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The relationship between the resting state functional connectivity and social cognition in schizophrenia: Results from the Italian Network for Research on Psychoses

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ABSTRACT

Deficits in social cognition (SC) interfere with recovery in schizophrenia (SZ) and may be related to resting state brain connectivity.

This study aimed at assessing the alterations in the relationship between resting state functional connectivity and the social-cognitive abilities of patients with SZ compared to healthy subjects.

We divided the brain into 246 regions of interest (ROI) following the Human Healthy Volunteers Brainnetome Atlas. For each participant, we calculated the resting-state functional connectivity (rsFC) in terms of degree centrality (DC), which evaluates the total strength of the most powerful coactivations of every ROI with all other ROIs during rest. The rs-DC of the ROIs was correlated with five measures of SC assessing emotion processing and mentalizing in 45 healthy volunteers (HVs) chosen as a normative sample. Then, controlling for symptoms severity, we verified whether these significant associations were altered, i.e., absent or of opposite sign, in 55 patients with SZ.

We found five significant differences between SZ patients and HVs: in the patients' group, the correlations between emotion recognition tasks and rsFC of the right entorhinal cortex (R-EC), left superior parietal lobule (L-SPL), right caudal hippocampus (R-c-Hipp), and the right caudal (R-c) and left rostral (L-r) middle temporal gyri (MTG) were lost.

An altered resting state functional connectivity of the L-SPL, R-EC, R-c-Hipp, and bilateral MTG in patients with SZ may be associated with impaired emotion recognition. If confirmed, these results may enhance the development of non-invasive brain stimulation interventions targeting those cerebral regions to reduce SC deficit in SZ.

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1. Introduction

Social cognition (SC) refers to the psychological processes of perceiving, encoding, storing, retrieving, and regulating information about others and ourselves (Green et al., 2019). Emotion processing and mentalizing are the SC domains most frequently assessed in neuropsychiatric disorders. The former involves both the ability to correctly identify others' emotions (emotion perception) and the ability to properly manage one's own emotions (emotion management), while mentalizing includes theory of mind (ToM) skills needed to represent others' mental states and make inferences about their intentions and beliefs (Green et al., 2005, 2008, 2019; Lysaker and Hasson-Ohayon, 2021; Maj et al., 2021).

Emotion processing and mentalizing are the two most impaired SC domains in schizophrenia (SZ) and deficits in these specific mental processes represent one of the main limits to patients' functional recovery (Vaskinn and Horan, 2020). Two meta-analyses showed that SC performance, particularly in ToM tests, was strongly associated with community functioning and mediated the relationship between neurocognition and functional outcomes (Fett et al., 2011; Halverson et al., 2019). Three studies from the Italian Network for Research on Psychoses (NIRP) found similar results. Based on deficits in mentalizing processes, different patients' clusters with different impairments in real-life functioning were identified at baseline (Rocca et al., 2016). Moreover, baseline SC and improvement in social inference were found among the strongest predictors of functional recovery evaluated after four years (Mucci et al., 2021; Rocca et al., 2023).

Many studies investigated the neural correlates of SC in people suffering from SZ. Most of them focused on functional magnetic resonance imaging (fMRI) data recorded during ToM tasks. According to three recent meta-analyses, altered activations were found in the prefrontal cortices, motor and premotor areas, cuneus and precuneus, temporoparietal junction, anterior insula, cingulate gyrus, and amygdala (Kronbichler et al., 2017; Vucurovic et al., 2020; Weng et al., 2022). Recently, some studies have taken a different approach by assessing resting state brain activity in terms of resting-state functional connectivity (rsFC), which reveals the temporal relations between the activation of different brain regions (Biswal et al., 1995). Rs-FC methods are a valuable complement to task-based approaches to study the neural basis of specific behaviors or symptoms (Abram et al., 2017) as RsFC has been shown to predict individual differences in task-evoked brain activity (Tavor et al., 2016) and may inform about the neural connectivity supporting or predisposing mental processes. Compared to task-based approaches, these neuroimaging methods also have some advantages: they are not confounded by individual differences in attention, effort, or comprehension that may emerge during a task and present fewer design constraints that could impede cross-sample replications (Abram et al., 2017). Some recent studies analyzed the association between rsFC and SC in patients with psychoses (Abram et al., 2017; Brady Jr et al., 2020; Choe et al., 2018; Jimenez et al., 2019; Kong et al., 2022; Narita et al., 2021; Peeters et al., 2015a, 2015b). Among them, some analyzed samples of mixed affective and non-affective psychoses (Brady Jr et al., 2020; Peeters et al., 2015a, 2015b), while others focused on patients with first-episode psychosis (Choe et al., 2018; Narita et al., 2021). Three investigated the associations between rs-FC and SC in patients with SZ (Abram et al., 2017; Jimenez et al., 2019; Kong et al., 2022). Abram et al. (2017) focused on brain areas involved in social cognition and grouped them into medial, temporal, and occipital components. In patients with SZ, the rsFC between the medial (medial prefrontal and anterior cingulate cortices) and temporal (superior temporal gyrus, temporoparietal junction, and temporal pole) components was negatively related to cognitive empathy accuracy, i.e., the ToM ability to understand the emotional perspective of others correctly. Kong et al. (2022) found an altered intrinsic network organization of the default mode network and a negative correlation between the intrinsic connectivity in the right cerebellum Crus I/Crus II and the right inferior temporal gyrus and emotion management in first-diagnosis drug-naïve SZ patients. Only Jimenez et al. (2019) used a whole-brain approach focusing on the relationship between nine resting state networks and SC measures. The Authors did not find any significant association between the altered connectivity of resting state functional networks and any of the SC domains assessed, namely emotion perception, emotion management, and metalizing, suggesting the need for further studies.

Following this line of research, we hypothesize that a higher degree of rsFC in brain areas involved in SC is associated with better SC skills in healthy subjects. A higher connection of these areas at rest would predispose subjects to better performance on tasks assessing SC. Having established these associations in the healthy group, we believe that some of the associations would be altered, i.e., absents or of opposite sign, in subjects with SZ. These differences, if present, could represent a neural correlate of the SC deficits found in patients with SZ. We expect to find significant differences between the two groups regarding the areas most involved in SC processes in healthy subjects (Diveica et al., 2021; Feng et al., 2021; Peelen and Downing, 2023; Redcay and Moraczewski, 2020; Schurz et al., 2021) and patients with SZ (Green et al., 2015; Henry et al., 2016; Hiser and Koenigs, 2018; Nejati et al., 2021; Porcelli et al., 2019; Saris et al., 2022; Vucurovic et al., 2020; Weng et al., 2022) consisting in the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), orbitofrontal cortex (OFC), premotor cortex (PMC), precuneus (PCun), inferior parietal lobule (IPL), temporoparietal junction (TPJ), superior temporal gyrus (STG), fusiform face area (FFA), temporal pole (TP), anterior insula (AI), dorsal anterior cingulate cortex (dACC), and amygdala (Amy). Therefore, the aim of this work is to test these hypotheses.

2. Material and methods

2.1. Participants

Participants were enrolled from five Italian university psychiatric services joining the Italian Network for Research on Psychoses (NIRP) (Galderisi et al., 2014, 2020).

Patients with a diagnosis of schizophrenia according to the DSM-IV and confirmed with the Structured Clinical Interview for DSM-IV - Patient version (SCID-I-P) were included in the study.

Exclusion criteria were more than mild extra-pyramidal symptoms, neurological diseases, history of head injury with loss of consciousness, moderate, severe, or profound intellectual developmental disorder, history of alcohol or substance abuse or dependence during the past six months, pregnancy, inability to provide informed consent, and changes in antipsychotics therapy in the past three months.

For healthy volunteers, additional exclusion criteria were current use of psychoactive drugs, personal history of psychiatric disorders, and a diagnosis of psychotic disorders in 1st-degree relatives. Each HV was screened with the SCID-I-Non-Patient version (SCID-I-NP).

After receiving a comprehensive explanation of the study procedures and goals, written informed consent was obtained from all subjects.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects were approved by local Ethics Committees of the participating centers, namely by the Comitato Etico -Interaziendale Azienda Ospedaliero-Universitaria 'Città della Salute e della Scienza di Torino' – Azienda Ospedaliera 'Ordine Mauriziano di Torino' – Azienda Sanitaria Locale 'Città di Torino' (approval number: 63143), Comitato Etico Università degli Studi della Campania 'Luigi Vanvitelli' (approval number: 1382), Comitato Etico Indipendente Azienda Ospedaliero-Universitaria 'Consorziale Policlinico' di Bari (approval number: 4205), Comitato Etico per le Province di L'Aquila e Teramo (approval number: 2243), and Comitato Etico Regionale, Regione Liguria (approval number: 007REG2016).

2.2. Clinical assessment

The severity of symptoms was rated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Positive symptoms were assessed according to the 5-factor solution proposed by Wallwork et al. (2012) using four items of the PANSS, namely P1 (delusions), P3 (hallucinatory behavior), P5 (grandiosity), G9 (unusual thought content). Disorganization was represented by the PANSS item "conceptual disorganization" (P2) to avoid overlap with cognitive functioning, as the PANSS disorganization factor of the 5-factors solution proposed by Wallwork et al. (2012) includes impairment in abstract thinking and poor attention (Giordano et al., 2023). Negative symptoms were evaluated by using the items 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) following the European Psychiatric Association (EPA) guidance on the assessment of negative symptoms in SZ (Galderisi et al., 2021). Negative symptoms were also assessed with a second-generation rating scale for negative symptoms, i.e., the Italian version of the Brief Negative Symptom Scale (BNSS; Kirkpatrick et al., 2011; Mucci et al., 2015). Depressive symptoms were evaluated with the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1993). Extrapyramidal symptoms were assessed with the St. Hans Rating Scale (SHRS; Gerlach et al., 1993). The SHRS has four components: hyperkinesia global, parkinsonism global, dystonia global, and akathisia global (Gerlach et al., 1993). Each component can range from absence of symptoms (0 points) to severe symptoms (6 points) (Gerlach et al., 1993). We excluded patients with more than mild extrapyramidal symptoms (i.e., >2 points) in one or more of the four components of the SHRS.

Clinical data were collected to provide an accurate description of the SZ sample. The SHRS was employed to verify whether there were subjects with movement disorders who should be excluded from the study because they could not stand still during the MR scan.

2.3. Assessment of social cognition

The assessment of SC included the Italian versions of the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT) managing emotion section, the Facial Emotion Identification Test (FEIT), and The Awareness of Social Inference Test (TASIT) (Kerr and Neale, 1993; Mayer et al., 2002; McDonald et al., 2006; Rocca et al., 2016).

The FEIT evaluates emotion perception abilities in terms of correctly recognizing facial emotions from pictures of actors' faces (Ekman and Friesen, 1976). Faces show basic emotions, namely fear, disgust, anger, happiness, sadness, surprise, and neutral expression. We considered the percentage of correct answers. The percentages were normalized for each subject by T-score transformation.

The TASIT proposes a collection of short videos showing everyday social interactions. During the test, participants have to correctly identify the emotions expressed by the actors and the type of communication showed in their interaction, i.e., sincere, deceitful, or sarcastic communication. The test consists of seven scales evaluating the recognition of spontaneous basic emotional expression (happy, surprised, sad, anxious, angry, disgusted, and neutral), sincere communication, lie, simple, paradoxical, and enriched sarcasm. These scales are organized into three sections: emotion recognition (section 1); social inference, minimal (section 2), which evaluates the comprehension of sincere versus simple and paradoxical sarcasm; and social inference, enriched (section 3), which assesses the recognition of lies versus enriched sarcasm. In contrast to FEIT, where emotion recognition is performed on photographs of actors' faces (Ekman faces), in TASIT section 1, this is done on movies of actors. Therefore, we decided to employ both tests since the former accurately assesses the ability to recognize fixed facial expressions while the latter is more ecological and considers other elements such as facial movements, voice, and gestures.

TASIT scores of each section were normalized for each subject by T-score transformation.

T-score transformations were applied on FEIT and TASIT to make results comparable between tests.

The MSCEIT is included in the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB). In the study, we employed the MSCEIT managing emotion section (MSCEIT-ME) that examines the regulation of emotions in oneself and in relationships with others by presenting written vignettes of various situations, along with ways to cope with the emotions depicted in these vignettes. These data were transformed into the corresponding percentiles according to the MCCB age and gender-specific normative values.

For all SC tests, higher T-scores or percentiles indicate a better performance.

2.4. Acquisition and preprocessing of MRI data

Participants performed SC tests in the morning and MR scans in the afternoon of the same day. MRI evaluations were performed at five different sites and with six different 3 Tesla scanners. All the sites involved used a 3 Tesla scanner to record one resting state-based functional MRI (rs-fMRI) sequence and one structural MRI (sMRI) for each participant. Rs-fMRI was carried out using a 5-min resting state paradigm. Participants were asked to stand still, eyes open, and stare at a crosshair on the screen. For the sMRI, the T1-weighted structural images used spoiled gradient echo or Magnetization Prepared - RApid Gradient Echo (MPRAGE) sequences. A gradient-echo echo-planar imaging (GE-EPI) sequence was used to acquire images during rs-fMRI acquisition. The GE-EPI sequence had the following characteristics in all sites: 300 s, 150 volumes; TR/TE = 2000/30; voxel size = $3.75 \times 3.75 \times 5\ mm^3$; and FOV = 240 mm/26 slices. Details on the scans and sequences of each site are summarized in Table S1 of the supplementary materials.

For sMRI, data processing was performed with Computational Anatomy Toolbox (2022) (CAT 12) included in SPM12. T1-weighted images were normalized on a standard brain (MNI152) using a diffeomorphic registration algorithm (DARTEL) and segmented into different tissue classes (gray matter, white matter, and cerebrospinal fluid) based on probability maps. All images were then modulated through Jacobian determinants to preserve initial volumes and smoothed with a 3-mm isotropic Gaussian filter. We used segmented gray matter images from sMRI, which reflect gray matter volume (GMV) information of the whole brain. The quality-based inclusion criteria were absence in the raw images of technical artifacts such as blurring, ringing, wrapping, and incomplete head coverage and absence in the segmented images of excessive noise, poor image contrast, and/or inadequate boundaries.

To compensate for differences between scanners in the MRI acquisition window, individual gray matter images were combined using the ImCalc toolbox in SPM12 with a multiplicative function to obtain a binary mask of voxels acquired only in each scanner. This mask containing only voxels common to all acquisitions (approximately 359,000 isotropic 1 mm voxels) was applied to all individual images. The resulting gray matter volume (GMV) maps were included in the multimodal group analyses. In subsequent analyses, individual total intracranial volume (TIV) was also calculated and used as a disturbance covariate.

Rs-fMRI data were preprocessed with SPM12. For each participant, functional volumes were realigned to correct for head movement. Individual motion parameters were extracted and used to calculate Friston 24 motion parameters. The realigned images were rescaled, co-registered to T1-weighted structural images, spatially normalized to a standard space (MNI 152) and masked using the gray matter mask. Finally, noise covariates, including Friston 24 head motion parameters, white matter signals, and cerebrospinal signals, were regressed and images were smoothed with an isotropic 6 mm FWHM kernel. Wavelet despiking was performed to remove motion-related distortions. The

quality-based inclusion criteria were absence of scan artifacts and low head motion (translation>3 mm, rotation>3°, change in Framewise Displacement between volumes - FD > 0.05). The individual mean value of FD was calculated and used as a disturbance covariate in subsequent analyses.

For the extraction of signal time courses in each anatomical district, we used the Human Brainnetome Atlas (BNA) (Fan et al., 2016). The BNA atlas divided the gray matter of the brain into 246 ROIs, 123 for each hemisphere, comprising 210 cortical and 36 subcortical ROIs. This parceling out covers the gray matter of the whole human brain. For each subject, we extracted the time courses from each of the 246 ROIs using the Data Processing Assistant for Resting-State fMRI (DPARSF). We chose to examine the rs-fMRI signal of the ROIs described in the BNA because this method reduces the dimensions of the data (from voxels to ROIs) and the ROIs are delimitated based on both anatomical and functional connections knowledge (Fan et al., 2016; Narita et al., 2021). The extracted data were then normalized within each subject by T-score transformation to minimize global signal differences between subjects.

For each participant, we calculated the rsFC in terms of degree centrality (DC) of each ROI during resting state. Resting-state DC (rs-DC) is a network connectivity measure that quantifies the connectivity of a node (in this case, a given ROI) with all other nodes (all the other ROIs of the brain) (Zuo et al., 2012). DC is an established functional connectivity metric representing for each node the number of Pearson's correlations with all other nodes exceeding a predefined threshold (Dukart and Bertolino, 2014). The threshold was set to $r > 0.25$ (Dukart and Bertolino, 2014; Buckner et al., 2009). All computations were restricted to a gray matter mask obtained by thresholding the MNI template used for spatial normalization by a value of 0.2, i.e., 20 % probability of being gray matter (Dukart and Bertolino, 2014). To account for the site effect, we applied the ComBat algorithm (Johnson et al., 2007) to rs-DC data. This algorithm is based on empirical Bayes and can be employed in studies with small sample sizes (Yu et al., 2018). It consists of a multivariate linear mixed effects regression with terms for rsFC and scanners variables to remove the site effect preserving the heterogeneity of the rsFC variables (Yu et al., 2018).

Nine subjects were excluded because of scan artifacts; four subjects were excluded because of excessive movement not related to extrapyramidal symptoms.

2.5. Statistical analyses

The normal distribution of the continuous variables was verified with the Kolmogorov-Smirnov test. The between-group comparison of sociodemographic variables and SC tests were performed with the χ^2 test, one-way analysis of variance (ANOVA), and the Kruskal-Wallis test according to the type of variable and its distribution. The false discovery rate (FDR) was controlled with the Benjamini-Hochberg (BH) procedure (Benjamini and Hochberg, 1995).

The between-group comparison of the correlations between the individual DC of each ROI and the five scores of the SC tests was performed as follows: (i) we calculated Spearman's partial correlation within each group (SZ and HV) controlling for age, sex, and years of education in both groups and for the severity of positive, disorganized, negative, and depressing symptoms in the SZ group only; (ii) we applied Fisher's transformations to obtain the correspondent Z score of each correlation; (iii) using the Z-test, we compared the Z scores of the significant correlation within the HV group with the Z scores of the correspondent correlations within the SZ group; (iv) to control the FDR, we applied the BH-procedure to the Z test results.

We employed non-parametric correlations, i.e., Spearman's, because most continuous variables were not normally distributed. We controlled for age and years of education as the HV and SZ groups showed significant differences in those two sociodemographic variables. HV subjects were chosen as the reference group to evaluate the alteration of the association between the rsFC and SC in patients with SZ. Therefore, we compared the two groups exclusively to the correlations that were significant within the HV group.

Analyses were conducted with IBM Statistical Package for Social Science (SPSS) version 28.0.1 and with Jamovi version 2.3.28, with a critical p_{FDR} of 0.05.

3. Results

3.1. Characteristics of the sample

One hundred and nineteen (70 SZ, 49 HV) subjects participated in the study. Five patients and four HVs were excluded because they performed no SC test. Four patients were excluded because they had more than mild extrapyramidal symptoms in at least one of the four components of the SHRS. Six patients were excluded from the statistical analysis because the severity of symptoms was not assessed. Finally, 55 patients and 45 HVs were included in the analyses.

Table 1 shows the clinical characteristics of the patients with SZ. The SZ and HV groups differed in age, years of education, and all SC variables (Table 1). Compared with HV, patients were older, reached a lower educational level, and performed worse in all SC tasks. SHRS scores are indicated as the sum of the four global components of the scale. Two patients had a total score of 3, three patients of 2, and four of 1. All other

Table 1
Characteristics of the sample and between-group comparisons.

	SZ (n = 55)	HV (n = 45)	F/χ^2	p	p_{FDR}
Sociodemographic variables					
Age, years	39.0 (29.2; 46.8)	28.0 (25.0; 31.0)	16.14	<.001	<.001
Gender, females	36 [41.8 %]	21 [46.6 %]	0.24	.630	.630
Education, years	13.0 (10.2; 13.0)	17.0 (15.0; 19.0)	37.71	<.001	<.001
Clinical variables					
PANSS Total score	58.0 (44.3; 74.5)	–	–	–	–
PANSS Positive	7.0 (4.0; 10.0)	–	–	–	–
PANSS Negative	11.0 (8.0; 18.0)	–	–	–	–
PANSS P2 item, conceptual disorganization	2.0 (1.0; 2.0)	–	–	–	–
BNSS Total score	27.0 (13.0; 43.0)	–	–	–	–
CDSS Total score	3.0 (0.0; 6.8)	–	–	–	–
SHRS, global Parkinsonism	0.0 (0.0; 0.0)	–	–	–	–
SC-related variables					
FEIT-NCA, st	−0.2 (−0.8; 0.5)	0.6 (0.4–0.9)	20.28	<.001	<.001
TASIT section 1, st	−0.4 (−2.8; 0.1)	0.1 (−0.4; 1.2)	20.89	<.001	<.001
TASIT section 2, st	−6.8 (−9.8; −4.5)	0.3 (−1.9; 1.5)	85.67	<.001	<.001
TASIT section 3, st	−4.4 (−6.9; −2.5)	0.2 (−1.3; 1.3)	125.08	<.001	<.001
MSCEIT-ME, %ile	28.0 (23.7–34.0)	42.0 (37.0–52.2)	49.20	<.001	<.001

Variables in italics showed a significant between-group difference; continuous variables are expressed as median and interquartile range (Q1; Q3); st: standardized score; SZ: subjects with schizophrenia; HV: healthy controls; FDR: false discovery rate correction; PANSS: Positive and Negative Syndrome Scale; BNSS: Brief Negative Symptom Scale; CDSS: Calgary Depression Scale for Schizophrenia; SHRS: St. Hans Rating Scale; SC: social cognition; FEIT: Facial Emotion Identification Test – Number of Correct Answers; TASIT: The Awareness of Social Inference Test; MSCEIT-ME: Mayer–Salovey–Caruso Emotional Intelligence Test Managing Emotion section.

patients showed no extrapyramidal symptoms.

3.2. Correlations between rs-DC and SC in HVs

Table S1 reports Spearman's correlations between the rs-DC of the 246 ROIs and SC-related variables within the HV group (see supplementary information). Table 2 reports significant correlations within the HV group, the corresponding correlations within the SZ group, the Z-values of the correlations within the two groups, and Z-test results for the between-group comparison.

In the HV group, we found significant positive correlations between rs-DC of ROIs belonging mainly to the bilateral frontal, temporal, and

Table 2
Correlations between resting-state degree centrality and social cognition measures.

SC measure	ROI		HV			SZ			Comparison (Z test)		
	N.	Description	Rho	p	Z-value	Rho	p	Z-value	Z	p	p_{FDR}
FEIT-NCA	5	L-SFG-A9l	0.494	.008	0.541	0.201	.213	0.204	1.390	.165	.815
	19	L-MFG-A46	0.489	.008	0.535	0.254	.114	0.260	1.133	.257	>.999
	20	R-MFG-A46	0.420	.026	0.448	0.210	.194	0.213	0.966	.334	>.999
	28	R-MFG-A10l	0.432	.022	0.462	−0.091	.577	−0.091	2.280	.023	.324
	33	L-IFG-A54c	0.497	.007	0.545	0.005	.975	0.005	2.225	.026	.324
	36	R-IFG-A45r	0.388	.041	0.409	−0.230	.153	−0.234	2.650	.008	.139
	38	R-IFG-A44op	0.450	.016	0.485	−0.177	.276	−0.179	2.733	.006	.139
	59	L-PrG-A4t	0.514	.005	0.568	0.304	.057	0.314	1.047	.295	>.999
	60	R-PrG-A4t	0.389	.041	0.411	0.010	.952	0.010	1.650	.099	.606
	68	R-PCL-A4ll	0.429	.023	0.459	0.052	.752	0.052	1.674	.094	.606
	70	R-STG-A38m	0.548	.003	0.616	−0.117	.471	−0.118	3.019	.003	.088
	82	R-MTG-A21c	0.447	.017	0.481	−0.017	.919	−0.017	2.051	.040	.381
	84	R-MTG-A21r	0.380	.046	0.400	−0.115	.481	−0.116	2.123	.034	.351
	91	L-ITG-A37elv	0.389	.041	0.411	−0.001	.993	−0.001	1.695	.090	.606
	92	R-ITG-A37elv	0.402	.034	0.426	0.005	.976	0.005	1.734	.083	.606
	94	R-ITG-A20r	0.446	.017	0.480	0.071	.661	0.071	1.683	.092	.606
	98	R-ITG-A37vl	0.398	.036	0.421	0.061	.707	0.061	1.483	.138	.755
	112	R-PhG-A35/6c	0.557	.002	0.628	−0.022	.892	−0.022	2.679	.007	.139
	114	R-lPPhG	0.471	.011	0.511	−0.022	.894	−0.022	2.196	.028	.324
	116	R-PhG-EC	0.616	<.001	0.719	−0.155	.340	−0.156	3.602	.000	.033*
	156	R-PoG-1/2/3ulhf	0.375	.049	0.394	0.138	.396	0.139	1.051	.293	>.999
	170	R-Ins-vdg/g	0.462	.013	0.500	0.295	.065	0.304	0.806	.420	>.999
	202	R-lOC-V5	0.384	.044	0.405	0.044	.785	0.044	1.485	.137	.755
	203	L-lOC-OPolC	0.573	.001	0.637	0.027	.867	0.027	3.198	.001	.072
	204	R-lOC-OPolC	0.563	.002	0.637	0.290	.069	0.299	1.395	.163	.815
	205	L-lOC-IOG	0.437	.020	0.469	−0.013	.936	−0.013	1.983	.047	.411
TASIT section 1	82	R-MTG-A21c	0.511	.002	−0.076	−0.076	.604	−0.196	3.065	.002	.031*
	83	L-MTG-A21r	0.507	.003	−0.148	−0.147	.314	−0.163	3.384	.001	.036*
	86	R-MTG-A37dl	0.368	.018	−0.136	−0.135	.356	−0.119	2.499	.012	.078
	89	L-ITG-A20iv	0.310	.048	−0.180	−0.178	.220	−0.268	2.396	.017	.088
	94	R-ITG-A20r	0.384	.013	0.008	0.008	.957	−0.136	1.900	.057	.230
	96	R-ITG-A20il	0.412	.007	−0.056	−0.056	.700	−0.154	2.366	.018	.088
	97	L-ITG-A37vl	0.320	.041	−0.072	−0.072	.625	−0.022	1.933	.053	.230
	101	L-ITG-A20cv	0.350	.025	−0.157	−0.156	.284	−0.230	2.503	.012	.078
	104	R-FuG-A20rv	0.386	.013	−0.157	−0.156	.284	−0.207	2.702	.007	.061
	133	L-SPL-A7r	−0.316	.044	0.270	0.264	.067	0.211	−2.861	.004	.046*
	218	R-cHip	0.353	.023	−0.263	−0.257	.074	−0.142	3.025	.002	.036*
TASIT section 2	33	L-IFG-A54c	0.315	.045	−0.281	−0.155	.246	−0.156	2.908	.004	.117
	82	R-MTG-A21c	0.374	.016	0.096	−0.079	.555	−0.079	1.421	.155	.994
	91	L-ITG-A37elv	0.359	.021	0.011	0.019	.889	0.019	1.746	.081	.820
	92	R-ITG-A37elv	0.350	.025	0.018	−0.076	.571	−0.076	1.664	.096	.820
	101	L-ITG-A20cv	0.322	.040	0.158	−0.040	.764	−0.040	0.841	.401	>.999
	102	R-ITG-A20cv	0.361	.021	0.037	−0.046	.732	−0.046	1.633	.103	.820
	110	R-PhG-A35/6r	0.315	.045	0.292	0.210	.113	0.213	0.163	.870	>.999
	194	R-mvOC-cCuG	0.321	.040	0.150	0.091	.495	0.091	0.874	.382	>.999
TASIT section 3	45	OrG-A11l	0.354	.023	−0.193	−0.191	.190	−0.186	2.697	.007	.307
	60	R-PrG-A4t	0.313	.046	0.196	0.194	.183	0.148	0.610	.542	>.999
	91	L-ITG-A37elv	0.312	.047	0.045	0.045	.758	0.136	1.330	.184	>.999
	92	R-ITG-A37elv	0.310	.049	0.011	0.011	.940	−0.031	1.482	.138	>.999
	101	L-ITG-A20cv	0.351	.025	0.020	0.020	.892	−0.002	1.659	.097	>.999
	102	R-ITG-A20cv	0.374	.016	0.106	0.106	.470	0.143	1.373	.170	>.999
	104	R-FuG-A20rv	0.341	.029	0.137	0.136	.350	0.146	1.046	.296	>.999
	110	R-PhG-A35/6r	0.402	.009	0.074	0.074	.615	0.107	1.685	.092	>.999
	130	R-SPL-A5l	0.382	.014	0.219	0.216	.137	0.254	0.876	.381	>.999
	156	R-PoG-A1/2/3ulhf	0.370	.017	0.231	0.227	.116	0.207	0.754	.451	>.999
	206	R-lOC-IOG	0.343	.028	0.187	0.185	.202	0.155	0.816	.415	>.999
MSCEIT-ME	No significant results		No significant results			NA	NA	NA	NA	NA	NA

SC: social cognition; ROI: region of interest; N.: number; rho: Spearman's correlation; FDR: false discovery rate correction; FEIT-NCA: Facial Emotion Identification Test, Number of Correct Answers; TASIT: The Awareness of Social Inference Test. MSCEIT-ME: Mayer–Salovey–Caruso Emotional Intelligence Test, Managing Emotion section; L: left; R: right; S: superior: M: medial; I: inferior; F: frontal; Or: orbital prefrontal; Pr: precentral frontal; PC: paracentral frontal; Po: postcentral parietal; Fu: fusiform temporal; Ins: insula; Ph: parahippocampal; Hip: hippocampus; O: occipital; G: gyrus; L: lobule; C: cortex; A: area; the number of the areas refers to Brodmann's Areas; E: entorhinal; Cu: cuneus; V5: visual area 5; Pol: polar; m: medial; l: lateral; v: ventral; d: dorsal; r: rostral; c: caudal; e: extreme; op: opercular; t: trunk region; ll: lower limbs region; dg: dysgranular; g: granular; NA: not applicable.

* Significant p values ($p < .05$).

lateral occipital cortices and the performance in facial emotion recognition assessed with the FEIT. The results of emotion recognition evaluated in Section 1 of the TASIT showed a positive correlation with the rs-DC of ROIs located mostly in the bilateral middle and inferior temporal gyri. For the performance in Sections 2 and 3 of the TASIT, which appraise minimal and enriched social inference, respectively, we also find a significant positive correlation with ROIs belonging to the middle and inferior temporal gyri but also to the frontal, parietal, and occipital lobes. This analysis also revealed one significant negative correlation between the rs-DC of the rostral portion of the Area 7 of the left superior parietal lobule (L-SPL; ROI 133) and the results in the TASIT Section 1. We did not find any significant correlation between the rs-DC of the 246 ROIs and the performance in the emotion management test (MSCEIT-ME).

3.3. Between-group comparison of correlations between rs-DC and SC

We found five significant between-group differences: four positive and one negative correlations found in the HC group were absent in the SZ sample. These correlations concerned two tasks assessing emotion recognition from pictures of faces (FEIT) and videos of interacting actors (TASIT Section 1). In the SZ group, we did not find significant correlations between the rs-DC of the right entorhinal cortex (R-EC; ROI 116) and the performance in the FEIT. Similarly, emotion recognition abilities assessed with the TASIT Section 1, were not significantly correlated with the rs-DC of the right caudal (ROI 82) and left rostral (ROI 83) middle temporal gyri (R-cMTG and L-rMTG respectively) and with the right caudal hippocampus (R-c-Hipp; ROI 218). Finally, the rs-DC of the L-SPL (ROI 133) was negatively associated with the performance in the TASIT Section 1 in the HV group while no significant correlation was found in SZ patients. These differences and the locations of the five ROIs are shown in Fig. 1.

4. Discussion

Our results showed positive correlations between the resting state

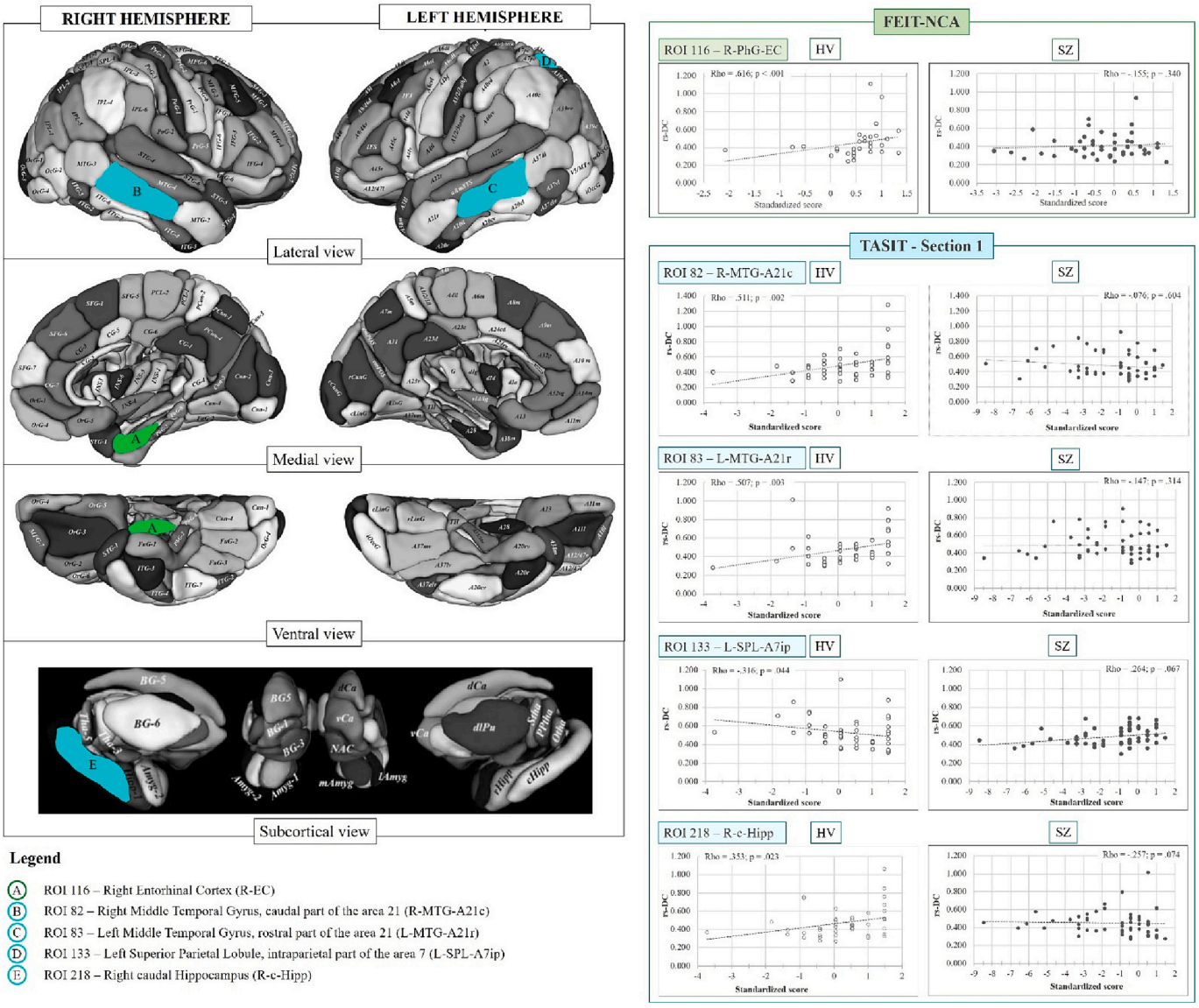

Fig. 1. Localization of the ROIs that showed a significant between-group difference in Spearman's partial correlations between emotion perception measures and resting state degree centrality and scatterplots of the correlations in the two groups.
FEIT-NCA: Facial Emotion Identification Test, Number of Correct Answers; TASIT: The Awareness of Social Inference Test; ROI: region of interest Rho: Spearman's correlation; HV: healthy volunteers' group; SZ: schizophrenia group; rs-DC: resting state degree centrality.
Brain maps adapted from Fan et al. (2016).

connectivity of the brain and the performance in emotion perception and mentalizing tasks in HVs, except for the L-SPL which exhibited a negative association. A link between rs-FC and SC performance was already described in healthy subjects and concerns specifically the default mode network (DMN), a pattern of brain co-activations typically suppressed during focused attention to external stimuli that emerges spontaneously during rest. (Menon, 2020; Mitchell, 2006; Raichle et al., 2001; Raichle, 2015; Schilbach et al., 2008; Smallwood et al., 2021; Spreng et al., 2009). This network is involved in multiple features of higher-order cognition, including theory of mind and emotion processing domains of SC (Smallwood et al., 2021) and is anchored in the posteromedial cortex, which comprises the posterior cingulate cortex, part of the inferior parietal lobule, and the medial precuneus of the parietal cortex, in the angular gyrus that is part of the temporoparietal junction, in the anterolateral middle temporal cortex, in some regions of the inferior frontal gyrus, and in the medial prefrontal cortex (Raichle, 2015; Smallwood et al., 2021). These brain areas are anatomically similar to those recruited during SC tasks and mainly overlap with the social brain network, which includes the precuneus, the temporoparietal junction, the posterior superior temporal sulcus, and the medial prefrontal cortex (Becht et al., 2021; Blakemore, 2012; Mills et al., 2014). Therefore, it has been proposed that the DMN may have a social function during resting state in terms of preparation and consolidation of social processes (Meyer, 2019).

In the current study, we found that five associations between rs-DC and the performance in two emotion recognition tasks (FEIT and TASIT section 1) were absent in people with SZ as compared to HVs. Four positive correlations were lost in the right entorhinal cortex (R-EC), in the right caudal and left rostral middle temporal gyri (R-cMTG and L-rMTG), and in the right caudal hippocampus (R-c-Hipp). Similarly, the negative correlation in the L-SPL was not found in the SZ group. We hypothesize that an altered rs-FC might reflect both a global and local disorganized brain activity during rest that could contribute to the SC deficit found in the SZ group. This atypical brain functioning during rest was demonstrated by many studies that showed a general dysconnectivity with an increased brain entropy and lower global modularity and modular segregation corresponding to abnormal connectivity of the brain hubs (Fornito et al., 2012; van den Heuvel and Fornito, 2014; Sapienza et al., 2023). In particular, Ma et al. (2020) reported higher participation in the whole brain rsFC of the bilateral dorsal prefrontal cortex, of the right angular gyrus, and of the left thalamus and a hyperconnectivity of the DMN with other resting state functional networks in patients with SZ as compared to healthy controls and patients with major depressive disorder or bipolar disorders. We suppose that the absence of significant correlations between the rs-DC of the R-EC, R-cMTG, L-rMTG, and R-c-Hipp and the emotion recognition abilities might interfere with the above-described putative role of resting-state in the preparation and consolidation of social processes, thus affecting patients' performance in SC tasks.

More in detail, focusing on the emotion recognition deficit in facial expression identification, patients did not show a significant association with the performance in the FEIT and the rs-DC of the R-EC (ROI 116). The EC is involved in emotional memory processes needed for emotion identification during the FEIT and structural and functional alterations of this area are commonly found in people with SZ (Cornblath et al., 2022; Hemby et al., 2002; Kesler-West et al., 2001; Pantazopoulos et al., 2010; Quidé et al., 2020).

Regarding correlations with emotion recognition results in the TASIT Section 1, we found a pivotal role for the MTG. This area is considered a core region for the cognitive processing of emotions (Wang et al., 2021) and speech processing (Branco et al., 2018) and its structure and activity are altered in many conditions including social anxiety (Wang et al., 2021), major depressive disorder (Gou et al., 2023; Li and Wang, 2021), and schizophrenia (Cui et al., 2018; Karnik-Henry et al., 2012; Morese et al., 2022). The positive correlations found in the HV group suggest that a higher rs-DC of both the R-cMTG and L-rMTG is associated with a better comprehension of basic emotions expressed by the actors during the short social interaction represented in the videos of the TASIT Section 1. We believe that the involvement of the MTG may be partially linked to the speech processing of the dialogues shown in the video. Indeed, the MTG plays a crucial role in language processes, particularly in pragmatics, both in healthy subjects (Bosco et al., 2017; Branco et al., 2018) and in patients with SZ (Morese et al., 2022). Also in this case, we suppose that these differences in terms of "loss" of correlation might be a sign of an altered architecture of the resting state activity of the brain in patients with SZ that could negatively influence patients' ability to understand basic emotion from verbal and non-verbal information showed in TASIT Section 1 social interactions.

Similar reasoning can be applied to the result regarding R-c-Hipp. In the general population, the hippocampus, especially the right one, is involved in various cognitive processes not only related to memory but also to SC (Palomero-Gallagher and Amunts, 2022; Vogel et al., 2020). The rsFC of the caudal hippocampus largely overlaps with the DMN (Ezama et al., 2021) and structural and functional hippocampal alterations due to general medical conditions like congenital adrenal hyperplasia and anti-*N*-methyl-D-aspartate receptor encephalitis can alter emotion perception and processing (Yang et al., 2024; Omary et al., 2023). Patients with SZ commonly show disruption of hippocampal rsFC (Dong et al., 2018) such that these alterations might represent a possible diagnostic and theranostic biomarker of the disorder (Alho et al., 2023; Blessing et al., 2020; Gangadin et al., 2021; Kraguljac et al., 2016; Mehta et al., 2021; Nelson et al., 2022; Shi et al., 2022; Zhou et al., 2008). As with MTG, we believe that in HVs greater rs-DC of the R-c-Hipp predisposes to a better aptitude for recognizing others' emotions. Therefore, the loss of this positive correlation in subjects with SZ could be a neural correlate of the deficit in this social cognitive task.

In contrast to the rs-DC of the other four ROIs, that of the L-SPL showed a negative correlation with the recognition of emotions from movies of interacting actors (TASIT Section 1) in the HV group. This cortical area is an element of the visual, attention, sensorimotor, and salience networks (Alahmadi, 2021) and has been associated with various processes of nonsocial cognition, mainly visuomotor integration (specifically body part localization and multiple visual stimuli processing), spatial attention shifting, and training of the working memory (Bruner et al., 2023; Felician et al., 2004; Molenberghs et al., 2007; Vialatte et al., 2021; Wang et al., 2015; Wolpert et al., 1998; Zhou et al., 2020). Unlike the other four ROIs, the SPL does not appear to be associated with any social cognitive function or with the DMN. Therefore, we assume that a high rs-DC not only does not predispose HVs to perform SC tasks correctly but hinders them by promoting a shift of attention to visuomotor and non-emotional elements. Specifically, with respect to the videos of the TASIT Section 1, a higher rs-DC of the L-SPL might favor a particular attention on the actors' movements limiting the ability to grasp the emotions they are expressing. This negative relationship between rs-DC and performance in TASIT Section 1 is absent in the SZ group suggesting that even the disappearance of a negative relationship, as well as positive ones, might impair the identification of emotions in subjects with SZ.

The current study has some limitations. The presence of only one clinical group does not allow comparison with other psychiatric conditions. Therefore, it cannot be ruled out that similar findings might emerge in other mental disorders as well, especially in other psychotic disorders (Carpenter, 2021; Kotov et al., 2020; Lahey et al., 2021). Another limitation is related to the sample characteristic: we included only clinically stable patients in treatment with antipsychotics with a predominance of negative symptoms, as compared to positive, disorganized, and depressive ones. This limits the generalizability to other populations, such as patients experiencing more severe psychotic symptoms or drug-naïve patients with a shorter duration of illness. Focusing on the fMRI methodology, the duration of the scan time of 5 min limits the power of the results, as a longer fMRI sequence could have detected more subtle connectivity alterations. A further limitation

comes from the choice to assess rsFC with only one specific DC measure. Other connectivity metrics or other ways of calculating rs-DC may have led to different results. Other limitations concern the statistical analyses. First, we did not control for the duration of illness and the psychopharmacological treatment, which were not assessed in this study. Therefore, we cannot rule out that these clinical variables may have affected our results. Finally, we decided to consider the HVs as a reference group and then to detect the differences in patients with SZ. Other approaches, e.g., starting from the SZ subjects or from the rsFC between-group differences, focusing exclusively on the results within the SZ group, or performing other analysis like multivariate regressions considering the group (SZ or HV) as an input variable may have led to different results. All these limitations should be addressed and overcome by further future studies aimed at confirming and expanding on the findings of this work.

As to the strengths, our sample represents a common clinical population, i.e., community-dwelling, clinically stable patients with SZ, in which the role of SC may greatly impact on real-life functioning. The selection of well-defined ROIs that cover the whole brain gray matter, the employ of a simple and easily understandable rsFC metric, i.e., DC, and the use of the Italian version of the FEIT, TASIT, and MSCEIT to assess social cognition represent sound, validated, and up-to-date methods. Furthermore, compared to task-related fMRI, the analysis of brain activity during resting state has some advantages. For example, it excludes phenomena that occur in the scan and that are not directly related to SC, such as reading or programming finger motion to answer task questions. It also allows the assessment of the relationship between fMRI data and different SC domains without the need to perform numerous tasks inside the MR scanner. Lastly, another strength of the present work depends on some methodological choices, which allowed us to identify, in a group of patients with stable SZ, alterations not related to the severity of symptoms of the whole-brain rs-DC of five well-defined cortical areas associated with emotion perception.

In conclusion, we found that the rs-DC in some brain areas was related to emotion perception abilities in HVs. In patients with SZ, these associations were lost in five cortical regions. This approach might enhance the identification of the cerebral areas more closely related to specific SC domains in SZ, thus facilitating the development of non-invasive brain stimulation interventions targeting those regions.

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CRediT authorship contribution statement

Paola Rocca: Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Claudio Brasso:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cristiana Montemagni:** Writing – review & editing. **Elisa Del Favero:** Writing – review & editing. **Silvio Bellino:** Writing – review & editing. **Paola Bozzatello:** Writing – review & editing. **Giulia Maria Giordano:** Writing – review & editing, Investigation, Data curation. **Edoardo Caporusso:** Writing – review & editing, Software. **Leonardo Fazio:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Giulio Pergola:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Giuseppe Blasi:** Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Mario Amore:** Writing – review & editing. **Pietro Calcagno:** Writing – review & editing. **Rodolfo Rossi:** Writing – review & editing. **Alessandro Bertolino:** Writing – review & editing. **Silvana Galderisi:** Writing – review & editing, Resources, Project administration, Methodology, Data curation. **Mario Maj:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

None.

Data availability

The data that support the findings of this study are available from the corresponding author [C.B.], upon reasonable request. The data are not publicly available as they contain information that could compromise the privacy of research participants.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2024.04.009.

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