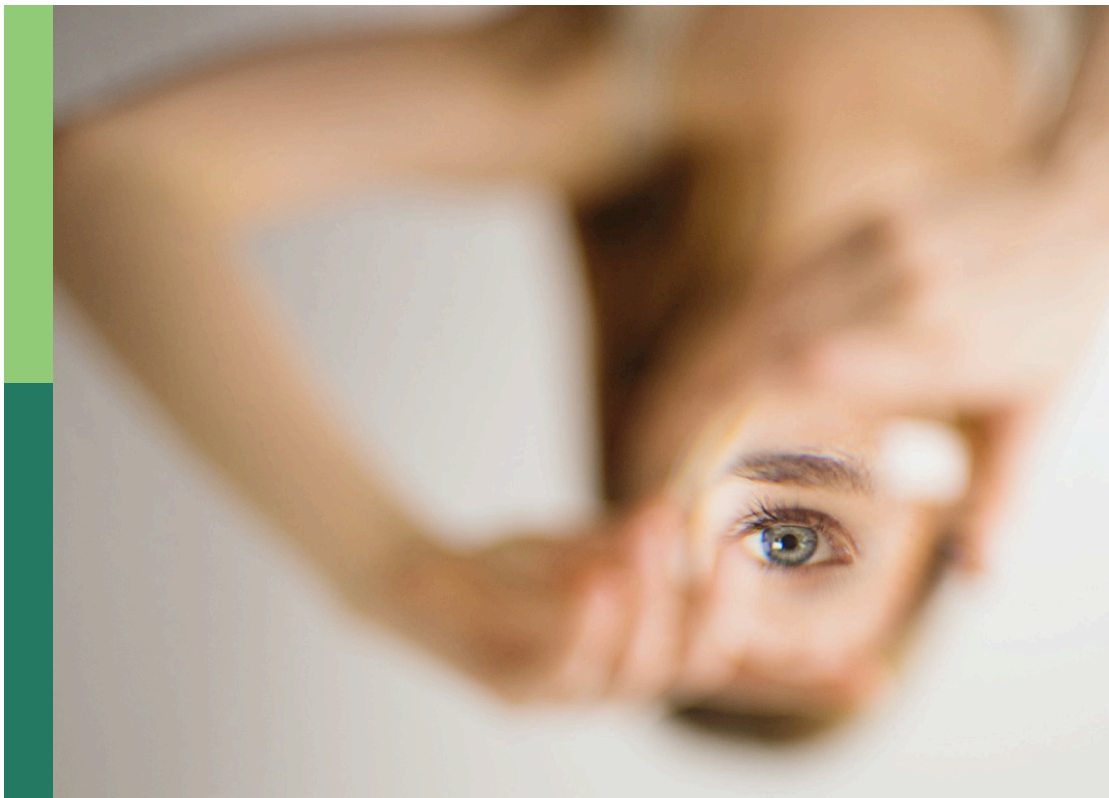
frontiers | Research Topics

Psychotic experiences, social cognition and pragmatic communication in the psychosis continuum

Edited by
Marta Bosia, Alberto Parola, Guillermo Soto and Ricardo R. Garcia

Published in
Frontiers in Psychology



ISSN 1664-8714
ISBN 978-2-83251-738-3
DOI 10.3389/978-2-83251-738-3

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

Psychotic experiences, social cognition and pragmatic communication in the psychosis continuum

Topic editors

Marta Bosia — Vita-Salute San Raffaele University, Italy
Alberto Parola — Aarhus University, Denmark
Guillermo Soto — University of Chile, Chile
Ricardo R. Garcia — University of Chile, Chile

Citation

Bosia, M., Parola, A., Soto, G., Garcia, R. R., eds. (2023). *Psychotic experiences, social cognition and pragmatic communication in the psychosis continuum*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83251-738-3

Table of contents

frontiers | Frontiers in Psychology

TYPE Editorial
PUBLISHED 08 February 2023
DOI 10.3389/fpsyg.2023.1127477

OPEN ACCESS

EDITED BY
Grigorios Nasios,
University of Ioannina, Greece

REVIEWED BY
Maria Skokou,
General University Hospital of Patras, Greece
Marinos Kyriakopoulos,
King's College London, United Kingdom

*CORRESPONDENCE
Alberto Parola
✉ alberto.parol@gmail.com

SPECIALTY SECTION
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

RECEIVED 19 December 2022
ACCEPTED 24 January 2023
PUBLISHED 08 February 2023

CITATION
Parola A, Bosia M, Soto G and Garcia R (2023) Editorial: Psychotic experiences, social cognition and pragmatic communication in the psychosis continuum.
Front. Psychol. 14:1127477.
doi: 10.3389/fpsyg.2023.1127477

Editorial: Psychotic experiences, social cognition and pragmatic communication in the psychosis continuum

Alberto Parola[1,2,3]*, Marta Bosia[4,5], Guillermo Soto[6] and Ricardo Garcia[6]

[1]Department of Linguistics, Cognitive Science and Semiotics, Aarhus University, Aarhus, Denmark, [2]The Interacting Minds Center - Institute of Culture and Society, Aarhus University, Aarhus, Denmark, [3]Department of Psychology, University of Turin, Turin, Italy, [4]School of Medicine, Vita-Salute San Raffaele University, Milan, Italy, [5]Department of Clinical Neurosciences, IRCCS San Raffaele Scientific Institute, Milan, Italy, [6]Department of Linguistics, Center of Cognitive Studies, University of Chile, Santiago, Chile

KEYWORDS

pragmatics, psychosis, schizophrenia, psychotic experience, social cognition, communication disorders, psychosis continuum

Editorial on the Research Topic
Psychotic experiences, social cognition and pragmatic communication in the psychosis continuum

Introduction

Psychotic experiences (PE), such as perceptual abnormalities and unusual beliefs, are widespread in the general population, but they often remain below the psychosis diagnostic threshold (Kelleher and Cannon, 2011; Linscott and Van Os, 2013). However, PE may represent a first point along a psychosis continuum, and identifying them in childhood and adolescence is crucial because of their association with an increased risk of developing psychosis, and with other psychosis-related features including social and cognitive disorders (Gregersen et al., 2022). In particular, deficits of social cognition and pragmatic communication seem to have a central role in the emergence and maintenance of PE in non-clinical populations, and can crucially contribute to transition to psychosis (e.g., Agostoni et al., 2021; Parola et al., 2021, see Figure 1).

In this Research Topic (RT), we aimed to gather new evidence and critical reappraisal from researchers addressing the relationship between PE and deficits of social cognition and pragmatic communication.

We focused on the nature of the interacting factors that determine the persistence of PE and the risk of transition to psychosis, and the relation between social cognition/pragmatic communication and other relevant cognitive and social domains in the context of PE.

The Research Topic

The RT is composed of 11 articles covering original research to reviews, conceptual analysis, and theoretical and perspectives articles from 74 researchers working in 12 different countries. More in detail, the main themes that emerged and were addressed are:

1) Psychosocial and cognitive factors that determine the development or persistence of psychotic experience in the psychosis spectrum and in subclinical populations.

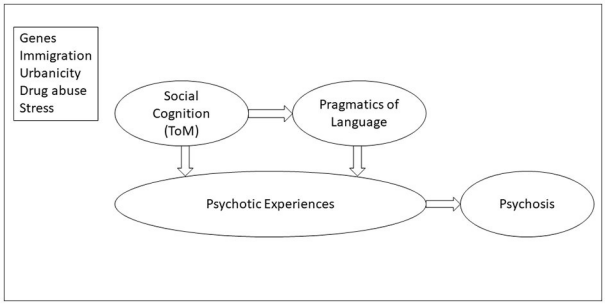


FIGURE 1
Psychotic experiences, social cognition, and pragmatics of language in the psychosis continuum. Social cognition (primarily, theory of mind) and pragmatics of language are associated with psychotic experiences and the transition to psychosis (Clemmensen et al., 2016; Sullivan et al., 2016). Social cognition determines, at least in part, linguistic pragmatics (Sullivan et al., 2016). The top panel shows risk factors for psychotic experiences and psychosis (schizophrenia): genes, immigration, urbanicity, drug abuse and stress.

- Krijnen et al. investigated the association between closeness of social contact, positive and negative affect and symptoms, and empathy in a sample of individuals with psychosis and healthy controls. The authors found that social contact, and especially contact with a close other, is beneficial for positive affect in the total sample and for positive symptoms in individuals with psychosis.
- Beals et al. aimed to characterize the relationship between paranoia, empathy and emotion recognition in a non-clinical sample of adults. They found that only a specific facet of cognitive empathy, i.e., imaginative perspective-taking, is related to paranoia in the general population; however, the association between empathy and paranoia did not appear to depend on emotion recognition. The author concluded that deficits in empathy and emotion recognition observed in schizophrenia may not be similarly detectable in subclinical populations.
- Csulak et al. present a meta-analysis and systematic review involving implicit mentalization in schizophrenia. Interestingly, the meta-analysis showed slower reaction time and low accuracy during implicit mentalization in schizophrenia. The systematic review also revealed different brain activation patterns and visual sensory motor alteration. Implicit mentalization alteration seems to play a role in schizophrenia, although not to the same extent as explicit mentalization.
- Chapellier et al. using the Mini Profile of Non-verbal Sensitivity, revealed that non-verbal social perception is impaired in patients with schizophrenia compared to controls, and that it is also related to the severity of psychopathology and functional disruption. These results underline the need for novel therapeutic approaches to alleviate non-verbal social perception deficits.
- Giugliano et al. using the Metacognition Self-Assessment Scale (MCAS) in a non-clinical population, revealed that metacognitive skills play a protective role in the occurrence of psychotic-like experiences in non-clinical individuals.
- Cavieres and López-Silva provided a precise and unitary definition of social perception, suggesting that it refers to low-level pre-reflective processes underlying the awareness of interpersonal interactions with and between others. The authors suggest that a better identification and assessment of this domain may be beneficial for developing new psychosocial rehabilitation programs.
- Bob et al. found, in a sample of drug naive women in their first psychotic episode, a relationship between epileptic-like symptoms and measures of chronic stress. Indeed, recent evidence indicates that early stressful and traumatic experiences may impact on the brain and increase the risk for psychosis, leading to neural processes similar to epilepsy which may occur in patients with mental disorders including schizophrenia. The present study provides useful information for diagnostic consideration of anticonvulsant therapy, also supporting its use in patients who do not respond to usual psychotropic medication.

2) New rehabilitative treatments aimed at recovering social and pragmatic deficits observed in the psychosis continuum.

- Lado-Codesido et al. conducted a randomized, single-blind, multicenter clinical trial to test the effectiveness of the "Voices 2" training program to improve emotion recognition through prosody in adults with schizophrenia. The authors found an improvement in recognition of emotional prosody in the patients which undergone the treatment, but not in control group.

3) New assessment tools aimed at detecting psychosocial factors that determine the development or persistence of psychotic experience.

- Kim et al. validated a Korean version of The Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS), a psychometric scale used indirectly to measure social anhedonia. The results showed that ACIPS revealed to be a useful psychometric instrument in non-help-seeking populations.

4) Neurobiological abnormalities associated with neuropsychiatric conditions and their symptoms.

- Sun et al., found that adult patients with early and late onset recurrent depression, compared to healthy controls, have abnormal neuronal fMRI activity in some brain regions, with differences closely related to the default mode network, and the salience network, and that patients of each age group exhibit regional homogeneity abnormalities relative to matched controls. The prevalence of depressive disorders in schizophrenia is reported to be very high (~40%), and these findings are therefore of great importance and relevance, even when taking into account the neurobiological abnormalities associated with schizophrenia spectrum disorder.
- Morese et al. found that patients with SCZ, compared to healthy controls, showed a higher fMRI neural activation of the left-middle temporal gyrus (L-MTG) while performing

a communicative pragmatic task; the involvement of the L-MTG was related to the increasing inferential effort required in correctly understanding the speaker's communicative intentions, and the higher integrative semantic processes involved in sentence processing.

Conclusions

This RT has contributed to identify which factors may contribute to the occurrence and persistence of PE in both the general population and the psychosis spectrum, and which aspects may instead play a protective role and reduce the risk of transition to psychosis.

The RT has explored the relationship between social cognition, pragmatic communication, and other relevant cognitive and social domains associated with PE and has shown, for example, that implicit mentalization and non-verbal social perception are two key skills that selectively distinguish patients with schizophrenia from controls.

Crucially, the RT has also revealed new ways to assess, conceptualize, and rehabilitate the psychosocial, cognitive, and clinical aspects involved in the development and persistence of PE. Indeed, new validated assessment tools—the ACIPS scale–, new conceptual views and new intervention treatments—the Voices 2 training program—were presented in the RT.

In summary, the RT has helped to uncover some of the complex interactions between multiple factors underlying the onset of PE and the transition to psychosis, and provided support to the idea of a continuum between the general population and the psychosis spectrum. Finally, the RT has also shown what is currently lacking and where future efforts might be directed: longitudinal design are essential to track over time the relationships between PE and deficits in social cognition and pragmatic communication and the onset of psychosis. We also need prospective studies that can track the development of PE since infancy and childhood and identify early signs of PE and psychosis and their association with clinical and psychosocial factors (Fried et al., 2022; Thorup et al., 2022).

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

AP was supported by a Marie Skłodowska-Curie Actions—H2020-MSCA-IF-2018 grant (ID: 832518, Project: MOVES).

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.

References

Agostoni, G., Bambini, V., Bechi, M., Buonocore, M., Spangaro, M., Repaci, F., et al. (2021). Communicative-pragmatic abilities mediate the relationship between cognition and daily functioning in schizophrenia. *Neuropsychology* 35, 42. doi: 10.1037/neu0000664

Clemmensen, L., van Os, J., Drukker, M., Munkholm, A., Rimvall, M. K., Væver, M., et al. (2016). Psychotic experiences and hyper-theory-of-mind in preadolescence - a birth cohort study. *Psychol Med.* 46, 87–101. doi: 10.1017/S0033291715001567

Fried, E. I., Rieble, C., and Proppert, R. K. K. (2022). Building an early warning system for depression: rationale, objectives, and methods of the WARN-D study. *PsyArXiv*. doi: 10.31234/osf.io/9qcvs

Gregersen, M., Møllegaard Jepsen, J. R., Rohd, S. B., Søndergaard, A., Brandt, J. M., Ellersgaard, D., et al. (2022). Developmental pathways and clinical outcomes of early childhood psychotic experiences in preadolescent children at familial high risk of schizophrenia or bipolar disorder: a prospective, longitudinal cohort study-the Danish High Risk and Resilience Study, VIA 11. *Am. J. Psychiatry* 179, 628–639. doi: 10.1176/appi.ajp.21101076

Kelleher, I., and Cannon, M. (2011). Psychotic-like experiences in the general population: characterizing a high-risk group for psychosis. *Psychol. Med.* 41, 1–6. doi: 10.1017/S0033291710001005

Linscott, R. J., and Van Os, J. (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychol. Med.* 43, 1133–1149. doi: 10.1017/S0033291712001626

Parola, A., Brasso, C., Morese, R., Rocca, P., and Bosco, F. M. (2021). Understanding communicative intentions in schizophrenia using an error analysis approach. *NPJ Schizophrenia* 7, 1–9. doi: 10.1038/s41537-021-00142-7

Sullivan, S. A., Hollen, L., Wren, Y., Thompson, A. D., Lewis, G., and Zammit, S. (2016). A longitudinal investigation of childhood communication ability and adolescent psychotic experiences in a community sample. *Schizophr Res.* 173, 54–61. doi: 10.1016/j.schres.2016.03.005

Thorup, A. A. E., Gantriis, D. L., Greve, A. N., Henriksen, M. T., Zahle, K. K., Stadsgaard, H., et al. (2022). Exploring protective and risk factors in the home environment in high-risk families-results from the Danish High Risk and Resilience Study-VIA 7. *BMC Psychiatry* 22, 1–11.

frontiers in Psychology

ORIGINAL RESEARCH
published: 16 December 2021
doi: 10.3389/fpsyg.2021.769091

Benefits of Social Contact in Individuals With Psychotic Symptoms: Do Closeness of the Contact and Empathic Skills Make the Difference?

Lisa J. G. Krijnen[1,2], Imke L. J. Lemmers-Jansen[2,3,4], Anne-Kathrin J. Fett[4,5] and Lydia Krabbendam[2,3]*

[1] Child and Adolescent Studies, Utrecht University, Utrecht, Netherlands, [2] Department of Clinical, Neuro and Developmental Psychology, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam, Netherlands, [3] Institute for Brain and Behavior (IBBA), Amsterdam, Netherlands, [4] CSI Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, London, United Kingdom, [5] Department of Psychology, City University of London, London, United Kingdom

OPEN ACCESS

Edited by:
Alberto Parola,
Aarhus University, Denmark

Reviewed by:
Irene Ceccato,
University of Studies G. d'Annunzio Chieti and Pescara, Italy
Philippe Delespaul,
Maastricht University, Netherlands

****Correspondence:***
Lisa J. G. Krijnen
lisa_krijnen@hotmail.com

Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: *01 September 2021*
Accepted: *25 November 2021*
Published: *16 December 2021*

Citation:
Krijnen LJG, Lemmers-Jansen ILJ, Fett A-KJ and Krabbendam L (2021) Benefits of Social Contact in Individuals With Psychotic Symptoms: Do Closeness of the Contact and Empathic Skills Make the Difference? Front. Psychol. 12:769091. doi: 10.3389/fpsyg.2021.769091

Objectives: Social contact is known to be beneficial for humans' mental health. Individuals with psychotic symptoms (PS) tend to show poorer social and interpersonal functioning. However, in this patient population, social contact may be crucial for their mental wellbeing and treatment success. Additionally, closeness of social contact (familiar versus less familiar others), rather than only the presence or absence of social contacts, may play an important role. Empathy may heighten the beneficial effects of social/close contact on mental health, facilitating interactions. We investigated the association between social contact and closeness of contact on mental health, defined as positive symptoms, positive affect and negative affect in PS and control participants, with empathy as a moderator.

Methods: Participants were 16–30 years old. Information regarding social/close contact and mental health was obtained using the experience sampling method in individuals with PS (n = 29) and healthy controls (n = 28). Empathy was measured using a self-report questionnaire.

Results: Social contact was associated with higher positive affect in the total sample. Contact with close as opposed to less close others was related to better mental health: It was associated with lower positive symptoms in the PS group, and with more positive affect in the total sample. Empathy moderated the association between closeness of contact and positive affect in the total sample, in which the combination of higher levels of empathy combined with the presence of close contact was associated with higher positive affect in the total sample. However, the direct association between empathy and positive affect was not significant per group of contact.

Conclusion: The results suggest that social contact, but especially contact with a close other is important for mental health outcomes: Contact with close others is beneficial for positive affect in the total sample and for positive symptoms in individuals with PS.

Keywords: first episode psychosis (FEP), clinical high risk (CHR) for psychosis, social contact, close contact, positive psychotic symptoms, positive and negative affect, experience sampling method (ESM)

INTRODUCTION

Psychotic disorders, including schizophrenia are severe conditions that have a significant impact on daily functioning of individuals experiencing psychotic symptoms (PS) (Cho et al., 2017). These disorders are characterized by positive symptoms (e.g., delusions and hallucinations), negative symptoms, such as diminished emotional expression and avolition, disorganized thinking (speech), grossly disorganized or abnormal motor behavior, and cognitive dysfunctions (American Psychiatric Association [APA], 2013). Psychotic disorders are also associated with poorer social and interpersonal functioning (Yager and Ehmann, 2006). However, a possible protective factor against the symptoms in this patient group is social contact. For individuals with PS, social contact has been linked to mental health and psychological wellbeing (Bengtsson-Tops and Hansson, 2001; Meyer-Lindenberg and Tost, 2012; Bjornestad et al., 2017). The concern, however, is that individuals with PS, including people at clinical high risk (CHR) for developing psychosis, have significantly poorer social networks in terms of quantity and quality of contact than healthy individuals (Bengtsson-Tops and Hansson, 2001; Pruessner et al., 2011), though social contact might be particularly important for this patient group.

Impaired social functioning (e.g., in terms of the number of close friends, quality of the friendship, number of social contacts, etc.) has been found to be predictive for developing a psychotic disorder in individuals at CHR (Cornblatt et al., 2007). In patients with schizophrenia, it was shown that a lack of social contact was predictive for more severe negative symptoms, lower psychosocial functioning and a worse quality of life (Millier et al., 2014). These findings support the idea that social contact is related to better outcomes for individuals with, or at high risk for, psychotic disorders.

The closeness of the contact might be the crucial element that determines whether social contact is beneficial or not. Research showed that though patients with psychotic disorders experienced more paranoia when being alone compared to having social company, both healthy people and patients experienced more paranoia when meeting with distant others compared to close others and that meeting close others was associated with lower paranoia over time (Fett et al., 2021). In a non-clinical sample of individuals at increased risk for psychosis, meeting with less close individuals was found to be associated with an increased risk of experiencing unusual perceptions when compared to being alone, whereas the presence of close contacts was associated with a lower risk (Verdoux et al., 2003). Individuals with low and medium paranoid traits showed more paranoia when being in company of less close individuals, than in company of close individuals (Collip et al., 2011). However, this association was not significant in individuals with high paranoia. In addition, it was found that individuals who were prone to psychosis showed an increase in negative affect (i.e., anxious and depressed moods) when they were likely to meet with less close others (Husky et al., 2004). These studies support the idea that the beneficial effect of social contact on mental health depends on the closeness of the contact.

The positive effect of social/close contact on mental health might be driven by empathy. Baron-Cohen and Wheelwright (2004) stated that "empathy is the glue of the social world" (p. 163), and it has been defined as the ability to understand and experience the thoughts and feelings of others. Generally, the ability to *understand* one's thoughts and feelings is called cognitive empathy, whereas the extent to being able to *experience* others' thoughts and feelings is referred to as affective empathy (Hogan, 1969). Empathy seems to be one of humans' core abilities to interpret actions of others (Price and Archbold, 1997), which is highly relevant when being in company of others. Empathy has been linked to prosocial and positive behaviors toward others, facilitating interactions and relationships (McDonald and Messinger, 2011). If empathy is lacking, the essence of a social exchange may get lost as the person would not fully understand or "feel" emotions of the other person. This can result in less satisfactory contact which in turn may affect mental health. Therefore, levels of empathy may determine the extent to which a person benefits from social contact in terms of their mental health. In other words, higher levels of empathy could boost the advantages of social contact on mental health.

Although the relationship between empathy, social/close contact and mental health is not clear yet, both empathy and social functioning show abnormal patterns in individuals with PS (Yager and Ehmann, 2006; Montag et al., 2007) and seem to be predictive for functional outcome (e.g., social skills and community functioning) (Brüne, 2005; Bora et al., 2006; Fett et al., 2011). These individuals tend to withdraw from social contact, which in turn negatively influences their social relationships. Abnormalities in social functioning and empathy are found along the psychosis continuum, in patients that experienced multiple psychotic episodes (Grant et al., 2001; Mazza et al., 2012), in first-episode psychosis patients (FEP) (Priebe et al., 2000; Grant et al., 2001; Mazza et al., 2012), and also in CHR (Häfner et al., 1999; Yung et al., 2004; Van Donkersgoed et al., 2015). Previous studies have investigated levels of empathy in these groups. In schizophrenia patients, cognitive empathy was found to be impaired (Montag et al., 2007, 2020; Derntl et al., 2009; Corbera et al., 2021), but results regarding affective empathy were inconsistent with some

studies reporting impairments in affective empathy (Derntl et al., 2009; Corbera et al., 2021), and others finding no impairment in both behavior measures and self-rated affective empathy compared to healthy controls (Montag et al., 2007; Berger et al., 2019). Furthermore, affective empathy has been found to be impaired in CHR compared to both schizophrenia patients and healthy controls, but cognitive empathy remained intact in this CHR group (Montag et al., 2020). Since social/close contact is associated with mental health and symptom severity, and empathy might strengthen this relationship, it is important to investigate the link between these factors in individuals with FEP and at CHR.

The aim of the current study was to investigate the link between being alone versus being in social contact, the closeness of the contact (with close versus less close others), empathy and mental health in individuals with PS, compared to healthy controls. Mental health consisted of three constructs: positive affect, negative affect and positive symptoms. Two research questions were addressed: (1) Is social contact compared to being alone associated with differential mental health (i.e., positive symptoms and positive/negative affect) in controls versus individuals with PS, and does the closeness of the contact (close versus less close others) affect mental health differently? (2) Does empathy function as a moderator in these associations? Based on the existing literature, we could not make a prediction regarding the direction of the effect of social contact on mental health, since the nature of the social contact (i.e., close versus less close) seems to play a pivotal role in this relationship. We hypothesized that close contact has a more beneficial effect on mental health than less close contact based on studies linking close contact to higher perceived social support and better outcomes (Nangle et al., 2003; Verdoux et al., 2003; Husky et al., 2004; Collip et al., 2011; Kingery et al., 2011; Manago et al., 2012). We expected this relation to be similar in individuals with PS and healthy participants (Verdoux et al., 2003; Collip et al., 2011). For the second research question, it was hypothesized that empathy functions as a moderator or a "booster," meaning that participants with high levels of empathy will benefit more from social contact as compared to being alone than participants with lower levels of empathy, as can be seen in lower levels of negative affect and positive symptoms, and more positive affect. It will also be explored whether empathy influences the relationship between closeness of the contact and mental health in individuals with PS and healthy participants.

MATERIALS AND METHODS

Participants

The current study was an add on to a larger study (Lemmers-Jansen et al., 2018, 2019) and included 37 individuals with PS and 30 healthy individuals. However, 8 individuals with PS and 2 controls were excluded because they had less than 20 experience sampling method (ESM) measurements. The final sample therefore consisted of 29 individuals with PS and 28 controls. CHR and FEP participants together formed the PS group, as studies have shown that both patient groups suffer from similar symptoms related to comparable impairments in social functioning (Niendam et al., 2006; Yung et al., 2008; Fusar-Poli et al., 2010; Pruessner et al., 2011).

Individuals of the PS group were recruited in the Academic Medical Center Amsterdam (AMC), the Amsterdam early intervention team psychosis ('Vroege Interventie Psychose' – VIP team) and PsyQ in The Hague and were contacted by their treating clinicians. Healthy controls were recruited at vocational and higher educational institutes in the area of Amsterdam and The Hague and were matched on education level, age, and sex. FEP patients were diagnosed at the AMC hospital by using DSM-IV criteria (American Psychiatric Association [APA], 2004), and included in the study within 18 months after diagnosis. CHR individuals were referred to PsyQ by their general practitioner or by other health care professionals. All new admissions were screened using the Comprehensive Assessment of At-Risk Mental States [CAARMS; (Yung et al., 2005)] which is a semi-structured interview used to assess psychotic experiences in the last year. Furthermore, patients had to obtain a score below 55 on the Social and Occupational Functioning Assessment Scale [SOFAS (Goldman et al., 1992; Morosini et al., 2000)] which indicates problems in work/study, relationships and self-care. CHR individuals were included in the study <1 year after the CAARMS assessment. In FEP and CHR, severity of symptoms was assessed with the Positive and Negative Syndrome Scale [PANSS; (Kay et al., 1987)]. Scores did not differ between CHR and FEP on the PANSS subscales and the total score, supporting the decision to merge the CHR and FEP participants into one patient group (PANSS total mean score CHR = 1.96 and FEP = 1.97, $p = 0.96$). The total symptom score of 58.52 of the patient group refers to "mildly ill" (Leucht et al., 2005). See **Table 1** for the participants' characteristics.

Sufficient knowledge of the Dutch language was required. An exclusion criterion for all participants was an IQ < 80, approximately. Individuals with PS were excluded when diagnosed with a primary diagnosis of a mood disorder or comorbid autism spectrum disorder (ASD). Healthy controls were excluded if they had a (family) history of psychiatric disorders or ASD.

Materials

Experience Sampling Method

The ESM, also referred to as Ecological Momentary Assessment (Stone and Shiffman, 1994), was developed to measure behavior, experiences and environment of daily life in a systematic and valid way (De Vries, 1992; Csikszentmihalyi and Larson, 2014). In the current study, the questions of the ESM were delivered on an iPod that the participants were carrying. Questionnaires were sent 10 times a day, for seven continuous days between 7.30 am and 22.30 pm. Within time frames of 1.5 h, measurements came at random intervals, but at least 15 min apart. Participants were alerted by a beep and had 15 min to fill out the questionnaire. The initial questionnaire consisted of 50 items, of which we used 17 items as these were the items measuring social/close contact and mental health (i.e., positive and negative affect and positive symptoms) and we used one additional item regarding to what

TABLE 1 | Participant characteristics.

Variable	Control group (*n* = 28)	PS group† (*n* = 29)
Sex		
Male (%)	15 (53.57%)	13 (44.83%)
Age		
Mean (*SD*)	20.36 (2.73)	21.33 (2.91)
Range	16–26	17–30
Education level‡		
Low, *n* (%)	14 (50.00%)	16 (57.14%)
Medium, *n* (%)	7 (25.00%)	7 (25.00%)
High, *n* (%)	7 (25.00%)	5 (17.86%)
Country of birth		
Netherlands, *n* (%)	25 (89.29%)	22 (78.57%)
Empathy		
Mean (*SD*)§	19.93 (3.22)	19.79 (3.17)
Medication type		
Antipsychotics, *n* (%)	–	10 (35.71%)
Other medication, *n* (%)¶	–	9 (32.14%)
No medication, *n* (%)	–	9 (31.03%)
PANSS scores[a]		
Positive symptoms, *M item* (*SD*)	–	1.77 (0.67)
Negative symptoms, *M item* (*SD*)	–	2.23 (0.71)
General symptoms, *M item* (*SD*)	–	1.91 (0.51)
Total mean score, *M (SD)*	–	1.97 (0.49)
Total sum score, *M (SD)*	–	58.52 (14.29)

SD, standard deviation; M, mean; PANSS, positive and negative syndrome scale; PS group, individuals with psychotic symptoms.
†*The patient group consists of both FEP and CHR.*
‡*Low, lower (pre-)vocational education (VMBO, MAVO, and MBO); Medium, higher (pre-)vocational education (HAVO and HBO); High, (pre-) university education (VWO and WO). One missing value in PS group.*
§*One missing value of empathy in the control group and one missing value in the PS group. Subscales for affective and cognitive empathy did not differ between groups.*
¶*Other medication consisted of antidepressants, benzodiazepines and in one case anticonvulsant medication. Medication use was unknown for one participant.*
[a]*PANSS data were only available for the PS group. Data of four participants were missing.*

extent the participant felt comfortable in the current company (see **Appendix A**).

Social Contact

The question "With whom am I now?" was used to investigate whether the person was in social contact. If the person answered that s/he was not with other people, the answer was coded as "alone." If the person answered that she/he was with others (answer options: "classmates," "colleagues," "friends," "1 friend," "partner," "family," "housemates," and "stranger"), it was coded as being in social contact.

Closeness of Contact

To investigate the closeness of contact, the same item was used as for measuring social contact. However, only answers referring to being with others were taken into account, as being alone did not form part of this concept. A distinction was made between close and less close contacts. In order to do so, we followed the procedure of Fett et al. (2021). Additionally we used the ESM question in which participants were asked to rate on a 7-point Likert scale whether they felt comfortable in the current company (1 = totally disagree to 7 = totally agree) (see **Appendix B** for more information). Based on this second method, results showed that housemates better fitted the concept of a close contact whereas Fett and colleagues grouped them as less close contacts. Therefore, the final distinction was as follows: Close contacts were considered "friends," "1 friend," "partner," "housemates," and "family," whereas "classmates," "colleagues," and "stranger" were considered as less close contacts. The contacts that were categorized as close contacts received significantly higher scores on the item regarding feeling comfortable within the company ($p < 0.001$) than the contacts that were considered as less close contacts.

Mental Health

Mental health was measured by 16 items, assessing positive symptoms (8 items, e.g., "I hear voices"), positive affect (4 items, e.g., "I feel relaxed") and negative affect (4 items, e.g., "I feel down") (Myin-Germeys et al., 2005). We calculated the internal consistency, reflecting an acceptable to good reliability (positive symptoms; $\alpha = 0.88$, positive affect, $\alpha = 0.71$, negative affect $\alpha = 0.83$). Answer options ranged from 1 = "totally disagree" to 7 "totally agree." Mean scores per outcome category were calculated, with higher scores reflecting more severe positive symptoms, higher negative affect, and higher positive affect. For an overview of the included questions, see **Appendix A**.

Positive and Negative Syndrome Scale

The PANSS is a semi-structured interview which aims to investigate the severity of the psychotic symptoms over the last 2 weeks (Kay et al., 1987). In the current study, the PANSS was used to investigate patients' symptoms at baseline. The scale consists of three subscales, measuring positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items). All items are rated on a 7-point Likert scale. Mean scores per subscale and sum scores for the total scale were calculated, with a higher score reflecting more severe symptoms. Total scores of 58, 75, 95, and 116 refer to "mildly ill," "moderately ill," "markedly ill," and "severely ill," respectively (Leucht et al., 2005).

Empathy Questionnaire for Children and Adolescents

Empathy was measured by using the EmQue-CA (Overgaauw et al., 2017). This is a 14-item self-report questionnaire measuring one's empathy during the past 2 months, consisting of three subscales. For the current study, only two subscales have been used: (1) Affective empathy, consisting of 6 items measuring the emotional arousal one experiences when confronted with other's emotion, and (2) Cognitive empathy, consisting of 3 items measuring the extent to which one understands other's emotions. A three-point scale was used, with 1 = "not true," 2 = "somewhat true," to 3 = "true." The sum score of these 9 items reflected the level of empathy, with a higher score indicating higher levels of empathy. The EmQue-CA has shown to be a reliable and valid instrument (Overgaauw et al., 2017).

Procedure

Participants were told that this study focused on social decision making in adolescents/young adults with and without psychosis/abnormal experiences. If the participant was willing to participate, one of the researchers made a home visit to provide the participant with the iPod after the informed consent form was signed. The participant filled in the questionnaire once together with the researcher, to ensure comprehension of the questions and the device. Under the age of 18, one of the parents also signed the informed consent. A week later the iPod was returned and the larger testing session took place, including the PANSS and the EmQue. In some of the cases, the iPod was given after the testing session. Two or three days after the start of the ESM, the researchers called the participants to inquire about the progress of filling in the questionnaires, and to encourage the participants to continue with the ESM. When returning the iPod with sufficient data, participants received 25 euros for participation. The study was approved by the Medical Ethics Committee of VU University Medical Center Amsterdam.

Statistical Analysis

Stata version 14.2 was used for data analysis (StataCorp, 2015). Simple linear regression analyses and chi-squared tests were performed to check for differences in characteristics between the control and PS group. Secondly, multilevel random regression analyses were conducted, in which repeated measures in time were considered as level 1, and participants as level 2. For every hypothesis, three separate outcome measures of mental health were used: positive symptoms, positive affect and negative affect. Age, sex, and education level were included as covariates in all analyses. For the first part of research question 1, the predictor social contact was added as a dichotomous variable (being in contact versus being alone). For the second part, the predictor was close (instead of social) contact (close contact versus less close contact). Furthermore, an interaction between contact and group (PS group versus healthy participants) was added to test for differences between the PS group and healthy participants. If this interaction was significant, analyses were run per group. If the interaction was non-significant, analyses were run excluding the interaction term. For the hypothesis regarding empathy as a moderator (centered composite score of affective and cognitive items), we used the same model but added empathy. Furthermore, we investigated whether there was an interaction between group and empathy, and social/close contact and empathy, for every outcome measure. To correct for multiple testing, we applied the Bonferroni adjustment – i.e., three outcome measures with four analyses each (i.e., social contact, close contact, social contact × empathy, and close contact × empathy) resulting in an alpha level of 0.05/12 = 0.004. See **Table 2** for an overview of the models.

RESULTS

Participant Characteristics

Demographics and participant characteristics are shown in **Table 1**. No significant differences between the PS group and healthy control participants were found in terms of sex, age, education level, and country of birth. The PANSS was only assessed in the PS group. Levels of empathy did not differ between the groups.

Social Contact and Mental Health

Experience sampling method variables are displayed in **Table 3**, showing no differences between the control and PS group in number of social contact ($b = -0.06$, $p = 0.25$) and close contact ($b = 0.07$, $p = 0.22$), but the control group filled out significantly more ESM measurements ($p = 003$). The PS group reported more positive symptoms ($b = 0.77$, $p < 0.001$), and

TABLE 2 | Presentation of the models.

Model 1 and 2	Group
	Contact[a]
	Group × Contact[a]
Model 3 and 4	Empathy
	Empathy × Group
	Empathy × Contact[a]

Model 3 and 4 are model 1 and 2, including empathy as extra factor. Age, sex, and education level were added to all models as covariates. All models were run 3 times: with the outcome measures positive symptoms, positive affect, negative affect.
[a]In model 1 and 3 "Contact" refers to the variable social contact. In model 2 and 4 "Contact" refers to closeness of contact.

TABLE 3 | ESM variables on social contact and mental health compared between the groups.

	Controls ($n = 28$)	PS group ($n = 29$)
Total *n* ESM obs	1,335**	1,018
Mean *n* ESM obs	47.68**	35.10
Social contact		
"Yes," obs, (%)	66.67%	60.32%
Close contact		
"Yes," obs, (%)	65.72%	72.24%
Family, obs (%)	34.73%	33.97%
1 friend, obs (%)	7.47%	11.80%
Roommates, obs (%)	5.41%	5.41%
Friends, obs (%)	14.64%	8.48%
Partner, obs (%)	3.47%*	12.58%
"No," obs (%)	34.28%	27.76%
Colleagues, obs (%)	11.82%	6.41%
Classmates, obs (%)	15.46%**	5.26%
Stranger, obs (%)	7.00%*	16.09%
Mental health		
Positive symptoms, *M* (*SD*)	1.33 (0.35)***	2.09 (0.95)
Positive affect, *M* (*SD*)	4.77 (0.57)†	4.31 (0.98)
Negative affect, *M* (*SD*)	1.72 (0.62)***	2.58 (1.14)

PS group, individuals with psychotic symptoms; ESM, experience sampling method; obs, observations; M, mean; SD, standard deviation. Groups significantly differed in number of ESM completions (p = 0.003). The other comparisons regarding type of contact were not significant after applying Bonferroni correction.
†p = 0.06.
**p < 0.05.*
***p < 0.01.*
****p < 0.001.*

more negative affect (b = 0.87, p < 0.001) than the control group. No differences were found for positive affect (b = −0.40, p = 0.06).

Mental Health

Results are presented in order of the hypotheses, first for social contact, followed by close contact.

Social Contact

Positive Symptoms

The analysis showed no significant interaction effect for social contact and group on positive symptoms, [b = −0.0001, 95% CI (−0.09 to 0.09), p = 1.00]. Further analyses, excluding the interaction, showed no significant effect for social contact [b = 0.04, 95% CI (−0.002 to 0.09), p = 0.06], indicating that social contact was not associated with positive symptoms in the total sample.

Positive and Negative Affect

There was no significant interaction effect between social contact and group on positive affect [b = 0.05, 95% CI (−0.12 to 0.23), p = 0.53] nor on negative affect [b = 0.01, 95% CI (−0.13 to 0.15), p = 0.91]. A main effect was found for social contact on positive affect [b = 0.22, 95% CI (0.14 to 0.30), p < 0.001], indicating that more social contact was associated with more positive affect, regardless of group. No main effect was found for social contact on negative affect [b = −0.06, 95% CI (−0.13 to 0.008), p = 0.08].

Close Contact

Positive Symptoms

An interaction effect was found for closeness of contact and group on positive symptoms, [b = −0.22, 95% CI (−0.35 to −0.08), p = 0.001]. Closeness of contact predicted positive symptoms in the patient group [b = −0.24, 95% CI (−0.35 to −0.13), p < 0.001], but not in the control group [b = −0.03, 95% CI (−0.10 to 0.05), p = 0.47], indicating that meeting with close others, as compared to less close others, was associated with lower positive symptoms only in the PS group.

Positive and Negative Affect

The analyses revealed no significant interaction of closeness of contact and group on positive affect nor on negative affect [b = −0.08, 95% CI (−0.31 to 0.16), p = 0.53; b = −0.08, 95% CI (−0.28 to 0.11), p = 0.40, respectively]. A main effect of closeness of contact on positive affect was found [b = 0.20, 95% CI (0.09 to 0.31), p < 0.001], but not on negative affect [b = −0.08, 95% CI (−0.17 to −0.02), p = 0.11], indicating that being with close contacts, as compared to company of less close others, was associated with more positive affect but not with negative affect in the total sample.

Empathy

Social Contact, Empathy, and Positive Symptoms

The analyses showed no interaction effects for group with empathy nor social contact with empathy on positive symptoms (b's ≤ −0.03 and p's ≥ 0.59).

Social Contact, Empathy, and Affect

No interaction was found between empathy and social contact on positive affect nor on negative affect (b's < −0.003, p's ≥ 0.83), nor of empathy and group on affect (b's ≥ −0.01 ≤ 0.05 and, p's ≥ 0.50).

Closeness of Contact, Empathy, and Positive Symptoms

No significant interaction between empathy and closeness of contact on positive symptoms was found for the total sample [b = 0.01, 95% CI (−0.01 to 0.03), p = 0.35], nor for empathy and group [b = −0.02, 95% CI (−0.14 to 0.10), p = 0.79].

Closeness of Contact, Empathy, and Affect

A significant interaction effect was found for empathy and close contact on positive affect for the total sample [b = 0.06, 95% CI (0.02 to 0.11), p = 0.003, see **Figure 1**] but not on negative affect for the total sample [b = −0.02, 95% CI (−0.05 to 0.02), p = 0.41]. There was no interaction between empathy and group on positive affect [b = 0.02, 95% CI (−0.11 to 0.16), p = 0.73] nor on negative affect [b = 0.01, 95% CI (−0.14 to 0.15), p = 0.93]. Follow-up analyses were carried out to interpret the interactions as shown in **Figure 1** and revealed a non-significant positive association between empathy and positive affect when being in company of close others [b = 0.02, 95% CI (−0.05 to 0.09), p = 0.58], and a non-significant negative association for being in company of less close others [b = −0.02, 95% CI (−0.10 to 0.06), p = 0.64].

DISCUSSION

The current study aimed to gain more insight into the relationship of social contact, closeness of contact, and empathy on mental health in individuals with PS versus controls. The results showed that being in company of others compared to being alone was associated with higher levels of positive affect in the total sample. However, social contact with close others (e.g., friends and partner) was significantly more related to higher positive affect than company of less close others. Furthermore, company of close others was associated with lower positive symptoms in the PS group only. This indicates that the nature of the contact (close versus less close) plays a relevant role, especially for individuals with PS, since it may lower their positive symptoms, although the direction of the effect could not be determined. In addition, the results for the total sample showed an interaction for closeness of contact and empathy on positive affect, suggesting that as levels of empathy increased, positive affect decreased when being in company of less close contacts but not when being in the company of close contacts. However, the results need to be considered with caution as these effects were not significant per type of contact (close versus less close) separately.

The results showed that being in social contact was not related to negative affect but it was related to more positive affect in the total sample. It was also found that close contact compared to less close contact was significantly related to more positive affect for the total sample. Furthermore, contact with

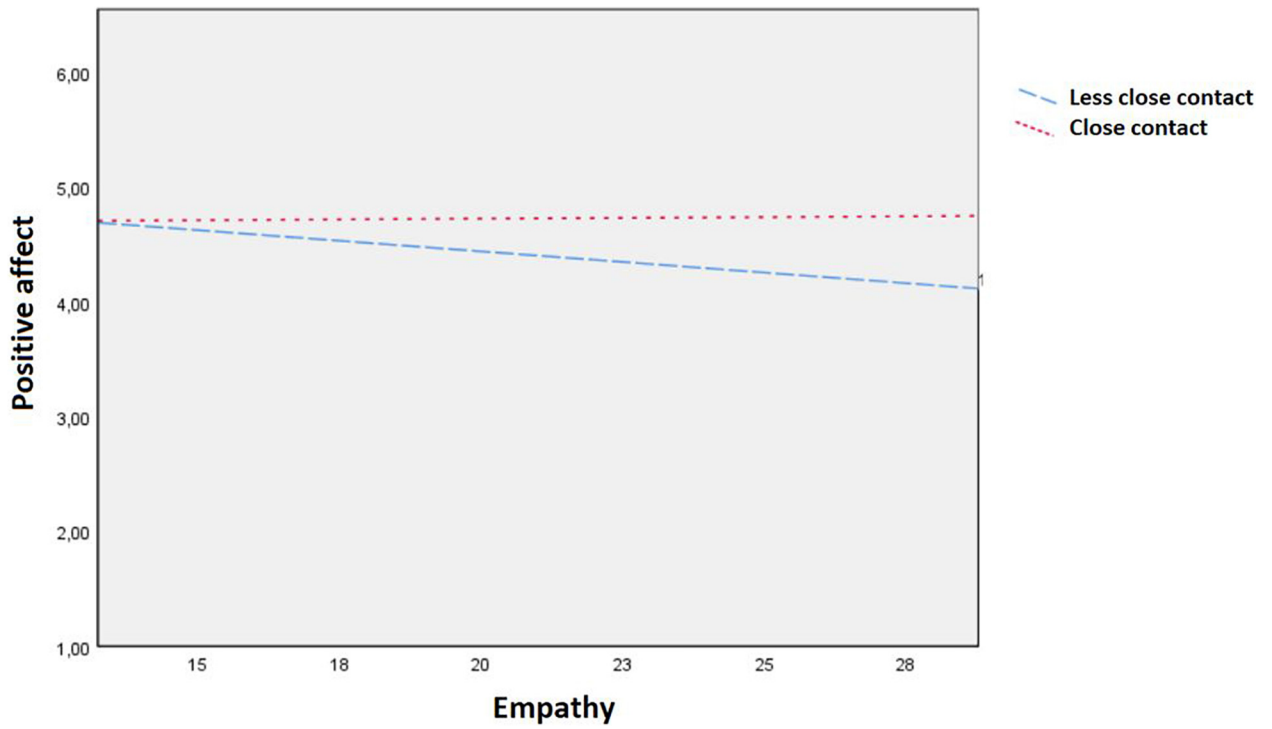


FIGURE 1 | Interaction effect of empathy as measured by the EmQue-CA and closeness of contact on positive affect as measured by the experience sampling method (ESM), for the total sample.

close others was related to lower positive symptoms in the patient group only. These findings are in agreement with previous research indicating that contact with close others is associated with a lower symptom severity (Verdoux et al., 2003; Husky et al., 2004; Collip et al., 2011). However, we could not test the direction of the effect. It may therefore also be possible that those who feel better, seek more contact with close others. Further research is needed to investigate the direction of this link. Nonetheless, these findings highlight the importance of the closeness of the contact and seem highly relevant for clinical practice. Therapies could focus more on involving close contacts in the life of the patient. Additionally, the role of empathy was investigated. It was assumed that the PS group would show lower levels of empathy than the control group, but this was not the case. This might be explained by the fact that we used a self-report questionnaire. This may lead to subjective biases and objective measures have been suggested to more accurately measure empathic skills (Chrysikou and Thompson, 2016; Van Donkersgoed et al., 2019). It may also be due to the fact that the PS group consisted of CHR and FEP participants and some studies suggest that empathic deficits are more visible in patients with chronic schizophrenia (Canty et al., 2021). Furthermore, we measured empathy as a trait rather than a state. Future research could incorporate ESM questions measuring empathy to investigate fluctuations of empathy and how it may affect the relationship between contact with others and mental health within one moment. It was hypothesized that individuals with higher levels of empathy benefited more from social contact resulting in a better mental health. Results showed that empathy only moderated the relationship between closeness of contact and positive affect and only for the total sample. The interaction plot suggested that for individuals with higher levels of empathy in combination with being with close others was related to higher positive affect compared to being with less close others. However, the direction of the effect is unclear as we could not investigate causality and more importantly, the effect of empathy on positive affect per type of contact (close versus less close) was non-significant. However, type of contact had a differential effect on positive affect dependent on levels of empathy. More research with larger sample sizes is needed to find a potential effect. Based on our results, empathy does not seem to play a pivotal role in boosting the relationship between contact and mental health.

Our results need to be considered in the light of several limitations. The sample size was relatively small and not all participants filled out every ESM measurement. We found that individuals with PS responded significantly less often than control participants. Although we have no insight in reasons for missing ESM measurements, it might be that with higher symptom severity, individuals with PS were less likely to fill out measurements which in turn may have influenced our results. For future research, we recommend to provide one pop-up question (e.g., multiple choice) for the participant to indicate why he/she did not fill out the measurement. Another point is that the PS group used different types of medication. For example, CHR were on medication for anxiety and depressive

symptoms whereas FEP were predominantly taking antipsychotic medication. These factors may have influenced their natural daily behavior and feelings. To avoid these biases, future studies should include more participants, and a more homogeneous group, preferably consisting of unmedicated individuals with PS. As we could not determine the directions of the effects, it would be valuable if future research included longitudinal data to show the temporal sequence, long-term effects and possibly causality. Furthermore, we did not have information regarding the bond of the company the participant was with, although we knew to what extent they felt comfortable in their company. However, it would have been best if participants rated how close they were to the specific person. Additionally, it would be valuable if future research investigated whether treatments involving close contacts are effective in individuals with PS. Furthermore, we were not able to measure perceived social support, but this may be a mediator between social contact and symptom severity as close contacts seem to be related to higher perceived social support (Manago et al., 2012), and social support has been linked to better outcomes in people with mental illnesses (McCorkle et al., 2008). Future research can investigate this link further. It is also interesting to investigate whether negative symptoms decrease when individuals with PS are motivated to engage in social contact with good friends or family. This could be done by providing therapy which involves the close contacts in order to strengthen their relationship and facilitate the contact. Lastly, it would be interesting to divide positive symptoms into manic and paranoid symptoms, as they may differ in terms of corresponding affect.

The current findings lead to several implications for clinical practice. Since the results showed that company of close contacts was associated with better outcomes, therapy should include ways to utilize these beneficial contexts either directly by involving close friends/family in therapy or indirectly by guiding the patient in seeking contact with close others. In the United Kingdom, family therapy is already a recommended psychological treatment for individuals with psychosis [National Institute for Health and Care Excellence (NICE), 2015].

In summary, we can conclude that social contact, especially with close others, is linked to a higher positive affect for both individuals with PS and healthy controls. Additionally, in individuals with PS, only close contacts were related to less positive symptoms. This seems an important finding for clinical practice as therapy could focus on this aspect, though we did not investigate the causality or long-term effects of this association. Levels of empathy might also play a role in terms of positive affect, but this should be further investigated in order to draw firm conclusions.

DATA AVAILABILITY STATEMENT

The data analyzed in this study can be shared upon reasonable request. Requests to access these datasets should be directed to IL-J and LJK, i.l.j.jansen@vu.nl and l.j.g.krijnen@uu.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam. Written informed consent to participate in this study was provided by the participant, and if under the age of 18, also by the participants' parent or guardian.

AUTHOR CONTRIBUTIONS

LJK: conceptualization, methodology, formal analysis, and writing – original draft. IL-J: conceptualization, methodology, formal analysis, and writing – review and editing. A-KF: writing – review and editing. LK: conceptualization, writing – review and editing, and funding acquisition. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by funding of the Hersenstichting Nederland [KS2011(1)-75], and an ERC Consolidator grant to LK, grant number 648082.

REFERENCES

American Psychiatric Association [APA] (2004). *Diagnostic and statistical manual of mental disorders (4th ed., Text Revision)*. Washington: American Psychiatric Association.

American Psychiatric Association [APA] (2013). *Statistical Manual of Mental Disorders: DSM-5^{TM}. Arlington*. Virginia: American Psychiatric Publishing. doi: 10.1176/appi.books.9780890425596

Baron-Cohen, S., and Wheelwright, S. (2004). The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. *J. Autism Dev. Disord.* 34, 163–175. doi: 10.1023/b:jadd.0000022607.19833.00

Bengtsson-Tops, A., and Hansson, L. (2001). Quantitative and qualitative aspects of the social network in schizophrenic patients living in the community. Relationship to sociodemographic characteristics and clinical factors and subjective quality of life. *Int. J. Soc. Psychiatry* 47, 67–77. doi: 10.1177/002076400104700307

Berger, P., Bitsch, F., Jakobi, B., Nagels, A., Straube, B., and Falkenberg, I. (2019). Cognitive and emotional empathy in patients with schizophrenia spectrum disorders: a replication and extension study. *Psychiatry Res.* 276, 56–59. doi: 10.1016/j.psychres.2019.04.015

Bjornestad, J., ten Velden Hegelstad, W., Joa, I., Davidson, L., Larsen, T. K., Melle, I., et al. (2017). "With a little help from my friends" social predictors of clinical recovery in first-episode psychosis. *Psychiatry Res.* 255, 209–214. doi: 10.1016/j.psychres.2017.05.041

Bora, E., Eryavuz, A., Kayahan, B., Sungu, G., and Veznedaroglu, B. (2006). Social functioning, theory of mind and neurocognition in outpatients with schizophrenia; mental state decoding may be a better predictor of social functioning than mental state reasoning. *Psychiatry Res.* 145, 95–103. doi: 10.1016/j.psychres.2005.11.003

Brüne, M. (2005). "Theory of mind" in schizophrenia: a review of the literature. *Schizophr. Bull.* 31, 21–42. doi: 10.1093/schbul/sbi002

Canty, A. L., Cao, Y., Neumann, D., and Shum, D. H. (2021). The functional significance of cognitive empathy and theory of mind in early and chronic schizophrenia. *Psychiatry Res.* 299:113852. doi: 10.1016/j.psychres.2021.113852

Cho, H., Gonzalez, R., Lavaysse, L. M., Pence, S., Fulford, D., and Gard, D. E. (2017). Do people with schizophrenia experience more negative emotion and less positive emotion in their daily lives? A meta-analysis of experience sampling studies. *Schizophr. Res.* 183, 49–55. doi: 10.1016/j.schres.2016.11.016

Chrysikou, E. G., and Thompson, W. J. (2016). Assessing cognitive and affective empathy through the interpersonal reactivity index: an argument against a two-factor model. *Assessment* 23, 769–777. doi: 10.1177/1073191115599055

Collip, D., Oorschot, M., Thewissen, V., Van Os, J., Bentall, R., and Myin-Germeys, I. (2011). Social world interactions: how company connects to paranoia. *Psychol. Med.* 41, 911–921. doi: 10.1017/S0033291710001558

Corbera, S., Wexler, B. E., Bell, M. D., Pearlson, G., Mayer, S., Pittman, B., et al. (2021). Predictors of social functioning and quality of life in schizophrenia and autism spectrum disorder. *Psychiatry Res.* 303:114087. doi: 10.1016/j.psychres.2021.114087

Cornblatt, B. A., Auther, A. M., Niendam, T., Smith, C. W., Zinberg, J., Bearden, C. E., et al. (2007). Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. *Schizophr. Bull.* 33, 688–702. doi: 10.1093/schbul/sbm029

Csikszentmihalyi, M., and Larson, R. (2014). "Validity and reliability of the experience-sampling method," in *Flow and The Foundations Of Positive Psychology*, ed. M. Csikszentmihalyi (Berlin: Springer), 35–54. doi: 10.1007/978-94-017-9088-8_3

De Vries, M. W. (ed.) (1992). *Practical issues in psychiatric applications of ESM. The Experience of Psychopathology: Investigating Mental Disorders In Their Natural Settings*. Cambridge: Cambridge University Press, 317–323.

Derntl, B., Finkelmeyer, A., Toygar, T. K., Hülsmann, A., Schneider, F., Falkenberg, D. I., et al. (2009). Generalized deficit in all core components of empathy in schizophrenia. *Schizophr. Res.* 108, 197–206. doi: 10.1016/j.schres.2008.11.009

Fett, A.-K. J., Hanssen, E., Eemers, M., Peters, E., and Shergill, S. S. (2021). Social isolation and psychosis: an investigation of social interactions and paranoia in daily life. *Eur. Arch. Psychiatry Clin. Neurosci.* [Online ahead of print] doi: 10.1007/s00406-021-01278-4

Fett, A.-K. J., Viechtbauer, W., Penn, D. L., van Os, J., and Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci. Biobehav. Rev.* 35, 573–588. doi: 10.1016/j.neubiorev.2010.07.001

Fusar-Poli, P., Byrne, M., Valmaggia, L., Day, F., Tabraham, P., Johns, L., et al. (2010). Social dysfunction predicts two years clinical outcome in people at ultra high risk for psychosis. *J. Psychiatr. Res.* 44, 294–301. doi: 10.1016/j.jpsychires.2009.08.016

Goldman, H. H., Skodol, A. E., and Lave, T. R. (1992). Revising axis V for DSM-IV: a review of measures of social functioning. *Am. J. Psychiatry* 149:9. doi: 10.1176/ajp.149.9.1148

Grant, C., Addington, J., Addington, D., and Konnert, C. (2001). Social functioning in first-and multiepisode schizophrenia. *Can. J. Psychiatry* 46, 746–749. doi: 10.1177/070674370104600808

Häfner, H., Löffler, W., Maurer, K., Hambrecht, M., and Heiden, W. A. D. (1999). Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. *Acta Psychiatr. Scand.* 100, 105–118. doi: 10.1111/j.1600-0447.1999.tb10831.x

Hogan, R. (1969). Development of an empathy scale. *J. Consult. Clin. Psychol.* 33:307.

Husky, M. M., Grondin, O. S., and Swendsen, J. D. (2004). The relation between social behavior and negative affect in psychosis-prone individuals: an experience sampling investigation. *Eur. Psychiatry* 19, 1–7. doi: 10.1016/j.eurpsy.2003.09.006

Kay, S. R., Fiszbein, A., and Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276.

Kingery, J. N., Erdley, C. A., and Marshall, K. C. (2011). Peer acceptance and friendship as predictors of early adolescents' adjustment across the middle school transition. *Merrill Palmer Q.* 57, 215–243. doi: 10.1353/mpq.2011.0012

Lemmers-Jansen, I. L. J., Fett, A.-K. J., Hanssen, E., Veltman, D. J., and Krabbendam, L. (2018). Learning to trust: social feedback normalizes trust behavior in first-episode psychosis and clinical high risk. *Psychol. Med.* 49, 780–790. doi: 10.1017/S003329171800140X

Lemmers-Jansen, I. L. J., Fett, A.-K. J., Van Doesum, N. J., Van Lange, P. A. M., Veltman, D. J., and Krabbendam, L. (2019). Social mindfulness and psychosis: neural response to socially mindful behavior in first-episode psychosis and patients at clinical high-risk. *Front. Hum. Neurosci.* 13:47. doi: 10.3389/fnhum.2019.00047

Leucht, S., Kane, J. M., Kissling, W., Hamann, J., Etschel, E., and Engel, R. R. (2005). What does the PANSS mean?. *Schizophr. Res.* 79, 231–238. doi: 10.1016/j.schres.2005.04.008

Manago, A. M., Taylor, T., and Greenfield, P. M. (2012). Me and my 400 friends: the anatomy of college students' Facebook networks, their communication patterns, and well-being. *Dev. Psychol.* 48:369. doi: 10.1037/a0026338

Mazza, M., Pollice, R., Pacitti, F., Pino, M. C., Mariano, M., Tripaldi, S., et al. (2012). New evidence in theory of mind deficits in subjects with chronic schizophrenia and first episode: correlation with symptoms, neurocognition and social function. *Riv. Psichiatr.* 47, 327–336. doi: 10.1708/1139.12561

McCorkle, B. H., Rogers, E. S., Dunn, E. C., Lyass, A., and Wan, Y. M. (2008). Increasing social support for individuals with serious mental illness: evaluating the compeer model of intentional friendship. *Community Ment. Health J.* 44:359. doi: 10.1007/s10597-008-9137-8

McDonald, N. M., and Messinger, D. S. (2011). "The development of empathy: How, when, and why," in *Moral Behavior And Free will: A Neurobiological And Philosophical Approach*, eds J. J. Sanguineti, A. Acerbi, and J. A. Lombo (London: IF Press), 333–359.

Meyer-Lindenberg, A., and Tost, H. (2012). Neural mechanisms of social risk for psychiatric disorders. *Nat. Neurosci.* 15:663.

Millier, A., Siegrist, K., Amri, I., Toumi, M., and Aballéa, S. (2014). Social contacts reduce negative symptoms, especially emotional withdrawal in patients with schizophrenia. *Value Health* 17:A455. doi: 10.1016/j.jval.2014.08.1244

Montag, C., Brandt, L., Lehmann, A., De Millas, W., Falkai, P., Gaebel, W., et al. (2020). Cognitive and emotional empathy in individuals at clinical high risk of psychosis. *Acta Psychiatr. Scand.* 142, 40–51. doi: 10.1111/acps.13178

Montag, C., Heinz, A., Kunz, D., and Gallinat, J. (2007). Self-reported empathic abilities in schizophrenia. *Schizophr. Res.* 92, 85–89.

Morosini, P. L., Magliano, L., Brambilla, L., Ugolini, S., and Pioli, R. (2000). Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social funtioning. *Acta Psychiatr. Scand.* 101, 323–329. doi: 10.1034/j.1600-0447.2000.101004323.x

Myin-Germeys, I., Delespaul, P., and Van Os, J. (2005). Behavioural sensitization to daily life stress in psychosis. *Psychol. Med.* 35, 733–741. doi: 10.1017/s0033291704004179

Nangle, D. W., Erdley, C. A., Newman, J. E., Mason, C. A., and Carpenter, E. M. (2003). Popularity, friendship quantity, and friendship quality: interactive influences on children's loneliness and depression. *J. Clin. Child Adolesc. Psychol.* 32, 546–555. doi: 10.1207/S15374424JCCP3204_7

National Institute for Health and Care Excellence (NICE) (2015). *Psychosis And Schizophrenia In Adults Quality standard [QS80]*. London: National Institute for Health and Care Excellence.

Niendam, T. A., Bearden, C. E., Johnson, J. K., McKinley, M., Loewy, R., O'Brien, M., et al. (2006). Neurocognitive performance and functional disability in the psychosis prodrome. *Schizophr. Res.* 84, 100–111. doi: 10.1016/j.schres.2006.02.005

Overgaauw, S., Rieffe, C., Broekhof, E., Crone, E. A., and Güroğlu, B. (2017). Assessing empathy across childhood and adolescence: validation of the Empathy Questionnaire for Children and Adolescents (EmQue-CA). *Front. Psychol.* 8:870. doi: 10.3389/fpsyg.2017.00870

Price, V., and Archbold, J. (1997). What's it all about, empathy?. *Nurs. Educ. Today* 17, 106–110.

Priebe, S., Roeder-Wanner, U.-U., and Kaiser, W. (2000). Quality of life in first-admitted schizophrenia patients: a follow-up study. *Psychol. Med.* 30, 225–230. doi: 10.1017/s0033291798008253

Pruessner, M., Iyer, S. N., Faridi, K., Joober, R., and Malla, A. K. (2011). Stress and protective factors in individuals at ultra-high risk for psychosis, first episode

psychosis and healthy controls. *Schizophr. Res.* 129, 29–35. doi: 10.1016/j.schres.2011.03.022

StataCorp, L. (2015). *Stata statistical software: release 14.[computer program]*. Texas: StataCorp LP.

Stone, A. A., and Shiffman, S. (1994). Ecological momentary assessment (EMA) in behavorial medicine. *Ann. Behav. Med.* 16, 199–202. doi: 10.1093/abm/16.3.199

Van Donkersgoed, R., De Jong, S., Aan het Rot, M., Wunderink, L., Lysaker, P., Hasson-Ohayon, I., et al. (2019). Measuring empathy in schizophrenia: the Empathic Accuracy Task and its correlation with other empathy measures. *Schizophr. Res.* 208, 153–159. doi: 10.1016/j.schres.2019.03.024

Van Donkersgoed, R., Wunderink, L., Nieboer, R., Aleman, A., and Pijnenborg, G. (2015). Social cognition in individuals at ultra-high risk for psychosis: a meta-analysis. *PLoS One* 10:e0141075. doi: 10.1371/journal.pone.0141075

Verdoux, H., Husky, M., Tournier, M., Sorbara, F., and Swendsen, J. D. (2003). Social environments and daily life occurrence of psychotic symptoms. *Soc. Psychiatry Psychiatr. Epidemiol.* 38, 654–661. doi: 10.1007/s00127-003-0702-8

Yager, J. A., and Ehmann, T. S. (2006). Untangling social function and social cognition: a review of concepts and measurement. *Psychiatry* 69, 47–68. doi: 10.1521/psyc.2006.69.1.47

Yung, A. R., Nelson, B., Stanford, C., Simmons, M. B., Cosgrave, E. M., Killackey, E., et al. (2008). Validation of "prodromal" criteria to detect individuals at ultra high risk of psychosis: 2 year follow-up. *Schizophr. Res.* 105, 10–17. doi: 10.1016/j.schres.2008.07.012

Yung, A. R., Phillips, L. J., Yuen, H. P., and McGorry, P. D. (2004). Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophr. Res.* 67, 131–142. doi: 10.1016/S0920-9964(03)00192-0

Yung, A. R., Yuen, H. P., McGorry, P. D., Phillips, L. J., Kelly, D., Dell'Olio, M., et al. (2005). Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Aust. N. Z. J. Psychiatry* 39, 964–971. doi: 10.1080/j.1440-1614.2005.01714.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.

APPENDIX A | ESM ITEMS USED IN THE CURRENT STUDY

"I feel comfortable in this company"
"With whom am I now?"
Alone/Alone with pet/colleague's/classmates/friends/1 friend/partner/family/roommates/stranger

Positive symptoms
"I sense that others do not like me"
"I sense that others intend to harm me"
"I am feeling suspicious"
"I feel surreal"
"My thoughts won't let me go"
"My thoughts are influenced by others"
"I hear voices"
"I see appearances"

Positive affect
"I feel lively"
"I feel relaxed"
"I feel content"
"I like myself"

Negative affect
"I feel insecure"
"I feel anxious"
"I feel irritated"
"I feel down"

APPENDIX B | PARTICIPANTS' ANSWERS REGARDING HOW COMFORTABLE THEY FELT WITH THEIR COMPANY

	Controls (n = 28)		PS group (n = 29)	
I feel comfortable in this company	**Close contact**	**Not a close contact**	**Close contact**	**Not a close contact**
No (scores 1–2)	9 (1.50%)	6 (2.1%)	5 (1.10%)	16 (10.40%)
Medium (scores 3, 4, 5)	47 (7.85%)	86 (29.66%)	168 (35.97%)	82 (53.25%)
Yes (scores 6–7)	543 (90.65%)	198 (68.28%)	294 (62.96%)	56 (36.36%)
Total obs, *n*	599	290	467	154

PS, individuals with psychotic symptoms; obs, number of ESM observations. Participants felt significantly more comfortable with company of close contacts ($p < 0.001$).

frontiers in Psychology

CLINICAL TRIAL
published: 24 December 2021
doi: 10.3389/fpsyg.2021.739252

Voices 2: Improving Prosodic Recognition in Schizophrenia With an Online Rehabilitation Program

*María Lado-Codesido[1,2], Rosa María Rey Varela[3], Marina Larios Quiñones[4], Luis Martínez Agulleiro[5], Julieta Ossa Basanes[2], María Martínez Querol[2], Raimundo Mateos[6], Carlos Spuch[7] and Alejandro García-Caballero[7,8]**

[1] University of Santiago de Compostela, Santiago de Compostela, Spain, [2] Department of Psychiatry, Donostia University Hospital, San Sebastián, Spain, [3] Department of Psychology, National University of Distance Education, Madrid, Spain, [4] Centro de Rehabilitación Laboral "Nueva Vida," Red Pública de Atención Social a Personas con Enfermedad Mental Grave y Duradera, Consejería de Políticas Sociales, Familias, Igualdad y Natalidad, Asociación Psiquiatría y Vida, Madrid, Spain, [5] Department of Psychiatry, Complexo Hospitalario Universitario de Ferrol, Ferrol, Spain, [6] Department of Psychiatry, University of Santiago de Compostela, Santiago de Compostela, Spain, [7] Translational Neuroscience Research Group, Galicia Sur Health Research Institute, University of Vigo, CIBERSAM, Vigo, Spain, [8] Department of Psychiatry, University Hospital Complex of Ourense, Ourense, Spain

OPEN ACCESS

Edited by:
Guillermo Soto,
University of Chile, Chile

Reviewed by:
Giulia Agostoni,
Vita-Salute San Raffaele University, Italy
Kara Hawthorne,
Gallaudet University, United States

***Correspondence:**
Alejandro García-Caballero
alejandro.alberto.garcia.caballero@sergas.es

Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: 10 July 2021
Accepted: 22 November 2021
Published: 24 December 2021

Citation:
Lado-Codesido M, Rey Varela RM, Larios Quiñones M, Martínez Agulleiro L, Ossa Basanes J, Martínez Querol M, Mateos R, Spuch C and García-Caballero A (2021) Voices 2: Improving Prosodic Recognition in Schizophrenia With an Online Rehabilitation Program. Front. Psychol. 12:739252. doi: 10.3389/fpsyg.2021.739252

Introduction: Emotion recognition of voices may play an important role in interpersonal communication and patients with schizophrenia present alterations in this regard. Several on-line rehabilitation tools have been developed for treatment in this area. *Voices* is an on-line prosodic recognition program consisting of identifying different emotional tones in neutral phrases, in different sessions of gradually increasing difficulty. This training tool has previously reported benefits, and a new version has been created called *Voices 2*. The main aim of this study is to test the capacity of the *Voices 2* program to improve emotion recognition through prosody for adults with schizophrenia. Secondly, it seeks to observe durability effects 1 month after intervention.

Method: A randomized, single-blind, multicenter clinical trial was conducted with 44 outpatients diagnosed with schizophrenia or schizoaffective disorder. The intervention group (also called *Voices*) was treated with *Voices 2*, whereas the control group was treated with auditory training that was not related to emotions. Sociodemographic and clinical data, clinical state (PANSS), Intelligence Quotient and prosodic recognition (RMV-SV) were measured at baseline. After intervention, RMV-SV and PANSS were assessed. One month later, the RMV-SV measure was repeated.

Results: The control group ($n = 19$) and the *Voices* group ($n = 22$) did not differ on χ^2, t or *U* tests in sociodemographic, clinical and psychometric variables at baseline or post-intervention (all p-values > 0.05). In the *Voices* group, statistically significant differences were observed in the RMV-SV scale applied post-intervention vs. that applied pre-intervention ($Z = 2.47$, $p = 0.013$). Similar results were observed in the 1-month follow-up RMV-SV vs. the pre-intervention RMV-SV ($Z = 1.97$, $p = 0.049$). PANSS scale was also assessed with no significant differences between pre vs. post measures in both groups. Lastly, *Voices 2* was rated relatively higher, based on its ease of understanding, entertainment value, usefulness and the appropriateness of use of its emotional glossary.

Discussion: Improvements were observed in prosodic recognition following intervention with *Voices 2* in the *Voices* group. Although these results are similar to other clinical trial rehabilitation programs, specific research on the matter remains scarce. Certain aspects, such as the durability of effects or adherence should be thoroughly studied and clarified.

Clinical Trial Registration: [https://doi.org/10.17605/OSF.IO/G95C4].

Keywords: prosodic recognition, emotion recognition, social cognition, natural semantic metalanguage, online cognitive training, computer based cognitive training, schizophrenia, schizoaffective disorder

INTRODUCTION

Schizophrenia is a severe and chronic mental disorder that affects 20 million people across the world (James et al., 2018). There are three types of main symptoms: positive symptoms (such as delusions, hallucinations, or disorganized speech); negative symptoms (affective flattening, alogia, or avolition) and cognitive symptoms (dysfunctions in working memory or processing speed, deficits in reasoning and abstract thinking, among others). Positive symptoms are manifested in acute episodes of the illness, while negative and cognitive symptoms are present during inter-episode phases, and they represent a significant factor in the limitation of the quality of life of patients. People with schizophrenia may present a high degree of social, occupational and academic dysfunction throughout their life (Ventura et al., 2009; Halverson et al., 2019).

The cognitive symptoms of the illness include deficits related to detection, processing and the use of social information, which enables integration and communication with other people. These tasks are part of Social Cognition (SC), and SC deficits are significantly related to deteriorating functionality in schizophrenia (Fett et al., 2011; Pinkham, 2014).

One of the bases of SC, which enables correct social interaction, is emotional processing. Emotional processing alterations do not improve with antipsychotic treatment (Penn et al., 2009), and they are related to the severity of the illness (Irani et al., 2012). Facial emotion processing deficits have been widely documented (Kohler et al., 2010; Gao et al., 2021). In studies related to other sensory channels, such as the auditory pathway, results are similar to those of facial recognition, although they are collected less frequently (Lin et al., 2018). In the auditory channel, emotional recognition is carried out through tone of voice, also called affective prosody.

Affective prosody is an important issue in the field of schizophrenia because it helps to clarify meanings and resolve ambiguity in human speech through the auditory channel, when no other channel is available (e.g., a phone call) (Paulmann and Pell, 2011). Moreover, prosodic recognition is integrated as part of the multisensory channels needed for emotion communication (composed of facial and linguistic expressions and paralinguistic inputs), and it is essential for interpersonal relations. If any of these channels fail to integrate emotional signals, interpersonal conflicts could arise (Lin et al., 2020).

Deficits in prosodic recognition are associated with negative and cognitive symptoms (Thomas et al., 2017). Basic auditory skills and auditory emotion processing are impaired in schizophrenia patients with cognitive disturbances (Kraus et al., 2019). The presence of negative symptomatology has been associated with worsening prosodic recognition (Leitman et al., 2005; Castagna et al., 2013). One of the hypotheses considered by Castagna et al. (2013) is that both the cognitive state and the negative symptoms that are altered in schizophrenia could bias the evaluation and discrimination of the auditory stimuli from the environment, making them less competitive, and therefore, more deficient than in non-pathological conditions.

Moreover, it has been shown that deficits in prosodic perception have a crucial effect on global functionality (Leitman et al., 2005, 2007). These prosodic deficits also have an impact on social skills, resulting in alterations, misunderstandings, and inappropriate social responses (Kee et al., 2003; Pinkham and Penn, 2006). Primary auditory processing has been directly related to social functioning, independently of cognition (Medalia et al., 2019).

Due to the impact of emotional processing on cognitive and social dysfunction, it is vitally important to study its treatment. Several research avenues have been developed in the treatment of prosodic recognition. Pharmacology, the use of oxytocin and neurostimulation are some of the possibilities under development, although sufficient evidence is still unavailable (Tan et al., 2018). Currently, the most effective treatment is cognitive rehabilitation (Horan and Green, 2019). According to the Cognitive Remediation Experts Workshop (Florence, Italy, April 2010), cognitive rehabilitation is defined as an intervention based on behavioral training, aimed at improving cognitive processes with the aim of achieving a durable and generalized improvement. The results of these objectives in the studies conducted are also varied. The generalized improvements observed after applying an intervention program, with regards to untrained cognitive functions, psychosocial functioning and symptomatology, have been verified in certain studies (McGurk et al., 2007; Kurtz and Richardson, 2012), although reviews point to a lack of attention to this objective (Fiszdon and Reddy, 2012). As for the durability of post-intervention effects, their short-term benefits have been demonstrated (Wykes et al., 2011; Fiszdon and Reddy, 2012; Revell et al., 2015), although research on the maintenance of these improvements in the long term continues to be limited.

Furthermore, among the cognitive rehabilitation programs published, the conditions that must be met to achieve greater

effectiveness are not clear. While certain reviews support the use of computerized methods compared to other types (Byrne et al., 2015), others maintain that the type of program does not necessarily entail differences in the results (Morin and Franck, 2017). Likewise, there does not appear to be significant association between a specific intervention based on a particular cognitive function and a global intervention based on several cognitive aspects when designing an intervention program (Grant et al., 2017). Studies agree that the number of tools is scarce and the methodological quality of studies is modest (Wykes et al., 2011; Grant et al., 2017). It is necessary to further examine the design of cognitive rehabilitation tools, by conducting studies with greater methodological rigor, making it possible to compare tools and draw valid conclusions.

At present, social cognition rehabilitation programs are continuously emerging. Emotion recognition is the subdomain that presents a greater number of developed tools for rehabilitation (Fiszdon and Reddy, 2012). One of the main effective SC programs in schizophrenia is called Training Affect Recognition (TAR) (Frommann et al., 2003), which focuses on facial expression recognition of basic emotions. Another program reviewed, called Social Cognition Interaction Training (SCIT) (Penn et al., 2005; Combs et al., 2007), includes various treatment modalities and is based on emotional perception, theory of mind and social perception. The final type of intervention, named Cognitive Enhancement Treatment (CET) (Eack et al., 2007), combines aspects of SC with neurocognition training and includes a prosodic rehabilitation module.

Despite this, literature on prosodic recognition rehabilitation remains scarce. Certain programs have been designed, such as Cognitive Pragmatic Treatment (Bosco et al., 2016), which is administered based on a group therapy model, in 20 half-hour sessions. Training is based on linguistics, paralinguistics and extra-linguistics, theory of mind and other cognitive functions. The results of this study did not provide affective prosodic measurements, and the sample was too small (n = 17). In another type of program created by Bechi et al. (2018), based on auditory and visual training and comprising of 8 h long sessions, the results showed an improvement in auditory abilities with training and an extended benefit in the auditory channel upon completion of the visual training. Finally, SocialVille (Nahum et al., 2014) is another relevant program in prosodic recognition rehabilitation. This program combines 40 working sessions of SC exercises, including auditory perception of basic emotion training, visual affect perception, social cue perception, theory of mind, self-referential style and empathy. The results showed an improvement in SC scales and functioning (Miley et al., 2020).

In this context, the web platform www.e-motionaltraining.com was developed, which includes different rehabilitation games in SC and social skills for schizophrenia and other mental illnesses (Vázquez-Campo et al., 2016; Maroño Souto et al., 2018). A specific intervention was created on this web platform, focused on affective prosody recognition, called *Voices*. The *Voices* program consists of eight sessions of varying levels in the form of a game with 15 different trials. In each trial, sentences of speech with neutral lexical content (e.g., "*I brought what you asked for*") are reproduced in different emotional valences (e.g., happy, angry, surprised. . .). These sentences are recorded by professional actors and actresses and uploaded to the program in an mp3 file. For each trial, two, three or four response options with different emotions are shown, with only one being the correct answer. Once the participant has chosen their answer, the program returns feedback regarding the correct/incorrect response. Trial difficulty increases gradually over the course of the sessions. A randomized, multicenter clinical trial was conducted, comparing the intervention with *Voices* in clinically stable patients with schizophrenia or schizoaffective disorder, compared to patients with the same diagnosis who regularly attended their routine treatment at psychosocial rehabilitation centers. The result of the prosodic recognition scale applied to evaluate the participants pre- and post-intervention was favorable for the *Voices* program, compared to conventional rehabilitation ($p < 0.05$). The participants following the *Voices* treatment filled out satisfaction surveys on the program, in which 80% of users considered the tool to be easy to use and entertaining (Lado-Codesido et al., 2019). Some of the limitations of the study include the scarcity of similar studies, hindering comparison between intervention programs, the minimal number of effective sessions and the lack of evaluation of other cognitive measures to ascertain the generalized effect of rehabilitation.

Following the initial results of the *Voices* program, the tool was optimized and adapted, creating the *Voices 2* program. New sentences were added, recorded by new voluntary actors and actresses, equipping the tool with greater diversity. A reference glossary was also created to understand certain complex emotional terms (called "emotional glossary"), which can be used by users independently. The study methodology was improved, adding an active control group and a more comprehensive post-intervention evaluation, in order to observe the durability of improvements in the short term. The *Voices 2* tool, like all the other programs on the platform www.e-motionaltraining.com, was developed in Spanish.

The main goal of this study was to assess improvements in prosodic recognition with a new version of a training tool called *Voices 2,* through a prosodic recognition scale, in clinically stable patients with schizophrenia or schizoaffective disorder. The second aim was to observe the maintenance of the benefits in a short period after intervention (1 month is proposed). The final objective was to evaluate the usability of *Voices 2* tasks from the participant's point of view.

MATERIALS AND METHODS

A randomized, single-blind, multicenter clinical trial was conducted with 44 outpatients diagnosed with schizophrenia or schizoaffective disorder. The patients were recruited from four psychosocial rehabilitation centers in A Coruña, Madrid and Guipúzcoa. All patients attended the centers as outpatients. The selected patients were randomized by a computer-generated randomization list. The allocation sequence was randomly assigned and concealed from the research team. Three of the recruited patients were lost to follow-up, 2 in the control group

(one of them refused to continue, the other moved house), and 1 in the intervention group (who refused to continue), also called the *Voices* group (Control $n = 19$, *Voices* $n = 22$). Therefore, the final sample was composed of 41 patients (**Figure 1**). The attrition rate of the intervention was 6.7%.

Inclusion and Exclusion Criteria

We included patients who voluntarily agreed to participate in the study, who were between 18 to 65 years of age, had a diagnosis of schizophrenia or schizoaffective disorder (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition), were clinically stable and followed up by the Department of Psychiatry, presented an intelligence quotient (IQ) within the normal range (> 70), who can read and write, and had no comorbidity with other psychiatric, neurological or severe auditory diseases or current substance abuse (except nicotine). We excluded patients with legal disability by reason of mental disability. During the informed consent process, the researchers confirmed that participants understood the voluntariness of their participation and the randomization strategy. Written informed consent was therefore obtained by researchers not pertaining to the clinical staff, to minimize social desirability biases. Recruitment was planned for March 2020, but it was postponed due to the COVID-19 pandemic situation from August 2020 until April 2021.

Initial Procedures and Characterization of the Sample

Before the intervention, participants were recruited at each center. An evaluation was conducted by the research team, consisting of the collection of personal, sociodemographic and clinical data, psychometric evaluation for IQ, measured by the K-BIT test, clinical state assessed by the PANSS scale, and prosodic recognition state by the RMV-SV scale (for further information on patient evaluation tools see point 2.5). The mean age of the sample was 43.22 (SD = 1.3), most of the participants were men, and were diagnosed with schizophrenia. For more information, see **Table 2**.

After these initial procedures, participants were randomized into the *Voices* and control group. The researchers were blind to the assignment.

Intervention Description

The control group participated using a free computerized music program called Lyrics Training[1]. This music program entails participants listening to different songs and guessing hidden words from the lyrics that are displayed on the screen while the song is playing. Each correct answer adds points to a total score that is shown at the end of the song. The difficulty of the program can be increased and adapted to the user's ability. This program can be used autonomously, with the support of the research team where necessary. Although prosody could be considered closely connected to music, this program is focused on semantic aspects of the lyrics, and is not related to social cognitive rehabilitation, or to emotion recognition training (the real aim of the Lyrics Training program is language learning). Moreover, this program is not specific to mental illness.

The *Voices* group participated in sessions using *Voices 2,* which is the optimized version of the *Voices* program (Lado-Codesido et al., 2019). Eighty-two new trials have been added to the sixty-three initial trials, with each sentence recorded by professional actors and actresses, while new sessions of progressive difficulty have also been designed. At the start of the game, the program automatically plays a sentence with neutral lexical content, which was produced with a specific emotion, and several response options are shown with different simple and complex emotions, as explained above. Feedback is given after each trial, and when each game has been completed, the final score is displayed. For each training session, participants can play the same game level as many times as they want, and the scores of each game will be compared on the final screen. In each game, different trials appear randomly. For more specific details about the *Voices* tool, see Lado-Codesido et al. (2019).

Intervention with Lyrics Training and *Voices 2* was composed of a total of eight sessions over the course of a month. These sessions were divided into 2 weekly sessions lasting approximately 30 min. The participants attended their reference center to undergo training. A common data collection protocol was established for all centers involved in the study. Training was conducted with a personal computer or tablet for each participant, in a quiet room, with the support of trained personnel from the research team to show the participant how to use the application. Both the control and the *Voices* groups underwent treatment as usual (including drug therapy, case management and individual and group psychotherapy).

Natural Semantic Metalanguage

One of the problems arising from our first *Voices* clinical trial was that users showed difficulties in comprehending the lexicon referring to complex emotions. However, explaining these complex terms was not easy and dictionary definitions were, on many occasions, circular, defining one complex term with a synonym of comparable difficulty. To resolve this issue, it was necessary to seek an operative definition model avoiding circularity, i.e., a "universal" language that could disambiguate complex emotions without recurring to synonyms. From a linguistic perspective, this solution was delivered by means of the so-called "Natural Semantic Metalanguage" (NSM). The NSM is an approach to explain human emotions that allows comprehension across different cultures, previously used in other pathologies such as autism (Mullan et al., 2020) and in other fields of medicine, to facilitate effective communication with patients (Peeters and Marini, 2018). It is a "mini-language" expressed through grammar and a reduced group of "primitive concepts," which represent the same meaning in every language (Wierzbicka, 1999). These "primitive concepts" are chosen and combined to construct a definition of emotional terms to facilitate the understanding of people with greater difficulties, such as those with psychosis. Further information

[1] www.lyricstrainning.com

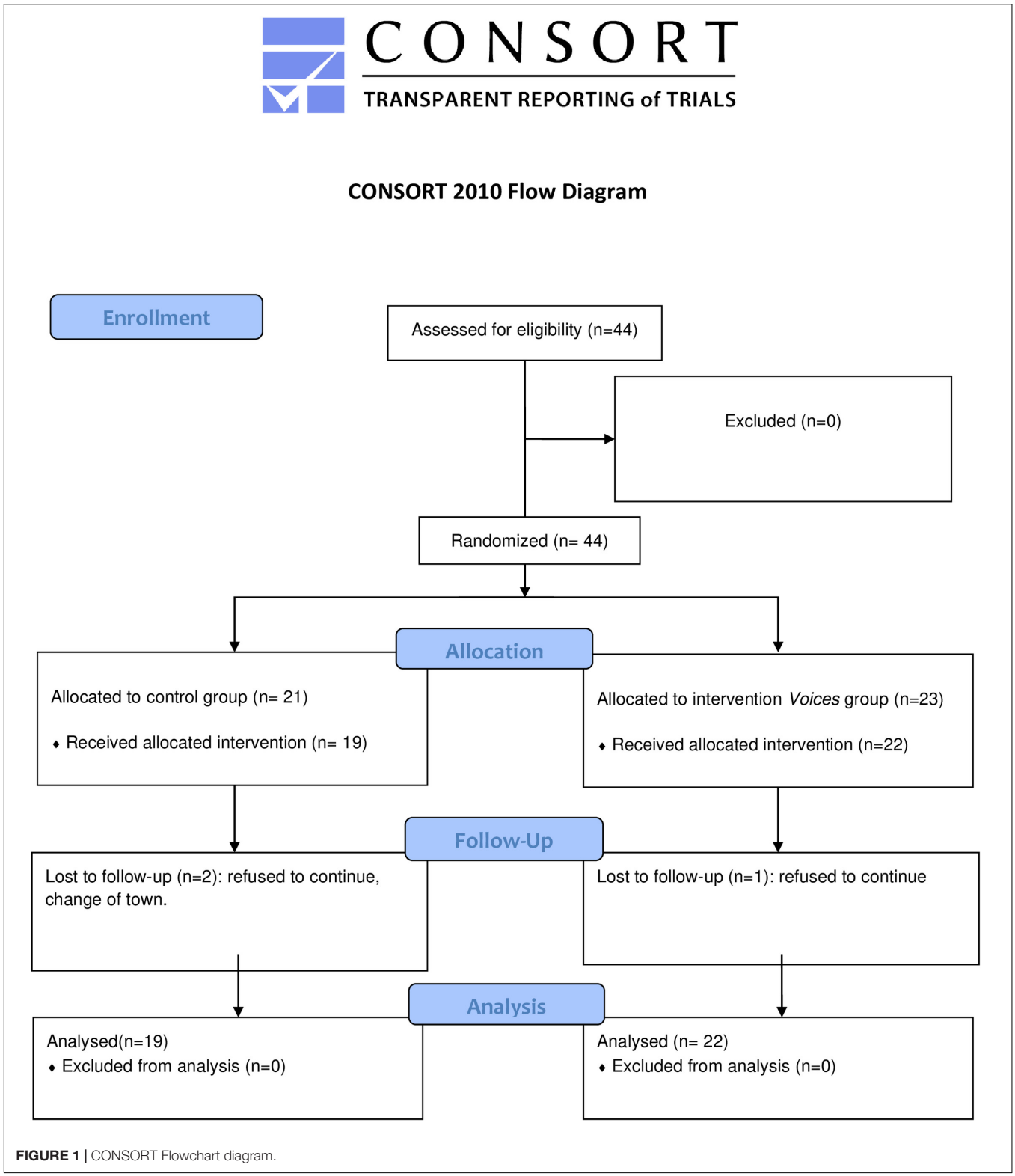


FIGURE 1 | CONSORT Flowchart diagram.

can be found on the NSM webpage: https://nsm-approach.net/.

Specialists in NSM voluntarily collaborated in the preparation of a consultation tool called "emotional glossary." Through NSM, they defined complex emotional terms that were used in the game, and which could pose greater difficulties to participants. This consultation tool was then made accessible from the program's main website and participants could check it

autonomously throughout the game and as many times as needed (**Figure 2**). Unfortunately, only two of the four centers could use the emotional glossary. The assessment questionnaire that was administered at the end of *Voices 2* intervention also asked participants to assess this tool and its ease of understanding.

Post-testing Procedures

At the end of the intervention with *Voices 2* and Lyrics Training, both groups were retested with RMV-SV and PANSS. The *Voices* group also completed a 5-min user experience questionnaire. One month after the post-intervention test, RMV-SV was tested once more in both groups (**Table 1**).

Evaluation Tools

Several tools were employed to assess the benefits of performing prosodic training, and to improve *Voices 2* tasks.

Patient Evaluation

All patients were assessed by the instruments described below. The results for all the scales mentioned below are provided in raw scores, except for IQ scores that are provided in standard scores:

- Customized datasheet designed by the authors for recording demographic and clinical data, including sex, age, occupation, educational level, marital status, current cohabitation, diagnosis and associated diagnoses, illness duration, handedness, and equivalence of antipsychotic treatment to chlorpromazine. The initial database characterization was obtained from this demographic data. This information was collected once at baseline, during a conventional clinical interview with the patient and based on their electronic medical history.
- *Reading the Mind in the Voices—Spanish Version, RMV-SV* (Sánchez-Reales et al., 2019). Validation of the Reading the Mind in the Voices—Test Revised (RMV-TR) scale (Golan et al., 2007), which includes 33 segments translated and adapted from English and recorded by professional actors, with four response options, with simple and complex emotions. This test was administered before, after and 1 month after finishing the intervention to both groups.
- *Positive and Negative Symptom Scale (PANSS)* (Kay et al., 1987). This scale assesses the positive and negative symptom severity. It was applied before and after intervention to both groups.
- *Kauffman Brief Intelligence Test (K-BIT)* (Kaufman and Kaufman, 2011). This test includes the measure of verbal and non-verbal intelligence in adults. It was applied before the intervention.
- User experience questionnaire, created for the evaluation of the *Voices* tool and re-adapted to the *Voices 2* tool. The questionnaire included 11 questions on a Likert-type scale (ranging from 1 = total disagreement, to 5 = total agreement) to assess different aspects of the intervention (frequency of PC or Internet use; ease of connection, ease of understanding, entertainment value, autonomy of use and usefulness of *Voices 2*; subjective perception of the benefits obtained after using the program in the usual environment, new relationships, work environment and self-esteem; duration of the intervention and assessment of the emotional glossary). It was applied post-intervention to the *Voices* group.

Ethical Aspects

This study has been designed respecting the rules of good clinical practice and the ethical principles for medical research of the World Medical Association, which are reflected in the Declaration of Helsinki and its subsequent amendments. Likewise, European and state regulations regarding medical research are respected, particularly Organic Law 15/1999 of December 13 on the protection of personal data. All patients included were adequately informed about the purpose of the study and were asked to sign an informed consent. This study was approved by the local ethics committee (Clinical Research Ethics Committee of Galicia, Registration code: 2019/530, Euskadi, Registration code: PI2019192).

The authors confirm that all ongoing and related trials of this intervention are registered and anonymized. This study has been registered in an international registry of clinical trials, with Clinical Trial Registry Number: https://doi.org/10.17605/OSF.IO/G95C4. Under no circumstances will personal information be published or disclosed to persons outside the investigation or to the Ethics Committee for Clinical Research.

The study complies with current regulations on Intellectual Property, in accordance with Legislative Royal Decree 1/1996 of April 12. The ability of patients to understand the voluntariness of the study was assessed by researchers, by employing a clinical interview.

Statistical Analyses

Statistical analyses were performed, using SPSS version 25.0 software. The accepted α risk was 0.05. The following tests were applied:

- A descriptive analysis was performed. The quantitative variables are presented as means (M) and standard deviation (SD) or medians (Med) and ranges. The qualitative variables are presented as frequencies and percentages.
- To compare characteristics at baseline between the control and *Voices* groups, normality of data was tested, using the Shapiro–Wilk test. All variables presented a normal distribution except for the following variables: equivalence to chlorpromazine, Total IQ, PANSS positive, general psychopathology and PANSS total at baseline. To compare two qualitative variables, the chi-squared test was used. To compare quantitative variables, Student's *t*-test for independent samples (in Gaussian distribution) and *U*-Mann–Whitney test (in non-Gaussian distribution) were applied.
- To assess significant differences in temporal changes in RMV-SV and PANSS pre-post intervention in each group, normality was again tested with Shapiro–Wilk test. In this case, distribution was non-normal in all variables.

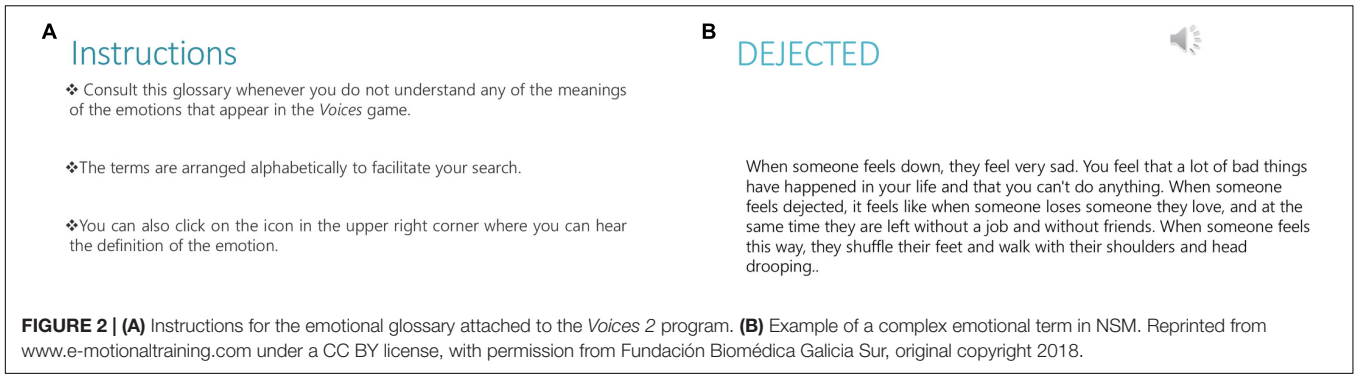


FIGURE 2 | (A) Instructions for the emotional glossary attached to the *Voices 2* program. **(B)** Example of a complex emotional term in NSM. Reprinted from www.e-motionaltraining.com under a CC BY license, with permission from Fundación Biomédica Galicia Sur, original copyright 2018.

TABLE 1 | Description of procedure of the clinical trial.

	Before intervention	Intervention	After intervention	1-month follow-up
Description	Recruitment, selection and randomization of *Voices* and control group	8 sessions in total over a month. Each week two sessions were administered of *Voices 2*/Lyrics Training program.		
Evaluation tools	Customized datasheet RMV-SV PANSS K-BIT		RMV-SV PANSS User experience questionnaire (*Voices* group)	RMV-SV

For our purpose, Wilcoxon's signed-rank non-parametric test was applied.

- Lastly, Cohens d statistic was obtained to estimate the effect size in the control and *Voices* groups.

RESULTS

A total of 44 participants were recruited and met the selected criteria. A single blinded, randomized assignation was carried out to select participants for the control group or for the *Voices* group. Three participants dropped out of the study. Finally, the statistical analysis was performed over a sample of 41 participants. All the descriptive analyses of the main variables of the sample are described in **Table 2**.

Baseline Characteristics and Analysis Between Subgroups

No significant differences were found between groups in χ^2, t or U test (all p-values > 0.05) in any sociodemographic or clinical measure at baseline (**Table 2**). RMV-SV raw mean was 19.91 (SD = 4.8) in the control group, and 21.11 (SD = 4.1) in the *Voices* group, with no statistical differences observed between groups ($t = 0.839$, $p = 0.406$). In the IQ test, no differences were observed in terms of the standard scores for total IQ ($U = 0.445$, $p = 0.657$), verbal IQ ($t = 0.132$, $p = 0.925$), or non-verbal IQ ($t = 0.662$, $p = 0.514$) between groups. Nor were any differences found in the raw PANSS scores between subgroups, confirming the homogeneity between subgroups.

Assessment of Changes in RMV-SV Before, After and 1 Month After Intervention in Each Group

Raw RMV-SV scores at baseline, after intervention and 1 month after intervention in both groups are reported in **Figure 3**. RMV-SV scores after intervention are progressively higher compared to the previous scores, for both subgroups (control RMV-SV post-intervention $M = 21.89$, SD = 3.60, *Voices* $M = 21.68$, SD = 4.68). Similarly, at the 1-month follow-up, the maintenance of scores can be observed (RMV-SV 1 month follow-up control $M = 21.44$, SD = 4.01 vs. *Voices* $M = 21.48$, SD = 4.42). In the comparison between groups, no significant differences were observed in RMV-SV post-intervention ($t = 0.161$, $p = 0.873$) and in RMV 1-month follow-up ($t = -0.23$, $p = 0.982$).

Time (pre-post) interaction effects were investigated for raw RMV-SV scores and raw PANSS scores (**Table 3**). Statistically significant differences were observed in the post-intervention RMV-SV scale vs. the pre-intervention RMV-SV ($Z = 2.47$, $p = 0.013$) in the *Voices* group. Likewise, statistically significant differences were observed between the 1-month follow-up RMV-SV, compared to the pre-intervention RMV-SV ($Z = 1.97$, $p = 0.049$) in the *Voices* group. However, there were no significant differences between the post-intervention and 1-month follow-up measures in the *Voices* group. In the case of the control group, there were no significant differences when contrasting the three raw RMV-SV means. The effect size of RMV-SV between the groups was calculated ($d = 0.26$, $r = 0.13$). Effect sizes for the pre-post intervention comparisons are included in **Table 3**.

Furthermore, raw PANSS total and PANSS subscales scores were also assessed before and after intervention to confirm

TABLE 2 | Demographic and clinical characteristics of the sample and by subgroups.

Variable		Group		*p*-value
	Total (*n* = 41)	**Control (*n* = 19)**	**Voices (*n* = 22)**	
Sex	Male 61% Female 39%	10 9	15 7	0.309
Age	43.22 (1.3)	43.4 (8.33)	43.(8.75)	0.890
Marital status	Single 95.1% Married 4.9%	17 2	22 0	0.209
Current cohabitation	Alone 7.3% With family 58.6% Others 34.1%	1 11 7	2 13 7	0.868
Occupation	Active 31.7% Inactive 68.3%	6 13	7 15	0.987
Education level	Primary studies 26.8% Second studies 73.2%	4 15	7 15	0.438
Diagnosis	Schizophrenia 87.8% SA disorder 12.2%	17 2	19 3	1.000
Illness duration, years	19.39 (1.4)	20.6 (10.2)	18.3 (8)	0.424
Equivalence to chlorpromazine, mg (SD)	971.76 (197.33)	1,305.9 (1,739.39)	683.1 (509.47)	0.360
PANSS	PANSS-P PANSS-N PANSS-GP PANSS-T	18.3 (8.47) 19.7 (8.7) 38.4 (15.76) 76.5 (18.3)	15.1 (7.85) 20.7 (8.8) 35.2 (16.36) 71.5 (30.1)	0.213 0.720 0.991 0.598
K-BIT	Total Verbal Non-verbal	98.95 (14.59) 106.00 (10.40) 94.89 (16.48)	97.41 (23.97) 105.64 (13.63) 91.64 (15.18)	0.657 0.925 0.514
RMV-SV		21.11 (4.1)	19.91 (4.8)	0.406

PANSS, Positive and Negative Syndrome Scale; GP, General Psychopathology, P, Positive, N, negative, T, total. P-value between subgroups. K-BIT, Kauffman Brief Intelligence Test; RMV-SV, Reading Mind in the Voice- Spanish Version. SA disorder, schizoaffective disorder.

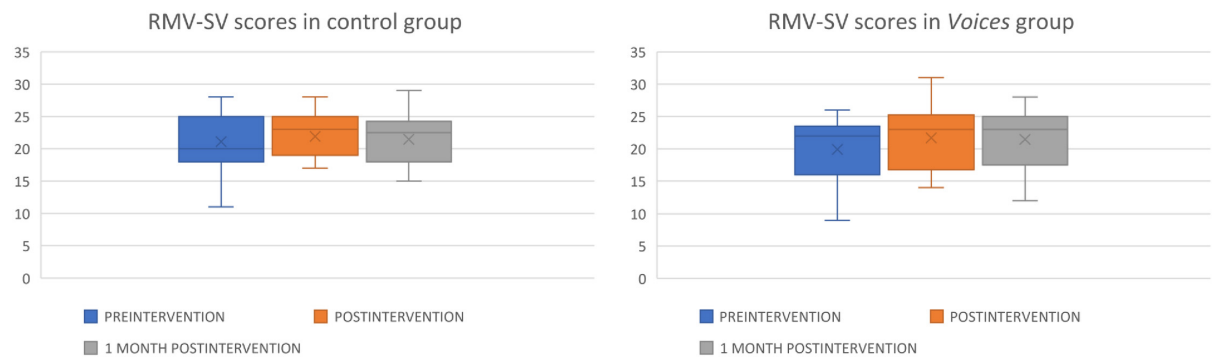


FIGURE 3 | This box plot shows raw RMV-SV scores in the control and *Voices* groups before (in blue), after (in orange) and 1 month after intervention (in gray). Inside each box, "X" represents the raw RMV-SV mean, and the horizontal line shows the median of each group. Error bars represent the maximum and minimum scores of this test in each subgroup.

clinical stability. No significant differences were found between pre- and post-intervention measures in both groups (**Table 3**).

In conclusion, significant improvements were observed in RMV-SV scores after *Voices 2* intervention and these improvements were maintained 1 month later. These differences were not reported in the control group. In the case of the clinical variable PANSS, there were no temporal significant differences despite the use of the *Voices 2* program.

User Experience Scale

All participants in the *Voices* group completed a 5-min self-reported questionnaire to describe their perception after using the *Voices 2* program. Medians and interquartile ranges can be observed in **Figure 4**. It should be noted that in the scores referring to the frequencies of PC or Internet use (from "not frequent" to "very frequent"), users obtained lower medians (2.5 for PC use and four for Internet use), with wider interquartile

TABLE 3 | RMV-SV analysis before, after and 1-month post-intervention.

	Control group				Voices group			
RMV-SV	**Z**	***p*-value**	***d***	***r***	***Z***	***p*-value**	***d***	***r***
Post vs. pre	0.727	0.467	0.20	0.09	2.472	**0.013**	0.37	0.18
1-month vs. pre	0.239	0.811	0.08	0.04	1.972	**0.049**	0.34	0.16
1-month vs. post	0.458	0.647	−0.11	−0.05	0.102	0.919	−0.04	−0.02
PANSS								
PANSS T post vs. pre	0.55	0.582	−0.04	−0.02	1.080	0.280	0.06	0.03
PANSS P post vs. pre	0.355	0.723	0.00	0.00	0.348	0.728	−0.01	−0.06
PANSS N post vs. pre	0.564	0.573	0.00	0.00	0.894	0.371	0.10	0.05
PANSS GP	0.735	0.462	−0.16	−0.08	0.996	0.319	0.00	0.00

Post, post-intervention; Pre, preintervention; PANSS T, Total; P, Positive; N, Negative; GP, General Psychopathology; Control, control group / Voices: intervention group; RMV-SV: Reading the Mind in the Voice – Spanish Version; Z, Wilcoxon signed-rank test; d, Cohen's d value; r, effect size.
In bold, p-values < 0.05 indicate statistically significative differences between post and pre-intervention scores and 1-month intervention and pre-intervention scores in Voices group.

ranges, so they are not highly familiar with this type of tool. Despite the fact that this could be an obstacle for the proper use of *Voices 2*, users rated the ease of understanding of the program (Med = 4), entertainment value (Med = 4.5), the utility of the program (Med = 4) and the convenience of the emotional glossary (Med = 4) highly.

DISCUSSION

In this randomized clinical study, a prosodic recognition program called *Voices 2* has been tested in patients with schizophrenia or schizoaffective disorder. A pre- and post-intervention assessment was conducted with the prosodic recognition scale RMV-SV and, in the case of clinical state, with the PANSS scale in each group. When comparing post-intervention RMV-SV between groups, no significant differences were observed. Despite this fact, the results confirmed significant differences in the post-intervention RMV-SV scale compared to the baseline values in the *Voices* group. In the control group, whose training entailed an auditory program that was not related to emotions, these results were not observed. The scores on this prosodic recognition scale also confirmed the significant differences observed 1 month after finalizing intervention in the *Voices* group, which were not observed in the control group. There were no significant differences in the clinical state of patients pre- and post-intervention in any of the subgroups. Users of the *Voices 2* program considered the tool as globally attractive and efficient. These results suggest that *Voices 2* could be useful as a specific intervention program for the rehabilitation of emotional prosody in patients with schizophrenia or schizoaffective disorder.

The results obtained in the scores of the RMV-SV are similar to the first version of the *Voices* study (Lado-Codesido et al., 2019). In the current study, it is worth noting that the improvements designed for *Voices 2* did not achieve better results compared to the first version of *Voices* (e.g., the emotional glossary, or the addition of new trials to the game). As explained above, the emotional glossary was applied in two of the four centers and, given that it was used autonomously, its impact was not strictly measured. Although participants found this tool appropriate, further research is needed to clarify its contribution. Likewise, the addition of new trials in *Voices 2* did not represent a greater improvement in results, but this variability could help avoid the repetition of phrases, thus reducing the memorization bias. The addition of an active control group in the present study implies increased methodological quality and gives the results greater rigor (Kurtz et al., 2016).

These findings are also in line with similar rehabilitation programs. For example, the SocialVille program, which we consider to be the most comparable with *Voices 2*, is based on PC games and includes specific auditory training and an active control group (Rose et al., 2015). Although significant results in the SC measures were not obtained in the initial trial (Nahum et al., 2014), when the study was repeated with a larger sample (n = 55), favorable results were observed for SC scales, including a prosodic identification scale (Nahum et al., 2021). At present, programs that include prosodic recognition measures, which would enable us to compare our results with other programs, continue to be extremely limited (Fiszdon and Reddy, 2012; Grant et al., 2017; Tan et al., 2018).

In this study, *Voices 2* shows the durability of the effects achieved 1 month after intervention, with results that are consistent with other rehabilitation programs. For example, SocialVille reported positive results in prosodic recognition after 6 months (Miley et al., 2020). In the review carried out by Fiszdon and Reddy (2012), 50 studies on SC treatments were reported. Six of these studies evaluate the short-term maintenance of effects (between 1 day to 6 weeks), with favorable results. Similar results can also be observed in other meta-analyses, with a low number of studies that include this variable (Grynszpan et al., 2011; Wykes et al., 2011). Other studies evaluate maintenance in the longer term (one and 2 years), such as the cognitive rehabilitation program Cognitive Enhancement Therapy (Hogarty et al., 2004; Eack et al., 2011). In a recent meta-analysis carried out by Nijman et al. (2020), it is concluded that improvements are maintained in the follow-up of studies evaluating this variable, but with lower values compared to post-treatment. These conclusions are consistent with the results of *Voices 2*. Given the significance of

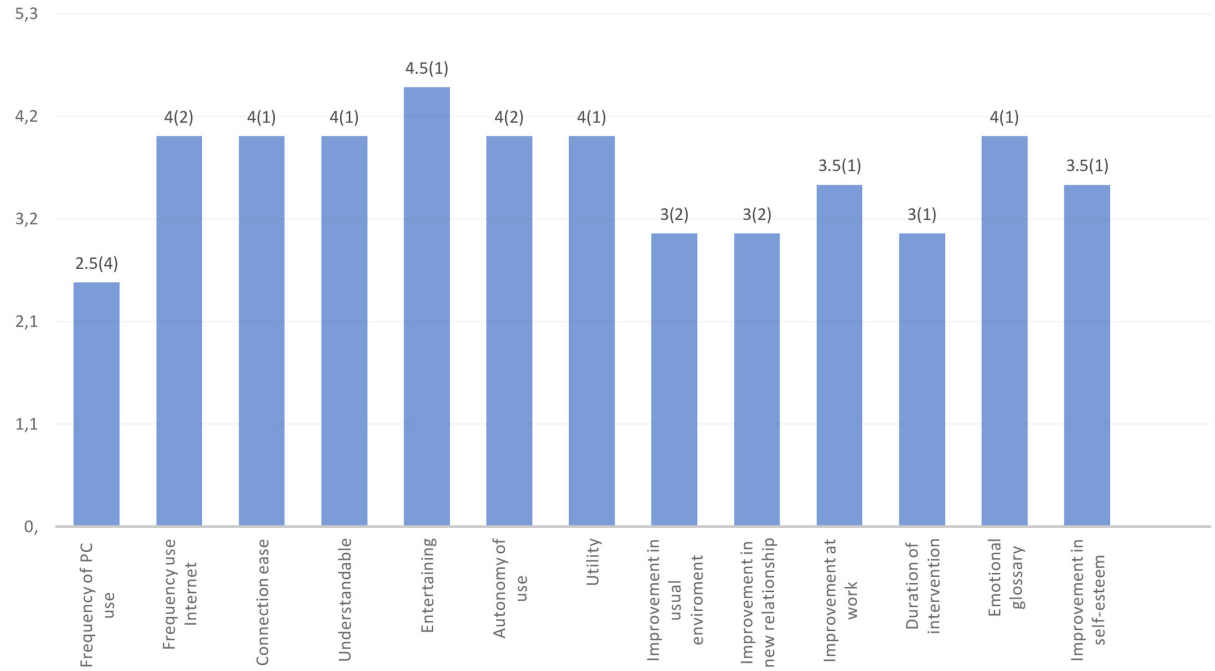


FIGURE 4 | User experience scale. Medians and interquartile ranges (in brackets) are represented in each bar.

the durability of these improvements, as the main objective of cognitive rehabilitation, it is crucial to continue to investigate the effects in the long term, as well as the underlying neoplastic changes brought about by cognitive rehabilitation.

The scores of the satisfaction survey on *Voices 2* are also similar to those of the first version of the program, confirming the perception of this tool as accessible and attractive. Other rehabilitation programs also include this type of subjective user evaluation (Nahum et al., 2014; Rus-Calafell et al., 2014; Palumbo et al., 2017). The positive evaluation of the tool, individual motivation, the subjective perception of improvements and feedback given to users during rehabilitation could all positively contribute to treatment response and program adherence (Fiszdon et al., 2020). These points were considered when designing the *Voices 2* program.

With regards to program adherence, it is worth noting the low dropout rate of 6.7%, compared to other studies reviewed, with rates of between 23–37% (Fernandez-Gonzalo et al., 2015; Fisher et al., 2017; Grant et al., 2017; Nahum et al., 2021). This could be due to the use of *Voices 2* at the regular care centers of participants, who take part in more extensive psychiatric rehabilitation. Furthermore, *Voices 2* seeks to represent situations that are similar to the real life of patients. These two factors could be key for treatment adherence (McGurk et al., 2007, 2012; Wykes et al., 2011; Parker et al., 2013). The duration of *Voices 2* (approximately 4 weeks, compared to 8–16 weeks for the aforementioned programs), could also be associated with the differences in dropout rates.

Finally, it is worth noting the innovative creation of the emotional glossary as an exploratory tool, with the use of NSM for the first time in a rehabilitation program. In the same way as the work carried out in autism, we find this approach to be very interesting, as a new avenue for the lexical understanding of emotional terms in populations that present deficits in emotional processing. Furthermore, such tools facilitate the autonomous use of the *Voices 2* program. Despite the fact that it has not been possible to use the glossary at all centers, users defined it as appropriate (Med = 4). After this first experience with NSM, we feel it would be interesting to expand on and further the study of the emotional glossary for future versions of the program.

LIMITATIONS

Certain limitations have been observed in this study. It is necessary to give cognitive rehabilitation studies sufficient methodological quality to enable comparison between studies. According to the criteria of the Clinical Trial Assessment Measure (CTAM), a larger clinical sample would be necessary. The small effect size is also a limitation. Moreover, repeating the RMV-SV scale on three different occasions could represent a learning bias, although this is not in line with the differences observed between subgroups. The repeated use of the RMV-SV is related to the lack of similar measures in Spanish, as well as its ease of application, without the need for prior training. In addition, the use of actors and actresses for play-acting vocal emotions

could be considered an artificial way of expressing emotions (Jürgens et al., 2011), and it does not represent natural conditions. Furthermore, following the objectives of cognitive rehabilitation, the inclusion of measures of other cognitive or psychosocial functioning aspects in this study could make it possible to clarify whether the effects of *Voices 2* are generalized, an objective that has not been investigated in this study.

CONCLUSION

Voices 2, the on-line prosodic recognition rehabilitation program, could be effective in improving prosodic recognition in patients with schizophrenia or schizoaffective disorder, as well as being described as attractive and efficient from the user's perspective. The durability of the improvements observed is maintained 1 month after intervention with *Voices 2*. These results support the use of *Voices 2* and promote the progress of aspects of psychiatric rehabilitation that still need to be developed. This new tool could provide benefits in terms of the interpersonal communication of patients with schizophrenia, and changes in prosodic recognition in the short term. Further studies could be conducted to continue to examine knowledge of prosodic rehabilitation, improving the quality of studies on emotion recognition intervention and promoting the personalization of rehabilitation treatment for schizophrenia.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://doi.org/10.17605/OSF.IO/G95C4.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Clinical Research Ethics Committee of Galicia, Registration code: 2019/530, Euskadi, Registration code: PI2019192. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AG-C and ML-C created the Voices 2 program, selected the participants, applied the intervention, extracted data, and supervised the study. AG-C, ML-C, and LM designed the study. ML-C, ML, RR, LM, JO, and MM participated in patient selection and obtained and extracted data. ML-C, AG-C, and RM wrote and revised the manuscript. All authors have had full access to the study data, have personally reviewed the manuscript and have given their final approval to the version attached.

FUNDING

Eighty percent of the project was originally funded by the Galician Department of Health with European Regional Development Funds through the PRIS program (Program for the Precommercial Development of Research Results of the public health system of Galicia). The project also received the 8th Edition of the Siota Grant of the College of Psychologists of Galicia, the 2013 Biannual Grant of the Medical-Surgical Academy of Ourense, the 2nd Spanish Innova-eVia award for 2015 and the National Award for the Best Health Videogame at the e-Health Spanish Congress in Madrid 2016. e-Motional training received an unrestricted grant for extending its free use in Spain by Janssen laboratories during the 2018–2019 period. The program is currently funded by the 2020/54 grant of the National Plan on Drugs, Secretary of State of Health of Spain, and freely available on request.

ACKNOWLEDGMENTS

We would like to thank participants for their collaboration as well as all the professional workers of the following associations: APEM Carballo (A Coruña), Saúde Mental Ferrol, Eume e Ortegal (A Coruña), Agifes (Guipúzcoa), and Centro de Rehabilitacion Psicosocial Nueva Vida (Madrid). We would also like to thank the indispensable contribution of Bert Peeters for his help and María Auxiliadora Barrios for her contribution to the emotional glossary. Lastly, we would like to thank Daniel González Vázquez and Gloria Cámara for their help in the creation of *Voices 2*.

REFERENCES

Bechi, M., Bosia, M., Spangaro, M., Pigoni, A., Buonocore, M., Scrofani, D., et al. (2018). Visual and audio emotion processing training for outpatients with schizophrenia: an integrated multisensory approach. *Neuropsychol. Rehabil.* 28, 1131–1144. doi: 10.1080/09602011.2016.1240698

Bosco, F. M., Gabbatore, I., Gastaldo, L., and Sacco, K. (2016). Communicative-Pragmatic Treatment in Schizophrenia: A Pilot Study. *Front. Psychol.* 7:1–12. doi: 10.3389/fpsyg.2016.00166

Byrne, L. K., Pan, L., Mccabe, M., Mellor, D., and Xu, Y. (2015). Assessment of a six-week computer-based remediation program for social cognition in chronic schizophrenia. *Shanghai Arch. Psychiatry* 27, 296–306. doi: 10.11919/j.issn.1002-0829.215095

Castagna, F., Montemagni, C., Maria Milani, A., Rocca, G., Rocca, P., Casacchia, M., et al. (2013). Prosody recognition and audiovisual emotion matching in schizophrenia: The contribution of cognition and psychopathology. *Psychiatry Res.* 205, 192–198. doi: 10.1016/j.psychres.2012.08.038

Combs, D. R., Adams, S. D., Penn, D. L., Roberts, D., Tiegreen, J., and Stem, P. (2007). Social Cognition and Interaction Training (SCIT) for inpatients with schizophrenia spectrum disorders: Preliminary findings. *Schizophr. Res.* 91, 112–116. doi: 10.1016/j.schres.2006.12.010

Eack, S. M., Greenwald, D., Hogarty, S. S., and Keshavan, M. S. (2011). One-Year Durability of the Effects of Cognitive Enhancement Therapy on Functional

Outcome in Early Schizophrenia. *Schizophr. Res.* 120, 210–216. doi: 10.1016/j.schres.2010.03.042.One-Year

Eack, S. M., Hogarty, G. E., Greenwald, D. P., Hogarty, S. S., and Keshavan, M. S. (2007). Cognitive enhancement therapy improves emotional intelligence in early course schizophrenia: Preliminary effects. *Schizophr. Res.* 89, 308–311. doi: 10.1016/j.schres.2006.08.018

Fernandez-Gonzalo, S., Turon, M., Jodar, M., Pousa, E., Hernandez Rambla, C., García, R., et al. (2015). A new computerized cognitive and social cognition training specifically designed for patients with schizophrenia/schizoaffective disorder in early stages of illness: A pilot study. *Psychiatry Res.* 228, 501–509. doi: 10.1016/j.psychres.2015.06.007

Fett, A.-K. J., Viechtbauer, W., Dominguez, M.-G., Penn, D. L., van Os, J., and Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neurosci. Biobehav. Rev.* 35, 573–588. doi: 10.1016/j.neubiorev.2010.07.001

Fisher, M., Nahum, M., Howard, E., Rowlands, A., Brandrett, B., Kermott, A., et al. (2017). Supplementing intensive targeted computerized cognitive training with social cognitive exercises for people with schizophrenia: An interim report. *Psychiatr. Rehabil. J.* 40, 21–32. doi: 10.1037/prj0000244

Fiszdon, J. M., and Reddy, L. F. (2012). Review of social cognitive treatments for psychosis. *Clin. Psychol. Rev.* 32, 724–740. doi: 10.1016/j.cpr.2012.09.003

Fiszdon, J. M., Kurtz, M. M., Parente, L., Choi, J., Connecticut, V. A., System, H., et al. (2020). What variables predict cognitive remediation associated improvement in individuals with psychosis? *Schizophr. Res. Cogn.* 19:100148. doi: 10.1016/j.scog.2019.100148

Frommann, N., Streit, M., and Wölwer, W. (2003). Remediation of facial affect recognition impairments in patients with schizophrenia: a new training program. *Psychiatry Res.* 117, 281–284. doi: 10.1016/S0165-1781(03)00039-8

Gao, Z., Zhao, W., Liu, S., Liu, Z., Yang, C., and Xu, Y. (2021). Facial Emotion Recognition in Schizophrenia. *Front. Psychiatry* 12:1–10. doi: 10.3389/fpsyt.2021.633717

Golan, O., Baron-Cohen, S., Hill, J. J., and Rutherford, M. D. (2007). The 'Reading the Mind in the Voice' Test-Revised: A Study of Complex Emotion Recognition in Adults with and Without Autism Spectrum Conditions. *J. Autism Dev. Disord.* 37, 1096–1106. doi: 10.1007/s10803-006-0252-5

Grant, N., Lawrence, M., Preti, A., Wykes, T., and Cella, M. (2017). Social cognition interventions for people with schizophrenia: a systematic review focussing on methodological quality and intervention modality. *Clin. Psychol. Rev.* 56, 55–64. doi: 10.1016/j.cpr.2017.06.001

Grynszpan, O., Perbal, S., Pelissolo, A., Fossati, P., Jouvent, R., Dubal, S., et al. (2011). Efficacy and specificity of computer-assisted cognitive remediation in schizophrenia: A meta-analytical study. *Psychol. Med.* 41, 163–173. doi: 10.1017/S0033291710000607

Halverson, T. F., Orleans-Pobee, M., Merritt, C., Sheeran, P., Fett, A., and Penn, D. L. (2019). Pathways to functional outcomes in schizophrenia spectrum disorders: Meta-analysis of social cognitive and neurocognitive predictors. *Neurosci. Biobehav. Rev.* 105, 212–219. doi: 10.1016/j.neubiorev.2019.07.020

Hogarty, G. E., Flesher, S., Ulrich, R., Carter, M., Greenwald, D., Pogue-Geile, M., et al. (2004). Cognitive Enhancement Therapy for Schizophrenia. *Arch. Gen. Psychiatry* 61, 866–876.

Horan, W. P., and Green, M. F. (2019). Treatment of social cognition in schizophrenia: Current status and future directions. *Schizophr. Res.* 203, 3–11. doi: 10.1016/j.schres.2017.07.013

Irani, F., Seligman, S., Kamath, V., Kohler, C., and Gur, R. C. (2012). A Meta-Analysis of Emotion Perception and Functional Outcomes in Schizophrenia. *Schizophr. Res.* 137, 203–211. doi: 10.1016/j.schres.2012.01.023.A

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., et al. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392, 1789–1858. doi: 10.1016/S0140-6736(18)32279-7

Jürgens, R., Hammerschmidt, K., and Fischer, J. (2011). Authentic and Play-Acted Vocal Emotion Expressions Reveal Acoustic Differences. *Front. Psychol.* 2:1–11. doi: 10.3389/fpsyg.2011.00180

Kaufman, A., and Kaufman, N. (2011). *K-BIT: Test Breve de Inteligencia de Kaufman*. London: Pearson.

Kay, S. R., Fiszbein, A., and Opfer, L. A. (1987). The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophr. Bull.* 13, 261–276. doi: 10.1093/schbul/13.2.261

Kee, K. S., Green, M. F., Mintz, J., and Brekke, J. S. (2003). Is emotion processing a predictor of functional outcome in schizophrenia? *Schizophr. Bull.* 29, 487–497. doi: 10.1093/oxfordjournals.schbul.a007021

Kohler, C. G., Walker, J. B., Martin, E. A., Healey, K. M., and Moberg, P. J. (2010). Facial Emotion Perception in Schizophrenia: A Meta-analytic Review. *Schizophr. Bull.* 36, 1009–1019. doi: 10.1093/schbul/sbn192

Kraus, M. S., Walker, T. M., Jarskog, L. F., Millet, R. A., and Keefe, R. S. E. (2019). Basic auditory processing de fi cits and their association with auditory emotion recognition in schizophrenia ☆. *Schizophr. Res.* 204, 155–161. doi: 10.1016/j.schres.2018.08.031

Kurtz, M. M., and Richardson, C. L. (2012). Social cognitive training for schizophrenia: A meta-analytic investigation of controlled research. *Schizophr. Bull.* 38, 1092–1104. doi: 10.1093/schbul/sbr036

Kurtz, M. M., Gagen, E., Rocha, N. B. F., Machado, S., and Penn, D. L. (2016). Comprehensive treatments for social cognitive deficits in schizophrenia: A critical review and effect-size analysis of controlled studies. *Clin. Psychol. Rev.* 43, 80–89. doi: 10.1016/j.cpr.2015.09.003

Lado-Codesido, M., Méndez Pérez, C., Mateos, R., Olivares, J. M., and García Caballero, A. (2019). Improving emotion recognition in schizophrenia with "VOICES": An on-line prosodic self-training. *PLoS One* 14:e0210816. doi: 10.1371/journal.pone.0210816

Leitman, D. I., Foxe, J. J., Butler, P. D., Saperstein, A., Revheim, N., and Javitt, D. C. (2005). Sensory contributions to impaired prosodic processing in schizophrenia. *Biol. Psychiatry* 58, 56–61. doi: 10.1016/j.biopsych.2005.02.034

Leitman, D. I., Hoptman, M. J., Foxe, J. J., Saccente, E., Wylie, G. R., Nierenberg, J., et al. (2007). The neural substrates of impaired prosodic detection in schizophrenia and its sensorial antecedents. *Am. J. Psychiatry* 164, 474–482. doi: 10.1176/appi.ajp.164.3.474

Lin, Y., Ding, H., and Zhang, Y. (2018). Emotional prosody processing in schizophrenic patients: A selective review and meta-analysis. *J. Clin. Med.* 7:363. doi: 10.3390/jcm7100363

Lin, Y., Ding, H., and Zhang, Y. (2020). Multisensory Integration of Emotion in Schizophrenic Patients. *Multisens. Res.* 33, 865–901. doi: 10.1163/22134808-bja10016

Maroño Souto, Y., Vázquez Campo, M., Díaz Llenderrozas, F., Rodríguez, Álvarez, M., Mateos, R., et al. (2018). Randomized Clinical Trial with e-MotionalTraining® 1.0 for Social Cognition Rehabilitation in Schizophrenia. *Front. Psychiatry* 9:1–9. doi: 10.3389/fpsyt.2018.00040

McGurk, S. R., Eack, S. M., Kurtz, M., and Mueser, K. T. (2012). Cognitive Remediation and Psychosocial Rehabilitation for Individuals with Severe Mental Illness. *Rehabil. Res. Pract.* 2012, 1–2. doi: 10.1155/2012/283602

McGurk, S. R., Twamley, E. W., Sitzer, D. I., McHugo, G. J., and Mueser, K. T. (2007). Reviews and Overviews A Meta-Analysis of Cognitive Remediation in Schizophrenia. *Am. J. Psychiatry* 164, 1791–1802.

Medalia, A., Saperstein, A. M., Qian, M., and Javitt, D. C. (2019). Impact of baseline early auditory processing on response to cognitive remediation for schizophrenia. *Schizophr. Res.* 208, 397–405. doi: 10.1016/j.schres.2019.01.012

Miley, K., Fisher, M., Nahum, M., Howard, E., Rowlands, A., Brandrett, B., et al. (2020). Six month durability of targeted cognitive training supplemented with social cognition exercises in schizophrenia. *Schizophr. Res. Cogn.* 20:100171. doi: 10.1016/j.scog.2019.100171

Morin, L., and Franck, N. (2017). Rehabilitation interventions to promote recovery from schizophrenia: A systematic review. *Front. Psychiatry* 8:100. doi: 10.3389/fpsyt.2017.00100

Mullan, K., Peeters, B., and Sadow, L. (2020). "Using Minimal English to Model a Parental Understanding of Autism," in *Studies in Ethnopragmatics, Cultural Semantics, and Intercultural Communication: Ethnopragmatics and Semantic Analysis*, eds K. Mullan, B. Peeters, and L. Sadow (Singapore: Springer Singapore), 1–256. doi: 10.1007/978-981-32-9983-2

Nahum, M., Fisher, M., Loewy, R., Poelke, G., Ventura, J., Nuechterlein, K. H., et al. (2014). A novel, online social cognitive training program for young adults with schizophrenia: A pilot study. *Schizophr. Res. Cogn.* 1, e11–e19. doi: 10.1016/j.scog.2014.01.003

Nahum, M., Lee, H., Fisher, M., Green, M. F., Hooker, C. I., Ventura, J., et al. (2021). Online Social Cognition Training in Schizophrenia: A Double-Blind,

Randomized, Controlled Multi-Site Clinical Trial. *Schizophr. Bull.* 47, 108–117. doi: 10.1093/schbul/sbaa085

Nijman, S. A., Veling, W., van der Stouwe, E. C. D., and Pijnenborg, G. H. M. (2020). Social Cognition Training for People With a Psychotic Disorder: A Network Meta-analysis. *Schizophr. Bull.* 46, 1086–1103. doi: 10.1093/schbul/sbaa023

Palumbo, D., Mucci, A., Piegari, G., D'Alise, V., Mazza, A., and Galderisi, S. (2017). SoCIAL – training cognition in schizophrenia: A pilot study. *Neuropsychiatr. Dis. Treat.* 13, 1947–1956. doi: 10.2147/NDT.S136732

Parker, S., Foley, S., Walker, P., and Dark, F. (2013). Improving the social cognitive deficits of schizophrenia: a community trial of Social Cognition and Interaction Training (SCIT). *Australas. Psychiatry* 21, 346–351. doi: 10.1177/1039856213486305

Paulmann, S., and Pell, M. D. (2011). Is there an advantage for recognizing multimodal emotional stimuli? *Motiv. Emot.* 35, 192–201. doi: 10.1007/s11031-011-9206-0

Peeters, B., and Marini, M. (2018). "Narrative Medicine Across Languages and Cultures: Using Minimal English for Increased Comparability of Patients' Narratives," in *Minimal English for a Global World: Improved Communication Using Fewer Words*, ed. C. Goddard (London: Palgrave Macmillan), 259–286. doi: 10.1007/978-3-319-62512-6

Penn, D. L., Keefe, R. S. E., Davis, S. M., Meyer, P. S., Perkins, D. O., Losardo, D., et al. (2009). The effects of antipsychotic medications on emotion perception in patients with chronic schizophrenia in the CATIE trial. *Schizophr. Res.* 115, 17–23. doi: 10.1016/j.schres.2009.08.016

Penn, D., Roberts, D. L., Munt, E. D., Silverstein, E., Jones, N., and Sheitman, B. (2005). A pilot study of social cognition and interaction training (SCIT) for schizophrenia. *Schizophr. Res.* 80, 357–359. doi: 10.1016/j.schres.2005.07.011

Pinkham, A. E. (2014). Social Cognition in Schizophrenia. *J. Clin. Psychiatry* 75, 14–19. doi: 10.4088/JCP.13065su1.04

Pinkham, A. E., and Penn, D. L. (2006). Neurocognitive and social cognitive predictors of interpersonal skill in schizophrenia. *Psychiatry Res.* 143, 167–178. doi: 10.1016/j.psychres.2005.09.005

Revell, E. R., Neill, J. C., Harte, M., Khan, Z., and Drake, R. J. (2015). A systematic review and meta-analysis of cognitive remediation in early schizophrenia. *Schizophr. Res.* 168, 213–222. doi: 10.1016/j.schres.2015.08.017

Rose, A., Vinogradov, S., Fisher, M., Green, M. F., Ventura, J., Hooker, C., et al. (2015). Randomized controlled trial of computer-based treatment of social cognition in schizophrenia: the TRuSST trial protocol. *BMC Psychiatry* 15:142. doi: 10.1186/s12888-015-0510-1

Rus-Calafell, M., Gutiérrez-Maldonado, J., and Ribas-Sabaté, J. (2014). A virtual reality-integrated program for improving social skills in patients with schizophrenia: A pilot study. *J. Behav. Ther. Exp. Psychiatry* 45, 81–89. doi: 10.1016/j.jbtep.2013.09.002

Sánchez-Reales, S., Caballero-Peláez, C., Prado-Abril, J., Inchausti, F., Lado-Codesido, M., García-Caballero, A., et al. (2019). Spanish validation of the "Reading the Mind in the Voice" task: A study of complex emotion recognition in adults with autism spectrum conditions. *Res. Autism Spectr. Disord.* 67:101421. doi: 10.1016/j.rasd.2019.101421

Tan, B., Lee, S., and Lee, J. (2018). Social cognitive interventions for people with schizophrenia: A systematic review. *Asian J. Psychiatr.* 35, 115–131. doi: 10.1016/j.ajp.2016.06.013

Thomas, M. L., Green, M. F., Hellemann, G., Sugar, C. A., Tarasenko, M., Calkins, M. E., et al. (2017). Modeling Deficits From Early Auditory Information Processing to Psychosocial Functioning in Schizophrenia. *JAMA Psychiatry* 74:37. doi: 10.1001/jamapsychiatry.2016.2980

Vázquez-Campo, M., Maroño, Y., Lahera, G., Mateos, R., and García-Caballero, A. (2016). e-Motional Training® : Pilot study on a novel online training program on social cognition for patients with schizophrenia. *Schizophr. Res. Cogn.* 4, 10–17. doi: 10.1016/j.scog.2015.11.007

Ventura, J., Hellemann, G. S., Thames, A. D., Koellner, V., and Nuechterlein, K. H. (2009). Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: A meta-analysis. *Schizophr. Res.* 113, 189–199. doi: 10.1016/j.schres.2009.03.035

Wierzbicka, A. (1999). *Emotions across Languages and Cultures: Diversity and Universals*, 1st Edn. Cambrigde: Cambrigde University Press.

Wykes, T., Huddy, V., Cellard, C., McGurk, S. R., and Czobor, P. (2011). A Meta-Analysis of Cognitive Remediation for Schizophrenia: Methodology and Effect Sizes. *Am. J. Psychiatry* 168, 472–485. doi: 10.1176/appi.ajp.2010.10060855

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 Psychology

SYSTEMATIC REVIEW
published: 02 February 2022
doi: 10.3389/fpsyg.2022.790494

Implicit Mentalizing in Patients With Schizophrenia: A Systematic Review and Meta-Analysis

Timea Csulak[1,2], András Hajnal[1], Szabolcs Kiss[3], Fanni Dembrovszky[3], Margit Varjú-Solymár[3], Zoltán Sipos[3], Márton Aron Kovács[1,2], Márton Herold[1,2], Eszter Varga[4], Péter Hegyi[3], Tamás Tényi[1] and Róbert Herold[1]*

[1] Department of Psychiatry and Psychotherapy, Medical School, University of Pécs, Pécs, Hungary, [2] Doctoral School of Clinical Neurosciences, Medical School, University of Pécs, Pécs, Hungary, [3] Medical School, Institute for Translational Medicine, University of Pécs, Pécs, Hungary, [4] Department of Pediatrics, Medical School, University of Pécs, Pécs, Hungary

Introduction: Mentalizing is a key aspect of social cognition. Several researchers assume that mentalization has two systems, an explicit one (conscious, relatively slow, flexible, verbal, inferential) and an implicit one (unconscious, automatic, fast, non-verbal, intuitive). In schizophrenia, several studies have confirmed the deficit of explicit mentalizing, but little data are available on non-explicit mentalizing. However, increasing research activity can be detected recently in implicit mentalizing. The aim of this systematic review and meta-analysis is to summarize the existing results of implicit mentalizing in schizophrenia

Methods: A systematic search was performed in four major databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science. Eleven publications were selected. Five studies were found to be eligible for quantitative synthesis, and 9 studies were included in qualitative synthesis.

Results: The meta-analysis revealed significantly lower accuracy, slower reaction time during implicit mentalizing in patients with schizophrenia. The systematic review found different brain activation pattern, further alterations in visual scanning, cue fixation, face looking time, and difficulties in perspective taking.

Discussion: Overall, in addition to the deficit of explicit mentalization, implicit mentalization performance is also affected in schizophrenia, if not to the same extent. It seems likely that some elements of implicit mentalization might be relatively unaffected (e.g., detection of intentionality), but the effectiveness is limited by certain neurocognitive deficits. These alterations in implicit mentalizing can also have potential therapeutic consequences.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, identifier: CRD42021231312.

Keywords: mentalizing, theory of mind, mentalization, implicit, schizophrenia, spontaneous

OPEN ACCESS

Edited by:
Ricardo R. Garcia, University of Chile, Chile

Reviewed by:
Alejandra Caqueo-Urízar, Universidad de Tarapacá, Chile
Martin Jáni, Masaryk University, Czechia

****Correspondence:***
Timea Csulak
timea.csulak@gmail.com

Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: *06 October 2021*
Accepted: *10 January 2022*
Published: *02 February 2022*

Citation:
Csulak T, Hajnal A, Kiss S, Dembrovszky F, Varjú-Solymár M, Sipos Z, Kovács MA, Herold M, Varga E, Hegyi P, Tényi T and Herold R (2022) Implicit Mentalizing in Patients With Schizophrenia: A Systematic Review and Meta-Analysis. Front. Psychol. 13:790494. doi: 10.3389/fpsyg.2022.790494

INTRODUCTION

Mentalizing (or mentalization, theory of mind) is a key aspect of social cognition. During the processes of mentalizing we attribute mental states (intentions, beliefs, desires, emotional states) to ourselves and others, which enables us to understand and predict social behavior. Mentalizing is a highly complex ability requiring the perception, processing, and interpretation of social

information. Traditionally mentalizing has been considered to develop in the early ages of life (3–6 years). However, more and more data suggest that children can intuitively attribute intentions much earlier (Apperly and Butterfill, 2009). According to these results, several researchers assume that mentalization is based on two systems, an explicit and an implicit one (Apperly and Butterfill, 2009; Butterfill and Apperly, 2013). Implicit mentalizing is supposed to be present very early, presumably from birth. It is characterized by fast and pre-reflexive non-verbal information processing, which is decoded without awareness. In contrast to this intuitive ability, the explicit form of mentalizing is inferential, relatively slow, and it relies heavily on verbal and conscious information processing. It develops parallelly with linguistic and cognitive skills (e.g., executive functions). The implicit-explicit systems are likely to persist and coexist throughout the lifespan (Apperly and Butterfill, 2009; Butterfill and Apperly, 2013; Vogeley, 2017). According to some recent hypotheses, different social neural networks are responsible for the processing of implicit lower-level information, and the explicit higher-level information (Vogeley, 2017). The former plays a role in the early, automatic detection of intentional bodily and spatial behavior. The latter is active in the late, controlled, and conscious evaluative and interpretive processing. However, not all researchers accept this sharp distinction between the implicit and explicit systems (Baillargeon et al., 2015; Scott and Baillargeon, 2017). Moreover, according to the submentalization approach, although certain behavioral elements may appear to be a process of implicit mentalization, it does not actually involve real mentalization, but rather domain-general cognitive processing (e.g., attention orientation, spatial perception, etc.) (Heyes, 2014).

Still there is no consensus either, whether implicit and explicit mentalizing rely on shared or distinct brain networks (Lieberman, 2007; Van Overwalle and Vandekerckhove, 2013). According to a recent meta-analysis of neuroimaging data the two types of processing overlap significantly, however important differences are also present (Molenberghs et al., 2016). Activation likelihood estimation revealed that the medial prefrontal cortex (mPFC), precuneus, bilateral inferior frontal gyrus (IFG), temporoparietal junction (TPJ), and temporal poles are activated both in implicit and explicit processing. At the same time explicit tasks activate the middle and superior temporal gyrus, the cingulate gyrus, and the medial frontal gyrus on the left side, while implicit tasks associate with the activation of left medial frontal gyrus, and right IFG. The meta-analytic connectivity modeling also revealed widespread overlapping co-activating areas during both explicit and implicit processing (Molenberghs et al., 2016). However, implicit mentalizing areas co-activate with bilateral middle frontal gyrus and the left superior frontal gyrus, while the explicit mentalizing regions co-activate with the right cingulate gyrus and left parietal lobule.

In the last 10–15 years an enormous number of studies dealt with the exploration of implicit mentalizing. Various paradigms have been developed, and their results suggest the existence of implicit mentalization. For example, Kovács et al. used an object detection task to investigate implicit mentalization, where participants' reaction time varied according to whether the other person's true or false belief was congruent or incongruent with the subject's belief. Based on their paradigm, the gaze times of 7-month-old infants have been shown to be influenced by their expectations, in the same way as for adults (Kovács et al., 2010). Although this paradigm was later contested by some (Phillips et al., 2015), more recent research has obtained results like Kovács et al. and found that one's own and the other's beliefs have a significant effect on reaction time (van der Wel et al., 2014; Nijhof et al., 2016; El Kaddouri et al., 2020). Interactive behavioral tasks (Buttelmann et al., 2009; Southgate et al., 2010); violation of expectation (Onishi and Baillargeon, 2005) is also frequently used paradigms in implicit mentalizing research. The anticipatory looking measures are widely used as well (Southgate et al., 2007; Schneider et al., 2012; Low and Watts, 2013), however the results are ambiguous because they have been found hardly replicable. Results from these paradigms are likely to be informative when they use ecologically relevant stimuli. In other situations, presumably participants just look back and forth without any anticipation, which can be one of the reasons for their non-replicability (Kulke et al., 2019; Kulke and Hinrichs, 2021). Moreover, a study using real-life mobile eye-tracking also failed to clearly confirm the suitability of anticipatory looking measures for implicit mentalization, which may also suggest that it is very difficult to detect (Kulke and Hinrichs, 2021). In summary, the existence of implicit mentalizing seems not to be questioned, however the results are still puzzling, and the appropriate tool for detecting implicit mentalizing is also missing.

In schizophrenia, it is now evident that social cognition is significantly affected and there is, among other things, a significant mentalizing deficit. Based on the research results, systematic reviews, and meta-analyses, it is clear that intention attribution of the patients is damaged (Sprong et al., 2007; Bora et al., 2009; Martin et al., 2014). Mentalizing impairments are characteristic both in the acute and the remission phases, and they can be detected in first-degree, clinically asymptomatic relatives (Herold et al., 2002, 2018; Bora and Pantelis, 2013; Healey et al., 2013). Mentalizing may be deficient even before the onset of the disease, may predict psychotic conversion, and often worsens before the first episode (Bora and Pantelis, 2013; Davidson et al., 2018; Tikka et al., 2020). Long-term studies of social functionality also suggest that functionality is already weaker in childhood and deteriorates markedly further in adolescence, which in turn significantly predicts impaired functionality over a 20 year period (Velthorst et al., 2017).

Imaging studies have also revealed significant abnormalities in schizophrenia. In addition to the brain volumetric abnormalities in pre-frontal and temporal areas (Benedetti et al., 2009; Herold et al., 2009; Koelkebeck et al., 2013) associated with deficient mentalization, studies using different functional imaging procedures have undoubtedly described atypical neural activation characterized by over- and underactivation in mentalizing regions (Marjoram et al., 2006). According to a meta-analysis, the mPFC, the left orbito-frontal cortex (OFC), and a small portion of the left posterior TPJ are regularly found under-activated, while over-activation was reported in the more dorsal part of the TPJ bilaterally, in the medial occipito-parietal cortex, right premotor areas, left cingulate gyrus, and lingual

gyrus (Kronbichler et al., 2017). Moreover, different activation has been shown in high-risk patients in the right TPJ, right middle temporal gyrus (MTG), and left precuneus (Vucurovic et al., 2021), and also in clinically asymptomatic relatives in dorsolateral PFC, dorsomedial PFC, and right inferior frontal gyrus (Marjoram et al., 2006; Herold et al., 2018).

Despite the extensive research on mentalizing in schizophrenia, the majority of studies has been focused only on explicit mentalizing. Relatively little is known about potential alterations of implicit mentalizing. Based on the neurodevelopmental hypothesis of schizophrenia (Weinberger, 1987) we cannot exclude that the implicit mentalizing is also impaired, as early neurodevelopmental abnormalities may affect the neural networks responsible for implicit mentalizing, which in turn may influence the development of later explicit mentalizing skills. Research data suggest that the impaired early embryonic and later adolescent maturation of the PFC is likely to play a role not just in the development of behavioral, but also in cognitive symptoms of the disorder (Selemon and Zecevic, 2015). Studies on childhood onset schizophrenia emphasize the role of steeper rate of tissue loss in parietofrontal and parietotemporal areas as well (Gogtay, 2008). Recently, abnormal growth process of the cingulo-fronto-termporal module development was also reported, which affect several structures repeatedly found impaired in mentalizing studies (right IFG, triangular and opercular part; right medial orbital superior frontal gyrus; right gyrus rectus; left posterior cingulate gyrus) (Alexander-Bloch et al., 2014). These disturbed maturational trajectories may interfere with the development of mentalizing, and indeed the infant research data highlights the role of temporoparietal areas in the early development of implicit mentalizing (Kampis et al., 2015; Hyde et al., 2018; Grosse Wiesmann et al., 2020).

Beyond its theoretical aspect, it may have even a therapeutic significance (Langdon et al., 2017), as unaffected implicit mentalizing skills may represent a significant base for remediating the impaired explicit mentalizing skills. However, impaired implicit mentalizing can be a significant limit in remediation. Recently, Langdon et al. highlighted the therapeutic implication of the differential effects of implicit and explicit aspects of mentalizing, as the remediation of explicit mentalizing may require interventions to strengthen compensatory strategies, while implicit mentalizing may require a more basic approach with using techniques to improve attentional processes to support a more efficacious detection of agency signals (Langdon et al., 2017).

Nevertheless, beside the dominance of research on explicit mentalizing in schizophrenia, more and more study focus on the implicit mentalizing. Unfortunately, the results are still not equivocal, so we found it important to summarize the results of the field. The aim of this systematic review and meta-analysis is to examine the nature of possible implicit mentalizing alterations in schizophrenia compared to healthy controls.

For theoretical clarity in our meta-analysis and systematic review we included only those studies that used non-verbal tasks to indirectly measure the accuracy with automatic behavioral signs without verbal answers. We excluded those studies that measure mentalizing skills with verbal answers or with spontaneous use of mental-state language. The latter type of performance can be described with the term of spontaneous mentalizing, although some studies use the phrase as a synonym for implicit mentalizing (e.g., Horan et al., 2009). In contrast, elsewhere, this term refers to indirect measurements, when the processing of social information happens without explicit instruction, but it is measured with the spontaneous use of mental state terms (Senju, 2013; Langdon et al., 2017). According to Senju (2012), spontaneous mentalizing is differ from implicit mentalizing as it does not require the lack of conscious awareness. Moreover, it is not so obligatory processing like automatic processing, and it can be interrupted with competing tasks. Usually, spontaneous mentalizing is tested with animated geometric forms stimuli, and measured by multiple choice questions or spontaneous use of mental-state language. Our systematic review on spontaneous mentalizing in schizophrenia will be presented in a separate article.

METHODS

This systematic review and meta-analysis were reported based on PRISMA Statement (Page et al., 2021). The review protocol was registered on PROSPERO (CRD42021231312). There was no protocol deviation.

Search Strategy

A systematic search was performed in four major databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science.

The search date was 02.11.2020. The following search key was used: [(implicit) OR (spontaneous)] AND [(theory of mind) OR (mentalizing) OR (mentalization)] AND (schizophrenia). We searched in all fields/all text in every database. There were no restrictions or filters.

Selection and Eligibility Criteria

The search results were combined in a reference manager software (EndNoteX9; Clarivate Analytics, Philadelphia, Pennsylvania). Records were screened (after automatic and manual removal of duplicates) based on title, abstract, full-text. Then the references and citations of the full text screening records were reviewed. The selection process was conducted by two independent researchers (AH, TC). Disagreements were resolved by an independent third investigator (RH). Reference lists, publication citing (Google Scholar search engine) of the included studies were screened to find additional studies.

We included case-control studies which reporting on implicit mentalization function in patients with schizophrenia. We also did not exclude studies that included schizoaffective patients, as both disorders belong to the same group of disorders, the schizophrenia spectrum disorders. The individuals of the control group were excluded if they met criteria for any psychiatric disorder. Studies which had overlapping populations were included only in the systematic review.

We included studies which measure implicit mentalization function with tasks taken unrelated to description of the paradigm or taken before questions of the paradigm (for

e.g., eye movements measures, perspective taking tasks). As described in the introduction, we excluded records, which examined spontaneous mentalization and the spontaneous use of mentalization terms or used verbal answers to measure mentalizing performance.

Data Extraction

Two independent review authors extracted the following data from each eligible studies: first author, publication year, study design, country, number of centers, studied population, gender distribution, age distribution, number of patients; accuracy (in percentage), reaction time (in ms), mentalizing cue looking percentage, fixation duration, face looking percentage. If the data was plotted on a bar graph, GetData Graph Digitizer was used to extract the data. We contacted the authors in case of missing data, and the data received were used during the processing. Disagreements were resolved by an independent third investigator.

Risk of Bias Assessment

The "Quality In Prognosis Studies" (QUIPS) tool (Hayden et al., 2013) was used based on the recommendations of The Cochrane Prognosis Methods Group (PMG) by two researchers. Any disagreement was resolved by a third reviewer.

Statistical Analysis

For continuous variables standardized mean difference (SMD) with 95% Confidence Intervals were calculated and since we had one study with sample size <20 we decided to use Hedges method. A $p < 0.05$ was considered statistically significant difference. Random effects model was used to calculate the overall estimates using the DerSimonian-Laird (DerSimonian and Laird, 1986) method. The results of the meta–analyses are presented on forest plots.

Heterogeneity was tested using Cochrane's Q and the I^2 statistics. As suggested by the Cochrane Handbook (Higgins and Green, 2011), I^2–values were interpreted with the following levels: 0–40, 30–60, 50–90, and 75–100%, meaning "Might not be important," "Moderate," "Substantial," and "Considerable," respectively. Heterogeneity, with a $p < 0.1$ considered significant.

(Egger's tests and funnel plots have not been carried out to assess any publication bias, because there was only a low amount of the studies included).

All analyses were performed by R environment (R Core Team, 2021).

To assess the certainty of the evidence we used the GRADE approach (Higgins and Green, 2011), which has four domains (risk of bias; inconsistency; indirectness; imprecision). The GRADE approach has four levels of evidence: high, moderate, low and very low. If there was a serious concern for any of the domains, we downgraded the evidence level.

RESULTS

Systematic Search and Selection

The systematic search yielded 541 records. After the automatic and manual removal of duplicates 502 records remained. The flowchart of the publication selection is presented in **Figure 1**. After checking the records and citation searching 11 publications remained. Five studies (Brunet et al., 2003; Eack et al., 2013; Roux et al., 2016a; Okruszek et al., 2018; Kronbichler et al., 2019) were included in the quantitative synthesis, and 9 studies (Das et al., 2012; Eack et al., 2013; Roux et al., 2014, 2015, 2016a,b; Okruszek et al., 2017; Kronbichler et al., 2019; Patel et al., 2020) in the qualitative synthesis.

All records found were used in either the meta-analysis or the systematic review.

The 5 studies (Brunet et al., 2003; Das et al., 2012; Eack et al., 2013; Roux et al., 2016a; Okruszek et al., 2017, 2018; Kronbichler et al., 2019) included in the quantitative synthesis examined 126 patients, while the 9 (Das et al., 2012; Eack et al., 2013; Roux et al., 2014, 2015, 2016a,b; Okruszek et al., 2017; Kronbichler et al., 2019; Patel et al., 2020) records included in the systematic review examined 157 patients (There is a complete overlap between patients in the studies by Roux et al. (2014, 2015, 2016a,b).

The characteristics of included studies are in **Table 1** and Table 1 in the **Supplementary Material**.

Accuracy

For accuracy, data from 5 studies (Brunet et al., 2003; Eack et al., 2013; Roux et al., 2016a; Okruszek et al., 2018; Kronbichler et al., 2019) (which used different paradigms) were used, involving 123 patients and 121 controls. There is a significant difference [SMD $= -0.40$; 95% CI (-0.70, -0.10); $p = 0.008$] between patients with schizophrenia and controls with negligible statistical heterogeneity ($I^2 = 22.0\%$) in performance during implicit mentalizing tasks. On average, schizophrenic patients have a weaker performance with an effect size of -0.40, which is considered medium effect. The results are shown in **Figure 2**.

As the performance of the two groups was identical in one study (Kronbichler et al., 2019) and we considered that the question asked was significantly simpler than in the other studies, we conducted a leave one out sensitivity analysis during which the heterogeneity decreased, the studies become completely homogeneous ($I^2 = 0.0\%$) and the result remained significant and the effect size increased [SMD: -0.50; 95% CI (-0.78, -0.21); $p = 0.001$]. The results are summarized in **Figure 3**.

Reaction Time

For reaction time, data from 4 studies (Brunet et al., 2003; Eack et al., 2013; Roux et al., 2016a; Kronbichler et al., 2019) (using different paradigms) were used, including 77 patients and 81 controls. There is a significant difference in reaction time between the two groups [SMD: 0.89; 95% CI (0.36, 1.42); $p = 0.001$]. On average, the reaction time was significantly longer in the schizophrenic group compared to the control group with a large effect size (effect size: 0.89). There is a moderate heterogeneity ($I^2 = 57.00\%$). The forest plot showing the results can be found in **Figure 4**.

GRADE Approach

The overall judgement of quality of evidence can be found in **Table 2**. The overall quality of evidence of the results was low/very low.

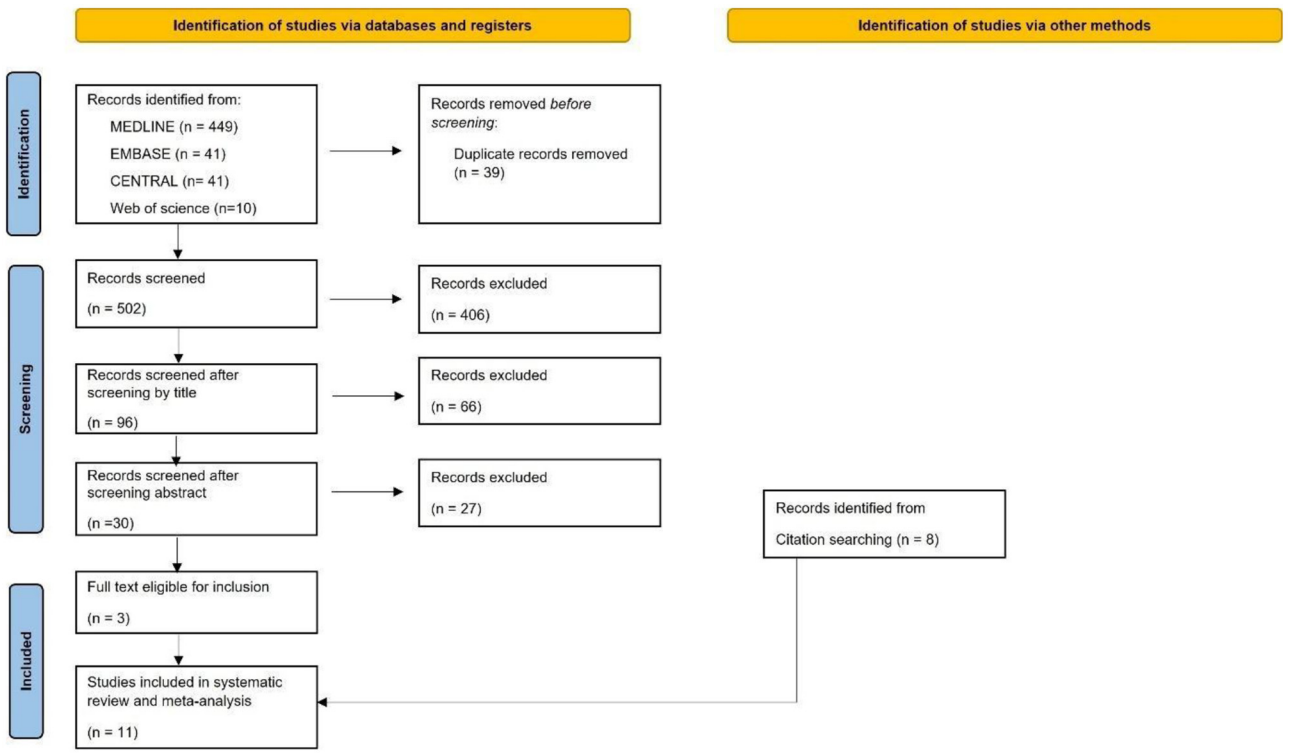


FIGURE 1 | PRISMA flowchart for the study selection process (Page et al., 2021).

TABLE 1 | Characteristics of the included studies.

	Task design	No. of patients (female of total %)	Age of patients (mean + SD)	No. of controls (female of total %)	Age of controls (mean + SD)	Medication (antipsychotic)
Brunet et al. (2003)	PET CT during non-verbal task (select a correct ending)	7 (0.0)	31.0 ± 6.5	8 (0.0)	23.3 ± 1.68	All
Das et al. (2012)	fMRI during animated triangle task	20 (0.0)	34.5 ± 8.4	21 (0.0)	33.5 ± 8.4	All except one
Eack et al. (2013)	Perspective-Taking task	20 (30.0)	27.8 ± 6.61	20 (35.0)	26.5 ± 5.8	All except one
Kronbichler et al. (2019)	Perspective-Taking task	24 (0.0)	26.0 ± 5.1	24 (0.0)	25.7 ± 4.5	All
Okruszek et al. (2017)	Interpersonal detection task	25 (3.0)	35.7 ± 6.9	26 (48.0)	35.3 ± 7.1	All except one
Okruszek et al. (2018)	Interpersonal detection task	46 (32.6)	33.4 ± 7.0	40 (50.0)	30.2 ± 10.7	–
Patel et al. (2020)	Eye movement measurement during TASIT videos	39 (25.6)	40.6 ± 11.0	27 (40.7)	35.2 ± 9.3	All
Roux et al. (2014)	Eye movements measurements during animated cartoons	29 (27.6)	39.0 ± 12.5	29 (34.5)	40.7 ± 13.5	All
Roux et al. (2015)	Eye movements measurements during intentional motion perception	29 (27.6)	39.0 ± 12.5	29 (34.5)	40.7 ± 13.5	All
Roux et al. (2016a)	Eye movement measurement during non-verbal task (select the correct ending)	29 (27.6)	39.0 ± 12.5	29 (34.5)	40.7 ± 13.5	All
Roux et al. (2016b)	Eye movement measurement during Frith-Happé animation	29 (27.6)	39.0 ± 12.5	29 (34.5)	40.7 ± 13.5	All

Systematic Review

FMRI Data

Concerning the comparison of activations/deactivations of schizophrenia patients and healthy subjects during mentalizing tasks, few data was available in the selected studies, which was not eligible for meta-analysis. Das et al. (2012) used an animated triangle task, consisting of mentalizing and control animations. In their study they emphasized a reduced activation in the right

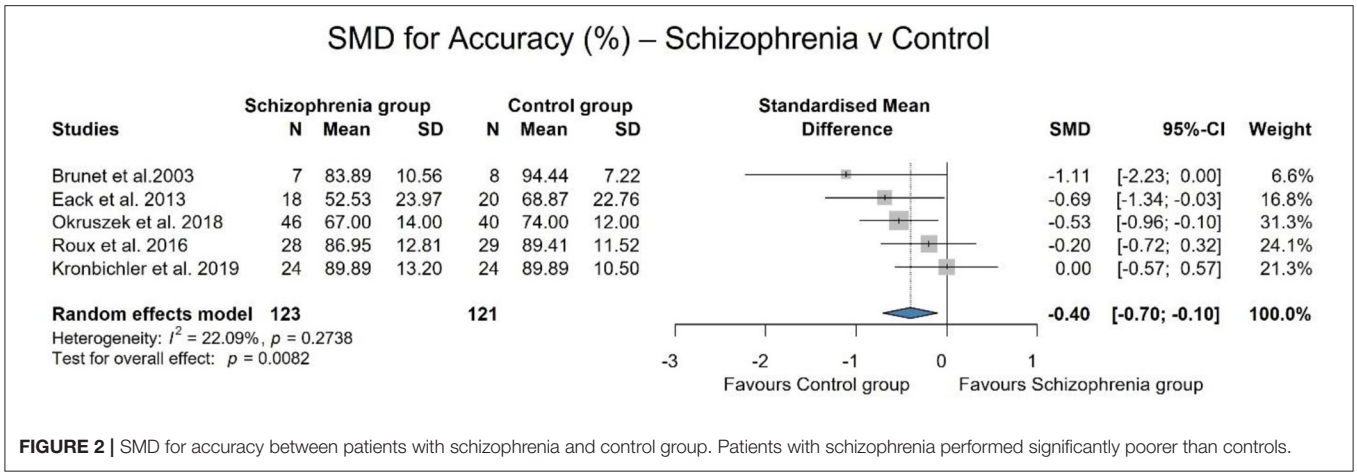


FIGURE 2 | SMD for accuracy between patients with schizophrenia and control group. Patients with schizophrenia performed significantly poorer than controls.

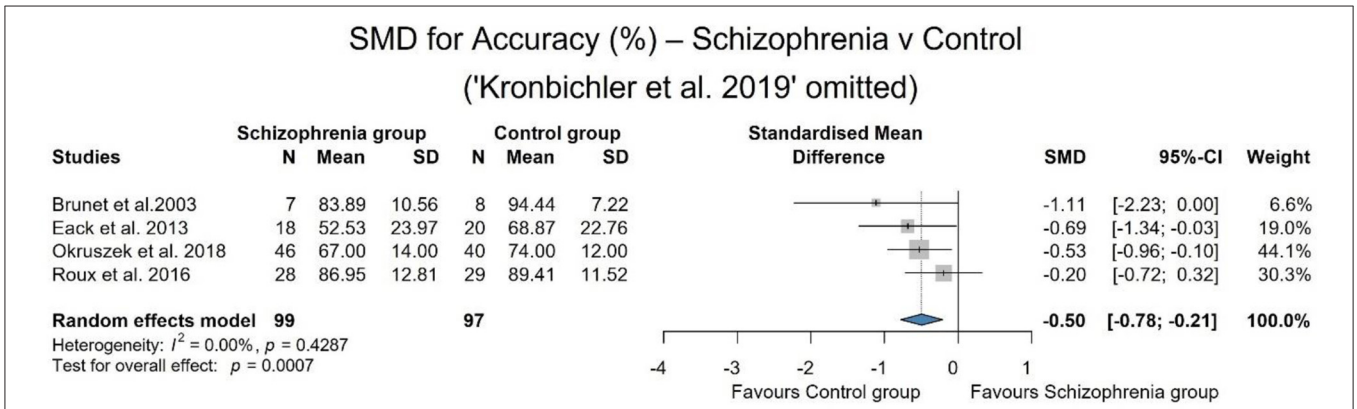


FIGURE 3 | SMD for accuracy after leaving one out sensitivity analysis. It demonstrates that when heterogeneity decreases, the sample becomes homogeneous.

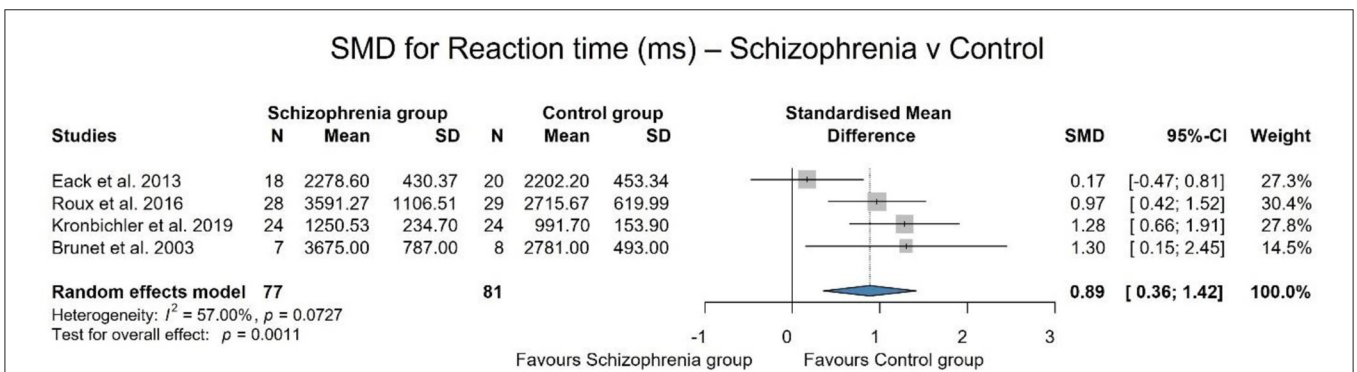


FIGURE 4 | Forest plot representing that patients with schizophrenia have significantly longer reaction times.

TABLE 2 | GRADE approach.

Outcome	No study/no patients/controls	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence
Accuracy	5/123/121	Not serious	Not serious	Not serious	Serious	Low
Reaction time	4/77/81	Not serious	Some	Not serious	Serious	Very low

TPJ and both the right and left IFG in patients with schizophrenia compared to healthy controls during processing of mentalizing animation, and a similar activation in the left TPJ. The workgroup of Eack et al. (2013) employed a visual perspective-taking task, during which the schizophrenia group showed a reduced activation in the left OFC and in both the left and right anterior cingulate cortex (ACC), when compared to healthy individuals. During the same task, functional connectivity analyses were also conducted, which showed deficits in negative functional connectivity between the anterior cingulate and fusiform/parahippocampal gyrus in patients with schizophrenia. In controls the deactivation of the ACC was associated with an increase in activation in the right fusiform and parahippocampal gyri, while the schizophrenia group had the opposite correlation. In the study of Kronbichler et al. (2019) a different visual perspective-taking task was used. Concerning the activations a difference was found: the activations in the bilateral middle occipital gyrus (MOG; marginal group difference in left MOG) in the schizophrenia group were indifferent across task conditions, whereas controls showed an increased BOLD response in situations of spontaneous perspective-taking. Okruszek et al. (2017) used a setting in which the subjects had to decide whether two agents, presented by point-light displays were either communicating or acting independently. They emphasized the lower activation of the right posterior sulcus temporalis superior (STS) in patients with schizophrenia during communicative interactions as their main finding. In the functional connectivity analysis of the same task the control group showed an increased connectivity of the right posterior STS with structures associated with the mentalizing (bilateral STS and TPJ, mPFC). The patients on the other hand, activated structures linked with mentalizing network (left posterior STS/TPJ, right anterior STS), but to a lesser extent.

Eye Movements Measurements

Five studies used this measurement (Roux et al., 2014, 2015, 2016a,b; Patel et al., 2020) from whose data we could not make meta-analysis due to overlapping populations. They used different paradigms. Except for one study (Roux et al., 2016b), all described different eye movements in patients with schizophrenia compared to controls (Roux et al., 2014, 2015, 2016a; Patel et al., 2020). Three studies described reduced viewing time on the face (Roux et al., 2014, 2016a; Patel et al., 2020), one described that patients spent more time observing contextual cues, which also highlighted the importance of time, based on which patients' mentalizing is delayed (Roux et al., 2016a).

Fixation Duration

Three (Roux et al., 2014, 2016b; Patel et al., 2020) studies measured the mean fixation duration which refers to the processing of information. Two studies found increased mean fixation duration in patients, which may indicate less saccades, shorter scanning paths (Roux et al., 2014, 2016b). In addition, Roux et al. (2016b) demonstrated that in patients and in controls the length of the fixation increases along with the complexity of the task, which referees an equal increase in cognitive processing in both groups. In contrast, Patel et al. described more saccades, shorter fixation duration time in patients with schizophrenia (Patel et al., 2020).

Looking at Cues of Mentalization

Three of the 5 studies found that patients spent less time looking at the cues of mentalization (Roux et al., 2014, 2016a; Patel et al., 2020). One study described that patients looked at intentional cues as long as controls while watching Firth—Happé animations (animated triangles interactions) (Roux et al., 2016b). One study demonstrated that patients have more center looking strategy during intentional motion perception (used chasing detection paradigm) (Roux et al., 2015). Patel et al. showed that patients' eye position was more variable than controls; the average area of the eye position was larger in patients during watching TASIT videos (Patel et al., 2020). Patients spent less time viewing action regions of interest during intentional attribution tasks based on comic strips (Roux et al., 2016a). On the other hand, the looking time of the contextual regions was greater in patients than in controls especially when the processing of social context required attribution of intention (Roux et al., 2016a). Roux et al. also demonstrated that looking time of a displaced object was the same in both groups when participants watched animated cartoons, but patients with schizophrenia spent less time looking at the head of the agent, and the decreased sensitivity to goal and belief attribution was associated with decreased attention to gaze orientation (Roux et al., 2014).

Face Looking Time

Three studies measured the face looking time of the participants. All of them found that patients spent less time looking at facial expressions (Roux et al., 2014, 2016a; Patel et al., 2020). Two of them (Roux et al., 2014, 2016a) examined the central field of view, the third one (Patel et al., 2020) described this discrepancy in peripheral field of view.

Risk of Bias Assessment

The overall risk of bias was low to high in the studies included. Detailed results of the quality assessment are found in **Supplementary Materials**.

DISCUSSION

Our meta-analysis and systematic review show that patients with schizophrenia have subtle impairments in implicit mentalizing. The results of the meta-analysis revealed more inaccurate performance, slower reaction times. The systematic review part of the analysis indicated different brain activation patterns; and different visual processing compared to control subjects during implicit mentalization tasks.

The patients with schizophrenia exhibited a small but significant impairment in accuracy with negligible statistical heterogeneity and a medium effect size. Decreasing heterogeneity during leave one out analysis may result from differences between the paradigms used in the studies, which may indicate the importance of the mentalizing tasks. The results suggest a subtle deficit compared to explicit mentalizing, which was found to be highly significantly impaired (Sprong et al., 2007; Bora et al.,

2009). It is important to point out that the accuracy probably may not directly reflect the implicit mentalization, since it is measured indirectly and appropriateness of present paradigms for detecting implicit mentalizing is still under debate (e.g., Heyes, 2014; Santiesteban et al., 2014; Phillips et al., 2015; Kulke et al., 2019).

In contrast to accuracy, reaction time may reflect implicit mentalizing more closely (Kovács et al., 2010; Edwards and Low, 2017). Our meta-analysis revealed a significantly slower reaction time among patients with schizophrenia with a large effect size. It also suggests that implicit mentalizing is affected in patients with schizophrenia. However, it may also mean that a less efficient processing speed is responsible for the lower performance in implicit mentalizing tasks. Some of the studies found intact mentalizing but delay in intention attribution due to a slowdown in context processing (Roux et al., 2016a,b). It is also essential to highlight that moderate heterogeneity was found, which may result from the markedly different paradigms, and the differences in the difficulties of the tasks. For this outcome, the effect size is high, which highlights its practical significance, but the certainty for outcome assessments is very low. It is important to note that two of the four studies were perspective taking studies. Some research assumed that perspective-taking tasks do not examine implicit mentalizing but are determined by domain-general processes (Santiesteban et al., 2014; Cole et al., 2016), whereas other studies confirmed that these tasks are driven by implicit mentalization (Samson et al., 2010; Ferguson et al., 2015; Gardner et al., 2018).

Concerning functional imaging, differences in activation patterns during implicit mentalization tasks were found. Patients with schizophrenia recruited several temporal regions (e.g., STG, TPJ, STS), however they showed lower activity in these areas compared to controls (Das et al., 2012; Okruszek et al., 2017). It may indicate a less effective processing of social situations. These regions have an important role in detecting intentionality from biological salient cues (Sugranyes et al., 2011; Frith and Frith, 2012; Ciaramidaro et al., 2014), and they were found to be active during implicit and during explicit mentalizing (Molenberghs et al., 2016). One study (Das et al., 2012) found reduced activation in the right TPJ, but not in the left TPJ in patients with schizophrenia. TPJ is active both in implicit and explicit processing (Molenberghs et al., 2016). The observed pattern (Das et al., 2012) is the opposite that has been found recently in healthy people, when stronger activation was detected in the right TPJ compared to the activity on the left side (Boccadoro et al., 2019). However, the activation of temporal regions and TPJ in patients with schizophrenia may point to the process of appreciating the communicative nature of the interaction being relatively unaffected, although it may rely on a slightly different brain network activity. On the other hand, controls activated several occipital and occipitotemporal regions which may suggest a less efficient computation of spontaneous visual perspective taking (Kronbichler et al., 2019). Some further common areas of explicit and implicit processing (Molenberghs et al., 2016), such as bilateral IFG (Das et al., 2012) and the cingulate gyrus (Eack et al., 2013) was found under-activated in subjects with schizophrenia relative to healthy controls. Furthermore, reduced activation of the OFC, which is thought to be an important part of the implicit mentalizing network (Molenberghs et al., 2016), was also reported in patients compared to controls (Eack et al., 2013). Overall, these results suggest that patients with schizophrenia are likely to detect communicative intentions, but they may activate a different, and possibly less integrated neural network during implicit mentalizing. As the connectivity analyses (Eack et al., 2013; Okruszek et al., 2017) revealed there are important differences in network connectivity in patients with schizophrenia. The decreased connectivity of the concerned areas (posterior STS, medial pre-frontal, and medial-temporal regions) possibly has a role in the less efficient implicit mentalizing. It may correspond to recent reports that found an alteration in the integrity of the neuronal network that is responsible for the processing of low-level pre-reflective intention detection, and also a diminished between-network connectivity of the low-level (implicit) and higher-level (explicit) mentalizing networks (Choe et al., 2018).

The qualitative synthesis revealed some further characteristics of implicit mentalizing in schizophrenia. Patients with schizophrenia showed subtle deficits in visual processing, which is not surprising since studies of implicit mentalizing have predominantly used visual paradigms. It seems a relatively consistent result that visual scanning is inadequate and slower in patients than in controls (Roux et al., 2015; Patel et al., 2020). Patients tend to focus more on contextual cues instead of processing socially relevant cues (Roux et al., 2014). In addition, patients fixate less on the head region (Roux et al., 2014, 2016a), especially when the face is in the peripheral field of view. They tend to bring faces less frequently into the central field of view for processing facial expressions (Patel et al., 2020). According to these results, patients with schizophrenia seem to focus less on socially relevant cues, especially on human faces, although face processing has a central role in detecting mental states (Itier and Batty, 2009). It is also important that interfering stimuli can significantly impair processing (e.g., stimulus overload) (Roux et al., 2016b). These results on visual processing and mentalizing seem to correspond with a recent meta-analysis, which found that mentalizing is linked to several neurocognitive deficits in schizophrenia, and that the type of the task used is a significant moderator in these relationships (Thibaudeau et al., 2020). This in turn also suggests that the complexity of the social situation and the deficient neurocognitive abilities may limit the efficiency of implicit mentalizing.

Our systematic review and meta-analysis have several limitations. The main limitation is the low number of eligible studies. However, we should mention that according to the Cochrane Handbook for Systematic Reviews a meta-analysis is the statistical combination of results from two or more separate studies (Higgins and Green, 2011). In addition, as claimed by Valentine et al. at least two studies are sufficient for a meta-analysis, because it is still the most transparent and valid way of synthesizing research data (Valentine et al., 2010). Based on this approach, we thought that the significance of the topic deserves a summary of the available data. We also found 8 studies via other methods than systematic search (e.g., checking the references of the selected articles), which is a significant limitation. Several search keys were tried, but the number of eligible records

found did not differ significantly. This was probably due to the lack of or inconsistent use of terms "implicit," "explicit," or "spontaneous" in publications that may have distorted the selection results. It is also important to mention that several different terms are used for mentalizing as well (Theory of Mind, mentalization, perspective taking, intentionality, mindreading, etc.) Unfortunately, a few studies were excluded (and included in the systematic part) because they did not provide sufficient data for meta-analysis. We contacted the authors, but not all missing data were received. Another limitation is that some studies have examined schizoaffective patients in addition to schizophrenic patients, which may also raise the bias. However, schizoaffective disorder is regularly included in schizophrenia studies as a schizophrenia-spectrum disorder.

It is important to highlight that other factors could also influence the results, but unfortunately, due to the small number of studies, we could not perform meta-regression [which requires at least 10 studies (Higgins and Green, 2011)], to assess the effect of moderator variables (e.g., symptom severity, general intelligence, age, education, gender ratio, duration of illness, etc.).

Another important limitation is the moderate heterogeneity due to different methods (different stimuli were used, different questions were asked) used to measure implicit mentalizing. Further limitations are that the studies involved have a small number of cases and most of the patients were taking medication at the time of the studies.

In conclusion, our results do not allow a firm conclusion at this moment. The substantial heterogeneity of the paradigms used in a small number of studies limit the generalizability of the results. Overall, in addition to the deficit of explicit mentalizing, implicit mentalizing performance is also affected in schizophrenia, if not to the same extent. It seems likely that some elements of implicit mentalizing might be relatively unaffected (e.g., detection of intentionality (Roux et al., 2016b; Okruszek et al., 2018), but the effectiveness may be limited by certain neurocognitive deficits. However, it would be important to have a clearer picture of the nature of implicit mentalizing in schizophrenia because it may significantly affect the remediation of mentalizing skills (Langdon et al., 2017), which in turn highlights the necessity of further studies.

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.

AUTHOR CONTRIBUTIONS

TC and AH: data collection, data analysis, writing article, and manuscript revision. SK, FD, MV-S, and ZS: data analysis and manuscript revision. MK, MH, and EV: data collection. PH: study design. TT: study design and manuscript revision. RH: study idea, study design, writing article, and manuscript revision. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by National Brain Research Program Grant No. NAP KTIA NAP-A-II/12(2017-2021) and the National Excellence programme (2019-2021, FIKP II).

ACKNOWLEDGMENTS

We would like to thank Lisa Kronbichler, Paul Roux, and Guarav H. Patel for providing missing data, and hence for the support with data collection.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.790494/full#supplementary-material

REFERENCES

Alexander-Bloch, A. F., Reiss, P. T., Rapoport, J., McAdams, H., Giedd, J. N., Bullmore, E. T., et al. (2014). Abnormal cortical growth in schizophrenia targets normative modules of synchronized development. *Biol. Psychiatry* 76, 438–446. doi: 10.1016/j.biopsych.2014.02.010

Apperly, I. A., and Butterfill, S. A. (2009). Do humans have two systems to track beliefs and belief-like states? *Psychol. Rev*. 116, 953–970. doi: 10.1037/a0016923

Baillargeon, R., Scott, R. M., He, Z., Sloane, S., Setoh, P., Jin, K.-S., et al. (2015). "Psychological and sociomoral reasoning in infancy," in *APA Handbook of Personality and Social Psychology, Vol. 1*, eds E. Borgida and J. A. Bargh (Washington, DC: American Psychological Association), 79–150. doi: 10.1037/14341-003

Benedetti, F., Bernasconi, A., Bosia, M., Cavallaro, R., Dallaspezia, S., Falini, A., et al. (2009). Functional and structural brain correlates of theory of mind and empathy deficits in schizophrenia. *Schizophr. Res.* 114, 154–160. doi: 10.1016/j.schres.2009.06.021

Boccadoro, S., Cracco, E., Hudson, A. R., Bardi, L., Nijhof, A. D., Wiersema, J. R., et al. (2019). Defining the neural correlates of spontaneous theory of mind (ToM): an fMRI multi-study investigation. *Neuroimage* 203, 116–193 doi: 10.1016/j.neuroimage.2019.116193

Bora, E., and Pantelis, C. (2013). Theory of mind impairments in first-episode psychosis, individuals at ultra-high risk for psychosis and in first-degree relatives of schizophrenia: systematic review and meta-analysis. *Schizophr. Res*. 144, 31–36. doi: 10.1016/j.schres.2012.12.013

Bora, E., Yucel, M., and Pantelis, C. (2009). Theory of mind impairment in schizophrenia: meta-analysis. *Schizophr. Res*. 109, 1–9. doi: 10.1016/j.schres.2008.12.020

Brunet, E., Sarfati, Y., Hardy-Bayle, M. C., and Decety, J. (2003). Abnormalities of brain function during a nonverbal theory of mind task in schizophrenia. *Neuropsychologia* 41, 1574–1582. doi: 10.1016/S0028-3932(03)00119-2

Buttelmann, D., Carpenter, M., and Tomasello, M. (2009). Eighteen-month-old infants show false belief understanding in an active helping paradigm. *Cognition* 112, 337–342. doi: 10.1016/j.cognition.2009.05.006

Butterfill, S. A., and Apperly, I. A. (2013). How to construct a minimal theory of mind. *Mind Lang.* 28, 606–637. doi: 10.1111/mila.12036

Choe, E., Lee, T. Y., Kim, M., Hur, J. W., Yoon, Y. B., Cho, K. K., et al. (2018). Aberrant within- and between-network connectivity of the mirror neuron system network and the mentalizing network in first episode psychosis. *Schizophr. Res*. 199, 243–249. doi: 10.1016/j.schres.2018.03.024

Ciaramidaro, A., Becchio, C., Colle, L., Bara, B. G., and Walter, H. (2014). Do you mean me? Communicative intentions recruit the mirror and the mentalizing system. *Soc. Cogn. Affect. Neurosci*. 9, 909–916. doi: 10.1093/scan/nst062

Cole, G. G., Atkinson, M., Le, A. T., and Smith, D. T. (2016). Do humans spontaneously take the perspective of others? *Acta Psychol*. 164, 165–168. doi: 10.1016/j.actpsy.2016.01.007

Das, P., Lagopoulos, J., Coulston, C. M., Henderson, A. F., and Malhi, G. S. (2012). Mentalizing impairment in schizophrenia: a functional MRI study. *Schizophr. Res*. 134, 158–164. doi: 10.1016/j.schres.2011.08.019

Davidson, C. A., Piskulic, D., Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., et al. (2018). Age-related trajectories of social cognition in youth at clinical high risk for psychosis: an exploratory study. *Schizophr. Res*. 201, 130–136. doi: 10.1016/j.schres.2018.05.001

DerSimonian, R., and Laird, N. (1986). Meta-analysis in clinical trials. *Control. Clin. Trials* 7, 177–188. doi: 10.1016/0197-2456(86)90046-2

Eack, S. M., Wojtalik, J. A., Newhill, C. E., Keshavan, M. S., and Phillips, M. L. (2013). Prefrontal cortical dysfunction during visual perspective-taking in schizophrenia. *Schizophr. Res*. 150, 491–497. doi: 10.1016/j.schres.2013.08.022

Edwards, K., and Low, J. (2017). Reaction time profiles of adults' action prediction reveal two mindreading systems. *Cognition* 160, 1–16. doi: 10.1016/j.cognition.2016.12.004

El Kaddouri, R., Bardi, L., De Bremaeker, D., Brass, M., and Wiersema, J. R. (2020). Measuring spontaneous mentalizing with a ball detection task: putting the attention-check hypothesis by Phillips and colleagues (2015) to the test. *Psychol. Res*. 84, 1749–1757. doi: 10.1007/s00426-019-01181-7

Ferguson, H. J., Apperly, I., Ahmad, J., Bindemann, M., and Cane, J. (2015). Task constraints distinguish perspective inferences from perspective use during discourse interpretation in a false belief task. *Cognition* 139, 50–70. doi: 10.1016/j.cognition.2015.02.010

Frith, C. D., and Frith, U. (2012). Mechanisms of social cognition. *Annu. Rev. Psychol*. 63, 287–313. doi: 10.1146/annurev-psych-120710-100449

Gardner, M. R., Bileviciute, A. P., and Edmonds, C. J. (2018). Implicit mentalising during level-1 visual perspective-taking indicated by dissociation with attention orienting. *Vision* 2, 3. doi: 10.3390/vision2010003

Gogtay, N. (2008). Cortical brain development in schizophrenia: insights from neuroimaging studies in childhood-onset schizophrenia. *Schizophr. Bull*. 34, 30–36. doi: 10.1093/schbul/sbm103

Grosse Wiesmann, C., Friederici, A. D., Singer, T., and Steinbeis, N. (2020). Two systems for thinking about others' thoughts in the developing brain. *Proc. Natl. Acad. Sci. U.S.A*. 117, 6928–6935. doi: 10.1073/pnas.1916725117

Hayden, J. A., van der Windt, D. A., Cartwright, J. L., Côté, P., and Bombardier, C. (2013). Assessing bias in studies of prognostic factors. *Ann. Intern. Med*. 158, 280–286. doi: 10.7326/0003-4819-158-4-201302190-00009

Healey, K. M., Penn, D. L., Perkins, D., Woods, S. W., and Addington, J. (2013). Theory of mind and social judgments in people at clinical high risk of psychosis. *Schizophr. Res*. 150, 498–504. doi: 10.1016/j.schres.2013.08.038

Herold, R., Feldmann, A., Simon, M., Tényi, T., Kövér, F., Nagy, F., et al. (2009). Regional gray matter reduction and theory of mind deficit in the early phase of schizophrenia: a voxel-based morphometric study. *Acta Psychiatr. Scand*. 119, 199–208. doi: 10.1111/j.1600-0447.2008.01297.x

Herold, R., Tényi, T., Lénárd, K., and Trixler, M. (2002). Theory of mind deficit in people with schizophrenia during remission. *Psychol. Med*. 32, 1125–1129. doi: 10.1017/S0033291702005433

Herold, R., Varga, E., Hajnal, A., Hamvas, E., Berecz, H., Tóth, B., et al. (2018). Altered neural activity during irony comprehension in unaffected first-degree relatives of schizophrenia patients-an fMRI study. *Front. Psychol*. 8:2309. doi: 10.3389/fpsyg.2017.02309

Heyes, C. (2014). Submentalizing: I am not really reading your mind. *Perspect. Psychol. Sci*. 9, 131–143. doi: 10.1177/1745691613518076

Higgins, J. P. T., and Green, S (Eds.). (2011). *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (Updated March 2011)*. The Cochrane Collaboration.

Horan, W. P., Nuechterlein, K. H., Wynn, J. K., Lee, J., Castelli, F., and Green, M. F. (2009). Disturbances in the spontaneous attribution of social meaning in schizophrenia. *Psychol. Med*. 39, 635–643. doi: 10.1017/S0033291708003838

Hyde, D. C., Simon, C. E., Ting, F., and Nikolaeva, J. I. (2018). Functional organization of the temporal-parietal junction for theory of mind in preverbal infants: a near-infrared spectroscopy study. *J. Neurosci*. 38, 4264–4274. doi: 10.1523/JNEUROSCI.0264-17.2018

Itier, R. J., and Batty, M. (2009). Neural bases of eye and gaze processing: the core of social cognition. *Neurosci. Biobehav. Rev*. 33, 843–863. doi: 10.1016/j.neubiorev.2009.02.004

Kampis, D., Parise, E., Csibra, G., and Kovács, Á. M. (2015). Neural signatures for sustaining object representations attributed to others in preverbal human infants. *Proc. R. Soc. B* 282:20151683. doi: 10.1098/rspb.2015.1683

Koelkebeck, K., Hirao, K., Miyata, J., Kawada, R., Saze, T., Dannlowski, U., et al. (2013). Impact of gray matter reductions on theory of mind abilities in patients with schizophrenia. *Soc. Neurosci*. 8, 631–639. doi: 10.1080/17470919.2013.837094

Kovács, Á. M., Téglás, E., and Endress, A. D. (2010). The social sense: susceptibility to others' beliefs in human infants and adults. *Science* 330, 1830–1834. doi: 10.1126/science.1190792

Kronbichler, L., Stelzig-schöler, R., Pearce, B. G., Tschernegg, M., Said-Yürekli, S., Crone, J. S., et al. (2019). Reduced spontaneous perspective taking in schizophrenia. *Psychiatry Res. Neuroimaging*. 292:5–12. doi: 10.1016/j.pscychresns.2019.08.007

Kronbichler, L., Tschernegg, M., Martin, A. I., Schurz, M., and Kronbichler, M. (2017). Abnormal brain activation during theory of mind tasks in schizophrenia: a meta-analysis. *Schizophr. Bull*. 43, 1240–1250. doi: 10.1093/schbul/sbx073

Kulke, L., and Hinrichs, M. A. B. (2021). Implicit theory of mind under realistic social circumstances measured with mobile eye-tracking. *Sci. Rep*. 11:1215. doi: 10.1038/s41598-020-80614-5

Kulke, L., Wübker, M., and Rakoczy, H. (2019). Is implicit theory of mind real but hard to detect? Testing adults with different stimulus materials. *R. Soc. Open Sci*. 6:190068. doi: 10.1098/rsos.190068

Langdon, R., Flynn, M., Connaughton, E., and Brüne, M. (2017). Impairments of spontaneous and deliberative mentalizing co-occur, yet dissociate, in schizophrenia. *Br. J. Clin. Psychol*. 56, 372–387. doi: 10.1111/bjc.12144

Lieberman, M. D. (2007). Social cognitive neuroscience: a review of core processes. *Ann. Rev. Psychol*. 58, 259–289. doi: 10.1146/annurev.psych.58.110405.085654

Low, J., and Watts, J. (2013). Attributing false beliefs about object identity reveals a signature blind spot in humans' efficient mind-reading system. *Psychol. Sci*. 24, 305–311. doi: 10.1177/0956797612451469

Marjoram, D., Job, D. E., Whalley, H. C., Gountouna, V. E., McIntosh, A. M., Simonotto, E., et al. (2006). A visual joke fMRI investigation into theory of mind and enhanced risk of schizophrenia. *Neuroimage* 31, 1850–1858. doi: 10.1016/j.neuroimage.2006.02.011

Martin, A. K., Robinson, G., Dzafic, I., Reutens, D., and Mowry, B. (2014). Theory of mind and the social brain: implications for understanding the genetic basis of schizophrenia. *Genes Brain Behav*. 13, 104–117. doi: 10.1111/gbb.12066

Molenberghs, P., Johnson, H., Henry, J. D., and Mattingley, J. B. (2016). Understanding the minds of others: a neuroimaging meta-analysis. *Neurosci. Biobehav. Rev*. 65:276–291. doi: 10.1016/j.neubiorev.2016.03.020

Nijhof, A. D., Brass, M., Bardi, L., and Wiersema, J. R. (2016). Measuring mentalizing ability: a within-subject comparison between an explicit and implicit version of a ball detection task. *PLoS ONE* 11:e0164373. doi: 10.1371/journal.pone.0164373

Okruszek, Ł., Piejka, A., Wysokiński, A., Szczepocka, E., and Manera, V. (2018). Biological motion sensitivity, but not interpersonal predictive coding is impaired in schizophrenia. *J. Abnorm. Psychol*. 127, 305–313. doi: 10.1037/abn0000335

Okruszek, L., Wordecha, M., Jarkiewicz, M., Kossowski, B., Lee, J., and Marchewka, A. (2017). Brain correlates of recognition of communicative interactions from biological motion in schizophrenia. *Psychol. Med*. 48, 1862–1871. doi: 10.1017/S0033291717003385

Onishi, K. H., and Baillargeon, R. (2005). Do 15-month-old infants understand false beliefs? *Science* 308, 255–258. doi: 10.1126/science.1107621

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372, n71. doi: 10.1136/bmj.n71

Patel, G. H., Arkin, S. C., Ruiz-Betancourt, D. R., DeBaun, H. M., Strauss, N. E., Bartel, L. P., et al. (2020). What you see is what you get: visual scanning failures of naturalistic social scenes in schizophrenia. *Psychol. Med.* doi: 10.1017/S0033291720001646. [Epub ahead of print].

Phillips, J., Ong, D. C., Surtees, A. D., Xin, Y., Williams, S., Saxe, R., et al. (2015). A second look at automatic theory of mind: reconsidering Kovács, Téglás, and Endress (2010). *Psychol. Sci*. 26, 1353–1367. doi: 10.1177/0956797614558717

R Core Team (2021). *R: A Language and Environment for Statistical Computing*. R version 4.1.2 (2021-11-01). Vienna: R Foundation for Statistical Computing.

Roux, P., Brunet-Gouet, E., Passerieux, C., and Ramus, F. (2016a). Eye-tracking reveals a slowdown of social context processing during intention attribution in patients with schizophrenia. *J. Psychiatry Neurosci*. 41, E13–E21. doi: 10.1503/jpn.150045

Roux, P., Forgeot D'arc, B., Passerieux, C., and Ramus, F. (2014). Is the theory of mind deficit observed in visual paradigms in schizophrenia explained by an impaired attention toward gaze orientation? *Schizophr. Res*. 157, 78–83. doi: 10.1016/j.schres.2014.04.031

Roux, P., Passerieux, C., and Ramus, F. (2015). An eye-tracking investigation of intentional motion perception in patients with schizophrenia. *J. Psychiatry Neurosci*. 40, 118–125. doi: 10.1503/jpn.140065

Roux, P., Smith, P., Passerieux, C., and Ramus, F. (2016b). Preserved implicit mentalizing in schizophrenia despite poor explicit performance: evidence from eye tracking. *Sci. Rep*. 6, 34728. doi: 10.1038/srep34728

Samson, D., Apperly, I. A., Braithwaite, J., and Andrews, B. (2010). Seeing it your way: evidence for altercentric intrusion effects in visual perspective taking. *J. Exp. Psychol. Hum. Percept. Perform*. 36, 1255–1266. doi: 10.1037/a0018729

Santiesteban, I., Catmur, C., Hopkins, S. C., Bird, G., and Heyes, C. (2014). Avatars and arrows: implicit mentalizing or domain-general processing? *J. Exp. Psychol. Hum. Percept. Perform*. 40, 929–937. doi: 10.1037/a0035175

Schneider, D., Bayliss, A. P., Becker, S. I., and Dux, P. E. (2012). Eye movements reveal sustained implicit processing of others' mental states. *J. Exp. Psychol. Gen*. 141, 433–438. doi: 10.1037/a0025458

Scott, R. M., and Baillargeon, R. (2017). Early false-belief understanding. *Trends Cogn. Sci*. 21, 237–249. doi: 10.1016/j.tics.2017.01.012

Selemon, L. D., and Zecevic, N. (2015). Schizophrenia: a tale of two critical periods for prefrontal cortical development. *Transl. Psychiatry* 8, e623. doi: 10.1038/tp.2015.115

Senju, A. (2012). Spontaneous theory of mind and its absence in autism spectrum disorders. *Neuroscientist* 18, 108–113. doi: 10.1177/1073858410397208

Senju, A. (2013). Atypical development of spontaneous social cognition in autism spectrum disorders. *Brain Dev*. 35, 96–101. doi: 10.1016/j.braindev.2012.08.002

Southgate, V., Chevallier, C., and Csibra, G. (2010). Seventeen-month-olds appeal to false beliefs to interpret others' referential communication. *Dev. Sci*. 13, 907–912. doi: 10.1111/j.1467-7687.2009.00946.x

Southgate, V., Senju, A., and Csibra, G. (2007). Action anticipation through attribution of false belief by 2-year-olds. *Psychol. Sci*. 18, 587–592. doi: 10.1111/j.1467-9280.2007.01944.x

Sprong, M., Schothorst, P., Vos, E., Hox, J., and van Engeland, H. (2007). Theory of mind in schizophrenia: meta-analysis. *Br. J. Psychiatry*. 191:5–13. doi: 10.1192/bjp.bp.107.035899

Sugranyes, G., Kyriakopoulos, M., Corrigall, R., Taylor, E., and Frangou, S. (2011). Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. *PLoS ONE* 6, e25322. doi: 10.1371/journal.pone.0025322

Thibaudeau, É., Achim, A. M., Parent, C., Turcotte, M., and Cellard, C. (2020). A meta-analysis of the associations between theory of mind and neurocognition in schizophrenia. *Schizophr. Res*. 216, 118–128. doi: 10.1016/j.schres.2019.12.017

Tikka, D. L., Singh, A. R., and Tikka, S. K. (2020). Social cognitive endophenotypes in schizophrenia: a study comparing first episode schizophrenia patients and, individuals at clinical- and familial- 'at-risk' for psychosis. *Schizophr. Res*. 215, 157–166. doi: 10.1016/j.schres.2019.10.053

Valentine, J. C., Pigott, T. D., and Rothstein, H. R. (2010). How many studies do you need? A primer on statistical power for meta-analysis. *J. Educ. Behav. Stat*. 2, 215–247. doi: 10.3102/1076998609346961

van der Wel, R. P., Sebanz, N., and Knoblich, G. (2014). Do people automatically track others' beliefs? Evidence from a continuous measure. *Cognition* 130, 128–133. doi: 10.1016/j.cognition.2013.10.004

Van Overwalle, F., and Vandekerckhove, M. (2013). Implicit and explicit social mentalizing: dual processes driven by a shared neural network. *Front. Hum. Neurosci*. 7, 560. doi: 10.3389/fnhum.2013.00560

Velthorst, E., Fett, A. J., Reichenberg, A., Perlman, G., van Os, J., Bromet, E. J., et al. (2017). The 20-year longitudinal trajectories of social functioning in individuals with psychotic disorders. *Am. J. Psychiatry* 174, 1075–1085. doi: 10.1176/appi.ajp.2016.15111419

Vogeley, K. (2017). Two social brains: neural mechanisms of intersubjectivity. *Philos. Trans. R. Soc. Lond. B Biol. Sci*. 372, 20160245. doi: 10.1098/rstb.2016.0245

Vucurovic, K., Caillies, S., and Kaladjian, A. (2021). Neural correlates of mentalizing in individuals with clinical high risk for schizophrenia: ALE meta-analysis. *Front Psychiatry* 12:634015. doi: 10.3389/fpsyt.2021.634015

Weinberger, D. R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Arch. Gen. Psychiatry* 44, 660–669. doi: 10.1001/archpsyc.1987.01800190080012

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 Psychology

ORIGINAL RESEARCH
published: 23 February 2022
doi: 10.3389/fpsyg.2022.804093

The Impact of Poor Nonverbal Social Perception on Functional Capacity in Schizophrenia

Victoria Chapellier†, Anastasia Pavlidou†, Lydia Maderthaner†, Sofie von Känel† and Sebastian Walther†*

Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland

OPEN ACCESS

Edited by:
Marta Bosia,
Vita-Salute San Raffaele University, Italy

Reviewed by:
Michal Hajdúk,
Comenius University, Slovakia
Giacomo Deste,
Civil Hospital of Brescia, Italy

***Correspondence:**
Victoria Chapellier
victoria.chapellier@upd.unibe.ch

†ORCID:
Victoria Chapellier
orcid.org/0000-0002-5102-1771
Anastasia Pavlidou
orcid.org/0000-0002-5590-3456
Lydia Maderthaner
orcid.org/0000-0003-3353-7229
Sofie von Känel
orcid.org/0000-0003-4875-7486
Sebastian Walther
orcid.org/0000-0003-4026-3561

Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: *28 October 2021*
Accepted: *07 January 2022*
Published: *23 February 2022*

Citation:
Chapellier V, Pavlidou A, Maderthaner L, von Känel S and Walther S (2022) The Impact of Poor Nonverbal Social Perception on Functional Capacity in Schizophrenia. Front. Psychol. 13:804093. doi: 10.3389/fpsyg.2022.804093

Background: Nonverbal social perception is the ability to interpret the intentions and dispositions of others by evaluating cues such as facial expressions, body movements, and emotional prosody. Nonverbal social perception plays a key role in social cognition and is fundamental for successful social interactions. Patients with schizophrenia have severe impairments in nonverbal social perception leading to social isolation and withdrawal. Collectively, these aforementioned deficits affect patients' quality of life. Here, we compare nonverbal social perception in patients with schizophrenia and controls and examine how nonverbal social perception relates to daily functioning.

Methods: We compared nonverbal social perception in 41 stable outpatients with schizophrenia and 30 healthy controls using the Mini Profile of Nonverbal Sensitivity (Mini-PONS). The participants evaluated 64 video clips showing a female actor demonstrating various nonverbal social cues. Participants were asked to choose one of two options that best described the observed scenario. We correlated clinical ratings (Positive and Negative Syndrome Scale, Brief Negative Syndrome Scale), Self-report of Negative Symptoms, and functional assessments (functional capacity and functional outcome) with Mini-PONS scores.

Results: Patients performed significantly poorer in the Mini-PONS compared to controls, suggesting deficits in nonverbal social perception. These deficits were not associated with either positive symptoms or negative symptoms (including self-report). However, impaired nonverbal social perception correlated with distinctive domains of BNSS (mainly avolition and blunted affect), as well as functional capacity and functional outcome in patients.

Conclusion: We demonstrate that nonverbal social perception is impaired in stable outpatients with schizophrenia. Nonverbal social perception is directly related to specific negative symptom domains, functional capacity and functional outcome. These findings underline the importance of nonverbal social perception for patients' everyday life and call for novel therapeutic approaches to alleviate nonverbal social perception deficits.

Keywords: communication, gesture, social cognition, functional domains, affect, social functioning, psychosis

INTRODUCTION

Schizophrenia is a severe and debilitating psychiatric disorder that affects nearly 1% of the world's population (McGrath et al., 2008). Schizophrenia is characterized by delusions, hallucinations, negative symptoms, disorganization symptoms according to DSM-5, including impaired social cognition (Goldsmith and McFall, 1975; Green et al., 2008a, 2019). Generally, social cognition refers to psychological processes that allow us to decode the behaviors and intentions of others (Frith and Frith, 2007; Adolphs, 2009). Impaired social cognition is not only prevalent in chronic schizophrenia patients, but also in early-onset psychosis and early psychosis patients (Fornells-Ambrojo and Garety, 2009; Barkl et al., 2014; Giannitelli et al., 2015; Healey et al., 2016). Therefore, these deficits occur across different stages of the disorder. Social cognitive deficits are assumed to be a stable trait that precedes and predicts the onset of schizophrenia (Frith and Corcoran, 1996; Riveros et al., 2010; Savla et al., 2013; Pinkham et al., 2014; Green et al., 2015), and informs on the frequency of patients' relapse (Mcglashan, 1986). In schizophrenia, social cognition acts as a mediator between neurocognition and functional outcome (Vauth et al., 2004; Brekke et al., 2005; Couture et al., 2006; Sparks et al., 2010; Mancuso et al., 2011; Galderisi et al., 2020). Hence, these impairments play a key role not only in the development of the disorder, but also in the functional outcome of patients. Social cognitive impairment in schizophrenia encompasses multiple domains.

In schizophrenia, all of the five well-established social cognitive domains are impaired (Pinkham et al., 2014): social perception (Toomey et al., 2002), social knowledge (Penn et al., 2002), emotion processing (Pollard et al., 1995), attributional processing (Green and Horan, 2010), and theory of mind (Greig et al., 2004; Green and Horan, 2010). A meta-analysis revealed that social perception and theory of mind were most severely impaired in schizophrenia (Savla et al., 2013). The majority of previous studies focused on theory of mind and emotion processing. However, only a few studies focused on the nonverbal aspects of social perception (emotional prosody, facial expressions, body movements) in schizophrenia and used heterogeneous tasks (Pinkham et al., 2017).

Nonverbal social perception, which is the ability to decode relevant nonverbal interpersonal cues (Morrison and Bellack, 1981; Toomey et al., 2002) is impaired in schizophrenia patients (Walther et al., 2015). For example, schizophrenia patients exhibit decreased ability to evaluate nonverbal cues such as prosody (Murphy and Cutting, 1990), facial expressions (Cutting, 1981; Colussy and Zuroff, 1985; Borod et al., 1990; Edwards et al., 2002; van t'wout et al., 2007; McIntosh and Park, 2014), as well as, hand and body movements (Monti and Fingeret, 1987; Toomey et al., 2002; Goldin-Meadow and Alibali, 2013; Walther et al., 2015). Incorrect interpretation of facial expressions and body movements limits schizophrenia patients' communication: they tend to perceive ambiguous gestures and direct gaze as self-referential or threatening (Bucci et al., 2008; White et al., 2016; Wastler and Lenzenweger, 2018). In addition, impaired gesture perception has been linked to deficits in domains of visual information processing (Matthews et al., 2013; Millman et al., 2014; Walther et al., 2015; Gupta et al., 2021), which affects patients' attention and working memory (Green et al., 2008b; Jahshan et al., 2012). In schizophrenia, associations between the ability to evaluate nonverbal cues and symptoms are unclear (Toomey et al., 2002; Walther et al., 2015, 2016).

Despite the progress made in understanding social cognitive deficits in schizophrenia, the role of nonverbal social perception in schizophrenia remains poorly understood (Green et al., 2005). While in most reports associations between poor nonverbal social perception and positive symptoms (Toomey et al., 2002; Giannitelli et al., 2015) as well as negative symptoms are lacking (Olbert et al., 2013; Walther et al., 2016), others report the opposite (Walther et al., 2015). Therefore, the relationship between nonverbal social perception and symptoms remains unresolved. However, impaired nonverbal social perception are assumed to be associated with disorganization symptoms (Toomey et al., 2002), which have shown to mediate between nonverbal social perception deficits and poor functioning in schizophrenia (Engelstad et al., 2017). In fact, nonverbal social perception deficits may have an important impact on schizophrenia patients' social interaction, as these deficits are linked to patients' gesture performance (Walther et al., 2015) and overall functioning (Morrison et al., 1988; Hooker and Park, 2002; Sergi et al., 2006; Walther et al., 2016).

In patients with schizophrenia, deficits in nonverbal social perception have been associated with poor functional outcome (Morrison et al., 1988; Hooker and Park, 2002; Sergi et al., 2006) and functional capacity (Walther et al., 2016). In general, functional capacity refers to the relevant real-world adaptive skills for daily functioning, such as managing finances or scheduling an appointment (Patterson et al., 2001). Nonverbal social perception deficits in schizophrenia have been shown to predict functional capacity and outcome at 6 months follow-up in schizophrenia patients (Walther et al., 2016). Consequently, nonverbal social perception is closely linked to overall functioning, and therefore should be a target for pharmacological and non-pharmacological interventions. While the association between the ability to decode facial expressions and functional capacity has intensively been investigated in schizophrenia (Olbert et al., 2013; Abram et al., 2014), studies investigating the link between nonverbal social perception as a whole (including body movements and emotional prosody perception) and functional capacity are scarce.

This study aimed at determining whether schizophrenia outpatients perform poorer in nonverbal social perception than healthy controls. We hypothesized that poor nonverbal social perception is linked to limited functional capacity and poor functional outcome. We expect nonverbal social perception to have different effects on different functional domains. Hence, we explored six functional domains separately: physical functioning, personal care skills, interpersonal relationships, social acceptability, activities and work skills. In addition, we investigated the impact of symptoms such as positive symptoms, negative symptoms (including the domains of anhedonia, asociality, avolition, blunted affect, and alogia, as well as the item gesture expression) and the severity of symptoms on nonverbal social perception.

MATERIALS AND METHODS

In total, 41 schizophrenia patients (mean age = 38.6 years, SD = 12.2; 51.2% male) and 30 healthy controls (mean age = 40.0 years, SD = 12.2; 50.0% male) were included in this study (**Table 1**). We recruited patients with a diagnosis of the schizophrenia spectrum (33 patients with schizophrenia and 8 patients with the schizoaffective disorder) according to DSM-5 at the outpatient clinics of the University Hospital of Psychiatry and Psychotherapy, Bern. The recruitment period of participants started in December 2019 and ended in June 2021. This study focuses on baseline data of a larger project (Brain Stimulation And Group Therapy to Improve Gesture and Social Skills in Psychosis trial, clinicaltrials.gov NCT04106427). All patients consented to participate in the entire interventional study, were symptomatically stable and all but three received antipsychotic treatment. Healthy control participants were recruited by word-of-mouth, through leaflets at public places and a post on the website of the University Hospital of Psychiatry and Psychotherapy. For every participant, we acquired all baseline data within 2 days. All participants met the following criteria: 18–65 years of age, ability to provide written informed consent as documented by signature, no substance abuse or dependence other than nicotine, no past or current medical or neurological condition associated with impaired or aberrant movement and no epilepsy. In addition, controls had no history of any psychiatric disorder or first-degree relatives with schizophrenia spectrum disorders.

TABLE 1 | Demographic and clinical characteristics.

	Patients (*N* = 41)	Controls (*N* = 30)	Comparison
Demographics			
Age (years)	38.6 ± 12.2	40.0 ± 12.2	$t = 0.5$; $p = 0.651$
Gender (%female)	51.2%	50.0%	
Education (years)	14.5 ± 3.3	16.2 ± 2.6	$t = 2.4$; $p =$ **0.021***
Digit span backwards	4.4 ± 1.0	4.6 ± 1.1	$t = 0.9$; $p = 0.371$
Medication (CPZ-eq in mg)	455.0 ± 417.3		
Assessments			
PANSS positive[a]	12.4 ± 6.1		
PANSS negative[a]	17.3 ± 7.9		
PANSS total[a]	60.9 ± 21.5		
BNSS[a]	27.5 ± 15.6		
SNS	15.1 ± 6.7	4.3 ± 2.9	$t = -9.1$; $p <$ **0.001*** **
Mini-PONS	43.6 ± 5.3	47.6 ± 4.4	$t = 3.5$; $p <$ **0.001*** **
UPSA-brief[b]	83.8 ± 11.0	90.5 ± 7.4	$t = 3.0$; $p =$ **0.003****
SLOF	183.5 ± 18.5	213.3 ± 4.0	$t = 10.2$; $p <$ **0.001*** **

*PANSS, positive and negative syndrome scale; BNSS, brief negative symptom scale; SNS, self-evaluation of negative symptoms; Mini-PONS, mini profile of nonverbal sensitivity; UPSA-brief, University of California San Diego performance-based assessment; SLOF, specific levels of functioning scale; Values represent the mean ± SD for each group. [a] was not assessed in healthy controls, [b] one missing value for one patient; * denotes a significant difference p-value < 0.05; ** denotes a significant difference p-value < 0.01, *** denotes significant differences p-value < 0.001. P-values marked with bold indicate statistically significant differences between the groups.*

TABLE 2 | Comparison of the four PONS subscales between patients and controls, whilst controlling for education and working memory.

	Patients (*N* = 41)	Controls (*N* = 30)	Comparison	Effect size
Emotional prosody (voice recordings)	10.3 ± 2.1	11.8 ± 2.0	$F_{(1,70)} = 6.6$, $p =$ **0.012***	$\eta_p^2 = 0.090$
Body movements	10.7 ± 2.3	11.2 ± 2.0	$F_{(1,70)} = 0.1$, $p = 0.706$	$\eta_p^2 = 0.002$
Facial expression	11.3 ± 1.8	11.8 ± 1.6	$F_{(1,70)} = 0.6$, $p = 0.453$	$\eta_p^2 = 0.008$
Emotional prosody and facial expression	11.2 ± 2.4	12.8 ± 1.5	$F_{(1,70)} = 5.7$, $p =$ **0.010***	$\eta_p^2 = 0.095$

*Values represent the mean ± SD for each group; * denotes significant differences p-value < 0.05. P-values marked with bold indicate statistically significant differences between the groups.*

Assessments

Behavioral Assessment

Nonverbal social perception was assessed with the Mini Profile of Nonverbal Sensitivity (Mini-PONS), which includes 64 videos (2 s each) showing a Caucasian woman (Rosenthal, 1980; Banziger et al., 2011). The Mini-PONS has four subscales (see **Table 2**): voice recordings/emotional prosody only (either content-filtered speech, or randomized splice speech), body movements only, facial expressions only, as well as, combined emotional prosody (content-filtered speech and randomized splice speech) and facial expression. The test was administered on a computer. Participants were asked to choose one of two options that best described the observed scenario. The total score for Mini-PONS ranges from 0 to 64 and the four Mini-PONS subscores range from 0 to 16. The test takes around 13 min.

Clinical and Functional Assessments

To assess the current psychopathology of patients, we used the Positive And Negative Syndrome Scale [PANSS; (Kay et al., 1987)] and the 13-item Brief Negative Symptom Scale [BNSS; (Strauss et al., 2012)]. In both patients and controls, we collected a self-report of negative symptoms: the Self-Evaluation of Negative Symptoms (SNS) scale, which includes 20 items with a 3-point Likert scale, total score ranging from 0 to 40 (Dollfus et al., 2016).

Functional capacity was assessed with the brief version of the University of California San Diego Performance-Based Assessment (UPSA-brief) (Patterson et al., 2001). The UPSA-brief evaluates a person's ability in managing finances (e.g., count money change) and communicating with others (e.g., reschedule an appointment). Functional outcome was measured with the Specific Levels of Functioning Scale (SLOF), which is a 43-item interview-based instrument rated on a 5-point Likert scale by a psychiatrist. The SLOF total score ranges from 43 to 215. SLOF does not focus on items relevant to

psychiatric symptoms, nor cognitive impairment, but assesses behaviors and abilities essential to function in the community (Schneider and Struening, 1983).

To ensure reliability, three MD clinical raters, all currently in psychiatric residency (LM, DA, DB), were trained by the principal investigator (SW). The interrater reliability resulted in a very good mean of 0.95.

Data Analyses

Data were analyzed using SPSS (version 28) and R (version 3.6.1). For this report, we excluded four patients due to visual impairment or difficulties to understand the experimental task. We used two-sample *t*-tests to compare the demographic data, nonverbal social perception, clinical assessments and functional outcomes, available for both patients and controls. Our Mini-PONS total scores were normally distributed ($W_{(71)} = 0.97$, $p = 0.105$). However, since three of the four Mini-PONS sub scores were not normally distributed ($W_{(71)} > 0.95$, $p < 0.014$) we applied a square root transformation to the Mini-PONS sub scores. As years of education differed between patients and controls ($t = 2.35$; $p = 0.021$; see **Table 1**) and as working memory has been reported to affect nonverbal social perception (Walther et al., 2015), we used education and working memory as covariates in our main analyses. We ran a parametric ANCOVA comparing Mini-PONS total score in patients and controls, as well as a parametric MANCOVA to compare the four Mini-PONS subscales in both groups, whilst controlling for education and working memory. Effect sizes estimates were calculated for the parametric ANCOVA and MANCOVA analyses.

In patients, we ran partial correlations between Mini-PONS total score and psychopathology as well as functional outcomes, whilst controlling for medication (CPZ-equivalent in mg per day; **Table 1**). Here, we corrected for multiple comparisons using the false discovery rate (FDR). Additionally, we ran explorative correlations between Mini-PONS total score and five BNSS subscales (Alogia, Blunted Affect, Asociality, Avolition, and Anhedonia), one BNSS item (Gesture Expression) as well as six SLOF subscales (Physical functioning, Personal care skills, Interpersonal relationships, Social acceptability, Activities of community living, and Work skills) in patients, whilst controlling for medication.

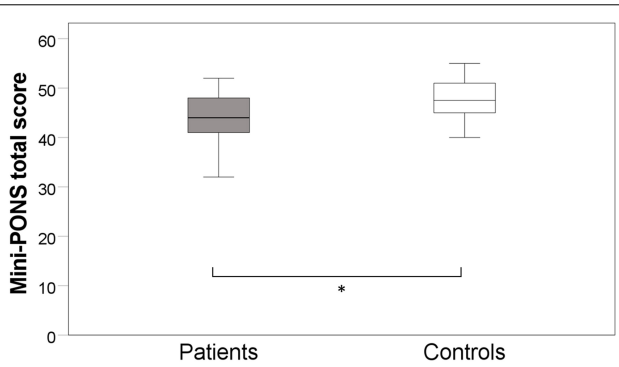


FIGURE 1 | Group difference in nonverbal social perception. * denotes significant differences *p*-value < 0.05, whilst controlling for education and working memory.

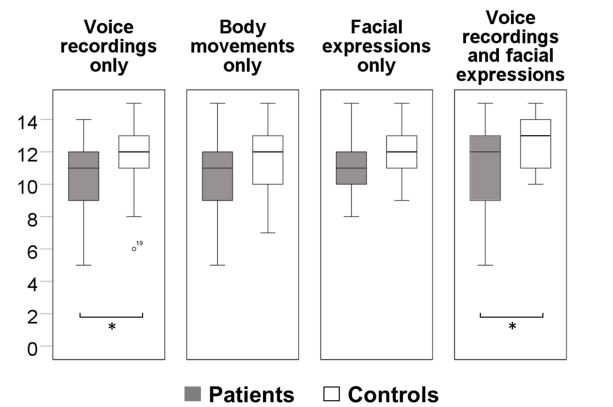


FIGURE 2 | Group differences in emotional prosody, face and body movement perception. * denotes significant differences *p*-value < 0.05 whilst controlling for education and working memory.

RESULTS

Comparison of Nonverbal Social Perception Between Patients and Controls

Schizophrenia patients performed significantly poorer than controls ($F_{(1,70)} = 7.1$, $p = 0.010$, $\eta_p^2 = 0.096$) in the Mini-PONS when controlling for education and working memory, suggesting impairments in nonverbal social perception (see **Figure 1**). Regarding the four Mini-PONS sub scores, patients performed poorer in both scenarios with emotional prosody (voice recordings) only and emotional prosody combined with facial expressions, whilst controlling for education and working memory (see **Table 2** and **Figure 2**). However, there was no significant group difference in videos with body movements only and facial expression only (see **Table 2** and **Figure 2**). Hence, there was only a significant difference between patients and controls when emotional prosody was incorporated in the scenario. Following up on this group difference, we explored a group × stimulus type interaction in an additional 2×2 ANCOVA controlling for education and working memory. While we found main effects for group (controls > patients) and for stimulus type (bimodal > unimodal), we failed to detect an interaction of the two factors [($F_{(1,70)} = 0.1$, $p = 0.760$, $\eta_p 2 = 0.001$)]; i.e., both groups improve with multimodal stimuli at comparable magnitude.

Correlation Between Nonverbal Social Perception and Clinical Assessments/Functional Outcomes

In patients, nonverbal social perception deficits failed to correlate with positive symptoms, negative symptoms (PANSS negative and BNSS), or overall symptom severity (PANSS total; see

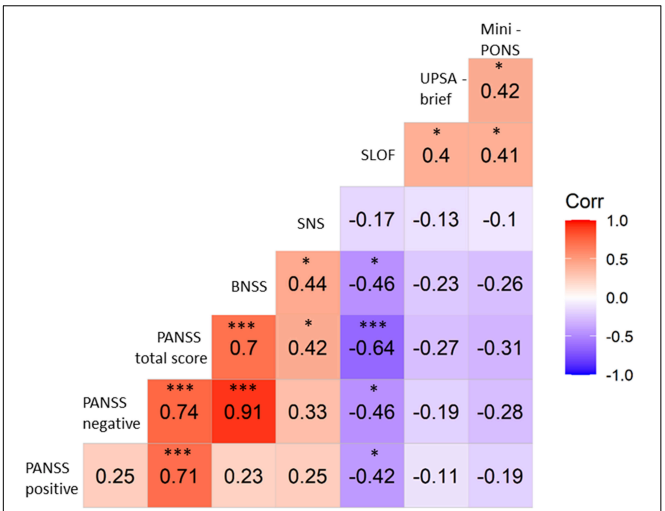


FIGURE 3 | Correlations between Mini-PONS total score and clinical/functional tests controlling for medication. PANSS, positive and negative syndrome scale; BNSS, brief negative symptom scale; SNS, self-evaluation of negative symptoms; SLOF, specific levels of functioning scale; UPSA-brief, University of California San Diego performance-based assessment; Mini-PONS, mini profile of nonverbal sensitivity; * denotes significant correlations p-value < 0.05; *** denotes significant correlations p-value < 0.001.

TABLE 3 | BNSS subscales/item correlations with PONS total score controlling for medication in patients.

	r	*p*
Anhedonia subscale	−0.1	0.574
Asociality subscale	−0.1	0.762
Avolition subscale	−0.3	**0.045***
Blunted affect subscale	−0.3	**0.031***
Alogia subscale	−0.2	0.188
Gesture expression item	0.5	**0.004****

** denotes significant correlations p-value < 0.05; ** denotes a significant correlation p-value < 0.01. P-values marked with bold indicate statistically significant correlations.*

Figure 3). However, the BNSS subscales and the gesture expression item in patients indicated that nonverbal social perception deficits were linked to avolition, blunted affect and gesture expression, but not to anhedonia, asociality or alogia (see **Table 3**). In addition, no correlation was observed in either patients or controls between Mini-PONS and subjective negative symptoms (SNS; see table **Figure 3**).

Poor nonverbal social perception highly correlated with limited functional capacity (UPSA-brief, see **Figures 3**, **4**) and reduced functional outcome in patients (SLOF, see **Figures 3**, **5**). While all symptom domains correlated with the rater-based SLOF total score, symptom domains failed to correlate with the performance-based UPSA-brief total score. When running correlations between Mini-PONS total score and all six SLOF subscales in patients, we observed that nonverbal social perception deficits are associated with impaired personal care skills, limited activities and reduced work skills, but not with physical functioning, poor interpersonal relationships and social acceptability (see **Table 4**).

TABLE 4 | SLOF subscales comparison between schizophrenia patients and healthy controls; SLOF subscales correlation with Mini-PONS total score controlling for medication in schizophrenia patients.

	Comparison with healthy controls	**Correlation with Mini-PONS in patients**
Physical functioning subscale	$t = -0.2$; $p = 0.855$	$r = 0.2$; $p = 0.149$
Personal care skills subscale	$t = 5.3$; $p <$ **0.001****	$r = 0.5$; $p =$ **0.002****
Interpersonal relationships subscale	$t = 9.0$; $p <$ **0.001****	$r = 0.2$; $p = 0.144$
Social acceptability subscale	$t = 1.8$; $p = 0.086$	$r = 0.0$; $p = 0.951$
Activities subscale	$t = 6.6$; $p <$ **0.001****	$r = 0.4$; $p =$ **0.008****
Work skills subscale	$t = 11.0$; $p <$ **0.001****	$r = 0.3$; $p =$ **0.026***

** denotes a significant correlation p-value < 0.05; ** denotes significant correlation p-value < 0.01; *** denotes significant differences p-value < 0.001. P-values marked with bold indicate statistically significant differences and correlations.*

DISCUSSION

This study on nonverbal social perception deficits in schizophrenia patients had three main findings. First, we confirmed that schizophrenia patients perform worse in nonverbal social perception (Mini-PONS) compared to healthy controls (see **Figure 1**), especially when the task requires them to recognize emotional prosody (Mini-PONS voice recordings only and Mini-PONS voice recordings with facial expressions, see **Figure 2**). Second, as expected, in patients with schizophrenia, impaired nonverbal social perception was associated with limited functional capacity (UPSA-brief, see **Figure 4**) and poor functional outcome (SLOF, see **Figure 5**). On the SLOF subscales, poor nonverbal social perception correlated with poor personal care skills, limited activities and impaired work skills (see **Table 4**). Third, nonverbal social perception deficits were not linked to symptom domains (PANSS positive, PANSS negative, PANSS total, BNSS and SNS), with the exception of two BNSS subscales: avolition, blunted affect and one BNSS item: gesture expression (see **Figure 3** and **Table 3**).

The first finding confirms that schizophrenia outpatients have nonverbal social perception deficits, which suggests that they have trouble recognizing nonverbal cues. This finding not only aligns with the well-established finding that patients with schizophrenia display difficulties at detecting emotions from facial expressions (Kohler et al., 2010; Olbert et al., 2013; Barkl et al., 2014), but also corroborates previous studies that used the same measure of nonverbal social perception (Monti and Fingeret, 1987; Bucci et al., 2008; Walther et al., 2016; Pinkham et al., 2017). Particularly, our findings demonstrate that schizophrenia patients have specific difficulties recognizing scenarios including voice recordings, while they

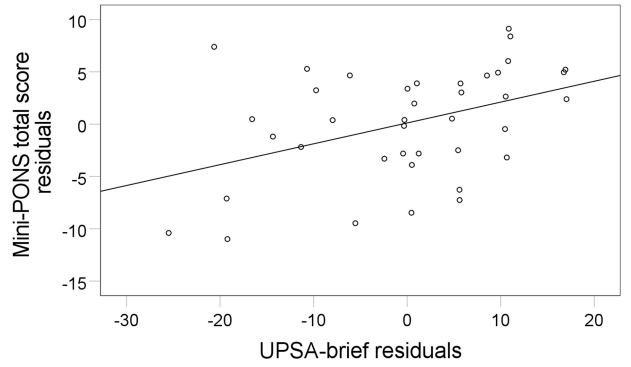


FIGURE 4 | Association between nonverbal social perception and functional capacity. Mini-PONS, mini profile of nonverbal sensitivity; UPSA-brief, University of California San Diego performance-based assessment. To plot the partial correlation between Mini- PONS total score and UPSA-brief whilst controlling for medication ($r = 0.42$, $p = 0.031$), we used Mini-PONS total score residuals and UPSA-brief total score residuals.

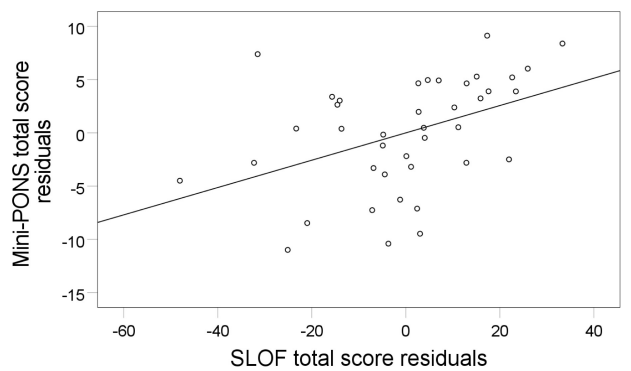


FIGURE 5 | Association between nonverbal social perception and functional outcome. Mini-PONS, mini profile of nonverbal sensitivity; SLOF, specific levels of functioning scale. To plot the partial correlation between Mini-PONS total score and SLOF whilst controlling for medication ($r = 0.41$, $p = 0.031$), we used Mini-PONS total score residuals and SLOF residuals.

performed similarly to controls on other scenarios, i.e., facial expressions only or body movements only. Hence, schizophrenia patients seem to have specific difficulties extracting emotional information from voice recordings, i.e., prosody. This is in contrast to previous papers reporting deficits in all Mini-PONS subscales (Toomey et al., 2002). Our findings also align with studies reporting that schizophrenia patients exhibit deficits in processing bimodal sensory information (Meiselman, 1973; Mussgay and Hertwig, 1990) and impairments in multisensory integration (de Jong et al., 2009; Tseng et al., 2015; Grohn et al., 2022), which suggest that individuals with schizophrenia have difficulties processing sensory signals from different modalities (e.g., visual and auditory modalities) of temporally and/or spatially coincident sources of information. However, in the current report we found schizophrenia patients to exhibit perceptual impairments in both unimodal and bimodal stimulus presentations. Similar to healthy controls, patients' performance improved with bimodal presentation vs. unimodal presentation, however, the group difference remained. Collectively, these findings suggest that bolstering nonverbal information with bimodal stimuli, such as video clips, enhances understanding in patients, who nevertheless perform poorer than healthy controls.

Our second finding confirms and extends previous studies noting nonverbal social perception to be associated with both performance-based functional capacity (UPSA-brief) and observer-rated functional outcome (SLOF). These associations hold true even after controlling for medication dosage (chlorpromazine equivalent doses – mg/day) and correcting for multiple comparisons (FDR). While earlier studies also reported poor nonverbal social perception to be correlated with low functional outcomes in schizophrenia patients (Green and Horan, 2010; Walther et al., 2016; Pinkham et al., 2017), the present study extends these findings by exploring the correlations in distinct functional domains and functional capacity. Impaired personal care skills, limited activities and reduced work skills were correlated with impaired nonverbal social perception, while reduced physical functioning, interpersonal relationships and social acceptability were not.

Previous studies failed to find a significant correlation between nonverbal social perception deficits and symptoms (Toomey et al., 2002; Giannitelli et al., 2015; Walther et al., 2016). However, we have found that some negative symptom domains correlate significantly with these deficits, while others do not. The absence of correlation between nonverbal social perception deficits and symptoms may suggest that nonverbal social perception impairment is a core feature of schizophrenia, independent of current symptom severity, duration of illness and medication. This finding calls for further investigation linking nonverbal social perception with distinct symptoms domains. We extend previous reports by exploring associations within negative symptom domains. Here, we found that nonverbal social perception deficits correlated with some negative symptom domains (avolition, blunted affect), but not with others (anhedonia, asociality, alogia). Furthermore, the BNSS gesture expression item strongly correlated with nonverbal social perception, suggesting that patients rarely using gestures themselves also have difficulties understanding nonverbal social cues of their encounters. A related concept is the (dis-)embodiment perspective (Stanghellini, 2009; Walther et al., 2014; Tschacher et al., 2017), which implies that the relationship between cognitive-emotional processes and the body is altered in schizophrenia patients. Moreover, the finding of the current study corroborates previous reports of a generalized nonverbal communication deficit in schizophrenia (including gesture perception and production) (Walther et al., 2015, 2020b). Considering that gesture performance is highly correlated with functional outcome in schizophrenia (Walther et al., 2016), future work should test interventions alleviating nonverbal communication deficits in schizophrenia.

The strengths of our study are a homogeneous patient sample, a comprehensive assessment of nonverbal social perception, the focus on multiple domains of functional outcome and functional capacity. At the same time, our study is limited by the selection of stable, chronic outpatients, therefore, our

results cannot be generalized to all patients with schizophrenia. Another limitation might be the absence of comprehensive neurocognitive assessments as cognitive deficits may have an effect on nonverbal social perception. We attempted to address this potential limitation by controlling for working memory in our main analyses. Furthermore, medication might also have an effect on our findings; however, we tried to tackle this problem by correcting for current medication dosage. Moreover, the Mini-PONS is only one of several potential tests of nonverbal social perception in schizophrenia and it takes some time to complete, but it offers sufficient internal consistency and retest-reliability (Pinkham et al., 2017). The assessment of the functional outcomes does not integrate information provided by caregivers or other informants (Harvey et al., 2019). However, we included the objective performance-based measure UPSA-brief to increase the reliability of our functional assessments. Finally, this cross-sectional study does not allow for inferences about causality. These issues will be addressed, once the interventional study is completed.

Future studies should determine whether specific interventions will alleviate nonverbal social perception deficits. Reducing nonverbal social perception deficits is considered to be important to improve social and community functioning in schizophrenia (Walther et al., 2016; Pinkham et al., 2017). Recently, studies using cognitive social remediation therapy (Kurtz and Richardson, 2012; Muller et al., 2014; Mueller and Roder, 2017; Bin Kitoko et al., 2020; Vita et al., 2021), non-invasive brain stimulation (Mehta et al., 2014; Walther et al., 2020a), as well as, virtual reality (Rus-Calafell et al., 2014; Torregrossa et al., 2018; Pavlidou and Walther, 2021) all show promising results in alleviating some of the social deficits schizophrenia patients' experience. This holds true for the reduction of symptom severity and improvement of emotional processing, theory of mind, social functioning, as well as interpretation and use of nonverbal social cues (i.e., gesture performance).

CONCLUSION

Schizophrenia outpatients exhibit nonverbal social perception deficits, which are linked to their ability to function in everyday life. Nonverbal social perception deficits are associated with some negative symptoms (avolition, blunted affect, and item gesture expression) and with multiple functional domains (impaired personal care skills, activities and work skills). These findings suggest that the difficulty to decode nonverbal cues in schizophrenia patients is key to function in daily life. Future studies should investigate whether interventions designed to improve nonverbal social perception deficits could alleviate negative symptoms and improve overall 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 Kantonale Ethikkommission Bern (KEK). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VC recruited participants, conducted assessments, analyzed the data and drafted the manuscript. AP supervised and contributed to the statistical analyses. LM carried out clinical assessments. SK recruited participants and conducted assessments. SW designed the study, obtained funding, wrote the protocol, and supervised assessments. All authors discussed the findings and critically revised the manuscript.

FUNDING

Swiss National Science Foundation (grant #184717 to SW) funded this study.

ACKNOWLEDGMENTS

We thank Daniel Baumann Gama and Danai Alexaki for assisting with some of the clinical assessments.

REFERENCES

Abram, S. V., Karpouzian, T. M., Reilly, J. L., Derntl, B., Habel, U., and Smith, M. J. (2014). Accurate perception of negative emotions predicts functional capacity in schizophrenia. *Psychiatry Res.* 216, 6–11. doi: 10.1016/j.psychres.2014.01.032

Adolphs, R. (2009). The social brain: neural basis of social knowledge. *Annu Rev. Psychol.* 60, 693–716. doi: 10.1146/annurev.psych.60.110707.163514

Banziger, T., Scherer, K. R., Hall, J. A., and Rosenthal, R. (2011). Introducing the minipons: a short multichannel version of the profile of nonverbal sensitivity (PONS). *J. Nonverbal Behav.* 35, 189–204. doi: 10.1007/s10919-011-0108-3

Barkl, S. J., Lah, S., Starling, J., Hainsworth, C., Harris, A. W. F., and Williams, L. M. (2014). Facial emotion identification in early-onset psychosis. *Schizophrenia Res.* 160, 150–156. doi: 10.1016/j.schres.2014.10.035

Bin Kitoko, G. M., Maurage, P., Miezi, S. M. M., Gillain, B., Kiswanga, A. P., and Constant, E. (2020). Inter-individual variability of social perception and social knowledge impairments among patients with schizophrenia. *Psychiatry Res.* 290:112951. doi: 10.1016/j.psychres.2020.112951

Borod, J. C., Welkowitz, J., Alpert, M., Brozgold, A. Z., Martin, C., Peselow, E., et al. (1990). Parameters of emotional processing in neuropsychiatric disorders - conceptual issues and a battery of tests. *J. Commun. Dis.* 23, 247–271. doi: 10.1016/0021-9924(90)90003-h

Brekke, J., Kay, D. D., Lee, K. S., and Green, M. F. (2005). Biosocial pathways to functional outcome in schizophrenia. *Schizophr. Res.* 80, 213–225. doi: 10.1016/j.schres.2005.07.008

Bucci, S., Startup, M., Wynn, P., Baker, A., and Lewin, T. J. (2008). Referential delusions of communication and interpretations of gestures. *Psychiatry Res.* 158, 27–34. doi: 10.1016/j.psychres.2007.07.004

Colussy, S. A., and Zuroff, D. C. (1985). Schizophrenic and depressed inpatients perceptions of congruent and incongruent communications. *J. Clin. Psychol.* 41, 331–337. doi: 10.1002/1097-4679(198505)41:3<331::aid-jclp2270410305>3.0.co;2-s

Couture, S. M., Penn, D. L., and Roberts, D. L. (2006). The functional significance of social cognition in schizophrenia: a review. *Schizophr. Bull.* 32, S44–S63.

Cutting, J. (1981). Judgment of emotional expression in schizophrenics. *Br. J. Psychiatry* 139, 1–6. doi: 10.1192/bjp.139.1.1

de Jong, J. J., Hodiamont, P. P., Van Den Stock, J., and De Gelder, B. (2009). Audiovisual emotion recognition in schizophrenia: reduced integration of facial and vocal affect. *Schizophr. Res.* 107, 286–293. doi: 10.1016/j.schres.2008.10.001

Dollfus, S., Mach, C., and Morello, R. (2016). Self-evaluation of negative symptoms: a novel tool to assess negative symptoms. *Schizophr. Bull.* 42, 571–578. doi: 10.1093/schbul/sbv161

Edwards, J., Jackson, H. J., and Pattison, P. E. (2002). Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review (vol 22, pg 789, 2002). *Clin. Psychol. Rev.* 22, 1267–1285. doi: 10.1016/s0272-7358(02)00130-7

Engelstad, K. N., Sundet, K. S., Andreassen, O. A., and Vaskinn, A. (2017). Body language reading of emotion in schizophrenia: associations with symptoms and functional outcome. *Scand. J. Psychol.* 58, 359–366. doi: 10.1111/sjop.12381

Fornells-Ambrojo, M., and Garety, P. A. (2009). Understanding attributional biases, emotions and self-esteem in 'poor me' paranoia: findings from an early psychosis sample. *Br. J. Clin. Psychol.* 48, 141–162. doi: 10.1348/014466508X377135

Frith, C. D., and Corcoran, R. (1996). Exploring 'theory of mind' in people with schizophrenia. *Psychol. Med.* 26, 521–530. doi: 10.1017/s0033291700035601

Frith, C. D., and Frith, U. (2007). Social cognition in humans. *Curr. Biol.* 17, R724–R732.

Galderisi, S., Rucci, P., Mucci, A., Rossi, A., Rocca, P., Bertolino, A., et al. (2020). 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* 19, 81–91. doi: 10.1002/wps.20700

Giannitelli, M., Xavier, J., Francois, A., Bodeau, N., Laurent, C., Cohen, D., et al. (2015). Facial, vocal and cross-modal emotion processing in early-onset schizophrenia spectrum disorder (vol 168, pg 252, 2015). *Schizophr. Res.* 169, 508–508. doi: 10.1016/j.schres.2015.07.039

Goldin-Meadow, S., and Alibali, M. W. (2013). Gesture's role in Speaking, learning, and creating language. *Ann. Rev. Psychol.* 64, 257–283. doi: 10.1146/annurev-psych-113011-143802

Goldsmith, J. B., and McFall, R. M. (1975). Development and evaluation of an interpersonal skill-training program for psychiatric inpatients. *J. Abnorm Psychol.* 84, 51–58. doi: 10.1037/h0076264

Green, M. F., and Horan, W. P. (2010). Social cognition in schizophrenia. *Curr. Direct. Psychol. Sci.* 19, 243–248.

Green, M. F., Horan, W. P., and Lee, J. (2015). Social cognition in schizophrenia. *Nat. Rev. Neurosci.* 16, 620–631.

Green, M. F., Horan, W. P., and Lee, J. (2019). Nonsocial and social cognition in schizophrenia: current evidence and future directions. *World Psychiatry* 18, 146–161. doi: 10.1002/wps.20624

Green, M. F., Olivier, B., Crawley, J. N., Penn, D. L., and Silverstein, S. (2005). Social cognition in schizophrenia: recommendations from the measurement and treatment research to improve cognition in schizophrenia new approaches conference. *Schizophr. Bull.* 31, 882–887. doi: 10.1093/schbul/sbi049

Green, M. F., Penn, D. L., Bentall, R., Carpenter, W. T., Gaebel, W., Gur, R. C., et al. (2008a). Social cognition in schizophrenia: an NIMH workshop on definitions, assessment, and research opportunities. *Schizophr. Bull.* 34, 1211–1220. doi: 10.1093/schbul/sbm145

Green, M. J., Waldron, J. H., Simpson, I., and Coltheart, M. (2008b). Visual processing of social context during mental state perception in schizophrenia. *J. Psychiatry Neurosci.* 33, 34–42.

Greig, T. C., Bryson, G. J., and Bell, M. D. (2004). Theory of mind performance in schizophrenia: diagnostic, symptom, and neuropsychological correlates. *J. Nerv. Ment. Dis.* 192, 12–18. doi: 10.1097/01.nmd.0000105995.67947.fc

Grohn, C., Norgren, E., and Eriksson, L. (2022). A systematic review of the neural correlates of multisensory integration in schizophrenia. *Schizophr. Res. Cogn.* 27:100219. doi: 10.1016/j.scog.2021.100219

Gupta, T., Osborne, K. J., and Mittal, V. A. (2021). Abnormal gesture perception and clinical high-risk for psychosis. *Schizophr. Bull.* 47, 938–947. doi: 10.1093/schbul/sbab056

Harvey, P. D., Deckler, E., Jones, M. T., Jarskog, L. F., Penn, D. L., and Pinkham, A. E. (2019). Autism symptoms, depression, and active social avoidance in schizophrenia: association with self-reports and informant assessments of everyday functioning. *J. Psychiatr. Res.* 115, 36–42. doi: 10.1016/j.jpsychires.2019.05.010

Healey, K. M., Bartholomeusz, C. F., and Penn, D. L. (2016). Deficits in social cognition in first episode psychosis: a review of the literature. *Clin. Psychol. Rev.* 50, 108–137. doi: 10.1016/j.cpr.2016.10.001

Hooker, C., and Park, S. (2002). Emotion processing and its relationship to social functioning in schizophrenia patients. *Psychiatry Res.* 112, 41–50. doi: 10.1016/s0165-1781(02)00177-4

Jahshan, C., Cadenhead, K. S., Rissling, A. J., Kirihara, K., Braff, D. L., and Light, G. A. (2012). Automatic sensory information processing abnormalities across the illness course of schizophrenia. *Psychol. Med.* 42, 85–97. doi: 10.1017/S0033291711001061

Kay, S. R., Fiszbein, A., and Opler, L. A. (1987). The positive and negative syndrome scale (panss) for schizophrenia. *Schizophr. Bull.* 13, 261–276.

Kohler, C. G., Walker, J. B., Martin, E. A., Healey, K. M., and Moberg, P. J. (2010). Facial emotion perception in schizophrenia: a meta-analytic review. *Schizophr. Bull.* 36, 1009–1019.

Kurtz, M. M., and Richardson, C. L. (2012). Social cognitive training for schizophrenia: a meta-analytic investigation of controlled research. *Schizophr. Bull.* 38, 1092–1104. doi: 10.1093/schbul/sbr036

Mancuso, F., Horan, W. P., Kern, R. S., and Green, M. F. (2011). Social cognition in psychosis: multidimensional structure, clinical correlates, and relationship with functional outcome. *Schizophr. Res.* 125, 143–151. doi: 10.1016/j.schres.2010.11.007

Matthews, N., Gold, B. J., Sekuler, R., and Park, S. (2013). Gesture imitation in schizophrenia. *Schizophr. Bull.* 39, 94–101. doi: 10.1093/schbul/sbr062

Mcglashan, T. H. (1986). The prediction of outcome in chronic-schizophrenia .4. the chestnut-lodge follow-up-study. *Arch. General Psychiatry* 43, 167–176. doi: 10.1001/archpsyc.1986.01800020077010

McGrath, J., Saha, S., Chant, D., and Welham, J. (2008). Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol. Rev.* 30, 67–76. doi: 10.1093/epirev/mxn001

McIntosh, L. G., and Park, S. (2014). Social trait judgment and affect recognition from static faces and video vignettes in schizophrenia. *Schizophr. Res.* 158, 170–175. doi: 10.1016/j.schres.2014.06.026

Mehta, U. M., Thirthalli, J., Basavaraju, R., and Gangadhar, B. N. (2014). Association of intracortical inhibition with social cognition deficits in schizophrenia: findings from a transcranial magnetic stimulation study. *Schizophr. Res.* 158, 146–150. doi: 10.1016/j.schres.2014.06.043

Meiselman, K. C. (1973). Broadening dual modality cue utilization in chronic nonparanoid schizophrenics. *J. Consul. Clin. Psychol.* 41, 447–453. doi: 10.1037/h0035360

Millman, Z. B., Goss, J., Schiffman, J., Mejias, J., Gupta, T., and Mittal, V. A. (2014). Mismatch and lexical retrieval gestures are associated with visual information processing, verbal production, and symptomatology in youth at high risk for psychosis. *Schizophr. Res.* 158, 64–68. doi: 10.1016/j.schres.2014.06.007

Monti, P. M., and Fingeret, A. L. (1987). Social-perception and communication-skills among schizophrenics and nonschizophrenics. *J. Clin. Psychol.* 43, 197–205. doi: 10.1002/1097-4679(198703)43:2<197::aid-jclp2270430206>3.0.co;2-1

Morrison, R. L., and Bellack, A. S. (1981). The role of social-perception in social skill. *Behav. Ther.* 12, 69–79. doi: 10.1016/s0005-7894(81)80107-4

Morrison, R. L., Bellack, A. S., and Bashore, T. R. (1988). Perception of emotion among schizophrenic-patients. *J. Psychopathol. Behav. Assess.* 10, 319–332. doi: 10.1007/bf00960625

Mueller, D., and Roder, V. (2017). Does cognitive remediation therapy prevent relapses in stabilized schizophrenia outpatients? a 1-year rct follow-up study. *Schizophr. Bull.* 43, S53–S54.

Muller, D. R., Benzing, V. J., and Roder, V. (2014). Effectiveness of integrated cognitive remediation therapy for schizophrenia outpatients: early versus long-term course of illness - results from an international rct. *Schizophr. Res.* 153, S117–S117.

Murphy, D., and Cutting, J. (1990). Prosodic comprehension and expression in schizophrenia. *J. Neurol. Neurosurg. Psychiatry* 53, 727–730. doi: 10.1136/jnnp.53.9.727

Mussgay, L., and Hertwig, R. (1990). Signal-detection indexes in schizophrenics on a visual, auditory, and bimodal continuous performance-test. *Schizophr. Res.* 3, 303–310. doi: 10.1016/0920-9964(90)90014-x

Olbert, C. M., Penn, D. L., Kern, R. S., Lee, J., Horan, W. P., Reise, S. P., et al. (2013). Adapting social neuroscience measures for schizophrenia clinical trials, part 3: fathoming external validity. *Schizophr. Bull.* 39, 1211–1218. doi: 10.1093/schbul/sbt130

Patterson, T. L., Goldman, S., Mckibbin, C. L., Hughs, T., and Jeste, D. V. (2001). UCSD performance-based skills assessment: development of a new measure of everyday functioning for severely mentally ill adults. *Schizophr. Bull.* 27, 235–245. doi: 10.1093/oxfordjournals.schbul.a006870

Pavlidou, A., and Walther, S. (2021). Using virtual reality as a tool in the rehabilitation of movement abnormalities in schizophrenia. *Front. Psychol.* 11:607312. doi: 10.3389/fpsyg.2020.607312

Penn, D. L., Ritchie, M., Francis, J., Combs, D., and Martin, J. (2002). Social perception in schizophrenia: the role of context. *Psychiatry Res.* 109, 149–159. doi: 10.1016/s0165-1781(02)00004-5

Pinkham, A., Penn, D., and Harvey, P. (2017). Social cognition psychometric evaluation (scope): results: of the final validation study. *Schizophr. Bull.* 43, S224–S225. doi: 10.1093/schbul/sbx117

Pinkham, A. E., Penn, D. L., Green, M. F., Buck, B., Healey, K., and Harvey, P. D. (2014). The social cognition psychometric evaluation study: results of the expert survey and RAND panel. *Schizophr. Bull.* 40, 813–823. doi: 10.1093/schbul/sbt081

Pollard, V. B., Hellewell, J. S. E., and Deakin, J. F. W. (1995). Performance of schizophrenic subjects on tests of recognition memory, perception and face processing. *Schizophr. Res.* 15, 122–122.

Riveros, R., Hurtado, E., Escobar, M., Ibanez, A., Manes, F., Cetkovich, M., et al. (2010). Context-sensitive social cognition is impaired in schizophrenic patients and their healthy relatives. *Schizophr. Res.* 116, 297–298. doi: 10.1016/j.schres.2009.10.017

Rosenthal, H. (1980). Verdi 'aroldo' + Caballe,M, Busching,M, Cecchele,G, Manno,V, Rogers,P, Juan Pons,J, Lebherz,L, opera-orchestra-of-New-York, oratorio-society-of-New-York, westchester-choral-society, Queler,E - Cbs-79328. *Opera* 31, 1014–1015.

Rus-Calafell, M., Gutierrez-Maldonado, J., and Ribas-Sabate, J. (2014). A virtual reality-integrated program for improving social skills in patients with schizophrenia: a pilot study. *J. Behav. Ther. Exp. Psychiatry* 45, 81–89. doi: 10.1016/j.jbtep.2013.09.002

Savla, G. N., Vella, L., Armstrong, C. C., Penn, D. L., and Twamley, E. W. (2013). Deficits in domains of social cognition in schizophrenia: a meta-analysis of the empirical evidence. *Schizophr. Bull.* 39, 979–992. doi: 10.1093/schbul/sbs080

Schneider, L. C., and Struening, E. L. (1983). Slof - a behavioral rating-scale for assessing the mentally-Ill. *Soc. Work Res. Abstr.* 19, 9–21. doi: 10.1093/swra/19.3.9

Sergi, M. J., Rassovsky, Y., Nuechterlein, K. H., and Green, M. F. (2006). Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. *Am. J. Psychiatry* 163, 448–454. doi: 10.1176/appi.ajp.163.3.448

Sparks, A., Mcdonald, S., Lino, B., O'donnell, M., and Green, M. J. (2010). Social cognition, empathy and functional outcome in schizophrenia. *Schizophr. Res.* 122, 172–178. doi: 10.1016/j.schres.2010.06.011

Stanghellini, G. (2009). Embodiment and schizophrenia. *World Psychiatry* 8, 56–59. doi: 10.1002/j.2051-5545.2009.tb00212.x

Strauss, G. P., Hong, L. E., Gold, J. M., Buchanan, R. W., Mcmahon, R. P., Keller, W. R., et al. (2012). Factor structure of the brief negative symptom scale. *Schizophr. Res.* 142, 96–98. doi: 10.1016/j.schres.2012.09.007

Toomey, R., Schuldberg, D., Corrigan, P., and Green, M. F. (2002). Nonverbal social perception and symptomatology in schizophrenia. *Schizophr. Res.* 53, 83–91. doi: 10.1016/s0920-9964(01)00177-3

Torregrossa, L., Adery, L. H., Ichinose, M., Nichols, H., Gizdic, A., Wade, J., et al. (2018). Novel virtual reality social skills training for individuals with schizophrenia. *Schizophr. Bull.* 44, S195–S196.

Tschacher, W., Giersch, A., and Friston, K. (2017). Embodiment and schizophrenia: a review of implications and applications. *Schizophr. Bull.* 43, 745–753. doi: 10.1093/schbul/sbw220

Tseng, H. H., Bossong, M. G., Modinos, G., Chen, K. M., Mcguire, P., and Allen, P. (2015). A systematic review of multisensory cognitive-affective integration in schizophrenia. *Neurosci. Biobehav. Rev.* 55, 444–452. doi: 10.1016/j.neubiorev.2015.04.019

van t'wout, M., Aleman, A., Kessels, R. P. C., Cahn, W., De Haan, E. H. F., and Kahn, R. S. (2007). Exploring the nature of facial affect processing deficits in schizophrenia. *Psychiatry Res.* 150, 227–235. doi: 10.1016/j.psychres.2006.03.010

Vauth, R., Rusch, N., Wirtz, M., and Corrigan, P. W. (2004). Does social cognition influence the relation between neurocognitive deficits and vocational functioning in schizophrenia? *Psychiatry Res.* 128, 155–165. doi: 10.1016/j.psychres.2004.05.018

Vita, A., Barlati, S., Ceraso, A., Nibbio, G., Ariu, C., Deste, G., et al. (2021). Effectiveness, core elements, and moderators of response of cognitive remediation for schizophrenia a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* 78, 848–858. doi: 10.1001/jamapsychiatry.2021.0620

Walther, S., Eisenhardt, S., Bohlhalter, S., Vanbellingen, T., Muri, R., Strik, W., et al. (2016). Gesture performance in schizophrenia predicts functional outcome after 6 months. *Schizophr. Bull.* 42, 1326–1333. doi: 10.1093/schbul/sbw124

Walther, S., Mittal, V. A., Stegmayer, K., and Bohlhalter, S. (2020b). Gesture deficits and apraxia in schizophrenia. *Cortex* 133, 65–75. doi: 10.1016/j.cortex.2020.09.017

Walther, S., Kunz, M., Muller, M., Zurcher, C., Vladimirova, I., Bachofner, H., et al. (2020a). Single session transcranial magnetic stimulation ameliorates hand gesture deficits in schizophrenia. *Schizophr. Bull.* 46, 286–293. doi: 10.1093/schbul/sbz078

Walther, S., Ramseyer, F., Horn, H., Strik, W., and Tschacher, W. (2014). Less structured movement patterns predict severity of positive syndrome, excitement, and disorganization. *Schizophr. Bull.* 40, 585–591. doi: 10.1093/schbul/sbt038

Walther, S., Stegmayer, K., Sulzbacher, J., Vanbellingen, T., Muri, R., Strik, W., et al. (2015). Nonverbal social communication and gesture control in schizophrenia. *Schizophr. Bull.* 41, 338–345. doi: 10.1093/schbul/sbu222

Wastler, H. M., and Lenzenweger, M. F. (2018). Cone of gaze in positive schizotypy: relationship to referential thinking and social functioning. *Personal. Dis. Theory Res. Treat.* 9, 324–332. doi: 10.1037/per0000258

White, T. P., Borgan, F., Ralley, O., and Shergill, S. S. (2016). You looking at me? Interpreting social cues in schizophrenia. *Psychol. Med.* 46, 149–160. doi: 10.1017/S0033291715001622

Conflict of Interest: SW received honoraria from Janssen, Lundbeck, Mepha, Neurolite, and Sunovion.

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 Psychology

ORIGINAL RESEARCH
published: 24 February 2022
doi: 10.3389/fpsyg.2022.804178

Empathy, Emotion Recognition, and Paranoia in the General Population

Kendall Beals[1], Sarah H. Sperry[2] and Julia M. Sheffield[1]*

[1] Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN, United States, [2] Michigan Medicine, University of Michigan, Ann Arbor, MI, United States

Background: Paranoia is associated with a multitude of social cognitive deficits, observed in both clinical and subclinical populations. Empathy is significantly and broadly impaired in schizophrenia, yet its relationship with subclinical paranoia is poorly understood. Furthermore, deficits in emotion recognition – a very early component of empathic processing – are present in both clinical and subclinical paranoia. Deficits in emotion recognition may therefore underlie relationships between paranoia and empathic processing. The current investigation aims to add to the literature on social cognition and paranoia by: (1) characterizing the relationship between paranoia and empathy, and (2) testing whether there is an indirect effect of emotion recognition on the relationship between empathy and paranoia.

Methods: Paranoia, empathy, and emotion recognition were assessed in a non-clinical sample of adults (n = 226) from the Nathan Kline Institute-Rockland (NKI-Rockland) dataset. Paranoia was measured using the Peters Delusions Inventory-21 (PDI-21). Empathy was measured using the Interpersonal Reactivity Index (IRI), a self-report instrument designed to assess empathy using four subscales: Personal Distress, Empathic Concern, Perspective Taking, and Fantasy. Emotion recognition was assessed using the Penn Emotion Recognition Test (ER-40). Structural equation modeling (SEM) was used to estimate relationships between paranoia, the four measures of empathy and emotion recognition.

Results: Paranoia was associated with the Fantasy subscale of the IRI, such that higher Fantasy was associated with more severe paranoia ($p < 0.001$). No other empathy subscales were associated with paranoia. Fantasy was also associated with the emotion recognition of fear, such that higher Fantasy was correlated with better recognition of fear ($p = 0.008$). Paranoia and emotion recognition were not significantly associated. The Empathic Concern subscale was negatively associated with emotion recognition, with higher empathic concern related to worse overall emotion recognition ($p = 0.002$). All indirect paths through emotion recognition were non-significant.

Discussion: These results suggest that imaginative perspective-taking contributes to paranoia in the general population. These data do not, however, point to robust global

OPEN ACCESS

Edited by:
Alberto Parola,
Aarhus University, Denmark

Reviewed by:
Kyle Minor,
Indiana University–Purdue University Indianapolis, United States
Silvia Corbera,
Central Connecticut State University, United States

****Correspondence:***
Kendall Beals
kendall.m.beals@vumc.org

Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: *28 October 2021*
Accepted: *28 January 2022*
Published: *24 February 2022*

Citation:
Beals K, Sperry SH and Sheffield JM (2022) Empathy, Emotion Recognition, and Paranoia in the General Population. Front. Psychol. 13:804178. doi: 10.3389/fpsyg.2022.804178

relationships between empathy and paranoia or to emotion recognition as an underlying mechanism. Deficits in empathy and emotion recognition observed in schizophrenia may be associated with the broader pathology of schizophrenia, and therefore not detectable with subclinical populations.

Keywords: paranoia, emotion recognition (ER), empathy, structural equation modeling (SEM), interpersonal reactivity index (IRI)

INTRODUCTION

Paranoia is one of the most common psychotic experiences, occurring in over 70% of individuals presenting with their first episode of psychosis (Coid et al., 2013) and 10–15% of the general population (Freeman and Freeman, 2008). Models of paranoia suggest that social cognitive abnormalities contribute to paranoid thinking by creating an information-processing bias (Locascio and Snyder, 1975; Freeman et al., 2002), leading to misinterpretation of others' emotions and intentions, fueling mistrust. Social cognition is comprised of multiple domains including emotion processing, social perception, theory of mind, attributional bias, and empathy (Decety and Svetlova, 2012; Pinkham, 2014). Evidence suggests that theory of mind, attributional bias, emotion processing and social perception are all associated with paranoid thinking (McKay et al., 2005; Combs et al., 2006), and these relationships are observed across clinical and non-clinical populations (Martin and Penn, 2001; Freeman et al., 2002; Combs et al., 2013). Given that both paranoid thinking and social cognitive deficits contribute to functional impairment (Minkowski, 1953; Shamay-Tsoory et al., 2007; Sparks et al., 2010; Pinkham et al., 2016; Bonfils et al., 2017), fully elucidating how different facets of social cognition relate to paranoia is critical for advancing models of and ultimately treatments for paranoia.

In schizophrenia, social cognitive deficits have been largely described in relationship to negative symptoms and deficits in social functioning (Green et al., 2019), with evidence that social cognition and negative symptoms predict social competence and social outcomes (Kalin et al., 2015) and are related to social cognitive processes, including empathy (Wang et al., 2021). Yet, as noted, social cognition is also relevant for "positive" psychotic experiences (Bliksted et al., 2017; Peyroux et al., 2019), including paranoid thinking (Green and Leitman, 2007). One robust relationship between paranoia and social cognition is via misinterpretation of social cues (Trotta et al., 2021). Individuals with heightened paranoia show evidence of misinterpreting ambiguous information more negatively (Bentall et al., 2009; Savulich et al., 2015), which may be shaped by negative prior beliefs about the intentions of others (Wellstein et al., 2020). Importantly, recent meta-analysis has shown that the relationship between paranoia and misinterpretation of ambiguous cues (including emotional cues) is present in both clinical and non-clinical populations, with more severe paranoia being related to worse interpretation bias (Trotta et al., 2021). This suggests that these experiences exist on a continuum across clinical and non-clinical populations. This evidence of a continuum of social cognition and paranoia, in addition to the impact of negative symptoms on social cognition, highlight the utility of examining relationships between social cognition and paranoia in a general population sample that is less impacted by co-occurring experiences of schizophrenia (e.g., negative symptoms and cognitive impairment).

Despite prior relationships between interpretation bias and paranoia, as well as other aspects of social cognition (e.g., theory of mind and social perception), there is a dearth of research examining associations between paranoia and empathy (Buck et al., 2017; Lee, 2017; Herms et al., 2022). Empathy may be a particularly important aspect of social cognition for understanding paranoia, because successful social interactions require the capacity for interpreting emotional states, beliefs, and motivations of others (Rochat and Striano, 1999; Decety and Meyer, 2008). Empathy is a multifaceted construct that involves both cognitive and affective components (Baron-Cohen and Wheelwright, 2004; Blair, 2005). Cognitive empathy involves a set of reflective processes that include perspective taking and distinguishing another's feelings from one's own, whereas affective empathy is a more automatic set of processes through which perceived social cues trigger an emotional response in oneself that is shared with an observed person (Michaels et al., 2014). In schizophrenia, both types of empathy are impaired (Bonfils et al., 2017) while those in the ultra-high risk phase of psychosis show impaired cognitive empathy (Jan Kuis et al., 2021). Studies have also found that heightened engagement with imaginative, perceptual, and ideational resources predicts delusional ideation in the general population (Tellegen and Atkinson, 1974; Humpston et al., 2016; Murphy et al., 2018). Whether distinct facets of empathy are differentially associated with paranoia has not been previously investigated.

Both cognitive and affective empathy depend, at least in part, on the ability to accurately recognize emotional expression. The ability to recognize basic facial expressions develops very early in life (Field et al., 1982), is universal across cultures (Ekman and Friesen, 1971) and is acquired in closely related animal species (Darwin, 1872). Emotion recognition is an early facet of the empathetic process and reflects a more intrinsic, biological aspect of social cognition (Besel and Yuille, 2010). Research investigating the relationship between empathy and emotion recognition has found that people with high levels of empathy are more sensitive to subliminally presented emotional face stimuli (Martin et al., 1996) and rated angry faces as expressing more anger and happy faces as being happier than people with low empathy (Dimberg et al., 2011). In individuals with polygenic risk for schizophrenia, emotion recognition deficits are evident by mid childhood and are related to severity of psychotic experiences (Germine et al., 2016). Research has also demonstrated that

paranoid patients show worse emotion recognition ability than non-paranoid patients (An et al., 2006; Russell et al., 2007; Williams et al., 2007), possibly due to a tendency for paranoid patients to inaccurately recognize neutral facial expressions as angry (Pinkham et al., 2011). Some research points to empathy being a factor in one's ability to accurately recognize facial expressions (Besel and Yuille, 2010; Wai and Tiliopoulos, 2012). Although emotion recognition ability contributes to empathy, and is impaired in paranoid patients, the unique and shared contribution of these social cognitive domains to paranoia has not been studied directly.

The current study aims to examine the relationship between paranoia, empathy, and emotion recognition in a large sample of individuals from the general population. Given previous findings that impaired social cognitive ability is related to worse paranoia in both clinical and non-clinical samples, and that emotion recognition is important for empathic ability, we hypothesized the following: (1) that greater deficits in empathic abilities and emotion identification would be related to more severe paranoid thinking, and (2) that there would be a significant indirect effect of emotion identification on the relationship between empathy and paranoia. As prior work on empathy and paranoia is sparse, we did not have strong predictions about the type of empathy that would be most related to paranoia, and hoped instead to address this knowledge gap.

MATERIALS AND METHODS

Participants

Participants were drawn from the Nathan Kline Institute-Rockland study (NKI-Rockland) a large (>1,000 individuals) community-ascertained sample representative of the broader United States population (age 6–85) based on the 2010 census (Nooner et al., 2012). From the total cohort, 226 adult participants (age 18–65) were identified who completed measures of paranoid thinking, empathy, and emotion recognition (described below) within a 5-day period (M_{age} = 38.64, SD_{age} = 15.91; 58.4% self-identified as female, 41.6% male; 64.6% White, 20.8% Black/African American, 14.6% Asian/Native Hawaiian/American Indian/Other Race).

Procedures

The NKI Rockland Sample was collected in a multi-phase National Institute of Mental Health (NIMH) funded study. Phase one collected psychiatric, behavioral, and cognitive data from 250 convenience sampled individuals from 4 to 89 years old. The second phase aimed to collect data from 1,000 participants from 6 to 85 years old who reflect the demographics of the 2009 United States census (Nooner et al., 2012). For each study visit, participants fill out self-report questionnaires (including the PDI-21 and IRI) at home within 28 days of the in-person study day. The baseline visit included 2 days of study related tasks including neuropsychological testing, neuroimaging, and behavioral tasks. A full overview of participant protocols can be found here: http://fcon_1000.projects.nitrc.org/indi/enhanced/ALGFullEndUserProtocol.pdf. The first and second phase were approved by the Institutional Review Board (Nathan Kline Institute Phase I #226781 and Phase II #239708; Montclair State University Phase I #000983A and Phase II #000983B) and participants were paid up to $200 for the baseline 2-day study or $250 if that baseline included an MRI.

Measures

Mean, standard deviation, range, and Cronbach's alpha are presented in **Table 1**.

Peters Delusions Inventory-21 Item

The Peters Delusions Inventory (PDI) is a self-report measure that assesses delusional thinking in the general population and has shown acceptable reliability and validity (Peters et al., 2004). The PDI measures a variety of delusional beliefs by asking participants whether or not they relate to different statements (e.g., "Do you ever feel as if you are being persecuted in some way?", "Do you ever feel as if there is a conspiracy against you?"). If they state "yes" then participants are asked to score the amount of distress, preoccupation, and conviction they experience on a scale of one to five. Prior factor analysis of the PDI-21 has identified four items that are associated with paranoid thinking (Verdoux et al., 1998; López-Ilundain et al., 2006). Scores for each of the four paranoia items were summed to determine a measure of paranoid thinking as previously reported (Preti et al., 2007; Sheffield et al., 2021). Total scores ranged from 0 to 64.

Interpersonal Reactivity Index

The Interpersonal Reactivity Index (IRI) is a well-validated 28-item self-report scale measuring empathy (Davis, 1980, 1983). The IRI is comprised of four scales: Fantasy (ability to put oneself into fictional situations and take the perspective of fictitious characters), Empathic Concern ("other-oriented" feelings of sympathy and concern for others), Perspective Taking (ability to adopt the psychological viewpoint of others), and Personal Distress ("self-oriented" feelings of personal distress in interpersonal settings). Each subscale was calculated separately, as recommended (Davis, 1980, 1983; Chrysikou and Thompson, 2016), by summing the seven items in each of the four subscales (Shamay-Tsoory et al., 2007; Bonfils et al., 2017). The Fantasy and Perspective Taking scales reflect cognitive empathy and

TABLE 1 | IRI, PDI, and ER-40 descriptive statistics.

	MEAN (SD)	RANGE	CRONBACH'S ALPHA
PARANOIA	9.51 (9.88)	0–57	0.88
FANTASY	14.27 (6.15)	0–28	0.79
EMPATHIC CONCERN	21.42 (4.3)	12–28	0.70
PERSONAL DISTRESS	11.87 (5.12)	2–29	0.76
PERSPECTIVE TAKING	16.68 (3.66)	5–24	0.66
ER TOTAL	35.17 (2.75)	24–40	
ER FEAR	6.85 (1.32)	2–8	
ER SADNESS	6.67 (1.17)	1–8	
ER ANGER	6.62 (1.12)	3–8	
ER HAPPY	7.96 (0.2)	7–8	
ER NO EMOTION	7.06 (1.26)	0–8	

the Empathic Concern and Personal Distress scales reflect affective empathy.

Example items for Fantasy include "I really get involved with the feelings of the characters in a novel", Empathic Concern includes "I often have tender, concerned feelings for people less fortunate than me," Perspective Taking includes "I try to look at everybody's side of a disagreement before I make a decision" and Personal Distress includes "I sometimes feel helpless when I am in the middle of a very emotional situation."

Davis (1983) explained how the IRI has a hierarchical structure, with each factor mirroring an aspect of the general empathy construct. More recent studies have supported the four-factor model (Cliffordson, 2002; Hawk et al., 2013). Separating the IRI into Cognitive and Affective empathy is known to be unsupported by psychometric analyses (Chrysikou and Thompson, 2016). Therefore, the four subscales were analyzed separately, to examine unique relationships with paranoia and emotion recognition.

Penn Emotion Recognition Test (ER-40)

The Penn Emotion Recognition Test was conducted as part of the Penn Computerized Neurocognitive Battery (Moore et al., 2015). The PEIT measures participants' ability to recognize five emotions (Happy, Sad, Anger, Fear, and No Emotion) and has good test-retest reliability (Weiss et al., 2007). Emotional faces are presented on individuals of both genders and multiple races. A total of 40 photos are presented on a computer screen where participants recognize the type of emotion shown in a forced-choice format. Correct responses are scored as 1 and incorrect as 0 for a maximum score as 40, where a score of 40 indicates better overall facial emotion recognition. Subscales were also calculated for each of the five expressions: Happy recognition, Sad recognition, Anger recognition, Fear recognition, and No Emotion recognition (Gur et al., 2001a,b; Moore et al., 2015).

Statistical Analysis

Relationships between paranoia, emotion recognition, and empathy, were first examined in zero-order correlations using SPSS v.25.0 (IBM Corp. Released, 2017). Next, *a priori* hypotheses were tested using structural equation modeling (SEM), conducted in R (lavaan R 4.0.2 package; Rosseel, 2012). In our *a priori* SEM model, each IRI subscale (exogenous variable) predicted paranoia (endogenous). Paths were also specified from each IRI subscale to overall emotion recognition ability and from emotion recognition ability to paranoia. To test our hypothesis that there would be a relationship between empathy and paranoia through emotion recognition, we estimated an indirect path from empathy (IRI subscales) to emotion recognition ability to paranoia. Our primary model used overall emotion recognition ability. Follow-up sensitivity analyses were conducted to examine whether specific types of emotion recognition (e.g., fear) were related to empathy and paranoia. All analyses included age, sex, and race as covariates. Standard errors were calculated based on 1000 bootstrapped samples. We evaluated model fit using CFI, RMSEA, and SRMR based on Hu and Bentler (1999) criteria.

RESULTS

In this general population sample, mean paranoia was a 9.51 (SD = 9.88; max. 60). For each empathy subscale the maximum score is 35, and participants had a mean score of 14.27 (SD = 6.15) for Fantasy, 21.42 (SD = 4.3) for Empathic Concern, 11.87 (SD = 5.12) for Personal Distress, and 16.68 (SD = 3.66) for Perspective Taking. Emotion recognition has a maximum score of 40 and participants in this sample had a mean score of 35.17 (SD = 2.75).

Zero-Order Correlations

Correlations between all variables are presented in **Table 2**. The Fantasy subscale was significantly positively correlated with paranoia ($p < 0.001$) and fear recognition ($p < 0.001$). Emotion recognition was significantly negatively correlated with Empathic Concern ($p = 0.037$). Paranoia and emotion recognition were not correlated with any other measure.

Structural Equation Model

The main hypothesized model (**Figure 1**) had poor fit (CFI = 0.46, RMSEA = 0.25, SRMR = 0.08) so results should be interpreted with caution. Fantasy was significantly positively associated with paranoia ($p < 0.001$) (**Figure 2A**) and Empathic Concern was significantly negatively associated with overall emotion recognition ability ($p = 0.002$) (**Figure 2B**). Contrary to expectation, there was not a significant indirect path between empathy subscales, emotion recognition, and paranoia.

Sensitivity Analyses

Given the relatively poor model fit of the *a priori* theorized model, we ran several *post hoc* sensitivity analyses to determine whether modeling relationships with specific emotions would better fit our data (**Supplementary Figures 1–4**). First, we examined the paths between Fantasy and paranoia through emotion recognition for each emotion separately (e.g., fear). When considering ability to recognize specific emotions, we found that Fantasy was positively associated with fear emotion recognition ($p = 0.008$) and paranoia ($p < 0.001$), but no significant indirect path (**Figure 3A**) emerged. Of note, this model was oversaturated (CFI = 1.00, RMSEA = 0.00, SRMR = 0.00) indicating that it did not fit the observed data. Next, we tested an exploratory model in which we alternated the order of the endogenous and exogenous variables – fear recognition (exogenous) predicting paranoia (endogenous) through Fantasy. This model was also oversaturated (CFI = 1.0, RMSEA = 0.00, SRMR = 0.00) and showed similar results: fear emotion recognition was positively associated with Fantasy ($p = 0.003$) and Fantasy was positively associated with paranoia ($p < 0.001$) (**Figure 3B**) with no significant indirect path. Please see **Table 3** for all SEM parameters.

DISCUSSION

This study investigated the relationship between empathy, emotion recognition, and paranoia in subclinical populations,

TABLE 2 | Zero-order correlations.

	Perspective taking	Fantasy	Empathic concern	Personal distress	Paranoia	ER total	ER anger	ER fear	ER happy	ER no emotion	ER sad
Perspective taking											
Fantasy	0.20										
Empathic concern	0.42**	0.33**									
Personal distress	−0.07	0.29**	0.14*								
Paranoia	−0.04	0.24**	0.05	0.09							
ER total	0.01	0.09	−0.14*	0.01	0.02						
ER anger	0.02	−0.04	−0.15*	0.01	−0.03	0.57**					
ER fear	−0.07	0.24**	−0.04	0.11	0.11	0.59**	0.12				
ER happy	0.03	0.00	−0.04	−0.07	0.07	0.17*	0.16*	0.08			
ER no emotion	0.01	0.00	−0.07	−0.09	0.04	0.48**	−0.02	0.03	−0.10		
ER sad	0.07	−0.02	−0.06	0.00	−0.10	0.60**	0.25**	0.09	0.10	0.06	

*ER, emotion recognition. **Correlation is significant at the 0.01 level (two-tailed). *Correlation is significant at the 0.05 level (two-tailed).*

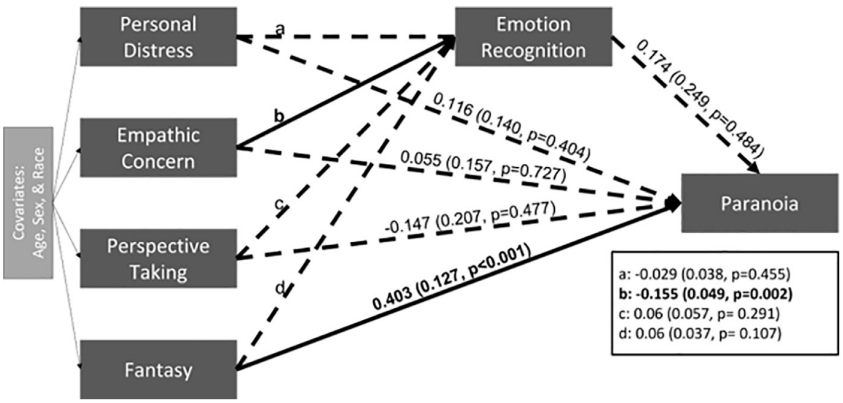


FIGURE 1 | The estimate and standard error are presented for each path. Significant paths are indicated with solid black lines and bolded coefficients. Non-significant pathways are indicated with dashed lines.

considering different types of empathy. Our findings suggest that increased scores on the Fantasy subscale of the IRI are associated with increased paranoia in the general population, but that this relationship is independent of one's overall ability to recognize emotional expressions. In addition, increased scores on Empathic Concern were related to decreased emotion recognition. Interestingly, higher Fantasy scores were significantly associated with both increased paranoia and better fear recognition, and no other facet of empathy showed this effect. Taken together, specific facets of cognitive empathy (Fantasy) are related to paranoia and fear recognition in the general population, but the association between empathy and paranoia does not appear to depend on ability to detect fearful faces.

Fantasy and Paranoia

In this general population dataset, empathic fantasy was positively associated with paranoia, suggesting that individuals who experience more paranoia report a tendency toward empathically relating to fictional characters. Previous studies in schizophrenia that have investigated empathy using the IRI have reported varying levels of disruption in empathic fantasy (Rankin et al., 2005; Sucksmith et al., 2013; Bonfils et al., 2017), with some research demonstrating deficits (Fujiwara et al., 2008; Hooker et al., 2011) while others have shown greater or similar Fantasy scores in schizophrenia as compared to healthy controls (Sparks et al., 2010; McCormick et al., 2012; Matsumoto et al., 2015). Meta-analysis reported slightly reduced Fantasy scores in schizophrenia, with a small effect size (Hedge's $g = 0.19$).

Although the IRI has been thoroughly investigated in patients with schizophrenia, there are fewer studies looking at the IRI and sub-clinical paranoia. In one study, Buck et al. (2017) found that distorted mind perception (perceiving that someone/something possesses a thinking, feeling mind) partially explained the association between paranoia and the perspective taking and empathic concern subscales but found no direct effects. In another study, Lee (2017) found that patients with paranoid personality disorder had diminished perspective taking and increased personal distress, but no differences in Fantasy. Interestingly, although Buck et al. (2017) did not specifically investigate the Fantasy subscale, they do report that paranoia is positively associated with a tendency to perceive mind in dead people, trees, robots and Superman. Mind perception of a character like Superman reflects the person's sense that the fictional character has memories, agency, and ability to feel

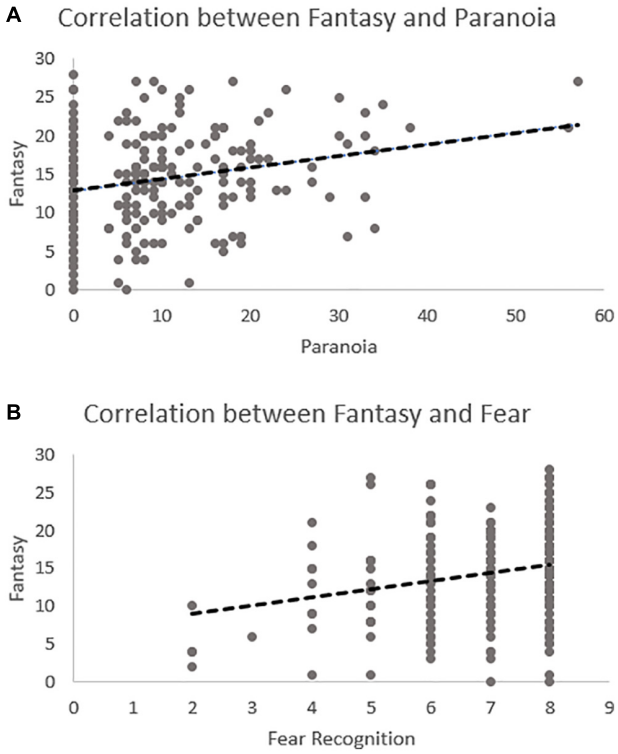


FIGURE 2 | Scatterplots demonstrating the significant relationship in the model between Fantasy and paranoia **(A)** and Fantasy and fear recognition **(B)**.

fear, pleasure and hunger. These findings in a larger sample may bear on our data, suggesting that those with greater tendency toward paranoia experience more empathy toward fictional characters.

Also relevant to our findings is a previous report of a significant relationship between Fantasy scores and delusion severity in individuals with schizophrenia (Sparks et al., 2010). Although Fantasy scores did not differ between patients and controls in this prior analysis, greater Fantasy was strongly related to more severe delusions. In addition, in a study looking at empathy and theory of mind in first-degree relatives of individuals with schizophrenia (i.e., those at elevated genetic risk), it was only the Fantasy subscale of the IRI (not theory of mind or other measures of empathy) that was associated with a history of subclinical delusional ideation, such that greater delusional ideation was related to greater Fantasy scores (Montag et al., 2012).

Our findings therefore add to a growing literature that connects delusional ideation and the Fantasy subscale of the IRI. The relationship between these two measures is somewhat confounding, in part because the Fantasy subscale is, itself, difficult to interpret (Nomura and Akai, 2012). The Fantasy scale measures the individual's tendency to use their imagination in order to take the perspective of a fictional character. Unlike the other IRI subscales, Fantasy is stable across adolescence, suggesting it may function slightly differently than other facets of empathy, which change over time (Davis and Franzoi, 1991). In factor analysis, Fantasy loads with Perspective Taking on a factor of cognitive empathy (Shamay-Tsoory et al., 2007), indicating it may reflect more advanced capabilities similar to theory of mind. In fact, scores on the Fantasy scale have been previously related to verbal measures and intellectual ability (Mayer and Geher, 1996; Montag et al., 2012). Paranoia is a facet of delusional ideation focused on a belief that one is under threat from others (Freeman, 2016). Delusions, including paranoia, are a self-conscious experience that are thought to be born from an unstable boundary between the self, the world, and others (Sass and Parnas, 2003). While speculative, relationships between Fantasy and paranoia may be an unexpected glimpse into this boundary disturbance that can occur in individuals on the delusion spectrum (Feyaerts et al., 2021). Its relationship with paranoia could also be a byproduct of the safety that fictional characters can provide. More paranoid individuals may feel more connected with fictional characters, because they cannot cause them imminent harm and may themselves be persecuted.

Emotion Recognition

Another contribution of the current study is our investigation into role that emotion recognition plays with empathy and paranoia. Both emotion recognition and empathy are critical for healthy social interactions, and impaired social functioning contributes to paranoia (Fiske and Taylor, 2013; Chen, 2014; Wickham et al., 2014). Emotion recognition is a more "basic" ability that supports interaction with the environment, underlying the more complex process of experiencing empathy (Duesenberg et al., 2016). Due to empathy's dependence on recognizing facial emotion, we expected to find an association between the IRI subscales and emotion recognition. After *post hoc* analyses, the only subscales we found to be associated with emotion recognition was the Fantasy subscale and the Empathic Concern subscale. Previous studies linking empathy and emotion recognition have found that emotion recognition capabilities correlate with higher dispositional empathy (Davis and Kraus, 1997; Hall et al., 2009). Soto et al. (1998) found that people who are empathically accurate (better at rating how a stranger feels from moment to moment) are better at identifying positive and negative emotions. Papers that have looked specifically at the IRI and ER-40 measures generally found increased emotion recognition in relationship to higher empathy (Martin et al., 1996; Gery et al., 2009).

In our study, emotion recognition was associated with both Fantasy and Empathic Concern, however, there was not an indirect relationship between these facets of empathy and paranoia through emotion recognition. Interestingly, Fantasy was specifically associated with recognition of the emotion of fear, such that better fear recognition was related to greater empathic fantasy. Expressions of fear are distress cues that can drive feelings of empathy (Panksepp and Panksepp, 2013), and better fear recognition is related to more pro-social behavior (Marsh et al., 2007). Relationships with Fantasy and fear recognition are novel, as prior work linking fear recognition and empathy have looked only at Empathic Concern (Besel and Yuille, 2010). Unlike

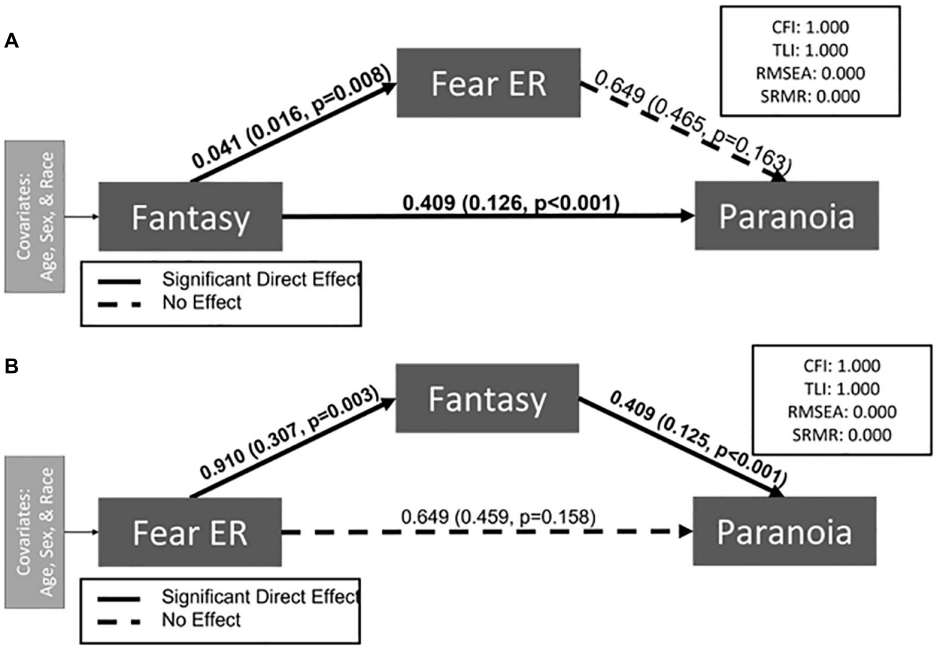


FIGURE 3 | Exploratory path models demonstrate associations between Fantasy, fear recognition, and paranoia. Indirect paths are designated either through fear recognition **(A)** or Fantasy **(B)**. Neither model demonstrated a significant indirect effect. The estimate and standard error are presented for each path. Significant paths are indicated with solid black lines and bolded coefficients. Non-significant pathways are indicated with dashed lines.

TABLE 3 | Test statistic.

	Test statistic	DF	Chi-square	CFI	TLI	RMSEA	90% CI low	90% CI upper	*P* RMSEA < = 0.05	SRMR
ER total	91.981	6	0.000	0.459	−1.975*	0.252	0.208	0.298	0.000	0.083
ER happy	91.981	6	0.000	0.394	−2.335*	0.252	0.208	0.298	0.000	0.081
ER no emotion	91.981	6	0.000	0.401	−2.293*	0.252	0.208	0.298	0.000	0.081
Anger	91.981	6	0.000	0.401	−2.292*	0.252	0.208	0.298	0.000	0.083
Fear	91.981	6	0.000	0.468	−1.925*	0.252	0.208	0.298	0.000	0.082
Sad	91.981	6	0.000	0.421	−2.184*	0.252	0.208	0.298	0.000	0.082
Fantasy-Fear-Paranoia	0.000	0	N/A	1.000	1.000	0.000	0.000	0.000	N/A	0.000
Fear-Fantasy-Paranoia	0.000	0	N/A	1.000	1.000	0.000	0.000	0.000	N/A	0.000

**Typically, TLI values range between 0 and 1. However, in models with smaller sample sizes and low degrees of freedom, TLI can have negative values. These can be rounded to 0. Anderson and Gerbing (1984) indicates that TLI is an inferior fit index for SEM models with small sample sizes.*

our findings, however, which revealed a negative relationship, prior work has demonstrated a positive relationship between Empathic Concern on the IRI and emotion recognition ability (Jiang et al., 2014). This finding was strongest for emotion recognition after a brief exposure (50 ms), which is much shorter than the current task parameters. This implies that sensitivity to the relationship between emotion recognition and Empathic Concern may depend on quick, automatic processing. Overall, the findings between empathy and emotion recognition in the current study are intriguing but require replication and further investigation.

The lack of a significant association between emotion recognition and paranoia is also somewhat surprising. Past research completed in the general population has shown that those with higher subclinical paranoia had lower overall emotion recognition ability (Combs and Penn, 2004; Klein et al., 2018), and misidentified neutral expressions for anger (Pinkham et al., 2011), although a recent study found that positive schizotypy was not associated with emotion recognition (Dawes et al., 2021). This relationship has also been studied extensively in patients with schizophrenia. In a study comparing schizophrenia participants and subclinical populations with varying levels of paranoia, schizophrenia participants had worse emotion recognition ability than those with low or moderate subclinical paranoia, but similar emotion recognition as subclinical participants with high paranoia (Combs et al., 2006). Lack of replication in the current sample may be due to our use of the PDI-21 to measure paranoia. Prior studies have used the Paranoia Scale – a 20-item self-report focused entirely on paranoia (Combs and Penn, 2004; Klein et al., 2018), allowing for more power to detect relationships within a subclinical population.

Strengths and Weaknesses

This investigation approached the relationship between empathy, emotion recognition and paranoia through a sophisticated statistic method that allowed us to test the relative contribution of different types of empathy on paranoia, as well as model our hypothesized pathways. However, this study was limited by relatively low power for a structural equation model, which may have affected the specificity and fit of each model (Anderson and Gerbing, 1984). Another limitation to this study is the nature of the Peters Delusion Inventory and Interpersonal Reactivity Index. Self-report questionnaires are often influenced by response biases like social desirability. As the Peters Delusion Inventory asks questions about thoughts that may be stigmatizing (e.g., Do you ever feel as if there is a conspiracy against you? Do you ever think people can communicate telepathically?), a participant may report lower levels of distress, preoccupation, and conviction. Furthermore, the IRI may be best interpreted as a participant's thoughts about their empathic abilities and not their actual abilities. Self-reported cognitive empathy abilities have been found to be unrelated to actual empathic accuracy during a brief interaction with another person (Ickes et al., 2000; Zaki and Ochsner, 2009). A more interactive or dynamic task may be necessary to tap into the social cognitive domain of empathy (Haut et al., 2019). Finally, Batson et al. (2002) has questioned whether empathy can be measured validly by self-reports and the internal consistency of the fantasy subscale as a measure of empathy has been previously questioned (Baldner and McGinley, 2014) and therefore should be interpreted carefully. One main note is that the fantasy subscale, unlike the other three subscales, was created from two sources [Stotland's (1969) Fantasy-Empathy scale and Davis (1983)]. Baron-Cohen and Wheelwright (2004) proposed that fantasy was not characterized by affective-cognitive dimensions of empathy and suggested that the scale assesses imagination, not empathy itself (Lawrence et al., 2004). In the schizophrenia literature, results of differences in fantasy are mixed (Horan et al., 2015; Bonfils et al., 2017). Therefore, while we are intrigued by the fairly consistent relationships between fantasy and delusional ideation across the literature, we acknowledge that its interpretation as a facet of empathy requires further validation.

Future Directions

This study was one of the first to identify relationships between a cognitive facet of empathy and paranoia, as well as fear recognition. The role of fear recognition in the relationship between Fantasy and paranoia should be explored further. If replicated, future studies should examine the directionality of these relationships, for instance testing whether increased Fantasy is present prior to paranoia onset. This would require longitudinal or temporal data that could truly capture directionality. This study provides future support for considering symptoms as a continuum and highlights the importance of studying the social-cognitive aspects of experiences like paranoia.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: http://fcon_1000.projects.nitrc.org/indi/enhanced/access.html.

ETHICS STATEMENT

Institutional Review Board Approval was obtained for this project at the Nathan Kline Institute (Phase I #226781 and Phase II #239708) and Montclair State University (Phase I #000983A and Phase II #000983B). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KB, SS, and JS conceptualized the study. SS conducted initial data analysis, and including suggestion of statistical approaches and provided feedback for the manuscript. KB conducted *post hoc* analyses and developed all figures and tables. KB and JS drafted the initial manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

Support for this project was given by the Vanderbilt University Medical Center, Department of Psychiatry and Behavioral Sciences.

ACKNOWLEDGMENTS

We thank Dr. Amy Pinkham (University of Texas, Dallas) for her invaluable insight into emotion recognition in psychosis, as well as her helpful consultation throughout this project.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.804178/full#supplementary-material

REFERENCES

An, S. K., Lee, E., Kim, J. J., Namkoong, K., Kang, J. I., Jeon, J. H., et al. (2006). Greater impairment in negative emotion evaluation ability in patients with paranoid schizophrenia. *Yonsei Med. J.* 47, 343–353. doi: 10.3349/ymj.2006.47.3.343

Anderson, J. C., and Gerbing, D. W. (1984). The effect of sampling error on convergence, improper solutions, and goodness-of-fit indices for maximum likelihood confirmatory factor analysis. *Psychometrika* 49, 155–173.

Baldner, C., and McGinley, J. J. (2014). Correlational and exploratory factor analyses (EFA) of commonly used empathy questionnaires: new insights. *Motiv. Emot.* 38, 727–744. doi: 10.1007/s11031-014-9417-2

Baron-Cohen, S., and Wheelwright, S. (2004). The empathy quotient: an investigation of adults with asperger syndrome or high functioning autism, and normal sex differences. *J. Autism Dev. Disord.* 34, 163–175. doi: 10.1023/B:JADD.0000022607.19833.00

Batson, C. D., Ahmad, N., Lishner, D. A., and Tsang, J. A. (2002). "Empathy and Altruism," in *Handbook of Positive Psychology*, (Eds) C. R., Snyder, J. L., Shane (Oxfordshire: Oxford University Press), 485–498.

Bentall, R. P., Rowse, G., Shryane, N., Kinderman, P., Howard, R., Blackwood, N., et al. (2009). The Cognitive and Affective Structure of Paranoid Delusions. *Arch. Gen. Psychiatry* 66, 236–247. doi: 10.1001/archgenpsychiatry.2009.1

Besel, L. D. S., and Yuille, J. C. (2010). Individual differences in empathy: the role of facial expression recognition. *Pers. Individ. Differ.* 49, 107–112. doi: 10.1016/j.paid.2010.03.013

Blair, R. J. R. (2005). Responding to the emotions of others: dissociating forms of empathy through the study of typical and psychiatric populations. *Conscious. Cogn.* 14, 698–718. doi: 10.1016/j.concog.2005.06.004

Bliksted, V., Videbech, P., Fagerlund, B., and Frith, C. (2017). The effect of positive symptoms on social cognition in first-episode schizophrenia is modified by the presence of negative symptoms. *Neuropsychology* 31, 209–219. doi: 10.1037/neu0000309

Bonfils, K. A., Lysaker, P. H., Minor, K. S., and Salyers, M. P. (2017). Empathy in schizophrenia: a meta-analysis of the Interpersonal Reactivity Index. *Psychiatry Res.* 249, 293–303. doi: 10.1016/j.psychres.2016.12.033

Buck, B., Hester, N., Penn, D. L., and Gray, K. (2017). Differential patterns in mind perception in subclinical paranoia: relationships to self-reported empathy. *Cogn. Neuropsychiatry* 22, 137–144. doi: 10.1080/13546805.2017.1287692

Chen, J. (2014). Face recognition as a predictor of social cognitive ability: effects of emotion and race on face processing. *Asian J. Soc. Psychol.* 17, 61–69. doi: 10.1111/ajsp.12041

Chrysikou, E. G., and Thompson, W. J. (2016). Assessing Cognitive and Affective Empathy Through the Interpersonal Reactivity Index. *Assessment* 23, 769–777. doi: 10.1177/1073191115599055

Cliffordson, C. (2002). The hierarchical structure of empathy: dimensional organization and relations to social functioning. *Scand. J. Psychol.* 43, 49–59. doi: 10.1111/1467-9450.00268

Coid, J. W., Ullrich, S., and Kallis, C. (2013). The relationship between delusions and violence: findings from the East London first episode psychosis study. *JAMA Psych.* 70, 465–471. doi: 10.1001/jamapsychiatry.2013.12

Combs, D. R., Finn, J. A., Wohlfahrt, W., Penn, D. L., and Basso, M. R. (2013). Social cognition and social functioning in nonclinical paranoia. *Cogn. Neuropsychiatry* 18, 531–548. doi: 10.1080/13546805.2013.766595

Combs, D. R., Michael, C. O., and Penn, D. L. (2006). Paranoia and emotion perception across the continuum. *Br. J. Clin. Psychol.* 45, 19–31. doi: 10.1348/014466505X29099

Combs, D. R., and Penn, D. L. (2004). The role of subclinical paranoia on social perception and behavior. *Schizophr. Res.* 69, 93–104. doi: 10.1016/S0920-9964(03)00051-3

Darwin, C. (1872). *The Descent of Man, and Selection in Relation to Sex (Vol. 2)*. Michigan: the University of Michigan

Davis, M. H. (1980). A multidimensional approach to individual differences in empathy. *JSAS Catalog Select. Doc. Psychol.* 10, 85–104. doi: 10.3389/fpsyg.2021.588934

Davis, M. H. (1983). Measuring individual differences in empathy: evidence for a multidimensional approach. *J. Pers. Soc. Psychol.* 44, 113–126. doi: 10.1037/0022-3514.44.1.113

Davis, M. H., and Franzoi, S. L. (1991). Stability and change in adolescent self-consciousness and empathy. *J Res. Pers.* 25, 70–87. doi: 10.1016/0092-6566(91)90006-C

Davis, M. H., and Kraus, L. A. (1997). "Personality and Empathic Accuracy," in *Empathic Accuracy*, ed. W. Ickes 144–168. New York: Guilford Press

Dawes, C., Danielmeier, C., Haselgrove, M., and Moran, P. M. (2021). High Schizotypy Predicts Emotion Recognition Independently of Negative Affect. *Front. Psychiatry* 12:738344. doi: 10.3389/fpsyt.2021.738344

Decety, J., and Meyer, M. (2008). From emotion resonance to empathic understanding: a social developmental neuroscience account. *Dev. Psychopathol.* 20, 1053–1080. doi: 10.1017/S0954579408000503

Decety, J., and Svetlova, M. (2012). Putting together phylogenetic and ontogenetic perspectives on empathy. *Dev. Cogn. Neurosci.* 2, 1–24. doi: 10.1016/j.dcn.2011.05.003

Dimberg, U., Andréasson, P., and Thunberg, M. (2011). Emotional empathy and facial reactions to facial expressions. *J. Psychophysiol.* 25, 26–31. doi: 10.1027/0269-8803/a000029

Duesenberg, M., Weber, J., Schulze, L., Schaeuffele, C., Roepke, S., Hellmann-Regen, J., et al. (2016). Does cortisol modulate emotion recognition and empathy? *Psychoneuroendocrinology* 66, 221–227. doi: 10.1016/j.psyneuen.2016.01.011

Ekman, P., and Friesen, W. V. (1971). Constants across cultures in the face and emotion. *J. Pers. Soc. Psychol.* 17, 124–129. doi: 10.1037/h0030377

Feyaerts, J., Kusters, W., van Duppen, Z., Vanheule, S., Myin-Germeys, I., and Sass, L. (2021). Uncovering the realities of delusional experience in schizophrenia: a qualitative phenomenological study in Belgium. *Lancet Psychiatry* 8, 784–796. doi: 10.1016/S2215-0366(21)00196-6

Field, T. M., Woodson, R., Greenberg, R., and Cohen, D. (1982). Discrimination and imitation of facial expressions by neonates. *Science* 218, 179–181. doi: 10.1126/science.7123230

Fiske, S. T., and Taylor, S. E. (2013). *Social Cognition from Brains to Culture* 2nd edition. Portland: Reference & Research Book News 28,

Freeman, D. (2016). Persecutory delusions: a cognitive perspective on understanding and treatment. *Lancet Psychiatry* 3, 685–692. doi: 10.1016/S2215-0366(16)00066-3

Freeman, D., and Freeman, J. (2008). *Paranoia: The 21st-Century Fear*. Oxford: Oxford University Press, doi: 10.1192/bjp.bp.108.061499

Freeman, D., Garety, P. A., Kuipers, E., Fowler, D., and Bebbington, P. E. (2002). A cognitive model of persecutory delusions. *Br. J. Clin. Psychol.* 41, 331–347. doi: 10.1348/014466502760387461

Fujiwara, H., Shimizu, M., Hirao, K., Miyata, J., Namiki, C., Sawamoto, N., et al. (2008). Female specific anterior cingulate abnormality and its association with empathic disability in schizophrenia. *Prog. NeuroPsychopharmacol. Biol. Psychiatry* 32, 1728–1734. doi: 10.1016/j.pnpbp.2008.07.013

Germine, L., Robinson, E. B., Smoller, J. W., Calkins, M. E., Moore, T. M., Hakonarson, H., et al. (2016). Association between polygenic risk for schizophrenia, neurocognition and social cognition across development. *Trans. Psychiatry* 6:e924. doi: 10.1038/tp.2016.147

Gery, I., Miljkovitch, R., Berthoz, S., and Soussignan, R. (2009). Empathy and recognition of facial expressions of emotion in sex offenders, non-sex offenders and normal controls. *Psychiatry Res.* 165, 252–262. doi: 10.1016/j.psychres.2007.11.006

Green, M. F., Horan, W. P., and Lee, J. (2019). Nonsocial and social cognition in schizophrenia: current evidence and future directions. *World Psychiatry* 18, 146–161. doi: 10.1002/wps.20624

Green, M. F., and Leitman, D. I. (2007). Social Cognition in Schizophrenia. *Schizophr. Bull.* 34, 670–672. doi: 10.1093/schbul/sbn045

Gur, R. C., Ragland, J. D., Moberg, P. J., Bilker, W. B., Kohler, C., Siegel, S. J., et al. (2001b). Computerized neurocognitive scanning: II. The profile of schizophrenia. *Neuropsychopharmacology* 25, 777–788. doi: 10.1016/S0893-133X(01)00279-2

Gur, R. C., Ragland, J. D., Moberg, P. J., Turner, T. H., Bilker, W. B., Kohler, C., et al. (2001a). Computerized neurocognitive scanning: I. Methodology and validation in healthy people. *Neuropsychopharmacology* 25, 766–776. doi: 10.1016/S0893-133X(01)00278-0

Hall, J. A., Andrzejewski, S. A., and Yopchick, J. E. (2009). Psychosocial correlates of interpersonal sensitivity: a meta-analysis. *J. Nonverbal Behav.* 33, 149–180. doi: 10.1007/s10919-009-0070-5

Haut, K. M., Dodell-Feder, D., Guty, E., Nahum, M., and Hooker, C. I. (2019). Change in Objective Measure of Empathic Accuracy Following Social Cognitive Training. *Front. Psychiatry* 10:894. doi: 10.3389/fpsyt.2019.00894

Hawk, S. T., Keijsers, L., Branje, S. J. T., van der Graaff, J., de Wied, M., and Meeus, W. (2013). Examining the Interpersonal Reactivity Index (IRI) among early and late adolescents and their mothers. *J. Pers. Assess.* 95, 96–106. doi: 10.1080/00223891.2012.696080

Herms, E., Bolbecker, A., and Wisner, K. (2022). The role of emotion regulation strategies and delusion proneness on empathetic tendencies in a community sample. *PsyArXiv* [Preprint]. doi: 10.31234/osf.io/7xqtv

Hooker, C. I., Bruce, L., Lincoln, S. H., Fisher, M., and Vinogradov, S. (2011). Theory of mind skills are related to gray matter volume in the ventromedial prefrontal cortex in schizophrenia. *Biol. Psychiatry* 70, 1169–1178. doi: 10.1016/j.biopsych.2011.07.027

Horan, W. P., Reise, S. P., Kern, R. S., Lee, J., Penn, D. L., and Green, M. F. (2015). Structure and correlates of self-reported empathy in schizophrenia. *J. Psychiatric Res.* 6, 60–66. doi: 10.1016/j.jpsychires.2015.04.016

Hu, L. T., and Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Struct. Equ. Modeling* 6, 1–55. doi: 10.1080/10705519909540118

Humpston, C. S., Walsh, E., Oakley, D. A., Mehta, M. A., Bell, V., and Deeley, Q. (2016). The relationship between different types of dissociation and psychosis-like experiences in a non-clinical sample. *Conscious. Cogn.* 41, 83–92. doi: 10.1016/j.concog.2016.02.009

IBM Corp. Released (2017). *IBM SPSS Statistics for Windows, Version 25.0.* Armonk, NY: IBM Corp.

Ickes, W., Gesn, P. R., and Graham, T. (2000). Gender differences in empathic accuracy: differential ability or differential motivation? *Pers. Relatsh* 7, 95–109. doi: 10.1111/j.1475-6811.2000.tb00006.x

Jan Kuis, D., van de Giessen, T., de Jong, S., Sportel, B. E., Boonstra, N., van Donkersgoed, R., et al. (2021). Empathy and its relationship with social functioning in individuals at Ultra-High Risk for psychosis. *Front. Psychiatry* 12:730092. doi: 10.3389/fpsyt.2021.730092

Jiang, Y., Hu, Y., Wang, Y., Zhou, N., Zhu, L., and Wang, K. (2014). Empathy and emotion recognition in patients with idiopathic generalized epilepsy. *Epilepsy Behav.* 37, 139–144. doi: 10.1016/j.yebeh.2014.06.005

Kalin, M., Kaplan, S., Gould, F., Pinkham, A. E., Penn, D. L., and Harvey, P. D. (2015). Social cognition, social competence, negative symptoms and social outcomes: inter-relationships in people with schizophrenia. *J. Psychiatric Res.* 68, 254–260. doi: 10.1016/j.jpsychires.2015.07.008

Klein, H. S., Kelsven, S., and Pinkham, A. E. (2018). Increased social cognitive bias in subclinical paranoia. *Schizophr. Res. Cogn.* 12, 74–76. doi: 10.1016/j.scog.2018.05.002

Lawrence, E. J., Shaw, P., Baker, D., Baron-Cohen, S., and David, A. S. (2004). Measuring empathy: reliability and validity of the Empathy Quotient. *Psychol. Med.* 34, 911–920. doi: 10.1017/S0033291703001624

Lee, R. J. (2017). Mistrustful and Misunderstood: a Review of Paranoid Personality Disorder. *Curr. Behav. Neurosci. Rep.* 4, 151–165. doi: 10.1007/s40473-017-0116-7

Locascio, J. J., and Snyder, C. R. (1975). Selective attention to threatening stimuli and field independence as factors in the etiology of paranoid behavior. *J. Abnorm. Psychol.* 84, 637–643. doi: 10.1037/0021-843X.84.6.637

López-Ilundain, J. M., Pèrez-Nievas, F., Otero, M., and Mata, I. (2006). Peter's delusions inventory in Spanish general population: internal reliability, factor structure and association with demographic variables (dimensionality of delusional ideation). *Actas. Esp. Psiquiatr.* 34, 94–104.

Marsh, A. A., Kozak, M. N., and Ambady, N. (2007). Accurate identification of fear facial expressions predicts prosocial behavior. *Emotion* 7, 239–251. doi: 10.1037/1528-3542.7.2.239

Martin, J. A., and Penn, D. L. (2001). Social cognition and subclinical paranoid ideation. *Br. J. Clin. Psychol.* 40, 261–265. doi: 10.1348/014466501163670

Martin, R. A., Berry, G. E., Dobranski, T., Horne, M., and Dodgson, P. G. (1996). Emotion perception threshold: individual differences in emotional sensitivity. *J. Res. Pers.* 30, 290–305. doi: 10.1006/jrpe.1996.0019

Matsumoto, Y., Takahashi, H., Murai, T., and Takahashi, H. (2015). Visual processing and social cognition in schizophrenia: relationships among eye movements, biological motion perception, and empathy. *Neurosci. Res.* 90, 95–100. doi: 10.1016/j.neures.2014.10.011

Mayer, J. D., and Geher, G. (1996). Emotional intelligence and the identification of emotion. *Intelligence* 22, 89–113. doi: 10.1016/S0160-2896(96)90011-2

McCormick, L. M., Brumm, M. C., Beadle, J. N., Paradiso, S., Yamada, T., and Andreasen, N. (2012). Mirror neuron function, psychosis, and empathy in schizophrenia. *Psychiatry Res. Neuroimag.* 201, 233–239. doi: 10.1016/j.pscychresns.2012.01.004

McKay, R., Langdon, R., and Coltheart, M. (2005). Paranoia, persecutory delusions and attributional biases. *Psychiatry Res.* 136, 233–245. doi: 10.1016/j.psychres.2005.06.004

Michaels, T. M., Horan, W. P., Ginger, E. J., Martinovich, Z., Pinkham, A. E., and Smith, M. J. (2014). Cognitive empathy contributes to poor social functioning in schizophrenia: evidence from a new self-report measure of cognitive and affective empathy. *Psychiatry Res.* 220, 803–810. doi: 10.1016/j.psychres.2014.08.054

Minkowski, E. (1953). Schizophrenic psychopathology: feeling and living. *G. Psichiatr. Neuropatol.* 81, 1–10.

Montag, C., Neuhaus, K., Lehmann, A., Krüger, K., Dziobek, I., Heekeren, H. R., et al. (2012). Subtle deficits of cognitive theory of mind in unaffected first-degree relatives of schizophrenia patients. *Eur. Arch. Psychiatry Clin. Neurosci.* 262, 217–226. doi: 10.1007/s00406-011-0250-2

Moore, T. M., Reise, S. P., Gur, R. E., Hakonarson, H., and Gur, R. C. (2015). Psychometric properties of the penn computerized neurocognitive battery. *Neuropsychology* 29, 235–246. doi: 10.1037/neu0000093

Murphy, P., Bentall, R. P., Freeman, D., O'Rourke, S., and Hutton, P. (2018). The paranoia as defence model of persecutory delusions: a systematic review and meta-analysis. *Lancet Psychiatry* 5, 913–929. doi: 10.1016/S2215-0366(18)30339-0

Nomura, K., and Akai, S. (2012). Empathy with fictional stories: reconsideration of the Fantasy scale of the interpersonal reactivity index. *Psychol. Rep.* 110, 304–314. doi: 10.2466/02.07.09.11.PR0.110.1.304-314

Nooner, K. B., Colcombe, S. J., Tobe, R. H., Mennes, M., Benedict, M. M., Moreno, A. L., et al. (2012). The NKI-Rockland sample: a model for accelerating the pace of discovery science in psychiatry. *Front. Neurosci.* 6:152. doi: 10.3389/fnins.2012.00152

Panksepp, J., and Panksepp, J. B. (2013). Toward a cross-species understanding of empathy. *Trends Neurosci.* 36, 489–496. doi: 10.1016/j.tins.2013.04.009

Peters, E., Joseph, S., Day, S., and Garety, P. (2004). Measuring delusional ideation: the 21-item Peters et al. Delusions Inventory (PDI). *Schizophr. Bull.* 30, 1005–1022. doi: 10.1093/oxfordjournals.schbul.a007116

Peyroux, E., Prost, Z., Danset-Alexandre, C., Brenugat-Herne, L., Carteau-Martin, I., Gaudelus, B., et al. (2019). From "under" to "over" social cognition in schizophrenia: is there distinct profiles of impairments according to negative and positive symptoms? *Schizophr. Res. Cogn.* 15, 21–29. doi: 10.1016/j.scog.2018.10.001

Pinkham, A. E. (2014). Social cognition in schizophrenia. *J. Clin. Psychiatry* 75, 14–19. doi: 10.4088/JCP.13065su1.04

Pinkham, A. E., Brensinger, C., Kohler, C., Gur, R. E., and Gur, R. C. (2011). Actively paranoid patients with schizophrenia over attribute anger to neutral faces. *Schizophr. Res.* 125, 174–178. doi: 10.1016/j.schres.2010.11.006

Pinkham, A. E., Harvey, P. D., and Penn, D. L. (2016). Paranoid individuals with schizophrenia show greater social cognitive bias and worse social functioning than non-paranoid individuals with schizophrenia. *Schizophr. Res. Cogn.* 3, 33–38. doi: 10.1016/j.scog.2015.11.002

Preti, A., Rocchi, M. B. L., Sisti, D., Mura, T., Manca, S., Siddi, S., et al. (2007). The psychometric discriminative properties of the Peters et al Delusions Inventory: a receiver operating characteristic curve analysis. *Compr. Psychiatry* 48, 62–69. doi: 10.1016/j.comppsych.2006.05.003

Rankin, K. P., Kramer, J. H., and Miller, B. L. (2005). Patterns of cognitive and emotional empathy in frontotemporal lobar degeneration. *Cogn. Behav. Neurol.* 18, 28–36. doi: 10.1097/01.wnn.0000152225.05377.ab

Rochat, P., and Striano, T. (1999). "Social-Cognitive development in the first year," in *Early Social Cognition: Understanding Others in the First Months of Life* (Ed) R. Philippe. Hove: Psychology Press. 3–34.

Rosseel, Y. (2012). Lavaan: an R package for structural equation modeling. *J. Stat. Softw.* 48, 1–36. doi: 10.18637/jss.v048.i02

Russell, T. A., Reynaud, E., Kucharska-Pietura, K., Ecker, C., Benson, P. J., Zelaya, F., et al. (2007). Neural responses to dynamic expressions of fear in schizophrenia. *Neuropsychologia* 45, 107–123. doi: 10.1016/j.neuropsychologia.2006.04.026

Sass, L. A., and Parnas, J. (2003). Schizophrenia, Consciousness and the Self. *Schizophr. Bull.* 29, 427–444. doi: 10.1093/oxfordjournals.schbul.a007017

Savulich, G., Freeman, D., Shergill, S., and Yiend, J. (2015). Interpretation Biases in Paranoia. *Behav. Ther.* 46, 110–124. doi: 10.1016/j.beth.2014.08.002

Shamay-Tsoory, S. G., Shur, S., Harari, H., and Levkovitz, Y. (2007). Neurocognitive Basis of Impaired Empathy in Schizophrenia. *Neuropsychology* 21, 431–438. doi: 10.1037/0894-4105.21.4.431

Sheffield, J. M., Brinen, A. P., and Freeman, D. (2021). Paranoia and Grandiosity in the General Population: differential Associations With Putative Causal Factors. *Front. Psychiatry* 12:668152. doi: 10.3389/fpsyt.2021.668152

Soto, J. A., Pole, N., Mccarter, L. M., and Levenson, R. W. (1998). Knowing Feelings and Feeling Feelings: Are they Connected?. *Paper Presented at the 38th Annual Meeting of the Society for Psychophysiological Research*. Denver: SPR.

Sparks, A., McDonald, S., Lino, B., O'Donnell, M., and Green, M. J. (2010). Social cognition, empathy and functional outcome in schizophrenia. *Schizophr. Res.* 122, 172–178. doi: 10.1016/j.schres.2010.06.011

Stotland, E. (1969). Exploratory Investigations of Empathy. *Adv. Exp. Soc. Psychol.* 4, 271–314. doi: 10.1016/S0065-2601(08)60080-5

Sucksmith, E., Allison, C., Baron-Cohen, S., Chakrabarti, B., and Hoekstra, R. A. (2013). Empathy and emotion recognition in people with autism, first-degree relatives, and controls. *Neuropsychologia* 51, 98–105. doi: 10.1016/j.neuropsychologia.2012.11.013

Tellegen, A., and Atkinson, G. (1974). Openness to absorbing and self-altering experiences ("absorption"), a trait related to hypnotic susceptibility. *J. Abnorm. Psychol.* 83, 268–277. doi: 10.1037/h0036681

Trotta, A., Kang, J., Stahl, D., and Yiend, J. (2021). Interpretation Bias in Paranoia: a Systematic Review and Meta-Analysis. *Clin. Psychol. Sci.* 9, 3–23. doi: 10.1177/2167702620951552

Verdoux, H., van Os, J., Maurice-Tison, S., Gay, B., Salamon, R., and Bourgeois, M. (1998). Is early adulthood a critical developmental stage for psychosis proneness? A survey of delusional ideation in normal subjects. *Schizophr. Res.* 29, 247–254. doi: 10.1016/S0920-9964(97)00095-9

Wai, M., and Tiliopoulos, N. (2012). The affective and cognitive empathic nature of the dark triad of personality. *Pers. Individ. Differ.* 52, 794–799. doi: 10.1016/j.paid.2012.01.008

Wang, W., Zhou, Y., Liu, R., Wei, S., Xu, H., Wang, J., et al. (2021). Association between empathy and clinical symptoms in chronic schizophrenia: a large sample study based on Chinese Han population. *J Psychiatric Res.* 139, 106–112. doi: 10.1016/j.jpsychires.2021.05.046

Weiss, E. M., Kohler, C. G., Brensinger, C. M., Bilker, W. B., Loughead, J., Delazer, M., et al. (2007). Gender differences in facial emotion recognition in persons with chronic schizophrenia. *Eur. Psychiatry* 22, 116–122. doi: 10.1016/j.eurpsy.2006.05.003

Wellstein, K. V., Diaconescu, A. O., Bischof, M., Rüesch, A., Paolini, G., Aponte, E. A., et al. (2020). Inflexible social inference in individuals with subclinical persecutory delusional tendencies. *Schizophr. Res.* 215, 344–351. doi: 10.1016/j.schres.2019.08.031

Wickham, S., Taylor, P., Shevlin, M., and Bentall, R. P. (2014). The impact of social deprivation on paranoia, hallucinations, mania and depression: the role of discrimination social support, stress and trust. *PLoS One* 9:e105140. doi: 10.1371/journal.pone.0105140

Williams, L., Lea, M., Das, P., Liddell, B. J., Olivieri, G., Peduto, A. S., et al. (2007). Fronto-limbic and autonomic disjunctions to negative emotion distinguish schizophrenia subtypes. *Psychiatry Res. Neuroimag.* 155, 29–44. doi: 10.1016/j.pscychresns.2006.12.018

Zaki, J., and Ochsner, K. (2009). The need for a cognitive neuroscience of naturalistic social cognition. *Ann. N.Y. Acad. Sci.* 1167, 16–30. doi: 10.1111/j.1749-6632.2009.04601.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 Psychology

ORIGINAL RESEARCH
published: 24 February 2022
doi: 10.3389/fpsyg.2022.805435

Metacognitive Abilities as a Protective Factor for the Occurrence of Psychotic-Like Experiences in a Non-clinical Population

Marco Giugliano[1], Claudio Contrada[1], Ludovica Foglia[1], Francesca Francese[1], Roberta Romano[1], Marilena Dello Iacono[1], Eleonora Di Fausto[1], Mariateresa Esposito[1], Carla Azzara[1], Elena Bilotta[1,2]*, Antonino Carcione[1,2] and Giuseppe Nicolò[1,2]*

[1] Società Italiana di Cognitivismo Clinico, Rome, Italy, [2] Terzo Centro di Psicoterapia, Rome, Italy

OPEN ACCESS

Edited by:
Ricardo R. Garcia,
University of Chile, Chile

Reviewed by:
Juan Francisco Rodríguez-Testal,
Sevilla University, Spain
Yan-yu Wang,
Weifang Medical University, China

***Correspondence:**
Marco Giugliano
mail.marco.giugliano@gmail.com
Elena Bilotta
bilotta.elena@gmail.com

Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: 30 October 2021
Accepted: 17 January 2022
Published: 24 February 2022

Citation:
Giugliano M, Contrada C, Foglia L, Francese F, Romano R, Dello Iacono M, Di Fausto E, Esposito M, Azzara C, Bilotta E, Carcione A and Nicolò G (2022) Metacognitive Abilities as a Protective Factor for the Occurrence of Psychotic-Like Experiences in a Non-clinical Population. Front. Psychol. 13:805435. doi: 10.3389/fpsyg.2022.805435

Psychotic-like experiences (PLEs) are a phenomenon that occurs in the general population experiencing delusional thoughts and hallucinations without being in a clinical condition. PLEs involve erroneous attributions of inner cognitive events to the external environment and the presence of intrusive thoughts influenced by dysfunctional beliefs; for these reasons, the role played by metacognition has been largely studied. This study investigates PLEs in a non-clinical population and discriminating factors involved in this kind of experience, among which metacognition, as well as psychopathological features, seems to have a crucial role. The aim of this study was to extend the knowledge about the relationship between metacognition, psychopathology, and PLEs, orienting the focus on metacognitive functioning. The sample consisted of 207 Italian participants (men = 32% and women = 68%) voluntarily recruited online, who gave consent to participate in the study. The average age of the sample was 32.69 years (SD: 9.63; range: 18–71). Subjects affected by psychosis, neurological disease, and drug addiction were excluded from the analyses. The following scales were used to investigate PLEs: Peters et al. Delusions Inventory (PDI), Launay-Slade Hallucinations Scale-Extended Revised (LSHSE), Prodromal Questionnaire-Brief (PQ-B), and Revised Hallucination Scale (RHS). To assess general psychopathological features, the Behavior and Symptom Identification Scale (BASIS-32) was administrated. The Metacognition Self-Assessment Scale (MSAS) was chosen to evaluate metacognitive functioning. From hierarchical regression analyses, it emerged that the presence of anxiety, depression, and impulsive/addictive symptoms constitute a remarkable vulnerability factor for PLEs, in line with previous evidence regarding the relationship between general psychopathology and PLEs. Metacognition negatively predicts PLEs, and its presence does not affect the significance of psychopathological variables, suggesting that metacognitive abilities seem to play a protective role for the occurrence of PLEs among non-clinical individuals, and such ability operates as an independent predictor along with other variables. These

results are explained by the role of metacognitive functions, which allow individuals to operate many mental processes such as interpreting sensorial events as real or illusory, understanding behaviors, thoughts, and drives of others, and questioning the subjective interpretation of facts.

Keywords: psychotic-like experiences, metacognition, delusions, hallucinations, Metacognition Self-Assessment Scale, psychopathology

INTRODUCTION

Psychotic-like experiences (PLEs) are a phenomenon that occurs in the general population experiencing delusional thoughts and hallucinations without being in a clinical condition (Kelleher and Cannon, 2011). Delusional thoughts are commonly experienced by the subclinical population (Heilskov et al., 2020) as well as hallucinations (Larøi et al., 2019), and recently, many studies suggested that between 5 and 7% of adults incur PLEs during their lifetimes (van Os et al., 2009; McGrath et al., 2015; Maijer et al., 2018; Healy and Cannon, 2020). Johns and Van Os reviewed the occurrence of psychotic symptoms within the general population (between 5 and 8%) and proposed an extended psychosis phenotype, suggesting that symptoms reported by the non-clinical population and symptoms reported by patients lie on the same multidimensional continuum (Johns and van Os, 2001), with non-psychotic individuals that may have less severe experiences compared with psychotic individuals and, moreover, better reality testing in the absence of clinical levels of distress or functional impairment. PLEs involve erroneous attributions of inner cognitive events to the external environment (Hoffman, 1986; Bentall, 1990a,b; Frith, 1992; Larøi and Woodward, 2007) and erroneous attributions of intrusive thoughts influenced by dysfunctional beliefs (Morrison et al., 1995), and for these reasons, the role played by metacognition was largely studied. Most of the publications on this topic refer to the self-regulatory executive function model (S-REF; Wells and Matthews, 1996), which defines metacognition as "the aspect of information processing that monitors, interprets, evaluates, and regulates the contents and processes of its organization" (Wells and Purdon, 1999). Studies using this perspective show that metacognitive beliefs involving worry and intrusive thoughts promote and maintain delusional and hallucinatory experiences in clinical and non-clinical populations (Larøi and Van Der Linden, 2005; García-Montes et al., 2006; Barkus et al., 2010). S-REF focuses on "thinking about thinking" declined into worry and rumination outcomes, this construct of metacognition is assessed with *Metacognitive Questionnaire* (MCQ; Cartwright-Hatton and Wells, 1997; Wells and Cartwright-Hatton, 2004), and this instrument is oriented to evaluate mental contents rather than mental functions (Faustino et al., 2021). *The Metacognitive Multi-Function Model* (MMFM; Semerari et al., 2003) intends metacognition as "the whole set of abilities that allows us to understand mental phenomena and work them out in order to tackle tasks and master mental states that are a source of subjective sufferance" (Carcione et al., 1997; Carcione and Falcone, 1999). This perspective considers a set of abilities that are crucial to (1) identify mental states and ascribe them to oneself and others based on facial expressions, somatic states, behaviors, and actions; (2) reflect and reason on mental states; and (3) use information about mental states to make decisions, solve problems or psychological and interpersonal conflicts, and cope with subjective suffering (Semerari et al., 2003; Carcione et al., 2019). In addition, the model identifies different metacognitive functions as follows: *monitoring* is the ability to detect emotion and thoughts forming mental states, *integration* is the ability to reflect on mental states and processes due to sorting them in a hierarchy of importance, which permit individuals to behave coherently with their own purposes, *differentiation* is the ability to differentiate between different classes of representation (e.g., dreams, fantasies, and beliefs) and between representations and reality, recognizing their subjectivity, and *decentration* is the ability to define mental states of others by forming hypothesis and *mastery* that is the use of psychological information to cope with problems of different levels of complexity. In comparison with the model suggested by Wells and Matthews, authors keep the subdivision into monitoring and regulating abilities and concentrate on the functional ability to perform certain operations, rather than on the contents (Faustino et al., 2021). Another important point about PLEs is their relationship with general psychopathology. Studies found a link between PLEs and PTSD (Bak et al., 2005; Scott et al., 2007), drug abuse/addiction (Mitchell and Vierkant, 1991; Rössler et al., 2007; Brewer and Collins, 2014), anxiety, and depression (Johns et al., 2004). Regarding metacognition, its interplay with PLEs and general psychopathology as the isolated factor is difficult to assess using MCQ (Brett et al., 2009) as the items of the scale represent peculiar psychopathological impairments particularly related to anxious and depressive symptomatology (Wells et al., 1997), and this can in part explain why there are no findings in the literature about the interplay between these factors. By the way, since MCQ does not allow testing metacognition decoupled from some psychopathological symptoms and there are many studies in support of correlation between PLEs and psychopathological features (Freeman and Fowler, 2009; Armando et al., 2010; Kelleher and Cannon, 2011; Varghese et al., 2011), the role of metacognition in the occurrence of PLEs is unclear. However, the hypothesis of previous studies is probably correct given that metacognitive contents provided in MCQ test the ability to provide mental processes allowing individuals to evaluate their own thoughts and thoughts of others as well as internal or external events. Therefore, the MMFM model understands metacognition in a similar way to the MCQ model but by implementing the construct with other

characteristics and through a different scale (Metacognition Self-Assessment Scale, MSAS) which defines metacognition as a set of skills that do not overlap with any psychopathological symptom. Therefore the hypothesis of the present work is that the metacognitive functions, measured with MSAS, can play a role in the PLE as well as in the metacognitive contents and the interaction with psychopathology can be verified given the nature of this model.

In view of the above, the aim of this study was to investigate both PLEs in non-clinical population and discriminating factors involved in these kinds of experiences, among which metacognition seems to have an important role. Since MCQ seems to not discriminate for the evaluation of metacognitive functioning, the MSAS (Pedone et al., 2017) was chosen to assess metacognitive functioning instead of metacognitive contents in order to identify the link between metacognition, psychopathology, and PLEs. The involvement of all the metacognitive functions is expected due to the heterogeneity of PLEs.

METHODS

Participants and Procedure

The sample consisted of 215 Italian participants (men = 32% and women = 68%) voluntarily recruited online, who gave consent to participate in the study. The average age of the sample was 32.69 years (SD: 9.63; range: 18–71). Education and professional demographics were also measured. As for education, 5.8% did not have a high school diploma, 30.9% had a high school degree, and 63.3% had a college degree. Students comprised 17.2% of the sample, while professionals were 31.2%, white-collar employees 38.1, housewives 3.3%, unemployed 5.1, and 1.4 retired seniors. Finally, 16.9% were currently married, and 27.5% were divorced or separated. Respondents affected by psychosis, neurological disease, and drug addiction were excluded from the analyses ($n = 8$) leaving the sample to 207.

The sample was recruited online during the months of May–July 2019 and was asked to voluntarily participate in the research about unusual experiences and wellbeing. Ten researchers advertised in their social network pages a link to voluntarily participate in the research, described as an inquiry about unusual experiences in everyday life. Every participant was informed about the anonymity of the study and gave consent to participate in the inquiry. The questionnaire took ∼20 min to be filled in.

The obtained sample size guaranteed 0.80 power for *r*s as low as 0.19.

Measures

Unusual Experience Scales

(1) Peters et al. Delusions Inventory

This is a 21-item Italian version of the *Peters et al. Delusions Inventory* (PDI) (Peters et al., 1999; Preti et al., 2007). The participant was required to rate the degree of distress, preoccupation, and conviction about delusional thoughts (e.g., "Do you ever feel as if you are being persecuted in some way?") on 5-point Likert scales (1–5) for each positively endorsed item. This scale is typically used to assess delusional ideation in the general population. The scale showed good reliability ($\alpha = 0.90$).

(2) **Launay-Slade Hallucinations Scale-Extended Revised**

The Italian version of Launay-Slade Hallucinations Scale-Extended Revised (LSHS-E) (Launay and Slade, 1981; Larøi et al., 2004; Larøi and Van Der Linden, 2005; Vellante et al., 2012) is a self-report scale, which investigates the hallucinatory experiences in every sensory modality in the general population (e.g., "I have been troubled by hearing voices in my head"). Subjects have to rate each item on a five-point scale: (0) "certainly does not apply to me"; (1) "possibly does not apply to me"; (2) "unsure"; (3) "possibly applies to me"; and (4) "certainly applies to me." The time interval considered for the appearance of these experiences is 5 years. The scale showed good reliability ($\alpha = 0.86$).

(3) Prodromal Questionnaire-Brief

This is the Italian version of the Prodromal Questionnaire-Brief (PQ-B) (Preti et al., 2018), which is a yes/no 21-item self-report questionnaire used to assess positive symptoms experienced in the past month in the general population. For each symptom, responders have to rate the level of distress and its related impairment in everyday life, in a range from 1 (strongly disagree) to 5 (strongly agree), with 4 or 5 indicating distress. The total distress score (range: 0–105) is obtained by summing up each item. The scale showed acceptable reliability ($\alpha = 0.79$).

(4) Revised Hallucination Scale

The Revised Hallucination Scale (RHS) is a 24-item questionnaire revised from Launay and Slade (1981) and Morrison et al. (2002). This version incorporates additional items measuring predisposition to auditory and visual hallucinations, vividness of imagery, and daydreaming. Items are endorsed with a 4-point scale measuring frequency. To date, an Italian validation of this instrument does not exist so a mother tongue translator independently translated the items, and international translation practices were employed (Beaton et al., 2002). The scale showed acceptable reliability ($\alpha = 0.79$).

Psychological Health and Metacognition Functioning

(1) Behavior and Symptom Identification Scale

The Italian version of this scale (Eisen et al., 1986; Conti, 1999) was used to assess the psychological health of subjects perceived during the antecedent week. Notably, 32 items clustered in five subscales compose the following: depression and anxiety, relation to self and others, psychosis, impulsive and addictive behavior, daily living and role functioning, and the overall score. The scale showed good reliability ($\alpha = 0.94$).

(2) The Metacognition Self-Assessment Scale

The MSAS (Pedone et al., 2017) was used to assess metacognitive functions (e.g., "I'm able to define and detect my emotions") according to the MMFM model (Semerari et al., 2003). The MSAS is scored using a five-point Likert scale (1 = never, 2 = rarely, 3 = sometimes, 4 = frequently, and 5 = almost always). The range of the total score is from 18 to 90. High scores on the MSAS indicate better self-evaluation of metacognitive abilities than low scores. The MSAS is designed to measure five sub-functions of metacognition as follows: (1) monitoring; (2) differentiation; (3) integration; (4) decentration;

TABLE 1 | Zero-order correlations and descriptive statistics.

	1	2	3	4	5	6	7	8	9	10	11	12
1. Age	1											
2. Gender	0.06	1										
3. Relationships self/other	0.02	0.03	1									
4 Anxiety/depression	0.01	0.07	0.74**	1								
5. Daily living/role functioning	−0.00	−0.01	0.79**	0.77**	1							
6. Impulsive/addictive behavior	−0.01	−0.01	0.64**	0.63**	0.64**	1						
7. Psychosis	0.08	0.03	0.48**	0.61**	0.55**	0.74**	1					
8. Metacognition	−0.13	−0.00	−0.09	−0.07	−0.07	−0.13	−0.09	1				
9. RHS	0.02	−0.05	0.20**	0.28**	0.24**	0.36**	0.27**	−0.16*	1			
10. PDI	−0.13	−0.05	0.19**	0.24**	0.24**	0.35**	0.29**	−0.17*	0.52**	1		
11. LSHS	0.04	0.04	0.25**	0.32**	0.28**	0.33**	0.25**	−0.14*	0.54**	0.41**	1	
12. PQB	0.16*	0.05	0.34**	0.46**	0.40**	0.50**	0.42**	−0.29**	0.64**	0.70**	0.61**	1
Means (SD)	32.7 (9.6)	-	0.73 (0.69)	0.65 (0.69)	0.69 (0.62)	0.30 (0.43)	0.19 (0.38)	3.9 (0.59)	1.2 (0.31)	4.9 (3.2)	0.55 (0.57)	3.8 (3.3)
Females Means (SD)	32.29 (9.85)	-	0.71 (0.69)	0.61 (0.63)	0.69 (0.61)	0.30 (0.43)	0.18 (0.38)	3.9 (0.61)	1.26 (0.31)	5.06 (3.2)	0.53 (0.54)	3.66 (3.27)
Makes Means (SD)	33.51 (9.17)	-	0.76 (0.73)	0.72 (0.73)	0.68 (0.64)	0.29 (0.43)	0.21 (0.39)	3.9 (0.54)	1.22 (0.32)	4.70 (3.30)	0.58 (0.63)	4.03 (3.4)

*N = 207; *p < 0.05; **p < 0.01; Gender (1 = F; 2 = M).*
RHS, Revised Hallucination Scale; PDI, Peters Delusions Inventory; LSHS, Launay-Slade Hallucinations Scale; PQ-B, Prodromal Questionnaire-Brief.

TABLE 2 | Hierarchical regression Models' fit indexes and standardized coefficients.

	Model 1	Model 2	Model 3
Gender	−0.01	−0.01	−0.01
Age	0.07	0.07	0.05
Relationships self/other		−0.21	−0.21
Anxiety/Depression		0.25*	0.25*
Daily living/role functioning		0.06	0.07
Impulsive/addictive behavior		0.43**	0.41**
Psychosis		−0.01	−0.02
Metacognition functioning			−0.16**
F(gdl)	0.45 (2,204)	10.28 (7,199)	10.14 (8,198)
R^2	0.004	0.266**	0.291**
ΔR^2		0.261**	0.025**
F change		(5,199) 14.157**	(1,198) 6,982*

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

and (5) mastery. The total score is obtained from the sum of the five subscale scores, and this represents the overall level of metacognitive functioning. The scale showed good reliability ($\alpha = 0.91$).

RESULTS

Table 1 reports zero-order Pearson correlations among the relevant variables of the study. In particular, we included age and gender because they were used as controls in subsequent analysis; variables in columns 3–7 correspond to facets of Behavior and Symptom Identification Scale (BASIS-32); and metacognition and all the unusual experience scales were used in the study.

Since all the variables concerning unusual experiences were highly correlated, we run a principal component analysis. Eigenvalues were 2.722, 0.596, 0.437, and 0.245. This pattern clearly conformed to a one-component solution. All variables loaded strongly on the first component (range: 0.77–0.90). In the following analysis, we used the factor score deriving from the principal component analysis as an index of "Unusual Experiences."

To investigate the associations of "Unusual Experiences" with its putative predictors, we run a series of hierarchical regression models. In Model 1, we entered age and gender as socio-demographic controls. In Model 2, we added the dimensions of BASIS 32. In Model 3, we added metacognition functioning. **Table 2** summarizes the results.

Demographic control did not relate to "Unusual Experiences." Entering the facets of BASIS32 significantly increased R^2. Finally, metacognition added a further significant increase in R^2.

Anxiety/depression and impulsive/addictive behavior showed positive and significant regression coefficients. Metacognition functioning showed a negative and significant regression coefficient. The coefficients for anxiety/depression and impulsive/addictive behavior remained significant.

DISCUSSION

The aim of this study was to extend the knowledge about the relationship between metacognition, psychopathology, and PLEs, redirecting the focus on metacognitive functioning rather than on metacognitive contents. Considering the existing evidence (Larøi and Van Der Linden, 2005; Stirling et al., 2007; Sellers et al., 2017), the levels of metacognitive abilities are expected to predict the outcome of PLEs in our sample, which includes non-clinical subjects.

As expected, the different psychopathological features were strongly correlated with the whole range of PLEs, in line with previous findings (Freeman and Fowler, 2009; Armando et al., 2010; Kelleher and Cannon, 2011; Varghese et al., 2011). Moreover, the specific PLEs turned out to be strongly interrelated as well, and this result allows us to speculate on the co-occurrence of such phenomena which has already been explained in the literature (Pechey and Halligan, 2011). Thus, a principal component analysis was run to pool the whole set of PLEs into a single factor to conduct the subsequent analyses. Concerning metacognition, from correlational analyses, it emerged that it was not related to any of the psychopathological domains explored, but it was significantly and negatively correlated with all the PLE scales, suggesting a potential role of metacognition.

To clarify these relationships, a hierarchical regression was performed, which showed the result that, as expected, age and gender did not predict PLEs (step 1), the subscales, namely, anxiety/depression and impulsive/addictive behavior, significantly predicted PLEs (step 2), and that metacognitive functioning significantly explained a further portion of variance after accounting for psychopathology (step 3).

The role of the subscales related to emotional and impulsive symptoms is in line with previous studies on the topic: a long tradition of research suggests a direct involvement of emotional features in the onset of hallucinations (Slade and Bentall, 1988), and recent empirical findings confirmed and clarified that high levels of anxiety constitute a remarkable vulnerability factor for PLE predisposition in non-clinical individuals as well as depression and stress (Freeman and Garety, 2003; Johns et al., 2004; Allen et al., 2005). Concerning *impulsive/addictive behavior*, results can be explained in light of the evidence regarding the relationship between substance addiction and PLEs (Mitchell and Vierkant, 1991; Rössler et al., 2007; Brewer and Collins, 2014).

Regarding step 3 of the hierarchical regression, it is possible to notice that metacognition negatively and significantly predicts PLEs conjunctly with psychopathological factors suggesting that metacognitive functioning does not overlap with psychopathological variables; however, the percentage of variance explained by metacognition is lower than the percentage explained by psychopathological variables. This result enlarges the present knowledge stemmed from the studies previously conducted (Larøi and Van Der Linden, 2005; Stirling et al., 2007; Sellers et al., 2017) measuring metacognition through the use of MCQ, which includes, among its factors, components related to the emotional sphere (e.g., worry and rumination). The use of MSAS allows us to assert that metacognitive functioning acts as an independent factor in predicting PLEs. Metacognitive abilities seem to play a protective role in the occurrence of PLEs among non-clinical individuals, and thus, it is possible to hypothesize that a good metacognitive functioning (that implies a balanced combination of different metacognitive distinct functions) allows for the interpretation of inner mental events and outer events to provide an explanation of the reality, which prevents the individual from experiencing PLEs.

CONCLUSION

This study delivers a new inspiring perspective on the complex interplay between psychopathology, metacognition, and PLEs, suggesting that poor metacognitive functioning predisposes to the occurrence of PLEs in individuals, and such ability operates as an independent predictor along with other variables. Although rigorously conducted, this study is not exempt from limits. First, the study adopted a cross-sectional design, preventing us from making further inferences on the causal relationships between the variables observed. It is desirable that future research would extend the present findings throughout longitudinal studies to confirm the protective role of metacognitive functioning on the onset and development of PLEs. To have a comparative value between metacognitive functioning and metacognitive contents and to verify what already showed in previous literature, the MCQ questionnaire could have been administered adopting a different study design. Another limit may be constituted by the adoption of self-report questionnaires that present a desirability bias: it would be interesting in the future to assess metacognition through an interview that provides more detailed information on the peculiar metacognitive functioning of the individual. Finally, the obtained sample size is of only moderate magnitude. Therefore, the generability of results may turn out to be limited, and power could be inadequate for small population effect sizes.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GN, AC, EB, MG, and CC: conceptualization. FF, MG, and CC: methodology. EB: formal analysis and visualization. MG: investigation. MD, FF, RR, CA, ED, and ME: resources. MG, FF, and EB: data curation. MG, CC, and EB: writing—original draft preparation. CA: writing—review and editing. AC and GN: supervision. EB and MG: project administration. All authors have read and agreed to the published version of the manuscript.

REFERENCES

Allen, P., Freeman, D., McGuire, P., Garety, P., Kuipers, E., Fowler, D., et al. (2005). The prediction of hallucinatory predisposition in non-clinical individuals: examining the contribution of emotion and reasoning. *Br. J. Clin. Psychol.* 44, 127–132. doi: 10.1348/014466504X20044

Armando, M., Nelson, B., Yung, A. R., Ross, M., Birchwood, M., Girardi, P., et al. (2010). Psychotic-like experiences and correlation with distress and depressive symptoms in a community sample of adolescents and young adults. *Schizophr. Res.* 119, 258–265. doi: 10.1016/j.schres.2010.03.001

Bak, M., Krabbendam, L., Janssen, I., de Graaf, R., Vollebergh, W., and van Os, J. (2005). Early trauma may increase the risk for psychotic experiences by impacting on emotional response and perception of control. *Acta Psychiatr. Scand.* 112, 360–366. doi: 10.1111/j.1600-0447.2005.00646.x

Barkus, E., Stirling, J., French, P., Morrison, A., Bentall, R., and Lewis, S. (2010). Distress and metacognition in psychosis prone individuals: comparing high schizotypy to the at-risk mental state. *J. Nerv. Ment. Dis.* 198, 99–104. doi: 10.1097/NMD.0b013e3181cc418a

Beaton, D., Bombardier, C., Guillemin, F., and Ferraz, M. B. (2002). Recommendations for the cross-cultural adaptation of health status measures. *New York: American Academy of Orthopaedic Surgeons,* 12, 1–9.

Bentall, R. P. (1990a). The syndromes and symptoms of psychosis. *Reconstructing Schizophr.* 23–60.

Bentall, R. P. (1990b). The illusion of reality: a review and integration of psychological research on hallucinations. *Psychol. Bull.* 107, 82–95. doi: 10.1037/0033-2909.107.1.82

Brett, C. M., Johns, L. C., Peters, E. P., and McGuire, P. K. (2009). The role of metacognitive beliefs in determining the impact of anomalous experiences: a comparison of help-seeking and non-help-seeking groups of people experiencing psychotic-like anomalies. *Psychol. Med.* 39, 939–950. doi: 10.1017/S0033291708004650

Brewer, T. L., and Collins, M. (2014). A review of clinical manifestations in adolescent and young adults after use of synthetic cannabinoids. *J. Spec. Pediatr. Nurs.* 19, 119–126. doi: 10.1111/jspn.12057

Carcione, A., and Falcone, M. (1999). *Il concetto di metacognizione come costrutto clinico fondamentale per la psicoterapia*. Psicoterapia cognitiva del paziente grave. Milano: Raffaello Cortina Editore.

Carcione, A., Falcone, M., Magnolfi, G., and Manaresi, F. (1997). La funzione metacognitiva in psicoterapia: Scala di Valutazione della Metacognizione (S. Va. M.). *Psicoterapia* 9, 91–107.

Carcione, A., Riccardi, I., Bilotta, E., Leone, L., Pedone, R., Conti, L., et al. (2019). Metacognition as a predictor of improvements in personality disorders. *Front. Psychol.* 10:170. doi: 10.3389/fpsyg.2019.00170

Cartwright-Hatton, S., and Wells, A. (1997). Beliefs about worry and intrusions: the meta-cognitions questionnaire and its correlates. *J. Anxiety Disord.* 11, 279–296. doi: 10.1016/S0887-6185(97)00011-X

Conti, L. (1999). *Repertorio delle scale di valutazione in psichiatria*. Firenze: SEE.

Eisen, S. V., Grob, M. C., and Klein, A. A. (1986). BASIS: the development of a self-report measure for psychiatric inpatient evaluation. *Psychiatr. Hosp.* 17, 165–171.

Faustino, B., Branco Vasco, A., Oliveira, J., Lopes, P., and Fonseca, I. (2021). Metacognitive self-assessment scale: psychometric properties and clinical implications. *Appl. Neuropsychol. Adult* 28, 596–606. doi: 10.1080/23279095.2019.1671843

Freeman, D., and Fowler, D. (2009). Routes to psychotic symptoms: trauma, anxiety and psychosis-like experiences. *Psychiatry Res.* 169, 107–112. doi: 10.1016/j.psychres.2008.07.009

Freeman, D., and Garety, P. A. (2003). Connecting neurosis and psychosis: the direct influence of emotion on delusions and hallucinations. *Behav. Res. Ther.* 41, 923–947. doi: 10.1016/S0005-7967(02)00104-3

Frith, C. D. (1992). *The Cognitive Neuropsychology of Schizophrenia*. Lawrence Erlbaum Associates, Inc.

García-Montes, J. M., Pérez-Alvarez, M., Soto Balbuena, C., Perona Garcelán, S., and Cangas, A. J. (2006). Metacognitions in patients with hallucinations and obsessive-compulsive disorder: the superstition factor. *Behav. Res. Ther.* 44, 1091–1104. doi: 10.1016/j.brat.2005.07.008

Healy, C., and Cannon, M. (2020). Psychotic-like experiences in the general population. In: *Risk Factors for Psychosis*. Academic Press. 119–141. doi: 10.1016/B978-0-12-813201-2.00007-7

Heilskov, S., Urfer-Parnas, A., and Nordgaard, J. (2020). Delusions in the general population: a systematic review with emphasis on methodology. *Schizophr. Res.* 216, 48–55. doi: 10.1016/j.schres.2019.10.043

Hoffman, R. E. (1986). Verbal hallucinations and language production processes in schizophrenia. *Behav. Brain Sci.* 9, 503–517. doi: 10.1017/S0140525X00046781

Johns, L. C., Cannon, M., Singleton, N., Murray, R. M., Farrell, M., Brugha, T., et al. (2004). Prevalence and correlates of self-reported psychotic symptoms in the British population. *Br. J. Psychiatry*, 185, 298–305. doi: 10.1192/bjp.185.4.298

Johns, L. C., and van Os, J. (2001). The continuity of psychotic experiences in the general population. *Clin. Psychol. Rev.* 21, 1125–1141. doi: 10.1016/S0272-7358(01)00103-9

Kelleher, I., and Cannon, M. (2011). Psychotic-like experiences in the general population: characterizing a high-risk group for psychosis. *Psychol. Med.* 41, 1–6. doi: 10.1017/S0033291710001005

Larøi, F., Bless, J. J., Laloyaux, J., Kråkvik, B., Vedul-Kjelsås, E., Kalhovde, A. M., et al. (2019). An epidemiological study on the prevalence of hallucinations in a general-population sample: effects of age and sensory modality. *Psychiatry Res.* 272, 707–714. doi: 10.1016/j.psychres.2019.01.003

Larøi, F., Marczewski, P., and Van der Linden, M. (2004). Further evidence of the multi-dimensionality of hallucinatory predisposition: factor structure of a modified version of the Launay-Slade Hallucinations Scale in a normal sample. *Eur. Psychiatry* 19, 15–20. doi: 10.1016/S0924-9338(03)00028-2

Larøi, F., and Van Der Linden, M. (2005). Nonclinical Participants' Reports of Hallucinatory Experiences. *Canadian Journal of Behavioural Science / Revue canadienne des sciences du comportement* 37, 33–43. doi: 10.1037/h0087243

Larøi, F., and Woodward, T. S. (2007). Hallucinations from a cognitive perspective. *Harv. Rev. Psychiatry* 15, 109–117. doi: 10.1080/10673220701401993

Launay, G., and Slade, P. D. (1981). The measurement of hallucinatory predisposition in male and female prisoners. *Pers. Individ. Dif.* 2, 221–234. doi: 10.1016/0191-8869(81)90027-1

Maijer, K., Begemann, M. J. H., Palmen, S. J. M. C., Leucht, S., and Sommer, I. E. C. (2018). Auditory hallucinations across the lifespan: a systematic review and meta-analysis. *Psychol. Med.* 48, 879–888. doi: 10.1017/S0033291717002367

McGrath, J. J., Saha, S., Al-Hamzawi, A., Alonso, J., Bromet, E. J., Bruffaerts, R., et al. (2015). Psychotic experiences in the general population: a cross-national analysis based on 31,261 respondents from 18 countries. *JAMA Psychiatry* 72, 697–705. doi: 10.1001/jamapsychiatry.2015.0575

Mitchell, J., and Vierkant, A. D. (1991). Delusions and hallucinations of cocaine abusers and paranoid schizophrenics: a comparative study. *J. Psychol.* 125, 301–310. doi: 10.1080/00223980.1991.10543294

Morrison, A. P., Haddock, G., and Tarrier, N. (1995). Intrusive thoughts and auditory hallucinations: a cognitive approach. *Behav. Cogn. Psychother.* 23, 265–280. doi: 10.1017/S1352465800015873

Morrison, A. P., Wells, A., and Nothard, S. (2002). Cognitive and emotional predictors of predisposition to hallucinations in non-patients. *Br. J. Clin. Psychol.* 41, 259–270. doi: 10.1348/014466502760379127

Pechey, R., and Halligan, P. (2011). The prevalence of delusion-like beliefs relative to sociocultural beliefs in the general population. *Psychopathology* 44, 106–115. doi: 10.1159/000319788

Pedone, R., Semerari, A., Riccardi, I., Procacci, M., Nicolò, G., and Carcione, A. (2017). Development of a self-report measure of metacognition: The Metacognition Self-Assessment Scale (MSAS). Instrument description and factor structure. *Clin. Neuropsychiatry.* 14, 185–194. doi: 10.1037/t82174-000

Peters, E. R., Joseph, S. A., and Garety, P. A. (1999). Measurement of delusional ideation in the normal population: introducing the PDI (Peters et al. Delusions Inventory). *Schizophr. Bull.* 25, 553–576. doi: 10.1093/oxfordjournals.schbul.a033401

Preti, A., Raballo, A., Kotzalidis, G. D., Scanu, R., Muratore, T., Gabbrielli, M., et al. (2018). Quick identification of the risk of psychosis: the Italian version of the prodromal questionnaire-brief. *Clin. Pract. Epidemiol. Ment. Health* 14, 120–131. doi: 10.2174/1745017901814010154

Preti, A., Rocchi, M. B., Sisti, D., Mura, T., Manca, S., Siddi, S., et al. (2007). The psychometric discriminative properties of the Peters et al. Delusions Inventory: a receiver operating characteristic curve analysis. *Compr. Psychiatry* 48, 62–69. doi: 10.1016/j.comppsych.2006.05.003

Rössler, W., Riecher-Rössler, A., Angst, J., Murray, R., Gamma, A., Eich, D., et al. (2007). Psychotic experiences in the general population: a twenty-year prospective community study. *Schizophr. Res.* 92, 1–14. doi: 10.1016/j.schres.2007.01.002

Scott, J., Chant, D., Andrews, G., Martin, G., and McGrath, J. (2007). Association between trauma exposure and delusional experiences in a large community-based sample. *Br. J. Psychiatry* 190, 339–343. doi: 10.1192/bjp.bp.106.026708

Sellers, R., Varese, F., Wells, A., and Morrison, A. P. (2017). A meta-analysis of metacognitive beliefs as implicated in the self-regulatory executive function model in clinical psychosis. *Schizophr. Res.* 179, 75–84. doi: 10.1016/j.schres.2016.09.032

Semerari, A., Carcione, A., Dimaggio, G., Falcone, M., Nicolo, G., Procacci, M., et al. (2003). How to evaluate metacognitive functioning in psychotherapy? The metacognition assessment scale and its applications. *Clin. Psychol. Psychother.* 10, 238–261. doi: 10.1002/cpp.362

Slade, P. D., and Bentall, R. P. (1988). *Sensory Deception: A Scientific Analysis of Hallucination.* Johns Hopkins University Press.

Stirling, J., Barkus, E., and Lewis, S. (2007). Hallucination proneness, schizotypy and meta-cognition. *Behav. Res. Ther.* 45, 1401–1408. doi: 10.1016/j.brat.2006.06.003

van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., and Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol. Med.* 39, 179–195. doi: 10.1017/S0033291708003814

Varghese, D., Scott, J., Welham, J., Bor, W., Najman, J., O'Callaghan, M., et al. (2011). Psychotic-like experiences in major depression and anxiety disorders: a population-based survey in young adults. *Schizophr. Bull.* 37, 389–393. doi: 10.1093/schbul/sbp083

Vellante, M., Larøi, F., Cella, M., Raballo, A., Petretto, D. R., and Preti, A. (2012). Hallucination-like experiences in the nonclinical population. *J. Nerv. Ment. Dis.* 200, 310–315. doi: 10.1097/NMD.0b013e31824cb2ba

Wells, A., and Cartwright-Hatton, S. (2004). A short form of the metacognitions questionnaire: properties of the MCQ-30. *Behav. Res. Ther.* 42, 385–396. doi: 10.1016/S0005-7967(03)00147-5

Wells, A., and Matthews, G. (1996). Modeling cognition in emotional disorder: The S-REF model. *Behav. Res. Ther.*, 34, 881–888. doi: 10.1016/S0005-7967(96)00050-2

Wells, A., and Purdon, C. (1999). Introduction: metacognition and cognitive–behaviour therapy [Special issue]. *Clin. Psychol. Psychother.* 6, 71–72. doi: 10.1002/(SICI)1099-0879(199905)6:23.0.CO;2-G

Wells, A., White, J., and Carter, K. (1997). Attention training: effects on anxiety and beliefs in panic and social phobia. *Clin. Psychol. Psychother.* 4, 226–232. doi: 10.1002/(SICI)1099-0879(199712)4:4<226::AID-CPP129>3.0.CO;2-M

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 | Frontiers in Psychology

ORIGINAL RESEARCH
published: 07 April 2022
doi: 10.3389/fpsyg.2022.849847

A Comparative Study of Regional Homogeneity of Resting-State fMRI Between the Early-Onset and Late-Onset Recurrent Depression in Adults

Ji-fei Sun[1,2†], Li-mei Chen[1,2†], Jia-kai He[2,3], Zhi Wang[1,2], Chun-lei Guo[1,2], Yue Ma[1,2], Yi Luo[1,2], De-qiang Gao[1], Yang Hong[1], Ji-liang Fang[1] and Feng-quan Xu[1*]*

[1]Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [2]Graduate School of China Academy of Chinese Medical Sciences, Beijing, China, [3]Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing, China

Background: Neurobiological mechanisms underlying the recurrence of major depressive disorder (MDD) at different ages are unclear, and this study used the regional homogeneity (ReHo) index to compare whether there are differences between early onset recurrent depression (EORD) and late onset recurrent depression (LORD).

Methods: Eighteen EORD patients, 18 LORD patients, 18 young healthy controls (HCs), and 18 older HCs were included in the rs-fMRI scans. ReHo observational metrics were used for image analysis and further correlation of differential brain regions with clinical symptoms was analyzed.

Results: ANOVA analysis revealed significant differences between the four groups in ReHo values in the prefrontal, parietal, temporal lobes, and insula. Compared with EORD, the LORD had higher ReHo in the right fusiform gyrus/right middle temporal gyrus, left middle temporal gyrus/left angular gyrus, and right middle temporal gyrus/right angular gyrus, and lower ReHo in the right inferior frontal gyrus/right insula and left superior temporal gyrus/left insula. Compared with young HCs, the EORD had higher ReHo in the right inferior frontal gyrus/right insula, left superior temporal gyrus/left insula, and left rolandic operculum gyrus/left superior temporal gyrus, and lower ReHo in the left inferior parietal lobule, right inferior parietal lobule, and left middle temporal gyrus/left angular gyrus. Compared with old HCs, the LORD had higher ReHo in the right fusiform gyrus/right middle temporal gyrus, right middle temporal gyrus/right angular gyrus, and left rolandic operculum gyrus/left superior temporal gyrus, and lower ReHo in the right inferior frontal gyrus/right insula. ReHo in the right inferior frontal gyrus/right insula of patients with LORD was negatively correlated with the severity of 17-item Hamilton Rating Scale for Depression (HAMD-17) scores ($r = -0.5778$, $p = 0.0120$).

OPEN ACCESS

Edited by:
Alberto Parola,
Aarhus University, Denmark

Reviewed by:
Yajun Zhao,
Southwest Minzu University, China
Xize Jia,
Hangzhou Normal University, China

***Correspondence:**
Ji-liang Fang
Fangmgh@163.com
Feng-quan Xu
xufengquan@gamyy.cn

[†]These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: *06 January 2022*
Accepted: *11 March 2022*
Published: *07 April 2022*

Citation:
Sun J-f, Chen L-m, He J-k, Wang Z, Guo C-l, Ma Y, Luo Y, Gao D-q, Hong Y, Fang J-l and Xu F-q (2022) A Comparative Study of Regional Homogeneity of Resting-State fMRI Between the Early-Onset and Late-Onset Recurrent Depression in Adults. Front. Psychol. 13:849847. doi: 10.3389/fpsyg.2022.849847

Conclusion: Adult EORD and LORD patients of different ages have abnormal neuronal functional activity in some brain regions, with differences closely related to the default mode network (DMN) and the salience network (SN), and patients of each age group exhibit ReHo abnormalities relative to matched HCs.

Clinical Trial Registration: [http://www.chictr.org.cn/], [ChiCTR1800014277].

Keywords: major depressive disorder, regional homogeneity, magnetic resonance imaging, early-onset recurrent depression, late-onset recurrent depression

INTRODUCTION

Major depressive disorder (MDD) is a common clinical psychiatric disorder that is characterized by depressed mood, slowed thinking, reduced interest, and diminished cognitive function as the main clinical manifestations, and is one of the main causes of disability (Rotenstein et al., 2016; Cladder-Micus et al., 2018). It is estimated that MDD will become the second leading cause of disability in the world (Ferrari et al., 2013). Approximately 25% of MDD patients relapse within 6 months of discharge (Harlev et al., 2021), approximately one-third of MDD patients are prone to relapse within a year (Cosci et al., 2020), and the severity of MDD increases with the number of depressive relapses (Harlev et al., 2021). There is a growing awareness that the challenge of depression is relapse prevention rather than recovery (Fava et al., 2017). Therefore, understanding the pathogenesis of recurrent depression is of great importance for clinical work.

Previous studies have found that patients with recurrent depression at different ages have different clinical features (Driscoll et al., 2005; Hammen et al., 2008; Sung et al., 2013). Early onset recurrent depression (EORD) is associated with a higher risk of life-long persistent depression, a higher risk of suicide, worse social cognitive function, and greater anxiety than late onset recurrent depression (LORD) (Hammen et al., 2008; Sung et al., 2013). And LORD is also associated with more cognitive dysfunction than EORD (Driscoll et al., 2005). A study has shown that EORD has a greater risk of relapse than LORD (Cassano et al., 1993). Therefore, recurrent depression in different age groups may be associated with different neuropathological mechanisms.

Moreover, recurrent depression is more heritable and increases the risk of depression in offspring (Burcusa and Iacono, 2007; Benjet et al., 2020; Jaffee et al., 2021). For example, one study found that adolescent children whose parents had recurrent depression had a 4.21-fold greater probability of reaching MDD than adolescents whose parents were never depressed (Jaffee et al., 2021). A meta analysis showed a degree of specificity in different subtypes of depression, and understanding their specificity can be a guide to clinical treatment (Harald and Gordon, 2012).

However, the clinical characteristics of EORD and LORD depend on the different cut-off ages (Cassano et al., 1993; Driscoll et al., 2005; Hammen et al., 2008). An age-specific study of recurrent depression in adolescents showed that EORD recurred between 15 and 20 years of age, and LORD after 20 years of age (Hammen et al., 2008). A study of recurrent depression in older adults showed that the age of EORD was defined as before 59 years of age, while LORD was defined as after 60 years of age (Driscoll et al., 2005). Another study defined the age of EORD before 44 years of age and LORD after 45 years of age (Cassano et al., 1993). The above studies suggest that the biological evidence for the age limits of EORD and LORD is unclear and there is no unified consensus on age classification criteria. In this study, the age of EORD was defined as 18 to 29 years and LORD was defined from 30 to 45 years based on previous studies to avoid the effect of (>45 years) cerebrovascular disease (Shen et al., 2017).

In recent years, with the development of neuroimaging technology, resting-state functional MRI (rs-MRI) has been widely used in insomnia (Li et al., 2019), schizophrenia (Huang et al., 2020), autism (Shi et al., 2020), and other psychiatric disorders. Regional homogeneity (ReHo) is an important indicator for the study of rs-fMRI. ReHo can reflect the synchronization of brain functional activity state in localized regions of whole-brain voxels and is used to assess the level of coordination of neural activity in local brain regions (Zang et al., 2004). In addition, the ReHo indicator has been used to study changes in neuronal functional activity in depressive subtypes of the brain, and abnormalities have been found in brain regions such as the frontal lobe, precuneus, and insula (Chen et al., 2012; Shen et al., 2017; Zhang et al., 2021). The ReHo values of these abnormal brain regions are closely correlated with the default mode network (DMN) and the salience network (SN). The correlation of ReHo values with abnormal brain regions in subtypes of depression is useful for understanding the degree of severity of the disease and neuroimaging markers (Shen et al., 2017; Liu et al., 2021). Previous studies have also found that differences in brain function across subtypes of depression are associated with abnormalities in DMN and SN (Li et al., 2017; Cai et al., 2021). However, there is a lack of neuroimaging studies on the differences between EORD and LORD, and the differences in regional neural activity between EROD and LORD are unclear.

In this study, we focused on the differences in local brain functional activity between EORD (18–29 years) and LORD (30–45 years) and whether there was a correlation between the depression group and clinical symptoms. Based on previous studies of age differences in subtypes of depression, we hypothesized that (1) differences in local brain functional

activity in EORD and LORD may be closely related to the DMN and SN. (2) Increased or decreased local brain function of ReHo in EORD and LORD may be associated with clinical depressive symptoms.

MATERIALS AND METHODS

Subjects

A total of 36 patients (18 with EORD and 18 with LORD) were diagnosed with recurrent depression from the Department of Psychosomatic Medicine, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, the Department of Psychiatry, Beijing First Hospital of Integrative Medicine, the Department of Psychiatry, Yuquan Hospital, Qinghua University, and the Department of Psychiatry, Xuanwu Hospital, Capital Medical University. The inclusion criteria were as follows: (1) According to the diagnostic criteria for depression in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) of the American Psychiatric Association, all patients were diagnosed by two experienced psychiatrists; (2) All patients recurred after antidepressant treatment, relapsed between the ages of 18 and 45 years, and were off medication for at least 4 weeks prior to admission; (3) 17-item Hamilton Rating Scale for Depression (HAMD-17) score > 17; and (4) right-handedness. 36 gender- and age-matched healthy controls (HCs; 25 females and 11 males) were also included in the HCs: (1) HAMD-17 score < 7; (2) right-handedness; and (3) no history of mental illness.

Exclusion criteria of patients and HCs include the following items: (1) suffering from serious mental illness and other diseases such as cardiovascular and cerebrovascular; (2) with a history of drug and alcohol abuse; (3) had any MRI contraindications, such as heart pacemaker, metal fixed false teeth, or severe claustrophobia; and (4) were pregnant or lactating.

Clinical Materials and Subgroups

Data were collected for the study population including gender, age, education level, frequency of recurrence, and duration of disease. Subjects were assessed for depressive symptoms by an experienced psychiatrist using the HAMD-17 scale. Based on previous studies on age division of first-episode depression to avoid the influence of cerebrovascular diseases (Shen et al., 2016, 2017), we initially divided all recurrent depression patients with recurrent depression into EORD group (18–29 years) and LORD group (30–45 years). The HCs were also matched corresponding to two subgroups: young HCs (18–29 years) and old HCs (30–45 years).

Scan Acquisition

All subjects in this study underwent data acquisition using a Magneton Skyra 3.0 T MRI scanner (Siemens, Germany). Subjects were informed prior to the scan to remain awake during the scan and to avoid active thinking activities. During the scan, the subject is required to use earplugs and wear noise-canceling headphones, use a hood to immobilize the head, and lie flat on the examination bed. The scanning procedure contains a localizer, a high resolution three-dimensional T1-weighted imaging (3D-T1WI), and a blood oxygenation level-dependent fMRI (BOLD-fMRI).

The scanning parameters were as follows: 3D-T1WI: time repetition (TR)/time echo (TE) = 2500/2.98 ms, flip angle = 7°, matrix = 64 × 64, field of view (FOV) = 256 mm × 256 mm, slice thickness = 1 mm, slice number = 48, slices =192, scanning time 6 min 3 s; BOLD-fMRI: TR/TE = 2000/30 ms, flip angle = 90°, matrix 64 × 64, field of view = 240 mm × 240 mm, slice number = 43, slice thickness/spacing = 3.0/1.0 mm, and 200 volumes were obtained, scanning time 6 min 40 s.

fMRI Data Analysis

fMRI Data Preprocessing

The rs-fMRI data were pre-processed using Data Processing Assistant for Resting-State fMRI (DPARSF) software (DPABI5.0; Chao-Gan and Yu-Feng, 2010) in MATLAB (Mathworks, Inc., Natick, MA, United States).[1] First, image format conversion was performed to convert the raw data DICOM format to NIFTI format. Next, the first 10 time points were excluded. Then, slice timing, realign, was performed to remove subjects with head movement translations exceeding 2.0 mm and rotations exceeding 2.0°. Spatial normalization was performed by normalizing the functional images to Montreal Neurological Institute (MNI) space. Linear regression was performed on the covariates of head movement, white matter (WM), and cerebrospinal fluid (CSF) signals to reduce the effects. Finally, we removed the linear drift and set the filter to 0.01–0.08 Hz to reduce the effect of noise.

ReHo Analysis

The pre-processed data images were analyzed using DPARSF software, and ReHo was calculated by Kendall correlation coefficient (Kendall & Gibbons, 1990), based on voxels to calculate the synchronization of the time series of a given voxel with the time series changes of its 26 adjacent voxels, and a ReHo map was obtained for each subject. The ReHo map of each subject was divided by the whole-brain mean ReHo value to obtain a normalized ReHo map. Finally, the smReHo maps were obtained by smoothing using a 6 mm × 6 mm × 6 mm Gaussian smoothing kernel for subsequent statistical analysis.

Statistical Analysis

Clinical Data Analysis

The clinical data were analyzed with SPSS 23.0 statistics software (IBM Corp, Somers, New York, United States). One-way analysis of variance (ANOVA) was used to compare age and education level between the four groups, and the chi-square test was used to compare gender. The duration of illness, frequency of recurrence, and HAMD-17 scores were compared between

[1]http://www.rfmri.org/DPARSF

patient groups using a two-sample *t*-test. $p < 0.05$ was statistically significant.

fMRI Data Analysis

Image data statistics were analyzed using the DPARSF toolbox, and a voxel-based one-way ANOVA was performed to compare whole-brain ReHo maps of the four groups. Gender, age, education level, and framewise displacement (FD) metric (derived from Jenkinson's formula) of the four groups of subjects were used as covariates, brain areas with ReHo differences between the four groups were corrected for Gaussian random fields (GRF), and corrected cluster levels were settled as $p < 0.05$ and threshold voxel levels $p < 0.005$ were defined as statistically different. The time series means of the peak voxel ReHo values of the four contrasting brain regions were extracted, and *post-hoc* two-sample *t*-tests were performed on the ReHo values between the paired groups (EORD *vs.* young HCs, LORD *vs.* old HCs, LORD *vs.* EORD) using SPSS 23.0 software, and the results were Bonferroni corrected ($p < 0.01$).

In order to verify the relationship between ReHo values and clinical symptoms, Pearson correlation analysis was performed by extracting ReHo values of abnormal brain regions and HAMD-17 scores in patient groups, separately, and $p < 0.05$ was statistically significant.

RESULTS

Characteristics of Research Samples

A total of 18 patients with EROD, 18 patients with LORD, 18 young HCs, and 18 old HCs met the study criteria. There were no statistical differences between the MDD group and the HCs and in terms of gender and years of education, and there were statistical differences in age comparisons between the four groups. There were no statistical differences in disease duration, frequency of recurrence, and HAMD-17 scores between the two MDD groups (**Table 1**).

ReHo: Group Differences

A one-way ANOVA was performed on the ReHo values of the four groups using age, gender, years of education, and mean frame displacement as covariates. ReHo was found to be significantly significant difference in the right inferior frontal gyrus/right insula, left superior temporal gyrus/left insula, left inferior parietal lobule, right inferior parietal lobule, right fusiform gyrus/right middle temporal gyrus, left middle temporal gyrus/left angular gyrus, right middle temporal gyrus/right angular gyrus, and left rolandic operculum gyrus/left superior temporal gyrus significant differences between superior gyrus groups (**Table 2**; **Figure 1**).

Compared with young HCs, the EORD had higher ReHo in the right inferior insular frontal gyrus/right insula, left superior temporal gyrus/left insula, and left rolandic operculum gyrus/superior temporal gyrus, and lower ReHo values in the left inferior parietal lobule, right inferior parietal lobule, and left middle temporal gyrus/left angular gyrus (**Figure 2**).

Abnormal ReHo in LORD Patients *vs* Old HC

Compared with old HCs, the LORD had higher ReHo in the right fusiform gyrus/right middle temporal gyrus, right middle temporal gyrus/right angular gyrus, left rolandic operculum gyrus/left superior temporal gyrus, and lower ReHo values in the right inferior frontal gyrus/right insula (**Figure 2**).

Abnormal ReHo in LORD Patients *vs* EORD

Compared with EORD, the LORD group had higher ReHo in the right fusiform gyrus/right middle temporal gyrus, left middle temporal gyrus/left angular gyrus, and right middle temporal gyrus/right angular gyrus, and lower ReHo in the

TABLE 1 | Demographic and clinical characteristics of the study participants.

Variables (mean ± SD)	HCs		MDD		$t(F)/\chi^2$	*p*
Age (years)	31.61 ± 7.01		31.58 ± 7.69		0.016	0.987[a]
Gender (male/female)	11/25		10/26		0.670	0.795[b]
Years of education	15.80 ± 3.90		15.02 ± 2.96		0.952	0.344[a]
HAMD-17 score	1.97 ± 0.99		23.61 ± 3.31		–37.501	0.000[a]
	Young HCs	**Old HCs**	**EORD**	**LORD**		
Age (years)	25.16 ± 3.36	38.00 ± 4.85	25.94 ± 2.31	37.27 ± 5.28	51.594	0.000[c]
Gender (male/female)	5/13	6/12	4/14	6/12	0.739	0.864[d]
Years of Education	16.72 ± 2.46	13.77 ± 4.27	15.38 ± 2.11	14.66 ± 3.64	2.643	0.056[e]
Frequency of recurrence			1.33 ± 0.59	1.44 ± 0.61	–0.551	0.585[a]
Illness duration (months)			19.77 ± 12.37	23.16 ± 15.64	–0.721	0.476[a]
HAMD-17 score	1.94 ± 1.05	2.00 ± 0.97	23.72 ± 3.23	23.38 ± 3.53	–0.397	0.694[f]

HCs, healthy controls; MDD, major depressive disorder; EORD, early onset recurrent depression; LORD, late onset recurrent depression; and HAMD-17, 17-item Hamilton Rating Scale for Depression.

[a]*Value of p obtained by two-sample t-test.*

[b]*Value of p for gender distribution in the two groups was obtained by chi-square test.*

[c]*Value of p were obtained by one-way analysis of variance tests. Post-hoc t-test: p = 0.964(EORD vs. Young HCs), p = 0.999(LORD vs. Old HCs).*

[d]*Value of p of gender distribution among the four groups were obtained by chi-square test: p = 0.717(EORD vs. Young HCs), p = 0.457(LORD vs. Old HCs).*

[e]*The values of p were obtained by one-way analysis of variance tests. Post-hoc t-test: p = 0.222(EORD vs. Young HCs), p = 0.507(LORD vs. Old HCs).*

[f]*Values of p were obtained by two-sample t-test p = 0.694 (EORD vs. LORD).*

TABLE 2 | One-way ANOVA between the four groups for differences in ReHo values Brain areas.

Brain regions	Side	Peak coordinates (MNI)			Cluster size	*F*-values
		X	Y	Z		
Inferior frontal gyrus/insula	R	48	12	9	26	12.06
Superior temporal gyrus/insula	L	−42	−6	−9	24	7.176
Inferior parietal lobule	L	−27	−42	39	75	15.99
Inferior parietal lobule	R	21	−42	54	74	14.1
Fusiform gyrus/middle temporal gyrus	R	45	−27	−9	67	14.4
Middle temporal gyrus/angular gyrus	L	−42	−51	21	27	9.305
Middle temporal gyrus/angular gyrus	R	39	−57	18	33	13.215
Rolandic operculum gyrus/superior temporal gyrus	L	−36	−30	18	23	7.576

F is the statistical value of the difference in peak voxel ReHo between the EORD and LORD groups and HCs. $p<0.05$, GRF corrected, $p<0.005$, cluster size > 10. Abnormal ReHo in EORD patients VS young HC.

right inferior frontal gyrus/right insula and left superior temporal gyrus/left insula (**Figure 2**).

Correlations Between the Abnormal ReHo and Depressive Symptoms in the Patients

To test whether there was a relationship between the severity of depressive symptoms and abnormal ReHo in the depressed group in this study, we performed further correlation analyses. We found a negative correlation between HAMD-17 scores and ReHo values in the right inferior frontal gyrus/right insula in the LORD group ($r=-0.5778$, $p=0.0120$; **Figure 3**).

DISCUSSION

To our knowledge, this is the first to analyze and compare the regional neural activity of LORD and EORD based on rs-MRI technique using the ReHo method. The results of this study found that adult EORD and LORD have abnormal neuronal activity in some of the same brain regions at different ages. And relative to matched controls, different ReHo abnormalities were demonstrated at each age. Correlation analysis showed that ReHo values in the right inferior frontal gyrus/right insula were negatively correlated with clinical scales and could be used as a neuroimaging marker to distinguish LORD from EORD. This study provides new insights into functional brain activity in recurrent depression at different ages.

The results of this study showed that LORD had higher ReHo in the right fusiform gyrus/right middle temporal gyrus, left middle temporal gyrus/left angular gyrus, and right middle temporal gyrus/right angular gyrus compared with EORD. The concept of DMN was introduced by (Raichle et al., 2001) in 2001, which suggests that some brain areas are more active than others in a quiet, resting state without a task and are "activated," while functional activity decreases when performing a task and becomes "negatively activated." This region consists of the ventral medial prefrontal cortex, posterior cingulate/retosplenial cortex, lateral temporal cortex, dorsal medial prefrontal cortex, and inferior parietal lobules (including the angular gyrus) and is involved in the extraction of situational memory, detection of surroundings, and introspective states (Raichle et al., 2001; Raichle and Snyder, 2007; Buckner et al., 2008). The results of this study showed that most of the brain regions belonged to DMN. Most studies have regarded abnormal DMN function as a neurobiological marker of MDD (Gao et al., 2018; Goldstein-Piekarski et al., 2018; Sendi et al., 2021), DMN also changes in different stages of disease and at different ages, which is closely related to changes in clinical depression symptoms, and different therapeutic effects will also produce different responses to DMN (Huang et al., 2020; Pan et al., 2020). The middle temporal gyrus and angular gyrus are important constituent parts of the DMN (Buckner et al., 2008). The middle temporal gyrus not only participates in self-referential processing, but also plays an important role in autobiographical memory and regulates human emotional and mental activities (Sheldon et al., 2016). The angular gyrus is located at the junction of the parietal, temporal, and occipital lobes and is primarily involved in ontological functions such as semantic processing, number processing, attention, and memory (Seghier, 2013). Previous studies have shown abnormal DMN functional activity in patients with recurrent depression (Marchetti et al., 2012; Yan et al., 2019; Berwian et al., 2020). It was found that the recurrent depression group had hyperactivation in the right middle temporal gyrus compared to the HCs (Liu et al., 2017, 2019). Another study also found that the recurrent depression had abnormal bold signaling in the angular gyrus compared to the HCs (Yüksel et al., 2018). All of the above studies suggest abnormalities in the middle temporal gyrus and angular gyrus in patients with recurrent depression. The fusiform gyrus belongs to the visual cognitive network and together with the inferior temporal gyrus forms the ventral visual pathway, which is involved in the recognition of objects, words, and faces. The neural response of the fusiform gyrus increases with the intensity of the sad stimulus (Wu et al., 2011). ReHo was higher in the left superior temporal gyrus (Chen et al., 2012) and right fusiform gyrus (Shen et al., 2017) in late onset depression (LOD) compared with early onset depression (EOD), suggesting that compensatory elevation of the left superior temporal gyrus and right fusiform gyrus may have a pathogenetic mechanism for LOD. This is broadly consistent with the results of the present study. Therefore, the

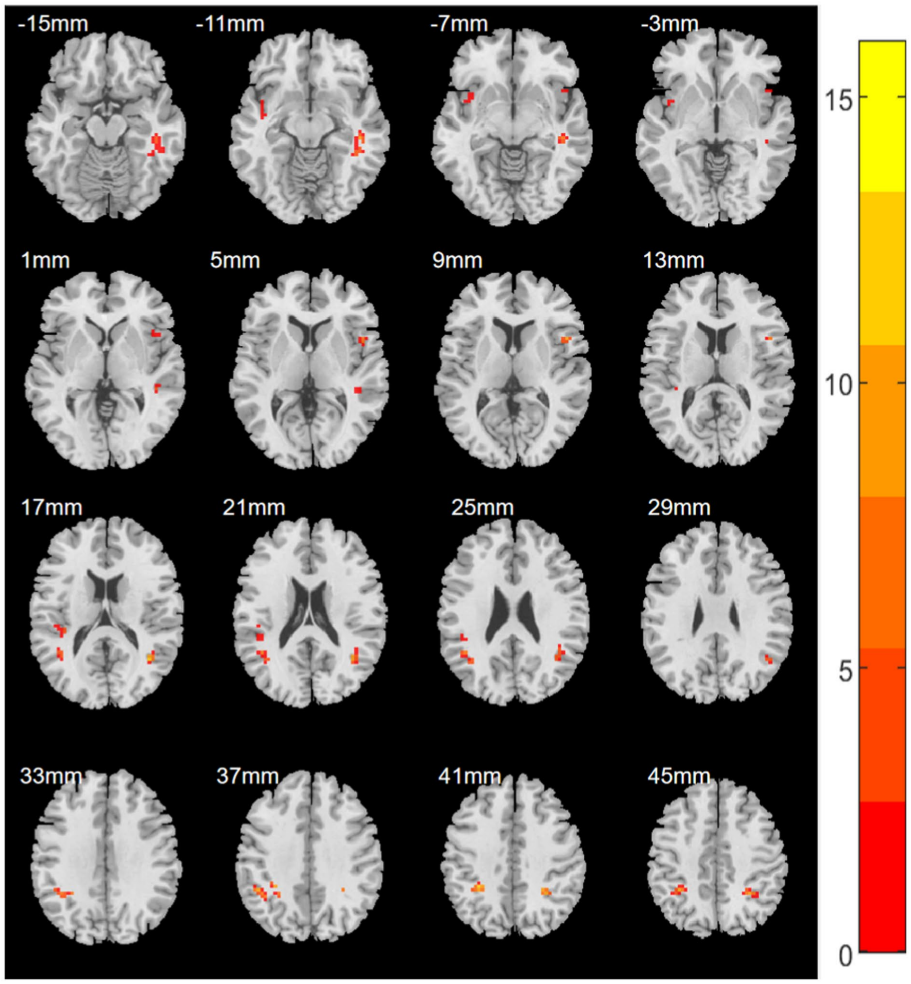


FIGURE 1 | Statistical maps showing ANOVA results for ReHo abnormalities between EORD or LORD patients and HCs (GRF corrected). Color bar indicates red to yellow showing enhancement of ReHo values.

results of the present study suggest that ReHo is elevated in the right fusiform/right middle temporal gyrus, left middle temporal/left angular gyrus, and right middle temporal/right angular gyrus in LORD compared with EORD, and this partial compensatory elevation of DMN may be one of the differences in the brain mechanisms of recurrent depression in these two subtypes.

We also found that LORD had lower ReHo than EORD in the right inferior frontal gyrus/right insula and left superior temporal gyrus/left insula. The right inferior frontal gyrus, part of the ventral lateral prefrontal cortex, plays an important role in response inhibition and is primarily responsible for downregulating negative emotional responses and inhibiting unwanted information or inappropriate behavior (Kravitz et al., 2011). The insula is a cortical structure located deep in the brain and is involved in the processing of information related to emotion, attention, visceral sensation, etc., that is transmitted to the brain, as well as being involved in taste and vision (Sprengelmeyer et al., 2011). The insula cortex is connected to the frontal limbic area (Guo et al., 2015). Previous studies have found that metabolism in the insula cortex is enhanced in HCs when they recall sad events (Reiman et al., 1997). These two brain areas are closely related to the SN, which has been shown to be a functional brain network involved in perception, cognition, emotion, and social awareness (Menon and Uddin, 2010; Ham et al., 2013; Uddin, 2015; Chand and Dhamala, 2016; Touroutoglou et al., 2016). The SN has an important regulatory role for the DMN and the executive control network (ECN) (Touroutoglou et al., 2016). Previous, it was found that patients with recurrent depression had lower amplitude of low frequency fluctuations (ALFF) (Liu et al., 2017) and gray matter volume (Stratmann et al., 2014) in the right insula compared to HCs. It has also been found that middle-aged and older women with a history of depression have reduced FC between SN (right insula seed) and ECN (Vega et al., 2020). All of the above studies found that abnormalities in the function of the insula were closely associated with recurrent depression. Previous studies have

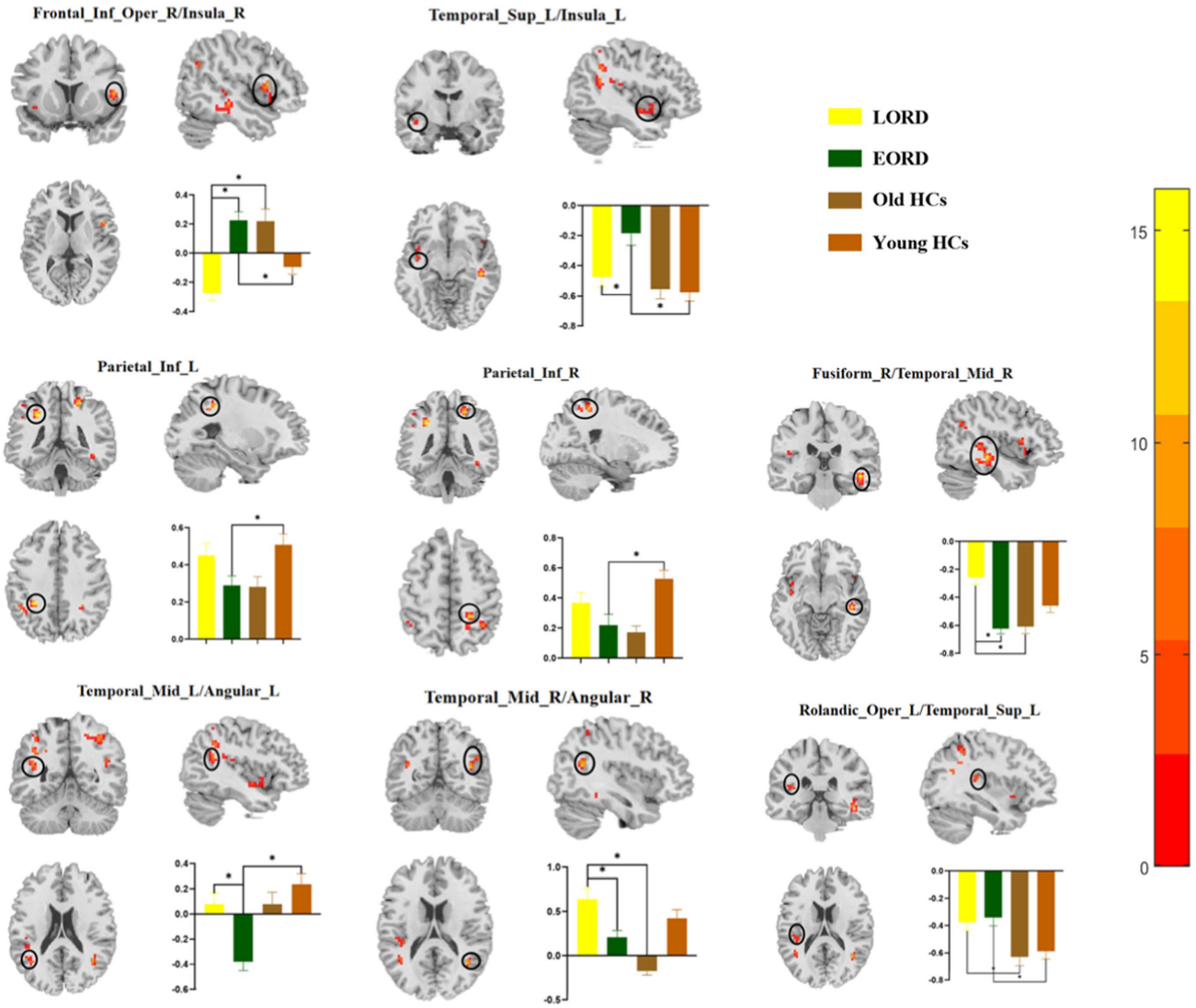


FIGURE 2 | *Post-hoc* two-sample *t*-tests (Bonferroni corrected) comparison showing ReHo values differences at peak voxel between each pair group (EORD vs. young HCs, LORD vs. old HCs, and LORD vs. EORD). EORD, early onset recurrent depression; LORD, late onset recurrent depression; young HCs, young healthy controls; and old HCs, old healthy controls. Frontal_Inf_Oper_R/Insula_R = right inferior frontal gyrus/right insula; Temporal_Sup_L/Insula_L = left superior temporal gyrus/left insula; Parietal_Inf_L = left inferior parietal lobule; Parietal_Inf_R = right inferior parietal lobule; Fusiform_R/Temporal_Mid_R = right fusiform gyrus/right middle temporal gyrus; Temporal_Mid_L/Angular_L = left middle temporal gyrus/left angular gyrus; Temporal_Mid_R/Angular_R = right middle temporal gyrus/right angular gyrus; and Rolandic_Oper_L/Temporal_Sup_L = left rolandic operculum gyrus/left superior temporal gyrus.

found significantly enhanced ReHo in the right insula of LOD compared to old HCs, suggesting SN abnormalities in patients with LOD depression (Shen et al., 2017). Therefore, the results of this study suggest that there are differences in SN between LORD and EORD, which may also be the neuropathological pathogenesis of these two subtypes of recurrent depression. Further correlation analysis in this study showed that ReHo values in the right inferior insular frontal gyrus/right insula of the LORD group were negatively correlated with HAMD-17 scale scores. It is suggested that this region can be used as a neuroimaging marker with high sensitivity and specificity to distinguish between the two subtypes of recurrent depression. More research is needed in the future to clarify this point.

On the other hand, we also found that the ReHo in the left superior temporal gyrus/left insula were lower in the LORD compared to the EORD. The superior temporal gyrus is part of the auditory-verbal center and plays an important role in the processing of emotions, memory, and mental activity (Yao et al., 2018). Previous studies found that the LOD had higher ReHo values in the left superior temporal gyrus compared to the EOD, suggesting that compensatory elevation of ReHo in the left superior temporal gyrus may be the pathogenesis of LOD patients (Chen et al., 2012). Therefore, the results of

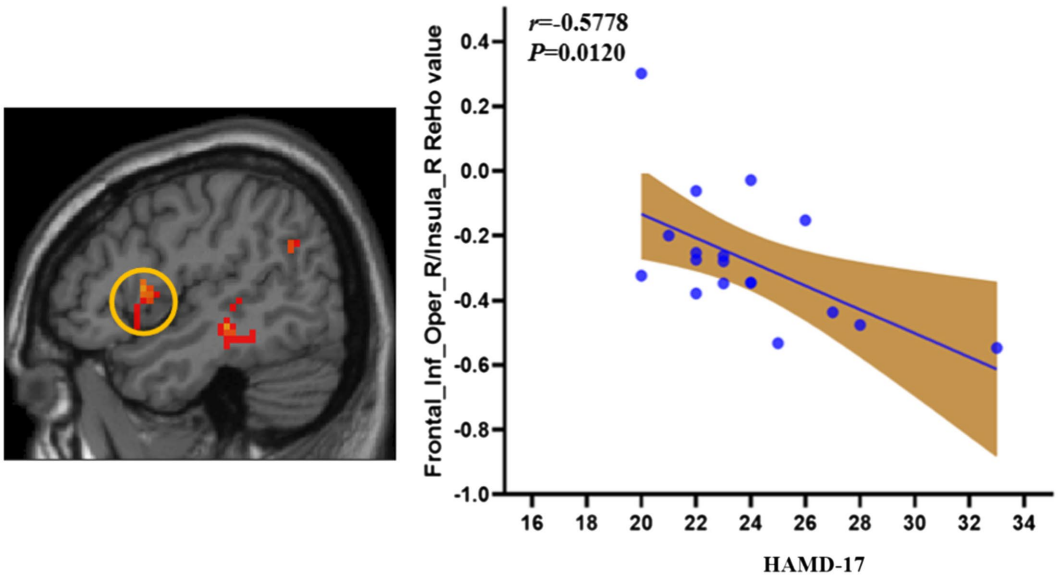


FIGURE 3 | The correlation of the ReHo and HDRS symptom in LORD patients. LORD, late onset recurrent depression.

this study suggest that the left superior temporal gyrus/left insula is also an important brain region in which differences exist between the two subgroups of patients with recurrent depression.

Interestingly, we observed that both the LORD and EROD groups together had increased ReHo in the left rolandic operculum gyrus/left superior temporal gyrus compared to HCs. The rolandic operculum gyrus and superior temporal gyrus belong to the auditory network (Oh et al., 2018; Koshiyama et al., 2020), which has the function of integrating auditory stimuli and processing them, and is closely related to human emotions (Phillips et al., 2001; Wang et al., 2019). Previous studies have found that depression scale scores are positively correlated with gray matter in the left rolandic operculum gyrus and left superior temporal gyrus, suggesting that these two brain regions also play a role in mood regulation (Besteher et al., 2017). One study showed that the insula is closely related to the operculum gyrus and that the insula/operculum gyrus is involved in interoception and interoceptive awareness, processes signals critical for self-awareness (Blefari et al., 2017). A meta-analysis showed that depressed patients had significantly increased activation of the right superior temporal gyrus during working memory (WM) compared to the HCs (Wang et al., 2015). In addition, abnormal fMRI connections between the right superior temporal lobe and subgenual cingulate cortex were also found in previous studies in patients with recurrent depression (Lythe et al., 2015). The above findings favorably support our observation of ReHo anomalies in the left rolandic operculum gyrus and left superior temporal gyrus. Therefore, these findings suggest that (Rotenstein et al., 2016) patients with recurrent depression may have features of auditory network dysfunction. (Rotenstein et al., 2016) ReHo abnormalities in the left rolandic operculum gyrus and left superior temporal gyrus may be important brain regions in distinguishing the recurrent depression group from the HCs, independent of age of onset.

However, there are still several limitations to this study. First, the small sample size of this study will affect the statistical validity to some extent, and a larger sample size is needed to confirm or overturn the current results. Second, only patients with recurrent depression were recruited in this study. Although there was a discontinuation period of at least 4 weeks, there may still be an influence of potential factors such as antidepressants. Finally, although there was no statistical difference in the frequency of recurrence between the two subtypes of depression groups, the study of first recurrence of depression in different age groups is more clinically relevant and further research in this area will be enhanced in the future.

CONCLUSION

In conclusion, this study was based on rs-fMRI technique and used ReHo index analysis to initially explore the differences in regional neural activity between LORD and EORD. We found that although LORD and EORD had similar clinical symptoms, abnormal changes in neurological functional activity existed in some of the same brain regions, suggesting that different pathogenesis may exist in patients with different age onset. In addition, patients of each age group also exhibited different ReHo abnormalities relative to HCs.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was reviewed and approved by the Ethics Committee of Guang'anmen Hospital, Chinese Academy of Traditional Chinese Medicine, China (NO. 2017-021-SQ). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

J-fS and L-mC drafted the manuscript and participated in data collection and analysis. J-kH, D-qG, C-lG, YM, YL, YH, and F-qX involved in data analysis and project design work. J-lF involved in the design of the experimental study and the revision of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by the Science and Technology Innovation Project of Chinese Academy of Traditional Chinese Medicine (CI2021A03301), and National Natural Science Foundation of China (82174282, 81774433), National Key Research and Development Program of China (2018YFC1705800).

ACKNOWLEDGMENTS

The authors thank all the patients and healthy people who participated in the experiment for their support.

REFERENCES

Benjet, C., Albor, Y. C., Bocanegra, E. S., Borges, G., Méndez, E., Casanova, L., et al. (2020). Incidence and recurrence of depression from adolescence to early adulthood: a longitudinal follow-up of the Mexican adolescent mental health survey. *J. Affect. Disord.* 263, 540–546. doi: 10.1016/j.jad.2019.11.010

Berwian, I. M., Wenzel, J. G., Kuehn, L., et al. (2020). The relationship between resting-state functional connectivity, antidepressant discontinuation and depression relapse. *Sci. Rep.* 10:22346. doi: 10.1038/s41598-020-79170-9

Besteher, B., Gaser, C., Langbein, K., Dietzek, M., Sauer, H., and Nenadić, I. (2017). Effects of subclinical depression, anxiety and somatization on brain structure in healthy subjects. *J. Affect. Disord.* 215, 111–117. doi: 10.1016/j.jad.2017.03.039

Blefari, M. L., Martuzzi, R., Salomon, R., Bello-Ruiz, J., Herbelin, B., Serino, A., et al. (2017). Bilateral Rolandic operculum processing underlying heartbeat awareness reflects changes in bodily self-consciousness. *Eur. J. Neurosci.* 45, 1300–1312. doi: 10.1111/ejn.13567

Buckner, R. L., Andrews-Hanna, J. R., and Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38. doi: 10.1196/annals.1440.011

Burcusa, S. L., and Iacono, W. G. (2007). Risk for recurrence in depression. *Clin. Psychol. Rev.* 27, 959–985. doi: 10.1016/j.cpr.2007.02.005

Cai, Y., Elsayed, N. M., and Barch, D. M. (2021). Contributions from resting state functional connectivity and familial risk to early adolescent-onset MDD: results from the adolescent brain cognitive development study. *J. Affect. Disord.* 287, 229–239. doi: 10.1016/j.jad.2021.03.031

Cassano, G. B., Akiskal, H. S., Savino, M., Soriani, A., Musetti, L., and Perugi, G. (1993). Single episode of major depressive disorder. First episode of recurrent mood disorder or distinct subtype of late-onset depression? *Eur. Arch. Psychiatry Clin. Neurosci.* 242, 373–380. doi: 10.1007/BF02190251

Chand, G. B., and Dhamala, M. (2016). The salience network dynamics in perceptual decision-making. *NeuroImage* 134, 85–93. doi: 10.1016/j.neuroimage.2016.04.018

Chao-Gan, Y., and Yu-Feng, Z. (2010). DPARSF: A MATLAB Toolbox for "Pipeline" Data Analysis of Resting-State fMRI. *Front. Syst. Neurosci.* 4:13. doi: 10.3389/fnsys.2010.00013

Chen, J. D., Liu, F., Xun, G. L., Chen, H. F., Hu, M. R., Guo, X. F., et al. (2012). Early and late onset, first-episode, treatment-naive depression: same clinical symptoms, different regional neural activities. *J. Affect. Disord.* 143, 56–63. doi: 10.1016/j.jad.2012.05.025

Cladder-Micus, M. B., Speckens, A. E. M., Vrijsen, J. N., Donders, A. R. T., Becker, E. S., and Spijker, J. (2018). Mindfulness-based cognitive therapy for patients with chronic, treatment-resistant depression: a pragmatic randomized controlled trial. *Depress. Anxiety* 35, 914–924. doi: 10.1002/da.22788

Cosci, F., Guidi, J., Mansueto, G., and Fava, G. A. (2020). Psychotherapy in recurrent depression: efficacy, pitfalls, and recommendations. *Expert. Rev. Neurother.* 20, 1169–1175. doi: 10.1080/14737175.2020.1804870

Driscoll, H. C., Basinski, J., Mulsant, B. H., Butters, M. A., Dew, M. A., Houck, P. R., et al. (2005). Late-onset major depression: clinical and treatment-response variability. *Int. J. Geriatr. Psychiatry* 20, 661–667. doi: 10.1002/gps.1334

Fava, G. A., Cosci, F., Guidi, J., and Tomba, E. (2017). Well-being therapy in depression: new insights into the role of psychological well-being in the clinical process. *Depress. Anxiety* 34, 801–808. doi: 10.1002/da.22629

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J. L., et al. (2013). Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med.* 10:e1001547. doi: 10.1371/journal.pmed.1001547

Gao, W., Chen, S., Biswal, B., Lei, X., and Yuan, J. (2018). Temporal dynamics of spontaneous default-mode network activity mediate the association between reappraisal and depression. *Soc. Cogn. Affect. Neurosci.* 13, 1235–1247. doi: 10.1093/scan/nsy092

Goldstein-Piekarski, A. N., Staveland, B. R., Ball, T. M., Yesavage, J., Korgaonkar, M. S., and Williams, L. M. (2018). Intrinsic functional connectivity predicts remission on antidepressants: a randomized controlled trial to identify clinically applicable imaging biomarkers. *Transl. Psychiatry* 8:57. doi: 10.1038/s41398-018-0100-3

Guo, W., Liu, F., Xiao, C., Zhang, Z., Liu, J., Yu, M., et al. (2015). Decreased insular connectivity in drug-naive major depressive disorder at rest. *J. Affect. Disord.* 179, 31–37. doi: 10.1016/j.jad.2015.03.028

Ham, T., Leff, A., de Boissezon, X., Joffe, A., and Sharp, D. J. (2013). Cognitive control and the salience network: an investigation of error processing and effective connectivity. *J. Neurosci.* 33, 7091–7098. doi: 10.1523/JNEUROSCI.4692-12.2013

Hammen, C., Brennan, P. A., Keenan-Miller, D., and Herr, N. R. (2008). Early onset recurrent subtype of adolescent depression: clinical and psychosocial correlates. *J. Child Psychol. Psychiatry* 49, 433–440. doi: 10.1111/j.1469-7610.2007.01850.x

Harald, B., and Gordon, P. (2012). Meta-review of depressive subtyping models. *J. Affect. Disord.* 139, 126–140. doi: 10.1016/j.jad.2011.07.015

Harlev, D., Ravona-Springer, R., Nuriel, Y., and Fruchter, E. (2021). Sleep monitoring using WatchPAT device to predict recurrence of major depression in patients at high risk for major depression disorder recurrence: a case report. *Front. Psychiatry* 12:572660. doi: 10.3389/fpsyt.2021.572660

Huang, H., Botao, Z., Jiang, Y., Tang, Y., Zhang, T., Tang, X., et al. (2020). Aberrant resting-state functional connectivity of salience network in first-episode schizophrenia. *Brain Imaging Behav.* 14, 1350–1360. doi: 10.1007/s11682-019-00040-8

Jaffee, S. R., Sligo, J. L., McAnally, H. M., Bolton, A. E., Baxter, J. M., and Hancox, R. J. (2021). Early-onset and recurrent depression in parents increases

risk of intergenerational transmission to adolescent offspring. *J. Child Psychol. Psychiatry* 62, 979–988. doi: 10.1111/jcpp.13356

Kendall, M. G., and Gibbons, J. D. (1990) in *Rank Correlation Methods. 5th Edn.* ed. E. Arnold (London New York, NY: Oxford University Press).

Koshiyama, D., Miyakoshi, M., Tanaka-Koshiyama, K., Joshi, Y. B., Molina, J. L., Sprock, J., et al. (2020). Neurophysiologic Characterization of Resting State Connectivity Abnormalities in Schizophrenia Patients. *Front. Psychiatry* 11:608154. doi: 10.3389/fpsyt.2020.608154

Kravitz, D. J., Saleem, K. S., Baker, C. I., and Mishkin, M. (2011). A new neural framework for visuospatial processing. *Nat. Rev. Neurosci.* 12, 217–230. doi: 10.1038/nrn3008

Li, W., Wang, Y., Ward, B. D., Antuono, P. G., Li, S. J., and Goveas, J. S. (2017). Intrinsic inter-network brain dysfunction correlates with symptom dimensions in late-life depression. *J. Psychiatr. Res.* 87, 71–80. doi: 10.1016/j.jpsychires.2016.12.011

Li, M., Wang, R., Zhao, M., Zhai, J., Liu, B., Yu, D., et al. (2019). Abnormalities of thalamus volume and resting state functional connectivity in primary insomnia patients. *Brain Imaging Behav.* 13, 1193–1201. doi: 10.1007/s11682-018-9932-y

Liu, C. H., Ma, X., Yuan, Z., Song, L. P., Jing, B., Lu, H. Y., et al. (2017). Decreased resting-state activity in the Precuneus is associated With depressive episodes in recurrent depression. *J. Clin. Psychiatry* 78, e372–e382. doi: 10.4088/JCP.15m10022

Liu, C. H., Tang, L. R., Gao, Y., Zhang, G. Z., Li, B., Li, M., et al. (2019). Resting-state mapping of neural signatures of vulnerability to depression relapse. *J. Affect. Disord.* 250, 371–379. doi: 10.1016/j.jad.2019.03.022

Liu, P., Tu, H., Zhang, A., Yang, C., Liu, Z., Lei, L., et al. (2021). Brain functional alterations in MDD patients with somatic symptoms: a resting-state fMRI study. *J. Affect. Disord.* 295, 788–796. doi: 10.1016/j.jad.2021.08.143

Lythe, K. E., Moll, J., Gethin, J. A., Workman, C. I., Green, S., Lambon Ralph, M. A., et al. (2015). Self-blame-selective hyperconnectivity between anterior temporal and subgenual cortices and prediction of recurrent depressive episodes. *JAMA Psychiat.* 72, 1119–1126. doi: 10.1001/jamapsychiatry.2015.1813

Marchetti, I., Koster, E. H., Sonuga-Barke, E. J., and De Raedt, R. (2012). The default mode network and recurrent depression: a neurobiological model of cognitive risk factors. *Neuropsychol. Rev.* 22, 229–251. doi: 10.1007/s11065-012-9199-9

Menon, V., and Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Struct. Funct.* 214, 655–667. doi: 10.1007/s00429-010-0262-0

Oh, S. Y., Boegle, R., Ertl, M., Stephan, T., and Dieterich, M. (2018). Multisensory vestibular, vestibular-auditory, and auditory network effects revealed by parametric sound pressure stimulation. *NeuroImage* 176, 354–363. doi: 10.1016/j.neuroimage.2018.04.057

Pan, F., Xu, Y., Zhou, W., Chen, J., Wei, N., Lu, S., et al. (2020). Disrupted intrinsic functional connectivity of the cognitive control network underlies disease severity and executive dysfunction in first-episode, treatment-naive adolescent depression. *J. Affect. Disord.* 264, 455–463. doi: 10.1016/j.jad.2019.11.076

Phillips, M. D., Lowe, M. J., Lurito, J. T., Dzemidzic, M., and Mathews, V. P. (2001). Temporal lobe activation demonstrates sex-based differences during passive listening. *Radiology* 220, 202–207. doi: 10.1148/radiology.220.1.r01jl34202

Raichle, M. E., Mac Leod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., and Shulman, G. L. (2001). A default mode of brain function. *Proc. Natl. Acad. Sci. U. S. A.* 98, 676–682. doi: 10.1073/pnas.98.2.676

Raichle, M. E., and Snyder, A. Z. (2007). A default mode of brain function: a brief history of an evolving idea. *NeuroImage* 37, 1083–1090. doi: 10.1016/j.neuroimage.2007.02.041

Reiman, E. M., Lane, R. D., Ahern, G. L., Schwartz, G. E., Davidson, R. J., Friston, K. J., et al. (1997). Neuroanatomical correlates of externally and internally generated human emotion. *Am. J. Psychiatry* 154, 918–925. doi: 10.1176/ajp.154.7.918

Rotenstein, L. S., Ramos, M. A., Torre, M., Segal, J. B., Peluso, M. J., Guille, C., et al. (2016). Prevalence of depression, depressive symptoms, and suicidal ideation Among medical students: a systematic review and meta-analysis. *JAMA* 316, 2214–2236. doi: 10.1001/jama.2016.17324

Seghier, M. L. (2013). The angular gyrus: multiple functions and multiple subdivisions. *Neuroscientist* 19, 43–61. doi: 10.1177/1073858412440596

Sendi, M. S. E., Zendehrouh, E., Sui, J., Fu, Z., Zhi, D., Lv, L., et al. (2021). Abnormal dynamic functional network connectivity estimated from default mode network predicts symptom severity in major depressive disorder. *Brain Connect.* 11, 838–849. doi: 10.1089/brain.2020.0748

Sheldon, S., Farb, N., Palombo, D. J., and Levine, B. (2016). Intrinsic medial temporal lobe connectivity relates to individual differences in episodic autobiographical remembering. *Cortex* 74, 206–216. doi: 10.1016/j.cortex.2015.11.005

Shen, Z., Cheng, Y., Yang, S., et al. (2016). Changes of grey matter volume in first-episode drug-naive adult major depressive disorder patients with different age-onset. *Neuroimage Clin.* 12, 492–498. doi: 10.1016/j.nicl.2016.08.016

Shen, Z., Jiang, L., Yang, S., et al. (2017). Identify changes of brain regional homogeneity in early and later adult onset patients with first-episode depression using resting-state fMRI. *PLoS One* 12:e0184712. doi: 10.1371/journal.pone.0184712

Shi, L. J., Zhou, H. Y., Wang, Y., Shen, Y. M., Fang, Y. M., He, Y. Q., et al. (2020). Altered empathy-related resting-state functional connectivity in adolescents with early-onset schizophrenia and autism spectrum disorders. *Asian J. Psychiatr.* 53:102167. doi: 10.1016/j.ajp.2020.102167

Sprengelmeyer, R., Steele, J. D., Mwangi, B., Kumar, P., Christmas, D., Milders, M., et al. (2011). The insular cortex and the neuroanatomy of major depression. *J. Affect. Disord.* 133, 120–127. doi: 10.1016/j.jad.2011.04.004

Stratmann, M., Konrad, C., Kugel, H., et al. (2014). Insular and hippocampal gray matter volume reductions in patients with major depressive disorder. *PLoS One* 9:e102692. doi: 10.1371/journal.pone.0102692

Sung, S. C., Wisniewski, S. R., Balasubramani, G. K., Zisook, S., Kurian, B., Warden, D., et al. (2013). Does early-onset chronic or recurrent major depression impact outcomes with antidepressant medications? A CO-MED trial report. *Psychol. Med.* 43, 945–960. doi: 10.1017/S0033291712001742

Touroutoglou, A., Bliss-Moreau, E., Zhang, J., Mantini, D., Vanduffel, W., Dickerson, B. C., et al. (2016). A ventral salience network in the macaque brain. *NeuroImage* 132, 190–197. doi: 10.1016/j.neuroimage.2016.02.029

Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. *Nat. Rev. Neurosci.* 16, 55–61. doi: 10.1038/nrn3857

Vega, J. N., Taylor, W. D., Gandelman, J. A., Boyd, B. D., Newhouse, P. A., Shokouhi, S., et al. (2020). Persistent intrinsic functional network connectivity alterations in middle-aged and older women with remitted depression. *Front. Psychiatry* 11:62. doi: 10.3389/fpsyt.2020.00062

Wang, X. L., Du, M. Y., Chen, T. L., et al. (2015). Neural correlates during working memory processing in major depressive disorder. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 56, 101–108. doi: 10.1016/j.pnpbp.2014.08.011

Wang, D., Xue, S. W., Tan, Z., Wang, Y., Lian, Z., and Sun, Y. (2019). Altered hypothalamic functional connectivity patterns in major depressive disorder. *Neuroreport* 30, 1115–1120. doi: 10.1097/WNR.0000000000001335

Wu, Q. Z., Li, D. M., Kuang, W. H., Zhang, T. J., Lui, S., Huang, X. Q., et al. (2011). Abnormal regional spontaneous neural activity in treatment-refractory depression revealed by resting-state fMRI. *Hum. Brain Mapp.* 32, 1290–1299. doi: 10.1002/hbm.21108

Yan, C. G., Chen, X., Li, L., Castellanos, F. X., Bai, T. J., Bo, Q. J., et al. (2019). Reduced default mode network functional connectivity in patients with recurrent major depressive disorder. *Proc. Natl. Acad. Sci. U. S. A.* 116, 9078–9083. doi: 10.1073/pnas.1900390116

Yao, X., Yin, Z., Liu, F., Wei, S., Zhou, Y., Jiang, X., et al. (2018). Shared and distinct regional homogeneity changes in bipolar and unipolar depression. *Neurosci. Lett.* 673, 28–32. doi: 10.1016/j.neulet.2018.02.033

Yüksel, D., Dietsche, B., Konrad, C., Dannlowski, U., Kircher, T., and Krug, A. (2018). Neural correlates of working memory in first episode and recurrent depression: an fMRI study. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 84, 39–49. doi: 10.1016/j.pnpbp.2018.02.003

Zang, Y., Jiang, T., Lu, Y., He, Y., and Tian, L. (2004). Regional homogeneity approach to fMRI data analysis. *NeuroImage* 22, 394–400. doi: 10.1016/j.neuroimage.2003.12.030

Zhang, Z., Chen, Y., Wei, W., et al. (2021). Changes in regional homogeneity of medication-free major depressive disorder patients with different

onset ages. *Front. Psychiatry* 12:713614. doi: 10.3389/fpsyt.2021.713614

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 Psychology

ORIGINAL RESEARCH
published: 14 April 2022
doi: 10.3389/fpsyg.2022.804628

Psychosocial Stress, Epileptic-Like Symptoms and Psychotic Experiences

Petr Bob[1], Tereza Petraskova Touskova[1], Ondrej Pec[1], Jiri Raboch[1], Nash Boutros[2] and Paul Lysaker[3]*

[1] Center for Neuropsychiatric Research of Traumatic Stress, Department of Psychiatry and UHSL, First Faculty of Medicine, and Department of Psychiatry, Faculty of Medicine Pilsen, Charles University in Prague, Prague, Czechia, [2] Rush University Medical Center, Chicago, IL, United States, [3] Roudebush VA Medical Center and the Indiana University School of Medicine, Indianapolis, IN, United States

Background: Current research suggests that stressful life experiences and situations create a substantive effect in the development of the initial manifestations of psychotic disorders and may influence temporo-limbic epileptic-like activity manifesting as cognitive and affective seizure-like symptoms in non-epileptic conditions.

Methods: The current study assessed trauma history, hair cortisol levels, epileptic-like manifestations and other psychopathological symptoms in 56 drug naive adult young women experiencing their initial occurrence of psychosis.

Results: Hair cortisol levels among patients experiencing their initial episode of psychosis, were significantly correlated with stress symptoms measured by Trauma Symptom Checklist-40 ($r = -0.48$, $p < 0.01$), and complex partial seizure-like symptoms measured by the Complex Partial Seizure-Like Symptoms Inventory ($r = -0.33$, $p < 0.05$) and LSCL-33 ($r = -0.33$, $p < 0.05$). Hair cortisol levels were not found to be significantly correlated with symptoms of anxiety and depression measured by Beck depression Inventory and Zung Anxiety Scale.

Conclusion: These findings suggest a significant relationship between epileptic-like symptoms and stress responses demonstrated by patients in their first psychotic episode. These findings may suggest the potential for research to explore usefulness of anticonvulsant treatment in patients who do not respond to usual psychotropic medication.

Keywords: stress, cortisol, epileptic like symptoms, psychosis, stress senzitization

OPEN ACCESS

Edited by:
Marta Bosia,
Vita-Salute San Raffaele University, Italy

Reviewed by:
Panayiotis Patrikelis,
Aristotle University of Thessaloniki, Greece
Federica Cuoco,
San Raffaele Scientific Institute (IRCCS), Italy

****Correspondence:***
Petr Bob
petrbob@netscape.net

Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: *29 October 2021*
Accepted: *17 March 2022*
Published: *14 April 2022*

Citation:
Bob P, Touskova TP, Pec O, Raboch J, Boutros N and Lysaker P (2022) Psychosocial Stress, Epileptic-Like Symptoms and Psychotic Experiences. Front. Psychol. 13:804628. doi: 10.3389/fpsyg.2022.804628

BACKGROUND

Current evidence suggests that stressful early life experiences influence psychological and neurobiological development and ultimately have enduring consequences for the development of psychosis over the lifespan (Eack et al., 2008; van Os et al., 2008; van Winkel et al., 2008; Howes et al., 2017; Mayo et al., 2017). Further, recent research suggests that initial episodes of psychotic disorders may also be closely related to current stressful events (Varese et al., 2012;

Reininghaus et al., 2016). As previously described, earlier or current stress may influence psychosis through its effects on the HPA axis (hypothalamic-pituitary adrenal) (Walker and Diforio, 1997; Faravelli et al., 2017; Pruessner et al., 2017)[8] and cortisol reactivity more specifically (Ryan et al., 2004; Girshkin et al., 2014; Chaumette et al., 2016).

More recent research has suggested even more subtle ways through which early stressful and traumatic experiences may influence the brain and potential for psychosis. One of these involves the possibility that trauma may lead to sensitization or kindling-like processes which then become underlying mechanisms for seizure-like activity in schizophrenia and other psychiatric disorders (Roberts et al., 1992; Teicher et al., 2006; Bob et al., 2016; Weidenauer et al., 2017). Sensitization and kindling represent phenomena where repeated stimulations lead to a progressive enhancement of the response to repeated stimuli that may determine heightened vulnerability to epileptic seizures and increased sensitivity to stress stimuli (Goddard et al., 1969; Bertram, 2007). Further recent evidence also indicates that these kindling-like mechanism and sensitization may lead to neural processes resembling epilepsy which may manifest in patients with mental disorders including schizophrenia, posttraumatic stress disorder (PTSD), depression and others (Castner and Williams, 2007; Yuii et al., 2007; Collip et al., 2008; van Winkel et al., 2008).

Stress-related sensitization has additionally been suggested to create changes in GABA postsynaptic receptors that may lead to overstimulation of neurons mainly in the limbic system, resulting in limbic system irritability occurring as markedly increased prevalence of symptoms suggesting a subclinical form of temporal lobe epilepsy (Teicher et al., 2006; Bertram, 2007). These symptoms may manifest symptomatically similar to temporal lobe epilepsy including occurrence of somatic, sensory, behavioral and memory symptoms which may occur also in non-epileptic conditions (Roberts et al., 1992; Teicher et al., 2003; Gomes et al., 2016).

The issue of whether stress may lead to epileptic activity in persons with psychosis is an important issue for several reasons. For one it may point to the need for treatments which target seizure like activity and may also offer clues about treatment resistance among some patients (Johannessen Landmark, 2008; Tiihonen et al., 2009; Bob et al., 2010, 2011; Kaufman, 2011). It may further help us understand how psychosis when linked to trauma may follow a different course than psychosis not linked to trauma. To explore this issue this study has tested the hypothesis that cortisol levels among patients with first episode psychosis would be associated with both a more severe traumatic stress symptoms and heightened levels of seizure like activity. To measure cortisol we have analyzed hair samples. Heightened cortisol levels have been found in schizophrenia and bipolar disorders (Streit et al., 2016) using this method. The measurement of hair cortisol concentrations (HCC) represents new methodological approach and potentially provides relatively long-term balanced indicator of cortisol levels (Meyer and Novak, 2012; Stalder et al., 2017; Steudte-Schmiedgen et al., 2017) which may reflect chronic stress. To rule out the possibility that any of our observed results were the product of heightened levels of general anxiety or depression we included measures of these constructs as potential covariates.

MATERIALS AND METHODS

Participants

The current study examines 56 adult women with whom the initial episode of psychosis was assessed immediately following admission to Psychiatric Hospital (mean of age 28.43, age range 20-38, SD = 5.32). All the patients were provided and assented to pre-informed consent at the onset of their hospitalization. Further, final written consent was obtained on remission, when the patients were able to deliver an informed decision. The study was approved by the University hospital ethical committee.

The subjects had predominantly high school education 14.35 (SD = 4.52) years. The subjects' diagnoses of the initial psychotic episode was confirmed by clinical interview according to DSM IV guidelines and according to first clinical assessments fulfilled the criteria for any of the following diagnosis: schizophreniform disorder, schizophrenia, brief psychotic disorder, affective psychoses, schizoaffective disorder, and other psychoses. Patients were additionally assessed by M.I.N.I. version 5.0.0 (Sheehan et al., 1998). All the patients had their first hospitalizations and were administered no medications which influenced the CNS. Exclusion criteria were substance, and/or alcohol abuse, organic diseases involving the CNS, antiepileptic treatment, analgetic medication and benzodiazepine, or mental disabilities. Two of the authors of this article have performed independent re-evaluations of the patient's diagnoses in accordance with DSM IV criteria (American Psychiatric Association, 1994).

Psychometric Measures

The patients were assessed utilizing the Positive and Negative Symptoms Scale- PANSS (Kay et al., 1987) enabling evaluation of the typical positive and negative symptoms of schizophrenia (Cronbach's alpha is 0.81 for positive symptoms and 0.88 for negative symptoms). The scale consists of 30 items divided into three subcategories: seven negative (PANSS-Neg), seven positive (PANSS-Pos), and 16 general (PANSS-Gen) psychopathological symptoms. Items may be rated from 1 (absent) to 7 (extremely present). Remission is typically defined as a score of <3 in all positive PANSS items.

Levels of experienced childhood trauma were evaluated with the TSC-40 (Trauma Symptom Checklist) (Elliott and Briere, 1992). The TSC-40 is a 40-item self-report style questionnaire utilizing a 4-point Likert scale. The TSC-40 evaluates symptomatology in adults associated with childhood or adult traumatic experiences and evaluates aspects of posttraumatic stress and other symptom clusters identified in some traumatized individuals.

Complex partial seizure-like symptoms were evaluated utilizing the complex partial seizure-like symptoms inventory–CPSI (Roberts et al., 1992). The CPSI was originally designed to evaluate sensory, somatic, behavioral and memory symptoms associated with temporal lobe epilepsy (i.e., brief hallucinations, dissociative disturbances, paroxysmal somatic disturbances, and

automatisms). The inventory consists of 35 questions and subjects indicate the degree of their experience on a 6-point Likert scale (Cronbach's alpha 0.95). Some recent evidence suggests a CPSI total score higher than 70 presents a significant criterion for the so-called epilepsy spectrum disorder although lower values also may indicate an underlying electrophysiological dysfunction (Roberts et al., 1992). Although these symptoms were originally described in patients with temporal lobe epilepsy, subsequent studies have found that transient sensory, cognitive, and affective phenomena occurring in patients with complex partial seizures may be more common in patients with affective disorders and also in other psychiatric diseases than is typically known (Silberman et al., 1985; Elliott and Briere, 1992).

The similar symptoms and experiences as those assessed by CPSI were also assessed by the Limbic System Checklist, LSCL-33 (Teicher et al., 1993). LSCL-33 is focused on evaluation and measurement of the temporo-limbic activity which may manifest as behavioral, sensory, memory and somatic symptoms which may include paroxysmal somatic disturbances, hallucinations and dissociative symptoms. Subjects indicate the degree of their experience on a four-point Likert scale (never, rarely, sometimes, often) (Cronbach's alpha 0.90).

The assessment of depressive symptoms utilized the Beck depression inventory BDI-II (Beck et al., 1961, 1987) which consists of a 21-items questionnaire to indicate levels of experienced depression. Subjects indicate the degree to which their experience best corresponds to how he/she feels over the preceding 14 days on 4-point Likert scale.

The Zung Self-Rating Anxiety Scale was utilized to assess anxiety levels (Zung, 1971). The SAS is 20-item self-reporting inventory focused into the most common general anxiety symptoms. Each question is evaluated on 4-point Likert scale ranging from 1 to 4.

Hair Cortisol Analysis

The hair samples utilized for biochemical assessment, were cut with clean scissors from the posterior vertex of the scalp due to the smallest hair variation in this position (Sauvé et al., 2007), stored at room temperature and sent in a sealed envelope. According to common procedures two 1 cm long hair segments were provided by each participant to assess ∼2 months of stress exposure, as hair grows at an average of 1 cm per month and there is a "wash-out" effect of cortisol from proximal to distal hair segments which enables to detect maximum of 3-6 month (Stalder et al., 2017). The analysis was performed on the average cortisol levels across the hair segments. Cortisol were evaluated utilizing an ELISA kit for cortisol in saliva (CORTISOL SALIVA ELISA, Diametra). The results were assessed utilizing photometric analysis ELISA (SPECTRA SLT) at the university biochemical department. This analysis of cortisol levels in hair was shown to provide valid and reliable results (Gow et al., 2010; Russell et al., 2012).

Statistical Analysis

Statistical evaluation for results of psychometric measures included means and standard deviations. Because hair cortisol values do not have normal distribution we have used non-parametric Spearman correlation coefficients. We considered $p < 0.05$ as statistically significant. All the methods of statistical evaluation were performed using the software package Statistica version 6.

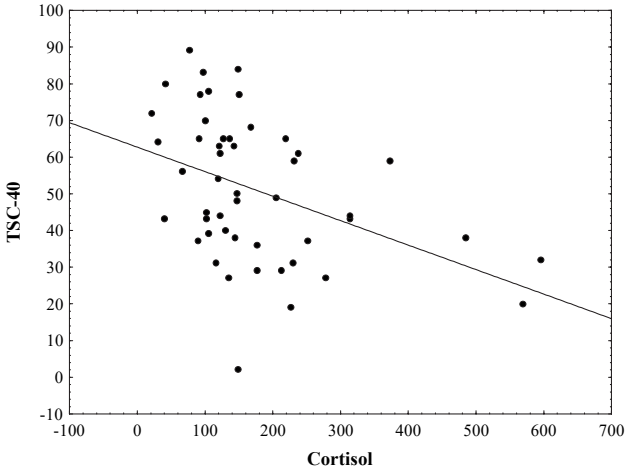


FIGURE 1 | Relationship between hair cortisol levels (pg/mg) and stress symptoms measured by TSC-40.

RESULTS

Results indicate that in the sample of initial psychotic episode onset subjects, hair cortisol levels are significantly correlated with stress symptoms measured by TSC-40 ($r = -0.48$, $p < 0.01$; **Figure 1**), and also with complex partial seizure-like symptoms measured by CPSI ($r = -0.33$, $p < 0.05$; **Figure 2**) and LSCL-33 ($r = -0.33$, $p < 0.05$; **Figure 3**), but no significant correlations of hair cortisol were found with symptoms of anxiety and depression measured by SAS and BDI. Further the results suggest that complex partial seizure-like symptoms as evaluated by CPSI and LSCL-33 are correlated significantly with psychopathological symptoms related to depression, anxiety and stress. Traumatic stress symptoms evaluated by TSC-40 are significantly correlated with CPSI ($r = 0.67$, $p < 0.01$) and LSCL ($r = 0.69$, $p < 0.01$), symptoms of depression measured by BDI are significantly correlated with CPSI ($r = 0.52$, $p < 0.01$) and LSCL-33 ($r = 0.42$, $p < 0.01$). Symptoms of anxiety measured by SAS are significantly correlated with CPSI ($r = 0.62$, $p < 0.01$) and LSCL-33 ($r = 0.80$, $p < 0.01$). No significant correlations between symptoms of schizophrenia measured by PANSS subscales for Positive, Negative and Global psychopathology and other psychopathological symptoms related to stress, depression, anxiety, hair cortisol levels and epileptic like activity symptoms were identified.

From the 56 patients 8 had (14%) CPSI higher than 70, representing psychometrically reliable criterion for epilepsy spectrum disorders (Roberts et al., 1992; Bob, 2013).

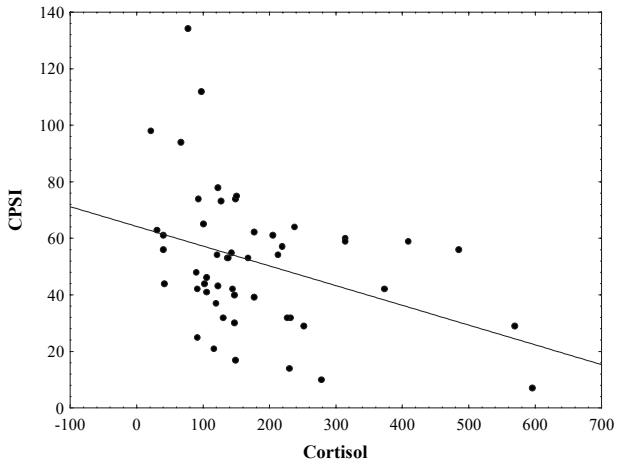


FIGURE 2 | Relationship between hair cortisol levels (pg/mg) and epileptic-like symptoms measured by CPSI.

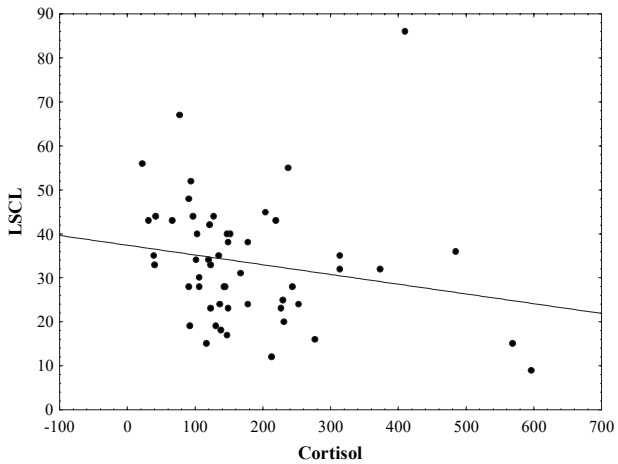


FIGURE 3 | Relationship between hair cortisol levels (pg/mg) and epileptic-like symptoms measured by LSCL-33.

DISCUSSION

The issue of whether stress may lead to epileptic activity in persons with psychosis seems to be supported by these findings suggesting underlying seizure like activity which may also offer clues about treatment resistance among some patients. In addition these findings may further help us to understand how psychosis when linked to traumatic stress may follow a different course than psychosis not linked to trauma. Results of this study provide first supportive indication as to the relationship between hair cortisol levels reflecting chronic stress conditions in patients with initial episode psychosis and epileptic-like symptoms.

These data based on the homogenous group of women reflect the drug naive mental and physiological states. This finding suggests "concomitant" correspondence of variables reflecting links between psychological experience and neurobiological changes related to stress. The results are in accordance with findings suggesting an influence of sensitization or "kindling-like" processes in etiology of psychiatric disorders such as drug addiction, schizophrenia, mood disorders, or posttraumatic stress disorder (Post and Weiss, 1996; Phillips et al., 1997; Post et al., 1997; Kraus, 2000; Collip et al., 2008; Weidenauer et al., 2017). The findings of the current study are also in agreement with evidence indicating that epileptic-like symptoms and mechanism of sensitization or kindling may be closely linked to stress conditions (Teicher et al., 2003, 2006; Yuii et al., 2007).

Some studies also indicate that similar sensitization or kindling-like processes may manifest in inhibitory systems due to local discharges of limbic and hypothalamic neurons and this dysbalance between excitation and inhibition leading to excessive inhibitory activities may manifest as psychotic disorders (Stephens et al., 2002, 2006). These patients who manifest the epileptic-like symptoms appear to be positively indicated for anticonvulsant treatment due to increased excitatory neural activity and regionally-specific compensatory upregulation of GABA-A receptors in response to decreased GABAergic input in hippocampal pyramidal cells (Heckers and Konradi, 2002; Mohler, 2006). The GABA neurons provide both inhibitory and disinhibitory modulation of cortical and hippocampal circuits and play an important role in gating of sensory information and attentional filtering within the corticolimbic system which are typically affected in schizophrenia (Glenthoj and Hemmingsen, 1997; Benes and Berretta, 2001; Costa et al., 2004; Gonzalez-Burgos and Lewis, 2008; Jacob et al., 2008). Further, the role of GABA neurons in cognitive functions suggests that disturbances in GABA systems may be linked to stressful conditions and alterations in the dopamine system (Benes and Berretta, 2001; Teicher et al., 2003, 2006; Yuii et al., 2007).

Numerous studies indicate that HCC is negatively related to hair washing frequency, hair treatment and oral contraceptive use, positively associated with ongoing chronic stress, some anthropometric measures, systolic blood pressure and with other confounding factors influencing hair cortisol such as gender, physical stressors and other psychiatric disorders (Meyer and Novak, 2012; Stalder et al., 2017). Some of these above mentioned variables were not addressed in this study, which represents a limitation with respect to more detailed analysis.

In summary, the current study suggests a link between epileptic-like symptoms and chronic stress response in the patients in the initial onset of psychosis. These data may be helpful in explaining the efficacy of anticonvulsant medication in patients who are resistant to usual psychotropic medication (Boutros et al., 2014). Patients with the epileptic-type manifestations likely may have decreased inhibition due to stress conditions manifesting as various mental and somatic states including complex partial seizure-like symptoms which may be assessed using psychometric measures (LSCL-33, CPSI). From the clinical perspective the link between complex partial seizure-like symptoms and stress may provide useful information for diagnostic consideration of anticonvulsant therapy and also how psychosis when linked to traumatic stress may follow a different course than psychosis not linked to trauma.

As for the limitations of this study the features of the sample limit the generalizability of these findings because the current data does not provide representative sample due to the number and gender of participants. Other limitations due to the novelty of this study do not allow to respond other interesting questions which this research might implicate. For example, the absence of significant correlations between symptoms of schizophrenia measured by PANSS subscales and symptoms related to stress, hair cortisol levels, and epileptic-like activity symptoms. Also further research focused on the efficacy of anticonvulsant medication in patients who are resistant to usual psychotropic medication their cognitive abilities and other psychopathological symptoms is warranted.

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 Charles University, First Faculty of Medicine Ethical Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PB and TT: writing manuscript. PB, TT, OP, JR, NB, and PL: data analysis: PB, TT, and JR: data collection and processing. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by Charles University projects Progress, Cooperatio, SVV.

REFERENCES

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders (4th ed.)*. American Psychiatric Publishing, Inc.

Beck, A. T., Steer, R., and Brown, G. (1987). *Beck Depression Inventory Manual*. San Antonio, TX: The Psychological Corporation.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., and Erbaugh, J. (1961). An inventory for measuring depression. *Arch. Gener. Psychiatry* 4, 561–571. doi: 10.1001/archpsyc.1961.01710120031004

Benes, F. M., and Berretta, S. (2001). GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. *Neuropsychopharmacology* 25, 1–27. doi: 10.1016/S0893-133X(01)00225-1

Bertram, E. (2007). The relevance of kindling for human epilepsy. *Epilepsia* 48, 65–74. doi: 10.1111/j.1528-1167.2007.01068.x

Bob, P. (2013). *Stress Sensitization and Anticonvulsant Medication in Psychiatric Patients in Polypharmacy in Psychiatry Practice*. Berlin: Springer, 233–242.

Bob, P., Jasova, D., and Raboch, J. (2011). Subclinical epileptiform process in patients with unipolar depression and its indirect psychophysiological manifestations. *PLoS One* 6:e28041. doi: 10.1371/journal.pone.0028041

Bob, P., Palus, M., Susta, M., and Glaslova, K. (2010). Sensitization, epileptic-like symptoms and local synchronization in patients with paranoid schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 34, 143–146. doi: 10.1016/j.pnpbp.2009.10.015

Bob, P., Pec, O., Mishara, A. L., Touskova, T., and Lysaker, P. H. (2016). Conscious brain, metacognition and schizophrenia. *Int. J. Psychophysiol.* 105, 1–8. doi: 10.1016/j.ijpsycho.2016.05.003

Boutros, N. N., Ghosh, S., Khan, A., Bowyer, S. M., and Galloway, M. P. (2014). Anticonvulsant medications for panic disorder: a review and synthesis of the evidence. *Int. J. Psychiatry Clin. Pract.* 18, 2–10. doi: 10.3109/13651501.2013.873053

Castner, S. A., and Williams, G. V. (2007). From vice to virtue: insights from sensitization in the nonhuman primate. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 31, 1572–1592. doi: 10.1016/j.pnpbp.2007.08.026

Chaumette, B., Kebir, O., Mam-Lam-Fook, C., Morvan, Y., Bourgin, J., Godsil, B. P., et al. (2016). Salivary cortisol in early psychosis: new findings and meta-analysis. *Psychoneuroendocrinology* 63, 262–270. doi: 10.1016/j.psyneuen.2015.10.007

Collip, D., Myin-Germeys, I., and Van Os, J. (2008). Does the concept of "sensitization" provide a plausible mechanism for the putative link between the environment and schizophrenia? *Schizophr. Bull.* 34, 220–225. doi: 10.1093/schbul/sbm163

Costa, E., Davis, J. M., Dong, E., Grayson, D. R., Guidotti, A., Tremolizzo, L., et al. (2004). A GABAergic cortical deficit dominates schizophrenia pathophysiology. *Crit. Rev. Neurobiol.* 16, 1–23. doi: 10.1615/critrevneurobiol.v16.i12.10

Eack, S. M., Prasad, K. M., Montrose, D. M., Goradia, D. D., Dworakowski, D., Miewald, J., et al. (2008). An integrated psychobiological predictive model of emergent psychopathology among young relatives at risk for schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 32, 1873–1878. doi: 10.1016/j.pnpbp.2008.08.024

Elliott, D. M., and Briere, J. (1992). Sexual abuse trauma among professional women: validating the Trauma Symptom Checklist-40 (TSC-40). *Child Abuse Negl.* 16, 391–398. doi: 10.1016/0145-2134(92)90048-v

Faravelli, C., Mansueto, G., Palmieri, S., Sauro, C. L., Rotella, F., Pietrini, F., et al. (2017). Childhood adversity, cortisol levels, and psychosis: a retrospective investigation. *J. Nervous Ment. Dis.* 205, 574–579. doi: 10.1097/NMD.0000000000000699

Girshkin, L., Matheson, S. L., Shepherd, A. M., and Green, M. J. (2014). Morning cortisol levels in schizophrenia and bipolar disorder: a meta-analysis. *Psychoneuroendocrinology* 49, 187–206. doi: 10.1016/j.psyneuen.2014.07.013

Glenthoj, B. Y., and Hemmingsen, R. (1997). Dopaminergic sensitization: implications for the pathogenesis of schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 21, 23–46. doi: 10.1016/s0278-5846(96)00158-3

Goddard, G. V., Mcintyre, D. C., and Leech, C. K. (1969). A permanent change in brain function resulting from daily electrical stimulation. *Exp. Neurol.* 25, 295–330. doi: 10.1016/0014-4886(69)90128-9

Gomes, R. R., Vicente, V. A., Azevedo, C. M., Salgado, C. G., Da Silva, M. B., Queiroz-Telles, F., et al. (2016). Molecular epidemiology of agents of human chromoblastomycosis in brazil with the description of two novel species. *PLoS Negl. Trop. Dis.* 10:5102.

Gonzalez-Burgos, G., and Lewis, D. A. (2008). GABA neurons and the mechanisms of network oscillations: implications for understanding cortical dysfunction in schizophrenia. *Schizophr. Bull.* 34, 944–961. doi: 10.1093/schbul/sbn070

Gow, R., Thomson, S., Rieder, M., Van Uum, S., and Koren, G. (2010). An assessment of cortisol analysis in hair and its clinical applications. *Forensic. Sci. Int.* 196, 32–37. doi: 10.1016/j.forsciint.2009.12.040

Heckers, S., and Konradi, C. (2002). Hippocampal neurons in schizophrenia. *J. Neural. Transm.* 109, 891–905. doi: 10.1007/s007020200073

Howes, O. D., Mccutcheon, R., Owen, M. J., and Murray, R. M. (2017). The role of genes, stress, and dopamine in the development of schizophrenia. *Biol. Psychiatry* 81, 9–20. doi: 10.1016/j.biopsych.2016.07.014

Jacob, T. C., Moss, S. J., and Jurd, R. (2008). GABA(A) receptor trafficking and its role in the dynamic modulation of neuronal inhibition. *Nat. Rev. Neurosci.* 9, 331–343. doi: 10.1038/nrn2370

Johannessen Landmark, C. (2008). Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. *CNS Drugs* 22, 27–47. doi: 10.2165/00023210-200822010-00003

Kaufman, K. R. (2011). Antiepileptic drugs in the treatment of psychiatric disorders. *Epilep. Behav.* 21, 1–11. doi: 10.1016/j.yebeh.2011.03.011

Kay, S. R., Fiszbein, A., and Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 13, 261–276. doi: 10.1093/schbul/13.2.261

Kraus, J. E. (2000). Sensitization phenomena in psychiatric illness: lessons from the kindling model. *J. Neuropsych. Clin. Neurosci.* 12, 328–343. doi: 10.1176/jnp.12.3.328

Mayo, D., Corey, S., Kelly, L. H., Yohannes, S., Youngquist, A. L., Stuart, B. K., et al. (2017). The role of trauma and stressful life events among individuals at clinical high risk for psychosis: a review. *Front. Psychiatry* 8:55. doi: 10.3389/fpsyt.2017.00055

Meyer, J. S., and Novak, M. A. (2012). Minireview: Hair cortisol: a novel biomarker of hypothalamic-pituitary-adrenocortical activity. *Endocrinology* 153, 4120–4127. doi: 10.1210/en.2012-1226

Mohler, H. (2006). GABA(A) receptor diversity and pharmacology. *Cell Tissue Res.* 326, 505–516. doi: 10.1007/s00441-006-0284-3

Phillips, T. J., Roberts, A. J., and Lessov, C. N. (1997). Behavioral sensitization to ethanol: genetics and the effects of stress. *Pharmacol. Biochem. Behav.* 57, 487–493. doi: 10.1016/s0091-3057(96)00448-0

Post, R. M., and Weiss, S. R. (1996). A speculative model of affective illness cyclicity based on patterns of drug tolerance observed in amygdala-kindled seizures. *Mol. Neurobiol.* 13, 33–60. doi: 10.1007/BF02740751

Post, R. M., Weiss, S. R., Smith, M., Li, H., and Mccann, U. (1997). Kindling versus quenching. Implications for the evolution and treatment of posttraumatic stress disorder. *Ann. NY Acad. Sci.* 821, 285–295. doi: 10.1111/j.1749-6632.1997.tb48287.x

Pruessner, M., Cullen, A. E., Aas, M., and Walker, E. F. (2017). The neural diathesis-stress model of schizophrenia revisited: an update on recent findings considering illness stage and neurobiological and methodological complexities. *Neurosci. Biobehav. Rev.* 73, 191–218. doi: 10.1016/j.neubiorev.2016.12.013

Reininghaus, U., Kempton, M. J., Valmaggia, L., Craig, T. K., Garety, P., Onyejiaka, A., et al. (2016). Stress sensitivity, aberrant salience, and threat anticipation in early psychosis: an experience sampling study. *Schizophr. Bull.* 42, 712–722. doi: 10.1093/schbul/sbv190

Roberts, R. J., Gorman, L. L., Lee, G. P., Hines, M. E., Richardson, E. D., Riggle, T. A., et al. (1992). The phenomenology of multiple partial seizure-like symptoms without stereotyped spells: an epilepsy spectrum disorder? *Epilep. Res.* 13, 167–177. doi: 10.1016/0920-1211(92)90073-3

Russell, E., Koren, G., Rieder, M., and Van Uum, S. (2012). Hair cortisol as a biological marker of chronic stress: current status, future directions and unanswered questions. *Psychoneuroendocrinology* 37, 589–601. doi: 10.1016/j.psyneuen.2011.09.009

Ryan, M. C., Sharifi, N., Condren, R., and Thakore, J. H. (2004). Evidence of basal pituitary-adrenal overactivity in first episode, drug naive patients with schizophrenia. *Psychoneuroendocrinology* 29, 1065–1070. doi: 10.1016/j.psyneuen.2003.08.011

Sauvé, B., Koren, G., Walsh, G., Tokmakejian, S., and Van Uum, S. H. (2007). Measurement of cortisol in human hair as a biomarker of systemic exposure. *Clin. Invest. Med.* 2007, E183–E191. doi: 10.25011/cim.v30i5.2894

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). 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* 59, 22–33.

Silberman, E. K., Post, R. M., Nurnberger, J., Theodore, W., and Boulenger, J. P. (1985). Transient sensory, cognitive and affective phenomena in affective illness. A comparison with complex partial epilepsy. *Br. J. Psychiatry* 146, 81–89. doi: 10.1192/bjp.146.1.81

Stalder, T., Steudte-Schmiedgen, S., Alexander, N., Klucken, T., Vater, A., Wichmann, S., et al. (2017). Stress-related and basic determinants of hair cortisol in humans: a meta-analysis. *Psychoneuroendocrinology* 77, 261–274. doi: 10.1016/j.psyneuen.2016.12.017

Stephens, D. W., Mclinn, C. M., and Stevens, J. R. (2002). Discounting and reciprocity in an Iterated Prisoner's Dilemma. *Science* 298, 2216–2218. doi: 10.1126/science.1078498

Stephens, D. W., Mclinn, C. M., and Stevens, J. R. (2006). Effects of temporal clumping and payoff accumulation on impulsiveness and cooperation. *Behav. Proc.* 71, 29–40. doi: 10.1016/j.beproc.2005.09.003

Steudte-Schmiedgen, S., Wichmann, S., Stalder, T., Hilbert, K., Muehlhan, M., Lueken, U., et al. (2017). Hair cortisol concentrations and cortisol stress reactivity in generalized anxiety disorder, major depression and their comorbidity. *J. Psychiatric Res.* 84, 184–190. doi: 10.1016/j.jpsychires.2016.09.024

Streit, F., Memic, A., Hasandedic, L., Rietschel, L., Frank, J., Lang, M., et al. (2016). Perceived stress and hair cortisol: differences in bipolar disorder and schizophrenia. *Psychoneuroendocrinology* 69, 26–34. doi: 10.1016/j.psyneuen.2016.03.010

Teicher, M. H., Andersen, S. L., Polcari, A., Anderson, C. M., Navalta, C. P., and Kim, D. M. (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neurosci. Biobehav. Rev.* 27, 33–44. doi: 10.1016/s0149-7634(03)00007-1

Teicher, M. H., Glod, C. A., Surrey, J., and Swett, C. Jr. (1993). Early childhood abuse and limbic system ratings in adult psychiatric outpatients. *J. Neuropsych. Clin. Neurosci.* 5, 301–306. doi: 10.1176/jnp.5.3.301

Teicher, M. H., Tomoda, A., and Andersen, S. L. (2006). Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? *Ann. NY Acad. Sci.* 1071, 313–323. doi: 10.1196/annals.1364.024

Tiihonen, J., Wahlbeck, K., and Kiviniemi, V. (2009). The efficacy of lamotrigine in clozapine-resistant schizophrenia: a systematic review and meta-analysis. *Schizophr. Res.* 109, 10–14. doi: 10.1016/j.schres.2009.01.002

van Os, J., Rutten, B. P., and Poulton, R. (2008). Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophr. Bull.* 34, 1066–1082. doi: 10.1093/schbul/sbn117

van Winkel, R., Stefanis, N. C., and Myin-Germeys, I. (2008). Psychosocial stress and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. *Schizophr. Bull.* 34, 1095–1105. doi: 10.1093/schbul/sbn101

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., et al. (2012). Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr. Bull.* 38, 661–671. doi: 10.1093/schbul/sbs050

Walker, E. F., and Diforio, D. (1997). Schizophrenia: a neural diathesis-stress model. *Psychol. Rev.* 104, 667–685. doi: 10.1037/0033-295x.104.4.667

Weidenauer, A., Bauer, M., Sauerzopf, U., Bartova, L., Praschak-Rieder, N., Sitte, H. H., et al. (2017). Making sense of: sensitization in schizophrenia. *Int. J. Neuropsychopharmacol.* 20, 1–10. doi: 10.1093/ijnp/pyw081

Yuii, K., Suzuki, M., and Kurachi, M. (2007). Stress sensitization in schizophrenia. *Ann. NY Acad. Sci.* 1113, 276–290. doi: 10.1196/annals.1391.013

Zung, W. W. (1971). A rating instrument for anxiety disorders. *Psychosomatics* 12, 371–379. doi: 10.1016/S0033-3182(71)71479-0

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 | Frontiers in Psychology

ORIGINAL RESEARCH
published: 29 April 2022
doi: 10.3389/fpsyg.2022.859234

Validation of the Korean Version of the Anticipatory and Consummatory Interpersonal Pleasure Scale in Non-help-seeking Individuals

*Eunhye Kim[1], Diane C. Gooding[2,3] and Tae Young Lee[1,4]**

[1] Department of Psychiatry, Yangsan Hospital, Pusan National University, Yangsan, South Korea, [2] PATHS Laboratory, Department of Psychology, University of Wisconsin-Madison, Madison, WI, United States, [3] Department of Psychiatry, University of Wisconsin-Madison, Madison, WI, United States, [4] Research Institute for Convergence of Biomedical Science and Technology, Yangsan Hospital, Pusan National University, Yangsan, South Korea

OPEN ACCESS

Edited by:
Ricardo R. Garcia, University of Chile, Chile

Reviewed by:
Gabriele Nibbio, University of Brescia, Italy
Giulia Agostoni, Vita-Salute San Raffaele University, Italy
Gwenole Loas, University of Picardie Jules Verne, France

***Correspondence:**
Tae Young Lee
tylee@pusan.ac.kr

Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: *21 January 2022*
Accepted: *21 March 2022*
Published: *29 April 2022*

Citation:
Kim E, Gooding DC and Lee TY (2022) Validation of the Korean Version of the Anticipatory and Consummatory Interpersonal Pleasure Scale in Non-help-seeking Individuals. Front. Psychol. 13:859234. doi: 10.3389/fpsyg.2022.859234

The Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) is a psychometric instrument that has been used to indirectly measure social anhedonia in many cross-cultural contexts, such as in Western (US), European (French, Spanish), Eastern (Chinese), and Israeli samples. However, little is known about the psychometric properties of the ACIPS in Korean samples. The primary goal of this study was to validate the Korean version of the ACIPS among non-help-seeking individuals. The sample consisted of 307 adult individuals who had no current or prior psychiatric history. Participants were administered the ACIPS, along with the Behavioral Inhibition and Behavioral Activation Scales (BIS/BAS) and Beck Depression Inventory (BDI). We examined the association of the total ACIPS scores with the other measures. The ACIPS showed good internal consistency. We also explored the factor structure of the Korean translation of the ACIPS using principal component analysis with Promax rotation and Kaiser normalization. Factor analysis yielded a three-factor structure that accounted for 58.8% of the variance. The three-factor model included the following subdomains: interactions involving close relationships, casual interactions, and interactions involving family members. Total BAS and BIS scores were significantly associated with total ACIPS scores, while BDI scores were inversely associated with total ACIPS scores. The current research indicates that the Korean version of the ACIPS is a useful and valid scale. Future directions include using the Korean translation of the ACIPS to elucidate the varying degrees of hedonic capacity in psychiatric patients.

Keywords: Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS), social anhedonia, social reward, validation, interpersonal pleasure

INTRODUCTION

Schizophrenia is a severe and persisting mental illness characterized by a neurocognitive deficits, functional decline, and a constellation of positive and negative symptoms, with up to 60% of patients experiencing negative symptoms (Correll and Schooler, 2020). Negative symptoms include anhedonia, apathy, avolition, blunted or restricted affect, and attentional impairment

(Andreasen, 1982; Bobes et al., 2010). Anhedonia, defined as the absence or diminution of the ability for pleasure, is one of the prominent symptoms of patients with major depressive disorder and schizophrenia (Andreasen, 1982; Leventhal et al., 2006; Winograd-Gurvich et al., 2006; Horan et al., 2008; Zhornitsky et al., 2012).

There is increasing evidence that social anhedonia, i.e., decreased interest in and/or reduced reward from social interactions, is distinct from other forms of anhedonia (Gooding and Pflum, 2014a,b, 2022). Social anhedonia is an indicator of heightened risk for the later development of a schizophrenia-spectrum disorder (Kwapil, 1998; Gooding et al., 2005, 2007). It appears across all phases of schizophrenia-spectrum disorders, including the prodromal phase (e.g., Jhung et al., 2016). Findings from patients (e.g., Blanchard et al., 2001; Ritsner et al., 2018), first-degree relatives of patients with schizophrenia (e.g., Docherty and Sponheim, 2014; Umesh et al., 2018), and psychometrically identified schizotypes (e.g., Gooding et al., 2005) provide compelling evidence that social anhedonia is a trait-related symptom for many individuals within the schizophrenia spectrum. Thus, evaluating social anhedonia can be crucial in terms of understanding contributory aspects underlying schizophrenia-spectrum disorder.

Social anhedonia is also observed among several other forms of psychopathology (Barkus and Badcock, 2019; Liang et al., 2020; Gooding and Pflum, 2022). Currently, there is strong evidence that social anhedonia is a state-related symptom in patients with depressive disorder, though there are increasing reports of social anhedonia in autism, eating disorders, post traumatic stress disorder (PTSD), and substance use disorders. While there are several self-report measures designed to assess anhedonia, to date there are two validated scales specifically designed to measure social anhedonia. The Revised Social Anhedonia Scale (RSAS; Eckbland et al., 1982) is a direct measure of social anhedonia, whereas the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS; Gooding and Pflum, 2014a,b) is an indirect measure. Scores on the RSAS and ACIPS are strongly and negatively correlated with each other, though the two measures tap distinct aspects of social anhedonia (Gooding and Pflum, 2014a,b; Gooding et al., 2015, 2017). Some characteristics of the ACIPS distinguish it from the RSAS. First, the ACIPS was developed to assess individual differences in social pleasure, while the RSAS was originally developed to detect proneness to develop psychosis. Second, the ACIPS contains more updated content, measuring individuals' ability to experience pleasure from social and interpersonal interactions that occur either in person or remotely (e.g., while texting). Recently, bivariate biometric analyses on twin data revealed that the ACIPS captures unique heritable contributions to social/interpersonal pleasure, in addition to sharing genetic variance with other self-report measures of positive affect (Gooding et al., 2021).

The ACIPS has been used in many cross-cultural contexts, such as in Western (US), European (Spanish), Eastern (Chinese), and Middle East (Israeli) samples. The internal consistency of the ACIPS has been high across all these contexts, regardless of whether the ACIPS was administered in English, European Spanish, Mandarin Chinese, or Hebrew, with ordinal alpha ranging from 0.85 to 0.96 (Chan et al., 2016; Gooding et al., 2016, 2017; Ritsner et al., 2018).

A few studies of the psychometric properties of the ACIPS have been conducted in cross-cultural contexts. For example, one research group (Gooding et al., 2016) examined the factor structure and construct validity of the ACIPS in a non-clinical Spanish adult sample. Using parallel analysis and maximum factor extraction, their analysis revealed a three-factor solution: Intimate Social Relations, Social bonding in the Context of Media, and Casual Socializing. Chan et al. (2016) examined the factor structure of the ACIPS in their non-clinical Chinese adult sample while also relying upon parallel analysis. They found a four factor structure characterized by Friendship, Family and Intimacy-Related Relationships, General Social Interactions, and Casual Interactions/Conversations. Chaix et al. (2017) compared one-, two-, and three- factor models using estimate fit testing for the French translation of the ACIPS. The best fitting solution was a three-factor model identifying Intimate Social Relations, Group Social Interactions, and Social Bonding and Making Connections as the factors. Thus far, there have been three cross-cultural validations of the ACIPS and they have been consistent in indicating the overall robustness of the measure.

Until now, the ACIPS has not been administered to any Korean samples. Prior to using the ACIPS in studies of Korean patients with schizophrenia-spectrum disorders, it is imperative that investigators first validate a Korean translation of the scale in a non-clinical sample. Therefore, the goal of the present study was to validate the Korean translation of the ACIPS for use with Korean populations. Given the previous findings that the translated versions of the ACIPS, like the original English version, are characterized by high internal consistency, we predicted that the Korean translation of the ACIPS would also be characterized by high internal consistency. We also hypothesized that factor analysis of the Korean translation of the ACIPS would reveal at least three but no more than four factors which could account for at least 50% of the variance. As a further examination of construct validity and measure of fidelity with the original English version of the ACIPS, we also examined the relationship between the Korean translation of the ACIPS with other measures of approach (the BAS), withdrawal (BIS), and affect (the BDI). Based on prior research (Gooding and Pflum, 2014b; Gooding et al., 2016, 2021), we expected the Korean version of the ACIPS to be associated with a measure of approach and reward sensitivity (i.e., the BAS) and withdrawal (the BIS) and inversely associated with a measure of negative affect (the BDI). No other *a priori* predictions were made.

MATERIALS AND METHODS

Participants

The sample consisted of 307 (108 male, 199 female) non-clinical participants who were recruited from an online survey platform in South Korea in August 2021. These participants had previously agreed to be notified about survey opportunities through email announcements. After enrolling in the online survey platform, participants who met study criteria were invited to take the

questionnaires. All participants were aged 17 years and older; the mean age of the sample was 25.1 (± 1.01) years. Exclusion criteria included no current or prior psychiatric history. The study was conducted as an online survey, with all individuals providing their informed consent through button press after the study was explained to them. This study was approved by the ethics committees of the Pusan National University and the Yangsan Hospital Institutional Review Board.

Measures

The investigation included the following questionnaires: the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS; Gooding and Pflum, 2014a,b), the Behavioral Inhibition and Behavioral Activation Scales (BIS/BAS; Carver and White, 1994), and the Beck Depression Inventory-II (BDI-II; Beck et al., 1996b).

The ACIPS is an indirect measure of social anhedonia that is suitable for use in patient groups and non-clinical samples as well as different age groups (i.e., children, adolescents, and adults). The adult version of the ACIPS (Gooding and Pflum, 2014a,b) is a 17-item self-report measure in which hedonic capacity for social and interpersonal engagement is rated on a Likert-like scale of 1 ("very false for me") to 6 (" very true for me"). Lower scores are associated with higher levels of social anhedonia. Translation of the ACIPS from English to Korean was conducted according to the international guidelines for translation of psychological measures (Hambleton et al., 2005). Two bilingual academic psychologists independently translated the ACIPS from English to Korean. The translations were reconciled and subsequently back-translated by an independent translator (another bilingual academic psychologist) in English who had not previously seen the original English version of the questionnaire. The back translations were reviewed with the primary developer of the measure (DCG) to verify the conceptual equivalence between the English and Korean versions of the ACIPS.

The Korean version of the BIS/BAS was used to examine convergent validity (Carver and White, 1994). The BIS/BAS consisted of 24 items that were rated on a Likert-type scale from 1 (very true) to 4 (very false). The BAS consisted of three subscales: Reward Responsiveness, Drive, and Sensation Seeking. The ordinal alpha for the BIS was 0.84. The ordinal alpha values for the BAS were 0.70, 0.69, and 0.80 for the Reward Responsiveness, Fun-Seeking, and Drive subscales, respectively.

The BDI-II (Beck et al., 1996a) is a self-report questionnaire based on the symptoms described by the Diagnostic and Statistical Manual of Mental Disorders-IV. The BDI consists of 21 items, in which four response options range from 0 to 3. Higher scores reflect greater symptom severity. The BDI showed a high level of internal consistency. The ordinal alpha for the BDI was 0.95.

Statistical Analysis

We conducted an exploratory factor analysis on the ACIPS items using principal component analysis with Promax rotation and Kaiser normalization. We examined the internal consistency for the ACIPS, BAS/BIS, and BDI by calculating the ordinal version of alpha coefficients (Zumbo et al., 2007) because the measures had Likert-type response scales. We evaluated the construct validity of the ACIPS by examining the association of the total ACIPS scores with the BAS, BIS, and BDI total scores. All *p*-values are two-tailed. We used Meng's test (Meng et al., 1992) to compare the strength of the correlations between the self-report measures. We used SPSS version 27 to perform the Meng's test. The remaining data analyses were performed using R v4.1.2 statistical package.

RESULTS

Demographics

Table 1 provides the demographic data for the sample. Independent samples *t*-test revealed that the mean total ACIPS scores of male (70.04 ± 15.25) and female participants (68.10 + 15.12) did not differ significantly, $t\,(305) = 1.91$, $p = 0.26$. Although the ages of participants ranged from 17 to 35 years, we observed no correlation between age and total ACIPS score in our sample, $r = -0.02$, $p = 0.70$. Accordingly, there was no significant between-group difference when participants were classified according to age, $F(2, 304) = 0.33$, $p = 0.72$.

Internal Consistency

The total ACIPS showed good internal consistency, with an ordinal coefficient of 0.94. As expected, the ACIPS items assessing anticipatory pleasure were significantly associated with the ACIPS items assessing consummatory pleasure ($r = 0.56$, $p < 0.001$).

Factor Structure of the Korean Translation of the Anticipatory and Consummatory Interpersonal Pleasure Scale

We explored the factor structure of the Korean translation of the ACIPS using factor analysis. Promax rotation of the ACIPS factor loadings using Kaiser normalization revealed a three-factor structure which together accounted for 58.81% of the variance. All three factors assessed both anticipatory and consummatory aspects of pleasure (**Table 2**). As indicated in both **Table 2** and **Figure 1**, nine ACIPS items loaded onto Factor I (close

TABLE 1 | Mean Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) scores by demographic group.

	Total sample (*n* = 307)	Mean	*SD*
Sex			
Male	108	70.04	15.25
Female	199	68.1	15.12
Age			
17∼19	14	71.73	15.78
20∼29	134	68.31	15.06
30∼35	159	68.91	15.28

Scores on the adult version of the ACIPS (Gooding and Pflum, 2014a,b) can range from 17 to 102, with lower scores reflecting greater likelihood of social anhedonia.

relationships), which accounted for 47.13% of the variance. Factor II (casual interactions) contained six items, assessing social and interpersonal interactions of a more casual nature and accounted for 6.06% of the variance. Factor III (interactions concerning family members) contained only two ACIPS items but accounted for 5.61% of the variance in the total ACIPS scores. The first two factors appeared to be more highly correlated than the third factor (**Table 3**).

Convergent and Discriminant Validity

Table 4 provides the descriptive statistics for the ACIPS, BAS/BIS, and BDI. To establish the convergent validity of the Korean translation of the ACIPS, we examined the associations between the ACIPS and a measure of approach-related affective behavior, namely, the BAS. Scores on the BAS were significantly correlated with ACIPS scores, $r = 0.47$, $p < 0.01$. The BIS of the BIS/BAS showed a small but significant association with total ACIPS scores, $r = 0.03$, $p < 0.01$. Further analyses revealed that the correlation between total ACIPS scores and total BAS scores was significantly stronger than the association between total ACIPS scores and total BIS scores, $Z = 5.50$, $p < 0.001$.

Total BDI scores were inversely associated with total ACIPS scores ($r = -0.36$, $p < 0.01$). The association between total ACIPS scores and BAS scores was stronger than the association between ACIPS scores and BDI scores, $Z = 7.24$, $p < 0.001$.

TABLE 2 | Factor structure and loading of the ACIPS.

ACIPS item	Factor 1 Close relationships	Factor II Casual interactions	Factor III Family relationships
4.	**0.748**	-0.007	0.070
5.	**0.859**	-0.207	0.101
6.	**0.593**	0.124	0.090
7.	**0.750**	-0.015	0.079
8.	**0.539**	0.226	0.023
10.	**0.628**	-0.024	0.257
11.	**0.594**	0.262	-0.083
12.	**0.865**	-0.038	-0.079
15.	**0.629**	0.338	-0.234
1.	0.050	**0.562**	0.191
9.	-0.134	**0.713**	0.279
13.	-0.145	**0.899**	0.022
14.	0.300	**0.493**	-0.028
16.	0.199	**0.620**	-0.245
17.	0.027	**0.742**	0.019
2.	0.204	0.185	**0.533**
3.	-0.012	0.049	**-0.858**

Rotated component matrix for the Korean version of the ACIPS. Extraction method = principal component analysis; rotation = Promax with Kaiser normalization; variance explained = 58.81%. The items that load on each factor are in boldface. ACIPS, Anticipatory and Consummatory Interpersonal Pleasure Scale; A, anticipatory pleasure item; C, consummatory pleasure item.

DISCUSSION

The main goal of this study was to validate the Korean translation of the ACIPS for use with Korean-speaking groups. This study provides the first evidence of cross-cultural validity of the ACIPS in a Korean-speaking context. Specifically, the results of the present study demonstrate that the adult version of the ACIPS could be successfully adapted from American English to Korean with semantic, linguistic, and contextual equivalence.

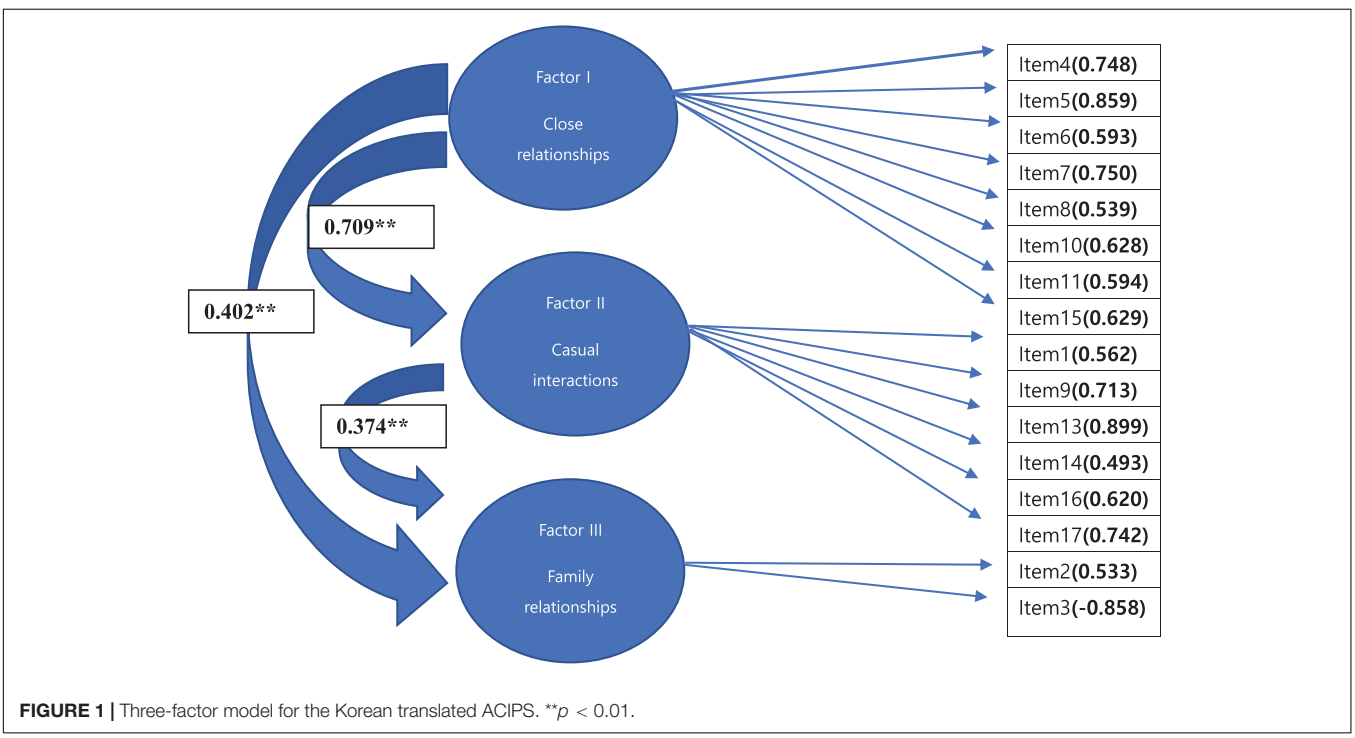


FIGURE 1 | Three-factor model for the Korean translated ACIPS. $^{**}p < 0.01$.

Our results revealed that the Korean translation of the adult version of the ACIPS had good internal consistency, as evidenced by the ordinal alpha coefficient. Results of exploratory factor analysis indicated a three-factor solution, namely, interaction in the context of close relationships, casual interactions, and family-related interactions. This factor structure is consistent with prior results of factor analyses conducted on different translations of the ACIPS. Overall, it appears that the ACIPS taps various types of social and interpersonal pleasure, including casual and intimate social interactions. It also appears that the factors include both anticipatory and consummatory items, rather than the ACIPS scale being subdivided into anticipatory and consummatory subdomains by factor analysis.

We did not observe any age effects on total ACIPS scores. However, there was not a large age range in the sample. Surprisingly, we did not observe any sex difference in the present sample. In prior reports based on adult samples, female respondents reported higher levels of social and interpersonal pleasure than males, regardless of age, or proportion of males in the sample. This pattern of sex difference was observed in American samples (Gooding et al., 2015), Spanish samples (Gooding et al., 2016), and Chinese samples (Chan et al., 2016). It is unclear whether the lack of sex differences in this Korean sample reflects a more "non-traditional" attitude toward gender roles in Korea (Choe, 2017) or whether it reflects a greater likelihood of a dampening of social pleasure amongst our female respondents.

In terms of total ACIPS mean scores, we observed lower mean scores in our Korean sample compared to other community-based adult samples, whether in the US (Bedwell et al., 2014; Gooding et al., 2015) or in China (Liang et al., 2020). We tried to identify reasons for the apparent differences in the mean total ACIPS scores. The differences in total mean scores cannot be attributed to differences in mode of survey administration (i.e., online versus in-person survey administration) because Gooding et al. (2015) used a similar mode of survey administration as the present study. One potential source of difference between the mean total ACIPS scores of the present sample (68.78 ± 15.17), the American sample of 305 adults (79.36 ± 13.40), and the Chinese sample of 74 adults (M = 74.1 ± 12.04) is the fact that our data collection occurred in the midst of the SARS-COVID-19 pandemic. This global epidemic may have had a dampening effect on the collective *joie de vivre* of an entire population. Indeed, it will be important to conduct further investigations of non-patient community-derived adults to determine whether these findings of relatively lowered total ACIPS scores reflect something about the sample itself or whether they reflect a cohort effect.

The Korean translation of the ACIPS displayed good construct validity. The total ACIPS scores were positively associated with total BAS scores, consistent with prior findings based on English versions of the measures (Gooding and Pflum, 2014a,b). The ACIPS was inversely associated with the BDI-II, consistent with a prior finding based on the Spanish version of ACIPS (Gooding et al., 2016). In the Spanish sample, participants who reported no or few depressive symptoms had significantly higher total ACIPS scores than those who reported moderate-to-severe depressive symptoms (Gooding et al., 2016). In terms of convergent validity, we expected that the ACIPS would be more closely related to measures of approach activation (i.e., the BAS) and inversely associated with scales that included direct measurement of anhedonia (i.e., the BDI) compared to measures of inhibition (i.e., the BIS).

TABLE 3 | Correlations between the ACIPS factors.

	Factor I	Factor II	Factor III
Factor I	1.000		
Factor II	0.709**	1.000	
Factor III	0.402**	0.374**	1.000

Associations between the Korean translation of the ACIPS factors. The three factors were empirically derived from factor analysis and are as follows: Factor I, close relationships; Factor II, casual interactions; Factor III, family relationships. All together, these factors accounted for 58.81% of the total variance.
ACIPS, Anticipatory and Consummatory Interpersonal Pleasure Scale.
$^{**}p < 0.01$.

TABLE 4 | Descriptive statistics for the psychometric measures (Mean ± *SD*).

	Total sample (n = 307)	Males (n = 108)	Females (n = 199)
Total ACIPS	68.78 (15.17)	70.04 (15.25)	68.10 (15.12)
Anticipatory	27.84 (5.49)	27.95 (5.98)	27.78 (5.23)
Consummatory	40.61 (9.27)	41.73 (9.49)	39.99 (9.13)
BAS	37.74 (6.77)	32.19 (7.08)	31.50 (6.59)
Reward responsiveness	5.63 (1.4)		
Fun seeking	9.05 (2.31)		
Drive	10.02 (2.57)		
BIS	17.15 (3.24)	16.19 (3.44)	17.67 (3.01)
BDI-II	37.71 (10.93)	32.19 (7.08)	31.5 (6.59)

Descriptive statistics are provided for the self-report measures used in the investigation: ACIPS, Anticipatory and Consummatory Interpersonal Pleasure Scale (Gooding and Pflum, 2014a,b); BAS, Behavioral Activation Scale (Carver and White, 1994); BIS, Behavioral Inhibition Scale (Carver and White, 1994); and BDI-II, Beck Depression Inventory-II (Beck et al., 1996a). Mean subscale scores for the ACIPS and the BAS are also provided. The group means (and standard deviations) are provided for the total sample as well as male and female participants separately.

Limitations

There are a few limitations in the present study. First, we conducted this study using an online survey. We do not think this affected the results, given that online data collection can be an effective and valid means of data collection. However, it should be noted that all of the measures involved self-reported feelings, attitudes, and emotions. The self-report approach assumes that respondents can accurately reflect upon and rate their affective experiences. There are data that indicate a relationship between self-reported social and interpersonal pleasure using the ACIPS and electromyograhic response (Kadison et al., 2014). Although the participants were limited to those without current or prior psychiatric history, there was no other clinical characterization of the sample. In the future, it would be helpful to measure participants' personality traits and clinical functioning to study the correlates

of social hedonic capacity. Another potential limitation of the present study concerns our inclusion of some 17-year-olds in the sample. These individuals were included because they had matriculated from high school and therefore were considered "adult status." We do not think this is a major limitation, given that only 3 of 307 (0.97%) participants fell into this category.

Future Directions

The Korean translation of the ACIPS is now ready to be used in clinical populations, such as persons living with schizophrenia and groups of individuals with lived experience of severe mental illness. One of the advantages of the ACIPS is its temporal stability (r = 0.78; Gooding and Pflum, 2014b) over a period of approximately 5–8 weeks. This suggests that the ACIPS is suitable for use in evaluating patients before and after targeted intervention. Working memory impairments are posited to serve as a key contributor to social anhedonia in schizophrenia (Gooding, 2022; Gooding and Pflum, 2022). As such, any evidence-based interventions such as cognitive remediation (see Vita et al., 2021), which might be effective in improving the cognitive functioning of people with schizophrenia, may partly ameliorate some of their social anhedonia.

Similarly, impairments in social cognition may cause or exacerbate the social anhedonia that characterizes many individuals with serious and persistent mental illness, including, but not limited to, schizophrenia-spectrum disorders (Favrod et al., 2019; Gooding and Pflum, 2022). There is a paucity of research in this area. Interventions which target social cognition and include the ACIPS pre- and post-intervention along with behavioral measures of *in vivo* social interactions would be useful in this regard.

CONCLUSION

Our results indicated that the ACIPS showed good construct validity in the Korean population. Future directions include using the Korean translation of the ACIPS to elucidate the varying degrees of hedonic capacity in patients with psychiatric disorders.

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 the Ethics Committees of the Pusan National University at Yangsan Hospital Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TL and DG designed the research and critically revised the article for important intellectual content. DG conceptualized and developed the scale. EK and TL acquired the data. EK, TL, and DG analyzed and interpreted the data. EK drafted the first version of the manuscript. All authors approved the final version for publication, agreed to be accountable for all aspects of the work by ensuring that any questions related to its accuracy and integrity can be appropriately investigated and resolved.

FUNDING

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (Grant No. 2021R1A2C1006718).

ACKNOWLEDGMENTS

We thank Dr. Wanju Park, Dr. Sohee Park, and Dr. Ji-Won Hur for their generous assistance in the process of translation and back translation of the ACIPS.

REFERENCES

Andreasen, N. C. (1982). Negative symptoms in schizophrenia. Definition and reliability. *Arch. Gen. Psychiatry* 39, 784–788. doi: 10.1001/archpsyc.1982.04290070020005

Barkus, E., and Badcock, J. C. (2019). A transdiagnostic perspective on social anhedonia. *Front. Psychiatry* 10:216. doi: 10.3389/fpsyt.2019.00216

Beck, A. T., Steer, R. A., Ball, R., and Ranieri, W. (1996b). Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *J. Pers. Assess* 67, 588–597. doi: 10.1207/s15327752jpa6703_13

Beck, A. T., Steer, R. A., and Brown, G. (1996a). *Beck Depression Inventory* (2nd edition). San Antonio, TX: The Psychological Corporation.

Bedwell, J. S., Gooding, D. C., Chan, C. C., and Trachik, B. J. (2014). Anhedonia in the age of RDoC. *Schiz. Res.* 160, 226–227. doi: 10.1016/j.schres.2014.10.028

Blanchard, J. J., Horan, W. P., and Brown, S. A. (2001). Diagnostic differences in social anhedonia: a longitudinal study of schizophrenia and major depressive disorder. *J. Abnorm. Psychol.* 110, 363–371. doi: 10.1037//0021-843x.110.3.363

Bobes, J., Arango, C., Garcia-Garcia, M., and Rejas, J. (2010). Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: findings from the CLAMORS study. *J. Clin. Psychiatry* 71, 280–286. doi: 10.4088/JCP.08m04250yel

Carver, C. S., and White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS Scales. *J. Personal. Soc. Psychol.* 67, 319–333. doi: 10.1037/0022-3514.67.2.319

Chaix, J., Golay, P., Fankhauser, C., Nguyen, A., Gooding, D. C., and Favrod, J. (2017). Confirmatory factor analysis of the french version of the anticipatory and consummatory interpersonal pleasure scale. *Front. Psychol.* 8:1296. doi: 10.3389/fpsyg.2017.01296

Chan, R. C., Yang, Z. Y., Li, Z., Xie, D. J., and Gooding, D. C. (2016). Validation of the chinese version of the anticipatory and consummatory interpersonal pleasure scale. *PsyCh. J.* 5, 238–244. doi: 10.1002/pchj.139

Choe, M. K. (2017). "Modernization, gender roles, and marriage behavior in South Korea," in *Transformations in Twentieth Century Korea*, eds C. Yun-Shik and S. H. Lee (New York, NY: Routledge), 295–309.

Correll, C. U., and Schooler, N. R. (2020). Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatr. Dis. Treat.* 16, 519–534. doi: 10.2147/NDT.S225643

Docherty, A. R., and Sponheim, S. R. (2014). "Anhedonia as an indicator of genetic liability in schizophrenia," in *Anhedonia: A Comprehensive Handbook*, ed. M. S. Ritsner (Berlin: Springer), 105–124. doi: 10.1007/978-94-017-8610-2_4

Eckbland, M. L., Chapman, L. J., Chapman, J. P., and Mishlove, M. (1982). *The revised Social Anhedonia Scale. Unpublished scale*. Madison: University of Wisconsin-Madison.

Favrod, J., Nguyen, A., Chaix, J., Pellet, J., Frobert, L., Fankhauser, C. et al. (2019). Improving pleasure and motivation in schizophrenia: a randomized controlled clinical trial. *Psychother. Psychosom.* 88, 84–95. doi: 10.1159/000496479

Gooding, D., Moore, M., Pflum, M., Schmidt, N., and Goldsmith, H. (2021). Genetic and environmental contributions to positive affect: insights from adolescent twins. *Affect. Sci.* 2, 289–300. doi: 10.1007/s42761-021-00041-1

Gooding, D. C. (2022). Brave new world: harnessing the promise of biomarkers to help solve the epigenetic puzzle. *Schiz. Res.* 242, 35–41. doi: 10.1016/j.schres.2022.01.020

Gooding, D. C., Fonseca-Pedrero, E., Pérez De Albéniz, A., Ortuño-Sierra, J., and Paino, M. (2016). Spanish adaptation of the adult version of the anticipatory and consummatory interpersonal pleasure scale. *Rev. Psiquiatr. Salud. Ment.* 9, 70–77. doi: 10.1016/j.rpsm.2015.10.006

Gooding, D. C., Padrutt, E. R., and Pflum, M. J. (2017). The predictive value of the NEO-FFI items: parsing the nature of social anhedonia using the revised Social Anhedonia Scale and the ACIPS. *Front. Psychol.* 8:147. doi: 10.33/fpsyg.201.00147

Gooding, D. C., and Pflum, M. (2022). The transdiagnostic nature of social anhedonia: Historical and current conceptualizations. *Curr. Top. Behav. Neurosci.* 2022:301. doi: 10.1007/7854_2021_301

Gooding, D. C., and Pflum, M. J. (2014a). Further validation of the ACIPS as a measure of social hedonic response. *Psychiatry Res.* 215, 771–777. doi: 10.1016/j.psychres.2013.11.009

Gooding, D. C., and Pflum, M. J. (2014b). The assessment of interpersonal pleasure: introduction of the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) and preliminary findings. *Psychiatry Res.* 215, 237–243. doi: 10.1016/j.psychres.2013.10.012

Gooding, D. C., Tallent, K. A., and Matts, C. W. (2005). Clinical status of at-risk individuals 5 years later: further validation of the psychometric high-risk strategy. *J. Abnorm. Psychol.* 114, 170–175. doi: 10.1037/0021-843X.114.1.170

Gooding, D. C., Tallent, K. A., and Matts, C. W. (2007). Rates of avoidant, schizotypal, schizoid, and paranoid personality disorders in psychometric high-risk groups at five year follow-up. *Schiz. Res.* 94, 373–374. doi: 10.1016/j.schres.2007.04.018

Gooding, D. C., Winston, T. M., Pflum, M. J., and Burgin, C. J. (2015). Individual differences in hedonic experience: further evidence for the construct validity of the ACIPS. *Psychiatry Res.* 229, 524–532. doi: 10.1016/j.psychres.2015.05.061

Hambleton, R. K., Merenda, P. F., and Spielberger, C. D. (2005). *Adapting educational and psychological tests for cross-cultural assessment*. London: Lawrence Erlbaum Associates.

Horan, W. P., Blanchard, J. J., Clark, L. A., and Green, M. F. (2008). Affective traits in schizophrenia and schizotypy. *Schiz. Bull.* 34, 856–874. doi: 10.1093/schbul/sbn083

Jhung, K., Park, J. Y., Song, Y. Y., Kang, J. I., Lee, E., and An, S. K. (2016). Experiential pleasure deficits in the prodrome: a study of emotional experiences in individuals at ultra-high risk for psychosis and recent-onset schizophrenia. *Compreh. Psychiat.* 68, 209–216. doi: 10.1016/j.comppsych.2016.04.021

Kadison, L. S., Ragsdale, K. A., Mitchell, J. C., Cassissi, J. E., and Bedwell, J. S. (2014). Subtypes of anhedonia and facial electromyography response to negative affective pictures in nonpsychiatric adults. *Cogn. Neuropsych.* 20, 31–40. doi: 10.1080/13546805.2014.955172

Kwapil, T. R. (1998). Social anhedonia as a predictor of the development of schizophrenia-spectrum disorders. *J. Abn. Psychol.* 107, 558–565. doi: 10.1037//0021-843x.107.4.558

Leventhal, A. M., Chasson, G. S., Tapia, E., Miller, E. K., and Pettit, J. W. (2006). Measuring hedonic capacity in depression: a psychometric analysis of three anhedonia scales. *J. Clin. Psychol.* 62, 1545–1558. doi: 10.1002/jclp.20327

Liang, Y. S., Wang, Y., Wang, Y. Y., Ni, K., Gooding, D. C., and Chan, R. C. K. (2020). Social anhedonia across mental disorders: a validation study of the anticipatory and consummatory interpersonal pleasure scale. *PsyCh. J.* 9, 160–162. doi: 10.1002/pchj.339

Meng, X.-L., Rosenthal, R., and Rubin, D. B. (1992). Comparing correlated correlation coefficients. *Psychol. Bull.* 111, 172–175. doi: 10.1037/0033-2909.111.1.172

Ritsner, M. S., Ratner, Y., Mendyk, N., and Gooding, D. C. (2018). The characterization of social anhedonia and its correlates in schizophrenia and schizoaffective patients. *Psychiatry Res.* 270, 922–928. doi: 10.1016/j.psychres.2018.11.003

Umesh, S., Nizamie, S. H., Goyal, N., Tikka, S., and Bose, S. (2018). Social anhedonia and gamma band abnormalities as a composite/multivariate endophenotype for schizophrenia: a dense array EEG study. *Early Intervent. Psychiat.* 2, 362–371. doi: 10.1111/eip.12327

Vita, A., Barlati, S., Ceranso, A., Nibbio, G., Ariu, C., Deste, G., et al. (2021). Effectiveness, core elements, and moderators of response of cognitive remediation for schizophrenia: A systematic Review and meta-analysis of randomized clinical trials". *JAMA Psychiat.* 78, 848–858. doi: 10.1001/jamapsychiatry.2021.0620

Winograd-Gurvich, C., Fitzgerald, P. B., Georgiou-Karistianis, N., Bradshaw, J. L., and White, O. B. (2006). Negative symptoms: a review of schizophrenia, melancholic depression and Parkinson's disease. *Brain Res. Bull.* 70, 312–321. doi: 10.1016/j.brainresbull.2006.06.007

Zhornitsky, S., Rizkallah, E., Pampoulova, T., Chiasson, J. P., Lipp, O., Stip, E., et al. (2012). Sensation-seeking, social anhedonia, and impulsivity in substance use disorder patients with and without schizophrenia and in non-abusing schizophrenia patients. *Psychiatry Res.* 200, 237–241. doi: 10.1016/j.psychres.2012.07.046

Zumbo, B., Gadermann, A., and Zeisser, C. (2007). Ordinal versions of coefficients alpha and theta for likert rating scales. *J. Mod. Appl. Stat. Methods* 2007, 21–29. doi: 10.22237/jmasm/1177992180

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 | Frontiers in Psychology

CONCEPTUAL ANALYSIS
published: 11 May 2022
doi: 10.3389/fpsyg.2022.805795

Social Perception Deficit as a Factor of Vulnerability to Psychosis: A Brief Proposal for a Definition

Álvaro Cavieres[1]* *and Pablo López-Silva*[2]

[1]Escuela de Medicina, Universidad de Valparaíso, Valparaíso, Chile, [2]Escuela de Psicología, Universidad de Valparaiso, Valparaíso, Chile

Disturbances in social cognition are a core feature of schizophrenia. While most research in the field has focused on emotion perception, social knowledge, theory of mind, and attribution styles, the domain of social perception has received little specific attention. In this paper, we suggest that this issue can be explained by the lack of a precise and unitary definition of the concept, this leads to the existence of different competing uses of the concept and their conflation with other domains of social cognition. Relying on resources coming from the ecological approach to psychology and the phenomenological tradition in psychiatry, we propose that the concept of Social Perception should be used to refer to low-level pre-reflective processes underlying the awareness of interpersonal interactions *with* and *between* others. Clinical data suggests that people with schizophrenia have problems perceiving social situations as opportunities for social engagement, so, in order to fulfil this explanatory need, we propose that the term should be used to capture this important—yet neglected—domain of social cognition. We conclude with the discussion of some future directions for research derived from our proposal.

Keywords: social cognition, social perception, social affordances, psychosis, schizophrenia

OPEN ACCESS

Edited by:
Marta Bosia,
Vita-Salute San Raffaele University, Italy

Reviewed by:
Marcel Riehle,
University of Hamburg, Germany
Stefano Zago,
IRCCS Ca 'Granda Foundation Maggiore Policlinico Hospital, Italy

***Correspondence:**
Álvaro Cavieres
cavieres.alvaro@gmail.com

Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: *31 October 2021*
Accepted: *27 April 2022*
Published: *11 May 2022*

Citation:
Cavieres Á and López-Silva P (2022) Social Perception Deficit as a Factor of Vulnerability to Psychosis: A Brief Proposal for a Definition. Front. Psychol. 13:805795. doi: 10.3389/fpsyg.2022.805795

THE SOCIAL DIMENSION OF SCHIZOPHRENIA

Schizophrenia is linked to a number of social difficulties, among them, reduced capacity for close relationships (Budziszewska et al., 2020), decrease in obtaining and keeping jobs (Hakkaart-van Roijen et al., 2015), decreased engagement in social activities (Bellack et al., 2007), and, in general, a less adequate social functioning (Gorostiaga et al., 2017). Although there is an important degree of causal overlapping with a general deficit in individual cognitive performance, most of these problems have been attributed to poor functioning in social cognition (Schmidt et al., 2011; Halverson et al., 2019). As a theoretical construct, social cognition has been defined as the ability to perceive, interpret, and process social information in real-world settings, or the capacity to be able to construct representations of the relationship between oneself and others and flexibly use these representations to guide social behavior (Green et al., 2008). Disturbed social cognition does not only limit the possibilities of an adequate psychosocial functioning in schizophrenia, but it also can lead to (a) distorted interpretations of the emotions and intentions of others in non-psychotic populations, and (b) false attribution of these emotions and intentions in neutral social contexts, predisposing genetically vulnerable subjects to develop psychotic symptoms (Mier and Kirch, 2017).

Over the last years, impairments in social cognition have been recognized as a core feature of schizophrenia (Green et al., 2015; Javed and Charles, 2018; Montag et al., 2020; D'Arma et al., 2021). Certainly, there are many processes involved in perceiving, interpreting, and generating responses to others intentions, dispositions, and behaviors; in this context, most described evidence point toward impairments in emotion perception, social perception, social knowledge, theory of mind, and attributional style (Ochsner, 2008; Haut et al., 2020; Montag et al., 2020). Broadly speaking, emotion perception has been regarded as the ability to identify the emotions of others accurately; social knowledge refers to the ability to perceive, understand, and appraise implicit and explicit social roles, rules, and context; theory of mind is conceptualized as the ability to interpret someone's speech or bodily actions in terms of their intentions; and, finally, the concept of attributional style refers to the usual mode of explaining events as a consequence of internal (personal), external (another person), or situational factors (Green et al., 2008; Savla et al., 2013; Montag et al., 2020). From an experimental point of view, research has shown that people with schizophrenia exhibit impaired recognition of emotions conveyed through facial expressions and verbal communication (Savla et al., 2013; Green et al., 2015). They also present problems representing affective mental states, but not more than straightforward cognitive mental states (Savla et al., 2013).

However, it is important to note that little to no research has been dedicated to the understanding of specific problems in social perception. In this paper, we first argue that this shortage in specific research might be explained as a consequence of the lack of a precise and unitary definition of the concept, thus leading to the existence of different competing uses of the notion and their conflation with other domains of social cognition which depend heavily on cognitive processes by which the subject interprets and understands the surrounding environment. Instead, we define social perception as one of the most fundamental functions of being in the world with others. On our view, altered social cognition would be a fundamental feature of schizophrenia as it has been described and linked to the origin of psychotic and deficit symptoms within the classic and contemporary phenomenological tradition in psychopathology (Kraepelin, 1904; Jaspers, 1948; Minkowski, 1966; Blankenburg, 1971; Fuchs, 2015a; Van Duppen, 2017; Parnas et al., 2021, among many others). In our view, psychotic symptoms such as delusions and hallucinations would not only imply disturbed ideas, thoughts, or perceptions. They would also include the impossibility of modifying or relativizing those mental states by sharing them in a common space with others. At the same, negative symptoms would be more than a deficit of expression or motivational drive; they would also be a failure to perceive the opportunity to interact and generate a shared lived reality with others. From a therapeutic point of view, incorporating the notion of a failure of social perception would broaden the current focus of treatment from improving the patient's cognitive abilities to better understand the world in front of them, to improving their abilities to be in the world with others.

By relying on resources coming from the ecological approach to psychology—especially on the concept of *affordance*—and the phenomenological tradition in psychiatry, we propose that the concept of *Social Perception* should be used to refer to low-level pre-reflective processes underlying the awareness of interpersonal interactions *with* and *between* others. Although direct empirical evidence is lacking, we believe that people with schizophrenia have problems perceiving social situations as opportunities for social engagement. In other words, subjects have problems perceiving social situations as social situations. For this reason, we propose that the term social perception might be useful to capture this important yet neglected domain of social cognition that appears to be altered in schizophrenia (Cavieres et al., 2020). Finally, we conclude by discussing some future directions for research derived from our brief and explorative proposal.

THE MANY FACES OF SOCIAL COGNITION

Definitions of *Social Cognition* found in the expert literature tend to differ in scope and the conceptual background underlying their main tenets. More importantly, these notions do not only differ in the way the term is defined or in the emphasis put on the social or individual aspects of social interactions; they also differ in the way in which the concept might—or might not—interact with other domains of social cognition. For example, Allison et al. (2000, p. 267) try to highlight the ability to rapidly perceive the intentions of others. The authors suggest that "social perception is the initial stage of evaluating intentions and psychological dispositions of others by analysis of gaze direction, body movement, and other types of biological motion." In this view, social perception is—mostly—an evaluative process aiming at translating behavioral clues into relevant information to guide adequate responses in social settings. Contrasting and emphasizing the importance of social context in human interactions, McCleery et al. (2014, p. 54) claim that social perception: "refers to identifying and utilizing social cues to make judgments about social roles, rules, relationships, context, or the characteristics (e.g., trustworthiness) of others." In this view, social perception would have a more active nature as it includes the process of identifying environmental cues. However, it is not clear the way that this process of identification is guided. McCleery et al. (2014, p. 54) also claim that social perception: "includes social knowledge, which refers to one's knowledge of social roles, norms, and schemas surrounding social situations and interactions." As a consequence, it is difficult to identify the specific conceptual differences between the notions of social knowledge and social perception. By contrast, Jacob and Jeannerod (2005) offer a more restrictive view of social perception and claim that only cues of actions and intentions directed toward conspecifics (intentions to affect the other's behavior) should be included within the domain of social perception.

In the context of the MATRICS initiative, Green and Leitman (2008) define social perception as one's ability to identify social roles and context including relationship perception, which refers

to the perception of the nature of relationships between people. In the authors' view, social knowledge would refer to the awareness of the roles, rules, and goals that characterize specific social situations and guide social interactions. Pinkham (2014, p. 14), on the other hand, ignores this difference and conceptualizes social perception as the decoding and interpretation of social clues in others, including "the ability to integrate contextual information and social knowledge into judgments of others' behaviors." Later on, Green et al. (2015) would revise these definitions, employing the term perception of social clues to refer to the ability to perceive the social information in others' faces, voices, and body movements, including gait, posture, and gestures. Apparently excluding context, the concept of social-clues perception is divided into (a) facial perception refers to the decoding of affective information from others' facial expressions, and (b) vocal perception, defined as the recognition and discriminating of acoustic properties of speech and the respective affective information they convey.

A brief literature review reveals the existence of a number of competing definitions of the notion of social perception, and with this, the existence of different alternatives for the way in which social perception might relate to other domains of social cognition (especially social knowledge). A more problematic issue seems to underlie this conceptual debate, namely, the contradictory use of the two basic concepts of the target debate, the concept of "social," and the concept of "perception." Within the debate, the concept of "social" is commonly used as a synonym for interpersonal, namely, as the source of information and the context in which this information is relevant. At the same time, perception seems to be used to refer to the initial impression caused by sensory stimuli or the set of cognitive operations originating from these stimuli. Contrasting with the many faces of the term "social perception," notions such as "social knowledge," "theory of mind," "emotion perception and processing," and "attributional style" seem to be both better-defined and researched within the domain of social cognition. Here, it is important to note that none of the aforementioned domains of social cognition specifically reflect, perhaps, one of the most relevant dimensions when trying to understand social cognition-related phenomena, namely, the capacity to *perceive a social situation as social,* that is, as an instance of interaction with and among others. In the next section, we will explore our proposal by looking closer at the way in which humans perceive the social world.

EXPERIENCING THE SOCIAL WORLD: HOW DO WE SOCIALLY PERCEIVE?

For human beings, the most prominent features in their environment are other humans. Although the humans we perceive in the environment might share some physical properties with the rest of the material world, we perceive them as different from mere material objects. We are aware of other humans as having emotions and intentions, namely, as having a mental life. However, the most striking difference between humans and other things we perceive is that other humans can meaningfully interact with us and other humans in the environment. In fact, perceiving the emotions and intentions of others helps us to understand these interactions so we can adequately navigate the social world. In a certain sense, situations become social when we become aware of these actual or potential interactions. The world is experienced as a social world as long as it offers opportunities for social engagement. According to Heider (2005), the critical differences between people and inanimate things are that as: (i) persons have phenomenally private experiences such as perceptions, imaginations, thoughts, feelings, and the like, which enable them to act as "centers of action" on the basis of their internal reasoning,[1] and additionally, (ii) people can establish a peculiar functional closeness and interaction in social encounters if they interact with each other.

Humans can rapidly perceive the emotions experienced by others (emotional perception; Jang and Elfenbein, 2015) and use them, together with other sources of information, to grasp their internal reasoning (Castelli, 2015). Some suggest that this process can take the form of a sequence where perceptual inputs from sensory stimuli are used to generate inferential interpretations of others' minds (Goldman, 2006; Pérez-Osorio et al., 2021). Others suggest that we can also *perceive* directly (rather than *inferring*) other people's intentions (Dokic, 2010; Kiverstein, 2015; Gallagher, 2017). Arguably, this is to say that we can perceive emotions and intentions in others, but such stimuli become truly social when they are used for processing cues of actions and intentions of a person directed to affect others' or our own behaviors.

Dokic (2010) describes two models of joint action with other people. In the first, joint action depends on mind reading. In the second, joint action involves the participants' non-mentalizing perceptions of social affordances. Adapting Gibson's definition of the term (see Gibson, 1966, 1977, 1986), we shall understand the term social affordances as the combination of a subject's features and possibilities for action that people in the environment offer to her and someone else. In this context, affordances can be either ego-centric when the agent is the perceiver or allo-centric when it concerns another agent. The latter type does not require mind reading abilities; all that is needed is the ability to represent other people and their bodily movements. Importantly, the perception of allo-centric affordances for others' actual or potential actions could reveal previously unperceived ego-centric affordances (and viceversa). This, in turn, would allow the emergence of interpersonal affordances as opportunities for joint actions integrating both ego and allo-centric aspects (Richardson et al., 2007).

This proposal seems to be compatible with the neural correlates of social information processing, comprising two distinct systems: the "mirror neuron system" (MNS) and the "mentalizing" system (MENT). Both systems are activated during interaction or communication with other human beings

[1]It is important to note that Heider's definition might also apply to animal perception. However, an analysis of this issues goes beyond the focus on our current work.

in social encounters (Bickart et al., 2014; Vogeley, 2017; Porcelli et al., 2019). However, although their precise functional roles are still unclear, it has been proposed that the MNS serves in early stages of social information processing related to the "detection" of spatial or bodily signals, whereas the MENT is recruited during later stages of social information processing related to the "evaluation" of emotional and psychological states of others (Vogeley, 2017; Geiger et al., 2019). While decreased connectivity has been observed both within the MNS and the MENT in subjects with schizophrenia compared to controls, only dysconnectivity of the MNS was related to symptom severity as assessed by the PANSS general and total scale. This could suggest differential patterns contributing to interpersonal difficulties (Schilbach et al., 2016). It has been argued that mirror neurons are linked to the production of information about the observer's *own* action opportunities, rather than a representation of the other agent's intention. In Dokic's terminology, mirror neurons underlie *ego-centric* perceptual representations of what the observer can do in a given situation generated from the perception of others' actions.

The aforementioned ideas can be connected with the way in which the concept of "intersubjectivity" has been explored within the phenomenological tradition. Fuchs (2015a) claims that as: "Intersubjectivity in its full sense is thus based on the ability to oscillate between an ego-centric, embodied perspective on the one hand, and an allo-centric or decentered perspective on the other, without thereby losing one's bodily center of self-awareness" (p. 179). Within this perspective, intersubjectivity implies a continuous "co-construction of meaning through mutual interaction and perspective taking" (p. 179). Observing others and their actions immediately opens the possibility of perceiving joint actions. This specific ability to anticipate actual or potential interactions is what we propose to call social perception, separating the term from the other domains of social cognition mentioned in section 1. According to Bickart et al. (2014), both the MNS and the MENT systems interact with other three, partially distinct, brain networks anchored in the amygdala; the network involved in the detection and processing of social stimuli; the social affiliation network and the social aversion network. Detection of social stimuli is rapid and automatic and directs attention to socially salient stimuli with subsequent activation of the other amygdala-centered circuits promoting or inhibiting pro-social behavior as well as the higher-order cognitive processes of the MENT and MNS systems (Porcelli et al., 2019). In sum, information about what others are doing is processed in our brains differently and in parallel to information about what they are feeling. Although this might sound like an oversimplification of a still insufficiently understood process, the brain seems to have a dynamic and hierarchical system of circuitries involved in simpler forms of more automated processing, like the immediate detection of socially relevant stimuli in amygdala-centered circuits, and a partially overlapping circuitry involved in the further interpretation of others actions, intentions, and emotions requiring the activation of the MENT and MNS systems.

HOW SOCIAL COGNITION GOES WRONG IN SCHIZOPHRENIA?

The distinction between general cognitive deficits and social cognitive functioning brought attention to the difficulties that people with schizophrenia have in recognizing other people's expressions and their emotional states and intentions. However, the lack of a more precise definition of social perception, including its conflation with other domains of social cognition, has resulted in a shortage in research on the specific problems in perceiving and understanding social interactions. Savla et al. (2013) reported the results of a meta-analysis of deficits in different domains of social cognition compared to controls, finding large effects for social perception, theory of mind, emotion perception, and emotion processing. Using a different classification, Green et al. (2015) found evidence of impairments in the perception of social cues (face and prosody perception), mentalizing and emotion regulation with emotion experience, and motor resonance (activation of the MNS) and affect sharing, largely intact in schizophrenia. Lee et al. (2013) reported that people with schizophrenia can use contextual social information provided to help them identify ambiguous facial expressions. Nikolaides et al. (2016) investigated gaze behavior in schizophrenia in relation to social interactions and its impact on social and role functioning. When observing social interaction scenes, subjects showed a shorter scan path length, fewer fixations, and a shorter mean distance between fixations. Furthermore, they exhibited fewer and shorter fixations on faces, but neither on the socially informative bodies nor in the background, suggesting a cue-specific abnormality.

Using a similar task, Sergi and Green (2003) and Sergi et al. (2006) suggested that social perception in schizophrenia is related to alterations in very early aspects of visual processing, although their results were heavily influenced by the educational status of the experimental subjects. Kitoko et al. (2020) report the results of a study using an integrated social perception and knowledge task on people with schizophrenia. Subjects had reduced performance in interpretation and awareness of social conventions. However, these deficits were not correlated with the severity of clinical symptoms, and individual profiles analyses showed a marked heterogeneity among subjects on their abilities. Karpouzian et al. (2016) used a facial affect perception task and video scenes of a single person displaying different facial expressions, voice intonations, and bodily gestures to evaluate social perception in a group of individuals with schizophrenia; they concluded that high, but not low functioning individuals have preserved social perception. In our own research, we asked people with schizophrenia to make sense of a scene depicting an ambiguous social situation with faces, thoughts, and facts about the scene hidden from view (Cavieres et al., 2020). Participants were required to select a limited number of these items before providing an answer. People with schizophrenia—as well as controls—had a strong preference for knowing the thoughts of the characters and their interpretations did not differ from the control group. The results of this study suggest that, despite difficulties perceiving clues about the mental state of others, people with

schizophrenia use this information when trying to understand social situations.

From a neurobiological perspective, Ebisch et al. (2017) examined the relationship between task-evoked neural activity during observation of social interaction and the functional organization of self-related brain networks during the resting state. Task-evoked activity in the dorsal posterior cingulate cortex during social perception co-varied with dorsal posterior cingulate cortex-ventromedial prefrontal cortex functional connectivity during resting state in controls not in people with schizophrenia. Using a different paradigm, they also reported the involvement of the dorsolateral prefrontal cortex and superior temporal sulcus in impaired social perception in schizophrenia. What these results show is that people with schizophrenia present problems in different and separate dimensions of social cognition, not only in perceiving the emotions and mental states of others and constructing hypotheses about their intentions but also in perceiving potential or actual interactions. This specific alteration might hinder the possibility of experiencing a social world where interactions with others can be had and shared.

The aforementioned idea seems to be present in some of the earliest descriptions of schizophrenia (e.g., in the descriptions offered by Bleuler and Minkowski). Later, psychopathological descriptions of the condition seem to have focused on psychotic symptoms and failures in the construction of the self. Nonetheless, disturbances of basic self-awareness and attunement to the social world seen in schizophrenia also impair the subject's ability to interact with others, not because they lack explicit knowledge, inferential or ToM abilities, but rather, because they seem to lack an implicit understanding of the "rules of the social game"; a sense of proportion for what is appropriate, likely and relevant in the social context (Fuchs, 2015a). From a phenomenological perspective, disturbances of pre-reflective self-awareness and embodiment—including a weakening of the basic sense of self and a disruption of implicit bodily functioning in the dimensions of both perception and action (Sass and Parnas, 2003, 2007)—would lead to a fundamental disturbance of the pre-reflective, embodied, and practical immersion of the self in the (social) world (Van Duppen, 2017).

HOW CAN FAILURES IN SOCIAL PERCEPTION LEAD TO PSYCHOTIC SYMPTOMS?

Early authors within the phenomenological tradition in psychiatry such as Bleuler, Kretschmer, and Minkowski considered interpersonal difficulties as a fundamental psychotic vulnerability, a hypothesis that has also been held by other authors in more recent times (Fuchs, 2015a,b; Pienkos, 2015; Henriksen and Nilsson, 2017; Van Duppen, 2017; Van Duppen and Feyaerts, 2020). All these authors seem to agree that, beyond difficulties in other areas of social cognition, schizophrenia would be characterized by a basic impairment in social perception in the sense in which we have just defined it in the previous sections. People with schizophrenia can recognize and identify other human beings and their actions but experience difficulties perceiving the interpersonal affordances of their presence. This can be interpreted as an inability to generate an adequate intersubjective space to share and construct meanings about everyday life experiences, including the use of pragmatic language. This leaves subjects vulnerable to the emergence of idiosyncratic and self-referential interpretations that might produce the core of psychotic experiences, especially delusions. Moreover, without an effective form of intersubjective communication, subjects also lose the possibility of developing metacognitive control over their own ideas. Thus, instead of common, shared meanings of everyday experiences, people with schizophrenia construct their peculiar interpretations in ways that are incomprehensible to others and which, escaping all metacognitive control, are held with apodictic certainty, foregoing verification or relativization in an intersubjective context.

Stanghellini (2001) employs the concept of *common sense* to refer to everything that members of a given society consider as obvious. It involves both practical knowledge about social situations and a basic intuitive attunement (social perception) with the social world aimed at understanding these situations. Whereas the concept of "social knowledge" refers to the background of constructs useful for organizing the everyday experiences, the concept of "attunement" reflects the affective-conative capacity to get involved in others' lives and to catch context-relevant cues to make sense of the others and of situations. According to Stanghellini, people with schizophrenia lose contact with this common sense through three mechanisms: (a) sensory (aberrant perception of self, body, and world), (b) typification disorders (disturbances of social knowledge network or lack of attunement), and (c) Attitudinal disorders (distrust toward common sense). These levels of vulnerability are coherently related to each other, in a way that, when intuitive attunement is disordered, not only do the others appear enigmatic and the social environment becomes uncanny, but also one's sense of the self and the boundaries between oneself and the others may become blurry. All these disruptions would lead to the onset of psychosis.

Fuchs (2015b) explicitly distinguishes between a faulty development or functioning of ToM module "inside" the subject (which renders other persons' thoughts, feelings, and actions strange and inaccessible) from an immediate, pre-reflective disturbance in the relationship between self and others in an emergent bi-personal field. When the perspectives of self and others are confused instead of being integrated, the subject may be left susceptible to experience symptoms where the subject's boundaries are diminished or altered such as thought-broadcasting, thought insertion, and auditory-verbal hallucinations. In this sense, traditional approaches focus on failures of self-integration and source monitoring as explanations for auditory hallucinations. Instead, Bell (2013) highlights "social" features of hallucinations such as possessing identities performing communicative acts and being perceived as interlocutors (McCarthy-Jones et al., 2014). There is also evidence that the neural circuits involved in the neurobiology of hallucinatory voices also perform tasks related to social cognition (Rushworth et al., 2013). Rushworth

hypothesizes that auditory-verbal hallucinations arise from the internalization of familiar people and their voices, which are used to make inferences about their behavior in imaginary situations. However, further research is needed in order to support this view in light of updated characterization of auditory hallucinatory phenomena (Woods et al., 2015; Rosen et al., 2016).

In relation to delusions, Fuchs (2015a) has argued that we create meanings about our experiences in a continuous circular process of mutual understanding, negotiation of intentions, alignment of perspectives, and reciprocal correction of perceptions—with others in every interaction and communication. However, if there are failures in the establishment of boundary conditions to these circular processes, then the co-construction of meaning will be disturbed, and mutual understanding will fail. These may include perceptual, cognitive, and affective alterations characteristic of schizophrenia, especially in its early stages. Here, our proposal integrates the specific ability to perceive social situations as shared instances with others (social perception). Delusions may be incompletely understood as merely individual false beliefs, they arise when the basic trust, that could help restore a consensual understanding of a situation and co-constitute a shared, commonsensical reality, is missing. Deluded subjects might be able to perceive (emotion recognition), understand, or even take the perspective of others (theory of mind); what they lack in our view is the independent position from which they could compare and integrate their own and another's point of view. Thus, among other factors, delusions might result from the failure of co-constituting the world through mutually taking and aligning one's perspectives.

CONCLUSION AND FUTURE DIRECTIONS

Disturbances in social cognition are one of the core features of schizophrenia. Most described socio-cognitive deficits in schizophrenia refer to impairments in emotion perception, social perception, social knowledge, theory of mind, and attributional style (Ochsner, 2008; Montag et al., 2020). We have noted an important shortage in specific research regarding social perception. We have proposed that this issue arises from the lack of a precise and unitary definition of the term, leading up to the existence of competing notions about the scope and the way in which social perception would interact with other dimensions of social cognition. In order to deal with this conceptual gap, we have proposed that the concept of Social Perception should be reserved to refer to low-level pre-reflective processes related to the awareness of interpersonal interactions *with* and *between* others. From this point of view, alterations in social perception might capture the fact that people with schizophrenia have problems perceiving social situations as social or, in other words, perceiving opportunities for social engagement.

It is important to note that our proposal is very explorative. Indeed, more research is needed to define the most appropriate way to study social perception and characterize its alterations in the different stages of schizophrenia including people at high risk of psychosis and its relation to the various symptoms of the condition. From a therapeutic and preventive approach, clarifying the relationship between social perception, intersubjectivity, and psychotic experiences and symptoms in schizophrenia is a critical issue that could potentially lead to new forms of psychosocial interventions or to the improvement of existing programs.

Much of the research cited in this article has been subject of criticism regarding the methodology employed. Teufel et al. (2013) pointed out that simple pictorial representations of other people are "social" only in the restricted sense that they reproduce their physical features but not their spatiotemporal properties. Even watching videos can be considered "non-social," because the observer knows that he is not seeing real persons and will not attribute mental states to the stimuli or do so qualitatively different from real social interaction. Pönkänen et al. (2011) demonstrated different information-processing mechanisms depending on whether or not the observers believe they are seeing a real person present at the time of viewing. Teufel et al. (2010) believe that another person's actual or assumed presence increases the tendency of observers to attribute mental states to viewed stimuli, which affects the perceptual processing of specific socially relevant information.

Regardless of the precise sequence in which it occurs, it seems clear that perceiving other people, and their actions, is a distinct process from emotion recognition and mindreading. Consequently, we believe that an ideal research design for this domain should be able to specifically investigate the ability to perceive other subjects as interacting with each other, independently of adequately identifying their intentions or emotional states. Moreover, being able to describe these actual or potential interactions does not necessarily require knowledge of the rules that apply to a specific social situation. For example, in our own unpublished research, patients recognize a group of subjects performing different tasks, following their own intentions in a common situation (opening the fridge, fetching cups, and boiling water for tea) but do not perceive them as performing a common task (preparing to have breakfast together). Normally, we observe others interacting with the world and the objects in it, but most importantly, with other persons and with ourselves. This is what allows us to perceive others as social intentional agents, whose actions and interactions are purposeful in contexts shared with others, and to learn to experience ourselves as intentional agents perceived by others in shared social spaces.

Fuchs (2015b) criticizes current paradigms based on a conception of the subject with schizophrenia as an enclosed individual with a clearly defined brain dysfunction. Instead, he states, most mental disorders imply more or less profound disturbances of intersubjectivity, which means, a restricted capacity to respond to the social environment in a flexible way and to reach a shared understanding through adequate interaction with others (p. 191). Nevertheless, emotion recognition, mind reading, attributional styles, and social

knowledge all occur mostly within the subject and so, are commonly studied in contexts with no real interactions. For instance, there is an important line of research and therapy for people diagnosed with schizophrenia based on the importance of the metacognitive aspects defined as an activity carried out by one person in order to know, monitor, and adjust their beliefs, memories, and behaviors (Moritz and Woodward, 2007). However, instead of a cognitive activity concretely located in an isolated mind, metacognition is entwined with intersubjective experience.

Psychosocial rehabilitation programs could benefit from incorporating this view in their design and methodology, favoring safe and shared working environments with other patients and therapists, where it is possible to examine experiences in a non-judgmental way and facilitate the incorporation of interpretations that include others' points of view, but above all, favoring constructive and real-life oriented social interactions. This could result in the generation of an intersubjective psychic space where it is possible to relativize one's own experiences and opinions without weakening ego-identity and self-confidence. It could be relevant in this sense to measure the impact of the programs on aspects such as trust in others, satisfaction with the therapy, improvement in self-esteem, and social skills.

We propose to define social perception as the awareness and comprehension of actual and potential interactions with and between others, including the understanding of individual and shared roles and intentions conveyed by expressions, speech, and behavior directed to other subjects and within a social environment. As such, this domain should be assessed independently from the ability to recognize facial expression and of mind reading, ideally in ecologically valid settings that allow re-enactment of emotionally relevant social interactions from a first-person perspective. Appraisals of experiences, including one's own thoughts, wishes, and feelings as well as the outcome of behavior, are necessarily shaped by the relative meanings assigned to different aspects of that experience. Those meanings that are assigned to an aspect of experience are naturally influenced and molded by how others do or might perceive and think about either those experiences or to how one is interpreting those experiences. Hasson-Ohayon et al. (2020) have reflected on this issue and proposed that while evidence is accumulating about the relationship between metacognition and recovery from schizophrenia, the role of intersubjectivity in the recovery process has been less studied. While we have explored literature on substantial alterations in metacognition, it is unclear to what extent intersubjective experience plays a role in persons who experience more negligible alterations. In addition, while we have advocated intersubjective consideration into the treatment of persons with schizophrenia, this is yet to be fully supported empirically.

AUTHOR CONTRIBUTIONS

AC and PL-S contributed to the conception and writing of the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

Allison, T., Puce, A., and McCarthy, G. (2000). Social perception from visual cues: role of the STS region. *Trends Cogn. Sci.* 4, 267–278. doi: 10.1016/S1364-6613(00)01501-1

Bell, V. A. (2013). Community of one: social cognition and auditory verbal hallucinations. *PLoS Biol.* 11:e1001723. doi: 10.1371/JOURNAL.PBIO.1001723

Bellack, A. S., Green, M. F., Cook, J. A., Fenton, W., Harvey, P. D., Heaton, R. K., et al. (2007). Assessment of community functioning in people With schizophrenia and other severe mental illnesses: A white paper based on an NIMH-sponsored workshop. *Schizophr. Res.* 33, 805–822. doi: 10.1093/schbul/sbl035

Bickart, K., Dickerson, B., and Barrett, L. (2014). The amygdala as a hub in brain networks that support social life. *Neuropsychologia* 63, 235–248. doi: 10.1016/j.neuropsychologia.2014.08.013

Blankenburg, W. (1971). *Der Verlust der Natürlichen Selbstverständlichkeit. Ein Beitrag zur Psychopa- thologie symptomarmer Schizophrenien*. Stuttgart: Ferinand Enkel Verlag.

Budziszewska, M. D., Babiuch-Hall, M., and Wielebska, K. (2020). Love and romantic relationships in the voices of patients who experience psychosis: An interpretive phenomenological analysis. *Front. Psychol.* 11:570928. doi: 10.3389/fpsyg.2020.570928

Castelli, F. (2015). "Mind, theories of," in *International Encyclopedia of the Social and Behavioral Sciences*. ed. J. Wright (Amsterdam: Elsevier), 539–544.

Cavieres, A., Acuña, V., Limarí, P., Zambrano, N., Maldonado, R., and Elliot, R. (2020). The type of information people with schizophrenia use in ambiguous social situations. *Rev. Colomb. Psiquiatr.* 51, 35–40. doi: 10.1016/j.rcp.2020.05.003

D'Arma, A., Isernia, S., Di Tella, S., Rovaris, M., Valle, A., Baglio, F., et al. (2021). Social cognition training for enhancing affective and cognitive theory of mind in schizophrenia: a systematic review and a meta-analysis. *J. Psychol.* 155, 26–58. doi: 10.1080/00223980.2020.1818671

Dokic, J. (2010). "Affordances and the sense of joint agency," in *Neuropsychology of the Sense of Agency: From Consciousness to Action*. ed. M. Balconi (Milan: Springer), 23–43.

Ebisch, S. J. H., Gallese, V., Salone, A., Martinotti, G., di Iorio, G., Mantini, D., et al. (2017). Disrupted relationship between "resting state" connectivity and task-evoked activity during social perception in schizophrenia. *Schizophr. Res.* 193, 370–376. doi: 10.1016/j.schres.2017.07.020

Fuchs, T. (2015a). The intersubjectivity of delusions. *World Psychiatry* 14, 178–179. doi: 10.1002/WPS.20209

Fuchs, T. (2015b). Pathologies of Intersubjectivity in autism and schizophrenia. *J. Conscious. Stud.* 22:191.

Gallagher, S. (2017). "Empathy and theories of direct perception," in *The Routledge Handbook of Philosophy of Empathy*. ed. H. Maibom (London: Routledge), 158–168.

Geiger, A., Bente, G., Lammers, S., Tepest, R., Roth, D., Bzdok, D., et al. (2019). Distinct functional roles of the mirror neuron system and the mentalizing system. *NeuroImage* 202:116102. doi: 10.1016/j.neuroimage.2019.116102

Gibson, J. J. (1966). *The Senses Considered as Perceptual Systems*. Boston: Houghton Mifflin.

Gibson, J. (1977). "The theory of affordances," in *Perceiving, Acting, and Knowing: Toward an Ecological Psychology*. eds. R. Shaw and J. Bransford (New Jersey: Lawrence Erlbaum), 67–82.

Gibson, J. J. (1986). *The Ecological Approach to Visual Perception*. New York: Psychology Press.

Goldman, A. (2006). *Simulating Minds*. Oxford: OUP.

Gorostiaga, A., Balluerka, N., Guilera, G., Aliri, J., and Barrios, M. (2017). Functioning in patients with schizophrenia: a systematic review of the literature using the international classification of functioning, disability and health (ICF) as a reference. *Qual. Life Res.* 26, 531–543. doi: 10.1007/s11136-016-1488-y

Green, M. F., Horan, W. P., and Lee, J. (2015). Social cognition in schizophrenia. *Nat. Rev. Neurosci.* 16, 620–631. doi: 10.1038/nrn4005

Green, M. F., and Leitman, D. I. (2008, 2008). Social cognition in schizophrenia. *Schizophr. Bull.* 34, 670–672. doi: 10.1093/schbul/sbn045

Green, M. F., Penn, D. L., Bentall, R., Carpenter, W. T., Gaebel, W., Gur, R. C., et al. (2008). Social cognition in schizophrenia: an NIMH workshop on definitions, assessment, and research opportunities. *Schizophr. Bull.* 34:1211, –1220. doi: 10.1093/SCHBUL/SBM145

Hakkaart-van Roijen, L., Bouwmans, C., de Sonneville, C., and Mulder, C. (2015). Employment and the associated impact on quality of life in people diagnosed with schizophrenia. *Neuropsychiatr. Dis. Treat.* 11, 2125–2142. doi: 10.2147/NDT.S83546

Halverson, T. F., Orleans-Pobee, M., Merritt, C., Sheeran, P., Fett, A. K., and Penn, D. L. (2019). Pathways to functional outcomes in schizophrenia spectrum disorders: meta-analysis of social cognitive and neurocognitive predictors. *Neurosci. Biobehav. Rev.* 105, 212–219. doi: 10.1016/j.neubiorev.2019.07.020

Hasson-Ohayon, I., Gumley, A., McLeod, H., and Lysaker, P. H. (2020). Metacognition and Intersubjectivity: reconsidering their relationship following advances From the study of persons With psychosis. *Front. Psychol.* 11:567. doi: 10.3389/FPSYG.2020.00567

Haut, K., Lee, A., Galindo, B., Lokey, S., Nahum, M., and Hooker, C. I. (2020). Altered connectivity in neural networks underlying social cognition in individuals at risk For psychosis. *Biol. Psychiatry* 87:S250. doi: 10.1016/j.biopsych.2020.02.646

Heider, F. (2005). *The Psychology of Interpersonal Relations*. London: Wiley & Sons.

Henriksen, M. G., and Nilsson, L. S. (2017). Intersubjectivity and psychopathology in the schizophrenia spectrum: complicated 'we', compensatory strategies, and self-disorders. *Psychopathology* 50, 321–333. doi: 10.1159/000479702

Jacob, P., and Jeannerod, M. (2005). The motor theory of social cognition: a critique. *Trends Cogn. Sci.* 9, 21–25. doi: 10.1016/j.tics.2004.11.003

Jang, D., and Elfenbein, H. A. (2015). "Emotion, perception and expression of," in *International Encyclopedia of the Social and Behavioral Sciences*. ed. J. Wright (Amsterdam: Elsevier), 483–489.

Jaspers, K. (1948). *Allgemeine Psychopathologie. 4th Edn*. Berlin: Springer Verlag.

Javed, A., and Charles, A. (2018). The importance of social cognition in improving functional outcomes in schizophrenia. *Front. Psych.* 9:157. doi: 10.3389/fpsyt.2018.00157

Karpouzian, T. M., Alden, E. C., Reilly, J. L., and Smith, M. J. (2016). High functioning individuals with schizophrenia have preserved social perception but not mentalizing abilities. *Schizophr. Res.* 171, 137–139. doi: 10.1016/j.schres.2016.01.029

Kitoko, G. M., Maurage, P., ma Miezi, S. M., Gillain, B., Kiswanga, A. P., and Constant, E. (2020). Inter-individual variability of social perception and social knowledge impairments among patients with schizophrenia. *Psychiatry Res.* 290:112951. doi: 10.1016/j.psychres.2020.112951

Kiverstein, J. (2015). Empathy and the responsiveness to social affordances. *Conscious. Cogn.* 36, 532–542. doi: 10.1016/j.concog.2015.05.002

Kraepelin, E. (1904). Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. 7., vielfach umgearbeitete Au age. II. Band. Leipzig: Verlag von Johan Ambrosius Barth.

Lee, J., Kern, R. S., Harvey, P. O., Horan, W. P., Kee, K. S., Ochsner, K., et al. (2013). An intact social cognitive process in schizophrenia: situational context effects on perception of facial affect. *Schizophr. Bull.* 39, 640–647. doi: 10.1093/schbul/sbs063

McCarthy-Jones, S., Trauer, T., Mackinnon, A., Sims, E., Thomas, N., and Copolov, D. L. (2014). A new phenomenological survey of auditory hallucinations: evidence for subtypes and implications for theory and practice. *Schizophr. Bull.* 40, 231–235. doi: 10.1093/SCHBUL/SBS156

McCleery, A., Horan, W. P., and Green, M. F. (2014). "Social cognition during the early phase of schizophrenia," in *Social Cognition and Metacognition in Schizophrenia: Psychopathology and Treatment Approaches*. eds. P. Lysaker, G. Dimaggio and M. Brune (London: Academic Press), 49–67.

Mier, D., and Kirch, P. (2017). Social-cognitive deficits in schizophrenia. *Curr. Top. Behav. Neurosci.* 30, 397–409. doi: 10.1007/7854_2015_427

Minkowski, E. (1966). *Traité de Psychopathologie*. Paris: Presses Universitaires de France.

Montag, C., Brandt, L., Lehmann, A., de Millas, W., Falkai, P., Gaebel, W., et al. (2020). Cognitive and emotional empathy in individuals at clinical high risk of psychosis. *Acta Psychiatr. Scand.* 142, 40–51. doi: 10.1111/acps.13178

Moritz, S., and Woodward, T. S. (2007). Metacognitive training for schizophrenia patients (MCT): A pilot study on feasibility, treatment adherence, and subjective efficacy. *German J. Psychiatry* 10, 69–78. doi: 10.1016/j.jbtep.2010.01.004

Nikolaides, A., Miess, S., Auvera, I., Müller, R., Klosterkötter, J., and Ruhrmann, S. (2016). Restricted attention to social cues in schizophrenia patients. *Eur. Arch. Psychiatry Clin. Neurosci.* 266, 649–661. doi: 10.1007/s00406-016-0705-6

Ochsner, K. N. (2008). The social-emotional processing stream: five core constructs and their translational potential for schizophrenia and beyond. *Biol. Psychiatry* 64, 48–61. doi: 10.1016/j.biopsych.2008.04.024

Parnas, J., Urfer-Parnas, A., and Stephensen, H. (2021). Double bookkeeping abd schizophrenia spectrum: dividedn unified phenomenal consciousness. *Eur. Arch. Psychiatry Clin. Neurosci.* 271, 1513–1523. doi: 10.1007/s00406-020-01185-0

Pérez-Osorio, J., Wiese, E., and Wikowska, A. (2021). "Theory of mind and joint attention," in *The Handbook on Socially Interactive Agents: 20 Years of Research on Embodied Conversational Agents, Intelligent Virtual Agents, and Social Robotic. Vol. 1*. eds. B. Lugrin, C. Pelachaud and D. Traum (New York: ACM Books), 311–348.

Pienkos, E. (2015). Intersubjectivity and its role in schizophrenic experience. *Humanist. Psychol.* 43, 194–209. doi: 10.1080/08873267.2014.990459

Pinkham, A. E. (2014). Social cognition in schizophrenia. *J. Clin. Psychiatry* 75(Suppl. 2), 14–19. doi: 10.4088/JCP.13065su1.04

Pönkänen, L. M., Alhoniemi, A., Leppänen, J. M., and Hietanen, J. K. (2011). Does it make a difference if I have an eye contact with you or with your picture? An ERP study. *Soc. Cogn. Affect. Neurosci.* 6, 486–494. doi: 10.1093/scan/nsq068

Porcelli, S., Van Der Wee, N., van der Werff, S., Aghajani, M., Glennon, J. C., van Heukelum, S., et al. (2019). Social brain, social dysfunction and social withdrawal. *Neurosci. Biobehav. Rev.* 97, 10–33. doi: 10.1016/j.neubiorev.2018.09.012

Richardson, M. J., Marsh, K. L., and Baron, R. M. (2007). Judging and actualizing intrapersonal and interpersonal affordances. *J. Exp. Psychol. Hum. Percept. Perform.* 33, 845–859. doi: 10.1037/0096-1523.33.4.845

Rosen, C., Jones, N., Chase, K. A., Gin, H., Grossman, L. S., and Sharma, R. P. (2016). The intrasubjectivity of self, voices and delusions: A phenomenological analysis. *Psychosis* 8, 357–368. doi: 10.1080/17522439.2016.1162839

Rushworth, M. F. S., Mars, R. B., and Sallet, J. (2013). Are there specialized circuits for social cognition and are they unique to humans? *Curr. Opin. Neurobiol.* 23, 436–442. doi: 10.1016/J.CONB.2012.11.013

Sass, L., and Parnas, J. (2003). Schizophrenia, consciousness, and the self. *Schizophr. Bull.* 29, 427–444. doi: 10.1093/oxfordjournals.schbul.a007017

Sass, L. A., and Parnas, J. (2007). "Explaining schizophrenia: the relevance of phenomenology," in *Recovering Schizophrenia*. eds. M. C. Chung, K. W. M. Fulford and G. Graham (New York: Oxford University Press), 63–95.

Savla, G. N., Vella, L., Armstrong, C. C., Penn, D. L., and Twamley, E. W. (2013). Deficits in domains of social cognition in schizophrenia: a meta-analysis of the empirical evidence. *Schizophr. Bull.* 39, 979–992. doi: 10.1093/schbul/sbs080

Schilbach, L., Derntl, B., Aleman, A., Caspers, S., Clos, M., Diederen, K. M. J., et al. (2016). Differential patterns of dysconnectivity in mirror neuron and mentalizing networks in schizophrenia. *Schizophr. Bull.* 42, 1135–1148. doi: 10.1093/schbul/sbw015

Schmidt, S. J., Mueller, D. R., and Roder, V. (2011). Social cognition as a mediator variable between neurocognition and functional outcome in schizophrenia: empirical review and new results by structural equation modeling. *Schizophr. Bull.* 37, S41–S54. doi: 10.1093/SCHBUL/SBR079

Sergi, M. J., and Green, M. F. (2003). Social perception and early visual processing in schizophrenia. *Schizophr. Res.* 59, 233–241. doi: 10.1016/S0920-9964(01)00405-4

Sergi, M. J., Rassovsky, Y., Nuechterlein, K. H., and Green, M. F. (2006). Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. *Am. J. Psychiatry* 163, 448–454. doi: 10.1176/appi.ajp.163.3.448

Stanghellini, G. (2001). Psychopathology of common sense. *Philo. Psych. Psychol.* 8, 201–218. doi: 10.1353/PPP.2001.0018

Teufel, C., Fletcher, P. C., and Davis, G. (2010). Seeing other minds: attributed mental states influence perception. *Trends Cogn. Sci.* 14, 376–382. doi: 10.1016/j.tics.2010.05.005

Teufel, C., von dem Hagen, E., Plaisted-Grant, K. C., Edmonds, J. J., Ayorinde, J. O., Fletcher, P. C., et al. (2013). What is social about social perception research? *Front. Integr. Neurosci.* 6:128. doi: 10.3389/fnint.2012.00128

Van Duppen, Z. (2017). The intersubjective dimension of schizophrenia. *Philo. Psych. Psychol.* 24, 399–418. doi: 10.1353/ppp.2017.0058

Van Duppen, Z., and Feyaerts, J. (2020). The phenomenology of psychosis: considerations for the future. *Philo. Psych. Psychol.* 28, 277–279. doi: 10.1353/ppp.2021.0041

Vogeley, K. (2017). Two social brains: neural mechanisms of intersubjectivity. *Philos. Trans. R Soc. B Biol. Sci.* 372:20160245. doi: 10.1098/rstb.2016.0245

Woods, A., Jones, N., Alderson-Day, B., Callard, F., and Fernyhough, C. (2015). Experiences of hearing voices: analysis of a novel phenomenological survey. *Lancet Psychiatry* 2, 323–331. doi: 10.1016/S2215-0366(15)00006-1

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 | Frontiers in Psychology

ORIGINAL RESEARCH
published: 14 June 2022
doi: 10.3389/fpsyg.2022.866160

Efforts for the Correct Comprehension of Deceitful and Ironic Communicative Intentions in Schizophrenia: A Functional Magnetic Resonance Imaging Study on the Role of the Left Middle Temporal Gyrus

R. Morese[1,2†], C. Brasso[3,4*†], M. Stanziano[3,5], A. Parola[6], M. C. Valentini[7], F. M. Bosco[6] and P. Rocca[3,4]*

[1] Faculty of Communication, Culture and Society, Università della Svizzera italiana, Lugano, Switzerland, [2] Faculty of Biomedical Sciences, Università della Svizzera italiana, Lugano, Switzerland, [3] Department of Neuroscience Rita Levi Montalcini, University of Turin, Turin, Italy, [4] Struttura Complessa di Psichiatria Universitaria, Dipartimento di Neuroscienze e Salute Mentale, Azienda Ospedaliera Universitaria "Città della Salute e della Scienza di Torino", Turin, Italy, [5] Neuroradiology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, [6] Research Group on Inferential Processes in Social Interaction (GIPSI), Department of Psychology, University of Turin, Turin, Italy, [7] Struttura Complessa di Neuroradiologia, Dipartimento Diagnostica per Immagini e Radiologia interventistica, Azienda Ospedaliera Universitaria "Città della Salute e della Scienza di Torino", Turin, Italy

Deficits in social cognition and more specifically in communication have an important impact on the real-life functioning of people with schizophrenia (SZ). In particular, patients have severe problems in communicative-pragmatics, for example, in correctly inferring the speaker's communicative intention in everyday conversational interactions. This limit is associated with morphological and functional alteration of the left middle temporal gyrus (L-MTG), a cerebral area involved in various communicative processes, in particular in the distinction of ironic communicative intention from sincere and deceitful ones. We performed an fMRI study on 20 patients with SZ and 20 matched healthy controls (HCs) while performing a pragmatic task testing the comprehension of sincere, deceitful, and ironic communicative intentions. We considered the L-MTG as the region of interest. SZ patients showed difficulties in the correct comprehension of all types of communicative intentions and, when correctly answering to the task, they exhibited a higher activation of the L-MTG, as compared to HC, under all experimental conditions. This greater involvement of the L-MTG in the group of patients could depend on different factors, such as the increasing inferential effort required in correctly understanding the speaker's communicative intentions, and the higher integrative semantic processes involved in sentence processing. Future studies with a larger sample size and functional connectivity analysis are needed to study deeper the specific role of the L-MTG in pragmatic processes in SZ, also in relation to other brain areas.

Keywords: pragmatic communication, fMRI, schizophrenia, sincere, deceitful, ironic, communicative intentions, left middle temporal gyrus

OPEN ACCESS

Edited by:
Fabio Giovannelli, University of Florence, Italy

Reviewed by:
Stéphanie Caillies, Université de Reims Champagne-Ardenne, France
Giorgio Arcara, San Camillo Hospital (IRCCS), Italy

***Correspondence:**
R. Morese
rosalba.morese@usi.ch
C. Brasso
claudio.brasso@unito.it

† These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: *30 January 2022*
Accepted: *18 May 2022*
Published: *14 June 2022*

Citation:
Morese R, Brasso C, Stanziano M, Parola A, Valentini MC, Bosco FM and Rocca P (2022) Efforts for the Correct Comprehension of Deceitful and Ironic Communicative Intentions in Schizophrenia: A Functional Magnetic Resonance Imaging Study on the Role of the Left Middle Temporal Gyrus. Front. Psychol. 13:866160. doi: 10.3389/fpsyg.2022.866160

INTRODUCTION

Deficits in social cognition and more specifically in communication have an important impact on the real-life functioning of people with schizophrenia (SZ) (Fett et al., 2011; Javed and Charles, 2018; Green et al., 2019). In particular, patients suffering from SZ have shown a wide range of deficits in the communicative-pragmatic domain, characterized by a severe impairment of the comprehension of the speaker's communicative intention in everyday conversational interactions (Brüne and Bodenstein, 2005; Mazza et al., 2008; Colle et al., 2013; Bambini et al., 2016; Bosco and Parola, 2017, Bosco et al., 2019; Parola et al., 2018, 2021a,b; Pawełczyk et al., 2018). Communicative-pragmatics, i.e., the ability to use language to convey meaning in a specific context (Levinson, 1983), is linked to the Theory of Mind (ToM), i.e., the ability to attribute mental states to oneself and others, however, these two abilities do not completely overlap (Bambini et al., 2016; Bosco et al., 2018, 2019; Parola et al., 2018). Rocca et al. (2016) showed that the clustering of patients according to their understanding of lies and complex sarcasm overlap well with their real-life functioning. Colle et al. (2013) showed that patients with SZ, compared to healthy controls (HC), have lower accuracy in the correct comprehension of sincere, deceitful, and ironic communicative acts.

Previous functional magnetic resonance imaging (fMRI) studies investigated brain activations during irony comprehension tasks in people with SZ (Rapp et al., 2013; Varga et al., 2013) and, by comparing the neural activations of patients and HC, revealed reduced activations in different cortical areas of the right hemisphere. In detail, a diminished BOLD signal was found in the middle temporal gyrus (MTG), rolandic operculum, post-central gyrus (Rapp et al., 2013), inferior parietal lobule (IPL), middle frontal gyrus (MFG), and temporal pole (Varga et al., 2013). A recent study proposed a pragmatic fMRI process on healthy subjects that simultaneously assessed the understanding of non-sense, literal or sincere, deceptive, and ironic communicative acts (Bosco et al., 2017). The authors found an activation of the left middle temporal gyrus (L-MTG) for the correct understanding of ironic communicative intentions when compared with the sincere and deceitful communicative acts. In particular, the activation of this cortical region was stronger under the ironic conditions as it was observed from the contrast between the correct understanding of ironic and deceptive communicative acts. The authors concluded that the L-MTG could play a pivotal role in the understanding of more complex communicative acts, like the ironic ones, that require demanding inferential steps. Several former neuroimaging studies on the samples of healthy populations demonstrated the activation of this cortical area in many language-related processes, from semantic integration (Noppeney and Price, 2004) to speech processing (Booth et al., 2002; Bitan et al., 2007; Hickok and Poeppel, 2007; Binder et al., 2009; Holle et al., 2010; Binder and Desai, 2011; Branco et al., 2018). A meta-analysis by Ferstl et al. (2008), for example, indicated that the L-MTG plays a key role in the comprehension and analysis of coherence of a text. Moreover, in subjects with SZ, a reduction of its gray matter (GM) volume was found in people with the first stage of schizophrenia (Kuroki et al., 2006; Hu et al., 2013; Guo et al., 2014), in healthy unaffected siblings of people with SZ (Hu et al., 2013; Guo et al., 2014), and in patients with a long duration of illness (Onitsuka et al., 2004). This finding was also confirmed by a large meta-analysis on GM alteration in SZ (van Erp et al., 2018). Moreover, a reduced thickness of this cortical area (Cui et al., 2018) and an altered resting-state functional connectivity with the left inferior frontal gyrus in the language network (Zhang et al., 2017) correlated with the presence of verbal hallucination. The functional connectivity of the L-MTG was also reduced during a specific process of gesture and speech integration. In particular, the reduced coactivation of this cortical area with the left superior temporal gyrus was associated with attention deficits and concretism in the proverb interpretation (Wroblewski et al., 2020). Furthermore, alterations of the functional connectivity of the L-MTG were reported in a meta-analysis on formal thought disorders (Cavelti et al., 2018). Reduced connectivity of the dorsal posterior part of this area was linked to a deficit in semantic discrimination, ToM, and social cognition (Wensing et al., 2017). Finally, alterations of the L-MTG connectivity were also found at a structural level in terms of increased fractional anisotropy and an augmented radial diffusivity in the white matter tract connecting the L-MTG with the ventral posterior cingulate cortex (Joo et al., 2018).

Considering the role played by the L-MTG in high–level inferential processes and the structural and functional alteration of this cortical region in patients with SZ, we performed an fMRI study on the comprehension of sincere, deceitful, and ironic communicative intentions in this clinical population. Indeed, the comprehension of both pragmatic phenomena requires to recognize the conflict between the literal meaning of a sentence and the speaker's private mental states (Bosco and Bucciarelli, 2008; Parola and Bosco, 2022), and it is associated with the activation of a cerebral network extending to the frontotemporal and frontoparietal areas (Harada et al., 2009; Bohrn et al., 2012; Spotorno et al., 2012; Uchiyama et al., 2012; Bosco et al., 2017; Filik et al., 2019). At the same time, previous studies have also shown that the comprehension of irony, compared to comprehension of deceit, can activate additional areas, in particular the L-MTG, since understanding irony may require more complex inferential processes necessary to recognize that the content of an ironic utterance also contrasts with the knowledge the speaker shares with the partner (Bosco et al., 2017).

Furthermore, in clinical samples of people suffering from SZ, differences in the correct understanding of deceitful and ironic communicative intentions were shown; patients performed worse in the linguistic and extralinguistic understanding of ironic communicative acts compared to deceitful ones (Colle et al., 2013; Parola et al., 2018). In addition, when assessing error patterns in understanding sincere, deceptive, and ironic communicative acts, patients with SZ, compared to HC, showed a bias in favor of deception, i.e., they tended to misclassify sincere and ironic communicative acts by attributing to them a deceptive communicative intention (Parola et al., 2021a).

The aim of this study was to investigate the neural correlations related to the correct understanding of sincere, deceitful, and ironic intentions in people with SZ, focusing, in particular, on the role of the L-MTG. The choice to compare the same speech act proffered with an ironic vs. deceitful intention is motivated by two reasons; the first is that no fMRI study has previously compared these two pragmatic phenomena in subjects with SZ and the second is to verify whether, even within a clinical sample, differential activation of the L-MTG discriminates against the correct understanding of ironic vs. deceitful communicative intentions. We expected that patients with SZ, as compared to HC, will perform worse in the comprehension of deceitful and ironic communicative acts while, at a neural level, the L-MTG will be differently activated in the clinical group as compared to HC.

MATERIALS AND METHODS

Participants

Individuals diagnosed with schizophrenia (n = 20) according to DSM-5 criteria (American Psychiatric Association, 2013) and healthy comparison individuals (n = 20) matched with average age, sex, and education were included in this study (**Table 1**). All participants gave their informed consent and took part in the study voluntarily. The study was approved by the Local Research Ethics Committee (protocol number: 0076364). All participants met the following inclusion criteria: (1) be aged between 18 and 65 years, (2) be right-handers, (3) have no history of neurological illness, and (4) demonstrate basic cognitive and linguistic abilities by achieving a cutoff score in the following neuropsychological tests, Test di Intelligenza Breve (TIB, Colombo et al., 2002), the Italian equivalent of the National Adult Reading Test (NART; Nelson and Willison, 1991; cutoff score 70) and two sub-scales (Comprehension of written words and comprehension of written sentences) of the Aachener Aphasie Test (AAT, Huber et al., 1983; cutoff score 112/120), and (5) be Italian native speakers. People diagnosed with SZ also met the following criteria: (1) have no other mental disorder and (2) be clinically stable, i.e., absence of hospitalization and treatment modification in the last 6 months. Finally, healthy controls (HC) met the following inclusion criteria: (1) no current use of psychoactive drugs and (2) no personal and familiar history of psychiatric disorders.

Psychiatric Assessment

The Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) was used to assess symptom severity. The dimensions "disorganization" and "positive symptoms" were calculated as proposed by Wallwork et al. (2012). Negative symptoms were rated with the Italian version of the Brief Negative Symptoms Scale (BNSS, Mucci et al., 2015) and grouped into the factors "avolition," consisting of anhedonia, asociality, and avolition, and "expressive deficit," including the blunted affect and alogia (Kirkpatrick et al., 2011; Strauss et al., 2012). Depressive symptoms were evaluated with the Calgary Depression Scale for Schizophrenia (CDSS, Addington et al., 1993). Functioning was evaluated with the Personal and Social Performance Scale (PSP, Morosini et al., 2000). Antipsychotic dosage was converted to chlorpromazine (CPZ) equivalent dose using the conversion methodology proposed by Leucht et al. (2016). Extrapyramidal symptoms were rated with the Simpson Angus Scale (SAS, Simpson and Angus, 1970).

TABLE 1 | Demographic characteristics.

	SZ group (n = 20)	HC group (n = 20)	Statistic (F/χ^2)	p-value
Age (years)	41,5 (11,3)	42,1 (10,8)	0.003	0.954
Gender (M/F)	13/7	13/7	0.000	1
Education (years)	13,7 (4,3)	13,85 (4,2)	0.012	0.912

SZ, schizophrenia; HC, healthy controls; M, male; F, female.
Continuous variables are expressed as means and standard deviations (SD).

Task and Functional Magnetic Resonance Imaging

Experimental Material

To test participants' comprehension of sincere, deceitful, and ironic communicative acts we used an experimental study consisting of 36 short written stories, each of them composed of two parts, i.e., a context scenario and a target sentence. The scenario described the context in which the target sentence was realized. In each context, two characters have a brief communicative interaction and the target sentence represents the final part of their short dialogue (see **Supplementary Section 1.1** for an example of the stories). We used three different context scenarios to represent three communicative intentions, namely, deceitful, ironic, and sincere (control condition). Context scenarios and target sentences were comparable to each other in terms of syllables, difficulty, and the number of words (Gulpease readability index–see **Supplementary Table 1**). The experimental material has already been validated in a previous study (see Bosco et al., 2017 for further methodological details).

Experimental Procedure

After the signing of the informed consent by each participant, we described, to each of them, the process that would be performed during the fMRI session. Participants also carried out training to familiarize themselves with the experimental task presented *via* a head coil-mounted display system (Resonance Technology, Inc.Los Angeles, California, United States) using the visual stimuli using the E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA, United States).

In line with the study of Bosco et al. (2017), each trial of the fMRI experimental study was displayed on the screen in the following order: (i) context- scenario (15 s); (ii) fixation cross ("+") (5–7 s); (iii) target sentence (6 s); (iv) fixation cross ("+") (5–7 s); (v) response (4 s); (vi) fixation cross ("+") (10–12 s) (see **Supplementary Figure 1**). During the response phase of the fMRI process [as described above "response (4 s)"], each participant was asked to identify the communicative intention expressed during the target sentence and to indicate it by choosing between sincere, deceptive, and ironic options presented on the screen. The indication of the choice was made by pushing a button corresponding to the option presented on the screen.

Statistical Analysis of Socio-Demographic and Behavioral Data

Statistical analyses of socio-demographic and behavioral data were performed using the software Statistical Package for Social Sciences, SPSS, version 25.0 for Windows (SPSS, Chicago, IL, United States).

Demographic characteristics and cognitive assessment variables of SZ and HC groups were compared using one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables.

Behavioral results, i.e., correct responses during the fMRI process, were analyzed using a two-way repeated-measure analysis of variance (RM-ANOVA). The within-subject factor had three repeated measures (i.e., sincere, deceitful, and ironic) to evaluate whether participants' accuracy differed between different experimental conditions. The group (SZ or CT) was selected as the between-subject factor.

Magnetic Resonance Imaging Data Acquisition

The MRI data were collected using a 3.0 T MRI Scanner (Philips Ingenia) using a 32-channel array head coil, provided with Philips specific eyeglasses (Resonance Technology, Inc.). MRI data acquisition was carried out at the Neuroimaging Center (Centro di Neuroimmagini–CNI) of the Neuroscience Institute of Turin (NIT) of the University of Turin, located in the Azienda Ospedaliera Universitaria "Città della Salute e della Scienza di Torino" in Turin, Italy. MRI acquisition parameters of a previous study (Bosco et al., 2017) were applied. In detail, Echo-Planar Image sequence (EPI) with TR/TE = 3,000/30 ms, 32 slices, matrix size = 96 × 96, slice gap = 0.5 mm, field of view (FOV) = 224 × 224 mm^2, and flip angle = 90°, with slices aligned on the AC-PC line, consisting of 230 volumes, was used during two runs for collecting functional images. Structural images were recorded applying a T1-weighted sequence (TR 8.1 ms, TI 900 ms, TE 3.7 ms, voxel size 1 × 1 × 1 mmł).

Functional Magnetic Resonance Imaging Data Analysis

The fMRI data were analyzed using SPM12 (Wellcome Department of Cognitive Neurology, London, United Kingdom) in Matlab (Mathworks, Cherborn, MA, United States). We applied the same analysis procedure as that used in a previous study (Bosco et al., 2017). In particular, for the preprocessing analysis of each participant, functional images were initially realigned spatially and then co-registered to their mean. They, subsequently, were normalized to the MNI (Montreal Neurological Institute) space and then smoothed applying an 8 mm Gaussian Kernel.

After preprocessing analysis, to investigate the participants' correct comprehension of the communicative intention compared to the HC, we convolved the onset times related to the target sentences with the canonical hemodynamic response function (HRF) using a General Linear Model (GLM) (Friston et al., 1995).

At the first level, we calculated, for each participant, three separate regressors of interest considering only correct responses, one for each experimental condition, sincere, deceitful, and ironic.

At the second level, we applied a full factorial design aiming at investigating the neural difference between SZ patients and HC comprehension of the communicative intentions. We employed a two-way RM-ANOVA with the within-subject factor, communicative intention, at three levels, i.e., sincere, deceitful, and ironic. At first, for an exploratory purpose, we applied a whole-brain analysis at $p < 0.001$ uncorrected thresholds. In this exploratory analysis, we checked whether the fMRI results of HC were in line with a previous study (Bosco et al., 2017) by performing the following contrasts within the HC group, deceitful condition vs. sincere condition and ironic condition vs. sincere condition. Within the SZ group, all possible contrasts among the three experimental conditions (i.e., sincere, deceitful, and ironic) were carried out.

Finally, the following between-group contrasts, Family-Wise Error (FEW) cluster-level corrected ($p < 0.05$), were examined, i.e., [SZ group (deceitful condition vs. sincere condition)] vs. [HC group (deceitful condition vs. sincere condition)] and [SZ group (ironic condition vs. sincere condition)] vs. [HC group (ironic condition vs. sincere condition)].

Then, given our hypothesis about the role of the L-MTG, a small volume correction applying a sphere of 10 mm radius centered on coordinates from our previous study ($x = -49$; $y = -37$; $z = -2$; Bosco et al., 2017) was used. In this analysis, a between-group contrast was analyzed for each condition (i.e., sincere, deceitful, and ironic) to compare the recruitment of the L-MTG in the correct comprehension of communicative intentions between patients with SZ and HC.

In addition, separately for the SZ group and HC group, correlations with task performance and with clinical and cognitive variables were evaluated using multiple regression analysis with Statistical Parametric Mapping 12.

RESULTS

Demographic and Clinical Characteristics

Demographic characteristics of SZ and HC groups were homogeneous (**Table 1**).

Clinical characteristics of the SZ group are shown in **Table 2**. The age at onset and the duration of illness were quite heterogeneous with a mean of 27.5 and 14.4 years, respectively. Scores of positive symptoms and disorganization dimensions were globally low, with an average of 7.45 (min 4–max 28) and 6.25 (min 3–max 21) reciprocally. Higher scores were observed in the avolition dimension (mean score 21.85; min 0–max 42) and to a lesser extent in the expressive deficit factor (mean score 11.60; min 0–max 30). Depressive symptoms were globally low or mild (mean 4.1; min 0–max 18). The personal and social functioning was partly reduced with a mean of the PSP score of 61.6 (min 0–max 100). A total of 18 subjects with SZ were treated with an atypical antipsychotic drug with an in-label daily dosage. Two patients were taking a typical antipsychotic drug. None of them was using clozapine. Extrapyramidal side effects were negligible (mean SAS = 0.75).

TABLE 2 | Clinical characteristics.

Age at Illness Onset, Years	27.50 (7.99)
Duration of Illness, Years	14.60 (9.81)
PANSS positive, Score	7.45 (1.82)
PANSS disorganization, Score	6.25 (2.63)
BNSS avolition, Score	21.85 (9.22)
BNSS expressive deficit, Score	11.65 (7.40)
CDSS, Total score	4.10 (5.08)
PSP, Score	61.60 (13.05)
CPZ equivalent, mg/day	371.80 (144.87)
SAS, Total score	0.75 (2.15)

PANSS, Positive and Negative Syndrome Scale; BNSS, Brief Negative Symptoms; CDSS, Calgary Depression Scale for Schizophrenia; PSP, Personal and Social Performance Scale; CPZ, chlorpromazine; SAS, Simpson Angus Scale.
Data are shown as means and standard deviations (SD).

TABLE 3 | Correct responses in the fMRI task.

	HC	SZ
Sincere	11.35 (10.45–12.24)	9.95 (9.06–10.84)
Deceitful	9.95 (8.72–11.17)	7.85 (6.62–9.08)
Ironic	10.15 (8.94–11.36)	7.30 (6.09–8.51)

HC, healthy controls; SZ, patients with schizophrenia.
Data are shown as means and 95% confidence intervals (95% CI).

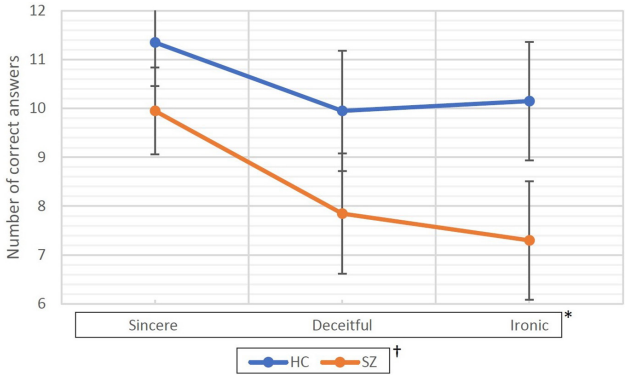


FIGURE 1 | Correct responses collected during the fMRI task. HC, healthy controls; SZ, patients with schizophrenia. Data are represented as the mean of correct answers (dots) and 95% confidence intervals (bars). * and † represent statistical significance of the two factors of the ANOVA for repeated measure. * represents within-subjects factor that are experimental conditions (i.e., sincere, deceitful, and ironic communicative intentions to be understood) chosen as repeated measure. The *p* associated with this factor was <0.001. † represents the between-subjects factor (group factor, HC vs. SZ) and was associated with a $p = 0.001$.

Behavioral Results

The mean rate (95% CI) of correct responses obtained during the process is shown in **Table 3** and **Figure 1**. In the HC group, the mean rate was 11.35/12 (94.6%) under the sincere condition, 9.95/12 (82.9%) under the deceitful condition, and 10.15/12 (84.6%) under the ironic one. Global accuracy was 31.45/36 (87.4%). The SZ group showed a poorer performance with a mean rate of correct answers of 9.95/12 (82.9%), 7.85/12 (65.4%), and 7.30/12 (60.3%) under the sincere, deceitful, and ironic conditions, respectively. Global accuracy was 25.10/36 (69.7%). The Mauchly's sphericity test performed for the two-way RM-ANOVA was not significant ($W = 0.84$; $p = 0.058$), therefore, we followed the sphericity assumption. The within-subject factor under sincere, deceitful, and ironic experimental conditions upon repeated measures and the between-subject factor (group HC vs. SZ) were both highly significant with $F = 12{,}503$ ($p < 0.001$) and $F = 12{,}096$ ($p = 0.001$), respectively. The interaction between the two factors, i.e., experimental condition × group, was not significant with $F = 1.451$ ($p = 0.241$).

Functional Magnetic Resonance Imaging Results

Between-group linear contrasts revealed significant stronger activations in the L-MTG in the SZ group vs. the HC group under all the experimental conditions (**Table 4** and **Figure 2**). Within-group linear contrasts are shown in **Supplementary Table 2** and **Supplementary Figures 2, 3**. In the linear contrasts performed within the HC group, we found activations in the left dorsolateral prefrontal cortex ($x = -42$; $y = 18$; $z = 29$), in the left inferior frontal gyrus ($x = -51$; $y = 27$; $z = 5$), and in the left middle frontal gyrus ($x = -50$; $y = 14$; $z = 37$) under the deceitful condition when compared to the sincere one (control condition). Under the ironic condition, as compared with the sincere one, activations were found in the left middle frontal gyrus ($x = -53$; $y = 18$; $z = 29$), in the left dorsolateral prefrontal cortex ($x = -45$; $y = 10$; $z = 32$), in the left inferior frontal gyrus ($x = -57$; $y = 25$; $z = 8$), and in the left middle temporal gyrus ($x = -52$; $y = -37$; $z = 4$). Within the SZ group, none of the contrasts performed showed differences between the sincere, deceptive, and ironic conditions. Between-group (SZ vs. HC) whole brain contrasts showed greater activation in the group of patients exclusively in the L-MTG under the ironic condition (**Supplementary Table 3**). No suprathreshold voxels (not statistically significant), emerged from the correlation between L-MTG activation and task performance and clinical and cognitive variables in the SZ and HC groups.

DISCUSSION

The aim of the study was to investigate the neural correlations related to the correct understanding of sincere, deceitful, and ironic intentions in people with SZ, focusing, in particular, on the role of the L-MTG. The contrasts between the SZ group and the HC group (SZ vs. HC) showed a higher recruitment of the L-MTG under all the experimental conditions. This phenomenon was also found at a whole-brain level in the comprehension of ironic communicative intentions. These results demonstrate a higher involvement of this cerebral area in patients with SZ when they answered correctly during the process.

Previous fMRI studies on healthy subjects have demonstrated that the activation of the L-MTG during communicative pragmatic tasks has been associated with the recognition of ironic (Eviatar and Just, 2006) and sarcastic statements (Uchiyama et al., 2006), with efforts in the comprehension of linguistic tasks (Bohrn et al., 2012; Rapp et al., 2013), with the pragmatic

inferential ability (Jang et al., 2013), and with the integration of information from different semantic systems (Davey et al., 2016). In patients with SZ, this cerebral area showed a reduction of the GM volume (Onitsuka et al., 2004; Kuroki et al., 2006; Hu et al., 2013; Guo et al., 2014; van Erp et al., 2018) and altered functional connectivity with other cerebral areas in the language network and in language-related fMRI processes (Wensing et al., 2017; Zhang et al., 2017; Joo et al., 2018; Wroblewski et al., 2020). According to this evidence, the L-MTG would play a key role in pragmatic communication processes and would be deficient in subjects with SZ. We assume that patients suffering from SZ could need a greater inferential effort and a stronger L-MTG activation to be able to understand correctly all the communicative acts, including the sincere ones. In other words, this stronger activation might be a form of over-compensation required by the patients to answer the questions of the fMRI process correctly. Moreover, as revealed by the whole-brain between-group comparison, this effort would be even more evident for the understanding of irony, which may require more complex inferential processes. However, since the L-MTG has been found to be involved in various linguistic processes, such as semantic integration of word meaning (Vandenberghe et al., 2002; Noppeney and Price, 2004), in the comprehension of texts and analysis of text coherence (Ferstl et al., 2008), and in controlling the retrieval of semantic information (Davey et al., 2016), the activation found in our results might be ascribed to some extent to other cognitive and linguistic processes involved in the correct understanding of communicative intentions.

Focusing on the within-group liner contrasts, fMRI results in the HC group partially replicated those of Bosco et al. (2017; see **Supplementary Results**: **Supplementary Table 2** and **Supplementary Figures 2, 3**). In detail, the following discrepancies emerged: in the deception vs. sincerity contrast, a greater activation of the right cerebellum was not detected, and in the irony vs. sincerity comparison, we did not observe a greater involvement of the left temporoparietal junction and of the right cerebellum. These inconsistencies in the cerebral hemodynamic response to the process (i.e., the BOLD signal) could be derived from the different demographic characteristics of the samples of healthy subjects in the two experiments, a homogeneous group of university students in Bosco et al. (2017), and a more heterogeneous group of participants (range 23–60 years old), which matched with patients with SZ in this study. Following this explanation, as reported by D'Esposito et al. (2003), higher age can negatively affect the BOLD signal, thus reducing the number of areas emerging from the linear contrasts. Despite these differences, within the HC group, the communicative pragmatic process was associated with the activation of brain areas partially overlapping with those described by Bosco et al. (2017), hence demonstrating a good degree of replicability of the experimental results.

Unexpectedly, within the group of patients with SZ, there was no difference between the experimental control condition (sincere) and the deceitful and ironic conditions. As previously proposed for the higher activation of L-MTG in the clinical group under all the experimental conditions, this phenomenon might be explained by the marked inferential effort made by patients to correctly understand communicative intentions regardless of the experimental conditions. Following this explanation, all experimental conditions, including the baseline (i.e., sincere), would facilitate a marked brain activation such as to "saturate" the BOLD signal. In other words, this putative high level of activation, regardless of the experimental conditions, makes it impossible to distinguish the brain areas specifically activated in

TABLE 4 | Functional magnetic resonance imaging results; activation of the L-MTG; SZ vs. HC.

Experimental condition	MNI coordinates			*Z*-score	*p* (FWE-corr.)
	X	*Y*	*Z*		
Sincere L-MTG	−53	−20	−2	3.07	0.048
*Deceitful*L-MTG	−62	−30	2	3.21	0.033
Ironic L-MTG	−51	−23	5	3.18	0.044

Activation of the L-MTG for the linear contrasts: (i) sincere SZ group vs. sincere HC group, (ii) deceitful SZ group vs. deceitful HC group, and (iii) ironic SZ group vs. ironic HC group.
L-MTG, left middle temporal gyrus; SZ, schizophrenia group; HC, healthy controls group; MNI, Montreal Neurological Institute; FEW-corr., family-wise error correction. Peak activity coordinates are given in MNI space.
Linear contrasts were computed using a small volume correction (SVC) with a sphere of 10 mm with a statistical threshold of $p < 0.05$ family-wise error corrected for multiple comparisons.

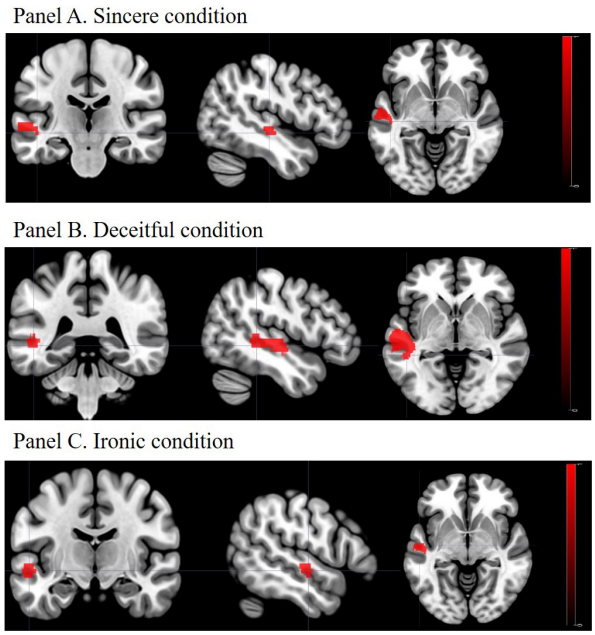


FIGURE 2 | Activation of the L-MTG: SZ vs. HC. **Panel A**. Sincere condition; **Panel B**. Deceitful condition; **Panel C**. Ironic condition. L-MTG, left middle temporal gyrus; SZ, schizophrenia group; HC, healthy controls group. In all the experimental conditions patients with SZ showed higher activation of the L-MTG, as compared to HC, when correctly comprehended the communicative intention proposed in the task.

the correct understanding of deceptive and ironic communicative intentions within the SZ group as also under the baseline condition, the same brain areas were strongly activated. However, this is only one possible interpretation of the result obtained. In fact, since no differences emerged between the three experimental conditions, what was observed could be the result of non-specific phenomena unrelated to the understanding of communicative intentions.

At a behavioral level, patients showed more difficulty than HC under all three experimental conditions, especially in irony understanding. This result is in accordance with previous pragmatic studies carried out on subjects with SZ (Brüne and Bodenstein, 2005; Mazza et al., 2008; Colle et al., 2013; Bambini et al., 2016; Bosco et al., 2019; Parola et al., 2021b). Moreover, we found that both patients and HC demonstrated greater difficulties in the correct comprehension of deceptive and ironic experimental conditions compared to the sincere one. This trend is coherent with the results of the previous study on healthy subjects (Bosco et al., 2017).

The impossibility to perform correlation analysis between the activation of L-MGT during the process and behavioral, clinical, and cognitive variables is probably due to the relatively small sample size. In fact, the relatively low number of subjects for each group (n = 20 for both SZ and HC groups) did not allow one to find any statistically significant voxel within the L-MTG, a prerequisite to carry out the correlation analysis.

The main limitation of this study is the relatively small sample that conditioned the types of fMRI analyses carried out. Analyses on multiple regions of interest belonging to the language network and analyses on functional connectivity of the L-MTG during the task and the resting state are needed to better understand the role of this specific cortical area in pragmatic abilities. With a similar aim, DTI analyses on the connectivity of WM of the L-MTG in relation to the performance in the task proposed might also be performed. These types of studies can verify the activity of L-MTG in relation to other cerebral areas and possibly bring out, also within the group of subjects with SZ, differences between the three different experimental conditions, but require a larger sample size.

Despite these limitations, this study has two important strengths. The first one is related to the fMRI task; for the first time. in a clinical sample of patients with SZ, the neural activation was investigated during the comprehension of both deceitful and ironic speech acts. In fact, in previous fMRI studies in people with SZ, only irony, and not deceit, comprehension, was investigated (Rapp et al., 2013; Varga et al., 2013). The second concerns the selection criteria of the sample as only clinically stable, right-handed, without marked cognitive deficits, and non-bilingual native Italian speaker patients were enrolled. This homogeneity of the sample has reduced possible confounding factors by limiting misleading results. Similarly, the choice of analyzing images related solely to the correct answers eliminated possible brain activations due to the misinterpretation of the communication intentions.

In conclusion, this study adds a small piece to the panorama of fMRI studies on pragmatics in schizophrenia characterizing the role of a brain area involved in the understanding of complex communicative acts, i.e., the L-MTG that is frequently altered for the structure and connectivity in subjects affected by the disorder. However, due to the poor generalizability of the results linked to the low sample size and the methods, this study needs to be integrated with more experiments using whole-brain techniques that confirm the role of L-MTG in pragmatic communication skills, possibly in response to specific rehabilitation programs, as proposed by Gabbatore et al. (2017).

DATA AVAILABILITY STATEMENT

Due to the anonymity guaranteed in the informed consent paperwork at the time when data were collected, data cannot be publicly shared, and are controlled by the Comitato Etico Interaziendale of the A.O.U. Città della Salute e della Scienza di Torino. Researchers who wish to request access to these data may contact the corresponding author (CB), claudio.brasso@unito.it.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RM: data collection, data curation, task preparation, fMRI data analysis, and writing–review and editing. CB: data collection, data curation, statistical analysis, methodology, and writing–original draft. MS and MV: data collection and writing–review and editing. AP: data collection, task preparation, and writing–review and editing. FB: conceptualization, methodology, task preparation, project administration, supervision, and writing–review and editing. PR: conceptualization, funding acquisition, project administration, supervision, and writing–review and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by Ministero dell'Istruzione, dell'Università e della Ricerca—MIUR projects "Dipartimenti di Eccellenza 2018–2022" to the Department of Neuroscience "Rita Levi Montalcini" and was performed in the Neuroimaging Center (CNI) of the Neuroscience Institute of Turin (NIT), originally funded by the Regione Piemonte.

ACKNOWLEDGMENTS

We acknowledge Raffaella Cravero for her help in performing this study and we thank all participants for their time and collaboration.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.866160/full#supplementary-material

REFERENCES

Addington, D., Addington, J., and Maticka-Tyndale, E. (1993). Assessing depression in schizophrenia: the calgary depression scale. *Br. J. Psychiatry* 163, 39–44.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders: DSM-5 (Vol. 10)*. Washington, DC: American Psychiatric Association.

Bambini, V., Arcara, G., Bechi, M., Buonocore, M., Cavallaro, R., and Bosia, M. (2016). The communicative impairment as a core feature of schizophrenia: frequency of pragmatic deficit, cognitive substrates, and relation with quality of life. *Compreh. Psychiatry* 71, 106–120. doi: 10.1016/j.comppsych.2016.08.012

Binder, J. R., and Desai, R. H. (2011). The neurobiology of semantic memory. *Trends Cogn. Sci.* 15, 527–536.

Binder, J. R., Desai, R. H., Graves, W. W., and Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb. Cortex* 19, 2767–2796.

Bitan, T., Cheon, J., Lu, D., Burman, D. D., Gitelman, D. R., Mesulam, M. M., et al. (2007). Developmental changes in activation and effective connectivity in phonological processing. *NeuroImage* 38, 564–575. doi: 10.1016/j.neuroimage.2007.07.048

Bohrn, I. C., Altmann, U., and Jacobs, A. M. (2012). Looking at the brains behind figurative language–a quantitative meta-analysis of neuroimaging studies on metaphor, idiom, and irony processing. *Neuropsychologia* 50, 2669–2683. doi: 10.1016/j.neuropsychologia.2012.07.021

Booth, J. R., Burman, D. D., Meyer, J. R., Gitelman, D. R., Parrish, T. B., and Mesulam, M. M. (2002). Modality independence of word comprehension. *Hum. Brain Mapp.* 16, 251–261. doi: 10.1002/hbm.10054

Bosco, F. M., Berardinelli, L., and Parola, A. (2019). The ability of patients with schizophrenia to comprehend and produce sincere, deceitful, and ironic communicative intentions: the role of theory of mind and executive functions. *Front. Psychol.* 10:827. doi: 10.3389/fpsyg.2019.00827

Bosco, F. M., and Bucciarelli, M. (2008). Simple and complex deceits and ironies. *J. Pragmat.* 40, 583–607. doi: 10.1006/brln.2000.2430

Bosco, F. M., and Parola, A. (2017). "Schizophrenia," in *Research in Clinical Pragmatics, Series: Perspectives in Pragmatics, Philosophy & Psychology*, Vol. 11, ed. L. Cummings (Cham: Springer-Verlag).

Bosco, F. M., Parola, A., Valentini, M. C., and Morese, R. (2017). Neural correlates underlying the comprehension of deceitful and ironic communicative intentions. *Cortex* 94, 73–86. doi: 10.1016/j.cortex.2017.06.010

Bosco, F. M., Tirassa, M., and Gabbatore, I. (2018). Why pragmatics and Theory of Mind do not (completely) overlap. *Front. Psychol.* 9:1453. doi: 10.3389/fpsyg.2018.01453

Branco, P., Seixas, D., and Castro, S. L. (2018). Temporal reliability of ultra-high field resting-state MRI for single-subject sensorimotor and language mapping. *NeuroImage* 168, 499–508. doi: 10.1016/j.neuroimage.2016.11.029

Brüne, M., and Bodenstein, L. (2005). Proverb comprehension reconsidered—'theory of mind and the pragmatic use of language in schizophrenia. *Schizophr. Res.* 75, 233–239. doi: 10.1016/j.schres.2004.11.006

Cavelti, M., Kircher, T., Nagels, A., Strik, W., and Homan, P. (2018). Is formal thought disorder in schizophrenia related to structural and functional aberrations in the language network? A systematic review of neuroimaging findings. *Schizophr. Res.* 199, 2–16. doi: 10.1016/j.schres.2018.02.051

Colle, L., Angeleri, R., Vallana, M., Sacco, K., Bara, B. G., and Bosco, F. M. (2013). Understanding the communicative impairments in schizophrenia: a preliminary study. *J. Commun. Disord.* 46, 294–308. doi: 10.1016/j.jcomdis.2013.01.003

Colombo, L., Sartori, G., and Brivio, C. (2002). Stima del quoziente intellettivo tramite l'applicazione del TIB (test breve di Intelligenza). *Giornale Ital. Psicol.* 29, 613–638.

Cui, Y., Liu, B., Song, M., Lipnicki, D. M., Li, J., Xie, S., et al. (2018). Auditory verbal hallucinations are related to cortical thinning in the left middle temporal gyrus of patients with schizophrenia. *Psychol. Med.* 48, 115–122. doi: 10.1017/S0033291717001520

Davey, J., Thompson, H. E., Hallam, G., Karapanagiotidis, T., Murphy, C., De Caso, I., et al. (2016). Exploring the role of the posterior middle temporal gyrus in semantic cognition: integration of anterior temporal lobe with executive processes. *NeuroImage* 137, 165–177. doi: 10.1016/j.neuroimage.2016.05.051

D'Esposito, M., Deouell, L. Y., and Gazzaley, A. (2003). Alterations in the BOLD fMRI signal with aging and disease: a challenge for neuroimaging. *Nat. Rev. Neurosci.* 4, 863–872. doi: 10.1038/nrn1246

Eviatar, Z., and Just, M. A. (2006). Brain correlates of discourse processing: an fMRI investigation of irony and conventional metaphor comprehension. *Neuropsychologia* 44, 2348–2359. doi: 10.1016/j.neuropsychologia.2006.05.007

Ferstl, E. C., Neumann, J., Bogler, C., and Von Cramon, D. Y. (2008). The extended language network: a meta-analysis of neuroimaging studies on text comprehension. *Hum. Brain Mapp.* 29, 581–593. doi: 10.1002/hbm.20422

Fett, A. K. J., Viechtbauer, W., Penn, D. L., van Os, J., and Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci. Biobehav. Rev.* 35, 573–588. doi: 10.1016/j.neubiorev.2010.07.001

Filik, R., Ţurcan, A., Ralph-Nearman, C., and Pitiot, A. (2019). What is the difference between irony and sarcasm? An fMRI study. *Cortex* 115, 112–122. doi: 10.1016/j.cortex.2019.01.025

Friston, K. J., Holmes, A. P., Poline, J. B., Grasby, P. J., Williams, S. C. R., Frackowiak, R. S., et al. (1995). Analysis of fMRI time-series revisited. *Neuroimage* 2, 45–53.

Gabbatore, I., Bosco, F. M., Geda, E., Gastaldo, L., Duca, S., Costa, T., et al. (2017). Cognitive pragmatic rehabilitation program in schizophrenia: a single case fMRI study. *Neural Plast.* 2017:1612078. doi: 10.1155/2017/1612078

Green, M. F., Horan, W. P., and Lee, J. (2019). Nonsocial and social cognition in schizophrenia: current evidence and future directions. *World Psychiatry* 18, 146–161. doi: 10.1002/wps.20624

Guo, W., Hu, M., Fan, X., Liu, F., Wu, R., Chen, J., et al. (2014). Decreased gray matter volume in the left middle temporal gyrus as a candidate biomarker for schizophrenia: a study of drug-naive, first-episode schizophrenia patients and unaffected siblings. *Schizophr. Res.* 159, 43–50. doi: 10.1016/j.schres.2014.07.051

Harada, T., Itakura, S., Xu, F., Lee, K., Nakashita, S., Saito, D. N., et al. (2009). Neural correlates of the judgment of lying: a functional magnetic resonance imaging study. *Neurosci. Res.* 63, 24–34. doi: 10.1016/j.neures.2008.09.010

Hickok, G., and Poeppel, D. (2007). The cortical organization of speech processing. *Nat. Rev. Neurosci.* 8, 393–402.

Holle, H., Obleser, J., Rueschemeyer, S. A., and Gunter, T. C. (2010). Integration of iconic gestures and speech in left superior temporal areas boosts speech comprehension under adverse listening conditions. *NeuroImage* 49, 875–884. doi: 10.1016/j.neuroimage.2009.08.058

Hu, M., Li, J., Eyler, L., Guo, X., Wei, Q., Tang, J., et al. (2013). Decreased left middle temporal gyrus volume in antipsychotic drug-naive, first-episode schizophrenia patients and their healthy unaffected siblings. *Schizophr. Res.* 144, 37–42. doi: 10.1016/j.schres.2012.12.018

Huber, W., Poeck, K., and Willmes, K. (1983). The aachen aphasia test. *Adv. Neurol.* 42, 291–303.

Jang, G., Yoon, S. A., Lee, S. E., Park, H., Kim, J., Ko, J. H., et al. (2013). Everyday conversation requires cognitive inference: neural bases of comprehending implicated meanings in conversations. *Neuroimage* 81, 61–72. doi: 10.1016/j.neuroimage.2013.05.027

Javed, A., and Charles, A. (2018). The importance of social cognition in improving functional outcomes in schizophrenia. *Front. Psychiatry* 9:157. doi: 10.3389/fpsyt.2018.00157

Joo, S. W., Chon, M. W., Rathi, Y., Shenton, M. E., Kubicki, M., and Lee, J. (2018). Abnormal asymmetry of white matter tracts between ventral posterior cingulate cortex and middle temporal gyrus in recent-onset schizophrenia. *Schizophr. Res.* 192, 159–166. doi: 10.1016/j.schres.2017.05.008

Kay, S. R., Fiszbein, A., and Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276.

Kirkpatrick, B., Strauss, G. P., Nguyen, L., Fischer, B. A., Daniel, D. G., Cienfuegos, A., et al. (2011). The brief negative symptom scale: psychometric properties. *Schizophr. Bull.* 37, 300–305.

Kuroki, N., Shenton, M. E., Salisbury, D. F., Hirayasu, Y., Onitsuka, T., Ersner-Hershfield, H., et al. (2006). Middle and inferior temporal gyrus gray matter volume abnormalities in first-episode schizophrenia: an MRI study. *Am. J. Psychiatry* 163, 2103–2110. doi: 10.1176/ajp.2006.163.12.2103

Leucht, S., Samara, M., Heres, S., and Davis, J. M. (2016). Dose equivalents for antipsychotic drugs: the DDD method. *Schizophr. Bull.* 42(suppl_1), S90–S94. doi: 10.1093/schbul/sbv167

Levinson, S. C. (1983). *Pragmatics*. Cambridge: Cambridge University Press.

Mazza, M., Di Michele, V., Pollice, R., Casacchia, M., and Roncone, R. (2008). Pragmatic language and theory of mind deficits in people with schizophrenia and their relatives. *Psychopathology* 41, 254–263. doi: 10.1159/000128324

Morosini, P. L., Magliano, L., Brambilla, L. A., Ugolini, S., and Pioli, R. (2000). 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.* 101, 323–329.

Mucci, A., Galderisi, S., Merlotti, E., Rossi, A., Rocca, P., Bucci, P., et al. (2015). The Brief Negative Symptom Scale (BNSS): independent validation in a large sample of Italian patients with schizophrenia. *Eur. Psychiatry* 30, 641–647. doi: 10.1016/j.eurpsy.2015.01.014

Nelson, H. E., and Willison, J. (1991). *National Adult Reading Test (NART)*. Windsor, ON: Nfer-Nelson, 1–26.

Noppeney, U., and Price, C. J. (2004). An fMRI study of syntactic adaptation. *J. Cogn. Neurosci.* 16, 702–713. doi: 10.1162/089892904323057399

Onitsuka, T., Shenton, M. E., Salisbury, D. F., Dickey, C. C., Kasai, K., Toner, S. K., et al. (2004). Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study. *Am. J. Psychiatry* 161, 1603–1611. doi: 10.1176/appi.ajp.161.9.1603

Parola, A., Berardinelli, L., and Bosco, F. M. (2018). Cognitive abilities and theory of mind in explaining communicative-pragmatic disorders in patients with schizophrenia. *Psychiatry Res.* 260, 144–151. doi: 10.1016/j.psychres.2017.11.051

Parola, A., and Bosco, F. M. (2022). EXPRESS: an eye-tracking investigation of the cognitive processes involved in the comprehension of simple and complex communicative acts. *Q. J. Exp. Psychol.* 11:17470218221079629. doi: 10.1177/17470218221079629

Parola, A., Gabbatore, I., Berardinelli, L., Salvini, R., and Bosco, F. M. (2021b). Multimodal assessment of communicative-pragmatic features in schizophrenia: a machine learning approach. *NPJ schizophr.* 7, 1–9. doi: 10.1038/s41537-021-00153-4

Parola, A., Brasso, C., Morese, R., Rocca, P., and Bosco, F. M. (2021a). Understanding communicative intentions in schizophrenia using an error analysis approach. *NPJ Schizophr.* 7, 1–9.

Pawełczyk, A., Kotlicka-Antczak, M., Łojek, E., Ruszpel, A., and Pawełczyk, T. (2018). Schizophrenia patients have higher-order language and extralinguistic impairments. *Schizophr. Res.* 192, 274–280. doi: 10.1016/j.schres.2017.04.030

Rapp, A. M., Langohr, K., Mutschler, D. E., Klingberg, S., Wild, B., and Erb, M. (2013). Isn't it ironic? Neural correlates of irony comprehension in schizophrenia. *PLoS One* 8:e74224. doi: 10.1371/journal.pone.0074224

Rocca, P., Galderisi, S., Rossi, A., Bertolino, A., Rucci, P., Gibertoni, D., et al. (2016). Social cognition in people with schizophrenia: a cluster-analytic approach. *Psychol. Med.* 46, 2717–2729. doi: 10.1017/S0033291716001100

Simpson, G. M., and Angus, J. W. S. (1970). A rating scale for extrapyramidal side effects. *Acta Psychiatr. Scand.* 45, 11–19.

Spotorno, N., Koun, E., Prado, J., Van Der Henst, J. B., and Noveck, I. A. (2012). Neural evidence that utterance-processing entails mentalizing: the case of irony. *NeuroImage* 63, 25–39. doi: 10.1016/j.neuroimage.2012.06.046

Strauss, G. P., Keller, W. R., Buchanan, R. W., Gold, J. M., Fischer, B. A., McMahon, R. P., et al. (2012). Next-generation negative symptom assessment for clinical trials: validation of the Brief Negative Symptom Scale. *Schizophr. Res.* 142, 88–92. doi: 10.1016/j.schres.2012.10.012

Uchiyama, H., Seki, A., Kageyama, H., Saito, D. N., Koeda, T., Ohno, K., et al. (2006). Neural substrates of sarcasm: a functional magnetic-resonance imaging study. *Brain Res.* 1124, 100–110. doi: 10.1016/j.brainres.2006.09.088

Uchiyama, H. T., Saito, D. N., Tanabe, H. C., Harada, T., Seki, A., Ohno, K., et al. (2012). Distinction between the literal and intended meanings of sentences: a functional magnetic resonance imaging study of metaphor and sarcasm. *Cortex* 48, 563–583. doi: 10.1016/j.cortex.2011.01.004

van Erp, T., Walton, E., Hibar, D. P., Schmaal, L., Jiang, W., Glahn, D. C., et al. (2018). Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. *Biol. Psychiatry* 84, 644–654. doi: 10.1016/j.biopsych.2018.04.023

Vandenberghe, R., Nobre, A. C., and Price, C. J. (2002). The response of left temporal cortex to sentences. *J. Cogn. Neurosci.* 14, 550–560. doi: 10.1162/08989290260045800

Varga, E., Simon, M., Tényi, T., Schnell, Z., Hajnal, A., Orsi, G., et al. (2013). Irony comprehension and context processing in schizophrenia during remission–A functional MRI study. *Brain Lang.* 126, 231–242. doi: 10.1016/j.bandl.2013.05.017

Wallwork, R. S., Fortgang, R., Hashimoto, R., Weinberger, D. R., and Dickinson, D. (2012). Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. *Schizophr. Res.* 137, 246–250. doi: 10.1016/j.schres.2012.01.031

Wensing, T., Cieslik, E. C., Müller, V. I., Hoffstaedter, F., Eickhoff, S. B., and Nickl-Jockschat, T. (2017). Neural correlates of formal thought disorder: an activation likelihood estimation meta-analysis. *Hum. Brain Mapp.* 38, 4946–4965. doi: 10.1002/hbm.23706

Wroblewski, A., He, Y., and Straube, B. (2020). Dynamic Causal Modelling suggests impaired effective connectivity in patients with schizophrenia spectrum disorders during gesture-speech integration. *Schizophr. Res.* 216, 175–183. doi: 10.1016/j.schres.2019.12.005

Zhang, L., Li, B., Wang, H., Li, L., Liao, Q., Liu, Y., et al. (2017). Decreased middle temporal gyrus connectivity in the language network in schizophrenia patients with auditory verbal hallucinations. *Neurosci. Lett.* 653, 177–182. doi: 10.1016/j.neulet.2017.05.042

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.

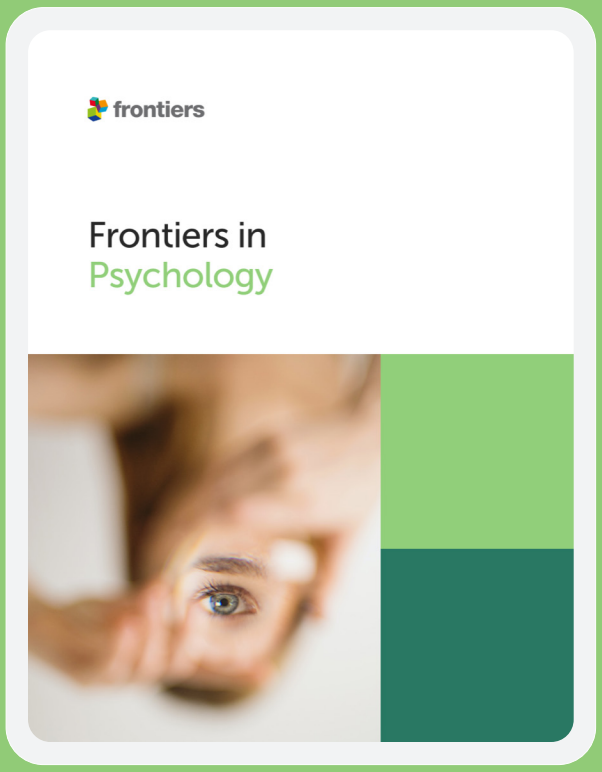
Frontiers in Psychology

Paving the way for a greater understanding of human behavior

The most cited journal in its field, exploring psychological sciences - from clinical research to cognitive science, from imaging studies to human factors, and from animal cognition to social psychology.

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