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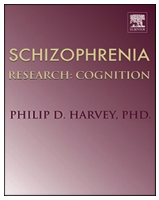

Social cognition among clinical subtypes of schizophrenia

Dear Editor,

Clozapine is the only available evidence-based treatment for those with Treatment-Resistant Schizophrenia (TRS). However, about 40–70 % of patients with TRS have suboptimal response to clozapine and are considered as Ultra Treatment-Resistant Schizophrenia (UTR) (Rajkumar et al., 2011). The resulting three subtypes of schizophrenia based on clinical response (treatment-responsive (TRpS), treatment-resistant and ultra-treatment-resistant) may implicate distinguishable pathophysiology (Lee et al., 2015). Identifying the three clinical subtypes may be important due to the dearth of literature surrounding prognostication, treatment trajectory, and contributing factors for TRS and UTR (Howes et al., 2021).

Social Cognition is a cognitive area prominently affected in schizophrenia and refers to the processing of an individual's perception of the intentions of others in social situations (Henry et al., 2015). Current evidence suggests that patients with schizophrenia experience a significantly greater likelihood of perceiving other individuals and situations as negative and hostile in nature (Henry et al., 2015). In particular, gross deviations from normal social cognition is known to be a strong determinant of patients' functional impairments due to reductions in empathy, social cue processing, and emotional regulation (Green et al., 2015). As such, the social cognitive symptom profile is often incorporated to diagnose, predict long-term prognosis, and to facilitate clinical decision-making (Harvey et al., 2019). The aim of the study was to compare socio-cognitive profiles among three clinical subtypes of schizophrenia and determine whether social cognition can be used as a predictor of treatment responsiveness.

For our study, 85 participants (mean age (SD) = 45.2 (SD) years; 70.6 % male) were recruited from the outpatient schizophrenia recovery program. TRpS, TRS, and UTRS were defined according to treatment type, which corresponded to non-clozapine antipsychotics, clozapine monotherapy, and clozapine with another therapeutic modality, respectively. Participants were asked to complete a one-time assessment of social cognition using the Ambiguous Intentions Hostility Questionnaire (AIHQ), where the self-reported blame score in Ambiguous and Accidental scenarios was used as a measure of social cognitive deficits. Relevant clinical data, including demographics, substance use, age of onset of illness, comorbidities and current medications were extracted from the electronic medical record. 5 incomplete questionnaires for which the analysis was omitted. Participants with TRS (n = 4) were excluded from comparative analysis owing to the small sample size.

Our results showed self-reported blame score total had good internal consistency with regards to both accidental and ambiguous scenarios, as well as combined across both scenario types. However, rater-measured items (i.e., aggression and hostility biases) had reduced internal consistency, which ranged poor to good overall for each scenario type as well as total (Table 1A). Furthermore, hostility biases in accidental scenario types were significantly associated with independent measures of overall symptom severity in schizophrenia, specifically the Clinical Global Impression Scale for Schizophrenia (CGI-SCH). Overall, correlations were strongest for accidental scenarios, but not for others (Table 1B).

Our participants' average blame scores ranged from 3.0 to 14.8 compared to the literature-reported range of 5.1–5.4 in the general population; overall blame biases in patients with schizophrenia were significantly higher in ambiguous (mean (SD):7.23(2.67)) than accidental scenarios (mean (SD) 6.04(2.8)), as well as across each of TRpS and UTR. In particular, participants with UTR (n = 18; mean age (SD) = 41.1y (11.1); 66.7 % male) demonstrated a mean ambiguous and accidental blame score of 7.38 and 6.62, respectively, as compared to participants with TRpS (n = 58; mean age (SD) = 45.5y (15.04); 74.1 % male) in which the mean scores were 7.27 and 5.941, respectively. Female participants demonstrated higher mean blame scores in both scenario types compared to male counterparts, though the differences were not statistically significant. Younger patients with schizophrenia (age 18–40) also demonstrated higher mean overall blame scores than older patients in both scenarios, but scores were higher in the elderly (age 61–74) compared to middle-aged patients (age 41–60).

These findings suggest that patients with UTR consistently exhibit higher blame biases than patients with TRpS. In general, some studies have shown that cognitive disorganization was higher in clozapine non-responders than responders (Rajkumar et al., 2011; Rodriguez et al., 1998). However, to our knowledge, no studies have looked at the differences in Social Cognition among the clinical subtypes. As such, our study suggests a distinguishable pathophysiology may exist in the social cognitive domain based on treatment-response to clozapine.

It is important to consider the clinical variates that may implicate social cognition. For instance, the differences in social cognitive profiles by age group may indicate a pattern of age-related social cognitive decline similar to other domains of cognition, as suggested, but not demonstrated, in a longitudinal study (McCleery et al., 2016). Another study hints that there may exist a transient stabilization phase of mental status from onset of first psychosis, which provides for the possibility of slight improvements in cognitive impairments before the onset of steady decline (Lee et al., 2020). Our study also reveals no significant sex differences in social cognitive deficits, potentially due to the small sample size. In general, it is thought that sexual dimorphism exists in schizophrenia across numerous neurobiological domains (Lee et al., 2020; Kubota et al., 2022). Nevertheless, we have shown that clinical trajectories will vary greatly between patients due to the multifactorial nature of social cognition (Green et al., 2015).

One limitation of the study stems from the inherent difficulty in conducting participatory studies in patients with schizophrenia. Another major limitation of our study was the small sample size of patients with

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Table 1
(A) AIHQ scale reliability for the blame score (self-reported), and hostility and aggression bases (rater-scored) with regards to internal consistency. (B) Convergent validity analysis as measured as Pearson correlations of AIHQ blame scores and hostility and aggression biases with measure of symptom severity via CGI-SCH.

	(A) Internal consistency (α)	(B) CGI-SCH Average
Accidental scenarios		
Blame score	0.82	0.21
Hostility bias	0.85	0.34**
Aggression bias	0.61	0.29*
Ambiguous scenarios		
Blame score	0.88	−0.02
Hostility bias	0.52	0.01
Aggression bias	0.52	0.08
Ambiguous + Accidental scenarios		
Blame score	0.89	0.1
Hostility bias	0.72	0.3*
Aggression bias	0.56	0.22

Note: For analysis in (B), sample sizes have been reduced accordingly after accounting for incomplete AIHQ questionnaire fields, given the following: AIHQ Blame Score ($n = 80$), AIHQ Hostility and Aggression biases ($n = 63$), CGI-SCH ($n = 46$).
* $p < 0.1$.
** $p < 0.05$.

TRS, and therefore we were unable to conduct analysis comparing clozapine responders to non-responders.

Schizophrenia continues to impose a multifaceted burden on patients, families, and caregivers, which manifests beyond the clinical setting (Crespo-Facorro et al., 2020). In summary, our findings are important in highlighting differences in social cognition in ultra-treatment psychosis. Future larger scale studies are required to confirm the findings of this study; however, this preliminary finding could lead us to better understanding of psychopathology and prediction of treatment response in schizophrenia.

Our results would further suggest clinicians may benefit from thorough assessments of various symptom domains to navigate tailored treatment options and increase predictive accuracy of treatment response. Efforts to increase patient education and social awareness must also be carefully considered.

Ethics approval

This study obtained research ethics approval from the Royal Ottawa Hospital Research Ethics Board (REB).

Informed consent

All procedures followed were in accordance with the ethical standards of the Royal Ottawa Mental Health Centre, Research Ethics Board (REB) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

CRediT authorship contribution statement

Seung Ho Lee: Data curation, Project administration, Writing – original draft. **Malik Ekhdoura:** Data curation, Investigation, Methodology, Project administration. **Sihyun Baek:** Data curation, Investigation, Methodology, Project administration. **Naista Zhand:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare no competing interests.

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