12, F14, and F17 was significantly different between the schizophrenia and healthy control groups ($p < 0.05$). The accuracy of the logistic regression model was 69.6% for predicting schizophrenia, 77.6% for predicting healthy controls, and 73.6% in total (**Table 3**).

The total score of BNSS was taken as the dependent variable, and the intensity of facial muscle activity was taken as the independent variable; $\alpha = 0.05$, excluding level $\beta = 0.10$. The results of multiple linear regression analysis using the enter method showed that the variables that were significant for negative symptoms were screened. Under positive, neutral, and negative emotional stimulation, the intensity of F16 facial muscle activity in patients was positively correlated with the total score of BNSS, and the model was statistically significant ($p < 0.05$). Positive emotion F12, neutral emotion F16, negative emotion F16 facial muscle activity intensity was positively correlated with the score of Anhedonia subscale; Neutral emotion F12 facial muscle activity intensity was positively correlated with the score of Depression subscale; Positive, neutral and negative emotion F16 facial muscle activity intensity was positively correlated with the score of Asociality subscale and Avolition subscale; Positive emotion F01 and F07, neutral emotion F15 facial muscle activity intensity was positively correlated with the score of Blunted affect subscale. This correlation was not statistically significant in other facial muscle activity intensity models ($p > 0.05$) (**Table 4**). See the **Supplementary Material** for other results.

TABLE 4 | Multiple linear regression analysis of facial muscle activity intensity related to negative symptoms of schizophrenia.

Variable	*β*	*SE*	*β'*	*t*	*p*
PSE F16	3.44	1.15	0.25	2.99	0.003**
NUE F16	3.07	1.14	0.23	2.70	0.008**
NGE F16	2.49	1.07	0.20	2.34	0.021*

*$p < 0.05$; **$p < 0.01$. *PSE, positive emotion; NUE, neutral emotion; NGE, negative emotion.*

DISCUSSION

Previous studies have shown that in addition to having impairments in facial emotion recognition, patients with schizophrenia also show a lack of facial expression. This study directly measured the facial muscle activity intensity of patients with schizophrenia under different emotional stimuli conditions to explore the attributes of negative symptoms that may lead to a reduction in facial activity. Our study had two main findings. First, we found that some facial muscle activity intensity in patients with schizophrenia was worse than that in healthy controls. Second, the weakening of some facial muscle activity intensity in patients with schizophrenia may be

related to negative symptoms, suggesting that schizophrenia may have some defects in the expression of basic social emotions, which provides a theoretical basis for further exploring the characteristics of schizophrenia in the expression of basic social emotions in the future.

This study showed that under the same emotional stimulation, the facial muscle activity intensity of patients with schizophrenia is lower than that of healthy controls; this suggests that this effect does not have emotional specificity, which is consistent with the results of previous studies (14–17) and may be related to face emotion recognition disorder in patients with schizophrenia. In this regard, corresponding psychological and physiological responses to different emotional stimuli cannot be fully expressed, which leads to the changes in facial muscle activities behind facial expressions. Some studies suggest that this may be related to changes in brain activation (18). Moreover, a small number of studies have reported that the facial muscle activity of patients with schizophrenia can be fully expressed (19, 20). Previous studies of basic socio-emotional perception primarily focused on facial emotion recognition and expression; however, cultural differences may affect patients in a variety of ways according to ethnicity, nationality, or race. This may be related to inconsistent measurement tools: those studies also used electromyography measurements with electrodes and sensors connected to the subject's face (21), while in this study, we used a full HD optical camera for computer automatic acquisition and measurement of facial muscle activity intensity, which is not affected by the above factors. Measurements were taken in positive, neutral, and negative emotional states rather than dichotomously divided into happiness and anger, and these were combined with clinical symptoms for effective results (22). The intensity may also be related to different stages of schizophrenia. Most of the patients in this study were long-term hospitalized patients in chronic remission. At the same time, this study also suggests that the decrease in facial muscle activity intensity in schizophrenia is related to negative symptoms, which is consistent with previous research results (4, 10). This may be related to the pathological mechanism of attention bias and memory loss related to emotional information (23) as well as to the defect of facial muscle activity caused by facial emotion recognition disorder, which is then followed by negative symptoms (24).

The findings of this study are also consistent with clinical experience; that is, patients with schizophrenia will show a decrease in overall facial muscle activity, poor richness of emotional expression, and more simplicity and repeatability, and they will exhibit basic socio-cognitive emotion impairment with negative symptoms as the core (25, 26).

This study has several limitations. First, this is a cross-sectional study, which cannot facilitate dynamic understanding of the changes of facial muscle activity over the course of the disease. Second, the patient group is still receiving drug treatment, and the effect of drugs and Parkinsonian side effects (caused by anti-psychotics) on facial muscle activity cannot be ruled out. Therefore, he current study can be viewed only as an exploratory study. In future studies, we plan to include patients at first onset or patients who are not undergoing drug treatment and to conduct follow-up studies to further understand the characteristics of facial muscle activity in patients with schizophrenia.

CONCLUSIONS

The intensity of some facial muscle activity of patients with schizophrenia is damaged to some degree, an effect that is may be related to the negative symptoms of schizophrenia. Whether the intensity of facial muscle activity can be used as an index to evaluate the negative symptoms and severity of schizophrenia needs to be further explored in future research.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing HuiLongGuan Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XD, HF, YW, JZ, XZ, YZ, and ST provided different contributions to this research, such as the collection of subjects, data sorting, and article writing guidance. All authors agreed to the publication of the article.

FUNDING

This work was supported by the Beijing Natural Science Foundation (Grant Number: 7162087, 2016), Capital Clinical Characteristic Application Research (Grant Number: z141107002514016, 2014), and the National Natural Science Foundation of China (Grant Number: 31671145, 2017).

ACKNOWLEDGMENTS

We thank the editors and reviewers for their careful review and professional suggestions. We would like to thank Editage (www.editage.cn) for English language editing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.829363/full#supplementary-material

REFERENCES

1. Huang Y, Wang YU, Wang H, Liu Z, Yu X, Yan J, et al. Prevalence of mental disorders in China: a cross-sectional epidemiological study. *Lancet Psychiatr.* (2019) 6:211–224. doi: 10.1016/S2215-0366 (18)30511-X
2. Wang Q, Xie Z. Comparative analysis of severe mental disorders patients managed by different registered residence in Beijing. *Chinese General Med.* (2018) 21:3714–7. doi: 10.3969/j.issn.1007-9572.2018.00.183
3. Zong D, Zhong Y, Jin L, Ye M, Lu H. Epidemiological characteristics of inpatients in a grade three class a psychiatric hospital in Hubei Province from 2014 to (2018). *Chinese Med Rec.* (2019) 20:42–5. doi: 10.3969/j.issn.1672-2566.2019.05.017
4. Pancotti F, Mele S, Callegari V, Bivi R, Saracino F, Craighero L. Efficacy of facial exercises in facial expression categorization in schizophrenia. *Brain Sci.* (2021) 11:7. doi: 10.3390/brainsci11070825
5. Caruana N, Stein T, Watson T, Williams N, Seymour K. Intact prioritisation of unconscious face processing in schizophrenia. *Cogn Neuropsychiatry.* (2019) 24:135–51. doi: 10.1080/13546805.2019.1590189
6. Grave J, Madeira N, Martins MJ, Silva S, Korb S, Soares SC. Slower access to visual awareness but otherwise intact implicit perception of emotional faces in schizophrenia-spectrum disorders. *Conscious Cogn.* (2021) 93:103165. doi: 10.1016/j.concog.2021.103165
7. Trémeau F, Malaspina D, Duval F, Corrêa H, Hager-Budny M, Coin-Bariou L, et al. Facial expressiveness in patients with schizophrenia compared to depressed patients and nonpatient comparison subjects. *Am J Psychiatry.* (2005) 162:92–101. doi: 10.1176/appi.ajp.162.1.92
8. Lotzin A, Haack-Dees B, Resch F, Romer G, Ramsauer B. Facial emotional expression in schizophrenia adolescents during verbal interaction with a parent. *Eur Arch Psychiatry Clin Neurosci.* (2013) 263:529–36. doi: 10.1007/s00406-012-0386-8
9. Chung YS, Mathews JR, Barch DM. The effect of context processing on different aspects of social cognition in schizophrenia. *Schizophr Bull.* (2011) 37:1048–56. doi: 10.1093/schbul/sbq012
10. Riehle M, Mehl S, Lincoln TM. The specific social costs of expressive negative symptoms in schizophrenia: reduced smiling predicts interactional outcome. *Acta Psychiatr Scand.* (2018) 138:133–44. doi: 10.1111/acps.12892
11. ASSOCIATION AP. *Diagnostic and Statistical Manual of Mental Disorders: (DSM-IV)*. Washington, DC: Encyclopedia of the Neurological Sciences (2003).
12. Yao J, Cui F, Chen N, Fan Z, Wang H, Li J. Validity and reliability test of Chinese version of concise negative symptom scale. *Chinese J Mental Health.* (2014) 28:302–307. doi: 10.3969/j.issn.1000-6729.2014.04.013
13. Eckman P, Friesen WV. *Facial Action Coding System: Investigator's Guide*. Palo Alto, CA: Consulting Psychologists Press. (1978).
14. Leszczyńska A. Facial emotion perception and schizophrenia symptoms. *Psychiatr Pol.* (2015) 49:1159–68. doi: 10.12740/PP/38919
15. Moody EJ, Reed CL, Van Bommel T, App B, McIntosh DN. Emotional mimicry beyond the face? rapid face and body responses to facial expressions. *Soc Psychol Pers Sci.* (2018) 9:844–52. doi: 10.1177/1948550617726832
16. Prochazkova E, Kret ME. Connecting minds and sharing emotions through mimicry: a neurocognitive model of emotional contagion. *Neurosci Biobehav Rev.* (2017) 80:99–114. doi: 10.1016/j.neubiorev.2017.05.013
17. Van Rheenen TE, Joshua N, Castle DJ, Rossell SL. Configural and featural face processing influences on emotion recognition in schizophrenia and bipolar disorder. *J Int Neuropsychol Soc.* (2017) 23:287–91. doi: 10.1017/S1355617716001211
18. Thakkar KN, Peterman JS, Park S. Altered brain activation during action imitation and observation in schizophrenia: a translational approach to investigating social dysfunction in schizophrenia. *Am J Psychiatry.* (2014) 171:539–48. doi: 10.1176/appi.ajp.2013.13040498
19. Chechko N, Pagel A, Otte E, Koch I, Habel U. Intact rapid facial mimicry as well as generally reduced mimic responses in stable schizophrenia patients. *Front Psychol.* (2016) 7:773. doi: 10.3389/fpsyg.2016.00773
20. Kring AM, Kerr SL, Earnst KS. Schizophrenic patients show facial reactions to emotional facial expressions. *Psychophysiology.* (1999) 36:186–92. doi: 10.1111/1469-8986.3620186
21. Torregrossa LJ, Bian D, Wade J, Adery LH, Ichinose M, Nichols H, et al. Decoupling of spontaneous facial mimicry from emotion recognition in schizophrenia. *Psychiatry Res.* (2019) 275:169–76. doi: 10.1016/j.psychres.2019.03.035
22. Bilgi MM, Taspinar S, Aksoy B, Oguz K, Coburn K, Gonul AS. The relationship between childhood trauma, emotion recognition, and irritability in schizophrenia patients. *Psychiatry Res.* (2017) 251:90–6. doi: 10.1016/j.psychres.2017.01.091
23. Jang SK, Park SC, Lee SH, Cho YS, Choi KH. Attention and memory bias to facial emotions underlying negative symptoms of schizophrenia. *Cogn Neuropsychiatry.* (2016) 21:45–59. doi: 10.1080/13546805.2015.1127222
24. Tseng HH, Chen SH, Liu CM, Howes O, Huang YL, Hsieh MH, et al. Facial and prosodic emotion recognition deficits associate with specific clusters of psychotic symptoms in schizophrenia. *PLoS ONE.* (2013) 8:e66571. doi: 10.1371/journal.pone.0066571
25. Ipser A, Cook R. Inducing a concurrent motor load reduces categorization precision for facial expressions. *J Exp Psychol Hum Percept Perform.* (2016) 42:706–18. doi: 10.1037/xhp0000177
26. Künecke J, Hildebrandt A, Recio G, Sommer W, Wilhelm O. Facial EMG responses to emotional expressions are related to emotion perception ability. *PLoS ONE.* (2014) 9:e84053. doi: 10.1371/journal.pone.0084053

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 17 March 2022
doi: 10.3389/fpsyt.2022.834333

Differential Effects of Aripiprazole and Amisulpride on Negative and Cognitive Symptoms in Patients With First-Episode Psychoses

Mette Ødegaard Nielsen[1,2,3,4]*, *Tina Dam Kristensen*[1,2,3], *Kirsten Borup Bojesen*[1,2,3], *Birte Y. Glenthøj*[1,2,3,4], *Cecilie K. Lemvigh*[1,2,3] and *Bjørn H. Ebdrup*[1,2,3,4]

[1] Center for Neuropsychiatric Schizophrenia Research (CNSR), Copenhagen University Hospital – Mental Health Services Copenhagen, Copenhagen, Denmark, [2] Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Copenhagen University Hospital – Mental Health Services Copenhagen, Copenhagen, Denmark, [3] Mental Health Center, Glostrup, Copenhagen University Hospital – Mental Health Services Copenhagen, Copenhagen, Denmark, [4] Department of Clinical Medicine, Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark

OPEN ACCESS

Edited by:
Joseph Ventura, UCLA Department of Psychiatry, United States

Reviewed by:
Hiroyoshi Takeuchi, Keio University School of Medicine, Japan
Armida Mucci, University of Campania Luigi Vanvitelli, Italy

***Correspondence:**
Mette Ødegaard Nielsen
mette@cnsr.dk

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *13 December 2021*
Accepted: *01 February 2022*
Published: *17 March 2022*

Citation:
Nielsen MØ, Kristensen TD, Borup Bojesen K, Glenthøj BY, Lemvigh CK and Ebdrup BH (2022) Differential Effects of Aripiprazole and Amisulpride on Negative and Cognitive Symptoms in Patients With First-Episode Psychoses. Front. Psychiatry 13:834333. doi: 10.3389/fpsyt.2022.834333

Introduction: Aripiprazole is hypothesized to have an effect on negative and cognitive symptoms in schizophrenia. Likewise, amisulpride is one of the only second-generation antipsychotics with which an effect on negative symptoms is reported. In the present study, we compare the effect of aripiprazole and amisulpride in initially antipsychotic-naïve patients with first-episode psychoses.

Methods: Psychopathology and cognitive measures from two consecutive cohorts of antipsychotic-naïve first episode psychotic patients were obtained before and after 6 weeks of antipsychotic monotherapy with either aripiprazole or amisulpride. Matched healthy controls were included to account for retest effects on the cognitive measures. Analyses of variance (repeated-measures ANOVA) were performed to detect effect of time and possible cohort*time interactions.

Results: Longitudinal data was obtained from 47 and 48 patients treated for 6 weeks with amisulpride or aripiprazole, respectively. For the Wallwork negative symptom dimension, there was a cohort*time interaction [$F_{(1,93)} = 4.29$, $p = 0.041$] and a significant effect of time [$F_{(1,93)} = 6.03$, $p = 0.016$], which was driven by an improvement in patients treated with aripiprazole [$t_{(47)} = 4.1$, $p < 0.001$] and not observed in patients treated with amisulpride ($p > 0.5$). For the eight cognitive measures, no cohort*time interaction was found and neither was cognitive improvement in any of the cohorts when accounting for retest effect.

Conclusion: Patients treated with aripiprazole improved on negative symptoms, which was not the case for patients treated with amisulpride. This may point to a general effect of a partial D2 receptor agonist on negative symptoms in patients with first-episode psychoses. There was, however, no improvement in cognitive functions.

Keywords: negative symptoms, cognitive deficits, antipsychotic treatment, dopamine antagonist, partial dopamine agonist

INTRODUCTION

Patients with schizophrenia often suffer from multiple symptoms. Antipsychotic medication ameliorates psychotic symptoms in most patients, but negative symptoms and cognitive deficits rarely improve during treatment (1–3). This constitutes a major clinical challenge because these symptoms are associated with worse outcomes in terms of lower levels of functioning and quality of life (4–6).

Psychotic symptoms are associated with a dopaminergic hyperactivity in ventral and associative parts of striatum (7–9). Although the neurobiological underpinnings of cognitive deficits and negative symptoms are not fully understood, they are both associated with disturbances in cerebral networks and may, to some degree, be related to a hypodopaminergic function in prefrontal cortex (10–12).

So-called first- and second-generation antipsychotic medication work by D2 antagonism thereby dampens an overactive dopamine turnover in the more ventral parts of striatum. Partial D2 agonists are denoted third-generation antipsychotics and are hypothesized to dampen the overactive dopamine system in striatal regions but increase dopamine-induced signaling in hypodopaminergic areas such as prefrontal cortex. Theoretically, this may improve negative symptoms and cognitive deficits (13).

Amisulpride is a relatively selective D2 receptor antagonist but is categorized as a second-generation antipsychotic because of a limbic selectivity (14). Due to an affinity for presynaptic D1 receptors in striatum, there should primarily be an effect on negative symptoms when given in doses below 300 mg, which has also been confirmed in two meta-analyses (15, 16). Few studies point to a small improvement in cognitive functions after treatment with amisulpride and other second-generation antipsychotics (17, 18); this may, however, primarily be caused by practice effects (19).

Aripiprazole was the first partial D2 receptor agonist registered for treating psychoses. Although it has been used for two decades, only a few studies focus on the effect on negative symptoms. In studies comparing the effect of aripiprazole to first-generation antipsychotics, aripiprazole showed a superior effect on negative symptoms (20, 21). Studies comparing aripiprazole with second-generation antipsychotics have primarily used risperidone and did not demonstrate a differential effect on the global negative symptom score (22–24) although a superior effect on the avolition-apathy subscore was found in one study (24).

Regarding a possible effect on cognitive impairments, a few open-label trials demonstrate a positive effect on verbal cognitive functions 8–26 weeks after switching to aripiprazole (25–27) although this was not the case in all studies (28). These studies were all carried out in patients who were already medicated and changed to aripiprazole from other antipsychotic drugs. One study examined the effect of using aripiprazole as adjunctive treatment and found a negative effect on verbal fluency and executive functions although motor speed was improved (29). None of the previous studies included a placebo or a healthy control group to correct for retest effects, which is of great importance in trials measuring cognitive functions (30). Further, there are no studies examining the effect of aripiprazole on cognitive functions in patients with first-episode psychoses.

In the Danish guidelines, both aripiprazole and amisulpride are recommended as first-line treatment for patients diagnosed with first-episode psychoses (31). Because both are also suggested to be effective for treating negative symptoms, we found it relevant to use the data from two consecutive cohorts of first-episode psychoses patients to compare their effect on negative symptoms. Based on the partial dopamine agonistic effect, we hypothesized that aripiprazole would show a superior effect on negative symptoms compared with amisulpride. Secondarily, we explored the effect on selected cognitive measures and hypothesized that patients treated with aripiprazole would improve in cognitive performance compared with patients treated with amisulpride.

MATERIALS AND METHODS

Data were collected in the Capital Region of Denmark, Copenhagen, as part of two consecutive longitudinal multimodal studies; the PECANS 1 cohort 2009–2013 (here denoted "amisulpride cohort") and the PECANS 2 cohort 2013–2019 (here denoted "aripiprazole cohort"). Detailed descriptions of the studies can be found in (32, 33) and www.clinicaltrials.gov (NCT01154829, NCT02339844). For a full overview of previous publications, please see www.cinsr.dk. Participants provided oral and written informed consent prior to inclusion, and both studies were approved by the regional Committee on Biomedical Research Ethics (H-D-2008-088, H-3-2013-149).

Participants

Patients were recruited from psychiatric hospitals and outpatient clinics in the Copenhagen catchment area. Diagnoses according to International Classification of Diseases 10th revision (ICD-10) were confirmed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), version 2.1 (34). For the amisulpride cohort, patients met the criteria for schizophrenia (DF20.x) or schizoaffective psychoses (DF25.x), whereas patients with diagnoses in the non-affective psychotic spectrum (DF2X.x except schizotypal disorder, DF21.x) were also included in the aripiprazole cohort. All patients were strictly antipsychotic-naïve and had never been treated with methylphenidate, whereas treatment with antidepressant medication more than a month before the baseline examinations was accepted. Previous or present use of benzodiazepines was allowed. Other exclusion criteria were current diagnosis of drug dependency, involuntary admission or treatment, or severe physical illness. Current occasional use of substances and benzodiazepines and previous substance abuse was accepted for patients.

Two consecutive groups of healthy controls (HC) matched to patients based on age (±2 years), sex, and parental socioeconomic status were recruited using online advertisement. Exclusion criteria for HCs were any physical or mental illness, substance abuse, and having a first-degree relative with psychotic symptoms. Data from the HCs are in the present study only used for calculating *z*-values for the cognitive measures.

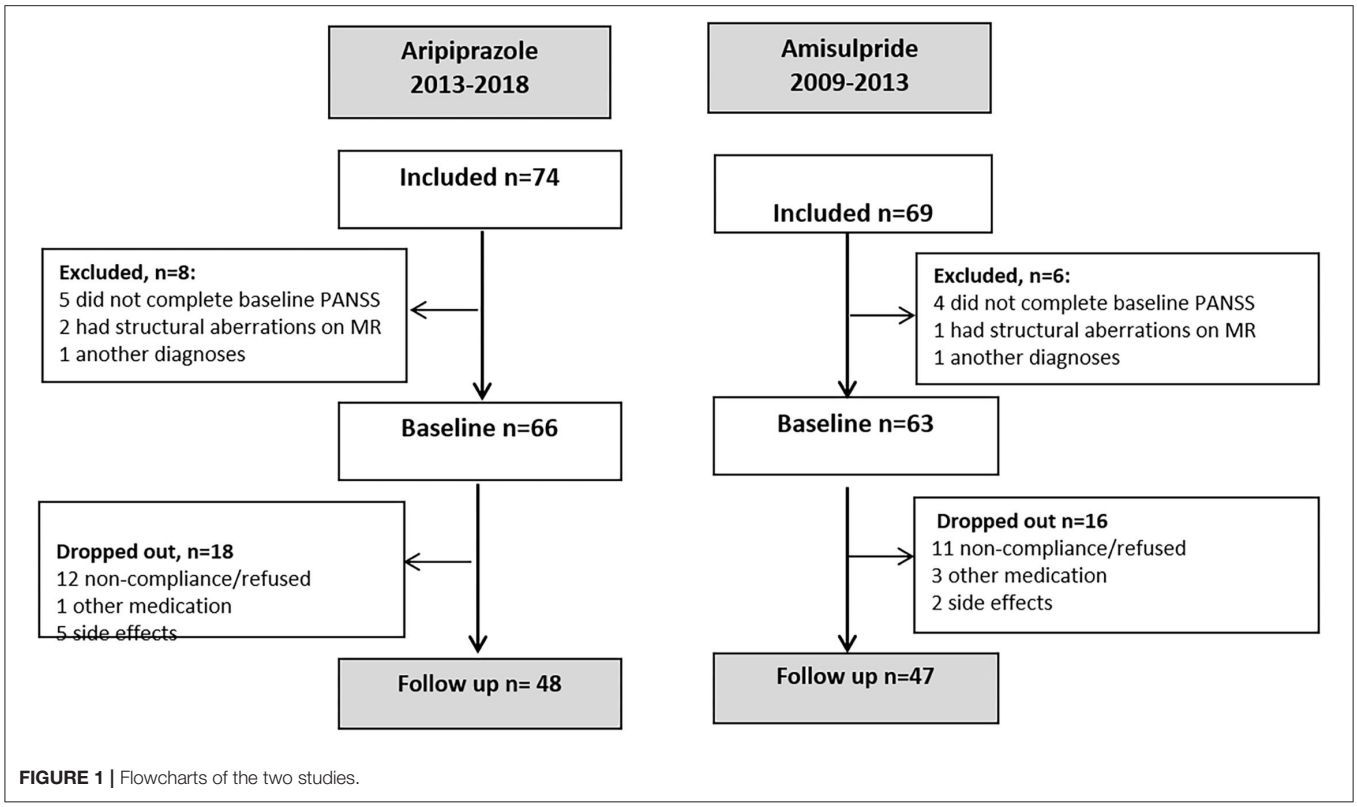


FIGURE 1 | Flowcharts of the two studies.

Clinical and Cognitive Assessments

At baseline and after 6 weeks, psychopathology in patients was assessed using the Positive And Negative Syndrome Scale (PANSS) (35). Because we were particularly interested in the effect on negative symptoms and the original PANSS negative symptom cluster has been criticized (36–38), our primary outcome was the negative symptom dimension described by Wallwork et al. (39), which is also found to be most ideal among patients with first-episode psychosis (40). In the Wallwork five-factor model, the negative dimension includes the following items from the PANSS scale: N1: Blunted affect; N2: Emotional withdrawal; N3: Poor rapport; N4: Passive/apathetic social withdrawal; N6: Lack of spontaneity and flow of conversation, and G7; Motor retardation. Additional analyses were performed on the original PANSS negative, positive, and general end total PANSS-scores.

Level of functions was estimated with the Global Assessment of Function scale (GAF) (41), and adverse effects were estimated with the Extrapyramidal Symptom Rating Scale (ESRS) (42).

Cognitive functions were examined using the Cambridge Neuropsychological Test Automated Battery (CANTAB) (43, 44) and the Brief Assessment of Cognition in Schizophrenia (BACS) (45). We focused our analyses on verbal working memory (number sequences, NSq), verbal fluency (VF), and processing speed (symbol coding, SC) from BACS and measures of spatial working memory, (strategy and between errors from Spatial Working Memory [SWM]), planning (Stockings of Cambridge [SOC]), mental flexibility (Intra-Extradimensional Set Shifting [IED]), and sustained attention (A' from Rapid Visual Information processing [RVP]) from CANTAB.

For each cohort separately, the means and standard deviations of the HCs at both time points were used to calculate *z*-scores for patients, thereby accounting for retest effect. *Z*-scores for SWM and IED were inverted to report all variables in the same direction

TABLE 1 | Demography, antipsychotic dose, and diagnoses for both cohorts.

	Amisulpride *N* = 47	Aripiprazole *N* = 48
Age (SD, range), years	24.5 (6; 18–43)	22.9 (4; 18–42)
Sex, female/male	20/27	24/24
Dose, mg (SD, range)	276 (173; 50–800)	10 (4.7; 2.5–25)
Chlorpromazine equivalent, mg	216 (124; 37.5–600)	201 (94; 50–500)
Diagnoses		
Schizophrenia	45	34
Persistent delusional disorder		2
Schizoaffective psychoses	2	1
Other nonorganic psychotic disorders		8
Unspecified nonorganic psychotic disorders		3

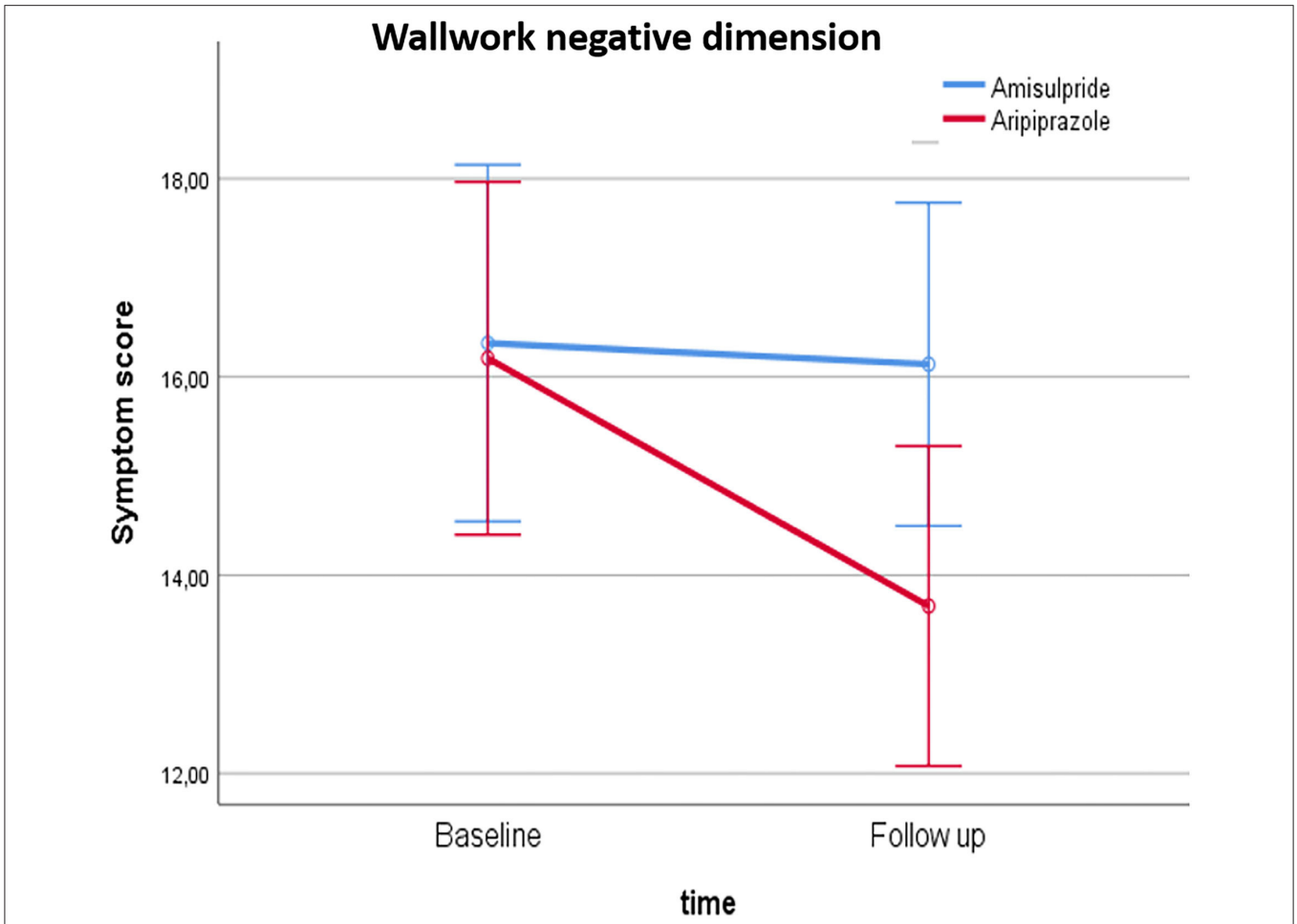


FIGURE 2 | Illustration of the group*time interaction on the Wallwork negative symptom dimension score.

and ease the interpretation; i.e., a negative *z*-score indicates less successful performance in patients compared with HCs.

Treatment

After baseline assessments, patients commenced treatment for 6 weeks with amisulpride or aripiprazole. The dose was individually adjusted according to the clinical impression of symptoms and report of adverse effects.

Statistics

Information on demography and baseline psychopathology was compared using Chi square and independent *t*-tests. Repeated-measures ANOVA was used to evaluate cohort*time interaction for the primary outcome; the Wallwork negative dimension; and for the secondary outcome, the selected cognitive measures. To account for the multiple comparison effect of analyzing eight cognitive measures, the corrected significance threshold for secondary analyses was $\leq$0.006 (0.05/8). *Post hoc* analyses were performed using independent and paired *t*-tests.

Explorative analyses were performed on the original PANSS symptom clusters, GAF, ESRS, weight and BMI. Because of a small difference in sex distribution and age, primary analysis was performed with sex and age as cofactors.

To account for patients who did not complete the follow up, analyses were repeated using mixed modeling, and dropout analyses were done using one-way ANOVA.

Finally, we repeated analyses including only the patients with schizophrenia/schizoaffective psychoses from the aripiprazole cohort ($n = 35$).

RESULTS

In total, 69 and 74 patients were included in the two cohorts. Baseline and follow-up measures on psychopathology were obtained from 47 patients from the amisulpride cohort and 48 patients from the aripiprazole cohort; numbers and reasons for exclusion are illustrated in **Figure 1**. For patients who completed the study, there were no differences between cohorts in age, sex, or baseline level of psychopathology except from a higher PANSS general mean score in the amisulpride cohort. In the amisulpride cohort, 96% ($n = 45$) had a schizophrenia diagnosis, and the remaining 4% ($n = 2$) were diagnosed with schizoaffective

TABLE 2 | Psychopathology, side effects and level of function for both cohorts at baseline and after six weeks.

Variable	Amisulpride 47		Aripiprazole 48		ANOVA, p-value		
	Baseline	Six weeks	Baseline	Six weeks	Time	Cohort	Cohort*time
Wallwork							
Negative	16.3	*16.1*	16.2	*13.7*	***0.016***	0.235	***0.041***
Positive	12.4	7.9	12.9	9.4	***<0.001***	0.065	0.083
Disorganized	8.8	7.5	7.4	5.7	***<0.001***	***0.003***	0.412
Excited	7.4	6.0	6.1	5.2	***<0.001***	***0.018***	0.352
Depressed	10.0	7.0	9.9	7.7	***<0.001***	0.552	0.156
PANSS							
Total	80.3	63.9	74.4	60.1	***<0.001***	0.076	0.449
Positive	20.2	14.1	18.6	13.8	***<0.001***	0.219	0.150
Negative	19.9	*19.3*	19.2	*16.5*	***0.002***	0.158	0.087
General	*40.2*	30.7	*36.6*	29.8	***<0.001***	0.083	0.071
ESRS	3.9	5.8	2.7	3.5	***0.034***	***0.018***	0.744
GAF	41.3	54.1	46.7	54.1	***<0.001***	0.063	0.410
Weight	77.7	80.2	71.6	71.7	***<0.001***	0.104	***0.001***
BMI	25.3	26.1	23.8	23.9	***<0.001***	***0.048***	***<0.001***

Wallwork the five dimensions from Wallwork five factor model; PANSS, Positive And Negative Syndrome Scale; ESRS, The extrapyramidal Symptom Rating Scale; GAF, Global Assessment of Function; BMI, Body Mass Index. Bold italics indicate p-values < .05.

psychoses. For the aripiprazole cohort, 71% ($n = 34$) had a schizophrenia diagnosis, 2% ($n = 1$) were diagnosed with a schizoaffective psychosis, and the remaining 27% ($n = 13$) were diagnosed with other non-affective psychoses (see **Table 1**). Mean dose of antipsychotic treatment at follow up was 276 (±173, range 50–800) mg for amisulpride and 10 (±4.7, range 2.5–25) mg for aripiprazole. Converted into chlorpromazine equivalent (46), the doses were comparable (216 vs. 201 mg).

Psychopathology

For the primary outcome, the Wallwork negative dimension, repeated-measure ANOVA showed a cohort*time interaction [$F_{(1,92)} = 4.29$, $p = 0.041$] and a significant effect of time [$F_{(1,92)} = 6.033$, $p = 0.016$] but no effect of cohort ($p = 0.235$). *Post hoc* analyses showed a difference between cohorts after 6 weeks [$t_{(92)} = 2.11$, $p = 0.037$], which was not found at baseline ($p = 0.93$) and a paired sample *t*-test showed an effect of time in the cohort treated with aripiprazole [$t_{(47)} = 4.1$, $p < 0.001$], but not in the cohort treated with amisulpride ($p = 0.23$), illustrated in **Figure 2**. Including sex and age as covariates made the cohort*time interaction slightly more significant [$F_{(1,92)} = 5.54$, $p = 0.021$]. There was no primary effect of either sex or age, but the effect of time disappeared, and a sex–time interaction was found [$F_{(1,92)} = 4.21$, $p = 0.043$]. Men improved in Wallwork negative symptoms score in both cohorts, whereas women improved on aripiprazole but worsened on amisulpride although none of these *post hoc* results reached significance.

The additional analyses on PANSS total and PANSS positive, negative, and general subscores, showed an effect of time and no effect of cohort and no cohort*time interaction although a trend was found for general and negative symptoms. All the Wallwork dimensions showed an effect of time: An effect of cohort was found in excitedness and disorganization with higher levels in the amisulpride cohort (**Table 2**). Both cohorts improved significantly in GAF score ($p < 0.001$), but there were no effects of cohort or cohort*time interactions. Likewise, there were no cohort*time interactions on ESRS score, but an overall effect of time ($p = 0.034$) and cohort ($p = 0.018$) was found. Both cohorts increased in ESRS score during treatment, and the amisulpride cohort had a higher rating at both baseline and follow up although this was not significant in the *post hoc* analyses (all *p*s > 0.09). Regarding weight and BMI, there was a cohort*time interaction ($p \leq 0.001$), an effect of time ($p < 0.001$), and for BMI also an effect of cohort ($p = 0.048$). The weight increase was driven by patients treated with amisulpride; these patients had a higher weight and BMI already at baseline although this was not significant ($p > 0.10$).

Cognitive Measures

For the secondary outcome, i.e., the eight selected cognitive measures, no cohort*time interaction survived the corrected significance threshold ($p < 0.006$). A main effect of time was found for verbal fluency ($p = 0.002$) and sustained attention ($p < 0.001$), where average *z*-scores became more negative, meaning that patients improved less after six weeks than HC. A main effect of cohort was found for spatial working memory strategy ($p = 0.002$) and at the trend level for mental flexibility ($p = 0.008$); for both measures the aripiprazole cohort had lower *z*-scores at both time points than the amisulpride cohort (**Figure 3**; **Supplementary Table S1**).

Mixed Modeling

For the primary outcome, the Wallwork negative dimension, there was a main effect of time and no effect of cohort, but a trend-level cohort*time interaction ($p = 0.067$) (**Table 3**). For the remaining analyses, please refer to **Table 4**.

Importantly, including the patients who dropped out introduced a main effect of cohort in PANSS total and general

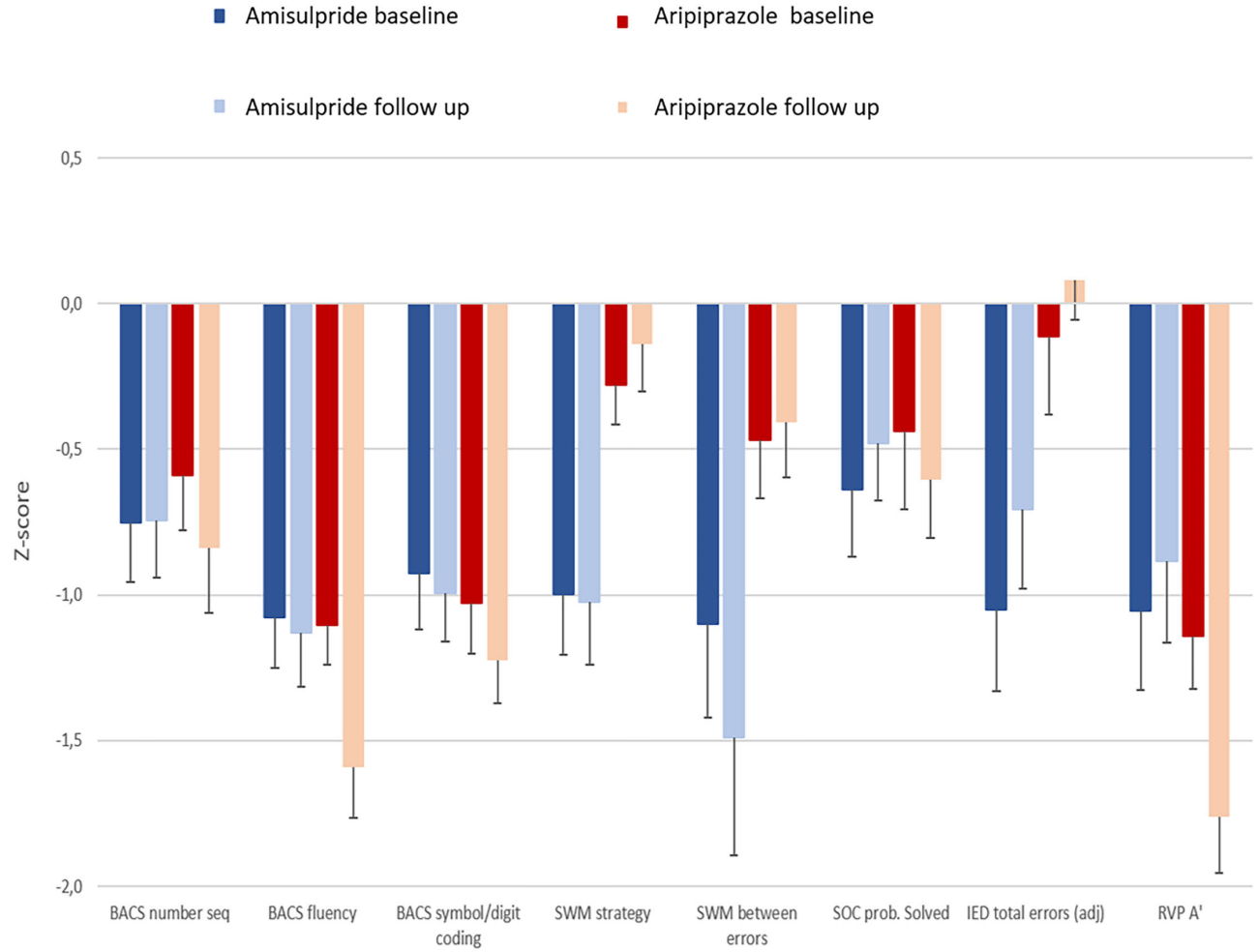


FIGURE 3 | Bar graph illustrating cognitive performance for patients in both cohorts at baseline and after 6 weeks as measured by *z*-score.

score, which was not observed in the original analyses. This was confirmed by dropout analyses showing a difference in baseline PANSS total and general score and in the disorganized and excitement dimension on the Wallwork five-factor model. Except for the Wallwork positive dimension, patients who dropped out had a higher baseline psychopathology score. This was most pronounced in the amisulpride cohort, where a *post hoc t*-test showed a significant difference for PANSS total and general score (both p-values < 0.02, all other p-values < 0.05).

Performing mixed modeling analyses on the cognitive measures resulted in results identical with the primary analyses: No cohort*time interaction survived the corrected significance threshold ($p < 0.006$). A main effect of time was found for verbal fluency ($p = 0.003$) and sustained attention ($p < 0.001$). A main effect of cohort was found for spatial working memory strategy ($p = 0.002$) and at the trend level for mental flexibility ($p = 0.031$, **Supplementary Table S2**).

Removing the 13 patients with other psychoses diagnoses resulted in less comparable groups as a group difference in baseline psychopathology was introduced (**Supplementary Table S4**). Further, removing 27% of the data in one of the cohorts reduced the power for detecting significant development over time. Therefore, these analyses are only presented in the **Supplementary Material**.

DISCUSSION

In the present analyses examining patients with first-episode psychoses who had not previously been treated with antipsychotic medication, we found a significant decrease in negative symptoms of 2.5 points in patients treated with aripiprazole for 6 weeks but not in patients treated with amisulpride. We found no indication of any positive effects on the cognitive performance of the two antipsychotic compounds when controlling for simple retest effect. In addition, we found a significant weight gain in the amisulpride cohort, whereas the aripiprazole cohort were weight stable during these first 6 weeks of antipsychotic treatment.

The primary aim of the presented analyses was to compare the effect on negative symptoms of two antipsychotic drugs that

TABLE 3 | Estimated means and *p* values from the mixed modeling analyses on the whole sample.

Variable	Amisulpride $n = 63$		Aripiprazole $n = 66$		Mixed modeling, *p*-value		
	Baseline	Six weeks	Baseline	Six weeks	Time	Cohort	Cohort*time
Wallwork							
Negative	16.6	16.2	16.2	13.8	***0.007***	0.144	0.067
Positive	12.2	7.8	12.8	9.5	***<0.001***	***0.017***	0.073
Disorganized	9.0	7.7	7.6	5.9	***<0.001***	***0.001***	0.369
Excited	7.9	6.2	6.2	5.3	***<0.001***	***0.001***	0.142
Depressed	10.2	7.1	10.2	7.9	***<0.001***	0.384	0.179
PANSS							
Total	83.0	65.4	75.7	60.7	***<0.001***	***0.013***	0.302
Positive	20.4	14.2	18.7	13.8	***<0.001***	0.106	0.114
Negative	20.6	19.5	19.4	16.7	***<0.001***	0.050	0.158
General	41.9	31.7	37.5	30.2	***<0.001***	***0.016***	***0.046***

Bold italics indicate p-values < .05.

TABLE 4 | Baseline psychopathology score on patients with and without follow up data and p-values for ANOVA comparing the four groups.

Variable	Amisulpride		Aripiprazole		
	Stayed $N = 47$	Dropped out $N = 16$	Stayed $N = 48$	Dropped out $N = 18$	ANOVA *p*-value
Wallwork					
Negative	16.3	18.1	16.5	16.1	0.761
Positive	12.4	11.8	12.9	12.5	0.529
Disorganized	8.8	10.0	7.4	8.7	***0.025***
Excited	7.4	9.4	6.1	6.7	***0.001***
Depressed	10.0	10.6	9.9	11.1	0.387
PANSS					
Total	*80.3**	*90.9**	74.4	79.3	***0.003***
Positive	20.2	21.1	18.6	18.9	0.130
Negative	19.9	23.4	19.2	20.1	0.172
General	*40.2**	*46.5**	36.6	40.3	***<0.001***

**Indicate group difference at baseline ($p < 0.05$). Bold italics indicate p-values < .05.*

are both recommended for first-line treatment in patients with first-episode psychoses. Treating negative symptoms is relevant because the level of negative symptoms has a high impact on the long-term outcome (47, 48). Although amisulpride in low doses (<300 mg) is registered for treatment of negative symptoms in Denmark, we were not able to measure a treatment effect on any of the negative symptom dimensions we analyzed. This was the case although patients were treated with relatively low doses, and therefore, they did not develop extrapyramidal side-effects (EPS), which could have induced secondary negative symptoms and affected their negative symptom score. The fact that there were no significant development of EPS and no group*time interaction on this measure is important because most previous studies compare aripiprazole with compounds such as haloperidol and risperidone, which are prone to induce EPS (21–24, 28). Our results indicate that the superior effect of aripiprazole on negative symptoms is not only accounted for by not inducing EPS. One could argue that ESRS only measures EPS, whereas it does not specifically address other important side effects such as feeling or being sedated. We can, therefore, not rule out that different level of sedation in the two cohorts may explain some of the difference in the negative symptom score.

Importantly, patients treated with amisulpride improved just as much on positive and general symptoms as the patients treated with aripiprazole, which indicates that the difference in treatment effect is not accounted for by an effect on secondary negative symptoms, such as being socially isolated because of anxiety or psychotic symptoms. This could indicate that aripiprazole due to the dopamine receptor agonistic properties has an effect on primary negative symptoms although primary negative symptoms are difficult to disentangle from secondary negative symptoms, especially in recently diagnosed first-episode patients. There is, however, other evidence pointing toward third-generation antipsychotics that may influence primary negative symptoms. In a recent study focusing specifically on patients with primary negative symptoms, an effect of cariprazine was found

on several different PANSS-derived factors (49). Future studies, including neurophysiological measures of specific neurocircuits while examining change in negative symptoms during treatment with a partial dopamine receptor agonist, may be able to establish a direct link between the influence on neurophysiology and negative symptoms.

Because the patients were all first-episode psychotic patients, we chose the Wallwork definition of the negative symptom dimension of PANSS items (39). It would have been optimal to use one of the newer negative symptom rating scales, such as the Brief Negative Symptom Scale (BNSS) (50) or the Clinical Assessment Interview for Negative Symptoms (CAINS) (51). Unfortunately, the data were collected in the period 2009–2019, when these scales were being developed, and the BNSS were not translated into Danish and validated in a Danish sample until 2019 (52). In future studies, it would be highly relevant to examine the effect of dopamine receptor agonists on negative symptoms using one of the new scales, in which also the effect on different subdomains could be explored.

We did not observe a treatment effect on any of the cognitive measures. This is interesting because the design of the present study corrected for the retest effect by calculating *z*-scores based on healthy controls examined at the same time point. Previous studies did not use this strategy. Some studies only included one group, and thus, any improvement may simply be a retest effect (25, 27). Other studies compared two groups of patients receiving different antipsychotics in which any group difference may reflect differences in retest effect rather than an actual improvement in cognitive functions (26, 28). Thus, the clinical evidence of aripiprazole having a superior effect on cognitive deficits is not convincing. Nonetheless, there is limited evidence in humans that a partial D2 receptor agonist can at least affect working memory. One study on seven patients with schizophrenia found a relation between the D2 receptor occupancy of aripiprazole in striatum and the performance on an *N*-back test (53). The occupancy in prefrontal cortex was not directly measured, but the authors assumed that the result could be extrapolated to include prefrontal cortex. Whether this is plausible can be debated, but the results are interesting and underline the importance of addressing this directly in future imaging studies.

Although metabolic issues were not a primary or secondary outcome in the present study, it is important to notice that we observed no weight gain in the cohort treated with aripiprazole, whereas this was the case for patients treated with amisulpride. Although we only collected data during the first 6 weeks of treatment, this is an important observation because metabolic side effects constitute a major clinical problem.

In our primary analyses, we did not include patients who dropped out of the studies. Including these patients by using mixed modeling changed our results on psychopathology slightly, and the different effect on negative symptoms was now only a trend. However, dropout analyses showed that psychopathology at baseline in the patients who dropped out differed between the two cohorts. Including these patients in the analyses decreased cohort comparability and may, therefore, not be the optimal approach for these data. Also, it is important to note that comparing the treatment effect between cohorts was not a main aim of the original studies, which is, of course, a major limitation. The data were collected consecutively, unblinded, and there were diagnostic differences between cohorts. Although collected consecutively, the data was collected by the same research group, which may decrease variability in rating traditions. Because the present analyses were not planned when any of the studies were carried out, raters were not biased toward one of the compounds. A randomized design would be optimal although the two cohorts were very similar regarding age, sex, level of symptoms, and functioning. Importantly, diagnostic differences are present: The amisulpride cohort only included patients with schizophrenia/schizoaffective psychoses, whereas 27% of the patients in the aripiprazole cohort had other psychoses diagnoses. One could argue that the subgroup with other psychoses diagnosis may not have the same level of negative symptoms because negative symptoms do not appear in the diagnostic criteria. This was not the case in our additional analyses, where we found that the cohorts became less comparable regarding psychopathology after excluding these patients. We do, therefore, not believe that the diagnostic difference explains the effect of aripiprazole on negative symptom. We chose to use the Wallwork negative symptom dimension because this has been suggested in literature (40). This dimension does, however, include motor retardation, which other guidelines recommend should be excluded (54). The use of Wallwork and not one of the newer scales is a limitation.

Negative symptoms and cognitive deficits remain a challenge in the treatment of psychosis, and so far, there are no medical treatment strategies showing convincing effect. Although we found no effect on cognitive performance when accounting for the retest effect, our results support the notion that partial dopamine receptor agonists may improve negative symptoms in first episode psychoses patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by De Videnskabsetiske Komitéer, Region Hovedstaden, København. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BG and BE initiated and designed the studies. MN, KB, and CL participated in data collection. MN, CL, and TK performed the analyses and interpreted the results. MN drafted the manuscript. All authors have revised and approved the final manuscript.

FUNDING

The study was financially supported by the Lundbeck Foundation (R25-A2701 and R155-2013-16337), and the Mental Health Service in the Capital Region of Denmark. The funding sources had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, the review or approval of the manuscript; or in the decision to submit the manuscript for publication.

ACKNOWLEDGMENTS

We thank the patients and all colleges who helped collecting data and treating patients in the two cohorts. BG has been (January 2009-December 2 2021) leader of a Lundbeck Foundation Centre of Excellence for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), which was partially financed by an independent grant from the Lundbeck Foundation based on international review and partially financed by the Mental Health Services in the Capital Region of Denmark, the University of Copenhagen, and other foundations. All grants are the property of the Mental Health Services in the Capital Region of Denmark and administrated by them.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.834333/full#supplementary-material

REFERENCES

1. Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull.* (2006) 32:214–9. doi: 10.1093/schbul/sbj053
2. Galderisi S, Rucci P, Kirkpatrick B, Mucci A, Gibertoni D, Rocca P, et al. Interplay among psychopathologic variables, personal resources, context-related factors, and real-life functioning in individuals with schizophrenia a network analysis. *JAMA Psychiatry*. (2018) 75:396–404. doi: 10.1001/jamapsychiatry.2017.4607
3. Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. *Lancet Psychiatry.* (2018) 5:664–77. doi: 10.1016/S2215-0366(18)30050-6
4. Galderisi S, Kaiser S, Bitter I, Nordentoft M, Mucci A, Sabé M, et al. EPA guidance on treatment of negative symptoms in schizophrenia. *Eur Psychiatry.* (2021) 64:e21. doi: 10.1192/j.eurpsy.2021.13
5. Faerden A, Barrett EA, Nesvåg R, Friis S, Finset A, Marder SR, et al. Apathy, poor verbal memory and male gender predict lower psychosocial functioning one year after the first treatment of psychosis. *Psychiatry Res.* (2013) 30:55–61. doi: 10.1016/j.psychres.2013.02.007
6. Halverson TF, Orleans-Pobee M, Merritt C, Sheeran P, Fett AK, Penn DL. Pathways to functional outcomes in schizophrenia spectrum disorders: Meta-analysis of social cognitive and neurocognitive predictors. *Neurosci Biobehav Rev.* (2019) 105:212–9. doi: 10.1016/j.neubiorev.2019.07.020
7. Howes OD, Montgomery AJ, Asselin M-C, Murray RM, Grasby PM, McGuire PK. Molecular imaging studies of the striatal dopaminergic system in psychosis and predictions for the prodromal phase of psychosis. *Br J Psychiatry Suppl.* (2007) 51:s13–8. doi: 10.1192/bjp.191.51.s13
8. McCutcheon R, Beck K, Jauhar S, Howes OD. Defining the locus of dopaminergic dysfunction in schizophrenia: a meta-analysis and test of the mesolimbic hypothesis. *Schizophr Bull.* (2017) 44:1301–11. doi: 10.1093/schbul/sbx180
9. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry.* (2003) 160:13–23. doi: 10.1176/appi.ajp.160.1.13
10. Carpenter W, Heinrichs D, Wagman A. Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry.* (1988) 145:578–83. doi: 10.1176/ajp.145.5.578
11. Abi-Dargham A, Moore H. Prefrontal DA transmission at D1 receptors and the pathology of schizophrenia. *Neuroscientist.* (2003) 9:404–16. doi: 10.1177/1073858403252674
12. Brady RO Jr, Gonsalvez I, Lee I, Öngür D, Seidman LJ, Schmahmann JD, et al. Breakdown of functional connectivity in cerebellar-prefrontal network underlies negative symptoms in schizophrenia. *Am J Psychiatry.* (2019) 176:512–20. doi: 10.1176/appi.ajp.2018.18040429
13. Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. *CNS Drugs.* (2004) 18:251–67. doi: 10.2165/00023210-200418040-00005
14. Mortimer AM. Update on the management of symptoms in schizophrenia: Focus on amisulpride. *Neuropsychiatr Dis Treat.* (2009) 5:267–77. doi: 10.2147/NDT.S3949
15. Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Silveira da Mota Neto JI, et al. Amisulpride versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev.* (2010) 1:1–106. doi: 10.1002/14651858.CD006624.pub2
16. Leucht S, Pitschel-Walz G, Engel RR, Kissling W. Amisulpride, an unusual "atypical{"} antipsychotic: a meta-analysis of randomized controlled trials. *Am J Psychiatry.* (2002) 159:180–90. doi: 10.1176/appi.ajp.159.2.180
17. Mortimer AM, Joyce E, Balasubramaniam K, Choudhary PC, Saleem PT. Treatment with amisulpride and olanzapine improveneuropsychological function in schizophrenia. *Hum Psychopharmacol Clin Exp.* (2007) 22:445–54. doi: 10.1002/hup.865
18. Davidson M, Galderisi S, Weiser M, Werbeloff N, Fleischhacker WW, Keefe RS, et al. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). *Am J Psychiatry.* (2009) 166:675–82. doi: 10.1176/appi.ajp.2008.08060806
19. Ahn YM, Lee KY, Kim CE, Kim JJ, Kang DY, Jun TY, et al. Changes in neurocognitive function in patients with schizophrenia after starting or switching to amisulpride in comparison with the normal controls. *J Clin Psychopharmacol.* (2009) 29:117–23. doi: 10.1097/JCP.0b013e31819a6995
20. Irismar B, Oliveira R De, Elkis H, Gattaz WF, Gomes F, Matos D, et al. Aripiprazole for patients with schizophrenia and schizoaffective. *CNS Sptr.* (2008) 14:93–102. doi: 10.1017/S1092852900000249
21. Kasper S, Lerman MN, McQuade RD, Saha A, Carson WH, Ali M, et al. Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. *Int J Neuropsychopharmacol.* (2003) 6:325–37. doi: 10.1017/S1461145703003651
22. Liemburg E, Aleman A, Bous J, Hollander K, Knegtering H. An open randomized pilot trial on the differential effects of aripiprazole versus risperidone on anhedonia and subjective well-being. *Pharmacopsychiatry.* (2011) 44:109–13. doi: 10.1055/s-0031-1271688
23. Potkin SG, Saha AR, Kujawa MJ, Carson WH, Ali M, Stock E, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaff ective disorder. *Psychiatry, Psychother Clin Psychol.* (2018) 9:236–45. doi: 10.1001/archpsyc.60.7.681
24. Robinson DG, Gallego JA, John M, Petrides G, Hassoun Y, Zhang JP, et al. A randomized comparison of aripiprazole and risperidone for the acute treatment of first-episode schizophrenia and related disorders: 3-month outcomes. *Schizophr Bull.* (2015) 41:1227–36. doi: 10.1093/schbul/sbv125
25. Riedel M, Spellmann I, Schennach-Wolff R, Musil R, Dehning S, Cerovecki A, et al. Effect of aripiprazole on cognition in the treatment of patients with schizophrenia. *Pharmacopsychiatry.* (2010) 43:50–7. doi: 10.1055/s-0029-1239539

26. Kern RS, Green MF, Cornblatt BA, Owen JR, McQuade RD, Carson WH, et al. The neurocognitive effects of aripiprazole: an open-label comparison with olanzapine. *Psychopharmacology (Berl).* (2006) 187:312–20. doi: 10.1007/s00213-006-0428-x
27. Bervoets C, Morrens M, Vansteelandt K, Kok F, De Patoul A, Halkin V, et al. Effect of aripiprazole on verbal memory and fluency in schizophrenic patients: results from the ESCAPE study. *CNS Drugs.* (2012) 26:975–82. doi: 10.1007/s40263-012-0003-4
28. Suzuki H, Gen K, Inoue Y. An unblinded comparison of the clinical and cognitive effects of switching from first-generation antipsychotics to aripiprazole, perospirone or olanzapine in patients with chronic schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* (2011) 35:161–8. doi: 10.1016/j.pnpbp.2010.10.021
29. Yasui-Furukori N, Kaneda A, Sugawara N, Tomita T, Kaneko S. Effect of adjunctive treatment with aripiprazole to atypical antipsychotics on cognitive function in schizophrenia patients. *J Psychopharmacol.* (2012) 26:806–12. doi: 10.1177/0269881111405555
30. Fagerlund B, Mackeprang T, Gade A, Hemmingsen R, Glenthøj BY. Effects of low-dose risperidone and low-dose zuclopenthixol on cognitive functions in fisrt-episode drug-naïve schizophrenic patients. *CNS Spectr.* (2004) 9:364–74. doi: 10.1017/S1092852900009354
31. Medicinrådet. *Medicinrådets behandlingsvejledning vedrørende antipsykotika til behandling af psykotiske tilstande hos voksne.* Copenhagen: Medicinraadet.dk. (2020) Available online at: https://medicinraadet.dk/anbefalinger-og-vejledninger/behandlingsvejledninger/antipsykotika-til-voksne
32. Nielsen MO, Rostrup E, Wulff S, Bak N, Broberg BV, Lublin H, et al. Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. *Arch Gen Psychiatry.* (2012) 69:1195–204. doi: 10.1001/archgenpsychiatry.2012.847
33. Bojesen KB, Ebdrup BH, Jessen K, Sigvard A, Tangmose K, Edden RAE, et al. Treatment response after 6 and 26 weeks is related to baseline glutamate and GABA levels in antipsychotic-naïve patients with psychosis. *Psychol Med.* (2020) 50:2182–93. doi: 10.1017/S0033291719002277
34. Rijnders CA. van den Berg, JF, Hodiamont PP, Nienhuis FJ, Furer JW, Mulder J, et al. Psychometric properties of the schedules for clinical assessment in neuropsychiatry (SCAN-21). *Soc Psychiatry Psychiatr Epidemiol.* (2000) 35:348–52. doi: 10.1007/s001270050249
35. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale for schizophrenia. *Schizophr Bull.* (1987) 13:261–76. doi: 10.1093/schbul/13.2.261
36. Daniel DG. Issues in selection of instruments to measure negative symptoms. *Schizophr Res.* (2013) 150:343–5. doi: 10.1016/j.schres.2013.07.005
37. Marder SR, Galderisi S. The current conceptualization of negative symptoms in schizophrenia. *World Psychiatry.* (2017) 16:14–24. doi: 10.1002/wps.20385
38. Baandrup L, Allerup P, Nielsen M, Bak N, Düring SW, Leucht S, et al. Rasch analysis of the PANSS negative subscale and exploration of negative symptom trajectories in first-episode schizophrenia – data from the OPTiMiSE trial. *Psychiatry Res.* (2020) 289:112970. doi: 10.1016/j.psychres.2020.112970
39. Wallwork RS, Fortgang R, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. *Schizophr Res.* (2012) 137:246–50. doi: 10.1016/j.schres.2012.01.031
40. Langeveld J, Andreassen OA, Auestad B, Færden A, Hauge LJ, Joa I, et al. Is there an optimal factor structure of the Positive and Negative Syndrome Scale in patients with first-episode psychosis? *Scand J Psychol.* (2013) 54:160–5. doi: 10.1111/sjop.12017
41. Pedersen G. Urnes, Hummelen B, Wilberg T, Kvarstein EH. Revised manual for the Global Assessment of Functioning scale. *Eur Psychiatry.* (2018) 51:16–9. doi: 10.1016/j.eurpsy.2017.12.028
42. Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). *Schizophr Res.* (2005) 76:247–65. doi: 10.1016/j.schres.2005.02.013
43. Robbins TW. The case for frontostriatal dysfunction in schizophrenia. *Schizophr Bull.* (1990) 16:391–402. doi: 10.1093/schbul/16.3.391
44. Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P. Cambridge neuropsychological test automated battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. *Dementia.* (1994) 5:266–81. doi: 10.1159/000106735
45. Keefe RSE, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The brief assessment of cognition in schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res.* (2004) 68:283–97. doi: 10.1016/j.schres.2003.09.011
46. Patel MX, Arista IA, Taylor M, Barnes TRE. How to compare doses of different antipsychotics: a systematic review of methods. *Schizophr Res.* (2013) 149:141–8. doi: 10.1016/j.schres.2013.06.030
47. Galderisi S, Rossi A, Rocca P, Bertolino A, Mucci A, Bucci P, et al. The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. *World Psychiatry.* (2014) 13:275–87. doi: 10.1002/wps.20167
48. Galderisi S, Mucci A, Maj M. Untangling the factors contributing to functional outcome in schizophrenia clinical implications of slower cognitive growth in the psychosis spectrum. *JAMA Psychiatry.* (2018) 75:2018–9. doi: 10.1001/jamapsychiatry.2018.0840
49. Fleischhacker W, Galderisi S, Laszlovszky I, Szatmári B, Barabássy Á, Acsai K, et al. The efficacy of cariprazine in negative symptoms of schizophrenia: Post hoc analyses of PANSS individual items and PANSS-derived factors. *Eur Psychiatry.* (2019) 58:1–9. doi: 10.1016/j.eurpsy.2019.01.015
50. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The brief negative symptom scale: psychometric properties. *Schizophr Bull.* (2011) 37:300–5. doi: 10.1093/schbul/sbq059
51. Horan WP, Kring AM, Gur RE, Reise SP, Blanchard JJ. Development and psychometric validation of the Clinical Assessment Interview for Negative Symptoms (CAINS). *Schizophr Res.* (2011) 132:140–5. doi: 10.1016/j.schres.2011.06.030
52. Gehr J, Glenthøj B, Ødegaard Nielsen M. Validation of the Danish version of the brief negative symptom scale. *Nord J Psychiatry.* (2019) 73:425–32. doi: 10.1080/08039488.2019.1648549
53. Shin S, Kim S, Seo S, Lee JS, Howes OD, Kim E, et al. The relationship between dopamine receptor blockade and cognitive performance in schizophrenia: A [11C]-raclopride PET study with aripiprazole. *Transl Psychiatry.* (2018) 8:87. doi: 10.1038/s41398-018-0134-6
54. Galderisi S, Mucci A, Dollfus S, Nordentoft M, Falkai P, Kaiser S, et al. EPA guidance on assessment of negative symptoms in schizophrenia. *Eur Psychiatry.* (2021) 64:e23. doi: 10.1192/j.eurpsy.2021.11

Conflict of Interest: BE is part of the Advisory Board of Eli Lilly Denmark A/S, Janssen-Cilag, Lundbeck Pharma A/S, and Takeda Pharmaceutical Company Ltd. and has received lecture fees from Bristol-Myers Squibb, Boehringer Ingelheim, Otsuka Pharma Scandinavia AB, Eli Lilly Company, and Lundbeck Pharma A/S.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 25 March 2022
doi: 10.3389/fpsyt.2022.841057

Cognitive and Global Functioning in Patients With First-Episode Psychosis Stratified by Level of Negative Symptoms. A 10-Year Follow-Up Study

Magnus Johan Engen[1,2*], *Anja Vaskinn*[3,4], *Ingrid Melle*[3,5], *Ann Færden*[6], *Siv Hege Lyngstad*[1], *Camilla Bärthel Flaaten*[2,5], *Line Hustad Widing*[3,5], *Kristin Fjelnseth Wold*[3], *Gina Åsbø*[2,5], *Beathe Haatveit*[3,5], *Carmen Simonsen*[7] *and Torill Ueland*[2,3,5]

[1] Division of Mental Health and Addiction, Nydalen DPS, Oslo University Hospital, Oslo, Norway, [2] Department of Psychology, Faculty of Social Sciences, University of Oslo, Oslo, Norway, [3] Norwegian Centre for Mental Disorders Research (NORMENT), Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [4] Centre for Research and Education in Forensic Psychiatry, Oslo University Hospital, Oslo, Norway, [5] Division of Mental Health and Addiction, Section for Psychosis Research, Oslo University Hospital, Oslo, Norway, [6] Division of Mental Health and Addiction, Department of Acute Psychiatry, Oslo University Hospital, Oslo, Norway, [7] Early Intervention in Psychosis Advisory Unit for South-East Norway, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

OPEN ACCESS

Edited by:
Eugenia Kravariti, King's College London, United Kingdom

Reviewed by:
Mei-Hua Hall, McLean Hospital, United States
Zahra Zargol Moradi, King's College London, United Kingdom

***Correspondence:**
Magnus Johan Engen
m.j.engen@psykologi.uio.no

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *21 December 2021*
Accepted: *07 March 2022*
Published: *25 March 2022*

Citation:
Engen MJ, Vaskinn A, Melle I, Færden A, Lyngstad SH, Flaaten CB, Widing LH, Wold KF, Åsbø G, Haatveit B, Simonsen C and Ueland T (2022) Cognitive and Global Functioning in Patients With First-Episode Psychosis Stratified by Level of Negative Symptoms. A 10-Year Follow-Up Study. Front. Psychiatry 13:841057. doi: 10.3389/fpsyt.2022.841057

Negative and cognitive symptoms are core features of schizophrenia that are correlated in cross-sectional designs. To further explore the relationship between these critical symptom dimensions we use a method for stratifying participants based on level and persistence of negative symptoms from absent to sustained levels over a 10-year follow-up period. We investigate associations with cognitive performance and level of global functioning. First-episode psychosis (FEP) participants (n = 102) and healthy controls (n = 116) were assessed at baseline and follow-up. A cognitive battery consisting of 14 tests derived into four domains and a composite score were used in the analyses. FEP participants were stratified based on negative symptom items from the Positive and Negative Syndrome Scale (PANSS-R) into four groups with either no, mild, transitory or sustained symptoms over the 10-year follow-up period. Global functioning was measured with Global Assessment of Functioning Scale-Split version. Multivariate and univariate analyses of variance were used to explore between-group differences in level and course of cognitive performance as global functioning. A multivariate analysis with four cognitive domains as dependent variables, showed significant group differences in performance when including healthy controls and the negative symptom groups. The groups with no and mild negative symptoms outperformed the group with sustained levels of negative symptoms on verbal learning and memory. The group with no negative symptoms also outperformed the group with sustained negative symptoms on the cognitive composite score. Significant improvements on verbal learning and memory, executive functioning and the cognitive composite were detected for the entire sample. No differences in cognitive course were detected. There was a significant improvement in global functioning as measured by the GAF-F over the follow-up period (p <0.001),

without any time x group interactions ($p = 0.25$). Participants with sustained negative symptoms had a significantly lower level of global functioning at 10-year follow-up with an additional independent effect of the cognitive composite score, compared to all other groups. Individuals with an early illness course characterized by absence of negative symptoms form a group with better cognitive and functional outcomes than the impairments typically associated with schizophrenia. Individuals with sustained levels of negative symptoms on the other hand may require a combined focus on both negative and cognitive symptoms.

Keywords: cognition, longitudinal, negative symptoms (schizophrenia), attention, processing speed, executive functions, global functioning

INTRODUCTION

Negative and cognitive symptoms are core features of schizophrenia (1–3). Both are consistently associated with poorer clinical and functional outcome (1, 4–8), yet currently few effective treatments for either exist (2). The suggestion of subtypes, such as type II schizophrenia (9), negative schizophrenia (10) or deficit schizophrenia (11) have highlighted the significant co-occurrence of negative and cognitive symptoms in a subset of patients. Although sustained negative symptoms is not currently seen as a marker of a distinct disease sub-group within the schizophrenia spectrum (12), the association between negative symptoms and cognition remains important. This association is present for a wide range of cognitive domains, including memory, processing speed, attention, and executive functions (13–16). Furthermore, both cognitive and negative symptom domains have been associated with early predictors of outcome suggesting possible targets for early intervention, prevention, and treatment planning (17, 18).

An important question regarding the relationship between negative and cognitive symptoms concerns their temporal relationship. Although negative symptoms are more stable than positive symptoms, longitudinal studies have shown that they do show variation over time (19–21). Using latent class analysis to identify symptom courses in a 10-year follow-up in the OPUS study, Austin et al. (21) identified four course types for negative symptoms (21). One group had symptoms that were consistently high, i.e., above moderate levels while another group showed only mild negative symptoms at baseline with no negative symptoms from 1 year until 10-year follow-up. The remaining two groups fell in-between and with more variability in symptom scores (21). It has been argued that distinguishing enduring high levels of negative symptoms from fluctuating negative symptoms or symptoms hovering around threshold levels is important, both from a theoretical and an empirical perspective (12, 22, 23). This distinction is also deserving of attention for clinical reasons, since the course of negative symptoms is related to functional outcome, especially social functioning, in individuals with schizophrenia (8, 24).

In a recent study, we used clinically meaningful cut-off values in a 1-year follow-up study (25) to investigate the longitudinal relationship between negative symptoms and cognitive functioning in first-episode psychosis (FEP) participants. The groups had either no (NNS), mild (MNS), transitory (TNS) or sustained (SNS) negative symptoms. We found a dose-effect type relationship between the level of negative symptoms and the level of cognitive functioning, with the largest group differences in cognitive functioning between FEP participants with SNS and NNS. The latter group did not differ significantly from healthy controls on any cognitive measure.

In the current study, our main aim was to follow-up these results and investigate how negative symptom severity over a longer (10-year) follow-up period was related to cognitive functioning in a group of FEP participants, using the same stratification as at 1-year follow-up but here based on baseline and 10-year symptom levels. As in our previous study we included a group of healthy controls to explore the relative cognitive performance of the four FEP groups, stratified for levels of negative symptoms, i.e., sustained, transitory, mild or no negative symptoms (25) over 10 years. To evaluate the clinical significance of any group differences, we added an assessment of global functioning as external validation. Based on our findings at 1-year follow-up we hypothesized that the main difference in cognitive functioning would be between the NNS and SNS groups. The specific research aims were as follows:

First, to investigate if the method of grouping participants according to negative symptoms at the 10-year follow-up would replicate the previous findings, i.e., would reproduce four groups of approximately the same size and with comparable clinical characteristics and differences in baseline cognitive functioning.

Second, to investigate the course of cognitive functioning over the follow-period, both in the entire sample and between groups.

Third, to investigate the course of global functioning over the follow-up period for the different negative symptom groups, and evaluate to what extent the putative difference between the negative symptom groups result from differences in cognitive functioning, in addition to the influence from other clinical symptoms.

METHODS

Participants

Participants were recruited through the "Thematically Organized Psychosis" (TOP) study, an ongoing prospective cohort study recruiting participants from in- and outpatient clinics in the

greater Oslo area and the Innlandet Hospital Trust region, in Norway. All FEP participants were assessed for the study within 1 year of starting their first adequate treatment for a psychotic episode (defined as hospital treatment in an acute/psychosis ward and/or antipsychotic medication in recommended dosage). For the current study, we included participants with broad schizophrenia spectrum disorder at baseline and at follow-up including the following DSM-IV diagnoses: schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder and psychosis NOS (12). Exclusion criteria were IQ below 70, not speaking a Scandinavian language, clinically significant head injury or age beyond the range 18–65.

One hundred forty-six from a total of 382 participants with a broad schizophrenia spectrum diagnosis at baseline met for follow-up assessment at 10 years, a retention rate of 38.2%. A final sample of 102 participants who had undergone cognitive assessment at the 10-year follow-up met all criteria to participate in the current study. **Figure 1** provides details about loss to follow-up and unmet inclusion criteria.

Healthy controls were recruited from the same catchment area as FEP participants and were invited by letter through random selection from the public population registry. They were screened using the Primary Care Evaluation of Mental Disorders (PRIME-MD) (26) to assess for symptoms of severe mental health disorders, and underwent a brief demographic interview at both baseline and 10-year follow-up including direct questions about mental disorders in the family. In addition to the listed exclusion criteria for FEP participants, healthy controls were excluded from the study if they met criteria for substance abuse or dependency in the last 6 months, or if they reported a history severe mental disorder in first-degree relatives. Only control participants who met for 1-year follow-up were contacted for 10-year follow-up. A total of 164 healthy controls from baseline were eligible for the 10-year follow-up study and a total of 120 met for reassessment, giving a retention rate of 73%. A total of 116 healthy controls completed necessary cognitive assessment at baseline and 10-year follow-up and were included and used to generate standardized scores on the cognitive tests. The resulting sample was significantly larger than any of the patient groups and had also different error variances. To meet the assumptions for conducting analyses of variance (ANOVAs) as the main statistical analyses, the sample was randomly reduced to 26 participants to fit the statistical purposes. Study participation required written informed consent using a form approved by the Regional Ethics Committee.

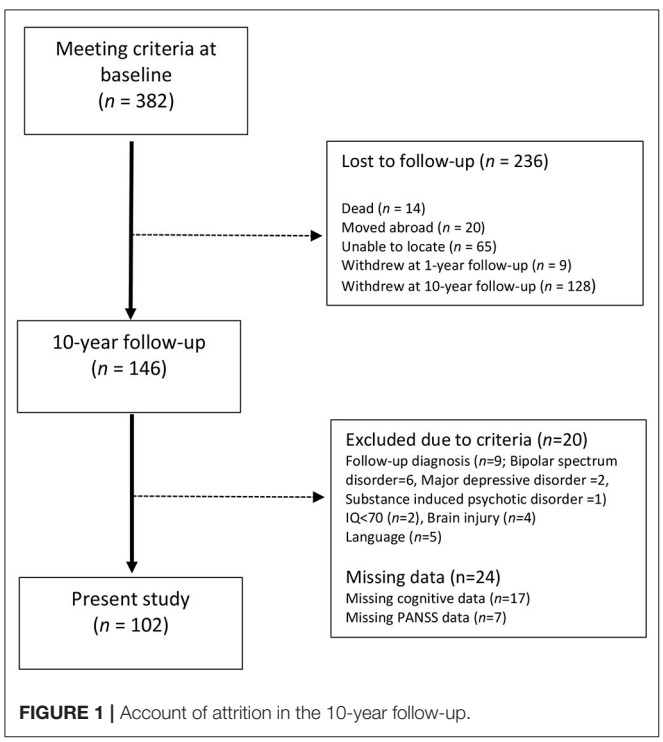


FIGURE 1 | Account of attrition in the 10-year follow-up.

Cognitive Assessment

A total of 14 tests were used to cover four cognitive domains which are known to be negatively influenced in schizophrenia: *Verbal learning and memory*, *attention*, *processing speed,* and *executive functions*. Cognitive assessments were carried out by psychologists or masters of neuroscience trained by senior research psychologists in the specific tests used and calibrated to ensure reliable test scores according to procedures developed at the research center. All test scores were converted into standardized Z-scores based on the total healthy control sample ($n = 116$).

The *verbal learning and memory* domain was comprised of trials 1–5 and delayed free recall from the California Verbal Learning Test (CVLT-II) (27), and the immediate and delayed recall conditions from the Logical Memory test in the Wechsler Memory Scale (WMS) (28). *Attention* was assessed using the Digit Span and Letter-Number Sequencing Test (28). *Processing speed* was assessed with the Digit Symbol Test (WAIS-III) (29), and the Color Naming and Word Reading subtest of the Color-Word Interference Test of the Delis-Kaplan Executive Function Scale (D-KEFS) (30). *Executive functions* were comprised of five separate scores from the D-KEFS test battery; the Inhibition and Inhibition/Switching subtests from the Color-Word Interference Test and Letter Fluency, Category Fluency and Category Switching from the Verbal Fluency Test. As a measure of general cognitive ability, a *cognitive composite score* was also calculated as the total sum of all test scores divided by the number of tests. *Current IQ* was measured with the abbreviated Wechsler intelligence scale WASI (31).

Clinical Assessment

Clinicians with formal background as licensed psychologists, psychiatrists or psychiatric residents conducted diagnostic interviews at baseline and follow-up using the Structured Clinical Interview for DSM IV Axis I disorders (SCID-I) (32). All interviewers were trained according to a program developed at UCLA prior to conducting interviews, and the inter-rater reliability from this program has previously been evaluated and found satisfactory with overall agreement for DSM-IV diagnostic categories of 82% and an overall κ of 0.77 (95% CI:0.60–0.94)

(33). The duration of untreated psychosis, time from onset of psychotic symptoms to first adequate treatment, was established based on information from interviews with participants and medical records. Symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) (34) using a validated five-factor model (35), but the depressive factor was excluded and instead measured by the Calgary Depression Scale for Schizophrenia (CDSS) (36) which is designed not to overlap with negative symptoms. Alcohol and substance use severity was assessed with the Alcohol Use Disorder Identification Test (AUDIT) and the Drug Use Disorder Identification Test (DUDIT) (37). The Global Assessment of Functioning Scale-Split version (GAF-F) (38) was used as a clinician rated measure of global functioning. The GAF-Split version assesses global symptoms and global functioning using two separate scales. The GAF-F thus serves the same purpose as the SOFAS.

Negative Symptom Subgroup Definition

PANSS items N1, N2, N3, N4 and N6 have been recommended for studying negative symptoms because they measure core negative symptoms and do not conceptually overlap with cognition (1). The PANSS items are rated 1–7, where 1–2 is within what is considered normal variation, 3 is a mild symptom and 4 is clear symptomatology with increasing values up to 7 indicating a more severe pathology (34). The distinction between 3 and 4 is pivotal because a score of 3 marks the upper limit for widely used and validated remission criteria (39, 40), and a score of 4 is also commonly used as a lower limit in studies investigating negative symptoms (22, 23). Here, we followed the same approach and logic as in a previous 1-year follow-up study (25), but with negative symptoms at 10-year follow-up as the endpoint.

Four groups based on levels of negative symptom severity at two time-points were thus determined based on baseline and 10-year follow-up assessment:

1. Sustained negative symptoms (SNS): Participants with at least one item ≥ 4 at both time points.

2. Transitory negative symptoms (TNS): Participants with at least one item ≥ 4 at only one time point.

3. Mild negative symptoms (MNS): Participants with at least one item $= 3$ at one or both time points, but no item ≥ 4.

4. No negative symptoms (NNS): Participants with no item > 2 at either time point.

Based on these criteria, the SNS group consists of participants with enduring levels of clear negative symptomatology, while the NNS group consists of participants who did not exceed normal levels for any negative symptom item as assessed at the two time points. The MNS group presents with only mild symptomatology, while the TNS group presents with clear negative symptomatology at one time-point without the stability of the SNS group.

Statistical Analyses

The Statistical Package for the Social Sciences version 27 (SPSS, Inc., Chicago, IL, USA) was used to perform all analyses.

Variables were inspected for normality and outliers. Due to skewness, the DUP variable was log-transformed before entering analyses, while median and range values were reported from the untransformed variable. ANOVA is sensitive to deviances in error variance when group size differences are large. Due to initial violations of assumptions made in analyses of variance (i.e., equality of covariance matrices and equality of error variances), the original group of healthy controls was randomly pruned from 116 to 26, the average size of the FEP groups ($n = 102$ divided into four groups; i.e., with an average size of $\sim$26). Following this operation, all assumptions concerning sample size and error variances were met. Alpha level was set at 0.05 for all statistical tests. All reported *p*-values are two-tailed.

Analyses of variance (ANOVAs), chi-square test, and independent samples *t*-tests were used to compare groups for differences in demographic and clinical characteristics, including investigations of differences between participants retained and those lost to follow-up, as reported in **Table 1**. We used the following approach to identify and correct for putative confounding factors in the analyses of cognition: First, to be a potential confounder the variable in question had to show significant associations with both the negative symptom groups *and* with the assessment of cognitive functioning. Second, the variable in question did not have any criteria overlaps with (i.e., was not measuring parts of the same phenomenon as) either negative symptom group or cognitive functioning, since entering these would lead to spurious findings. Based on this, IQ, PANSS negative, and PANSS disorganized/concrete symptoms factor (41) were not included in any evaluations as putative confounders. For the remaining, we investigated associations between negative symptom-based groups, cognitive domains, and clinical characteristics using Spearman's rank correlations. The group variable was here treated as an ordinal scale based on putative severity, with healthy controls = 0, NNS = 1, MNS = 2, TNS = 3, and SNS = 4 (see **Supplementary Table 1**).

Analysis of Differences in Baseline Cognitive Functioning

To investigate whether there was an overall difference in baseline cognitive functioning based on the level of negative symptoms over the follow-up period, we first performed a *multivariate analysis of variance (MANOVA)* as an omnibus test with "group" (the four negative symptom groups and healthy controls) as the independent variable and the four cognitive domains as dependent variables (Wilk's Λ). Further, given a significant group effect, follow-up explorations were done with separate ANOVAs for each cognitive domain and for the cognitive composite score, reporting partial η^2 as effect size and *post-hoc* Bonferroni correction for multiple comparisons when relevant. There were no clinical symptoms that were statistically significantly associated with both negative symptoms-based groups and cognitive domains, and we thus did not proceed with ANCOVAs.

Analysis of Differences in the Cognitive Course Between Groups

Differences between groups in the cognitive course over the 10-year study period were investigated by performing a series of repeated measures ANOVAs for each cognitive domain and the

cognitive composite score (Pillai's Trace reported). As validation of the repeated measures ANOVAs, we performed additional linear mixed models for the five cognitive variables. Time (baseline vs. follow-up), group (HC and four negative symptom groups) and the time x group interaction were fixed. The models included a random intercept and were conducted with maximum likelihood estimation. The linear mixed models were undertaken with the complete HC sample ($n = 116$).

Analysis of Global Functioning in Negative Symptom Groups

Our third aim was to investigate differences in global functioning between negative symptom groups and to assess the independent contributions of both group and cognition on GAF-F. We investigated group differences in GAF-F scores at baseline and follow-up using ANOVAs, and the development of GAF-F scores over time with separate repeated measures ANOVA (Pillai's Trace reported). Finally, we investigated the added contribution of cognitive functioning to global functioning using multiple linear regression analysis, with GAF-F at follow-up as the dependent variable and with the cognitive composite score and coming from the SNS group (vs. all other groups) as the two independent variables, corrected for differences in other clinical symptoms. Since the aim here was to identify the added contribution of cognition and not primarily to rule out confounder effects, the different symptom domains were entered independent of their association or lack of association to cognition. Symptom domains that did not have a significant contribution to the variation in functioning was not retained in the final model. Residual plots and evaluation of outliers were used to ascertain that the statistical requirements were met.

RESULTS

Demographic and Clinical Characteristics

Participants lost to follow-up did not differ from those who met for 10-year assessment on IQ, age, gender, or any clinical measure at baseline. The age of the healthy control group ($M = 32.7$, $SD = 7.9$) and their IQ (M = 114.7, SD = 8.5) was statistically significantly higher than the clinical groups ($F_{4,123} = 3.53$, $p = 0.009$) and ($F_{4,123} = 5.94$, $p < 0.001$). Clinical and demographic characteristics of the negative symptom groups are presented in **Table 1**. As expected, there were several significant between-group differences for clinical measures at baseline, including

TABLE 1 | Baseline descriptive information for the different patient groups.

Variable	NNS	MNS	TNS	SNS	F/X^2	*df*	*P*
N 102 total (%)	18 (18)	31 (30)	36 (35)	17 (17)			
Age (yr)[a]	28.9 ± 8.4	26.6 ± 9.1	25.7 ± 8.2	24.1 ± 5.6	1.10	3	0.35
Women *N* (%)	9 (50)	15 (48)	19 (53)	5 (29)	2.68	3	0.44
Education (yr)[b]	13.5 ± 2.8	13.7 ± 3.3	12.5 ± 2.5	11.9 ± 2.4	2.23	3	0.09
IQ[c]	109.5 ± 12.9	105.4 ± 13.7	100.6 ± 13.6	97.6 ± 19.5	2.54	3	0.06
Age at onset (Psychosis)[d]	24.4 ± 8.7	22.7 ± 8.1	21.1 ± 6.8	21.6 ± 4.0	0.92	3	0.43
Duration of untreated psychosis, median (range)[e]	19.5 (780)	26 (1,299)	104 (1,039)	76 (774)	2.64	3	0.06
PANSS positive	9.3 ± 3.8	10.5 ± 3.5	11.8 ± 3.9	12.9 ± 4.8	3.18	3	**0.03**
PANSS disorganized	4.4 ± 1.9	5.1 ± 2.0	5.9 ± 2.2	8.1 ± 3.5	8.35	3	**<0.001**
PANSS excited[f]	5.6 ± 2.0	5.9 ± 1.9	6.2 ± 2.1	7.3 ± 3.1	2.00	3	0.12
AUDIT[g]	9.7 ± 7.9	7.1 ± 5.4	7.2 ± 8.0	6.5 ± 5.9	0.70	3	0.71
DUDIT[h]	6.1 ± 8.1	2.8 ± 6.4	1.4 ± 2.6	4.8 ± 6.9	3.00	3	**0.04**
Leverl of Antipsychotic medication in DDD	0.6 ± 0.6	0.7 ± 0.8	0.7 ± 0.6	0.9 ± 0.9	0.70	3	0.55
Antipsychotic medication yes/no	11/7	23/8	29/7	15/2	4.09	3	0.25
GAF-F	52.4 ± 16.5	46.8 ± 12.6	38.2 ± 9.3	37.5 ± 7.6	8.27	3	**<0.001**
Depression (CDSS total)[i]	4.7 ± 4.3	6.7 ± 4.5	9.4 ± 4.4	5.8 ± 3.5	5.69	3	**0.001**
Schizophrenia *N* (%)	7	13	22	13			
Schizophreniform *N* (%)	5	2	2	1			
Schizoaffective *N* (%)	1	4	6	1			
Psychosis NOS *N* (%)	5	7	6	2			
Delusional disorder (%)	-	4	1	-			
Brief psychotic disorder (%)	-	1	-	-			

AUDIT, Alcohol Use Disorders Identification Test; CDSS, Calgary Depression Scale for Schizophrenia; DDD, defined daily dosage; DUDIT, Drug Use Disorders Identification Test; GAF-F, Global Assessment of Functioning-Functioning; IQ, intelligence quotient; MNS, mild negative symptoms; NOS, not otherwise specified; NNS, no negative symptoms; PANSS, Positive and Negative Syndrome Scale; SNS, sustained negative symptoms; TNS, transitory negative symptoms. [a]When including the healthy controls age difference was significant $F_{4,123} = 3.53$, $p = 0.009$. [b]Education years: number of missing scores: TNS = 2. [c]When including the healthy controls IQ difference was significant $F_{4,123} = 5.94$, $p < 0.001$. [d]Age at onset (Psychosis): number of missing scores: TNS = 2. [e]Duration of untreated psychosis: missing data: MNS = 1, TNS = 1. [f]PANSS excited: number of missing scores: MNS = 1. [g]AUDIT: number of scores missing: NNS = 1, MNS = 3, TNS = 3. [h]DUDIT: number of scores missing: MNS = 1, TNS = 3. [i]CDSS: number of scores missing: NNS = 1, TNS = 2. P-values in bold are statistically significant (p > 0.05).

TABLE 2 | Baseline cognitive scores for the different patient groups and healthy controls.

	NNS (18)	MNS (31)	TNS (36)	SNS (17)	HC (26)	ANOVA			
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*F*	*P*-value	η^2	*Post-hoc* analysis
Processing speed	−0.71 (1.1)	−1.05 (1.4)	−1.32 (1.4)	−1.98 (1.9)	0.14 (0.7)	7.88	$P < 0.001$	0.20	HC > MNS, TNS, SNS
Verbal learning and memory[a]	−0.28 (0.8)	−0.58 (1.1)	−0.80 (0.9)	−1.56 (1.2)	0.02 (0.7)	7.95	$P < 0.001$	0.21	HC > TNS, SNS|NNS>SNS|MNS>SNS
Attention[b]	−0.43 (1.0)	−0.76 (0.7)	−0.97 (0.9)	−0.86 (1.3)	−0.02 (0.9)	4.22	$P = 0.003$	0.13	HC > MNS, TNS
Executive functioning	−0.70 (1.1)	−0.97 (1.1)	−1.30 (1.2)	−1.48 (1.4)	0.05 (0.7)	7.55	$P < 0.001$	0.20	HC > MNS, TNS, SNS
Cognitive composite	−0.54 (0.8)	−0.83 (0.8)	−1.06 (0.9)	−1.47 (1.2)	0.05 (0.6)	9.75	$P < 0.001$	0.24	HC > MNS, TNS, SNS|NNS>SNS

ANOVA, analysis of variance; NNS, No negative symptoms; MNS, Mild negative symptoms; TNS, Transitory negative symptoms; SNS, Sustained negative symptoms; HC, Healthy contols.

[a,b]*NNS (n = 16), MNS (n = 30) and TNS (n = 34) due to missing data.*

PANSS positive, depressive, and disorganized symptoms and GAF-F. As shown in **Table 1**, the negative symptom groups varied in size from 17 to 36 out of the total $N = 102$. As a proportion of the total, the NNS group was 18%, the MNS 30%, the TNS 35%, and the SNS 17%.

Analysis of Differences in Baseline Cognitive Functioning

Our first research question concerned differences in cognitive functioning at baseline. The main multivariate analysis (MANOVA) done to compare all five groups on overall baseline cognitive performance was significant, $F_{16,352} = 3.18$, $p < 0.001$; Wilk's $\Lambda = 0.662$, partial $\eta^2 = 0.10$. The following separate ANOVAs for each cognitive domains are presented in **Table 2** with a graphical illustration of the five groups according to cognitive domain and the cognitive composite score is presented in **Figure 2**. The observed differences between groups from the Bonferroni-corrected *post-hoc* analyses are given in **Table 2**. For any cognitive domain and for the cognitive composite score, the healthy controls did not differ significantly from the NNS group. The remaining negative symptom groups were outperformed by healthy controls on all domains and the cognitive composite score except for the MNS group on verbal learning and memory and the SNS group on attention. The NNS and the MNS group outperformed the SNS group on verbal learning and memory. The NNS group also differed significantly from the SNS group with superior performance on the cognitive composite. As displayed in **Figure 2**, the mean values for cognitive performance decreased stepwise with an increase in the burden of negative symptoms, and with the largest difference between the NNS and SNS groups. There were no differences in age between negative symptom groups, but since there was a significant age difference when including healthy controls, we conducted a follow-up analysis controlling for age. This analysis did not provide different results. Between-group differences in cognitive functioning at 10-year follow-up are presented in **Supplementary Table 3**.

Analysis of Differences in the Cognitive Course Between Groups

Between-group differences in cognitive course over the 10-year follow-up for each domain and the cognitive composite score are displayed in **Figure 3**. There was a significant improvement in verbal learning ($F_{1,118} = 17.87$, $p < 0.001$; Pillai's Trace = 0.132), executive functioning ($F_{1,121} = 4.86$, $p = 0.03$; Pillai's Trace = 0.039), and the cognitive composite ($F_{1,123} = 8.34$, $p = 0.005$; Pillai's Trace = 0.063) over time. Visual inspection of means plots suggested that these improvements were mainly due to the healthy controls, the NNS and MNS groups, but there were no significant time x group interaction effects. The linear mixed model analyses, which included the complete HC sample, confirmed these results. All five analyses yielded significant effects of group. In addition, the effects of time were significant for verbal learning [$b = 0.28$, $t(213.61) = 3.28$, $p = 0.001$], executive function [$b = 0.21$, $t(217.79) = 2.05$, $p = 0.041$], and the composite score [$b = 0.16$, $t(218.00) = 2.53$, $p = 0.012$]. None of the interaction effects were significant.

Analysis of Global Functioning in Negative Symptom Groups

Global functioning at baseline, follow-up, and in the course over the 10-year follow-up is displayed in **Figure 4**. There was a significant improvement in global functioning as measured by the GAF-F over the follow-up period ($F_{1,97} = 49.97$, $p < 0.001$; Pillai's Trace = 0.340), without any time x group interactions ($F_{1,97} = 1.40$, $p = 0.25$; Pillai's Trace = 0.041). There were significant between-group differences in GAF-F at follow-up. The SNS group had the poorest level of global functioning, and the largest differences in GAF-F score were between this group and the NNS (mean difference 13.34, $p = 0.018$) and the MNS (mean difference 13.35, $p = 0.007$) groups. To explore the potential added contribution of cognitive functioning to the groups-based differences in global functioning, we performed a multiple linear regression analysis with GAF-F as the dependent variable and with the cognitive composite score and coming from the SNS group (vs. all other groups) as the independents, correcting for differences in other symptom areas, Both the cognitive composite score (beta = 0.98, $p < 0.001$), the PANSS positive component score (beta = 0.28, $p < 0.001$) and the PANSS depressive component score (beta 0.30, $p < 0.001$) had significant contributions to the variation in GAF-F at follow-up. Still, belonging to the SNS group had an independent and statically significant contribution to GAF-F when entered at the last step of the analysis (beta = 3.4, $p = 0.038$) (adjusted model $R^2 = 0.49$, $F = 42.6$, $p < 0.001$).

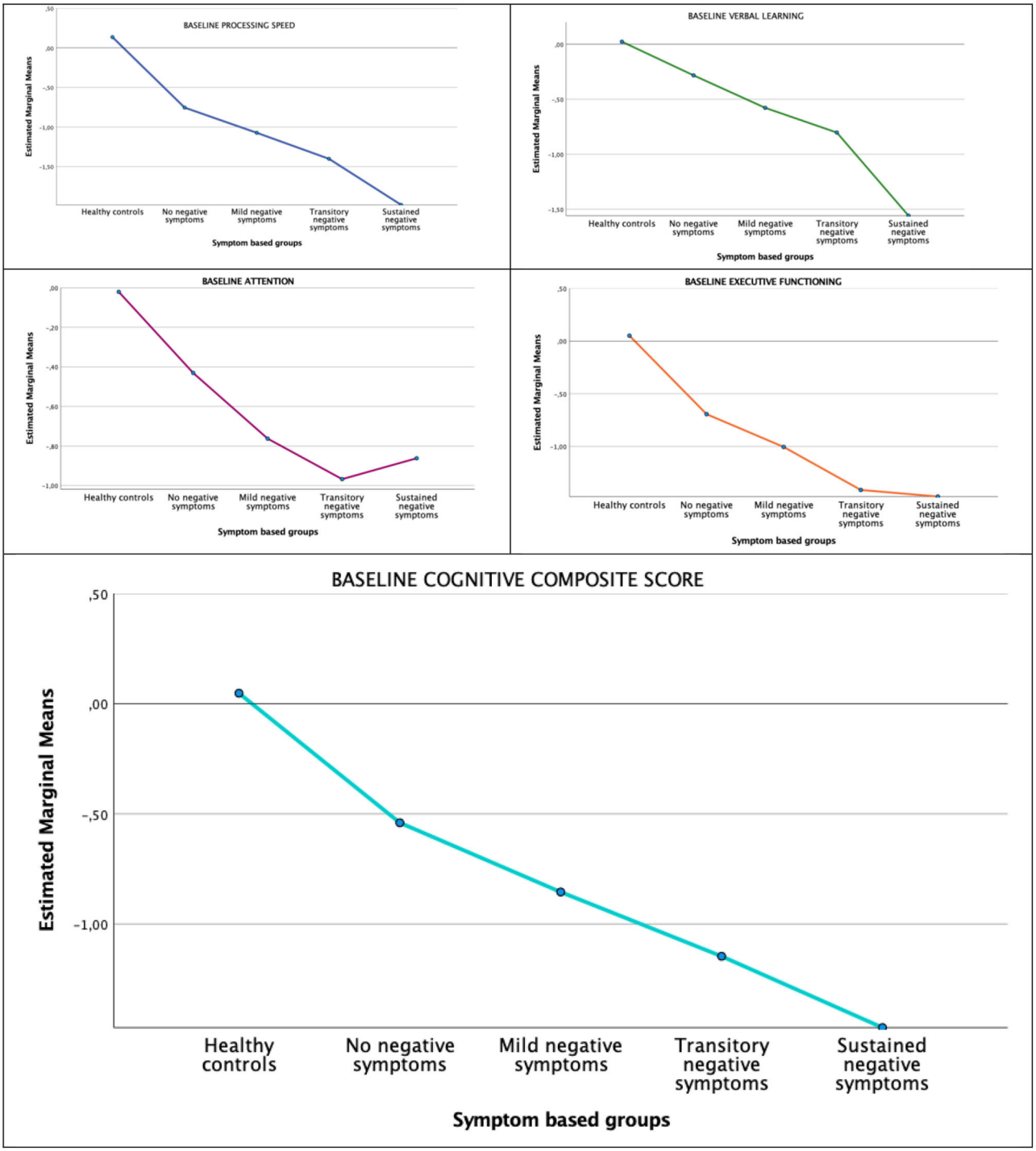


FIGURE 2 | Cognitive domains by negative symptom groups at baseline.

DISCUSSION

Using baseline and 10-year follow-up data to group FEP patients based on negative symptom severity, the current study largely replicates findings from our previous 1-year follow-up study, albeit with minor variations in group size (25). The SNS group which comprised 17% of the FEP sample is approximately the same size as reported for groups with deficit schizophrenia (42) or persistent negative symptoms (43) elsewhere. We also replicate our previous finding of group differences in cognitive

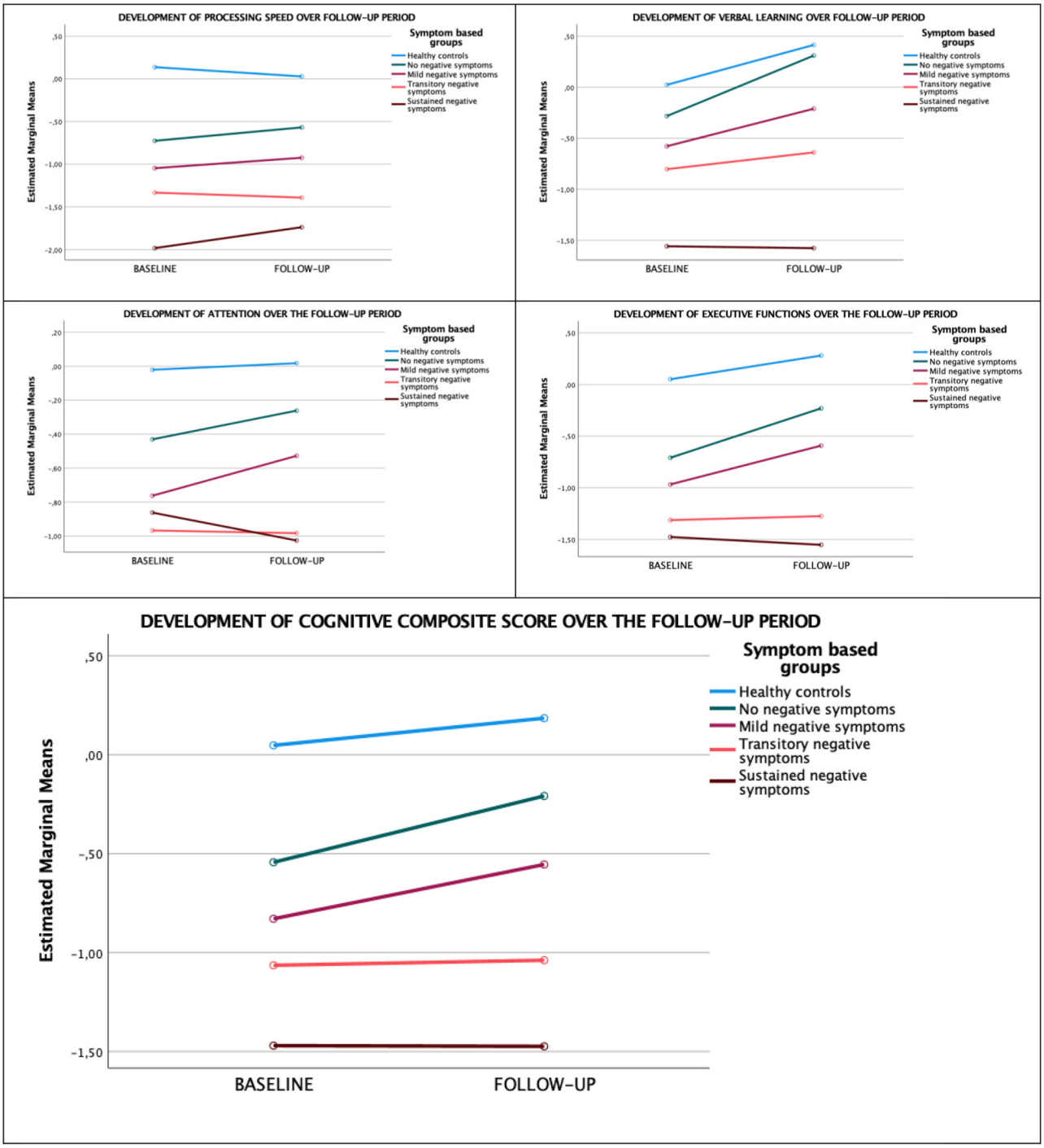


FIGURE 3 | Development of cognitive domains over the 10-year follow-up.

functioning at baseline between the four groups. The *post-hoc* analyses showed that the NNS group was not significantly outperformed by healthy controls on any domain or on the cognitive composite score. With some minor exceptions the healthy controls outperformed the remaining negative symptom groups on the four cognitive domains and on the cognitive composite. In the FEP sample, the NNS group significantly outperformed the SNS group on the verbal learning and memory domain and on the cognitive composite score. Our findings indicate that we already after 1 year of treatment in FEP

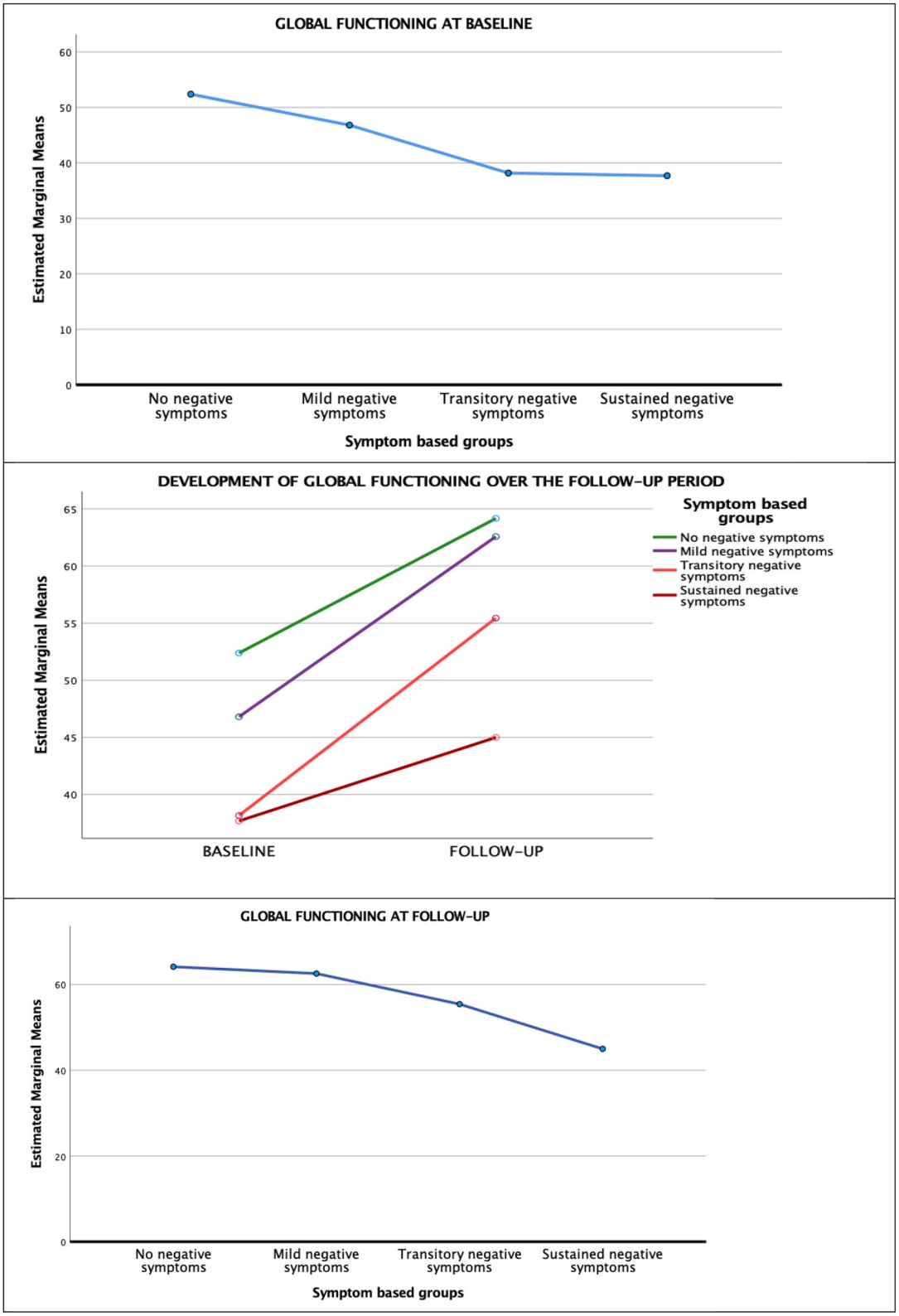


FIGURE 4 | Global functioning (gaf-f) over the 10-year follow-up.

can identify valid subgroups based on stratification of negative symptoms that have relevance for long-term outcome.

Concerning our second aim, we found parallel courses in the cognitive domains across subgroups. Significant improvements were detected for the cognitive composite and the domains of verbal learning and memory and executive function. The domains of processing speed and attention remained stable. These results add to the mixed findings in FEP, suggesting mainly stability (44), but improvements have also been reported (45). A recent 10-year follow-up study with healthy controls and a similar FEP sample size as the present, also reported a generally stable cognitive course (46). Although the authors reported finding a subgroup with a deteriorating course, they were unable to identify significant predictors. Upon visual inspection of slopes the SNS group did not show the same tendency toward improvement as the other groups, but there were no statistically significant interaction effects that would indicate a difference in course.

Concerning our third aim, we found that the groups differed significantly in their level of global functioning at baseline but did not differ in their course of global functioning over the 10-year follow-up period. The main difference in global functioning was as expected between the NNS and the SNS groups. However, the SSN group mainly showed a stable course and not clear deterioration. This is in line with some (47, 48), but not all (49–51), studies of the development of functioning over time in FEP. We also found that the differences in cognitive functioning had an independent contribution to global functioning, beyond the effect of severe negative symptoms as represented by belonging to the SNS group. Since the addition of a measure of functioning was added to serve as an external validator of clinical relevance, we conducted analyses of global functioning and the cognitive composite score not including functional- and/or cognitive subdomains. The latter type of analyses could give a more in-depth understanding of the relationship between cognition and functioning but was outside the focus of the current paper which was the relationship between negative symptoms and cognition.

In addition to the significant and long-term effect of sustained negative symptoms, the most interesting finding in the current study is that the NNS group did not differ significantly from healthy controls for any cognitive measure. This replicates our previous findings from the 1-year follow-up of the current group and strengthens our argument that comparting the extreme groups of patients with stable absence or presence of negative symptoms would enhance our ability to explore the relationships between cognitive and negative symptoms. Future research would profit from more theory-driven approaches to the study of negative symptoms.

Moreover, our findings add to the broader discussion of the defining features of schizophrenia, as they show that a stable absence of negative symptoms is linked to more subtle deficits in cognition and less functional impairment. As noted by a recent review, there is a growing literature questioning the emphasis on positive symptoms to define the diagnostic category of schizophrenia (52). According to this view, both negative and cognitive symptoms are more specific to schizophrenia than positive symptoms, in line with the former Bleulerian concept of the disorder (52). In the absence of clear biomarkers, the "correct" diagnostic criteria remain elusive. Our findings do, however, suggest that characteristics important to the original concept of schizophrenia (i.e., cognitive, and functional impairments) are more closely associated with negative symptoms, rather than the positive symptoms often used to define the diagnosis. This is an additional argument for more in-depth studies of negative syndromes and their neuroscientific underpinnings.

Future Research

Contrasting individuals with NNS and SNS has the potential to give new insights into negative symptoms, their association with cognitive symptoms, and relevant biomarkers including genetics and brain phenotypes captured by imaging techniques. In addition, more specific and elaborate measures of functional domains and particularly real-world functioning would also add to our understanding of their functional consequences. Furthermore, including frequent measurement points based on smart phone technology could provide more detailed data on the course of negative symptoms in critical periods of their developments. Finally, our study was planned before general access to good and reproducible measures of social cognition and thus did not include any such assessments at baseline.

Strengths and Limitations

The strengths of this study are the longitudinal design, and the inclusion of a sample recruited through the Norwegian public health system, which covers all citizens regardless of socioeconomic status. The sample is also well-characterized, with validated assessments for both clinical and cognitive variables.

A clear limitation is a 10-year period without any in-between measurements that could map variability in negative symptoms. However, previous studies have indicated considerable stability in negative symptoms from 1- to 10-year follow-up (53).

Also, the loss of participants from baseline to follow-up is always a threat to the representativeness of the sample, and the retention rate in this study is low. However, a study simulating the effect of losing participants in long-term longitudinal studies found that association between variables was not affected even with high rates of attrition (54). Moreover, there were no significant differences in baseline demographic and clinical variables between participants included compared to those lost to follow-up in the current study. We are, however, not able to rule out attrition bias due to different courses of illness.

The statistical tests used do not make assumptions about the equality of sample sizes, and type I errors are not increased by this limitation. However, there might be an increase of type II error due to the small and unequal sample sizes, particularly concerning the main groups of interest, the NNS and SNS groups, since they were the smallest. This could cause a conservative bias in the statistical interpretation overlooking group differences that in fact are present.

Finally, our study was planned before general access to good and reproducible measures of social cognition and thus did not include any such assessments at baseline. This can be considered a limitation as social cognition has been found to mediate the relationship between neurocognition and functioning (55).

CONCLUSION

Stratifying FEP patients based on the severity of negative symptoms over time could be key to understanding important aspects of heterogeneity in schizophrenia, such as the differences in cognitive functioning. This particularly applies to the differences between patients with persistently absent and persistently present negative symptoms. In the current study, participants with persistently low levels of negative symptoms over the 10-year follow-up period did not differ significantly from healthy controls and largely outperformed participants with sustained moderate-severe negative symptoms on verbal learning and memory. The group with persistent negative symptoms also demonstrated inferior global functioning, with an additional independent contribution from the difference in cognitive functioning. Clinical implications of the study are that differences in course of negative symptoms may indicate different treatment needs, and that the SNS group may need interventions specifically targeting cognitive impairments such as cognitive remediation. Although cognitive remediation does not primarily target negative symptoms, several studies have shown that in addition to improving cognition (56) this intervention may also have a beneficial effect on negative symptoms (57).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Etisk Komite Sør Øst. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TU, CS, AV, and ME formed the idea and planned the study. ME wrote the first draft and did the initial data analyses. IM contributed with data analysis and making of graphical presentation. GÅ, KW, BH, LW, CF, SL, and AF contributed with data collection. All authors have commented and contributed to the final submitted text.

FUNDING

The study was supported by grants from the Research Council of Norway to NORMENT CoE (grant number c, under the Centers of Excellence funding scheme), Stiftelsen Kristian Gerhard Jebsen (SKGJ-MED-008), the Southern and Eastern Norway Regional Health Authority (#2006233, #2006258, #2011085, #2014102, #2015088), and the Research Council of Norway (#287714). The funding bodies had no role in the analyses or writing of the manuscript, or the decision to submit this work for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.841057/full#supplementary-material

REFERENCES

1. Marder SR, Galderisi S. The current conceptualization of negative symptoms in schizophrenia. *World Psychiatry*. (2017) 16:14–24. doi: 10.1002/wps.20385
2. Owen M, Sawa A, Mortensen P. Schizophrenia seminar. *The Lancet*. (2016) 388:86–97. doi: 10.1016/s0140-6736(15)01121-6
3. Green MF, Harvey PD. Cognition in schizophrenia: past, present, and future. *Schizophr Res Cogn*. (2014) 1:e1–9. doi: 10.1016/j.scog.2014.02.001
4. Fenton WS, McGlashan T. Natural history of schizophrenia subtypes: II. positive I, and negative symptoms and long-term course. *Arch Gen Psychiatry*. (1991) 48:978–86. doi: 10.1001/archpsyc.1991.01810350018003
5. Fervaha G, Foussias G, Agid O, Remington G. Motivational and neurocognitive deficits are central to the prediction of longitudinal functional outcome in schizophrenia. *Acta Psychiatr Scand*. (2014) 130:290–9. doi: 10.1111/acps.12289
6. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull*. (2000) 26:119–36. doi: 10.1093/oxfordjournals.schbul.a033430
7. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res*. (2004) 72:41–51. doi: 10.1016/j.schres.2004.09.009
8. Milev P, Ho B-C, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am J Psychiatry*. (2005). doi: 10.1176/appi.ajp.162.3.495
9. Crow TJ. Molecular pathology of schizophrenia: more than one disease process? *Br Med J*. (1980) 280:66. doi: 10.1136/bmj.280.6207.66
10. Andreasen NC, Olsen S. Negative v positive schizophrenia. Definition and validation. *Arch Gen Psychiatry*. (1982) 39:789–94. doi: 10.1001/archpsyc.1982.04290070025006
11. Carpenter WT, Heinrichs DW, Wagman AM. Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry*. (1988) 145:578. doi: 10.1176/ajp.145.5.578
12. Peralta V, Cuesta MJ. The deficit syndrome of the psychotic illness. *Eur Arch Psychiatry Clin Neurosci*. (2004) 254:165–71. doi: 10.1007/s00406-004-0464-7
13. Hovington CL, Lepage M. Neurocognition and neuroimaging of persistent negative symptoms of schizophrenia. *Expert Rev Neurother*. (2012) 12:53–69. doi: 10.1586/ern.11.173
14. Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship? *Schizophr Bull*. (2005) 32:250–8. doi: 10.1093/schbul/sbj011
15. Aleman A, Hijman R, de Haan EH, Kahn RS. Memory impairment in schizophrenia: a meta-analysis. *Am J Psychiatry*. (1999) 156:1358–66. doi: 10.1176/ajp.156.9.1358
16. Ince E, Üçok A. Relationship between persistent negative symptoms and findings of neurocognition and neuroimaging in schizophrenia. *Clinical EEG Neurosci*. (2018) 49:27–35. doi: 10.1177/1550059417746213
17. Bucci P, Galderisi S, Mucci A, Rossi A, Rocca P, Bertolino A, et al. Premorbid academic and social functioning in patients with schizophrenia and its associations with negative symptoms and cognition. *Acta Psychiatr Scand*. (2018) 138:253–66. doi: 10.1111/acps.12938
18. Tan EJ, Rossell SL, Subotnik KL, Ventura J, Nuechterlein KH. Cognitive heterogeneity in first-episode psychosis and its relationship

with premorbid developmental adjustment. *Psychol Med.* (2021). doi: 10.1017/S0033291721000738. [Epub ahead of print].
19. Savill M, Banks C, Khanom H, Priebe S. Do negative symptoms of schizophrenia change over time? A meta-analysis of longitudinal data. *Psychol Med.* (2015) 45:1613–27. doi: 10.1017/S0033291714002712
20. Lyne J, O'Donoghue B, Roche E, Renwick L, Cannon M, Clarke M. Negative symptoms of psychosis: a life course approach and implications for prevention and treatment. *Early Interv Psychiatry.* (2018) 12:561–71. doi: 10.1111/eip.12501
21. Austin SF, Mors O, Budtz-Jorgensen E, Secher RG, Hjorthoj CR, Bertelsen M, et al. Long-term trajectories of positive and negative symptoms in first episode psychosis: A 10 year follow-up study in the OPUS cohort. *Schizophr Res.* (2015) 168:84–91. doi: 10.1016/j.schres.2015.07.021
22. A Mucci, Merlotti E, Ucok A, Aleman A, Galderisi S. Primary and persistent negative symptoms: concepts, assessments and neurobiological bases. *Schizophr Res.* (2017) 186:19–28. doi: 10.1016/j.schres.2016.05.014
23. Buchanan RW. Persistent negative symptoms in schizophrenia: an overview. *Schizophr Bull.* (2007) 33:1013–22. doi: 10.1093/schbul/sbl057
24. Strassnig MT, Raykov T, O'Gorman C, Bowie CR, Sabbag S, Durand D, et al. Determinants of different aspects of everyday outcome in schizophrenia: the roles of negative symptoms, cognition, functional capacity. *Schizophr Res.* (2015) 165:76–82. doi: 10.1016/j.schres.2015.03.033
25. Engen MJ, Simonsen C, Melle I, Faerden A, Lyngstad SH, Haatveit B, et al. Cognitive functioning in patients with first-episode psychosis stratified by level of negative symptoms: a 1-year follow-up study. *Psychiatry Res.* (2019) 281:112554. doi: 10.1016/j.psychres.2019.112554
26. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *JAMA.* (1999) 282:1737–44. doi: 10.1001/jama.282.18.1737
27. Delis D, Kramer J, Kaplan E, Ober B, *CVLT-II. California Verbal Learning Test Manual Adult Version.* San Antonio, Texas: The Psychological Corporation (2000).
28. Wechsler D. *WMS-III: Wechsler Memory Scale Administration and Scoring Manual*. Psychological Corporation (1997).
29. *W.D.Scale WAI, III (WAIS-III) Manual*. San Antonio, TX: The Psychological Corporation (1997).
30. Delis DC, Kaplan E, Kramer JH. *Delis-Kaplan Executive Function System (D-KEFS), Psychological Corporation* (2001).
31. Wechsler D. *WAS Manual*. San Antonio: Psychological Corporation (1999).
32. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV Axis I Disorders.* New York: New York State Psychiatric Institute (1995).
33. Ringen PA, Melle I, Birkenaes AB, Engh JA, Faerden A, Vaskinn A, et al. The level of illicit drug use is related to symptoms and premorbid functioning in severe mental illness. *Acta Psychiatr Scand.* (2008) 118:297–304. doi: 10.1111/j.1600-0447.2008.01244.x
34. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* (1987) 13:261–76. doi: 10.1093/schbul/13.2.261
35. Wallwork RS, Fortgang R, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of the positive and negative syndrome scale for schizophrenia. *Schizophr Res.* (2012) 137:246–50. doi: 10.1016/j.schres.2012.01.031
36. Addington D, Addington J, Maticka-Tyndale E, Joyce J. Reliability and validity of a depression rating scale for schizophrenics. *Schizophr Res.* (1992) 6:201–8.
37. Hildebrand M, Noteborn MG. Exploration of the (interrater) reliability and latent factor structure of the Alcohol Use Disorders Identification Test (AUDIT) and the Drug Use Disorders Identification Test (DUDIT) in a sample of Dutch probationers. *Subst Use Misuse.* (2015) 50:1294–306. doi: 10.3109/10826084.2014.998238
38. Pedersen G, Hagtvet KA, Karterud S. Generalizability studies of the global assessment of functioning–split version. *Compr Psychiatry.* (2007) 48:88–94. doi: 10.1016/j.comppsych.2006.03.008
39. Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry.* (2005) 162:441–9. doi: 10.1176/appi.ajp.162.3.441
40. Opler MG, Yang LH, Caleo S, Alberti P. Statistical validation of the criteria for symptom remission in schizophrenia: preliminary findings. *BMC Psychiatry.* (2007) 7:35. doi: 10.1186/1471-244X-7-35
41. Rodriguez-Jimenez R, Bagney A, Mezquita L, Martinez-Gras I, Sanchez-Morla EM, Mesa N, et al. Cognition and the five-factor model of the positive and negative syndrome scale in schizophrenia. *Schizophr Res.* (2013) 143:77–83. doi: 10.1016/j.schres.2012.10.020
42. Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT. A separate disease within the syndrome of schizophrenia. *Arch Gen Psychiatry.* (2001) 58:165–71. doi: 10.1001/archpsyc.58.2.165
43. Galderisi S, Mucci A, Bitter I, Libiger J, Bucci P, Fleischhacker WW, et al. Persistent negative symptoms in first episode patients with schizophrenia: results from the European first episode schizophrenia trial. *European Neuropsychopharmacol.* (2013) 23:196–204. doi: 10.1016/j.euroneuro.2012.04.019
44. Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ. Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology.* (2009) 23:315–36. doi: 10.1037/a0014708
45. Bora E, Murray RM. Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: do the cognitive deficits progress over, or after, the onset of psychosis? *Schizophr Bull.* (2014) 40:744–55. doi: 10.1093/schbul/sbt085
46. Rodríguez-Sánchez JM, Setién-Suero E, Suárez-Pinilla P, Mayoral Van Son J, Vázquez-Bourgon J, Gil López P, et al. Ten-year course of cognition in first-episode non-affective psychosis patients: PAFIP cohort. *Psychol Med.* (2020). doi: 10.1017/S0033291720002408. [Epub ahead of print].
47. Secher RG, Hjorthøj CR, Austin SF, Thorup A, Jeppesen P, Mors O, et al. Ten-year follow-up of the OPUS specialized early intervention trial for patients with a first episode of psychosis. *Schizophr Bull.* (2015) 41:617–26. doi: 10.1093/schbul/sbu155
48. Evensen J, Røssberg JI, Barder H, Haahr U, Hegelstad WT, Joa I, et al. Flat affect and social functioning: a 10 year follow-up study of first episode psychosis patients. *Schizophr Res.* (2012) 139:99–104. doi: 10.1016/j.schres.2012.04.019
49. Velthorst E, Fett AJ, Reichenberg A, Perlman G, van Os J, Bromet EJ, et al. The 20-year longitudinal trajectories of social functioning in individuals with psychotic disorders. *Am J Psychiatry.* (2017) 174:1075–85. doi: 10.1176/appi.ajp.2016.15111419
50. Hall MH, Holton KM, Ongur D, Montrose D, Keshavan MS. Longitudinal trajectory of early functional recovery in patients with first episode psychosis. *Schizophr Res.* (2019) 209:234–44. doi: 10.1016/j.schres.2019.02.003
51. Chang WC, Chu AOK, Kwong VWY, Wong CSM, Hui CLM, Chan SKW, et al. Patterns and predictors of trajectories for social and occupational functioning in patients presenting with first-episode non-affective psychosis: a three-year follow-up study. *Schizophr Res.* (2018) 197:131–7. doi: 10.1016/j.schres.2018.01.021
52. Loch AA. Schizophrenia, not a psychotic disorder: bleuler revisited. *Front Psychiatry.* (2019) 10:328. doi: 10.3389/fpsyt.2019.00328
53. Lyngstad SH, Gardsjord ES, Engen MJ, Haatveit B, Ihler HM, Wedervang-Resell K, et al. Trajectory and early predictors of apathy development in first-episode psychosis and healthy controls: a 10-year follow-up study. *Eur Arch Psychiatry Clin Neurosci.* (2020) 270:709–22. doi: 10.1007/s00406-020-01112-3
54. Gustavson K, von Soest T, Karevold E, Roysamb E. Attrition and generalizability in longitudinal studies: findings from a 15-year population-based study and a Monte Carlo simulation study. *BMC Public Health.* (2012) 12:918. doi: 10.1186/1471-2458-12-918
55. Schmidt SJ, Mueller DR, Roder V. Social cognition as a mediator variable between neurocognition and functional outcome in schizophrenia: empirical review and new results by structural equation modeling. *Schizophr Bull.* (2011) 37(Suppl. 2):S41–54. doi: 10.1093/schbul/sbr079
56. Vita A, Barlati S, Ceraso A, Nibbio G, Ariu C, Deste G, et al. Effectiveness, core elements, and moderators of response of cognitive remediation for schizophrenia: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry.* (2021) 78:848–58. doi: 10.1001/jamapsychiatry.2021.0620
57. Cella M, Preti A, Edwards C, Dow T, Wykes T. Cognitive remediation for negative symptoms of schizophrenia: a network

meta-analysis. *Clin Psychol Rev*. (2017) 52:43–51. doi: 10.1016/j.cpr.2016.11.009

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Psychiatry

ORIGINAL RESEARCH
published: 27 April 2022
doi: 10.3389/fpsyt.2022.865226

The Relationship Between the Recognition of Basic Emotions and Negative Symptoms in Individuals With Schizophrenia Spectrum Disorders – An Exploratory Study

Marco Zierhut[1,2]*, *Kerem Böge*[1], *Niklas Bergmann*[1], *Inge Hahne*[1], *Alice Braun*[3], *Julia Kraft*[3], *Thi Minh Tam Ta*[1], *Stephan Ripke*[3], *Malek Bajbouj*[1] and *Eric Hahn*[1]

[1] Department of Psychiatry and Psychotherapy, Charité – Universitätsmedizin Berlin, Berlin, Germany, [2] BIH Charitè Junior Clinician Scientist Program, BIH Biomedical Innovation Academy, Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, Germany, [3] Department of Psychiatry and Psychotherapy, Charité – Universitätsmedizin Berlin, Berlin, Germany

OPEN ACCESS

Edited by:
Armida Mucci,
University of Campania Luigi Vanvitelli, Italy

Reviewed by:
Massimo Ballerini,
Usl Tuscany Center, Italy
Stefano Barlati,
University of Brescia, Italy

***Correspondence:**
Marco Zierhut
marco.zierhut@charite.de

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *29 January 2022*
Accepted: *04 April 2022*
Published: *27 April 2022*

Citation:
Zierhut M, Böge K, Bergmann N, Hahne I, Braun A, Kraft J, Ta TMT, Ripke S, Bajbouj M and Hahn E (2022) The Relationship Between the Recognition of Basic Emotions and Negative Symptoms in Individuals With Schizophrenia Spectrum Disorders – An Exploratory Study. Front. Psychiatry 13:865226. doi: 10.3389/fpsyt.2022.865226

Current research suggests that emotion recognition is impaired in individuals affected by schizophrenia spectrum disorders (SSD). However, the specific impact of negative symptoms on the ability to recognize single basic emotions has not yet been explored sufficiently and is the aim of the present study. A sample of $N = 66$ individuals diagnosed with SSD was recruited at the Charité – Universitätsmedizin Berlin. In a first step, correlation analyses were conducted between seven different negative symptom subdomains of the Positive and Negative Syndrome Scale (PANSS) and the accuracy and latency in recognizing the six basic emotions (anger, disgust, fear, happiness, sadness, surprise) using the Emotion Recognition Task (ERT) of the Cambridge Neuropsychological Test Automated Battery (CANTAB). The significant correlations were subjected to linear regression models that controlled for the significant covariates diagnoses, age, sex, and education. Results revealed that in individuals with SSD the negative symptom domain of blunted affect significantly predicted the accuracy of emotion recognition performance ($p < 0.05$), particularly, when recognizing happiness ($p < 0.05$). Additionally, we found that stereotyped thinking also predicted the performance of emotion recognition, especially the response latency ($p < 0.05$) and difficulty in abstract thinking predicted the recognition of fear ($p < 0.05$). However, the nominal significances did not withstand correction for multiple tests and therefore need to be followed up in further studies with a larger sample.

Keywords: schizophrenia spectrum disorders, negative symptoms, emotion recognition, schizophrenia, psychosis

INTRODUCTION

Social cognition is a crucial domain for interacting with other people and participation in society. It has been defined as the psychological processes that underlie social interactions, including perception, experience sharing, mentalizing, and experiencing and regulating emotion and information about other people and about ourselves (1, 2). Among this heterogeneous category

of processes, the most important domains of social cognition include the perception of social cues like emotion perception (1–4). Individuals affected by schizophrenia spectrum disorders (SSD) show significant impairments in their ability to recognize and express emotions, as already described by Kraepelin (2, 5, 6). Previously, studies of emotion deficits in schizophrenia focused on three main domains: expression, experience, and recognition of emotions. A review of 110 studies revealed marked impairment in all three domains in individuals with SSD (7). It is essential to differentiate between emotion recognition – which refers to the ability to recognize an expression of emotion such as disgust - and finding a face disgusting, which is called subjective appraisal (7). Emotion recognition has been linked to emotional intelligence and social perception, whereas appraisal has been linked to emotion processing (7). Gur et al. (8) reported an association of greater impairment for individuals with SSD in emotion recognition via facial stimuli with the severity of negative symptoms. Social cognitive impairments and negative symptoms are core features of SSD closely associated with high burden due to impairments in social functioning and quality of life already apparent prior to illness onset (2, 5, 6, 9–12). For example attenuated impairment in emotion recognition manifests in unaffected first-degree relatives, ultra-high-risk individuals (13, 14), and young individuals with first-episode schizophrenia (5, 15, 16). A study found that young individuals with schizophrenia were impaired in their ability to recognize faces and gestures from movie scenes during the first two to 3 years of their illness after symptom onset (15, 17). According to Comparelli, Corigliano (13), facial emotion recognition impairment already present in ultra-high-risk individuals remained stable across the course of illness. Deficits in emotion recognition may be one of the most consistent and severe aspects of interpersonal problems (15) and impairment of social skills (18) and are related to poorer social outcomes in schizophrenia (19). Some researchers argue emotion recognition deficits are long-term stable features of schizophrenia (20). In one model, negative symptoms, emotion recognition latency, and processing speed were significant predictors of social functioning in individuals at ultra-high risk for psychosis (21, 22). Another model for schizophrenia onset included face emotion processing and negative symptoms as predictors of transition in individuals at high clinical risk to schizophrenia with an accuracy of 96% (11). Accordingly, this represents a particularly relevant field of research since both negative symptoms and impairments in social cognition could be apparent prior to illness onset with psychotic symptoms (10, 11).

Impaired emotional functioning has been linked to negative symptoms and can be conceptualized as a fundamental clinical feature in SSD (7, 23, 24). Newer discussions on deficits in emotion recognition raise the question of whether those belong to the negative symptom spectrum or form a separate domain in SSD (1, 25, 26). According to recent models, negative symptoms are also described as deficient social cognitions (27). The existing data non-etheless suggest that negative symptoms and social cognition are related, yet distinct constructs. Over time, deficits in social cognition could manifest behaviourally as negative symptoms (1). There are different models for a possible connection between social cognition and negative symptoms. On the one hand it is assumed that specific impairments in social cognition are linked to one or some negative symptoms but not others, which means there is a mechanistic heterogeneity. In support of this model, associations between only specific social cognition domains and negative symptoms have been reported (1). On the other hand, findings support broad impairments in basic sensory and cognitive processes (e.g., visual perception, motor output, processing speed, and implicit attention), which affect downstream processes. These are directly involved in social cognitive operations, which, in turn, result in the development of a range of negative symptoms and functional impairment (1). In studies looking at various factor models no correlations were found between the social cognitive factors and negative symptoms suggesting that social cognition and negative symptoms are largely separate constructs. They can be seen as relatively independent causes of dysfunction and disability and can be used to meaningfully classify non-acute patients (12, 28, 29). Furthermore, the entry level of negative symptoms was significantly associated with poor social functioning. Important predictive links have been found in the early course of schizophrenia, mostly indicating that higher negative symptom severity is associated with poor daily functioning and worse long-term outcomes (30–33). Given this, there is increasing interest in understanding to what amount negative symptoms reflect the expression of deficits in social cognition and the relationship between the two symptom domains (1). However, little is known about the dependence of these dimensions of illness and, whether individuals with schizophrenia can be meaningfully classified based on these dimensions and potentially differentially treated. Ruocco et al. (34), who compared emotion recognition deficits in individuals with schizophrenia, schizoaffective disorders, and bipolar disorders, discovered that compared to healthy controls, emotion recognition deficits among individuals increased progressively from bipolar disorder to schizoaffective disorder to schizophrenia. The researchers concluded that emotion recognition deficits are apparent at the first psychotic episode and prominent but different across psychotic disorders and relatively independent of mood state and antipsychotic treatment dosages (34–36). Conclusively illness-related characteristics like negative symptoms need further investigation (34–36). A priority of negative over positive symptoms in determining deficits in social cognition and functioning in chronic schizophrenia was concluded by many researchers (5, 37). To develop intervention approaches in the early phase of SSD, it is crucial to understand the longitudinal course of negative symptoms, especially in relationship to functioning (30).

There are, however, no sufficient treatment options for negative symptoms. The most often employed approaches as medication, psychotherapy, psychosocial interventions, and electroconvulsive therapy have only small effect sizes (38–40). A model of negative symptoms as the behavioral manifestation of altered social cognition has the potential to reveal areas of intact functioning, including domains of social cognition that remain unaffected by the illness, which novel treatments could rely upon to enhance the recovery of individuals with schizophrenia (1). The findings regarding social cognition in schizophrenia have treatment implications and the social processes that are

aberrant in schizophrenia may each require their own specific therapeutic intervention. Training programmes that target facial emotion perception and mentalizing deficits have been validated in individuals with schizophrenia (2, 41, 42).

Some researchers, such as Schneider et al. (43), concluded that especially impairments in facial emotion perception were strongly associated with the severity of negative symptoms. Since then, several studies have investigated the connection between negative symptoms and emotion deficits, but findings on the relationship between emotion recognition and negative symptoms remain inconclusive (5, 15, 43–56). There are various explanations for these mixed results. Most of the studies did not differentiate subdomains of negative symptoms and only considered negative symptoms overall. Also, some studies did not include all six basic emotions in their experimental designs but presented the subjects with a smaller selection of emotional stimuli. Paul Ekman first defined the six basic emotions: anger, disgust, fear, happiness, sadness and surprise (15, 57). Furthermore, different operationalizations and instruments for negative symptoms could be a source of variation (58, 59). To better understand the link between specific negative symptoms and emotion recognition, this study aims to explore the relationship between recognizing the six basic emotions and seven distinct negative symptoms in individuals with SSD in an exploratory approach by using the Positive and Negative Syndrome Scale (PANSS) (60) and the Emotion Recognition Test of the Cambridge Neuropsychological Test Automated Battery (ERT-CANTAB) (61).

According to the current state of research, five key subdomains of negative symptoms have been identified: (1) avolition, (2) anhedonia, (3) blunted affect (4) social withdrawal, and (5) alogia (9, 62–64). Negative symptoms can be assessed via various instruments [e.g., PANSS, Scale for the Assessment of Negative Symptoms (SANS) (65), Brief Negative Symptom Scale (BNSS) (66), Clinical Assessment Interview for Negative Symptoms (CAINS) (67), Negative Symptom Assessment (NSA) (68)]. So, it is necessary to consider the nature of each measurement instrument, especially with the aim of relating each symptom domain to the recognition of individual basic emotions. The domain of negative symptomatology is very complex encompassing primary and secondary symptoms as a result of medication side effects, depressive symptomatology and other causes (64). In SSD, studies confirmed moderate to large associations between negative symptoms and deficits in social cognition using the SANS (65) and/or the PANSS (1, 5, 12, 28, 30, 60, 69) as well as newer negative symptom scales like the BNSS (1, 5, 12, 66, 70). In many older studies, the negative syndrome scale of the classic PANSS was used to assess the individual domains of negative symptoms. However, according to recent factor analytic studies, it must be considered that the two symptom domains difficulty in abstract thinking (N5) and stereotyped thinking (N7) are now no longer regarded as negative symptoms but are assigned to the domain of cognitive symptoms (56) and difficulty in abstract thinking (N5) to the domain of disorganization, depending on the study design (71). This should therefore be considered when evaluating results using the PANSS. Nevertheless, in the context of an explorative approach of our study and for comparability with previous studies, especially older ones, we selected the PANSS as the primary rating tool for negative symptoms as a still frequently used third-party rating instrument in clinical studies (1, 5, 12, 28, 30, 60, 69). Depending on our results, a selection of the other measurement instruments should also be included in follow-up studies for an even better understanding of the relationships between negative symptoms and social cognition. We selected the Emotion Recognition Test of the CANTAB to measure the recognition of basic emotions. It contains all six basic emotions and is easy to use as a tablet-based measurement instrument in different settings (61). It is explicitly part of the Schizophrenia Test Battery of the CANTAB and several studies with patients with SSD have already been conducted with it. For example, Gica et al. (20) could show with the ERT-CANTAB, that emotion recognition deficits are long term stable features of schizophrenia and Kanchanatawan et al. (72) showed associations of anxiety and depressive symptoms in individuals with SSD with social cognition by using the ERT-CANTAB. Glenthøj et al. (22) could show impairments in social cognition with the ERT-CANTAB in ultra-high risk for psychosis individuals and that hereby emotion recognition latency but not accuracy relates to real life functioning in these individuals (21).

MATERIALS AND METHODS

Sample and Procedure

The recruitment of participants was based on recommendations of a multiprofessional team. A sample of $N = 66$ individuals diagnosed with SSD was recruited at the in- ($n = 36$) and out-patients ($n = 30$) clinic of the Department for Psychiatry and Psychotherapy at the Charité – Universitätsmedizin Berlin, Germany (see **Table 1**). Of these, $n = 54$ were diagnosed with schizophrenia and $n = 12$ with a schizoaffective disorder. For inclusion, participants had to a) be aged between 18 to 65, b) meet diagnostic criteria for SSD (ICD-10: F2X.X) assessed by an attending psychiatrist and c) be able to give informed consent to participate in the study. Exclusion criteria encompassed (a) a score > 6 on any item of the positive scale of the Positive and Negative Syndrome Scale (PANSS) (60), which suggests an acute psychotic episode with severe psychotic symptoms, (b) acute suicidality assessed with the Clinical Decision Support System (CDSS) (item $8 > 1$) (73), (c) current substance use other than nicotine or (d) the existence of neurological disorders or brain damages. For inpatients, the surveys were conducted within the first 8 weeks of treatment to avoid long hospitalization as a possible influencing factor on negative symptoms, respectively the exclusion criteria of an acute psychotic episode. The prescribed psychotropic medication and dosage was systematically recorded (see **Table 2**). Trained clinical staff assessed the seven different negative symptoms using the PANSS (60). The individuals' ability to recognize the six basic emotions happiness, sadness, fear, anger, surprise and disgust was measured using the Emotion Recognition Task (ERT) of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (61) on an Apple® iPad Air using the software iPadOs 15.2. Basic demographic information of the study sample is summarized in **Table 1**.

TABLE 1 | F2-Diagnoses and demographic data of the sample.

Variable	Overall, $N = 66$	Schizoaffective disorder (F25), $n = 12$	Schizophrenia (F20), $n = 54$
Sex			
Female	25 (38%)	8 (67%)	17 (31%)
Male	41 (62%)	4 (33%)	37 (69%)
Age			
N	66	12	54
Mean (SD)	41 (13)	50 (14)	40 (12)
Range	19, 69	26, 69	19, 67
Education			
Gymnasium (ISCED 3)	30 (46%)	6 (50%)	24 (45%)
Realschule (ISCED 2)	22 (34%)	5 (42%)	17 (32%)
Hauptschule (ISCED 2)	13 (20%)	1 (8.3%)	12 (23)
Missing	1	0	1

N, sample size; SD, Standard Deviation; ISCED, International standard classification of education.

Measures

The Positive and Negative Syndrome Scale (PANSS)

The Positive and Negative Syndrome Scale (PANSS) is a clinical instrument specifically designed to measure symptoms associated with SSD on a 7-point scale (1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate severe, 6 = severe and 7 = extreme). It encompasses three subscales; seven items to measure positive symptoms, seven items for negative symptoms and 16 on general symptomatology (60). Furthermore, the scale allows the calculation of a global score of overall symptom severity. These items are rated based on a comprehensive interview carried out by a trained clinician. The Negative Scale of the PANSS was used to assess the seven itemized negative symptoms: blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive and apathetic social withdrawal (N4), difficulty in abstract thinking (N5), lack of spontaneity and flow of conversation (N6) and stereotyped thinking (N7). Regarding the psychometric properties of the Negative Scales of the PANSS, it can be said that the PANSS scores are normally distributed, and negative scales showed good interrater reliability. Negative syndromes also proved their factorial validity. The Negative Scale also held a high concurrent validity with the Scale for the Assessment of Negative Symptoms (SANS) (60, 65, 74).

Emotion Recognition Task (ERT)

The assessment of emotion recognition was carried out with the iPad version of the validated Cambridge Neuropsychological Test Automated Battery (CANTAB) in German language. The CANTAB is a computerized assessment developed from animal behavior paradigms and human neuropsychology, initially developed in the late 1980s (61). It has been widely used in many neurocognitive examinations of individuals with and without SSD (75). The largely non-verbal nature of the tests makes the CANTAB practical for use across multisite and multilingual clinical trials. The CANTAB schizophrenia test battery comprises computerized neuropsychological tests presented on a touchscreen system assessing eight cognitive domains most impaired in people affected by SSD. These captured cognitive domains were prioritized by the National Institute of Mental Health (NIMH) sponsored Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program (76). To assess social cognition within this study, we used the tablet-based Emotion Recognition Task (ERT), a facial emotion labeling task recently added to the battery, including testing for all six basic emotions: anger, disgust, fear, happiness, sadness, and surprise. Within this task participants are presented with computer-morphed faces expressing one specific emotion out of six basic emotions. Each face image is shown for 200 ms. The study participants are then asked to indicate the displayed emotion out of the six primary emotions or choose a neutral option. The task takes around 12 min to complete (61). Key outcome measures of the ERT are the overall median reaction time to select an emotion (ERTOMDRT), the total number of correct responses (total hits, ERTTH) and the unbiased hit rate for each of the six emotions: anger (ERTUHRA), disgust (ERTUHRD), fear (ERTUHRF), happiness (ERTUHRH), sadness (ERTUHRS) and surprise (ERTUHRSU).

Ethical Approval

The current study was reviewed and approved by the Ethics Committee of Charité – Universitätsmedizin Berlin (EA4/225/19). All participants provided written informed consent to participate in this study.

Statistical Analysis

The statistical analysis was carried out in R Studio Version 1.2.5033 running R version 4.0.4 and IBM SPSS Version 25. The following steps were performed for the statistical analyses in an exploratory approach of the study:

1. The Pearson's correlation coefficient was calculated between the seven negative symptoms and the accuracy and latency of recognition for each basic emotion.

2. Multiple linear regression models followed up the significant correlations to investigate the relationship while controlling for the covariates diagnoses, age, sex, and education. For covariate analysis, multiple linear regressions were run to examine the effect of each potential covariate on each CANTAB variable.

3. Each significant correlation between a negative symptom and a CANTAB variable was tested as a linear regression model by including the significant covariates in the regression models.

4. Bonferroni corrections for multiple testing were performed despite a not sufficient sample size for statistical completeness. The Bonferroni adjusted p-value is reported as p_{Bonf} respectively (77). Power and sample size calculations followed.

TABLE 2 | Overview of the antipsychotics taken during the study.

Medication	Generation / potency	Mean (SD) (mg)	Administration	Number of patients
Flupentixol	FG / HP	4.7 (3.1)	p.o.	3
Haloperidol	FG / HP	3	p.o.	1
Melperone	FG / LP	75	p.o.	1
Pipamperone	FG / LP	43.3 (29.4)	p.o.	6
Amisulpride	SG	553.9 (281)	p.o.	14
Aripiprazole	SG	13.4 (8.3)	p.o.	13
Aripiprazole	SG	300	i.m.	1
Cariprazine	SG	3 (0)	p.o.	2
Clozapine	SG	266 (239)	p.o.	22
Olanzapine	SG	19 (8.1)	p.o.	11
Paliperidone	SG	5.3 (4.5)	p.o.	5
Paliperidone	SG	112.5 (25)	i.m.	4
Quetiapine	SG	240 (176.1)	p.o.	10
Risperidone	SG	3.2 (1.2)	p.o.	12
Risperidone	SG	37.5	i.m.	1
Ziprasidone	SG	50 (42.4)	p.o.	2

FG, First Generation; SG, Second generation; HP, High potency; LP, Low potency; mg, milligram; p.o., per os; i.m., intramuscular.

RESULTS

In **Figure 1**, a correlational matrix with an overview of the findings that emerged after data collection is presented. Positive correlations within the respective scales can also be found in the literature (60, 78–80). There was a significant negative correlation between blunted affect (N1) and the total number of correct responses in emotion selection ($r = -0.291$, $p < 0.05$), the recognition of happiness ($r = -0.034$, $p = < 0.05$), fear ($r = -0.246$, $p < 0.05$) and disgust ($r = -0.253$, $p < 0.05$). A significant negative correlation of difficulties in abstract thinking (N5) with fear recognition ($r = -0.337$, $p < 0.05$) was found. There was also a significant positive correlation of the response latency in emotion recognition with difficulties in abstract thinking (N5) ($r = 0.289$, $p < 0.05$) and stereotyped thinking (N7) ($r = 0.349$, $p < 0.05$). There were no significant correlations between the negative symptom domains emotional withdrawal (N2), poor rapport (N3), passive and apathetic social withdrawal (N4), and lack of spontaneity and flow of conversation (N6) and the assessed CANTAB variables among those with SSD. In the next step, linear regressions were run to examine a significant effect of the covariates age, education, sex and diagnoses on each CANTAB variable.

When controlling for age and education, a multiple linear regression analysis was conducted to assess whether blunted affect (N1) significantly predicted the total number of correct responses in emotion selection. Hereby blunted affect (N1) significantly predicted the total number of correct responses in emotion selection [$B = -0.919$, $t = -2.199$, $p = 0.032$]. Blunted affect (N1) could also be identified as a significant predictor of the accurate recognition of happiness when controlling for the covariates [$B = -0.241$, $t = -2.113$, $p = 0.039$]. Likewise, the negative symptom domain of difficulties in abstract thinking (N5) was identified as a significant predictor of fear recognition in the regression analyses [$B = -0.037$, $t = -2.044$, $p = 0.045$] when controlling for education. A linear regression analysis was conducted to assess whether difficulties in abstract thinking (N5) and stereotyped thinking (N7) predicted the response latency when controlling for age. In this model stereotyped thinking (N7) significantly predicted the response latency [$B = 195.921$, $t = 2.400$, $p = 0.019$], whereas the negative symptom difficulties in abstract thinking (N5) was not a significant predictor in this model [$B = 117.474$, $t = 1.535$, $p = 0.130$]. Linear regression analysis models showed that that blunted affect (N1) was not a significant predictor for recognizing either fear [$B = -0.023$, $t = -1.607$, $p = 0.113$] or disgust [$B = -0.027$, $t = -1.699$, $p = 0.094$], while controlling for the significant covariate education. For an overview of the above significant regression analyses, please refer to **Table 3**. The complete respective regression tables are provided in the **Supplementary Material**.

The demonstrated nominal significances did not withstand correction for 111 multiple tests. After Bonferroni correction, none of the mentioned correlation and regression analyses between PANSS and the ERT items, respectively, reached statistical significance (see **Supplementary Material**). With a power of 0.8, an expected small effect of $f2 = 0.054$ of the PANSS negative scales on emotion recognition based on preliminary studies (81), and a p-value of 0.00045 corrected for 111 multiple tests, a sample size of 446 subjects would be necessary to detect a significant effect. According to the guidelines of Cohen (82) $f2 \geq 0.02$, $f2 \geq 0.15$, and $f2 \geq 0.35$ represent small, medium, and large effect sizes, respectively.

DISCUSSION

Summary of the Main Results

In the present study, blunted affect (N1) emerged as the negative symptom most strongly predicting the total number

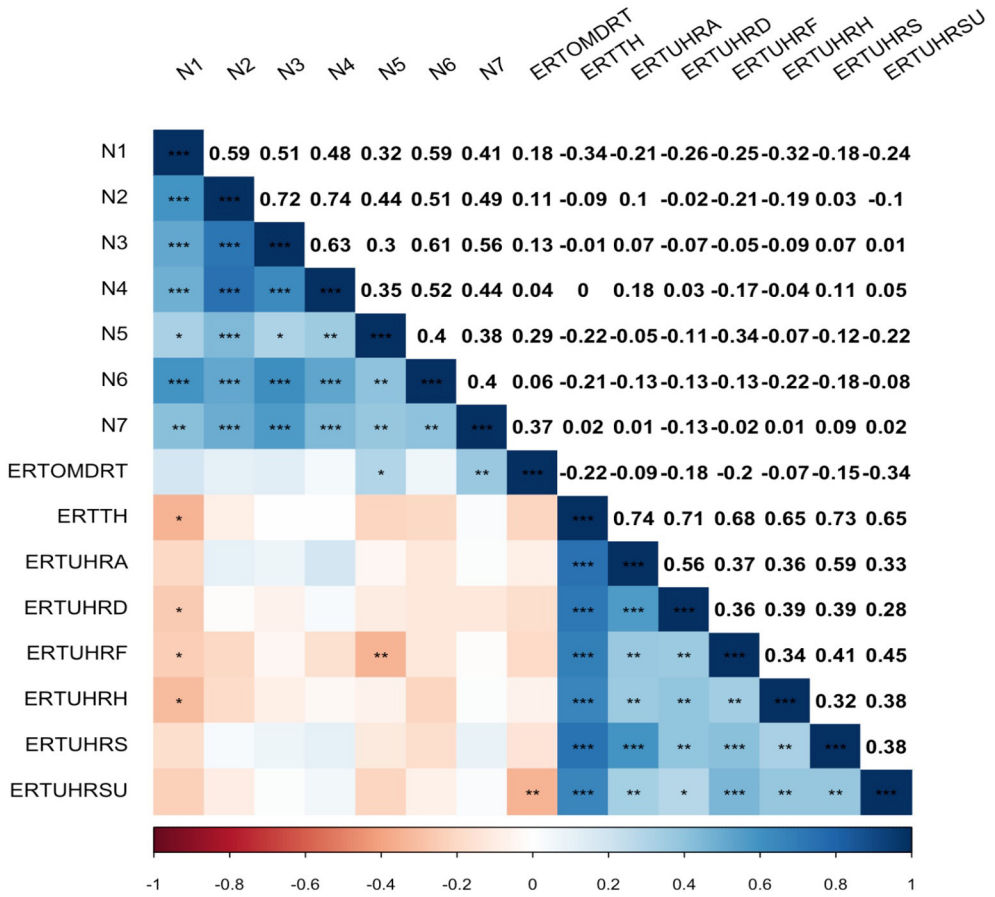


FIGURE 1 | Correlation Matrix of Positive and Negative Syndrome Scale (PANSS) Negative Scale and Emotion Recognition Test (ERT) key outcomes in form of a heat map with Pearson correlation coefficient and significance level with unadjusted *p*-values (***p < 0.001, **p < 0.01, *p < 0.05); N1, blunted affect; N2, emotional withdrawal; N3, poor rapport; N4, passive and apathetic social withdrawal; N5, difficulty in abstract thinking; N6, lack of spontaneity and flow of conversation; N7, stereotyped thinking; ERTOMDRT, the overall median reaction time to select an emotion; ERTTH, the total number of correct responses; ERTUHRA, the unbiased hit rate for the emotion anger; ERTUHRD, the unbiased hit rate for the emotion disgust; ERTUHRF, the unbiased hit rate for the emotion fear; ERTUHRH, the unbiased hit rate for the emotion happiness; ERTUHRS, the unbiased hit rate for the emotion sadness; ERTUHRSU, the unbiased hit rate for the emotion surprise.

of correct responses, especially happiness recognition. First, a significant correlation was shown between blunted affect (N1) and happiness, fear and disgust. After controlling for the significant covariates, blunted affect (N1) only significantly predicted the recognition of happiness. We also found a prediction of difficulties in abstract thinking (N5) for recognizing the basic emotion of fear. Additionally, a significant correlation between difficulties in abstract thinking (N5) and response latency and a significant prediction of stereotyped thinking (N7) for the response latency in emotion recognition was found. However, results must be weighed against the methodological limitations of the study.

Prediction for Response Latency in Emotion Recognition

With reference to the results regarding response latency and the association with stereotyped thinking (N7) and difficulty in abstract thinking (N5), some authors assign stereotyped thinking, difficulties in abstract thinking alongside conceptual disorganization, disorientation, and poor attention rather to a cognitive symptom dimension than to the negative symptom dimension (56). This could explain the prediction for the response latency, where cognitive processing of impressions may play a role. Glenthøj et al. (21), also using the CANTAB for emotion recognition, reported that latency in emotion recognition, but not accuracy, related to real-life functioning for individuals at ultra-high risk for psychosis (21). More studies have been conducted on the relationship between cognitive capabilities and the ability to recognize emotions in individuals with SSD, but again with inconclusive results. According to Turetsky et al. (83), emotion recognition deficits could be assumed to be secondary to problems in a structural encoding of faces, and a specific signal recognition could play a role that precedes emotion recognition. Additionally, several studies reported a clear association between neuropsychological functions and emotion recognition (43, 56, 84, 85).

TABLE 3 | Regression analysis predicting the ERT items resulting from the correlation analyses.

Independent Variable	Unstandardized coefficient		Standardized coefficient	*t*	*p*	p_{Bonf}	Dependent variable
	B	SE	Beta				
N1	−0.919	0.418	−0.241	−2.199	0.032	1.000	ERTTH
N1	−0.034	0.016	−0.241	−2.113	0.039	1.000	ERTUHRH
N5	−0.037	0.018	−0.270	−2.044	0.045	1.000	ERTUHRF
N7	195.921	81.634	0.287	2.400	0.019	1.000	ERTOMDRT

Constant = 555.393, F(3,62) = 6,402, p = 0.001, $R^2 = 0.200$; p_{Bonf}, Bonferroni adjusted p-value; N1, blunted affect; N5, difficulty in abstract thinking; N7, stereotyped thinking; ERTTH, the total number of correct responses; ERTUHRH, the unbiased hit rate for the emotion happiness; ERTUHRF, the unbiased hit rate for the emotion fear; ERTOMDRT, the overall median reaction time to select an emotion.

Prediction for the Correct Recognition of the Six Emotions

Blunted affect (N1) significantly predicted the recognition of happiness. The current study results have been confirmed in the literature, while other studies reported inconclusive results and need further classification (15). On the one hand some authors like Turetsky et al. (83) showed that recognizing happy faces correlated with the severity of negative symptoms, especially in individuals with SSD. On the other hand, ratings in the blunted effect's subdomain uniquely predicted performance on the emotion processing tasks. They were associated with better speed and accuracy than other negative symptom domains (8). Blunted affect being more evident in men than women is in line with the findings of Kohler et al. (84), showing a poorer performance of men in emotion recognition. Several studies examined the relationship between impaired emotion perception with different symptom rating scales, e.g., the Brief Psychiatric Rating Scale (BPRS) (86), the Scale for the Assessment of the Positive Symptoms (SAPS) (87), the SANS (65), and the PANSS (60). Their impact and differences in the sample recruitment may have contributed to the inconsistencies reported in the literature (44) and should be further pursued. Since emotional impairments are connected to negative symptoms such as blunted affect and influence the course of illness from the onset on (8, 23, 55, 88), it would be important to focus on emotion recognition and early detection, especially regarding young individuals with SSD.

In some studies, the impaired recognition of positive emotions was found to be a prominent deficit in individuals with schizophrenia (34, 89) and significant group differences between individuals with SSD and healthy individuals were only limited to positive emotions like happiness (55, 56, 84). Tsoi et al. (89) showed that recognizing happy faces was more impaired than recognizing sad or fearful faces in a sample with individuals with schizophrenia. It could be shown that the perception of happy and sad emotions also relates differently to significant illness parameters such as age, intelligence quotient (IQ), cumulated time in hospital and negative symptoms (7, 48, 90). This supports the idea of the existence of an emotion-specific deficit in the perception of emotions in individuals with schizophrenia and of at least two separate neurobiological pathways for processing positive and negative emotions (18, 48, 89, 91–95). The inconsistencies of the findings on differential abilities to recognize positive vs. negative affect states could also be due to methodological, stimuli and sampling differences or other as yet unknown variables (18, 56).

Implications for Future Research and Future Practice

Despite the needs and hopes for therapeutic interventions in the field of emotion recognition for individuals with SSD, many aspects in this field of research must be further clarified in future studies. Finally, a study design with a larger sample to follow up on the investigated predictors within the framework of our exploratory study would be helpful. This study initially pursued an exploratory approach to shed more light on the associations between negative symptoms and emotion recognition. Each significant correlation between a negative symptom and a CANTAB variable was tested as a linear regression model by including the significant covariates in the regression models. The nominal significances of our exploratory study did not withstand Bonferroni correction for multiple tests, which was performed despite a not sufficient sample size for statistical completeness in the exploratory approach. Nevertheless, this explorative approach yielded results that can be built upon in follow-up studies with larger sample sizes, additional measurement instruments, and covariates. The correlation matrix (see **Figure 1**) shows significant within-correlations of all negative symptoms, some of which remain significant even after Bonferroni correction (see **Supplementary Material**). Therefore, the question arises whether the individual negative symptoms can even independently predict the ERT variables. Also, a larger sample could be used to calculate additional regression models in which all negative symptoms are included in future studies.

For covariate analysis, multiple linear regressions were run to examine the effect of each potential covariate on each CANTAB variable in our sample. Due to the initially exploratory approach of our study with a small sample size, the analyses were initially performed with a limited and selected number of covariates to control for. The variables that were expected to be most informative in the context of the study were diagnosis, gender, age, and education, as these include biological and cognitive components. The antipsychotic medication of the patients was systematically recorded and can be seen in **Table 2**. Due to the exploratory approach of our study with a small sample and the heterogeneity in medication, we did not statistically control for these. Since it could be

shown that emotion recognition is relatively independent of the influence of antipsychotics (34–36) and most antipsychotics of our sample belonged to second generation antipsychotics with only a minor influence on negative symptoms and cognitive functions (96), medication was considered as a negligible influence factor concerning the sample size. However, the heterogeneity of the collected medication in our sample reflects the treatment of patients with SSD for generalizability of the results. To allow generalizability of our study sample in this exploratory approach, we wanted to recruit as heterogeneous a cohort as possible, which also reflects a realistic representation of individuals with SSD in the inpatient and outpatient setting. In a large-scale follow-up study based on our results, further covariates like neurocognition, positive symptoms, medication and duration of illness and hospitalization should be therefore considered. A distinction between individuals with schizophrenia, schizoaffective disorders, and other diagnoses of SSD especially according to the ICD-11 classification regarding emotion recognition would be also of interest for future research in a larger sample. To reach the potential of personalized medicine, associations with the severity of predominant symptom manifestations should also be further illuminated in the framework of larger samples (34).

Additionally different measurements for negative symptoms are needed to ensure comparability. We initially chose the PANSS as the primary rating tool for negative symptoms within the framework of an explorative approach for the purpose of comparability with previous studies, especially older studies and due to inconsistencies in literature. The PANSS is a still frequently used external rating instrument in clinical studies. However, the limitations of the PANSS with respect to the nature of the negative symptom domains must certainly be considered in the interpretation of the results. Thus, as already mentioned, in factor analyses difficulty in abstract thinking (N5) and stereotyped thinking (N7) are attributed to the cognitive symptom domain (56) and difficulty in abstract thinking (N5) can be also accounted to the domain of disorganization (71). New generation scales like BNSS, CAINS and NSA should be included in follow-up studies to assess negative symptoms for an even broader understanding of their relationships with social cognition. Since most of the scales evaluate the behavioral side of negative symptoms, while the emotion recognition tasks assess the subjective experience, the new Self-evaluation of Negative Symptoms (SNS) (97) as a self-rating instrument would be an option for an additional perspective. Another alternative measure to be included is the recently introduced PANSS Autism Severity Score (PAUSS) (98, 99). The PAUSS is a score obtained from – essentially – the negative scale of the PANSS aimed to resemble autism spectrum disorder features in people with schizophrenia. It is a new construct with respect to autism conceptualized by classical continental psychopathology, as in the Autism Rating Scale (ARS) (100) and has already been studied in relation to social cognition (98).

Another reason for using the PANSS for our study was the ERT-CANTAB as an already relatively new measurement instrument to be chosen to capture emotion recognition. Hereby an advantage is the feasibility on a tablet and the thereby simple manageability. In addition, in studies by Glenthøj et al. (21) ERT-CANTAB was used in UHR for psychosis, so that in follow-up studies these individuals could be also included regarding the fact that impairments in emotion recognition and negative symptoms can already be determined before the onset of other symptoms (10, 11). However, different survey instruments for emotion recognition should be considered in follow-up studies to obtain a better insight independent of the measurement instrument. A comparison should therefore be made with likewise established measurement instruments for emotion recognition such as the Facial Emotion Identification Test (FEIT) (95), the Bell-Lysaker Emotion Recognition Task (BLERT) (101) or The Awareness of Social Inference Test (TASIT) (102). A systematic comparison of the measurement instruments would be of great benefit for clarifying the inconclusive results in literature. Research should be also expanded on all modalities of emotion recognition impaired in individuals with SSD (7, 15), including visual, verbal, and auditory channels (15). In addition, a longitudinal study and a study design for causality statements would be useful.

Consequently, impairments identified in the subdomains of negative symptoms and emotion recognition should be considered for early detection and individualized treatment as one of the research goals in social cognition in individuals with SSD, considering the enormous social burden. For example, specific interaction and emotion recognition training for a subgroup of individuals with specific profiles of negative symptoms, for instance in analogy to training programs for individuals with autism spectrum disorders (103, 104), could be developed to improve the recovery of individuals with SSD. Another treatment option that should be examined more closely in this area is the use of the neuropeptide oxytocin. In some studies, nasal oxytocin administration could improve the social performance of individuals with SSD (105).

Strength and Limitations

Concerning the size and selection of our exploratory study sample, larger diverse samples are needed to allow more precise analyses regarding the different variables. Our sample size calculations showed a sample size of 446 subjects required to detect a significant effect after correction for multiple testing. As could be expected, the nominal significances of our exploratory study did not withstand correction for multiple tests. Therefore, follow-up studies are necessary and recruitment for the present study is continued. Our research focused on negative symptoms, so we did not include positive symptom scores or total PANSS scores as well as further covariates like neurocognition. Only the CANTAB was used as a measurement instrument for emotion recognition. No comparison was made with other measurement instruments so that individual characteristics of the battery could have influenced the results. Additionally, different measurements for negative symptoms are needed to avoid bias and ensure comparability. Our results were collected in a cross-sectional design, so statements are limited to significant predictors in emotion recognition.

CONCLUSION

Conclusively in our exploratory study individuals with SSD and high scores of the negative symptoms blunted affect (N1), difficulty in abstract thinking (N5) and stereotyped thinking (N7) showed impairments in recognizing basic emotions and, here, particularly happiness. However, results must be weighed against the methodological limitations of the study and follow-up studies are necessary.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Charité's Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MZ, KB, NB, IH, AB, and JK designed and executed the study and conducted the data analyses. MZ wrote the article. TT, SR, EH, and MB collaborated with the design and editing of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

MZ is a participant in the BIH-Charité Junior Clinician Scientist Program funded by the Charité – Universitätsmedizin Berlin and the Berlin Institute of Health (BIH). In addition, the study was funded through the internal performance-based funding (LoM) of our research group at Charité – Universitätsmedizin Berlin.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.865226/full#supplementary-material

REFERENCES

1. Pelletier-Baldelli A, Holt DJ. Are negative symptoms merely the "real world" consequences of deficits in social cognition? *Schizophr Bull.* (2019) 46:236–41. doi: 10.1093/schbul/sbz095
2. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. *Nat Rev Neurosci.* (2015) 16:620–31. doi: 10.1038/nrn4005
3. Bora E, Yucel M, Pantelis C. Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. *Br J Psychiatry.* (2009) 195:475–82. doi: 10.1192/bjp.bp.108.055731
4. Gold J, Green M, Sadock B, Sadock V. *Comprehensive Textbook of Psychiatry*. Philadelphia: Lippincott Williams & Wilkins (2004).
5. Andrzejewska M, Wójciak P, Domowicz K, Rybakowski J. Emotion recognition and theory of mind in chronic schizophrenia: association with negative symptoms. *Arch Psychiatry Psychother.* (2017) 19:7–12. doi: 10.12740/APP/79878
6. Kraepelin E. *Dementia Praecox and Paraphrenia (R. Mary Barclay, Trans.)*. Edinburgh: Livingstone (1919).
7. Trémeau F, A. review of emotion deficits in schizophrenia. *Dialogues Clin Neurosci.* (2006) 8:59. doi: 10.31887/DCNS.2006.8.1/ftremeau
8. Gur RE, Kohler CG, Ragland JD, Siegel SJ, Lesko K, Bilker WB, et al. Flat affect in schizophrenia: relation to emotion processing and neurocognitive measures. *Schizophr Bull.* (2006) 32:279–87. doi: 10.1093/schbul/sbj041
9. Marder SR, Galderisi S. The current conceptualization of negative symptoms in schizophrenia. *World Psychiatry.* (2017) 16:14–24. doi: 10.1002/wps.20385
10. Yung AR, Nelson B, McGorry PD, Wood SJ, Lin A. Persistent negative symptoms in individuals at ultra high risk for psychosis. *Schizophr Res.* (2019) 206:355–61. doi: 10.1016/j.schres.2018.10.019
11. Corcoran C, Keilp J, Kayser J, Klim C, Butler P, Bruder G, et al. Emotion recognition deficits as predictors of transition in individuals at clinical high risk for schizophrenia: a neurodevelopmental perspective. *Psychol Med.* (2015) 45:2959. doi: 10.1017/S0033291715000902
12. Bell MD, Corbera S, Johannesen JK, Fiszdon JM, Wexler BE. Social cognitive impairments and negative symptoms in schizophrenia: are there subtypes with distinct functional correlates? *Schizophr Bull.* (2013) 39:186–96. doi: 10.1093/schbul/sbr125
13. Comparelli A, Corigliano V, De Carolis A, Mancinelli I, Trovini G, Ottavi G, et al. Emotion recognition impairment is present early and is stable throughout the course of schizophrenia. *Schizophr Res.* (2013) 143:65–9. doi: 10.1016/j.schres.2012.11.005
14. Bediou B, Asri F, Brunelin J, Krolak-Salmon P, D'Amato T, Saoud M, et al. Emotion recognition and genetic vulnerability to schizophrenia. *Br J Psychiatry.* (2007) 191:126–30. doi: 10.1192/bjp.bp.106.028829
15. Edwards J, Jackson HJ, Pattison PE. Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. *Clin Psychol Rev.* (2002) 22:789–832. doi: 10.1016/S0272-7358(02)00130-7
16. Bliksted V, Videbech P, Fagerlund B, Frith C. The effect of positive symptoms on social cognition in first-episode schizophrenia is modified by the presence of negative symptoms. *Neuropsychology.* (2017) 31:209. doi: 10.1037/neu0000309
17. Berndl K, Grüsser O-J, Martini M, Remschmidt H. Comparative studies on recognition of faces, mimic and gestures in adolescent and middle-aged schizophrenic patients. *Eur Arch Psychiatry Neurol Sci.* (1986) 236:123–30. doi: 10.1007/BF00454022
18. Bell M, Bryson G, Lysaker P. Positive and negative affect recognition in schizophrenia: a comparison with substance abuse and normal control subjects. *Psychiatry Res.* (1997) 73:73–82. doi: 10.1016/S0165-1781(97)00111-X
19. Germine LT, Garrido L, Bruce L, Hooker C. Social anhedonia is associated with neural abnormalities during face emotion processing. *Neuroimage.* (2011) 58:935–45. doi: 10.1016/j.neuroimage.2011.06.059
20. Gica S, Poyraz BC, Gulec H. Are emotion recognition deficits in patients with schizophrenia states or traits? a 6-month follow-up study indian. *J Psychiatry.* (2019) 61:45. doi: 10.4103/psychiatry.IndianJPsychiatry_307_18
21. Glenthøj LB, Albert N, Fagerlund B, Kristensen TD, Wenneberg C, Hjorthøj C, et al. Emotion recognition latency, but not accuracy, relates to real life functioning in individuals at ultra-high risk for psychosis. *Schizophr Res.* (2019) 210:197–202. doi: 10.1016/j.schres.2018.12.038
22. Glenthøj LB, Kristensen TD, Wenneberg C, Hjorthøj C, Nordentoft M. Investigating cognitive and clinical predictors of real-life functioning, functional capacity, and quality of life in individuals at ultra-high risk for psychosis. *Schizophr Bull.* (2020) 1:1. doi: 10.1093/schizbullopen/sgaa027

23. Goldman RS, Axelrod BN, Tandon R, Ribeiro SC, Craig K, Berent S. Neuropsychological prediction of treatment efficacy and one-year outcome in schizophrenia. *Psychopathology.* (1993) 26:122–6. doi: 10.1159/00028 4811
24. Andreasen NC. The evolving concept of schizophrenia: from kraepelin to the present and future. *Schizophr Res.* (1997) 28:105–9. doi: 10.1016/S0920-9964(97)00112-6
25. Correll CU, Schooler NR. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatr Dis Treat.* (2020) 16:519. doi: 10.2147/NDT.S225643
26. Charernboon T. Different subdomains of negative symptoms in clinically stable patients with schizophrenia: determining the nature of their relationships with emotion recognition, theory of mind and neurocognition. *Cogent Psychol.* (2020) 7:1849892. doi: 10.1080/23311908.2020.1849892
27. Bartholomeusz CF, Ganella EP, Labuschagne I, Bousman C, Pantelis C. Effects of oxytocin and genetic variants on brain and behaviour: implications for treatment in schizophrenia. *Schizophr Res.* (2015) 168:614–27. doi: 10.1016/j.schres.2015.06.007
28. Sergi MJ, Rassovsky Y, Widmark C, Reist C, Erhart S, Braff DL, et al. Social cognition in schizophrenia: relationships with neurocognition and negative symptoms. *Schizophr Res.* (2007) 90:316–24. doi: 10.1016/j.schres.2006.09.028
29. Mancuso F, Horan WP, Kern RS, Green MF. Social cognition in psychosis: multidimensional structure, clinical correlates, and relationship with functional outcome. *Schizophr Res.* (2011) 125:143–51. doi: 10.1016/j.schres.2010.11.007
30. Ventura J, Subotnik KL, Gitlin MJ, Gretchen-Doorly D, Ered A, Villa KF, et al. Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later. *Schizophr Res.* (2015) 161:407–13. doi: 10.1016/j.schres.2014.10.043
31. Chang WC, Tang JYM, Hui CLM, Wong GHY, Chan SKW, Lee EHM, et al. The relationship of early premorbid adjustment with negative symptoms and cognitive functions in first-episode schizophrenia: a prospective 3-year follow-up study. *Psychiatry Res.* (2013) 209:353–60. doi: 10.1016/j.psychres.2013.02.014
32. Evensen J, Røssberg JI, Barder H, Haahr U. ten Velden Hegelstad W, Joa I, et al. Flat affect and social functioning: a 10 year follow-up study of first episode psychosis patients. *Schizophr Res.* (2012) 139:99–104. doi: 10.1016/j.schres.2012.04.019
33. Hovington CL, Bodnar M, Joober R, Malla AK, Lepage M. Identifying persistent negative symptoms in first episode psychosis. *BMC Psychiatry.* (2012) 12:1–11. doi: 10.1186/1471-244X-12-224
34. Ruocco AC, Reilly JL, Rubin LH, Daros AR, Gershon ES, Tamminga CA, et al. Emotion recognition deficits in schizophrenia-spectrum disorders and psychotic bipolar disorder: findings from the bipolar-schizophrenia network on intermediate phenotypes (b-snip) study. *Schizophr Res.* (2014) 158:105–12. doi: 10.1016/j.schres.2014.07.001
35. Daros AR, Ruocco AC, Reilly JL, Harris MS, Sweeney JA. Facial emotion recognition in first-episode schizophrenia and bipolar disorder with psychosis. *Schizophr Res.* (2014) 153:32–7. doi: 10.1016/j.schres.2014 01.009
36. Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho B-C. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. *Biol Psychiatry.* (2010) 67:255–62. doi: 10.1016/j.biopsych.2009.08.040
37. Fett A-KJ, Maat A, Investigators G. Social cognitive impairments and psychotic symptoms: what is the nature of their association? *Schizophr Bull.* (2013) 39:77–85. doi: 10.1093/schbul/sbr058
38. Zierhut MM, Bernard RM, Turner E, Mohamad S, Hahn E, Bajbouj M. Electroconvulsive therapy for negative symptoms in schizophrenia: a literature review from 2000 to. current psychology. *Curr Psychol.* (2021):1–22. doi: 10.1007/s12144-021-01989-w
39. Leucht S, Barabássy Á, Laszlovszky I, Szatmári B, Acsai K, Szalai E, et al. Linking panss negative symptom scores with the clinical global impressions scale: understanding negative symptom scores in schizophrenia. *Neuropsychopharmacology.* (2019) 44:1589–96. doi: 10.1038/s41386-019-0363-2
40. Bighelli I, Rodolico A, García-Mieres H, Pitschel-Walz G, Hansen W-P, Schneider-Thoma J, et al. Psychosocial and psychological interventions for relapse prevention in schizophrenia: a systematic review and network meta-analysis. *Lancet Psychiatry.* (2021) 8:969–80. doi: 10.1016/S2215-0366(21)00243-1
41. Kurtz MM, Richardson CL. Social cognitive training for schizophrenia: a meta-analytic investigation of controlled research. *Schizophr Bull.* (2012) 38:1092–104. doi: 10.1093/schbul/sbr036
42. Penn DL, Roberts DL, Combs D, Sterne A. Best Practices: The development of the social cognition and interaction training program for schizophrenia spectrum disorders. *Psychiatr serv.* (2007) 58:449–51. doi: 10.1176/ps.2007.58.4.449
43. Schneider F, Gur RC, Gur RE, Shtasel DL. Emotional processing in schizophrenia: neurobehavioral probes in relation to psychopathology. *Schizophr Res.* (1995) 17:67–75. doi: 10.1016/0920-9964(95) 00031-G
44. Bozikas VP, Kosmidis MH, Anezoulaki D, Giannakou M, Karavatos A. Relationship of affect recognition with psychopathology and cognitive performance in schizophrenia. *J Int Neuropsychol Soc.* (2004) 10:549–58. doi: 10.1017/S1355617704104074
45. Catalan A, Gonzalez de. Artaza M, Bustamante S, Orgaz P, Osa L, Angosto V, et al. Differences in facial emotion recognition between first episode psychosis, borderline personality disorder and healthy controls. *PLoS ONE.* (2016) 11:e0160056. doi: 10.1371/journal.pone.0160056
46. Borod JC, Martin CC, Alpert M, Brozgold A, Welkowitz J. Perception of facial emotion in schizophrenic and right brain-damaged patients. *J Nerv Ment Dis.* (1993). doi: 10.1097/00005053-199308000-00004
47. Lewis SF, Garver DL. Treatment and diagnostic subtype in facial affect recognition in schizophrenia. *J Psychiatr Res.* (1995) 29:5–11. doi: 10.1016/0022-3956(94)00033-N
48. Silver H, Shlomo N, Turner T, Gur RC. Perception of happy and sad facial expressions in chronic schizophrenia: evidence for two evaluative systems. *Schizophr Res.* (2002) 55:171–7. doi: 10.1016/S0920-9964(01) 00208-0
49. Bellack AS, Blanchard JJ, Mueser KT. Cue availability and affect perception in schizophrenia. *Schizophr Bull.* (1996) 22:535–44. doi: 10.1093/schbul/22.3.535
50. Salem JE, Kring AM, Kerr SL. More evidence for generalized poor performance in facial emotion perception in schizophrenia. *J Abnorm Psychol.* (1996) 105:480. doi: 10.1037/0021-843X.105.3.480
51. Silver H, Shlomo N. Perception of facial emotions in chronic schizophrenia does not correlate with negative symptoms but correlates with cognitive and motor dysfunction. *Schizophr Res.* (2001) 52:265–73. doi: 10.1016/S0920-9964(00)00093-1
52. Wölwer W, Streit M, Gaebel W, Polzer U. Facial affect recognition in the course of schizophrenia. *Eur Arch Psychiatry Clin Neurosci.* (1996) 246:165–70. doi: 10.1007/BF02189118
53. Mueser KT, Doonan R, Penn DL, Blanchard JJ, Bellack AS, Nishith P, et al. Emotion recognition and social competence in chronic schizophrenia. *J Abnorm Psychol.* (1996) 105:271. doi: 10.1037/0021-843X.105.2.271
54. Mueser KT, Penn DL, Blanchard JJ, Bellack AS. Affect recognition in schizophrenia: a synthesis of findings across three studies. *Psychiatry.* (1997) 60:301–8. doi: 10.1080/00332747.1997.11024808
55. Sachs G, Steger-Wuchse D, Kryspin-Exner I, Gur RC, Katschnig H. Facial recognition deficits and cognition in schizophrenia. *Schizophr Res.* (2004) 68:27–35. doi: 10.1016/S0920-9964(03)00131-2
56. Larøi F, Fonteneau B, Mourad H, Raballo A. Basic emotion recognition and psychopathology in schizophrenia. *J Nerv Ment Dis.* (2010) 198:79–81. doi: 10.1097/NMD.0b013e3181c84cb0
57. Ekman P, Oster H. Facial expressions of emotion. *Annu Rev Psychol.* (1979) 30:527–54. doi: 10.1146/annurev.ps.30.020179.002523
58. Daniel DG. Issues in selection of instruments to measure negative symptoms. *Schizophr Res.* (2013) 150:343–5. doi: 10.1016/j.schres.2013.07.005
59. Ahmed AO, Kirkpatrick B, Granholm E, Rowland LM, Barker PB, Gold JM, et al. Two factors, five factors, or both? external validation studies of negative symptom dimensions in schizophrenia. *Schizophr Bull.* (2022) 10:148. doi: 10.1093/schbul/sbab148

60. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (panss) for schizophrenia. *Schizophr Bull.* (1987) 13:261–76. doi: 10.1093/schbul/13.2.261
61. Barnett JH, Robbins TW, Leeson VC, Sahakian BJ, Joyce EM, Blackwell AD. Assessing cognitive function in clinical trials of schizophrenia. *Neurosci Biobehav Rev.* (2010) 34:1161–77. doi: 10.1016/j.neubiorev.2010.01.012
62. Foussias G, Agid O, Fervaha G, Remington G. Negative symptoms of schizophrenia: clinical features, relevance to real world functioning and specificity versus other cns disorders. *Eur Neuropsychopharmacol.* (2014) 24:693–709. doi: 10.1016/j.euroneuro.2013.10.017
63. Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR. The nimh-matrics consensus statement on negative symptoms. *Schizophr Bull.* (2006) 32:214–9. doi: 10.1093/schbul/sbj053
64. Remington G, Foussias G, Fervaha G, Agid O, Takeuchi H, Lee J, et al. Treating negative symptoms in schizophrenia: an update. *Curr Treat Options Psychiatry.* (2016) 3:133–50. doi: 10.1007/s40501-016-0075-8
65. Andreasen N. *Scale for the Assessment of Negative Symptoms (Sans).* Iowa City, LA: The University of Iowa (1984).
66. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The brief negative symptom scale: psychometric properties. *Schizophr Bull.* (2011) 37:300–5. doi: 10.1093/schbul/sbq059
67. Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The clinical assessment interview for negative symptoms (cains): final development and validation. *Am J Psychiatry.* (2013) 170:165–72. doi: 10.1176/appi.ajp.2012.12010109
68. Alphs L, Summerfelt A, Lann H, Muller R. The negative symptom assessment: a new instrument to assess negative symptoms of schizophrenia. *Psychopharmacol Bull.* (1989) 25:159–63.
69. Shamay-Tsoory SG, Shur S, Harari H, Levkovitz Y. Neurocognitive basis of impaired empathy in schizophrenia. *Neuropsychology.* (2007) 21:431. doi: 10.1037/0894-4105.21.4.431
70. Strauss GP, Keller WR, Buchanan RW, Gold JM, Fischer BA, McMahon RP, et al. Next-generation negative symptom assessment for clinical trials: validation of the brief negative symptom scale. *Schizophr Res.* (2012) 142:88–92. doi: 10.1016/j.schres.2012.10.012
71. Vignapiano A, Koenig T, Mucci A, Giordano GM, Amodio A, Altamura M, et al. Disorganization and cognitive impairment in schizophrenia: new insights from electrophysiological findings. *Int J Psychophysiol.* (2019) 145:99–108. doi: 10.1016/j.ijpsycho.2019.03.008
72. Kanchanatawan B, Thika S, Anderson G, Galecki P, Maes M. Affective symptoms in schizophrenia are strongly associated with neurocognitive deficits indicating disorders in executive functions, visual memory, attention and social cognition. *Prog Neuro-Psychopharmacol Biol Psychiatry.* (2018) 80:168–76. doi: 10.1016/j.pnpbp.2017.06.031
73. Horrocks M, Michail M, Aubeeluck A, Wright N, Morriss R. An electronic clinical decision support system for the assessment and management of suicidality in primary care: protocol for a mixed-methods study. *JMIR Res Protoc.* (2018) 7:e11135. doi: 10.2196/11135
74. Peralta V, Cuesta MJ. Psychometric properties of the positive and negative syndrome scale (panss) in schizophrenia. *Psychiatry Res.* (1994) 53:31–40. doi: 10.1016/0165-1781(94)90093-0
75. Levaux M-N, Potvin S, Sepehry AA, Sablier J, Mendrek A, Stip E. Computerized assessment of cognition in schizophrenia: promises and pitfalls of cantab. *Eur psychiatry.* (2007) 22:104–15. doi: 10.1016/j.eurpsy.2006.11.004
76. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophr Res.* (2004) 72:29–39. doi: 10.1016/j.schres.2004.09.007
77. Wright SP. Adjusted *P*-values for Simultaneous Inference. *Biometrics.* (1992) 48:1005–13. doi: 10.2307/2532694
78. Wallwork R, Fortgang R, Hashimoto R, Weinberger D, Dickinson D. Searching for a consensus five-factor model of the positive and negative syndrome scale for schizophrenia. *Schizophr Res.* (2012) 137:246–50. doi: 10.1016/j.schres.2012.01.031
79. Jiang J, Sim K, Lee J. Validated five-factor model of positive and negative syndrome scale for schizophrenia in chinese population. *Schizophr Res.* (2013) 143:38–43. doi: 10.1016/j.schres.2012.10.019
80. Backx R, Skirrow C, Dente P, Barnett JH, Cormack FK. Bringing home cognitive assessment: initial validation of unsupervised web-based cognitive testing on the cambridge neuropsychological test automated battery (cantab) using a within-subjects counterbalanced design. *J Med Internet Res.* (2020) 22:e16792. doi: 10.2196/preprints.16792
81. Won S, Lee WK, Kim S-W, Kim JJ, Lee BJ Yu J-C, et al. Distinct differences in emotional recognition according to severity of psychotic symptoms in early-stage schizophrenia. *Front Psychiatry.* (2019) 10:564. doi: 10.3389/fpsyt.2019.00564
82. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* 2nd ed. Hillsdale NJ: Erlbaum (1988).
83. Turetsky BI, Kohler CG, Indersmitten T, Bhati MT, Charbonnier D, Gur RC. Facial emotion recognition in schizophrenia: when and why does it go awry? *Schizophr Res.* (2007) 94:253–63. doi: 10.1016/j.schres.2007.05.001
84. Kohler CG, Bilker W, Hagendoorn M, Gur RE, Gur RC. Emotion recognition deficit in schizophrenia: association with symptomatology and cognition. *Biol Psychiatry.* (2000) 48:127–36. doi: 10.1016/S0006-3223(00)00847-7
85. Heimberg C, Gur RE, Erwin RJ, Shtasel DL, Gur RC. Facial emotion discrimination: Iii. behavioral findings in schizophrenia. *Psychiatry Res.* (1992) 42:253–65. doi: 10.1016/0165-1781(92)90117-L
86. Mueser KT, Curran PJ, McHugo GJ. Factor structure of the brief psychiatric rating scale in schizophrenia. *Psychol Assess.* (1997) 9:196. doi: 10.1037/1040-3590.9.3.196
87. Andreasen NC. *Scale for the Assessment of Positive Symptoms (Saps).* Iowa City: University of Iowa (1984).
88. Shtasel DL, Gur RE, Gallacher F, Heimberg C, Cannon T, Gur RC. Phenomenology and functioning in first-episode schizophrenia. *Schizophr Bull.* (1992) 18:449–62. doi: 10.1093/schbul/18.3.449
89. Tsoi DT, Lee K-H, Khokhar WA, Mir NU, Swalli JS, Gee KA, et al. Is facial emotion recognition impairment in schizophrenia identical for different emotions? a signal detection analysis. *Schizophrenia Res.* (2008) 99:263–9. doi: 10.1016/j.schres.2007.11.006
90. Norton D, McBain R, Holt DJ, Ongur D, Chen Y. Association of impaired facial affect recognition with basic facial and visual processing deficits in schizophrenia. *Biol Psychiatry.* (2009) 65:1094–8. doi: 10.1016/j.biopsych.2009.01.026
91. Berretz G, Wolf OT, Güntürkün O, Ocklenburg S. Atypical lateralization in neurodevelopmental and psychiatric disorders: what is the role of stress? *Cortex.* (2020) 125:215–32. doi: 10.1016/j.cortex.2019.12.019
92. Reuter-Lorenz P, Davidson RJ. Differential contributions of the two cerebral hemispheres to the perception of happy and sad faces. *Neuropsychologia.* (1981) 19:609–13. doi: 10.1016/0028-3932(81)90030-0
93. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception ii: implications for major psychiatric disorders. *Biol Psychiatry.* (2003) 54:515–28. doi: 10.1016/S0006-3223(03)00171-9
94. Kring AM, Kerr SL, Smith DA, Neale JM. Flat affect in schizophrenia does not reflect diminished subjective experience of emotion. *J Abnorm Psychol.* (1993) 102:507. doi: 10.1037/0021-843X.102.4.507
95. Kerr SL, Neale JM. Emotion perception in schizophrenia: specific deficit or further evidence of generalized poor performance? *J Abnorm Psychol.* (1993) 102:312. doi: 10.1037/0021-843X.102.2.312
96. Galderisi S, Mucci A, Dollfus S, Nordentoft M, Falkai P, Kaiser S, et al. Epa guidance on assessment of negative symptoms in schizophrenia. *Eur Psychiatry.* (2021) 64:1. doi: 10.1192/j.eurpsy.2021.11
97. Dollfus S, Mach C, Morello R. Self-evaluation of negative symptoms: a novel tool to assess negative symptoms. *Schizophr Bull.* (2016) 42:571–8. doi: 10.1093/schbul/sbv161
98. Deste G, Vita A, Nibbio G, Penn DL, Pinkham AE, Harvey PD. Autistic symptoms and social cognition predict real-world outcomes in patients with schizophrenia. *Front Psychiatry.* (2020) 11:524. doi: 10.3389/fpsyt.2020.00524
99. Deste G, Barlati S, Gregorelli M, Lisoni J, Turrina C, Valsecchi P, et al. Looking through autistic features in schizophrenia using the

panss autism severity score (pauss). *Psychiatry Res.* (2018) 270:764–8. doi: 10.1016/j.psychres.2018.10.074

100. Palumbo D, Stanghellini G, Mucci A, Ballerini M, Giordano GM, Lysaker PH, et al. Autism rating scale: a new tool for characterizing the schizophrenia phenotype. *Front Psychiatry.* (2021) 7:622359. doi: 10.3389/fpsyt.2021.622359
101. Bryson G, Bell M, Lysaker P. Affect recognition in schizophrenia: a function of global impairment or a specific cognitive deficit. *Psychiatry Res.* (1997) 71:105–13. doi: 10.1016/S0165-1781(97)00050-4
102. McDonald S, Flanagan S, Rollins J, Kinch J. Tasit: A new clinical tool for assessing social perception after traumatic brain injury. *J Head Trauma Rehabil.* (2003) 18:219–38. doi: 10.1097/00001199-200305000-00001
103. van Elst LT, Fangmeier T, Schaller UM, Hennig O, Kieser M, Koelkebeck K, et al. Faster and scott&eva trainings for adults with high-functioning autism spectrum disorder (Asd): study protocol for a randomized controlled trial. *Trials.* (2021) 22:1–19. doi: 10.1186/s13063-021-05205-9
104. Parpart H, Krankenhagen M, Albantakis L, Henco L, Friess E, Schilbach L. Schematherapie-informiertes, soziales interaktionstraining: interventionsansatz für erwachsene mit hochfunktionalem autismus. *Psychotherapeut.* (2018) 63:235–42. doi: 10.1007/s00278-018-0271-7
105. Averbeck B, Bobin T, Evans S, Shergill S. Emotion recognition and oxytocin in patients with schizophrenia. *Psychol Med.* (2012) 42:259–66. doi: 10.1017/S0033291711001413

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Psychiatry

MINI REVIEW
published: 12 May 2022
doi: 10.3389/fpsyt.2022.826692

Splitting Things Apart to Put Them Back Together Again: A Targeted Review and Analysis of Psychological Therapy RCTs Addressing Recovery From Negative Symptoms

*Hamish J. McLeod**

Institute of Health and Wellbeing, College of Medical Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom

Negative symptoms have attracted growing attention as a psychological treatment target and the past 10 years has seen an expansion of mechanistic studies and clinical trials aimed at improving treatment options for this frequently neglected sub-group of people diagnosed with schizophrenia. The recent publication of several randomized controlled trials of psychological treatments that pre-specified negative symptoms as a primary outcome warrants a carefully targeted review and analysis, not least because these treatments have generally returned disappointing therapeutic benefits. This mini-review dissects these trials and offers an account of why we continue to have significant gaps in our understanding of how to support recovery in people troubled by persistent negative symptoms. Possible explanations for mixed trial results include a failure to separate the negative symptom phenotype into the clinically relevant sub-types that will respond to mechanistically targeted treatments. For example, the distinction between experiential and expressive deficits as separate components of the wider negative symptom construct points to potentially different treatment needs and techniques. The 10 negative symptom-focused RCTs chosen for analysis in this mini-review present over 16 different categories of treatment techniques spanning a range of cognitive, emotional, behavioral, interpersonal, and metacognitive domains of functioning. The argument is made that treatment development will advance more rapidly with the use of more precisely targeted psychological treatments that match interventions to a focused range of negative symptom maintenance processes.

Keywords: negative symptoms, motivation, apathy, psychological treatment, recovery

OPEN ACCESS

Edited by:
Armida Mucci, University of Campania Luigi Vanvitelli, Italy

Reviewed by:
Stefano Barlati, University of Brescia, Italy
Marcel Riehle, University of Hamburg, Germany

***Correspondence:**
Hamish J. McLeod
hamish.mcleod@glasgow.ac.uk

Specialty section:
This article was submitted to Schizophrenia, a section of the journal Frontiers in Psychiatry

Received: *01 December 2021*
Accepted: *28 March 2022*
Published: *12 May 2022*

Citation:
McLeod HJ (2022) Splitting Things Apart to Put Them Back Together Again: A Targeted Review and Analysis of Psychological Therapy RCTs Addressing Recovery From Negative Symptoms. Front. Psychiatry 13:826692. doi: 10.3389/fpsyt.2022.826692

INTRODUCTION

Providing psychological therapies for paranoia and distressing hallucinations alongside pharmacotherapy and other medical treatments is now well-established in clinical guidelines (1) and there continues to be considerable innovation in the types of therapies being developed for positive symptoms [e.g. (2, 3)]. However, the negative symptoms of schizophrenia such as avolition-apathy and diminished expressive abilities

have remained a major source of distress and arrested recovery that frequently present a significant treatment challenge (4, 5). Furthermore, surveys of people with a diagnosis of schizophrenia suggest that loss of emotional engagement and low motivational drive are a high priority for treatment (6) but at present there are very few effective psychological or pharmacological treatment options (7–9). This lack of progress in the development of viable treatments is particularly frustrating as earlier meta-analytic evidence suggested that even general CBTp led to medium effect size reductions on negative symptoms [$d = 0.437$, 95% CI: 0.171–0.704; (10)]. Also, it has become clearer that negative symptoms fluctuate more than previously assumed (11), leading to renewed hope that psychological interventions could be deployed to accelerate recovery. Reasons for cautious optimism can be drawn from recent meta-analytic evidence that suggests psychological treatments for negative symptoms can be beneficial, although the effects are less substantial when trial quality is factored in (12). To help accelerate the refinement of viable treatment packages this mini-review set out to analyze a range of negative symptom treatment trials conducted in the past decade with the aim of identifying ways that the targeting of treatments could be improved in future studies. Psychological treatment RCTs with the pre-specified aim of evaluating effects on negative symptoms were selected for review and analysis. The eligible papers were closely scrutinized, descriptive information was extracted, and themes and patterns across the studies were explored. **Table 1** presents the key summary information from each paper with the emphasis placed on describing which negative symptoms were targeted, what therapeutic techniques were applied, the proposed mechanisms of therapeutic change, and the effects observed including acceptability and implementation outcomes such as attrition. Where the authors presented effect sizes these are reported to support description and comparison across studies.

ONE PROBLEM OR MANY? SUBDIVIDING THE NEGATIVE SYMPTOM CLINICAL PHENOTYPE

One feature of this set of studies is that there is considerable heterogeneity in the clinical profile of people recruited into the trials and just about every study specifies a different constellation of primary and co-primary outcomes. This is an important issue as it is recognized that negative symptoms are more helpfully understood as comprising at least two separable sub-factors (27, 28) and that a very similar clinical phenotype can be seen when withdrawal and isolative behaviors are secondary to different underlying mechanisms such as positive symptoms or medication side effects (4, 29). Although nine of the included studies set some threshold for negative symptom severity as part of trial eligibility, only three clearly specified patient exclusion criteria based on the co-presence of positive symptoms or depressive features. These variations in method also extend to the ways that the primary outcomes were measured with seven studies using established negative symptom scales (e.g. CAINS, PANSS, SANS, BNSS) and the remaining three studies using measures of global functioning, social functioning, or independent living skills. There were also variations in practice across studies using established negative symptom measures as the outcome with some using a composite score of all negative symptoms and others selecting relevant subscale scores that indexed the negative symptom domain of interest [e.g. Favrod et al. (23) combined SANS avolition-apathy and anhedonia-asociality subscale scores as their primary outcome of the PEPS intervention programme]. As a result, the selected set of papers do not describe findings for a clearly delineated group of people with negative symptoms.

WHAT WORKS, ON WHAT AND FOR WHOM?

Six of the 10 studies returned results suggestive of at least some impact of the tested therapies on the targeted primary outcomes and the effect sizes reported are of a similar magnitude to those presented in previous meta-analyses (10). However, in several instances both the intervention and control arm patients showed improvements, possibly suggesting that for some people with negative symptoms giving *any* kind of supportive contact may be beneficial (30). The past 10 years has also seen a substantial increase in the studies testing one of the main tenets of the cognitive model of negative symptoms (31)—that self-defeating cognitions are a key cause and maintenance factor (32, 33). As described in **Table 1** and depicted in **Figure 1**, helping people with negative symptoms to identify, challenge, and modify self-defeating beliefs is explicitly mentioned in eight of the 10 studies analyzed here. This is by far the most common strategy deployed across the studies. As highlighted in the mechanisms of change column of **Table 1**, two studies have supplementary analyses which suggest that modification of defeatist cognitions at least partially mediate treatment outcomes (15). The analysis of treatment mediators across other studies suggests that factors such as patient gender (20) and group climate (21) may also influence some treatment effects.

However, one of the key observations of this review is that understanding the mechanisms of change and the doses of therapy needed to produce beneficial effects is obscured by the extensive array of techniques, procedures, and therapy combinations that have been deployed to support people struggling to recover from negative symptoms. **Figure 1** portrays this information in schematic form and shows that while the treatment protocols tested to date may share some features (e.g. attention to reducing defeatist cognitions), heterogeneity of treatment packages is the norm. It should be noted that the constellation of treatment techniques and the domains of therapeutic action depicted in **Figure 1** does not fully capture all of the nuances and complex processes involved in the negative symptom therapy packages described. But, it does provide a framework for deconstructing and analyzing the psychological treatment methods that have been used to support people with negative symptoms. Splitting treatment packages into constituent parts provides one way of identifying testable hypotheses about plausible mechanisms of therapeutic change that can be then used to refine future therapy protocols.

TABLE 1 | A descriptive summary of selected psychological treatment RCTs with negative symptoms specified as a primary or co-primary outcome 2009–2021.

References	Sample Characteristics	Therapy Type, Format, and Dose	Outcomes Measured	Mechanism(s) of Change	Therapy Techniques	Observed Effects	Reported Primary Outcome Effect Size
Klingberg et al. (13) Germany	198 people (44% female) with a SCID DSM-IV diagnosis of schizophrenia and at least one moderate severity PANSS negative syndrome factor and no PANSS positive or depression symptom score $\geq$ 6.	Two active treatment arms CBT vs. Cognitive Remediation delivered individually. Two phase modular CBT: Phase 1—psychoeducation, destigmatizing, and development of shared formulation. Phase 2—two out of five modules based on patient needs (e.g. support with planning, social skills) Twenty session over 9 months. Mean number of sessions: *CBT* = 16.6; *CR* = 13.7	Primary outcome was total PANSS Modified Negative Symptom Score (MNS; items N1, N2, N3, N4, N6, G7, G16) at 12 months post enrolment. Secondary outcomes were SANS subscale scores.	Social skills training Modification of self-defeating thought patterns Improvement of neurocognitive abilities	CBT: Shared formulation, improving self-understanding and acceptance, social skills training and feedback, Modifying expectations of failure. CR: Restitution and compensation based cognitive training focused on attention, memory, and executive functions.	No difference on primary outcome for CBT vs. CR. Both conditions improved.	Pre-post change on PANSS-MNS CBT $d = -0.42$ (95% CI: −0.70 to −0.13) CR $d = -0.53$ (95% CI: −0.82 to −0.25)
Grant et al. (14) USA	60 people with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. At least moderate severity rating on 2 SANS subscales or marked severity on 1 subscale. Mean neurocognitive profile at least −1 SD below normal.	Individual outpatient sessions delivered weekly for 18 months. Average dose 50.5 sessions (range 16 to 81 sessions).	Clinician rated single item Global Assessment Scale (GAS) at post-treatment (18 months after randomization). Secondary outcomes were SANS subscale total scores and total SAPS score.	Modifying defeatist beliefs about reduced cognitive capacity, reduced behavioral competence, and reduced emotional competence [see Staring et al. (15)]	Collaborative goal setting, activity scheduling, behavioral experiments, challenging defeatist cognitions.	CBT treated patients showed greater improvement on Global Assessment of Functioning.	CT group GAS score $d = -1.36$ SANS Apathy $d = -0.66$.
Granholm et al. (16) USA	149 people with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. No inclusion restrictions based on symptom profile.	Cognitive Behavioural Social Skills Training (CBSST) delivered in 36 weekly 2-h group sessions over 9 months. Monthly booster sessions were offered during 12-month post-treatment follow-up.	Primary outcome was self-reported functioning on the Independent Living Skills Survey (ILSS) at 9 months.	Asocial beliefs and defeatist performance beliefs (17)	Thought identification and change processes (e.g. 3c's), structured problem solving skills training, supported goal setting	CBSST arm showed significant improvements on the primary outcome. Retention was low across both the active and control treatment arms (54% retained at 9 months)	ILSS at 9 months d=0.55

(Continued)

TABLE 1 | Continued

References	Sample Characteristics	Therapy Type, Format, and Dose	Outcomes Measured	Mechanism(s) of Change	Therapy Techniques	Observed Effects	Reported Primary Outcome Effect Size
Velligan et al. (18) USA	51 people with schizophrenia marked by clinically meaningful and persistent negative symptoms and no more than moderate positive symptoms, mild depression, and no significant movement disorder.	MOtiVation and Engagement (MOVE) Training—a manualized community delivered individual treatment. Sessions last for approximately 90 min once per week over 9 months.	Primary outcome was negative symptom assessed with the Negative Symptom Assessment 16 (NSA-16). The CAINS and BNSS were used in secondary analyses.	Negative symptoms are viewed as defense against the distress associated with judging the self as unable to cope. Maintenance cycles are established where atrophy of the capacity for initiation of behavior exacerbates loss of competence and self-confidence.	Five targeted domains of intervention including: Goal setting; social-cognitive skill rehearsal including social cue processing and social reciprocity; re-activation of leisure interests; anticipating and rating pleasure experiences; and linking of action plans to personally meaningful goals.	MOVE treated patients showed improvements on negative symptom measures at 9 months (post-treatment) compared to standard care.	
Priebe et al. (19) UK	275 people with an ICD diagnosis of schizophrenia and PANSS negative symptom subscale score ≥18.	20 sessions of body psychotherapy delivered in group format twice weekly for 10 weeks.	Primary outcome was PANSS negative symptom scale score immediately post treatment.	Gender (20) Group Climate (21)	Structured group tasks to strengthen awareness of the self, one's body, the boundaries between the self and others, and the use of movement as a mode of expression.	No difference between body psychotherapy and an active control (Pilates) on PANSS negative symptom score at post treatment. Improvements on expressive symptoms are small and not clinically meaningful.	
Mueller et al. (22) Switzerland	61 people with severe negative symptoms	Integrated Neurocognitive Therapy (INT)—a manualized CRT approach delivered over 15 weeks in group format. Organized into four therapy modules addressing 11 NIMH-MATRICS neurocognitive and social cognition problems.	Primary outcome was reduction of negative symptoms measured with the PANSS using Remission in Schizophrenia Working Group (RSWG) thresholds. Secondary outcomes included GAF and neurocognitive measures (e.g. Wisconsin Card Sorting Test).	Severe negative symptoms are argued to be under-pinned by neurocognitive deficits and problems with social cognition which may be targeted through structured remediation strategies.	Therapy techniques teach cognitive coping strategies (compensation), repeated skill practice (restitution), and *in vivo* application (generalization and "real-world" practice).	A significantly greater proportion of INT treated participants showed remission of severe negative symptoms at 3 months compared to standard care. Remission rate at 12 months showed a trend in favor of INT.	PANSS negative symptom score change at 3 months $d = 0.31$.
Favrod et al. (23) Switzerland	80 people with ICD diagnosis of schizophrenia (F20 or F25) and who scored at least 2 on the SANS Anhedonia scale.	8 x 60-min Positive Emotions Programme for Schizophrenia (PEPS) group treatment sessions for 5–8 patients.	Primary outcome was combined SANS avolition-apathy and anhedonia-asociality subscale scores.	Training of positive emotion regulation skills such as savoring, anticipation of pleasure, emotional expression training, challenging defeatist cognitions	Didactic and experiential delivery in group format. Verbally describing and sharing pleasant experiences	Primary outcome of combined SANS apathy-anhedonia scores improved in the treatment arm. Secondary outcomes of improved consummatory pleasure experiences also improved	Combined SANS apathy and anhedonia subscale scores $d = -0.55$.

(Continued)

TABLE 1 | Continued

References	Sample Characteristics	Therapy Type, Format, and Dose	Outcomes Measured	Mechanism(s) of Change	Therapy Techniques	Observed Effects	Reported Primary Outcome Effect Size
Pos et al. (24) Netherlands	99 people in early phase of psychosis with DSM-IV-TR diagnosis of a schizophrenia spectrum disorder. Social withdrawal scores on PANSS and BNSS had to be at least in the mild range to be eligible for inclusion.	Combined group (8 sessions) and individual treatment (6 sessions) delivered over 3 months. 16 to 20 sessions.	Co-primary outcomes were Social Withdrawal scores on the PANSS and Brief Negative Symptom Scale score total and asociality scores.	Challenging defeatist beliefs and reducing self-stigma.	Psychoeducation, developing social goals, problem solving guidance	Both the intervention and control arm improved over time. Twenty percent attrition in active treatment vs. 30% in control.	
Buchanan et al. (25) USA	62 people with DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder. SANS asociality item needed to score $\geq$ 2 at baseline.	Four six session modules delivered over 24 weeks with repetition of each session to compensate for learning problems (total dose = 48 sessions). Treatment arm patients received intranasal oxytocin; controls received a placebo.	Birchwood Social Functioning Scale (BSFS) was the primary outcome at 24 weeks.	Enhancing social-affiliative information processing through exogenous oxytocin	Behavioral social skills practice, motivational interviewing, behavioral self-regulation strategy support, problem solving skills training	No post treatment between group differences in social functioning, defeatist beliefs, asocial beliefs.	-
Granholm et al. (26) USA	55 people with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder with moderate to severe negative symptoms on the CAINS (total score $\geq$19). People with severe positive symptoms or depression were ineligible.	25 twice weekly 1 h group sessions for 12.5 weeks. Mean number of sessions attended was 8.65 (*SD* = 8.16 sessions) out of 25.	Total negative symptom scores (CAINS and SANS).	Modification of defeatist cognitions and augmentation of capacity to use psychological therapy through targeted cognitive remediation.	Cognitive-behavioural social skills training augmented with up to 8 sessions of cognitive remediation strategies focused on attention, prospective memory, and learning.	Main effect on SANS total at end of treatment (12 weeks) was mostly due to improvements on SANS Diminished Motivation score. Attrition was very high with 42% drop out in active treatment and 45% in standard care.	CAINS total $r = -0.09$; SANS total $r = -0.22$; SANS Diminished motivation $r = -0.24$.

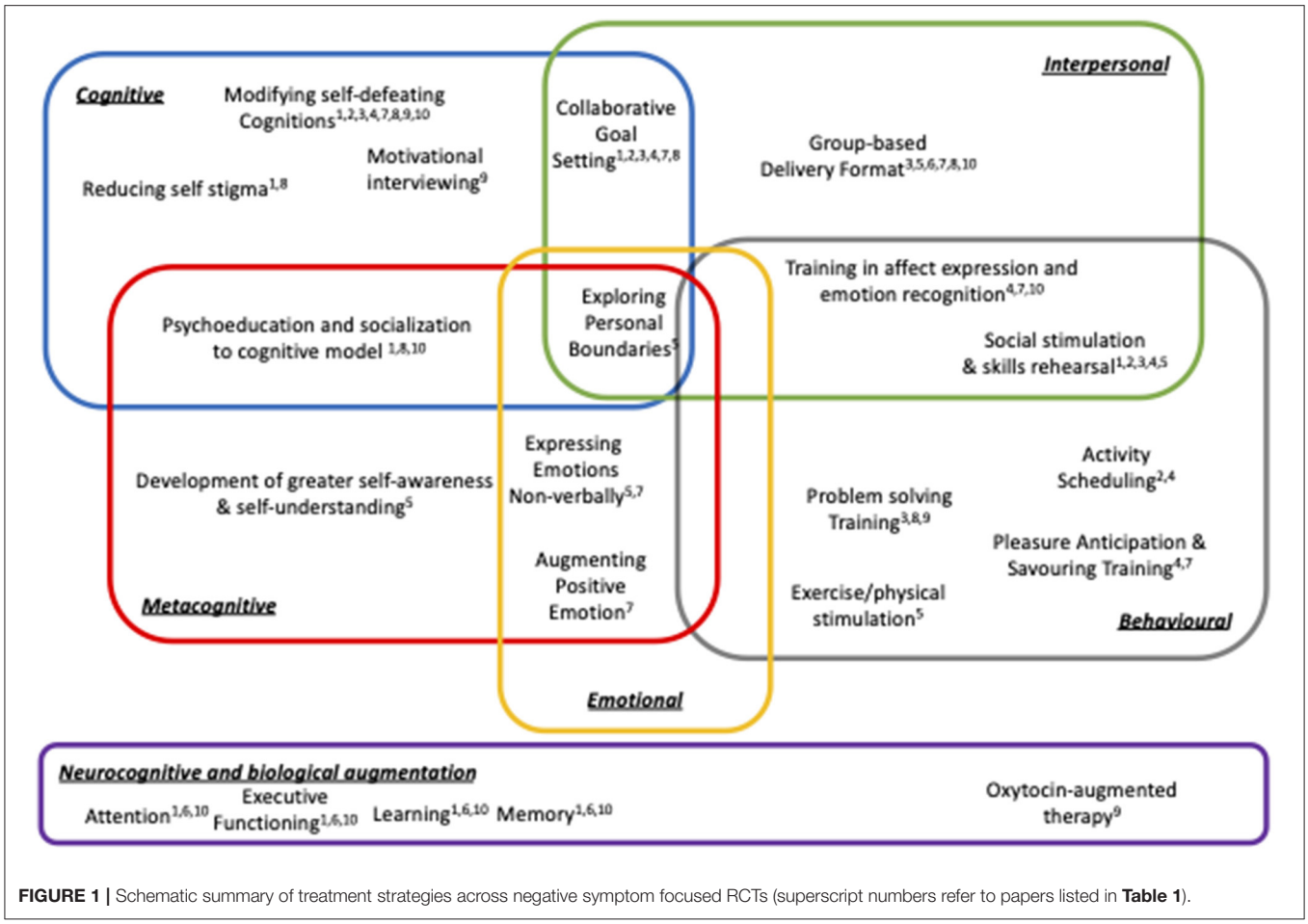


FIGURE 1 | Schematic summary of treatment strategies across negative symptom focused RCTs (superscript numbers refer to papers listed in **Table 1**).

SPLITTING THINGS APART

To advance our understanding of promising psychological treatment strategies for negative symptoms the therapeutic procedures described in each of the trials was "split apart" into constituent techniques. In some trials there was a clear link between the therapy techniques and the underlying theory of symptom formation and/or maintenance. For example, eliciting and challenging defeatist cognitions is a core feature of the dominant CBT model of negative symptoms and this leads to use of strategies such as belief modification and associated behavioral experiments. But, in other trials the link between the techniques and mechanisms of change were more opaque, or there were compound techniques that involved a mixture of potential change processes. **Figure 1** depicts five overlapping categories of intervention that addressed cognitive, interpersonal, emotional, behavioral, and metacognitive domains. These are underpinned by a sixth neurocognitive/biological domain which has been introduced in a number of trials to convey how neural factors may provide a substrate that can constrain the potential for recovery (34, 35). By mapping the variety of therapy techniques reported across studies to this framework we can also see that some therapeutic strategies will require the operation of overlapping systems. For example, successfully exploring personal boundaries described in Body Oriented Psychotherapy may involve successful coordination of metacognitive, interpersonal, emotional and behavioral systems and a breakdown in any one domain may make it difficult for a person to fully capitalize on therapy. Other therapeutic strategies may be simpler to implement because they make less complex demands on the patient and can be structured and scaffolded by a therapist (e.g. activity scheduling). Hence, **Figure 1** summarizes the candidate processes involved in supporting recovery from negative symptoms and tries to capture some of the reasons why the understanding of psychological treatment for negative symptoms is still very much a work in progress.

This approach to refining negative symptom treatments is warranted given the evidence that psychological treatments for positive psychotic symptoms have advanced through the use of causal manipulationist techniques that specify and modify psychological processes causally related to the clinical phenomenon of interest (2, 36). Currently the negative symptom treatment literature is dominated by multicomponent treatments, some elements of which are offshoots of experimental studies, but the specification of mechanistic targets is often incomplete. Next generation psychological treatment studies for negative symptoms are likely to benefit from a more explicit bottom-up development approach (37).

PUTTING THINGS BACK TOGETHER AGAIN

A symptom rather than syndrome focus has been highly successful for psychological treatment research over the past 30 years (38) and in psychosis treatment studies the focus on specific symptoms has driven several therapy refinements (39). In some notable instances, treatment trials focused on discrete symptoms such as command hallucinations have produced some of the largest treatment effect sizes in the literature (40). When considering which negative symptoms to focus on in future treatment development, the current evidence suggests that at least the experiential and expressive subdomains should be treated as different types of problems in need of suitably tailored treatment approaches (41). The therapeutic value of more precisely matching treatments strategies to problem subtypes is beginning to be shown by meta-analytic results which suggest that CBT may be more effective for amotivation while cognitive remediation approaches may address problems of diminished expression (12). Future success in improving treatments will also be helped by following consensus guidelines that support the assessment and appropriate sub-classification of persistent, predominant, prominent, primary, and secondary negative symptoms (42). However, in taking specific symptom focused approach it is also important that future negative symptom treatment development does not lose sight of the whole person receiving care. In addition to "splitting things apart" to target specific symptoms we must also ensure that treatments also use person-centered formulation to help re-construct the fragmented self-experience that underpins schizophrenia (43). As highlighted in **Figure 1**, a number of the therapeutic strategies evident in existing treatment protocols are likely to be beneficial because they enrich the persons capacity to understand themselves, the boundary between the self and other people, and the operation of key experiences such as emotional self-regulation and the modulation of social interactions. Supporting these integrative processes is likely to be a necessary component of any successful psychosis intervention (44). This maps to the process of individual case formulation which has been shown to enhance the outcome of CBT for hallucinations (45) and may be particularly relevant to the improvement of interventions for negative symptoms. For example, some people with negative symptoms exhibit such severe disturbances of metacognitive functioning that they may find it extraordinarily difficult to even think about and reflect on their own mental state (46). Matching therapeutic techniques to both the reflective and neurocognitive capacities of the patient provides a way to help people with problematic negative symptoms regain the ability to link their ongoing experiences into the autobiographical narrative needed to support effective social and interpersonal functioning (47, 48). An important challenge for the next phase of negative symptom treatment development will be to convert the increasingly refined set of models used to understand specific negative symptoms into targeted and personalized therapies.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

1. Killaspy H, Baird G, Bromham N, Bennett A, Guideline Committee. Rehabilitation for adults with complex psychosis: summary of NICE guidance. *BMJ.* (2021) 372:n1. doi: 10.1136/bmj.n1
2. Freeman D, Emsley R, Diamond R, Collett N, Bold E, Chadwick E, et al. Comparison of a theoretically driven cognitive therapy (the Feeling Safe Programme) with befriending for the treatment of persistent persecutory delusions: a parallel, single-blind, randomised controlled trial. *Lancet Psychiatry.* (2021) 8:696–707. doi: 10.1016/S2215-0366(21)00158-9
3. Garety P, Edwards CJ, Ward T, Emsley R, Huckvale M, McCrone P, et al. Optimising AVATAR therapy for people who hear distressing voices: study protocol for the AVATAR2 multi-centre randomised controlled trial. *Trials.* (2021) 22:366. doi: 10.1186/s13063-021-05301-w
4. Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. *Lancet Psychiatry.* (2018) 5:664–77. doi: 10.1016/S2215-0366(18)30050-6
5. Aleman A, Lincoln TM, Bruggeman R, Melle I, Arends J, Arango C, et al. Treatment of negative symptoms: where do we stand, and where do we go? *Schizophr Res.* (2016) 186:55–62. doi: 10.1016/j.schres.2016.05.015
6. Sterk B, Winter RI, Muis M, Haan L de. Priorities, satisfaction and treatment goals in psychosis patients: an online consumer's survey. *Pharmacopsychiatry.* (2013) 46:88–93. doi: 10.1055/s-0032-1327732
7. Fusar-Poli P, Papanastasiou E, Stahl D, Rocchetti M, Carpenter W, Shergill S, et al. Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. *Schizophr Bull.* (2015) 41:892–9. doi: 10.1093/schbul/sbu170
8. Velthorst E, Koeter M, Gaag M van der, Nieman DH, Fett AKJ, Smit F, et al. Adapted cognitive–behavioural therapy required for targeting negative symptoms in schizophrenia: meta-analysis and meta-regression. *Psychol Med.* (2014) 45:453–65. doi: 10.1017/S0033291714001147
9. Lutgens D, Gariepy G, Malla A. Psychological and psychosocial interventions for negative symptoms in psychosis: systematic review and meta-analysis. *Br J Psychiatr.* (2017) 210:324–32. doi: 10.1192/bjp.bp.116.197103
10. Wykes T, Steel C, Everitt B, Tarrier N. Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. *Schizophr Bull.* (2008) 34:523–37. doi: 10.1093/schbul/sbm114
11. Savill M, Banks C, Khanom H, Priebe S. Do negative symptoms of schizophrenia change over time? A meta-analysis of longitudinal data. *Psychol Med.* (2014) 45:1613–27. doi: 10.1017/S0033291714002712
12. Riehle M, Böhl MC, Pillny M, Lincoln TM. Efficacy of psychological treatments for patients with schizophrenia and relevant negative symptoms: a meta-analysis. *Clin Psychol Eur.* (2020) 2:1–23. doi: 10.32872/cpe.v2i3.2899
13. Klingberg S, Wittorf A, Herrlich J, Wiedemann G, Meisner C, Buchkremer G, et al. Cognitive behavioural treatment of negative symptoms in schizophrenia patients: study design of the TONES study, feasibility and safety of treatment. *Eur Arch Psychiatry Clin Neurosci.* (2009) 259:149–54. doi: 10.1007/s00406-009-0047-8
14. Grant PM, Huh GA, Perivoliotis D, Stolar NM, Beck AT. Randomized trial to evaluate the efficacy of cognitive therapy for low-functioning patients with schizophrenia. *Arch Gen Psychiatry.* (2012) 69:121. doi: 10.1001/archgenpsychiatry.2011.129
15. Staring ABP, Huurne M-AB ter, Gaag M van der. Cognitive behavioral therapy for negative symptoms (CBT-n) in psychotic disorders: a pilot study. *J Behav Ther Exp Psychiatry.* (2013) 44:300–6. doi: 10.1016/j.jbtep.2013.01.004

16. Granholm E, Holden J, Link PC, McQuaid JR. Randomized clinical trial of cognitive behavioral social skills training for schizophrenia: improvement in functioning and experiential negative symptoms. *J Consult Clin Psych.* (2014) 82:1173–85. doi: 10.1037/a0037098
17. Granholm E, Holden J, Worley M. Improvement in negative symptoms and functioning in cognitive-behavioral social skills training for schizophrenia: mediation by defeatist performance attitudes and asocial beliefs. *Schizophrenia Bull.* (2017) 44:653–61. doi: 10.1093/schbul/sbx099
18. Velligan DI, Roberts D, Mintz J, Maples N, Li X. A randomized pilot study of MOtiVation and Enhancement (MOVE) Training for negative symptoms in schizophrenia. *Schizophr Res.* (2015) 165:175–80. doi: 10.1016/j.schres.2015.04.008
19. Priebe S, Savill M, Wykes T, Bentall RP, Reininghaus U, Lauber C, et al. Effectiveness of group body psychotherapy for negative symptoms of schizophrenia: multicentre randomised controlled trial. *Br J Psychiatry.* (2016) 209:54–61. doi: 10.1192/bjp.bp.115.171397
20. Savill M, Orfanos S, Bentall R, Reininghaus U, Wykes T, Priebe S. The impact of gender on treatment effectiveness of body psychotherapy for negative symptoms of schizophrenia: a secondary analysis of the NESS trial data. *Psychiatry Res.* (2017) 247:73–8. doi: 10.1016/j.psychres.2016.11.020
21. Orfanos S, Priebe S. Group therapies for schizophrenia: initial group climate predicts changes in negative symptoms. *Psychosis.* (2017) 9:1–10. doi: 10.1080/17522439.2017.1311360
22. Mueller DR, Khalesi Z, Benzing V, Castiglione CI, Roder V. Does Integrated Neurocognitive Therapy (INT) reduce severe negative symptoms in schizophrenia outpatients? *Schizophr Res.* (2017) 188:92–7. doi: 10.1016/j.schres.2017.01.037
23. Favrod J, Nguyen A, Chaix J, Pellet J, Frobert L, Fankhauser C, et al. Improving pleasure and motivation in schizophrenia: a randomized controlled clinical trial. *Psychother Psychosom.* (2019) 88:84–95. doi: 10.1159/000496479
24. Pos K, Franke N, Smit F, Wijnen BFM, Staring ABP, Gaag MV der, et al. Cognitive behavioral therapy for social activation in recent-onset psychosis: randomized controlled trial. *J Consult Clin Psych.* (2019) 87:151–60. doi: 10.1037/ccp0000362
25. Buchanan RW, Kelly DL, Strauss GP, Gold JM, Weiner E, Zaranski J, et al. Combined oxytocin and cognitive behavioral social skills training for social function in people with schizophrenia. *J Clin Psychopharm.* (2021) 41:236–43. doi: 10.1097/JCP.0000000000001397
26. Granholm E, Twamley EW, Mahmood Z, Keller AV, Lykins HC, Parrish EM, et al. Integrated cognitive-behavioral social skills training and compensatory cognitive training for negative symptoms of psychosis: effects in a pilot randomized controlled trial. *Schizophr Bull.* (2021) 48:359–70. doi: 10.1093/schbul/sbab126
27. Marder SR, Kirkpatrick B. Defining and measuring negative symptoms of schizophrenia in clinical trials. *Eur Neuropsychopharmacol.* (2014) 24:737–43. doi: 10.1016/j.euroneuro.2013.10.016
28. Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull.* (2006) 32:214–9. doi: 10.1093/schbul/sbj053
29. Farreny A, Savill M, Priebe S. Correspondence between negative symptoms and potential sources of secondary negative symptoms over time. *Eur Arch Psy Clin N.* (2018) 268:603–9. doi: 10.1007/s00406-017-0813-y
30. Radhakrishnan R, Kiluk BD, Tsai J. A meta-analytic review of non-specific effects in randomized controlled trials of cognitive remediation for schizophrenia. *Psychiatr Q.* (2015) 87:57–62. doi: 10.1007/s11126-015-9362-6
31. Rector NA, Beck AT, Stolar N. The negative symptoms of schizophrenia: a cognitive perspective. *Can J Psychiatr.* (2005) 50:247–57. doi: 10.1177/070674370505000503
32. Luther L, Coffin GM, Firmin RL, Bonfils KA, Minor KS, Salyers MP, et al. test of the cognitive model of negative symptoms: associations between defeatist performance beliefs, self-efficacy beliefs, and negative symptoms in a non-clinical sample. *Psychiatry Res.* (2018) 269:278–85. doi: 10.1016/j.psychres.2018.08.016
33. Campellone TR, Sanchez AH, Kring AM. Defeatist performance beliefs, negative symptoms, and functional outcome in schizophrenia: a meta-analytic review. *Schizophr Bull.* (2016) 42:1343–52. doi: 10.1093/schbul/sbw026
34. Kring AM, Barch DM. The motivation and pleasure dimension of negative symptoms: Neural substrates and behavioral outputs. *Eur Neuropsychopharmacol.* (2014) 24:725–36. doi: 10.1016/j.euroneuro.2013.06.007
35. Kaiser S, Lyne J, Agartz I, Clarke M, Mørch-Johnsen L, Faerden A. Individual negative symptoms and domains – relevance for assessment, pathomechanisms and treatment. *Schizophr Res.* (2016) 186:39–45. doi: 10.1016/j.schres.2016.07.013
36. Brand RM, Rossell SL, Bendall S, Thomas N. Can we use an interventionist-causal paradigm to untangle the relationship between trauma, PTSD and psychosis? *Front Psychol.* (2017) 8:306. doi: 10.3389/fpsyg.2017.00306
37. Cristea IA, Vecchi T, Cuijpers P. Top-down and bottom-up pathways to developing psychological interventions. *Jama Psychiat.* (2021) 78:593–4. doi: 10.1001/jamapsychiatry.2020.4793
38. Costello CG. Research on symptoms versus research on syndromes. Arguments in favour of allocating more research time to the study of symptoms. *Br J Psychiatry.* (1992) 160:304–8. doi: 10.1192/bjp.160.3.304
39. Lincoln TM, Peters E. A systematic review and discussion of symptom specific cognitive behavioural approaches to delusions and hallucinations. *Schizophr Res.* (2019) 203:66–79. doi: 10.1016/j.schres.2017.12.014
40. Birchwood M, Michail M, Meaden A, Tarrier N, Lewis S, Wykes T, et al. Cognitive behaviour therapy to prevent harmful compliance with command hallucinations (COMMAND): a randomised controlled trial. *Lancet Psychiatry.* (2014) 1:23–33. doi: 10.1016/S2215-0366(14)70247-0
41. Strauss GP, Horan WP, Kirkpatrick B, Fischer BA, Keller WR, Miski P, et al. Deconstructing negative symptoms of schizophrenia: avolition-apathy and diminished expression clusters predict clinical presentation and functional outcome. *J Psychiatr Res.* (2013) 47:783–90. doi: 10.1016/j.jpsychires.2013.01.015
42. Galderisi S, Mucci A, Dollfus S, Nordentoft M, Falkai P, Kaiser S, et al. EPA guidance on assessment of negative symptoms in schizophrenia. *Eur Psychiat.* (2021) 64:e23. doi: 10.1192/j.eurpsy.2021.11
43. Lysaker PH, Minor KS, Lysaker JT, Hasson-Ohayon I, Bonfils K, Hochheiser J, et al. Metacognitive function and fragmentation in schizophrenia: relationship to cognition, self-experience and developing treatments. *Schizophr Res Cogn.* (2020) 19:100142. doi: 10.1016/j.scog.2019.100142
44. Leonhardt BL, Huling K, Hamm JA, Roe D, Hasson-Ohayon I, McLeod HJ, et al. Recovery and serious mental illness: a review of current clinical and research paradigms and future directions. *Expert Rev Neurother.* (2017) 17:1117–30. doi: 10.1080/14737175.2017.1378099
45. Turner DT, Burger S, Smit F, Valmaggia LR, Gaag M van der. What constitutes sufficient evidence for case formulation–driven CBT for psychosis? Cumulative meta-analysis of the effect on hallucinations and delusions. *Schizophr Bull.* (2020) 46:1072–85. doi: 10.1093/schbul/sbaa045
46. McLeod HJ, Gumley AI, MacBeth A, Schwannauer M, Lysaker PH. Metacognitive functioning predicts positive and negative symptoms over 12 months in first episode psychosis. *J Psychiatr Res.* (2014) 54:109–15. doi: 10.1016/j.jpsychires.2014.03.018
47. Berna F, Potheegadoo J, Aouadi I, Ricarte JJ, Allé MC, Coutelle R, et al. Meta-analysis of autobiographical memory studies in schizophrenia spectrum disorder. *Schizophr Bull.* (2015) 42:56–66. doi: 10.1093/schbul/sbv099
48. Edwards CJ, Garety PA, Hardy A. Remembering the past to live better in the future: a feasibility randomised controlled trial of memory specificity training for motivation in psychosis. *J Behav Ther Exp Psychiatry.* (2020) 68:101564. doi: 10.1016/j.jbtep.2020.101564

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Psychiatry

TYPE Systematic Review
PUBLISHED 21 September 2022
DOI 10.3389/fpsyt.2022.884828

OPEN ACCESS

EDITED BY
Joseph Ventura,
UCLA Department of Psychiatry,
United States

REVIEWED BY
Katharine Thakkar,
Michigan State University,
United States
Gianluca Ursini,
Lieber Institute for Brain Development,
United States
Armida Mucci,
University of Campania Luigi
Vanvitelli, Italy

*CORRESPONDENCE
Amir Valizadeh
thisisamirv@gmail.com

SPECIALTY SECTION
This article was submitted to
Schizophrenia,
a section of the journal
Frontiers in Psychiatry

RECEIVED 27 February 2022
ACCEPTED 16 August 2022
PUBLISHED 21 September 2022

CITATION
Valizadeh A, Mbwogge M, Rasouli
Yazdi A, Hedayati Amlashi N, Haadi A,
Shayestefar M and Moassefi M (2022)
The mirror mechanism in
schizophrenia: A systematic review
and qualitative meta-analysis.
Front. Psychiatry 13:884828.
doi: 10.3389/fpsyt.2022.884828

The mirror mechanism in schizophrenia: A systematic review and qualitative meta-analysis

Amir Valizadeh [1]*, Mathew Mbwogge [2], Anita Rasouli Yazdi [3], Nazanin Hedayati Amlashi [3], Ainaaz Haadi [3], Monir Shayestefar [1] and Mana Moassefi [1]

[1]Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran, [2]Independent Researcher, London, United Kingdom, [3]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Background: Mirror neuron system (MNS) consists of visuomotor neurons that are responsible for the mirror neuron activity (MNA), meaning that each time an individual observes another individual performing an action, these neurons encode that action, and are activated in the observer's cortical motor system. Previous studies report its malfunction in autism, opening doors to investigate the underlying pathophysiology of the disorder in a more elaborate way and coming up with new rehabilitation methods. The study of MNA function in schizophrenia patients has not been as frequent and conclusive as in autism. In this research, we aimed to evaluate the functional integrity of MNA and the microstructural integrity of MNS in schizophrenia patients.

Methods: We included case-control studies that have evaluated MNA in schizophrenia patients compared to healthy controls using a variety of objective assessment tools. In August 2022, we searched Embase, PubMed, and Web of Science for eligible studies. We used an adapted version of the NIH Quality Assessment of Case-Control Studies tool to assess the quality of the included studies. Evidence was analyzed using vote counting methods of the direction of the effect and was tested statistically using the Sign test. Certainty of evidence was assessed using CERQual.

Results: We included 32 studies for the analysis. Statistical tests revealed decreased MNA ($p = 0.002$) in schizophrenia patients. The certainty of the evidence was judged to be moderate. Investigations of heterogeneity revealed a possible relationship between the age and the positive symptoms of participants in the included studies and the direction of the observed effect.

Discussion: This finding contributes to gaining a better understanding of the underlying pathophysiology of the disorder by revealing its possible relation to some of the symptoms in schizophrenia patients, while also highlighting a new commonality with autism.

Systematic review registration: PROSPERO identifier: CRD42021236453.

KEYWORDS

mirror neuron activity, schizophrenia, meta-analysis, systematic review, schizophrenia spectrum disorder, mirror neuron system, mirror neurons

Introduction

Rationale

Mirror neuron system; An introduction

The mirror neuron system (MNS), which is a physiological substrate that may subserve certain mechanisms underlying social cognition has recently gained a lot of attention from the research community. MNS is a system consisting of visuomotor neurons that are responsible for the mirror mechanisms, meaning that each time an individual observes another individual performing an action, these neurons which encode that action, are activated in the observer's cortical motor system (1). Observed activations of this system are referred to as mirror neuron activity (MNA). MNA is considered a subdomain of social cognition (2). Several important functions beyond the action domain have been theorized for MNS, such as being a fundamental building block for understanding others' actions (3), encoding the intentions of the actor (4, 5), facilitating imitation (6, 7), and playing a role in human infants' ability to map similarities between self and others (8). Additionally, there has been an emphasis on the possible ties between MNA and empathy (9), and language (10). Mirror neurons were first discovered in the premotor area F5 of macaque monkeys (11). Later, similar neurons were found in the inferior parietal lobule, area PF, of macaque monkeys, and the concept of MNS was established (12). Some studies have claimed the discovery of similar neurons in various regions of the human brain, including the ventral premotor cortex (PMv) (13, 14), inferior frontal gyrus (IFG) (15–17), superior temporal sulcus (STS) (18–20), and inferior parietal lobule (IPL) (14, 21). In the meantime, some counter-arguments exist that question the function and even the very existence of the human MNS, with the strongest argument being the absence of single-cell recording data for human subjects (22). These counter-arguments were assuaged following single-cell recording studies in pre-surgical patients (23), the repetition suppression functional magnetic resonance imaging (fMRI) procedure in healthy volunteers (17), and lesion study in the human brain regions that have been proposed to be associated with human MNS (24). Nevertheless, MNS has been one of the most widely investigated domains of social cognition in psychiatric disorders within human beings. Even a recent paper by Heyes and Catmur (25) has called for more research on this phenomenon.

Other regions have also been proposed as an extension to MNS, one of the most important of them being the Brodmann area 2 (BA2) (26), which is the strongest generator of the mu rhythm (27). Mu rhythm (oscillations from 8 to 13 Hz) suppression has been proposed to be an indication of the MNA, as it is seen both when an individual performs and observes an action (28–30). A meta-analysis has demonstrated that there might also be other brain regions that do not have mirror properties but may convey necessary information to MNS including the primary visual cortex, supplementary motor area, dorsal premotor cortex, superior parietal lobe, cerebellum, and parts of the limbic system (31).

MNA in psychological disorders; Broken mirror theory and autism

In the context of psychological disorders, MNA has been mostly investigated in autism. This is due to the "broken mirror" hypothesis and its role in explaining the social and language deficits of this disorder (32). However, research has produced insufficient evidence to support this hypothesis in its pure form, and instead, two alternative models have been proposed: the EP-M model and the social top-down response modulation (STORM) model. The STORM model proposes that autism symptoms originate from abnormalities within the top-down regulation of the MNS, rather than within the MNS itself, while the EP-M model proposes that imitation behavior in autistic individuals is served by the pathways between brain areas associated with MNS (33). Nevertheless, both these alternative models also suggest that there might be some possible dysfunction in the MNA in these patients, either within the MNS itself or within the systems that regulate MNA (32, 33). The discovery of such dysfunction has opened the doors to investigate and explain the underlying pathophysiology of the disorder in a more elaborate way and to come up with new rehabilitation methods (34–36).

MNA dysfunction in schizophrenia and autism; A commonality?

Schizophrenia is one of the most debilitating and common neuropsychiatric disorders, with an estimated prevalence between 0.28 and 0.75% in the population worldwide (37–40). Deficits in a variety of cognitive domains are well-known for this disorder, such as impaired attention, verbal memory, and social cognition, and these are listed as specifiers for schizophrenia in the 11th revision of the International Classification of Diseases (ICD-11) (41). There are several reports of individuals with both autism and schizophrenia (42–45), which reveal that deficits in the theory of mind (ToM) exist in both disorders. Also, there are reports that both disorders share several genetic signals (46). A previous meta-analysis (47) of fMRI studies on autism and schizophrenia patients during ToM tasks revealed hypoactivation in the STS area, one of the main brain regions associated with MNA, in both groups, yet again emphasizing the deficits in ToM in both disorders, and possibly, hypothesizing the presence of MNA impairments in schizophrenia similar to the already known MNA impairments in autism patients.

MNA dysfunction might be another commonality between these disorders. Investigations of MNA in schizophrenia have

not been as profound and conclusive as in autism. Based on a recent review (48) that partly examined this subject, findings of the state of MNA function in schizophrenia are mixed, with some studies suggesting impaired MNA function in the patients, while others did not find such a phenomenon. If such dysfunction is proven to be present in schizophrenia patients, it might potentially serve for implementing new rehabilitation treatments based on MNA training, as such treatment options have been previously found in multiple reports to be beneficial for autism patients (49–53).

Objectives

To date, there has not been a systematic review with a qualitative analysis of studies that examine MNA/MNS in schizophrenia patients. Although a previous systematic review of the studies exists (54), that paper is a review of the evidence with little data analysis, and thus, considering the importance of the functions theorized to be associated with MNA, and the new studies published since that review, a new systematic examination of studies on this subject with a more in-depth analysis of the findings seems necessary. Results of such investigations may also help in gaining a more in-depth understanding of the mechanisms underlying schizophrenia and its possible common pathogenesis with autism. Specifically, we aim to evaluate the following:

- Primary objective: The functional integrity of MNA in schizophrenia patients. By functional integrity, we mean evaluating MNA using brain function measurement methods to investigate if it is identical to those in healthy control subjects.
- Secondary objective: The microstructural integrity of MNS in schizophrenia patients. By microstructural integrity, we mean evaluating MNS using brain microstructure evaluation methods to investigate if it is identical to those in healthy control subjects.

Methods

The design and methods used for this review comply with the Center for Reviews and Dissemination (CRD) Guidance for Undertaking Reviews in Healthcare (55), a guideline that presents rigor methods for undertaking systematic reviews, and Meta-analyses of Observational Studies in Epidemiology (MOOSE) (56), a guide on methods for conducting systematic reviews and meta-analyses specifically on observational studies. This review is reported in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (57) guideline. The review protocol has been published elsewhere (58).

Eligibility criteria

Eligibility criteria for including studies were informed using the SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, Research type) framework (59):

Sample: Patients of any age and sex diagnosed with schizophrenia or schizoaffective disorder confirmed by a physician in line with the International Classification of Diseases (ICD) or Diagnostic and Statistical Manual of Mental Disorders (DSM), irrespective of the severity or duration of illness, compared to healthy controls. Participants with any other macrostructural or functional neurologic disorders were excluded.

Phenomenon of interest: MNA and microstructural integrity of main brain regions (PMv, IFG, STS, IPL, and BA2) that are theorized to be associated with MNS.

Design: Observational case-control studies.

Evaluation:

- Functional methods: Electroencephalography (EEG), Magnetoencephalography (MEG), Transcranial magnetic stimulation (TMS), Electromyography (EMG), Proton Emission Tomography (PET), and Functional magnetic resonance imaging (fMRI). These methods are indirect measurements of what may reflect MNA, based on prior literature, as we cannot directly measure MNA in humans yet.
- Microstructural methods: Diffusion Tensor Imaging (DTI), Diffusion-Weighted Imaging (DWI), and Diffusion Spectrum Imaging (DSI). Only studies that specifically aimed to evaluate the microstructural integrity of the MNS were included.

Research type: Qualitative, quantitative, and mixed-methods.

Information sources and search strategy

In August 2022, AV searched Embase (*via* Ovid), PubMed, and Web of Science for eligible studies. We also carried out a "snowball" search through forward-citation and backward-citation tracking using Scopus on all of the included studies. Our search strategy is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature search extension (PRISMA-S) (60). No restriction or search filter was used. The search strategy is presented in Data sheet 1.

Selection process

Records were imported to EndNote version X9. NH and AH independently reviewed the titles and abstracts of

the retrieved records. AV was consulted to make the final decision in cases of disagreements. The full texts of all potentially eligible records were retrieved. MMb and AR independently screened full-text studies. A study was included when both reviewers independently assessed it as satisfying the inclusion criteria.

Data collection process

A data extraction form was developed, pilot tested, and then refined. After finalizing the data extraction form, MMb, AR, and MSh independently used it to extract data from eligible studies. Extracted data were compared, with any discrepancies being resolved through discussion. AV entered data into Microsoft Excel, double-checking them for accuracy. When information regarding any data was unclear, we contacted the authors of the reports to provide further details.

Data items

We extracted the following information from the included studies:

- Sample size and characteristics such as age, gender, handedness, and ethnicity;
- Inclusion and exclusion criteria of the study;
- Assessment tool information (paradigm class and equipment properties);
- Ethical considerations;
- Severity score of the disease;
- Brain regions with different activation patterns between patients and controls (for task-based fMRI, MEG, and PET);
- Results and conclusions of the study; and
- Funding sources and conflicts of interest.

Ethnicities were categorized according to the NIH Racial and Ethnic Categories (61). Severity scores included the Positive and Negative Syndrome Scale (PANSS) (62), the Scale for the Assessment of Negative Symptoms (SANS) (63), and the Scale for the Assessment of Positive Symptoms (SAPS) (64). To achieve a better comparison state, SANS and SAPS were converted to PANSS (65) scores.

Study methodological and reporting quality assessment

We used an adapted version of the NIH Quality Assessment Tool for Case-Control Studies (66). This tool is originally developed to evaluate the internal validity of case-control studies, is consisted of 11 questions, and assesses the following factors: risk of potential for selection bias, information bias, measurement bias, confounding, exposures occurring before outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, sufficient time frame to see an effect, and appropriate control for confounding. Using this tool, the overall methodological and reporting quality of a study should be judged as either poor, fair, or good.

After consensus, we made some changes to the tool, so it better suits our review. As sample size justification does not apply to our topic, we changed the third question to check if the authors included a considerable sample size. Considering the multimodal nature of this review, it was not possible to use power analysis to calculate the minimum required sample size for each study. Considering a recent analytical study (67), a sample size of 34 participants is required to surpass 80% power to detect an effect size of $D = 0.5$ at $\alpha = 0.05$ (though usually in functional neuroimaging studies $\alpha = 0.001$ is the standard). Nevertheless, investigations revealed that 90% of the highly cited fMRI papers had a sample size smaller than that (67). Considering these facts, by consensus, we decided to define the minimum required sample size as at least 34 participants (17 for each group). We changed the fourth question to address one of the most important possible confounders in our review, unrelated concurrent psychiatric and neurologic disorders. We considered the minimum required inclusion/exclusion criteria to address substance dependence, and other possible medical disorders, and having specified the diagnostic criteria used to diagnose patients. Also, as the 8th and 9th (concurrent control and exposures occurring before outcomes) questions don't apply to our subject, we changed them to address if controls were matched with cases for age, gender, and handedness because they might be important confounders in our study. We defined matching for age as having a $p > 0.05$ for the difference between groups, while for gender, we defined it as having a $p > 0.5$. We modified the 10th question to assess the validity and sufficient report of the paradigm used in the study. We considered a paradigm valid if at least some methodological studies have previously confirmed its reliability for the assessment of MNA. In the case of methodological innovations, the validity of the paradigm was assessed subjectively by discussion among the reviewers. Also, in cases of the inadequate report of paradigm parameters (e.g., not reporting acquisition parameters of an fMRI experiment), the study was ranked poor for this domain. The reviewers' arguments for each subjective decision behind the validity and report of the paradigms used in each study are presented in detail in Data sheet 2. We also removed the 11th question which addressed blinding of outcome assessors, since interventional methods (where blinding is of paramount concern) do not apply to our subject. Finally, we changed the last question to check if ethical issues were considered in the study design.

The adapted version of the tool was pilot-tested before use. MMb and AR independently evaluated included studies and recorded supporting information and justifications for their judgments. In cases of disagreements, AV was consulted.

Analysis methods

Eligibility and preparing for analysis

As we included data from multiple paradigms, with different outcomes, quantitative analysis was not feasible. Thus, we aimed for qualitative analysis. The full texts of the included studies were read and evaluated by AV and MMo. We determined the direction of the effect based on the studies' results, as either "decreased," "intact," or "increased MNA" for the primary outcome and "intact" or "altered MNS" for the secondary outcome. Regarding the primary outcome, we only included studies that have directly evaluated MNA. We did not consider studies that assessed other cognitive domains hypothesized to be related to MNA (e.g., empathy, etc.) as eligible for analysis. For the secondary outcome, we did not perform any analysis as there were very few studies for this purpose.

Statistical analyses

AV analyzed the data using Microsoft Excel and dmetar (68) package for R version 4. A qualitative meta-analysis was performed for the primary outcome based on vote counting of the direction of the effect. Vote counting, a simple method for analyzing evidence from multiple evaluations, involves comparing the number of studies showing benefit (reduced MNA in the case of our study) with the number of studies showing harm (intact/increased MNA in the case of our study) (69). A harvest plot was designed to present results from the analysis. We also designed graphics to represent evaluated domains of methodological and reporting quality for each study and the quality across all studies.

To test for the statistical significance of the vote counting analyses, we used the sign test. The sign test is a non-parametric test that uses a binary measure of either a positive or a negative effect to test whether there is sufficient evidence to reject the null hypothesis of an equal number of positive and negative results (70). The *P*-value from a sign test represents the probability of observing the given number of positive and negative results if the null hypothesis was true. To perform the test, we counted the number of studies in each effect direction for the outcome. Also, to explore the results of the most commonly used paradigms, we conducted separate analyses on paradigms with more than 5 studies, which were EEG with 7 studies and task-based fMRI with 9 studies. We used GraphPad (Link) to calculate the two-tailed *P*-value for the sign test. We considered a $p < 0.05$ as significant (alpha error).

Subgroup analyses

To explore heterogeneity in the results, we compared the outcome between subgroups. We conducted a test for subgroup differences between studies that evaluated MNA in "drug-naïve/drug-free for at least 1 month" patients, against studies on "medicated" patients. To check for this difference, we conducted Fisher's exact test (Link). Also, knowing that gray matter volumes atypically decline with age in schizophrenia patients (71), we conducted a logistic meta-regression test by comparing the mean age of the participants in each study, against the direction of the effect. We used the weighted least squares (WLS) method for this regression, with the weight associated with each study being the square root of its sample size ($\sqrt{N}$). Similar subgroup analyses were done for the gender of the participants (female to male ratio), mean positive PANSS scores of patients, and mean negative PANSS scores of the patients against the direction of the effect.

Sensitivity analyses

To evaluate the robustness of our results, we conducted a sensitivity analysis by excluding studies that were judged to be of poor methodological and reporting quality. We used the same previous methods above for this analysis.

Certainty assessment

The strength of the overall body of evidence was assessed using the Confidence in Evidence from Reviews of Qualitative Research Methods (CERQual) (72). This approach evaluates four components to score confidence in the review findings. These include methodological limitations, relevance, coherence, and adequacy. Each finding starts with a "high confidence" score which could be downgraded to "moderate confidence," "low confidence," or "very low confidence" if the CERQual process revealed concerns. AV and MMo evaluated each finding using the tool and attributed a score to it based on the four-point scoring system. We resolved discrepancies through discussion.

Results

Study selection

We identified 486 records through database searching. After deduplication and screening titles and abstracts of the records, 424 records were excluded. After reviewing the full texts of these reports, 28 were found to be eligible for inclusion in the review. Following citation searching of these studies, 6 more eligible studies were found. In the end, 32 studies (34 reports) were included in this review, 29 for

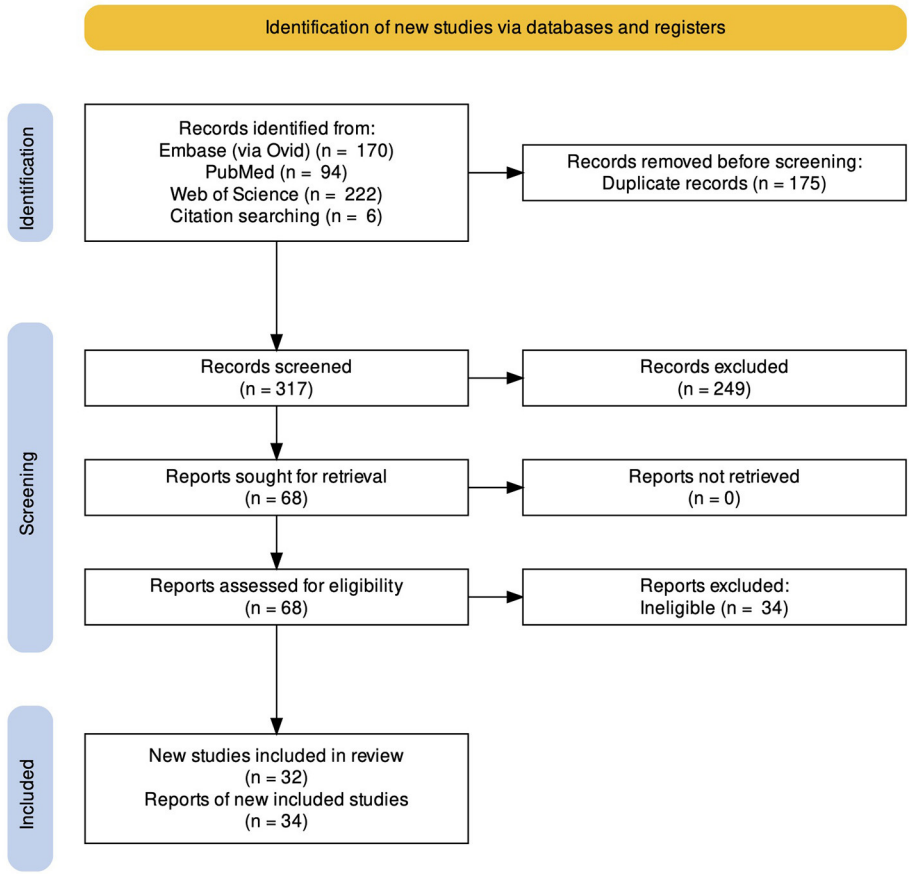


FIGURE 1
PRISMA Flow diagram of the study. We identified 486 records through database searching and six records through citation searching. Following deduplication, 317 records were screened, from which, 32 relevant studies (34 reports) were found and included in the review.

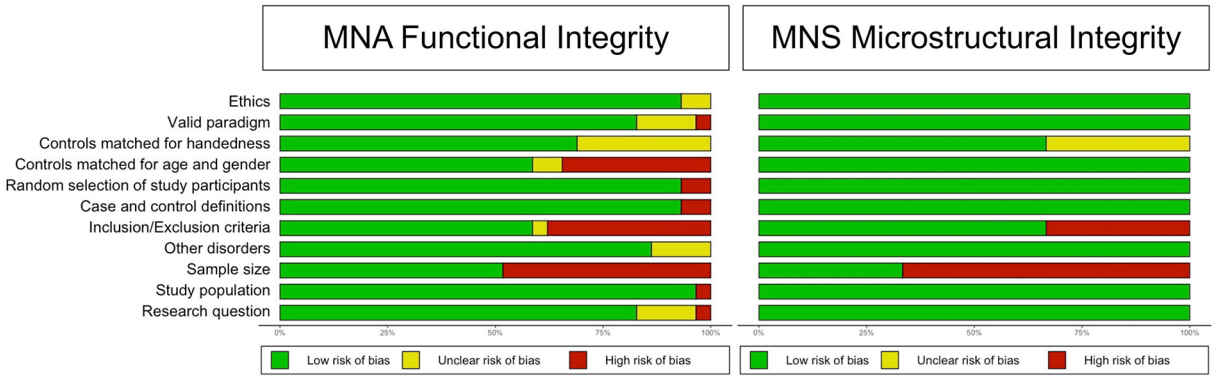


FIGURE 2
Methodological and reporting quality graph: Review authors' judgments about each methodological and reporting quality item presented as percentages across all included studies.

the main outcome (functional integrity of MNA) and 3 for the secondary outcome (microstructural integrity of MNS). A detailed report of the study selection process is presented in Figure 1. It is of special notice that the three papers of Horan et al. were considered as one study for the statistical analyses (since they were performed on the same patients in

the same setting), but were assessed for methodological quality separately (because they reported three different phases of a study).

Study characteristics

We included 29 studies (73–103) with 1,542 participants for the primary outcome and 3 studies (104–106) with 126 participants for the secondary outcome. Overall, 32 studies were included in this systematic review. For a detailed summary of the characteristics of the included studies, see Data sheet 3.

Methodological and reporting quality of studies

Sixteen studies (14 for the primary outcome, 2 for the secondary outcome) were judged to have good methodological and reporting quality, eight (7 for the primary outcome, 1 for the secondary outcome) were judged to have fair quality, and ten (all for the primary outcome) were judged to have poor quality. For more information on the quality domains for each study, please check Data sheets 2, 3. Figure 2 shows the judgments for each domain in each included study for each outcome. Judgments for each domain and each outcome across all studies are presented in Figure 3.

Results of individual studies

Regarding the primary outcome, the direction of the effect in most studies was toward decreased MNA. Four studies concluded that MNA in schizophrenia patients was not different from healthy controls, while two studies indicated that they detected increased MNA in these patients. For a detailed summary of the results of individual studies for this outcome, see the harvest plot in Figure 4. All three studies that evaluated the secondary outcome concluded that MNS microstructural integrity was altered in patients.

Results of analyses

Characteristics of contributing studies

A summary of the characteristics of the included studies is presented in Table 1. The comments section for this table is built upon the comments provided in a similar table in the systematic review of Mehta et al. (54). For a more detailed report of the characteristics of contributing studies, see Data sheet 3.

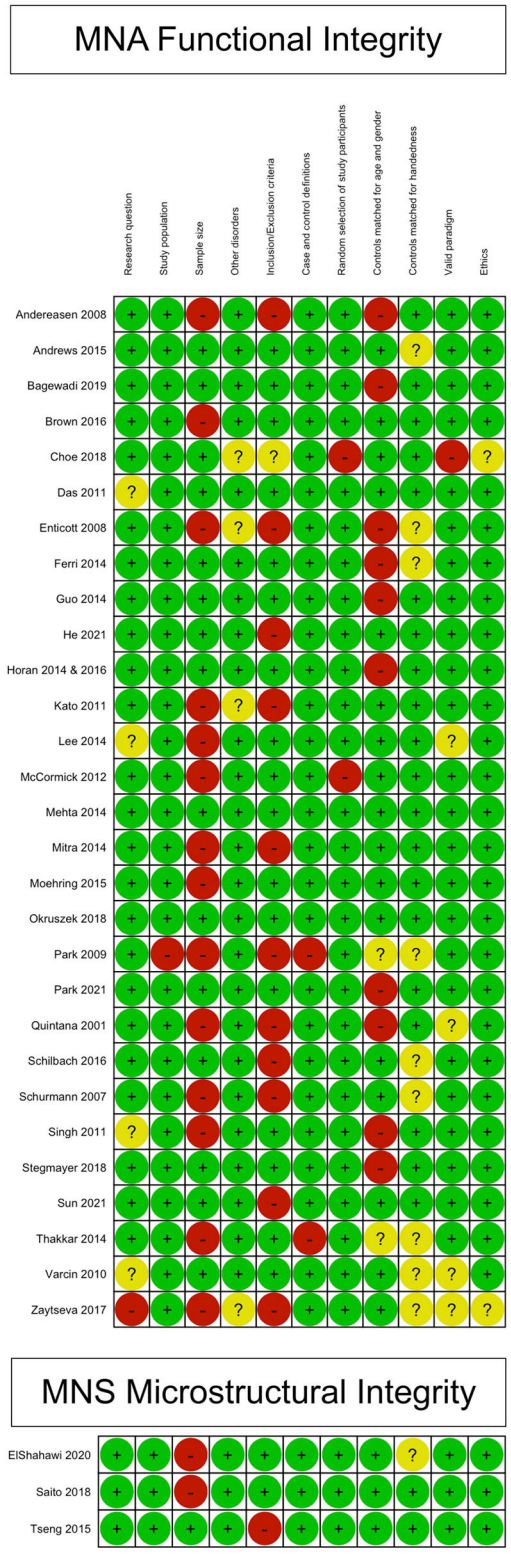


FIGURE 3
Methodological and reporting quality summary: review authors' judgments about each methodological and reporting quality item for each included study.

TABLE 1 The effect direction of the outcome table.

References	Direction	N (SCZ/HC)	Mean age	Medicated	+PANSS	−PANSS	Setting	Paradigm	Experimental condition
Microstructural methods									
Tseng et al. (106)	Altered	32/32	32	✓	–	–	Inpatient	DSI	Microstructural data
ElShahawi et al. (104)	Altered	15/15	29	✓	–	–	Mixed	DWI/DTI	Microstructural data
Saito et al. (105)	Altered	16/16	21	✓	–	–	Mixed	DWI/DTI	Microstructural data
Functional methods									
Brown et al. (76)	◀▶	17/17	40	✓	19 (7)	25 (8)	Inpatient	EEG	(a) Rest: inanimate motion, (b) Action-observation: observing video clips of two people sitting at a table, transferring coins from one bowl to the other bowls at the table
Horan et al. (84)	◀▶	32/26	46	✓	–	–	Outpatient	EEG	(a) Rest: inanimate motion (two bouncing balls), (b) Action-observation: hand movements, people playing a throw and catch game by throwing a ball to themselves, to each other, and to and from the observer
McCormick et al. (87)	▲	16/16	37	✓	17 (12)	16 (10)	Inpatient	EEG	(a) Rest: watching snow-fall, (b) Action-observation: bouncing balls and hand movements
Mitra et al. (89)	▼	15/15	29	×	–	–	Inpatient	EEG	(a) Rest: White screen, (b) Action-observation: video of handshakes, repeated at a rate of 1 per second
Möhring et al. (90)	▼	15/15	35	✓	16 (4)	20 (5)	Outpatient	EEG	(a) Action-observation: observing a static image of gestures of a hand for the rock–paper–scissors game, (b) Action-execution: participants actively executed hand gestures when stimuli depicting rock, paper, or scissors were displayed
Singh et al. (95)	▼	20/12	21	✓	15 (15)	17 (13)	Outpatient	EEG	(a) Rest: inanimate motion (two bouncing balls), (b) Action-observation: hand movements, point light display animation of a jumping human, people playing a game of throw and catch
Zaytseva et al. (101)	▼	11/32	23	✓	–	–	–	EEG	Imaginary representation of one's own walking on a familiar street (2 min) followed by the subjects' self-reports
Varcin et al. (99)	▼	25/25	42	✓	15 (13)	16 (10)	Outpatient	EMG	Watching facial expressions of happiness and anger displayed in 4 male and 4 female faces, while EMG was recorded from zygomaticus major and corrugator supercilii
Das et al. (78)	▼	20/19	34	✓	10 (3)	18 (5)	Inpatient	fMRI	16 blocks: 8 experimental in which two triangles mimicked human behavior (bluffing, persuading, surprising, and mocking), and 8 controls in which two triangles moved randomly
Ferri et al. (80)	▼	22/22	28	≈	14 (4)	12 (5)	Outpatient	fMRI	336 trials where subjects watched either "emotion action," "emotion," or "action" stimuli and 32 imitation trials where subjects were given a request to imitate either the action or the emotion
He et al. (102)	◀▶	17/18	32	✓	26 (17)	16 (13)	Inpatient	fMRI	Two runs of 182 trials each. Each run consisted of 3 stimuli: (a) observing videos of an actor making incomprehensible Russian sentences with gestures, (b) making comprehensible German sentences without any gestures, (c) making German sentences with accompanying gestures

(Continued)

10.3389/fpsyt.2022.884828

TABLE 1 (Continued)

References	Direction	N (SCZ/HC)	Mean age	Medicated	+PANSS	−PANSS	Setting	Paradigm	Experimental condition
Horan et al. (82)	◀▶	23/23	47	✓	–	–	Outpatient	fMRI	Five runs of 6 blocks, each block consisted of 6 trials (3 fingers and 3 faces). The trials required subjects to either (a) observe: observe finger movements or a facial expression, (b) imitate: imitate the fingers movement or the facial expression, and (c) execute: make the movement or facial expression described by each word. Words included the following in a random order: Lift Index, Lift Middle, Happy, Sad, Angry, Afraid
Horan et al. (83)	◀▶	21/21	47	✓	–	–	Outpatient	fMRI	Four runs of a mixed blocked/event-related paradigm. Each run consisted of two components: (a): (i) observing videos of patients receiving a painful sound stimulation treatment; (ii) listening to the painful sounds (to create ROIs). (b): manipulations of perspective-taking (imagine "Self" vs. "Other" experiencing pain) and cognitive appraisal (treatment was "Effective" vs. "Not Effective")
Lee et al. (86)	▼	15/16	37	✓	10 (3)	13 (3)	Outpatient	fMRI	180-trials (0.5 s of watching phase for each); (a) observation phase: subjects watched either facial or word stimuli, (b) expression phase: subjects actively expressed the emotions displayed, (c) returning phase: subjects returned to neutral facial expression after watching a neutral cue on the screen
Okruszek et al. (100)	▼	25/26	35	✓	11 (3)	18 (4)	Outpatient	fMRI	112 trials–each trial consisted of (a) watching phase: watching animations displaying actions of agents presented as point-light walkers, (b) behavioral response phase: responding to the question "Are the two persons acting together or separately?," (c) ISI phase
Park et al. (91)	▼	15/16	–	✓	13 (2)	17 (4)	Outpatient	fMRI	24 blocks; each block consisted of perceiving, inferring, and selecting appropriate responses (30, 20, and 10 s, respectively), to ambiguous or certain emotional events narrated by a graphical avatar. The neutral certain condition was the control condition
Quintana (92)	▲	8/8	33	✓	–	–	Outpatient	fMRI	Four runs of block-design paradigms–each run consisted of 3 resting blocks scattered among 2 sets (colored circles or drawings of facial expressions) of 6 task trials, where the subject was required to match the cues
Stegmayer et al. (96)	▼	22/25	38	✓	18 (7)	19 (5)	Mixed	fMRI	Two runs of event-related paradigm–each run consisted of 3 phases: (a) visual command phase (3 s), (b) planning phase (3 s): participants had to plan movements, (c) execution phase (3 s): participants should've executed the gesture that was stated in the visual command phase
Thakkar et al. (98)	▼	16/16	39	≈	14 (10)	23 (12)	Inpatient	fMRI	Four runs of 14 blocks–each block consisted of 3 trials (3 movement conditions in each). Subjects were required to either execute actions of pressing buttons while viewing these stimuli or observe (a) a hand pressing buttons, (b) an image of a hand and a button box, (c) inanimate marks
Kato et al. (85)	▼	15/15	33	×	18 (4)	18 (8)	-	MEG	(a) Rest: eyes fixed on a cross, (b) Action-observation: mouth opening movements.

(Continued)

10.3389/fpsyt.2022.884828

TABLE 1 (Continued)

References	Direction	N (SCZ/HC)	Mean age	Medicated	+PANSS	–PANSS	Setting	Paradigm	Experimental condition
Schürmann et al. (94)	▼	11/11	54	✓	-	-	Outpatient	MEG	(a) Rest: resting in a relaxed state, (b) Action-observation: manipulation of a small object with a hand; (c) Action-execution: participants manipulated the small object with their hand
Andereasen et al. (73)	▼	18/13	30	×	12 (11)	9 (8)	Outpatient	PET	Subjects were asked to say narrative stories explaining a given social situation. The control task required subjects to read aloud a neutral story that was presented on the monitor
Choe et al. (77)	▼	26/26	23	≈	16 (4)	16 (4)	Outpatient	rs-fMRI	Resting-State
Guo et al. (81)	▼	69/62	31	✓	12 (5)	14 (6)	Inpatient	rs-fMRI	Resting-State
Park et al. (103)	▼	37/80	23	≈	16 (4)	17 (5)	Outpatient	rs-fMRI	Resting-State
Schilbach et al. (93)	▼	116/133	34	✓	–	–	Multi-centric	rs-fMRI	Resting-State
Sun et al. (97)	▼	28/22	17	×	23 (7)	17 (7)	Inpatient	rs-fMRI	Resting-State
Bagewadi et al. (75)	▼	30/28	27	✓	21 (16)	20 (16)	Inpatient	TMS	(a) Rest: observing a static image, (b) Natural action-observation: a key held in pinch grasp, performing locking and unlocking, (c) Context-based action-observation: observing a video clip of a mother trying to unlock the door of a house that is on fire and her child is stuck in calling for help
Enticott et al. (79)	▼	15/15	38	✓	15 (4)	15 (5)	-	TMS	(a) Rest: not specified, (b) Action-observation: non-goal directed and goal-directed finger movements
Mehta et al. (88)	▼	54/45	31	≈	24 (6)	23 (9)	Mixed	TMS	(a) Rest: observing a static image, (b) Action-observation: a key held in pinch grasp, performing locking, and unlocking movements
Andrews et al. (74)	◄►	19/19	41.0	✓	16 (6)	16 (5)	Outpatient	TMS/EEG	(a) Rest: observing a black screen, (b) Action-observation: 6 video clips: 2 static hands; a hand reaching out and clasping a mug; a hand pantomiming clasping a mug; and 2 interactive movements, one with hands from two different people, and a similar movement carried out by one person

▲ indicates increased mirror neuron activity (MNA) ◄► indicates intact MNA, and ▼ indicates decreased MNA. Colors represent the methodological quality of the study (green = good, yellow = fair, red = poor). ✓, Mostly medicated patients; ×, Mostly drug-naïve/drug-free for at least a month; ≈, Mixed. + PANSS: + Positive and Negative Syndrome Scale (PANSS) scores [mean (SD)] round to the nearest integer; –PANSS, –PANSS scores [mean (SD)] round to the nearest integer; DSI, Diffusion spectrum imaging; DTI, Diffusion tensor imaging; DWI, Diffusion-weighted imaging; EEG, Electroencephalography; EMG, Electromyography; fMRI, Functional magnetic resonance imaging; HC, Healthy controls; MEG, Magnetoencephalography; PET, Proton emission tomography; rs-fMRI, Resting-state fMRI; SCZ, Schizophrenia; TMS, Transcranial magnetic stimulation.

10.3389/fpsyt.2022.884828

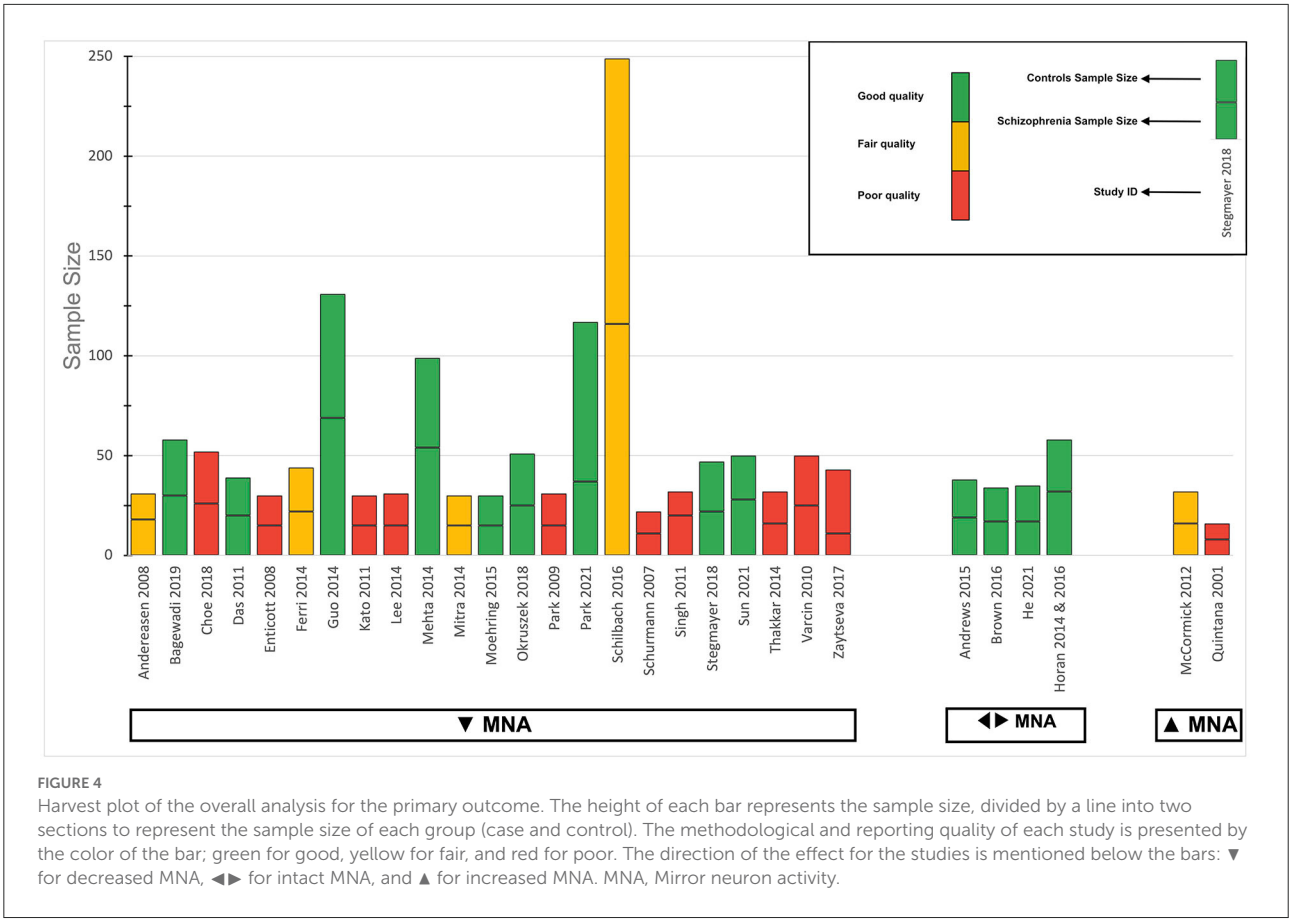


FIGURE 4
Harvest plot of the overall analysis for the primary outcome. The height of each bar represents the sample size, divided by a line into two sections to represent the sample size of each group (case and control). The methodological and reporting quality of each study is presented by the color of the bar; green for good, yellow for fair, and red for poor. The direction of the effect for the studies is mentioned below the bars: ▼ for decreased MNA, ◄► for intact MNA, and ▲ for increased MNA. MNA, Mirror neuron activity.

Patterns of activity in MNA-specific brain regions

MEG, fMRI, and PET are known to provide good spatial resolutions. The different patterns of activity in MNA-specific brain regions between cases and controls in the included studies are provided in Table 2.

IFG was the most investigated area across the literature where 6/7 studies reported the detection of a decreased MNA in that region. IPL was the second most investigated area, but interestingly, it was also the one with the most controversial results. Of the 6 studies that evaluated this area, 3 reported the detection of decreased MNA and the other 3 reported the detection of increased MNA. Also, MNA was reported to be decreased in PMv in 3 of the 4 studies that investigated this area. Results for the STG area were pretty consistent with 3 of 3 studies reporting decreased MNA. Only 2 studies reported a difference in the insula activation, where their results were in the opposite direction.

Results of statistical analyses

The results of the analysis for the primary outcome are presented as a harvest plot in Figure 4. Most studies concluded that MNA was significantly reduced in schizophrenia patients, compared to controls (23/29, 79.3%). The two-tailed sign test *P*-value was calculated to be 0.002, meaning that the chance of observing either 23 or more studies, or 6 or fewer studies in 29 studies, in that direction, is 0.2%. Only two studies (87, 92) found significant results in the opposite direction (2/29, 7.9%). Four studies (74, 75, 82–84, 102) concluded that there was no significant difference between patients and healthy controls (4/29, 13.8%).

We also conducted a vote-counting analysis for the direction of the effect for studies that only used task-based fMRI as their assessment tool. In this group, seven studies concluded that MNA was reduced in cases, although this finding was not statistically significant (7/10, 70.0%; $P = 0.344$). A similar analysis was also conducted for studies that only used EEG. In this group, four studies concluded that MNA was reduced in cases (4/7, 57.1%; $\underline{P} = 1.000$), showing almost no statistical significance. Also, two studies showed an intact MNA and one concluded that MNA was increased in cases. Results were very contradictory for the EEG group and demanded explicit evaluation.

TABLE 2 The difference in the pattern of activation of different mirror neuron activity (MNA)-specific brain regions between schizophrenia and healthy control participants in task-based fMRI, MEG, and PET studies of MNA.

References	Modality	PMv	IFG	IPL	STG	Insula
Andereasen et al. (73)	PET	–	Lower	–	–	–
Das et al. (78)	Task-Based fMRI	–	Lower	Lower	Lower	–
Ferri et al. (80)	Task-Based fMRI	–	Lower	Lower	–	Lower
Kato et al. (34)	MEG	–	-	Lower	–	-
Lee et al. (35)	Task-Based fMRI	Lower	Lower	Higher	–	Higher
Okruszek et al. (100)	Task-Based fMRI	–	–	–	Lower	–
Park et al. (91)	Task-Based fMRI	Lower	Lower	–	–	–
Quintana (92)	Task-Based fMRI	Higher	Higher	–	–	–
Schurmann et al. (94)	MEG	Lower	–	–	–	–
Stegmayer et al. (96)	Task-Based fMRI	–	Lower	Higher	–	–
Thakkar et al. (98)	Task-Based fMRI	–	–	Higher	Lower	–

Lower means lower activity in patients compared to controls, while higher means higher activity. IFG, Inferior frontal gyrus; IPL, Inferior parietal lobule; STG, Superior temporal gyrus; PMv, Ventral premotor cortex.

Results of subgroup analyses

Regarding the primary outcome, for the patients in the "drug-naïve/free for at least 1 month" subgroup, 4/4 studies, and the patients in the "medicated" subgroup, 14/20 studies were in the direction of decreased MNA, while 6 studies were in the direction of either intact or increased MNA. The test for subgroup differences revealed no significant difference between them ($P = 0.539$).

Results for the logistic meta-regression analyses for age, gender (female to male ratio), positive PANSS scores, and negative PANSS scores against the direction of the effect for the primary outcome are presented in Table 3 and Figure 5. There seems to be a relationship between the age of participants and the direction of the effect. A similar relationship was observed between the positive PANSS scores and the direction of the effect. Studies that found intact/increased MNA, were performed on patients of higher age and higher positive PANSS scores. These relationships were found to be statistically significant ($P < 0.001$ for age and $P = 0.004$ for positive PANSS scores).

TABLE 3 Results of the logistic meta-regression analyses for investigating the possible causes of heterogeneity.

Dependent variable	Independent variable	β_0 (Intercept)	β_1	*p*-value
Direction of the effect	Age	−7.42	0.16	<0.001
	Female to male ratio	−0.82	−1.86	0.070
	Positive PANSS	−4.75	0.17	0.004
	Negative PANSS	−3.31	0.09	0.226

Results of sensitivity analyses

To check the robustness of our results for the primary outcome, we performed an analysis on studies that were judged to have fair or good methodological and reporting quality. Most of these studies were in favor of decreased MNA in cases, although this finding was not statistically significant (13/18; $P = 0.096$).

Publication bias

Given the multi-modal nature of the included studies, it was not possible to use statistical tests or funnel plots to check for the possible role of publication bias in our results. We figured the best way for checking any potential publication bias in our review is to check for the time-lag phenomenon, defined as "an initial wave of studies reporting positive or expected results, followed by a secondary wave of negative results" which is an indicator of possible publication bias (107). Our investigations on a quarter of the most recent included studies [8 studies (75, 96, 97, 100, 102–105), from 2018 to 2021] revealed that 87.5% (7/8 studies) were in the same direction as the results of our main analysis (reduced MNA, altered MNS). Although this finding does not rule out the publication bias for certain, it ascertains the absence of it to some considerable degree.

Certainty of evidence

For the primary outcome, we believed there were some concerns for the "methodological limitations" domain as the considerable presence of bias across the included studies might have affected our results. We also believed there were minor concerns for the "coherence" domain because some studies reported contradictory results. No

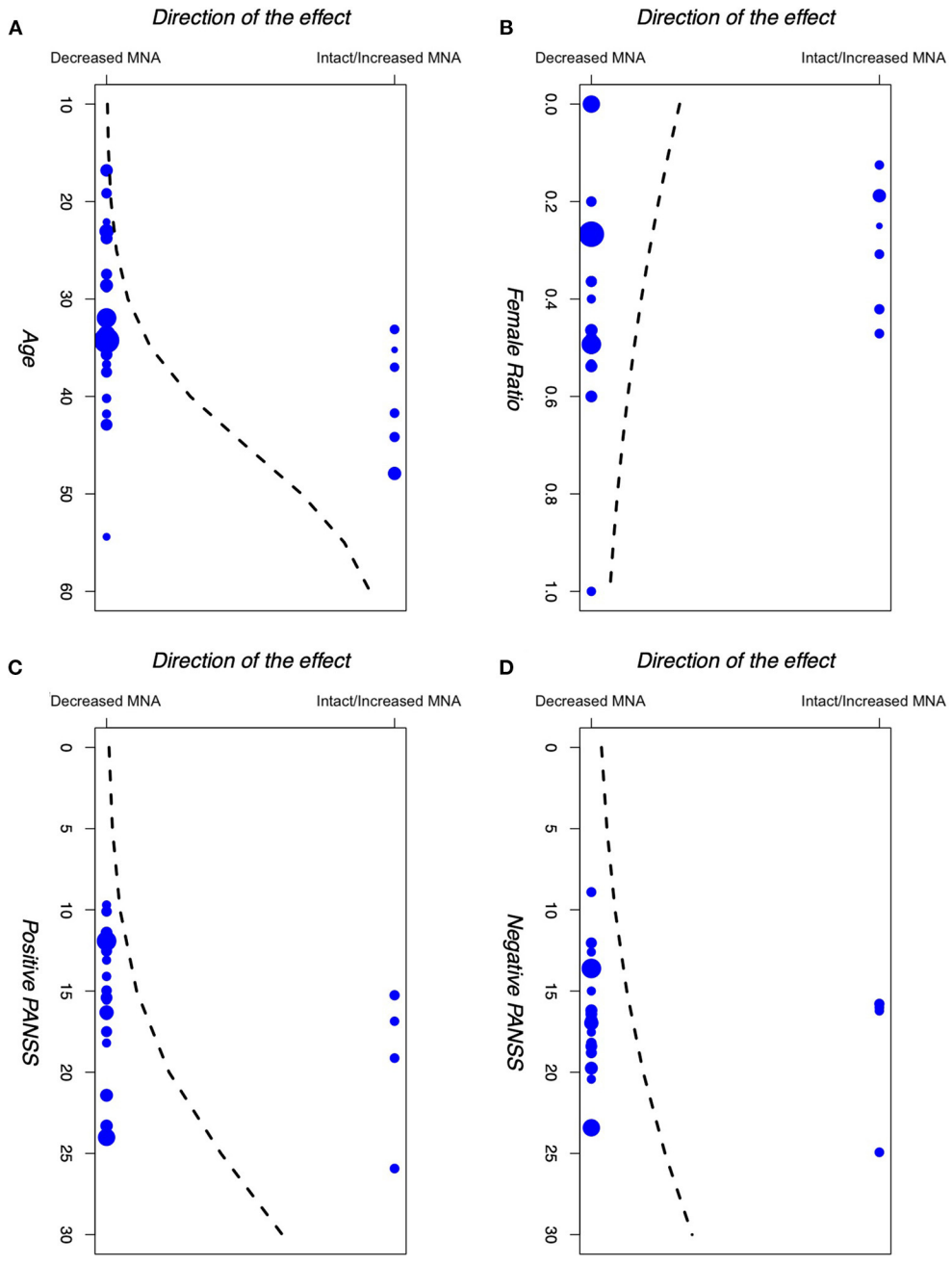


FIGURE 5
Logistic meta-regression analyses for **(A)** age, **(B)** gender (female to male ratio), **(C)** +PANSS scores, and **(D)** −PANSS scores of participants in the included studies against the direction of the effect of those studies. PANSS: Positive and Negative Syndrome Scale.

concerns were identified for the "adequacy" and "relevance" domains. Overall, given that the frequent presence of bias across the included studies might have affected our results, we decided to downgrade the certainty of the evidence by one level because of the "methodological limitations" domain. Thus, we believe there was moderate confidence in our findings.

Discussion

Interpretation of the results

MNA in schizophrenia; What did we find?

Mehta et al. (54) conducted a systematic review on the same subject in 2014. However, to our knowledge, this

is the first systematic review that has also incorporated qualitative data analysis to evaluate the mirror mechanism in schizophrenia patients and identify some of the possible sources of heterogeneity in the findings.

Some hypothesize that schizophrenia might be a disorder of the "social brain" (108). Mirror neurons are collections of neurons that are believed to be part of this social brain network (109). From this point of view, it has been hypothesized that MNA is impaired in schizophrenia. Our study reveals, with moderate confidence, that there is indeed an impaired MNA system in these patients.

Contradictory results; Some possible explanations

Although most findings were in the same direction, one might question why others found contradictory results. We aim to describe here some of the potential causes underlying those results.

First, our meta-regression analyses found a statistically significant relationship between the mean positive PANSS scores and age of the participants in each study and the direction of the observed effect in that study. Studies that demonstrated intact/increased MNA enrolled patients with higher positive PANSS scores and age, compared to the studies that demonstrated decreased MNA.

Regarding the relationship between the positive PANSS scores and the direction of the effect, our results indicate that patients with higher positive PANSS scores are more likely to have intact/increased MNA. Positive PANSS measures the severity of the positive symptoms of the disorder, such as delusions, conceptual disorganization, hallucinations, and hostility (62). McCormick et al. (87) found a similar pattern in their study, suggesting that MNS may be overactive when positive symptoms are most prevalent (especially hallucinations). Mitra et al. (89) reported a negative correlation between the mu wave suppression and the thought disturbance cluster on PANSS, proposing that according to the theory that dopamine levels in the brain and the performance of the brain circuits have an "inverted-U" shaped relationship, an increase in brain dopamine levels during schizophrenia possibly disrupts the MNS circuit, leading to psychopathology manifestations. Other studies did not find a significant correlation between positive PANSS scores and MNA (74, 78, 80, 84, 86, 88, 90, 96, 99, 102). These contradictory results could be due to differences in experimental conditions, stage of disease, or the measures used to assess symptoms. Nevertheless, the idea of MNA correlating with patients' symptoms seems to be a plausible hypothesis. Indeed, this hypothesis was previously mentioned by Mehta et al. (54), making it an explanation worth further investigation. This is also in line with Frith and Corcoran's theoretical model of the relationship between social cognitive processes and psychotic symptoms (110).

Regarding age, similar results were found previously in autism, suggesting that individuals with autism may outgrow any mirror neuron deficit after a certain age (111, 112), although some other studies question these results (113, 114). One recent study indicates that in general, there might be some differences in the MNA between younger and older adults (115), where older adults showed Mu suppression in frontal and frontotemporal regions during a memory task, in contrast with young adults who showed Mu enhancement. Besides these, some studies have also shown that the social cognitive performance of schizophrenia patients may actually increase by age (116). Linke et al. (117) found a similar pattern in their study as well, but after including the patient's age at onset in their models, they concluded that this observed increase in social cognitive performance is not really due to the patients' age, but it is actually due to their later onset of the disease, as older patients are usually those with a later onset of psychosis as well. This is in line with previous studies that revealed age at the onset of the disease is negatively correlated with patients' cognitive performance (118, 119).

In the study of Horan et al. (82–84), they used a mask before group-level analyses, which might "bias against finding significant between-group differences," as stated by the authors. In the study of Andrews et al. (73), they used a combination of TMS and EEG that may have reduced the quality of the EEG signals from some participants. Also, the baseline stimulus used to directly compare the EEG and TMS measures (blank screen) was not the same for the two measures. The studies of McCormick et al. (87) and Quintana (92) found increased MNA in patients. Quintana (91) study made a controversial decision by excluding BOLD signal changes during incorrect responses. The authors proposed that patients may have a compensatory increase in MNA while correctly performing the task. In the study of McCormick et al. (87), subgroup analyses showed only a subgroup of patients had greater mu suppression, the active psychosis subgroup. These findings indicate the need for more research on these subgroups of schizophrenia patients.

Most notably, we found the results of EEG studies to be very contradictory. Some possible explanations for such results have been previously mentioned in the study of Hobson and Bishop (120). First, they suggested that because the mu frequency band overlaps with the alpha frequency band (which is sensitive to attentional fluctuation), mu suppression could potentially be confounded by changes in attentional engagement. They also report that there is little consistency in how the specific baseline against which mu suppression is assessed should be defined. Finally, they examined mu suppression in 61 typical adults and reported that even in an optimal evaluation condition, 16–21% of participants showed no mu suppression to action observation task. Overall, they concluded that mu suppression can be used to index the human

MNS, but the effect seems to be weak and unreliable, and it may also easily be confounded by alpha rhythm suppression. More interestingly, a recent study found that observation tasks may sometimes elicit mu rhythm enhancement rather than suppression (121). All these results question the reliability of the EEG paradigm for assessing MNA. Also, the validity of the TMS/EEG paradigm has been seriously questioned by another recent study (122). With all of those in mind, we still didn't consider these paradigms as invalid in our bias assessment process, as this domain required subjective judgments (where we tried to be conservative) and there are still some counter-arguments supporting the possible reliability of these paradigms.

MNA and negative symptoms in schizophrenia

Negative symptoms account for a substantial portion of the morbidity associated with schizophrenia (123). Empirical research has argued for an association between negative symptoms and anomalous MNA (124). We found the same association in some of the studies included in this review (85, 86, 95, 98). The study of Singh et al. (95) found lower mu wave suppression to positively correlate with negative PANSS scores, suggesting MNS may be underactive when negative symptoms predominate. However, the study of Brown et al. (76) found a statistically significant correlation between mu wave suppression and negative PANSS scores in the opposite direction of Singh's et al. Also, the study of Kato et al. (85) reported a negative correlation between the amplitudes of root-mean-square (RMS) of MEG responses and negative PANSS scores. Finally, Park et al. (91) reported the presence of a negative correlation between the functional deficits in MNS and negative PANSS scores. Although we didn't find any significant correlation between MNA and negative PANSS scores ($P = 0.226$), future studies should provide an in-depth assessment of the relationship between these two factors.

MNA and communication skills in schizophrenia

Deficits in communications skills have been previously documented in schizophrenia (125), but there has not been a comprehensive explanation for the etiology of this phenomenon up to this date. Indeed, MNS has been linked to developing communication skills v*ia* integrating auditory, visual, and motor stimulation (126). A study by Cantisani et al. reported a negative linear association between resting-state cerebral blood flow in the left inferior and middle frontal gyrus of schizophrenia patients with their communication skills, measured through the Social and Occupational Functioning Assessment Scale (SOFAS) (127). Our results indicate that across the literature, the inferior frontal gyrus (IFG) was the most investigated area for MNA in schizophrenia patients, where most studies indicated decreased MNA detection in this area. Putting these findings together, the disruption in MNA might be suggested as a possible explanation for communication skills in schizophrenia patients. Further studies are required to validate this hypothesis.

MNA and echopraxia in schizophrenia

Echopraxia is the pathological repetition by imitation of the movements of another person. In the context of schizophrenia, it has been mostly associated with the catatonic form (128). A previous speculative paper by Pridmore et al. suggested that pathologically handled MNS-generated representations, especially in IFG, might be involved in this dysfunction (129). Indeed, this was in line with the findings of the study of Zaytseva et al. (101) where the authors reported altered mu rhythm suppression in the right frontal and central brain regions in patients with catatonic schizophrenia. More studies on catatonic patients in the future are suggested to further evaluate the validity of this finding.

MNS and the "plasticity" hypothesis in schizophrenia

Previously, some have argued that MNS might have a plastic feature (130), meaning that after receiving treatment, disruptions in this system might at least partially resolve. However, a study by Mitra et al. (131) found that following 8 weeks of antipsychotic treatment, no significant changes took place in the MNA of patients. This is partly in line with our results that revealed there was no significant MNA difference between medicated and drug-free patients. These indicate that even though antipsychotic medications may improve cognitive deficits for some schizophrenia patients, they may not affect MNA significantly.

Another commonality between autism and schizophrenia

Our results indicate that MNA is altered in schizophrenia patients, similar to the individuals with autism. This finding contributes to the efforts of exploring the dimensions of mental disorders to integrate many levels of information to understand the nature of mental health and illness, such as efforts taking place in the projects of RdoC (132).

Rehabilitation through MNS-based training

Deriving clinical impact from such results could be an existing area of research. In a pilot study in 2020 (133), Hadoush et al. evaluated the effect of bilateral anodal transcranial direct current stimulation (tDCS) applied over the MNS of autism patients. They concluded that this intervention has a moderate therapeutic effect on children with autism in terms of their

sociability, behavior, health, and even physical conditions. This pilot study reveals the potential of new rehabilitation methods through MNS-based training, which might benefit patients. It might be interesting to evaluate if similar results could be obtained for schizophrenia patients.

Another study that evaluated the effect of add-on yoga therapy on schizophrenia patients, revealed that MNA increased in the intervention group following 6 weeks of yoga therapy. They also found significant improvements in social cognition composite score (SCCS), negative symptoms (SANS), and positive symptoms (SAPS). One hypothesis is that the improvements in those clinical symptoms might have been achieved through the training of the MNS. Indeed, a previous study on yoga therapy for 2 years on 12 autism patients (6 in the interventional arm and 6 in the comparator arm) revealed improvements in imitation and other social skills of the participants (134). The authors hypothesized that guided imitation of therapist body positions might have stimulated MNA, resulting in an improved sense of self. Investigating the causal relationship between such findings might benefit future research.

Limitation of evidence

All the included studies used indirect measures of MNA. It is known that intracranial electrodes give the most reliable evidence of MNA, but understandably, such procedures cannot be used for research on humans. Nevertheless, the indirect nature of the assessment tools used in the included studies, compared to the definitive direct sell recording techniques, should be considered as a limitation of the evidence. Also, a considerable proportion of the included studies had a sample size of <34, which decreased the power of their statistical analysis. By the way, some studies did not use valid and comprehensive inclusion/exclusion criteria, which might increase the chance of confounding in their results. Finally, a proportion of the included studies did not report if controls were matched with cases for handedness.

Limitations of review processes

We acknowledge several limitations in our study. Firstly, we used a weak statistical test for our analyses. Although it requires mentioning that considering the wide range of assessment paradigms we included in this review, more powerful statistical tests were not feasible. Secondly, we didn't assess the same outcome in other populations with almost the same pathology (i.e., schizoaffective disorder). Finally, some important information was not reported in the included studies. We tried to reach out to the authors to ask for that information but did not get any response. Nevertheless, we believe that possible none of these methodological limitations would significantly change the overall conclusions of this review.

Overall, we acknowledge that presenting a quantified summary for such a highly debated and controversial topic, given so few studies with vastly different modalities, would have its challenges and may require some methodological innovations. With that in mind, we still believe that our study managed to provide a clearer picture of the current state of knowledge on this subject, while also pointing to some of the existing biases and limitations in the literature.

Implications

From our findings, one can claim, with moderate confidence, that MNA is altered in schizophrenia patients. This finding provides clues for a more in-depth understanding of the disorder and helps find a more comprehensive revision of the underlying pathophysiology of psychosis spectrum disorders. As more findings are being discovered that help to achieve a more in-depth understanding of psychiatric disorders, adjustments to our definitions for these illnesses seem necessary. Future researchers may evaluate the same deficits in patients with other disorders (e.g., bipolar disorder, depression, etc.) to come up with a better understanding of the common features across these disorders and facilitate the process of finding new semantic definitions for psychiatric illnesses.

We also urge future researchers on this subject to try to compensate for the existing biases and limitations in the literature. This may include conducting studies with larger sample sizes, using rigor eligibility criteria to minimize confounding effects, and utilizing valid paradigms to ensure the reliability of the results. Also, research on deriving potential clinical impact using MNS-based training methods could be an exciting topic for future investigations.

Data availability statement

The original contributions presented in the study are included in Supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

AV: conception and coordination of the review, designing the protocol, search, study selection, data extraction, methodological and reporting quality assessment, analysis of evidence, interpretation of the results, assessing the certainty of the evidence, and writing the review. MMb: data extraction, methodological, and reporting quality assessment. AR: data extraction, methodological, and reporting quality assessment. NH and AH: study selection. MS: data extraction. MMo:

data extraction and assessing the certainty of the evidence. All authors contributed to the article and approved the submitted version.

Acknowledgments

Special thanks to Prof. Giacomo Rizzolatti for his comments on the protocol.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.884828/full#supplementary-material

References

1. Rizzolatti G, Craighero L. The mirror-neuron system. *Annu Rev Neurosci.* (2004) 27:169–92. doi: 10.1146/annurev.neuro.27.070203.144230

2. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med.* (2013) 11:126. doi: 10.1186/1741-7015-11-126

3. Bonini L, Rozzi S, Serventi FU, Simone L, Ferrari PF, Fogassi L. Ventral premotor and inferior parietal cortices make distinct contribution to action organization and intention understanding. *Cerebral Cortex.* (2010) 20:1372–85. doi: 10.1093/cercor/bhp200

4. Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G. Parietal lobe: from action organization to intention understanding. *Science.* (2005) 308:662–7. doi: 10.1126/science.1106138

5. Rizzolatti G, Sinigaglia C. The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. *Nat Rev Neurosci.* (2010) 11:264–74. doi: 10.1038/nrn2805

6. Brass M, Heyes C. Imitation: is cognitive neuroscience solving the correspondence problem? *Trends Cogn Sci.* (2005) 9:489–95. doi: 10.1016/j.tics.2005.08.007

7. Buccino G, Vogt S, Ritzl A, Fink GR, Zilles K, Freund HJ, et al. Neural circuits underlying imitation learning of hand actions. *Neuron.* (2004) 42:323–34. doi: 10.1016/S0896-6273(04)00181-3

8. Marshall PJ, Meltzoff AN. Neural mirroring mechanisms and imitation in human infants. *Philos Trans R Soc B Biol Sci.* (2014) 369:20130620. doi: 10.1098/rstb.2013.0620

9. Iacoboni M. Imitation, empathy, and mirror neurons. *Annu Rev Psychol.* (2009) 60:653–70. doi: 10.1146/annurev.psych.60.110707.163604

10. Théoret H, Pascual-Leone A. Language acquisition: do as you hear. *Curr Biol.* (2002) 12:R736–7. doi: 10.1016/S0960-9822(02)01251-4

11. di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G. Understanding motor events: a neurophysiological study. *Exp Brain Res.* (1992) 91:176–80. doi: 10.1007/BF00230027

12. Gallese V. Mirror neurons and the simulation theory of mind-reading. *Trends Cogn Sci.* (1998) 2:493–501. doi: 10.1016/S1364-6613(98)01262-5

13. Dinstein I, Hasson U, Rubin N, Heeger DJ. Brain areas selective for both observed and executed movements. *J Neurophysiol.* (2007) 98:1415–27. doi: 10.1152/jn.00238.2007

14. Gazzola V, Keysers C. The observation and execution of actions share motor and somatosensory voxels in all tested subjects: single-subject analyses of unsmoothed fMRI data. *Cereb Cortex.* (2009) 19:1239–55. doi: 10.1093/cercor/bhn181

15. Buccino G, Binkofski F, Fink GR, Fadiga L, Fogassi L, Gallese V, et al. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *Euro J Neurosci.* (2001) 13:400–4. doi: 10.1111/j.1460-9568.2001.01385.x

16. Grèzes J, Armony JL, Rowe J, Passingham RE. Activations related to "mirror" and "canonical" neurones in the human brain: an fMRI study. *Neuroimage.* (2003) 18:928–37. doi: 10.1016/S1053-8119(03)00042-9

17. Kilner JM, Neal A, Weiskopf N, Friston KJ, Frith CD. Evidence of mirror neurons in human inferior frontal gyrus. *J Neurosci.* (2009) 29:10153–9. doi: 10.1523/JNEUROSCI.2668-09.2009

18. Buccino G, Binkofski F, Riggio L. The mirror neuron system and action recognition. *Brain Lang.* (2004) 89:370–6. doi: 10.1016/S0093-934X(03)00356-0

19. Iacoboni M. Neurobiology of imitation. *Curr Opin Neurobiol.* (2009) 19:661–5. doi: 10.1016/j.conb.2009.09.008

20. de la Rosa S, Schillinger FL, Bülthoff HH, Schultz J, Uludag K. fMRI adaptation between action observation and action execution reveals cortical areas with mirror neuron properties in human BA 44/45. *Front Hum Neurosci.* (2016) 10:78. doi: 10.3389/fnhum.2016.00078

21. Chong TTJ, Cunnington R, Williams MA, Kanwisher N, Mattingley JB. fMRI adaptation reveals mirror neurons in human inferior parietal cortex. *Curr Biol.* (2008) 18:1576–80. doi: 10.1016/j.cub.2008.08.068

22. Hickok G. Eight problems for the mirror neuron theory of action understanding in monkeys and humans. *J Cogn Neurosci.* (2009) 21:1229–43. doi: 10.1162/jocn.2009.21189

23. Mukamel R, Ekstrom AD, Kaplan J, Iacoboni M, Fried I. Single-Neuron responses in humans during execution and observation of actions. *Curr Biol.* (2010) 20:750–6. doi: 10.1016/j.cub.2010.02.045

24. Binder E, Dovern A, Hesse MD, Ebke M, Karbe H, Saliger J, et al. Lesion evidence for a human mirror neuron system. *Cortex.* (2017) 90:125–37. doi: 10.1016/j.cortex.2017.02.008

25. Heyes C, Catmur C. What happened to mirror neurons? *Perspect Psychol Sci.* (2022) 17:153–68. doi: 10.1177/1745691621990638

26. Caspers S, Zilles K, Laird AR, Eickhoff SB. ALE meta-analysis of action observation and imitation in the human brain. *Neuroimage.* (2010) 50:1148–67. doi: 10.1016/j.neuroimage.2009.12.112

27. Salmelin R, Hari R. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. *Neuroscience.* (1994) 60:537–50. doi: 10.1016/0306-4522(94)90263-1

28. Oberman LM, McCleery JP, Ramachandran VS, Pineda JA. EEG evidence for mirror neuron activity during the observation of human and robot actions: toward an analysis of the human qualities of interactive robots. *Neurocomputing.* (2007) 70:2194–203. doi: 10.1016/j.neucom.2006.02.024

29. Muthukumaraswamy SD, Johnson BW, McNair NA. Mu rhythm modulation during observation of an object-directed grasp. *Cogn Brain Res.* (2004) 19:195–201. doi: 10.1016/j.cogbrainres.2003.12.001

30. Muthukumaraswamy SD, Johnson BW. Changes in rolandic mu rhythm during observation of a precision grip. *Psychophysiology.* (2004) 41:152–6. doi: 10.1046/j.1469-8986.2003.00129.x

31. Molenberghs P, Cunnington R, Mattingley JB. Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. *Neurosci Biobehav Rev.* (2012) 36:341–9. doi: 10.1016/j.neubiorev.2011.07.004

32. Ramachandran VS, Oberman LM. Broken mirrors: a theory of autism. *Sci Am.* (2006) 295:62–9. doi: 10.1038/scientificamerican1106-62

33. Yates L, Hobson H. Continuing to look in the mirror: a review of neuroscientific evidence for the broken mirror hypothesis, EP-M model and STORM model of autism spectrum conditions. *Autism.* (2020) 24:1945–59. doi: 10.1177/1362361320936945

34. Iacoboni M, Mazziotta JC. Mirror neuron system: basic findings and clinical applications. *Ann Neurol.* (2007) 62:213–8. doi: 10.1002/ana.21198

35. Ramachandran VS, Seckel EL. Synchronized dance therapy to stimulate mirror neurons in autism. *Med Hypotheses.* (2011) 76:150–1. doi: 10.1016/j.mehy.2010.10.047

36. Khalil R, Tindle R, Boraud T, Moustafa AA, Karim AA. Social decision making in autism: on the impact of mirror neurons, motor control, and imitative behaviors. *CNS Neurosci Ther.* (2018) 24:669–76. doi: 10.1111/cns.13001

37. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, et al. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. *Schizophr Bull.* (2018) 44:1195–203. doi: 10.1093/schbul/sby058

38. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med.* (2005) 2:e141. doi: 10.1371/journal.pmed.0020141

39. Moreno-Küstner B, Martín C, Pastor L. Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. *PLoS ONE.* (2018) 13:e0195687. doi: 10.1371/journal.pone.0195687

40. Pacific W, Hasan SAW. *Magnitude and Impact*. World Health Organization (2021). Available online at: https://www.who.int/news-room/fact-sheets/detail/schizophrenia

41. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems: Alphabetical Index.* World Health Organization; International Statistical Classification of Diseases and Related Health Problems (2004).

42. Mouridsen SE, Rich B, Isager T. Psychiatric disorders in adults diagnosed as children with atypical autism. A case control study. *J Neural Transm.* (2008) 115:135–8. doi: 10.1007/s00702-007-0798-1

43. Rapoport J, Chavez A, Greenstein D, Addington A, Gogtay N. Autism spectrum disorders and childhood-onset schizophrenia: clinical and biological contributions to a relation revisited. *J Am Acad Child Adolesc Psychiatry.* (2009) 48:10–8. doi: 10.1097/CHI.0b013e31818b1c63

44. Solomon M, Olsen E, Niendam T, Ragland JD, Yoon J, Minzenberg M, et al. From lumping to splitting and back again: atypical social and language development in individuals with clinical-high-risk for psychosis, first episode schizophrenia, and autism spectrum disorders. *Schizophr Res.* (2011) 131:146–51. doi: 10.1016/j.schres.2011.03.005

45. Stahlberg O, Soderstrom H, Rastam M, Gillberg C. Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. *J Neural Transm.* (2004) 111:891–902. doi: 10.1007/s00702-004-0115-1

46. King BH, Lord C. Is schizophrenia on the autism spectrum? *Brain Res.* (2011) 1380:34–41. doi: 10.1016/j.brainres.2010.11.031

47. Sugranyes G, Kyriakopoulos M, Corrigall R, Taylor E, Frangou S. Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. *PLoS ONE.* (2011) 6:e25322. doi: 10.1371/journal.pone.0025322

48. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. *Nat Rev Neurosci.* (2015) 16:620–31. doi: 10.1038/nrn4005

49. Field T, Field T, Sanders C, Nadel J. Children with autism display more social behaviors after repeated imitation sessions. *Autism.* (2001) 5:317–23. doi: 10.1177/1362361301005003008

50. Escalona A, Field T, Nadel J, Lundy B. Brief report: imitation effects on children with autism. *J Autism Dev Disord.* (2002) 32:141–4. doi: 10.1023/A:1014896707002

51. Ingersoll B, Lewis E, Kroman E. Teaching the imitation and spontaneous use of descriptive gestures in young children with autism using a naturalistic behavioral intervention. *J Autism Dev Disord.* (2007) 37:1446–56. doi: 10.1007/s10803-006-0221-z

52. Ingersoll B, Schreibman L. Teaching reciprocal imitation skills to young children with autism using a naturalistic behavioral approach: effects on language, pretend play, and joint attention. *J Autism Dev Disord.* (2006) 36:487–505. doi: 10.1007/s10803-006-0089-y

53. Ingersoll B, Gergans S. The effect of a parent-implemented imitation intervention on spontaneous imitation skills in young children with autism. *Res Dev Disabil.* (2007) 28:163–75. doi: 10.1016/j.ridd.2006.02.004

54. Mehta UM, Thirthalli J, Aneelraj D, Jadhav P, Gangadhar BN, Keshavan MS. Mirror neuron dysfunction in schizophrenia and its functional implications: a systematic review. *Schizophr Res.* (2014) 160:9–19. doi: 10.1016/j.schres.2014.10.040

55. Tacconelli E. Systematic reviews: CRD's guidance for undertaking reviews in health care. *Lancet Infect Dis.* (2010) 10:226. doi: 10.1016/S1473-3099(10)70065-7

56. Stroup DF. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA.* (2000) 283:2008–12. doi: 10.1001/jama.283.15.2008

57. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Int J Surg.* (2021) 88:105906. doi: 10.1016/j.ijsu.2021.105906

58. Valizadeh A, Amlashi NH, Rasooli A, Mbwogge M, Haadi A. The mirror mechanism in schizophrenia spectrum disorders: protocol for a systematic review and meta-synthesis. *Res Square*. (2021). doi: 10.21203/rs.3.rs-264432/v3

59. Cooke A, Smith D, Booth A. Beyond PICO. *Qual Health Res.* (2012) 22:1435–43. doi: 10.1177/1049732312452938

60. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst Rev.* (2021) 10:39. doi: 10.1186/s13643-020-01542-z

61. National Institutes of Health. *Racial and Ethnic Categories and Definitions for NIH Diversity Programs and for Other Reporting Purposes*. National Institutes of Health (2015). Available online at: https://grants.nih.gov/grants/guide/notice-files/not-od-15-089.html

62. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* (1987) 13:261–76. doi: 10.1093/schbul/13.2.261

63. Andreasen NC. The scale for the assessment of negative symptoms (SANS): conceptual and theoretical foundations. *Br J Psychiatry.* (1989) 155:49–52. doi: 10.1192/S0007125000291496

64. Andreasen NC. *Scale for the Assessment of Positive Symptoms (SAPS).* Iowa City, IA: University of Iowa (1984)

65. van Erp TGM, Preda A, Nguyen D, Faziola L, Turner J, Bustillo J, et al. Converting positive and negative symptom scores between PANSS and SAPS/SANS. *Schizophr Res.* (2014) 152:289–94. doi: 10.1016/j.schres.2013.11.013

66. National Institute of Health. *NIH Quality Assessment of Case-Control Studies*. National Institute of Health (2014). Available online at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

67. Szucs D, Ioannidis JPA. Sample size evolution in neuroimaging research: an evaluation of highly-cited studies (1990–2012) and of latest practices (2017–2018) in high-impact journals. *Neuroimage.* (2020) 221:117164. doi: 10.1016/j.neuroimage.2020.117164

68. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. *Doing Meta-Analysis With R*. Boca Raton, FL: Chapman and Hall/CRC (2021). doi: 10.1201/9781003107347

69. Lewis JJ, Pattanayak SK. Who adopts improved fuels and cookstoves? A systematic review. *Environ Health Perspect.* (2012) 120:637–45. doi: 10.1289/ehp.1104194

70. Starnes DS, Yates D, Moore DS. *The Practice of Statistics*. Macmillan (2010). Available online at: https://www.google.com/books/edition/The_Practice_of_Statistics/r0Z-AN_T2hIC?hl=en&gbpv=0

71. Cropley VL, Klauser P, Lenroot RK, Bruggemann J, Sundram S, Bousman C, et al. Accelerated gray and white matter deterioration with age in schizophrenia. *Am J Psychiatry.* (2017) 174:286–95. doi: 10.1176/appi.ajp.2016.16050610

72. Lewin S, Glenton C, Munthe-Kaas H, Carlsen B, Colvin CJ, Gülmezoglu M, et al. Using qualitative evidence in decision making for health and social interventions: an approach to assess confidence in findings from qualitative evidence syntheses (GRADE-CERQual). *PLoS Med.* (2015) 12:e1001895. doi: 10.1371/journal.pmed.1001895

73. Andereasen N, Calage C, O'Leary D. Theory of mind and schizophrenia: a positron emission tomography study of medication-free patients. *Schizophr Bull.* (2009) 35:1030. doi: 10.1093/schbul/sbp069

74. Andrews SC, Enticott PG, Hoy KE, Thomson RH, Fitzgerald PB. No evidence for mirror system dysfunction in schizophrenia from a multimodal TMS/EEG study. *Psychiatry Res.* (2015) 228:431–40. doi: 10.1016/j.psychres.2015.05.067

75. Bagewadi VI, Mehta UM, Naik SS, Govindaraj R, Varambally S, Arumugham SS, et al. Diminished modulation of motor cortical reactivity during context-based action observation in schizophrenia. *Schizophr Res.* (2019) 204:222–9. doi: 10.1016/j.schres.2018.07.043

76. Brown EC, Gonzalez-Liencres C, Tas C, Brüne M. Reward modulates the mirror neuron system in schizophrenia: a study into the mu rhythm suppression, empathy, and mental state attribution. *Soc Neurosci.* (2016) 11:175–86. doi: 10.1080/17470919.2015.1053982

77. Choe E, Lee TY, Kim M, Hur JW, Yoon YB, Cho KIK, et al. Aberrant within- and between-network connectivity of the mirror neuron system network and the mentalizing network in first episode psychosis. *Schizophr Res.* (2018) 199:243–9. doi: 10.1016/j.schres.2018.03.024

78. Das P, Lagopoulos J, Coulston CM, Henderson AF, Malhi GS. Mentalizing impairment in schizophrenia: a functional MRI study. *Schizophr Res.* (2012) 134:158–64. doi: 10.1016/j.schres.2011.08.019

79. Enticott P, Hoy K, Herring S, Johnston P, Daskalakis Z, Fitzgerald P. Reduced motor facilitation during action observation in schizophrenia: a mirror neuron deficit? *Schizophr Res.* (2008) 102:116–21. doi: 10.1016/j.schres.2008.04.001

80. Ferri F, Costantini M, Salone A, Ebisch S, de Berardis D, Mazzola V, et al. Binding action and emotion in first-episode schizophrenia. *Psychopathology.* (2014) 47:394–407. doi: 10.1159/000366133

81. Guo S, Kendrick KM, Yu R, Wang HLS, Feng J. Key functional circuitry altered in schizophrenia involves parietal regions associated with sense of self. *Hum Brain Mapp.* (2014) 35:123–39. doi: 10.1002/hbm.22162

82. Horan WP, Iacoboni M, Cross KA, Korb A, Lee J, Nori P, et al. Self-reported empathy and neural activity during action imitation and observation in schizophrenia. *NeuroImage Clin.* (2014) 5:100–8. doi: 10.1016/j.nicl.2014.06.006

83. Horan WP, Jimenez AM, Lee J, Wynn JK, Eisenberger NI, Green MF. Pain empathy in schizophrenia: an fMRI study. *Soc Cogn Affect Neurosci.* (2016) 11:783–92. doi: 10.1093/scan/nsw002

84. Horan WP, Pineda JA, Wynn JK, Iacoboni M, Green MF. Some markers of mirroring appear intact in schizophrenia: evidence from mu suppression. *Cogn Affect Behav Neurosci.* (2014) 14:1049–60. doi: 10.3758/s13415-013-0245-8

85. Kato Y, Muramatsu T, Kato M, Shibukawa Y, Shintani M, Mimura M. Magnetoencephalography study of right parietal lobe dysfunction of the evoked mirror neuron system in antipsychotic-free schizophrenia. *PLoS ONE.* (2011) 6:e28087. doi: 10.1371/journal.pone.0028087

86. Lee JS, Chun JW, Yoon SY, Park HJ, Kim JJ. Involvement of the mirror neuron system in blunted affect in schizophrenia. *Schizophr Res.* (2014) 152:268–74. doi: 10.1016/j.schres.2013.10.043

87. McCormick LM, Brumm MC, Beadle JN, Paradiso S, Yamada T, Andreasen N. Mirror neuron function, psychosis, and empathy in schizophrenia. *Psychiatry Res Neuroimaging.* (2012) 201:233–9. doi: 10.1016/j.pscychresns.2012.01.004

88. Mehta UM, Thirthalli J, Basavaraju R, Gangadhar BN, Pascual-Leone A. Reduced mirror neuron activity in schizophrenia and its association with theory of mind deficits: evidence from a transcranial magnetic stimulation study. *Schizophr Bull.* (2014) 40:1083–94. doi: 10.1093/schbul/sbt155

89. Mitra S, Nizamie SH, Goyal N, Tikka SK. Mu-wave activity in schizophrenia: evidence of a dysfunctional mirror neuron system from an indian study. *Indian J Psychol Med.* (2014) 36:276–81. doi: 10.4103/0253-7176.135380

90. Möhring N, Shen C, Hahn E, Ta TMT, Dettling M, Neuhaus AH. Mirror neuron deficit in schizophrenia: evidence from repetition suppression. *Schizophr Res.* (2015) 168:174–9. doi: 10.1016/j.schres.2015.07.035

91. Park KM, Kim JJ, Ku J, Kim SY, Lee HR, Kim SI, et al. Neural basis of attributional style in schizophrenia. *Neurosci Lett.* (2009) 459:35–40. doi: 10.1016/j.neulet.2009.04.059

92. Quintana J. A compensatory mirror cortical mechanism for facial affect processing in schizophrenia. *Neuropsychopharmacology.* (2001) 25:915–24. doi: 10.1016/S0893-133X(01)00304-9

93. Schilbach L, Derntl B, Aleman A, Caspers S, Clos M, Diederen KMJ, et al. Differential patterns of dysconnectivity in mirror neuron and mentalizing networks in schizophrenia. *Schizophr Bull.* (2016) 42:1135–48. doi: 10.1093/schbul/sbw015

94. Schürmann M, Järveläinen J, Avikainen S, Cannon TD, Lönnqvist J, Huttunen M, et al. Manifest disease and motor cortex reactivity in twins discordant for schizophrenia. *Br J Psychiatry.* (2007) 191:178–9. doi: 10.1192/bjp.bp.106.024604

95. Singh F, Pineda J, Cadenhead KS. Association of impaired EEG mu wave suppression, negative symptoms and social functioning in biological motion processing in first episode of psychosis. *Schizophr Res.* (2011) 130:182–6. doi: 10.1016/j.schres.2011.04.004

96. Stegmayer K, Bohlhalter S, Vanbellingen T, Federspiel A, Wiest R, Müri RM, et al. Limbic interference during social action planning in schizophrenia. *Schizophr Bull.* (2018) 44:359–68. doi: 10.1093/schbul/sbx059

97. Sun F, Zhao Z, Lan M, Xu Y, Huang M, Xu D. Abnormal dynamic functional network connectivity of the mirror neuron system network and the mentalizing network in patients with adolescent-onset, first-episode, drug-naïve schizophrenia. *Neurosci Res.* (2021) 162:63–70. doi: 10.1016/j.neures.2020.01.003

98. Thakkar KN, Peterman JS, Park S. Altered brain activation during action imitation and observation in schizophrenia: a translational approach to investigating social dysfunction in schizophrenia. *Am J Psychiatry.* (2014) 171:539–48. doi: 10.1176/appi.ajp.2013.13040498

99. Varcin KJ, Bailey PE, Henry JD. Empathic deficits in schizophrenia: the potential role of rapid facial mimicry. *J Int Neuropsychol Soc.* (2010) 16:621–9. doi: 10.1017/S1355617710000329

100. Okruszek Ł, Wordecha M, Jarkiewicz M, Kossowski B, Lee J, Marchewka A. Brain correlates of recognition of communicative interactions from biological motion in schizophrenia. *Psychol Med.* (2018) 48:1862–71. doi: 10.1017/S0033291717003385

101. Zaytseva Y, Morozova A, Bendova M, Garakh Z. Is motor imagery different in catatonic schizophrenia? *Psych J.* (2017) 6:137–8. doi: 10.1002/pchj.155

102. He Y, Steines M, Sammer G, Nagels A, Kircher T, Straube B. Modality-specific dysfunctional neural processing of social-abstract and non-social-concrete information in schizophrenia. *NeuroImage Clin.* (2021) 29:102568. doi: 10.1016/j.nicl.2021.102568

103. Park SH, Kim T, Ha M, Moon SY, Lho SK, Kim M, et al. Intrinsic cerebellar functional connectivity of social cognition and theory of mind in first-episode psychosis patients. *NPJ Schizophr.* (2021) 7:59. doi: 10.1038/s41537-021-00193-w

104. ElShahawi HH, Sakr HM, Hashim MA, Mohamed HH, Abdeen MS. Social cognition correlation to white matter integrity alteration in mirror neurons of schizophrenic patients: DTI study. *Neurol Psychiatry Brain Res.* (2020) 38:65–73. doi: 10.1016/j.npbr.2020.10.004

105. Saito Y, Kubicki M, Koerte I, Otsuka T, Rathi Y, Pasternak O, et al. Impaired white matter connectivity between regions containing mirror neurons, and relationship to negative symptoms and social cognition, in patients with first-episode schizophrenia. *Brain Imaging Behav.* (2018) 12:229–37. doi: 10.1007/s11682-017-9685-z

106. Tseng CEJ, Chien YL, Liu CM, Wang HLS, Hwu HG, Tseng WYI. Altered cortical structures and tract integrity of the mirror neuron system in association with symptoms of schizophrenia. *Psychiatry Res Neuroimaging.* (2015) 231:286–91. doi: 10.1016/j.pscychresns.2015.01.010

107. Ioannidis JPA. Why most published research findings are false. *PLoS Med.* (2005) 2:e124. doi: 10.1371/journal.pmed.0020124

108. Burns J. The social brain hypothesis of schizophrenia. *World Psychiatry.* (2006) 5:77–81.

109. Spunt RP, Lieberman MD. The busy social brain. *Psychol Sci.* (2013) 24:80–6. doi: 10.1177/0956797612450884

110. Frith CD, Corcoran R. Exploring 'theory of mind' in people with schizophrenia. *Psychol Med.* (1996) 26:521–30. doi: 10.1017/S0033291700035601

111. Bastiaansen JA, Thioux M, Nanetti L, van der Gaag C, Ketelaars C, Minderaa R, et al. Age-Related increase in inferior frontal gyrus activity and social functioning in autism spectrum disorder. *Biol Psychiatry.* (2011) 69:832–8. doi: 10.1016/j.biopsych.2010.11.007

112. Chan MMY, Han YMY. Differential mirror neuron system (MNS) activation during action observation with and without social-emotional components in autism: a meta-analysis of neuroimaging studies. *Mol Autism.* (2020) 11:72. doi: 10.1186/s13229-020-00374-x

113. Nedelko V, Hassa T, Hamzei F, Weiller C, Binkofski F, Schoenfeld MA, et al. Age-independent activation in areas of the mirror neuron system during action observation and action imagery. A fMRI study. *Restor Neurol Neurosci.* (2010) 28:737–47. doi: 10.3233/RNN-2010-0542

114. Enticott PG, Kennedy HA, Rinehart NJ, Tonge BJ, Bradshaw JL, Taffe JR, et al. Mirror neuron activity associated with social impairments but not age in autism spectrum disorder. *Biol Psychiatry.* (2012) 71:427–33. doi: 10.1016/j.biopsych.2011.09.001

115. Kladi A, Iliadou P, Tsolaki M, Moraitou D. Age-related differences in Mu rhythm during emotional destination memory task. *Curr Aging Sci.* (2022) 15:26–36. doi: 10.2174/1874609814666210607154838

116. Rajji TK, Voineskos AN, Butters MA, Miranda D, Arenovich T, Menon M, et al. Cognitive performance of individuals with schizophrenia across seven

decades: a study using the MATRICS consensus cognitive battery. *Am J Geriatr Psychiatry*. (2013) 21:108–18. doi: 10.1016/j.jagp.2012.10.011

117. Linke M, Jankowski KS, Ciołkiewicz A, Jedrasik-Styła M, Parnowska D, Gruszka A, et al. Age or age at onset? Which of them really matters for neuro and social cognition in schizophrenia? *Psychiatry Res*. (2015) 225:197–201. doi: 10.1016/j.psychres.2014.11.024

118. Rajji TK, Ismail Z, Mulsant BH. Age at onset and cognition in schizophrenia: meta-analysis. *Br J Psychiatry*. (2009) 195:286–93. doi: 10.1192/bjp.bp.108.060723

119. Smeets-Janssen MMJ, Meesters PD, Comijs HC, Eikelenboom P, Smit JH, de Haan L, et al. Theory of mind differences in older patients with early-onset and late-onset paranoid schizophrenia. *Int J Geriatr Psychiatry*. (2013) 28:1141–6. doi: 10.1002/gps.3933

120. Hobson HM, Bishop DVM. Mu suppression – a good measure of the human mirror neuron system? *Cortex*. (2016) 82:290–310. doi: 10.1016/j.cortex.2016.03.019

121. Krivan SJ, Caltabiano N, Cottrell D, Thomas NA. I'll cry instead: Mu suppression responses to tearful facial expressions. *Neuropsychologia*. (2020) 143:107490. doi: 10.1016/j.neuropsychologia.2020.107490

122. Bekkali S, Youssef GJ, Donaldson PH, Hyde C, Do M, He JL, et al. Is there a relationship between EEG and sTMS neurophysiological markers of the putative human mirror neuron system? *J Neurosci Res*. (2021) 99:3238–49. doi: 10.1002/jnr.24969

123. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. Vol. 5. Washington, DC: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596

124. Gur RE, Kohler CG, Ragland JD, Siegel SJ, Lesko K, Bilker WB, et al. Flat affect in schizophrenia: relation to emotion processing and neurocognitive measures. *Schizophr Bull*. (2006) 32:279–87. doi: 10.1093/schbul/sbj041

125. Dickinson D, Bellack AS, Gold JM. Social/Communication skills, cognition, and vocational functioning in schizophrenia. *Schizophr Bull*. (2007) 33:1213–20. doi: 10.1093/schbul/sbl067

126. le Bel RM, Pineda JA, Sharma A. Motor–auditory–visual integration: the role of the human mirror neuron system in communication and communication disorders. *J Commun Disord*. (2009) 42:299–304. doi: 10.1016/j.jcomdis.2009.03.011

127. Cantisani A, Stegmayer K, Federspiel A, Bohlhalter S, Wiest R, Walther S. Blood perfusion in left inferior and middle frontal gyrus predicts communication skills in schizophrenia. *Psychiatry Res Neuroimaging*. (2018) 274:7–10. doi: 10.1016/j.pscychresns.2018.02.002

128. Wong E, Ungvari GS, Leung SK, Tang WK. Rating catatonia in patients with chronic schizophrenia: Rasch analysis of the bush-francis catatonia rating scale. *Int J Methods Psychiatr Res*. (2007) 16:161–70. doi: 10.1002/mpr.224

129. Pridmore S, Brüne M, Ahmadi J, Dale J. Echopraxia in schizophrenia: possible mechanisms. *Austral N Z J Psychiatry*. (2008) 42:565–71. doi: 10.1080/00048670802119747

130. Mehta UM, Waghmare A v., Thirthalli J, Venkatasubramanian G, Gangadhar BN. Is the human mirror neuron system plastic? Evidence from a transcranial magnetic stimulation study. *Asian J Psychiatr*. (2015) 17:71–7. doi: 10.1016/j.ajp.2015.06.014

131. Mitra S, Nizamie SH, Goyal N. Putative mirror neuron activity in patients with schizophrenia remains unchanged after 8 weeks of antipsychotic treatment. *Asian J Psychiatr*. (2018) 38:70–1. doi: 10.1016/j.ajp.2017.10.016

132. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. (2010) 167:748–51. doi: 10.1176/appi.ajp.2010.09091379

133. Hadoush H, Nazzal M, Almasri NA, Khalil H, Alafeef M. Therapeutic effects of bilateral anodal transcranial direct current stimulation on prefrontal and motor cortical areas in children with autism spectrum disorders: a pilot study. *Autism Res*. (2020) 13:828–36. doi: 10.1002/aur.2290

134. Radhakrishna S, Nagarathna R, Nagendra H. Integrated approach to yoga therapy and autism spectrum disorders. *J Ayurveda Integr Med*. (2010) 1:120. doi: 10.4103/0975-9476.65089

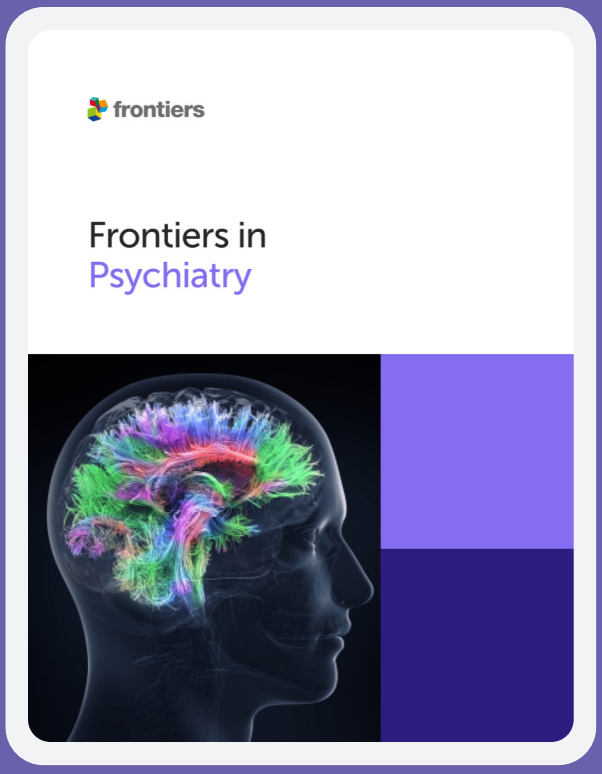
Frontiers in Psychiatry

Explores and communicates innovation in the field of psychiatry to improve patient outcomes

The third most-cited journal in its field, using translational approaches to improve therapeutic options for mental illness, communicate progress to clinicians and researchers, and consequently to improve patient treatment outcomes.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact