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Research Article

Loneliness is associated with mentalizing and emotion recognition abilities in schizophrenia, but only in a cluster of patients with social cognitive deficits

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Abstract

Objective: Loneliness is a concern for patients with schizophrenia. However, the correlates of loneliness in patients with schizophrenia are unclear; thus, the aim of the study is to investigate neuro- and social cognitive mechanisms associated with loneliness in individuals with schizophrenia. **Method:** Data from clinical, neurocognitive, and social cognitive assessments were pooled from two cross-national samples (Poland/USA) to examine potential predictors of loneliness in 147 patients with schizophrenia and 103 healthy controls overall. Furthermore, the relationship between social cognition and loneliness was explored in clusters of patients with schizophrenia differing in social cognitive capacity. **Results:** Patients reported higher levels of loneliness than healthy controls. Loneliness was linked to increased negative and affective symptoms in patients. A negative association between loneliness and mentalizing and emotion recognition abilities was found in the patients with social-cognitive impairments, but not in those who performed at normative levels. **Conclusions:** We have elucidated a novel mechanism which may explain previous inconsistent findings regarding the correlates of loneliness in individuals with schizophrenia.

Keywords: social cognition; theory of mind; cluster analysis; social isolation; loneliness; psychosis

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Introduction

Social functioning deficits constitute one of the greatest therapeutic challenges in treatment of patients with schizophrenia (SCZ). Lower social functioning in patients with schizophrenia compared to a healthy control group (HC) with large effect sizes is found consistently across all methods of clinical assessment, including self-report, clinical interview, and performance-based measures (Schneider et al., 2017). The low frequency of social contacts observed in this group is a long-term predictor of more severe disability in patients (Siegrist et al., 2015). Moreover, clinical and cognitive predictors of social dysfunction experienced by individuals with schizophrenia have been extensively studied for the last two decades, with multiple studies supporting the notion that social cognition (SC) is a better predictor of community functioning than nonsocial cognition (Halverson et al., 2019).

Despite extensive research examining the mechanisms underlying reduced social functioning observed in individuals with schizophrenia, the issue of loneliness in this clinical group is still being explored (Badcock et al., 2020). Furthermore, loneliness is driven by one's appraisal of his/her social relationships, rather than by objective characteristics of one's social network, thus it is not synonymous with objective social disconnection, even though there is a correlation between loneliness and social disconnection (Cacioppo & Cacioppo, 2018). Importantly, findings from a large scale meta-analysis demonstrate that loneliness (26%) and objective social disconnection (29%) similarly increase mortality (Holt-Lunstad et al., 2015).

As evidenced by two recent meta-analyses (Chau et al., 2019; Michalska et al., 2018), there is a significant relationship between loneliness and psychotic symptoms in clinical and nonclinical samples. Findings from a large-scale Australian cohort study showed that over 80% of individuals with schizophrenia experience loneliness, and over one out of three patients (37.2%) identify loneliness and social disconnection as a top-most challenge in their everyday functioning (Stain et al., 2012). Loneliness in patients has been also linked to certain aspects of cardiometabolic health

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(Badcock et al., 2019). This finding is particularly important given the fact that cardiovascular disorders are the major contributor to increased mortality in individuals with schizophrenia (Ringen et al., 2014).

Cognitive impairments are robustly identified as one of the core aspects of schizophrenia (e.g Green, 2006). Even though cognitive variables have not been included in the theoretical model of loneliness in individuals with psychosis (M. H. Lim et al., 2018), increasing effort has been devoted to identifying such correlates of loneliness in patients. An association between loneliness and psychomotor speed was observed in a large cohort of Australian outpatients (Badcock et al., 2015), however no relationship between loneliness and executive functioning was found in a sample of 116 noninstitutionalized patients (Eglit et al., 2018).

Social cognitive correlates of loneliness have also been investigated due to the postulates of the evolutionary theory of loneliness formulated by Cacioppo and Cacioppo (ETL; Cacioppo & Cacioppo, 2018). The ETL posits that salutary companionship is crucial for the survival of socially-oriented species such as humans, and thus a lack of beneficial social interactions elicits aversive signals that evolved to warn individuals about an increased probability of potential aggression or abuse. While potentially helpful in the short term, in case of prolonged loneliness, these mechanisms can have a lasting impact on the ability to accurately perceive and recognize mental states and intentions of other people. Therefore, on the one hand, increased vigilance to social threats could result in abnormal emotion recognition (Pinkham et al., 2011); while on the other hand, focusing solely on one's view and reduced perspective taking could hinder one's mentalizing capacity. An exploratory study by Trémeau et al. (2016) found a significant negative association between loneliness and both performance-based and self-report measures of SC in HC. However, a recent review of social information processing mechanisms in lonely individuals has found conflicting findings about the association between loneliness and emotion recognition in non-clinical populations (Spithoven et al., 2017). Moreover, when we administered a battery of SC tests to nonclinical controls, no associations were found between lower-level social cue processing or higher-order mentalizing abilities and loneliness (Okruszek et al., 2021).

Interestingly, the connection between SC and loneliness may be more nuanced within clinical populations. For example, in the Trémeau et al., (2016) study, loneliness reported by participants with schizophrenia was correlated with self-report, but not performance-based measures of SC. However, there was no association between SC variables and loneliness reported by persons with schizophrenia in the study that was part of the multi-site US project [Social Cognition Psychometric Evaluation (SCOPE) project (Ludwig et al., 2020)]. However, based on the results of the study, Ludwig et al., (2020) proposed a testable hypothesis that the association between SC and loneliness may be limited to a specific subset of participants with schizophrenia rather than all diagnosed individuals. While there is still no consensus with regard to the exact stratification of patients with schizophrenia with regard to the number and type of clusters based on cognitive or SC performance, previous studies have found at least one cognitively spared cluster of patients and either one or several clusters of patients with various levels of cognitive impairment (M. J. Green et al., 2020). As proposed by Ludwig et al., (2020), individuals with a psychotic disorder but "adequate social cognition and functioning may feel lonelier when experiencing a mismatch between their desired and current relationship quantity, quality or type" (p. 555). Thus, the lack of observed relationships between loneliness and SC in patients could stem from examining both constructs at the level of the whole clinical group instead of particular subgroups of patients differing in social cognitive capacity. As evidenced by recent large scale studies (e.g. Rocca et al., 2016; Viviano et al., 2018), clusters of patients stratified with regard to social cognitive capacity also show marked differences with regard to neurocognition, symptomatology and social functioning. Furthermore, social cognitive capacity in patients has been shown to be more strongly associated with a wider range of social outcomes than neurocognitive skills, which has been attributed to its proximity to community functioning variables (Fett et al., 2011). Taken together, these findings support Ludwig et al., (2020) suggestion that the association between social functioning and loneliness may be observed only in the subgroup of patients who display specific levels of social cognitive capacity. Yet, as various factors may precipitate loneliness in patients with either intact (e.g., good clinical insight) or impaired (e.g., more pronounced problems in interactions) SC, this hypothesis and its directionality needs further investigation.

Thus, the aim of the current study is to explore social cognitive and neurocognitive mechanisms that may be associated with loneliness in schizophrenia through the process of mega-analysis (pooling raw data across studies) of two datasets, including data from the original Ludwig et al. study (2020). First, we aim to re-examine the associations between demographic, clinical and cognitive variables, and loneliness in a large set of cross-national participants. Given the results of the previous studies (Lim et al., 2018), we expect to observe the robust association between affective symptoms and loneliness in patients. Second, we test the „cluster hypothesis", by investigating the association between SC and loneliness across subgroups of patients differing in SC capacity, as we expect that the association between loneliness and social cognitive capacity may be limited only to a subgroup of patients. Ludwig et al., (2020) suggested that the group of patients with an intact SC may show greater loneliness; yet it also seems possible that a group with social cognitive impairments may show greater loneliness, e.g. due to limited resources and capabilities. Thus, due to the lack of the previous data in this area we decided to abstain from predicting specific patterns of associations between loneliness and social cognitive capacity in the current study.

Methods

Participants: This study includes patients with a diagnosis of schizophrenia or schizoaffective disorder who participated in the original SCOPE study at the University of North Carolina site, which was the only SCOPE site that examined loneliness in participants (n=60; UNC; for details please see Ludwig et al., (2020). The second sample included in the mega-analysis comprised patients treated at the Institute of Psychiatry and Neurology in Warsaw who were examined as a part of the Polish National Centre of Science Sonata grant no 2016/23/D/HS6/02947 (SONATA; n=88). Adults (>18 years old) diagnosed with schizophrenia according to ICD-10 criteria were recruited for the study. Only clinically stable patients who had not undergone any treatment changes and did not endorse any significant changes in symptom severity during the 4 weeks preceding the baseline study assessment visit were included in the study. Patients with intellectual disability, a history of comorbid neurological or psychiatric disorders, or drug abuse were excluded from the project.

Participants for the control group included healthy volunteers who responded to online advertisements. In both UNC and

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SONATA, healthy individuals were screened for exclusion criteria (history of psychiatric or neurological disorders, substance abuse), and groups were matched according to sex, age, and parental education. Each participant received written information about the study procedure and provided signed written consent before participating in the study. The study protocol was approved by the respective ethics boards at UNC and the Institute of Psychology, Polish Academy of Sciences. Human data included in this manuscript was obtained in compliance with the Helsinki Declaration. SONATA participants were reimbursed at the rate of 100 PLN (approx 25 USD), and UNC participants received 60 USD. The SONATA project had a more restrictive age criteria compared to the SCOPE study. As such, only participants aged 18–51 were included from the UNC sample into the current project.

For the pooled analysis, only individuals with no missing data for any of the variables of interest (loneliness score, PANSS scores, five neurocognitive tests and four SC measures) were included in the analyses. This produced a final sample of 251 individuals, including 148 patients (88 from SONATA) and 103 HC (65 from SONATA). One patient was excluded from further analysis due to extreme outlier values in TMT-A, thus leaving 250 participants for pooled analyses. Detailed description of the final sample may be found in Supplemental Online Materials. Given the size of the patients' group, the current study should be able to detect small-to-medium effects (Pearson's r=.23 at p=.05 with 80% power), as estimated by *pwr* R library.

Neurocognitive and SC tests: For the SONATA sample, the full Polish Academic version of MATRICS Consensus Cognitive Battery (MCCB) (Jędrasik-Styła et al., 2015) was used to examine cognitive functioning in participants. MCCB is a standardized battery consisting of ten tests that assess seven cognitive domains (speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning, and problem-solving, SC). UNC participants completed only a subset of the MCCB, which included three tests measuring speed of processing (Trail Making Test – A, BACS Symbol Coding, Animal Fluency), one verbal learning task (Hopkins Verbal Learning Test – Revised) and one working memory test (Letter Number Span). For this reason, the current mega-analysis only included the five neurocognitive tests administered in both projects.

Four of the SC measures in the SCOPE battery are available in Polish, including two measures of mentalizing (Reading the Mind in the Eyes Task; RMET (Baron-Cohen et al., 2001); Hinting Task (Krawczyk et al., 2020)), a social perception task (the Mini Profile of Nonverbal Sensitivity; MiniPONS (Bänzigeret al., 2011)), and a test of emotion processing (Penn Emotion Recognition Task, PENN ER-40 (Gur et al., 2002)).

Social cognitive tasks used in the current study were taken from the Social Cognition Psychometric Evaluation Study (SCOPE; Pinkham et al., 2018), which the UNC study was part of. All of the original versions of the tasks showed acceptable internal consistency and, apart from PONS, were recommended for further use in research with patients with schizophrenia. The Polish versions of the task are also characterized by the satisfactory psychometric properties (Krawczyk et al., 2020), and have been previously effectively applied in the nonclinical populations (Okruszek et al., 2021).

Clinical assessment: Clinical symptom severity was assessed in both samples using the Positive and Negative Syndrome Scale (Kay & Opler, 1987). The four clinical domain scores (positive [P1, P3, P5, G9], negative [N1, N2, N3, N4, N6, G5, G7], affective [P6, G1, G2, G4, G6, G16], cognitive [P2, P4, P7, N5, N7, G8, G10, G11, G12, G13, G14, G15]) were calculated in line with recent PHAMOUS (The Pharmacotherapy Monitoring and Outcome Survey) consortium recommendations, as it has been based on the large multinational sample and has been strongly linked to neurobiological markers (Chen et al., 2020). As the specific PANSS items N4 (Passive/apathetic social withdrawal) and G16 (Active social avoidance) are highly semantically linked to the constructs measured by loneliness questionnaires, the pattern of results was also re-investigated after dropping these two items from respective subscales.

Loneliness measurement: Loneliness in the SONATA sample was measured using the Polish version of the Revised UCLA Loneliness scale (Kwiatkowska et al., 2017). The scale includes 20 statements which are reflective of one's loneliness and has been shown to have excellent internal consistency when administered to a large group of non-clinical Polish participants ($\alpha = .92$). Loneliness in the UNC sample was examined using the initial version of the UCLA Loneliness Scale, which has been reworded to produce R-UCLA Loneliness scale. Considering the Likert scale for responses on the initial version of the UCLA scale range from 0 to 3, instead of 1 to 4 as is the case for the updated R-UCLA scale, total scores for the UNC sample have been shifted by adding 20 points to the overall score for participants from UNC to produce a common scale for both samples.

Statistical analysis: Data analyses were performed using Statistical Package for the Social Sciences (SPSS 27) and R libraries. We completed a two-factor ANOVA with site (Poland *vs* USA) and group (SCZ vs HC) as between-subject factors to examine differences in neurocognitive and SC variables. Regarding loneliness, an additional factor (gender) was also investigated, as it has been significantly associated with loneliness in the original Ludwig et al., (2020) analysis. To examine the relationship between age, clinical, and cognitive variables and loneliness, Pearson correlation coefficients have been calculated separately for SCZ and HC.

Next, Latent Class Analysis (LCA) was implemented using Mclust (version 5.4.7) library to identify latent classes of patients who present similar SC profiles (Scruccaet al., 2016). Mclust provides functions for parameter estimation using the expectation-maximization algorithm for normal mixture models. One of the main advantages of using Mclust is the use of the Bayesian information criterion (BIC) which selects the optimal covariance structure and number of clusters. Furthermore, LCA has been demonstrated to produce fewer misclassifications compared to k-means clustering (Magidson & Vermunt, 2002). LCA classification was produced on the basis of the patients' performance in four SC tests (Mini-PONS, ER-40, RMET, Hinting) that were entered into the clustering algorithm. As most of the studies observed non-impaired cognitive performance in at least one cluster of patients, SC scores from LCA clusters were compared with HC. Finally, the pattern of correlations between cognitive variables and loneliness were reinspected separately for each LCA cluster.

Results

Neurocognitive and SC tests: In the first step of the analysis, we have examined the factors associated with neurocognitive and social cognitive scores in the current study. Patients performed worse than HC on all assessments (effect sizes ranging from d=0.30 to d=1.23, Table 1).

Main effects of site were found for the UNC sample demonstrating worse performance on Trails A ($d = 0.28$), animal fluency ($d = 0.49$), HVLT-R ($d = 0.32$), and Hinting Task ($d = 0.73$),

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Table 1. Between-group differences for neurocognitive and social cognitive tasks

	SCZ (n = 147)	HC (n = 103)	Cohen's d and statistics
TMT-A (time)	35.92 (13.23)	28.14 (8.59)	d = .67 $p < .001$ $F_{1,249} = 26.73$
BACS (coded symbols)	45.55 (10.82)	59.29 (11.73)	d = 1.23 $p < .001$ $F_{1,249} = 85.35$
HVLT-R (words)	24.08 (5.48)	26.95 (4.52)	d = .56 $p < .001$ $F_{1,249} = 17.35$
LNS (points)	13.67 (3.72)	15.36 (3.02)	d = .49 $p < .001$ $F_{1,249} = 13.12$
Animal Fluency (no of items)	22.52 (6.03)	27.41 (5.93)	d = .81 $p < .001$ $F_{1,249} = 35.60$
PENN ER-40 (correct answers)	32.00 (3.92)	33.04 (2.80)	d = .30 $p < .05$ $F_{1,249} = 5.87$
PONS (correct answers)	44.13 (5.37)	47.80 (5.40)	d = .68 $p < .001$ $F_{1,249} = 27.93$
HT (points)	14.46 (3.07)	16.44 (2.64)	d = .68 $p < .001$ $F_{1,249} = 25.26$
RMET (correct answers)	23.68 (5.06)	26.02 (3.87)	d = .51 $p < .001$ $F_{1,249} = 12.95$

Note. Abbreviations: RMET - Reading Minds in the Eyes Test; PENN-ER-40 - Penn Emotion Recognition Test; HT- Hinting Task; PONS - Profile of Nonverbal Sensitivity; HVLT-R - Hopkins Verbal Learning Test - Revised; TMT-A - The Trail Making Test, version A; BACS - The Brief Assessment of Cognition in Schizophrenia; LNS - Letter Number Span.

but better performance for Mini-PONS ($d = 0.28$). However, differences became non-significant after age was entered as a covariate on TMT and HVLT-R. No group by site interactions were observed for any of the tests.

Loneliness: In the second step of analysis, we examined the factors associated with loneliness in the current study. Patients reported higher levels of loneliness (44.31±12.73) compared to HC (34.17±10.23; $F_{1,249}$=52.20; $p < .001$; $d = 0.86$). This effect was not moderated by gender. A group by site interaction was found ($F_{1,249} = 5.82$; $p = .017$), such that in each sample, patients were lonelier than HC. However, UNC HC were less lonely compared to SONATA HC (d = .20), while the reverse pattern was observed in patients (d = .29). Furthermore, no correlation between age and loneliness was found in patients with schizophrenia (r = .06; $p = .47$), whereas these variables were negatively correlated in HC (r = −.22; $p = .02$). A robust correlation was found for loneliness with PHAMOUS negative (r = .25; $p = .002$) and affective (r = .49 $p < .001$) dimensions and a trend-level correlation with positive symptoms (r = .15; $p = .08$). The same pattern of results remained even after excluding N4 (Passive/apathetic social withdrawal) and G16 (Active social avoidance) from PHAMOUS Negative and Affective dimensions, respectively.

Association between loneliness and cognitive variables in groups: During the final stage of the whole-group analyses, we examined the association between neurocognitive and social cognitive scores and loneliness at the level of whole groups. There were no significant relationships between loneliness and any of the cognitive variables within the full group of patients (r from -.10 to .14). In HC, loneliness was negatively associated with performance on the Mini-PONS (r = −.22; $p < .05$; Table 2).

SC clusters: Before examining the "cluster hypothesis", the results of the LCA were investigated. The lowest BIC was observed for the diagonal model assuming unequal volume, but equal shape of the clusters (model "VEI"; Figure S1). Each of the top three models based on the BIC criterion had two clusters, thus the VEI two-cluster solution with 65 and 82 patients, respectively, was further investigated. Clusters did not differ in age ($t_{145} = .18$; $p = .86$; $d = 0.03$), gender (females: 16/65 vs. 31/82; $X^2_1 = .3$; $p = .11$), percentage of participants from each site (UNC participants: 29/65 vs. 30/82; $X^2_1 = 1.0$; $p = .40$), or loneliness ($t_{145} = 1.09$; $p = .28$; $d = 0.18$). Finally, no between-clusters differences were observed for PHAMOUS positive ($t_{145} = 1.55$; $p = .12$; $d = 0.26$), negative ($t_{145} = .58$; $p = .57$; $d = 0.10$) or affective ($t_{145} = .04$; $p = .97$; $d < 0.01$) symptoms. The smaller cluster, however, had more cognitive symptoms compared to the larger one ($t_{145} = 2.42$; $p = .02$; $d = 0.40$). Within the UNC sample a higher percentage of non-Caucasian participants was found in the smaller cluster (18 out of 29) compared to the larger cluster (4 out of 30; $X^2_4 = 15.4$; $p = .004$). For each of the four SC tests, the same pattern of results was found, confirming previous findings suggesting the existence of two clusters differing in social cognitive capacity in patients with schizophrenia: patients fell into either a normal-performance group (SC-NP; n = 82) that did not differ from HC, or an SC-impaired group (SC-IMP, n = 65) who performed worse on all four measures compared both to SC-NP and HC (all *p*s < .001). Between-cluster differences are shown in Table 3.

Table 2. Zero-order correlations between loneliness and neurocognitive and social cognitive tasks

	SCZ (n = 147)	HC (n = 103)	SC-NP (n = 82)	SC-IMP (n = 65)
Age	.059	−.223*	−.166	−.090
RMET	.137	−.043	.047	.170
PENN ER-40	−.095	−.099	−.116	−.219
HT	−.010	.152	.085	−.248*
PONS	.076	−.221*	−.054	.129
HVLT-R	−.008	−.075	−.092	−.002
TMT-A	.142	.095	.134	.221
BACS	−.046	−.154	−.054	−.165
Animal Fluency	−.016	−.077	−.032	−.116
LNS	.064	−.048	.162	−.186
PHAMOUS NEGATIVE	.250**	--	.228*	.300*
PHAMOUS POSITIVE	.145	–	.238*	.053
PHAMOUS COGNITIVE	−.008	–	−.004	.027
PHAMOUS AFFECTIVE	.487***	–	.527***	.429***

Note. Abbreviations: RMET - Reading Minds in the Eyes Test; PENN-ER-40 - Penn Emotion Recognition Test; HT- Hinting Task; PONS - Profile of Nonverbal Sensitivity; HVLT-R - Hopkins Verbal Learning Test - Revised; TMT-A - The Trail Making Test, version A; BACS - The Brief Assessment of Cognition in Schizophrenia; LNS - Letter Number Span; PHAMOUS - The Pharmacotherapy Monitoring and Outcome Survey * - $p < .05$, ** $p < .01$, *** - $p < .001$.

Association between loneliness and cognitive variables in SC clusters: In the last step of analysis, the "cluster hypothesis" was evaluated by examining the association between neurocognitive and social cognitive variables and loneliness separately in SC-NP and SC-IMP clusters. No correlations between loneliness and social cognitive or neurocognitive scores were observed for the SC-NP cluster. However, in the SC-IMP cluster a negative association was found between loneliness and mentalizing abilities (Hinting: r = −.25; $p < .05$). Moreover, trend-level associations were found for emotion-recognition (PENN ER-40: r = −.22; $p < .08$) and speed of processing (TMT-A: r = .22; $p < .08$) with loneliness. To further evaluate the independent and combined contributions of neurocognitive and social cognitive processes on loneliness in the SC-IMP cluster, the three variables were entered in subsequent steps of a regression model. Mentalizing abilities

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Table 3. Between-cluster differences in main variables of interest

	SCZ NP (n = 82)	SCZ IMP (n = 65)	Cohen's d and statistics
Age	34.18 (8.62)	34.45 (8.66)	$t_{145} = -.18$, NS; d = −0.03
RMET	26.37 (3.48)	20.29 (4.71)	$t_{145} = 8.99$, $p < .001$; d=1.49
PENN ER-40	84.23 (6.34)	74.58 (10.48)	$t_{145} = 6.91$, $p < .001$; d = 1.15
HT	16.20 (1.77)	12.26 (2.97)	$t_{145} = 9.96$, $p < .001$; d = 1.66
PONS	46.81 (3.96)	40.75 (5.03)	$t_{145} = 8.16$, $p < .001$; d=1.36
HVLT-R	26.09 (4.56)	21.54 (5.53)	$t_{145} = 5.46$, $p < .001$; Cohen's d = 0.91
TMT-A	33.06 (12.46)	39.52 (13.39)	$t_{145} = -3.02$, $p < .05$; d = .50
BACS	49.43 (11.12)	40.66 (8.19)	$t_{145} = 5.31$, $p < .001$; d = .88
Animal Fluency	25.04 (5.28)	19.34 (5.40)	$t_{145} = 6.43$, $p < .001$; d=1.07
LNS	15.33 (3.26)	11.57 (3.19)	$t_{145} = 7.01$, $p< .001$; d = 1.16
PHAMOUS NEGATIVE	14.68 (6.28)	15.26 (5.77)	$t_{145} = -.57$, ns; d = .10
PHAMOUS POSITIVE	8.96 (4.08)	10.05 (4.37)	$t_{145} = -1.55$, ns; d = −.26
PHAMOUS COGNITIVE	21.34 (5.24)	23.69 (6.55)	$t_{145} = -2.42$, $p < .05$; d = −.40
PHAMOUS AFFECTIVE	15.92 (5.79)	15.88 (5.25)	$t_{145} = .04$, ns; d = .01

Note. Abbreviations: RMET - Reading Minds in the Eyes Test; PENN-ER-40 - Penn Emotion Recognition Test; HT- Hinting Task; PONS - Profile of Nonverbal Sensitivity; HVLT-R - Hopkins Verbal Learning Test - Revised; TMT-A - The Trail Making Test, version A; BACS - The Brief Assessment of Cognition in Schizophrenia; LNS - Letter Number Span; PHAMOUS - The Pharmacotherapy Monitoring and Outcome Survey.

explained 5% of the loneliness in the SC-IMP cluster (adjusted $R^2 = 4.7\%$; $F_{1,63}$ 4.12; $p < .05$). Emotion recognition skills entered after mentalizing skills contributed an additional 4% of variance in loneliness scores (R^2-change = 4.4%; $p < .05$). Plots illustrating the association between SC and loneliness for both clusters are shown in Figure S2. The incremental increase in variance for TMT was not significant (R^2-change = 1.2%; $p = .18$).

Discussion

The current study extends previous knowledge about the factors which may underlie loneliness in patients with schizophrenia. First, in line with previous studies, we observed increased levels of loneliness reported by individuals with schizophrenia compared to individuals without the disorder. In fact, the magnitude of the effect was similar to that reported in the meta-analysis of thirteen studies on the association between psychotic symptoms and loneliness (Michalska da Rocha et al., 2018). This effect was not modulated by age or gender of patients and was consistently observed in both samples from different cultures included in the current mega-analysis, thus suggesting that loneliness may be seen as a universal problem across individuals with schizophrenia. Additionally, it is worth noting that none of the between-group differences observed in SC tasks was moderated by the site of the study. Lack of cross-cultural validation has been recently listed among the main challenges in research on SC impairment in patients with schizophrenia (Vaskinn & Horan, 2020). Thus, the similarity of findings across Polish and American participants in the current study adds to the previous results suggesting stability of findings with SCOPE battery across cultures (K. Lim et al., 2020). This notion is also consistent with the findings of a recent meta-analysis, which pooled data from 156 studies comparing SC capacity in patients with schizophrenia and healthy controls from 34 countries (Weinreb et al., 2022). Stable effects have been found across the globe for all social cognitive domains with an exception for hostile attribution bias. Still, studies that would establish social cognitive measurement invariance across cultures are urgently needed.

Second, similarly to previous studies demonstrating a robust association between depression and loneliness in both the general population (Cacioppo et al., 2006) and in individuals with mental health crises (Wang et al., 2020), we have found that more severe affective symptoms were the most robust clinical predictor of loneliness in patients. However, it is worth noting that chronic loneliness has been shown to increase the risk of depressive symptoms in healthy individuals, but the reverse relationship was not found (Cacioppo et al., 2010). As the cross-sectional design of the current study precludes establishing the direction of the causality between affective symptoms and loneliness in patients, further longitudinal investigation is needed to establish whether this observation applies to patients with schizophrenia. Given that negative symptoms are often considered as closely related with social dysfunction in schizophrenia (Robertson et al., 2014), it is notable that we observed a stable and small-to-medium relationship between negative symptoms and loneliness in patients. Finally, we believe that the site by group interaction with regard to levels of loneliness may be partially attributed to the higher levels of affective symptoms observed in the US sample of patients compared to the Polish sample of patients. As affective symptoms were found to be the most robust factor predicting loneliness in patients in the current study, more pronounced affective symptoms in the UNC sample of patients (Supplementary material) may have produced between sample effects in loneliness levels in patients. Still, as the between sample effects were also observed for the healthy controls, other sources of cross-cultural variance in factors which are known to affect loneliness levels in patients (e.g. societal perception of schizophrenia, social support or treatment-related variables; Lim et al., 2018) can be considered.

Consistently with the "cluster hypothesis", we did not observe an association between SC capacity and loneliness in the whole sample of patients. The size of the current sample was large enough to detect small-to-medium correlations, which confirms that previous null-findings in smaller samples (e.g. 74 patients reported by Ludwig et al. (Ludwig et al., 2020) or 87 patients included in Trémeau et al., (2016) were not due to insufficient statistical power. In contrast to the two previous studies, we employed a data-driven latent profile analysis of SC performance to stratify the sample of patients into clusters differing in SC-capacity. We identified a two-cluster structure, with the normal-performance cluster of patients outperforming the SC-impaired cluster on all neuro- and social cognitive tasks. Importantly, no between-group differences across key demographic characteristics or loneliness levels were observed. Yet, while no association was found between loneliness and SC in unimpaired groups, poorer theory of mind and emotion recognition was linked to higher levels of loneliness in the SC-impaired sample.

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This finding is congruent with Ludwig et al.'s notion that the association between social cognitive ability and loneliness may be limited to a specific subgroup of patients. However, while Ludwig et al., (2020) proposed that patients with "adequate" SC and functioning may feel lonelier as they are better suited to appraise the mismatch between their desired and actual social functioning, we have observed no significant relationship between SC and loneliness in SC-NP sample. This finding is similar to the previous findings from healthy individuals (Okruszek et al., 2021). Moreover, a recent review concluded that problems with understanding and interpreting social situations in lonely individuals may be attributed to negative cognitive bias rather than perceptual or attentional deficits (Spithoven et al., 2017). Thus, it may be suggested that in individuals with intact SC (whether HC or SC-NP), loneliness may be associated with SC tendencies (e.g. hostile attribution bias (Okruszek et al., 2021)) rather than SC capacity per se. At the same time, previous findings suggest a negative association between SC capacity and loneliness in other cognitively-impaired samples, e.g. stroke patients (Adams et al., 2020). Accordingly, the current study found that the relationship between loneliness and SC capacity may be limited to the individuals with schizophrenia with SC impairments.

Taken together, it may be proposed that in individuals with unimpaired SC, more subtle mechanisms associated with tendencies to interpret social situations in a negative way may be associated with loneliness, while relationship between loneliness and baseline SC capacity is nonsignificant. However, after reaching a SC-deficit threshold, overall SC capacity may become important for one's level of loneliness, e.g. with less impaired SC serving as a buffer against loneliness in SC-impaired participants. Consistent with precision psychiatry postulates (Williams, 2016), the findings of the current study stress the importance of embracing social cognitive heterogeneity in patients with schizophrenia while developing psychosocial interventions targeting loneliness in this clinical group. A recent large scale study focused solely on social cognitive processes found a significant difference in the outcome and clinical variables between clusters demonstrating varied SC impairment (Rocca et al., 2016). Similarly, decreased social functioning was found in a poorly-performing cluster in a study which utilized neuroimaging data for biophenotyping (Viviano et al., 2018). Here, we extend these findings by showing that even in the absence of differences in loneliness between normal-performing and SC-impaired clusters, different mechanisms may be associated with loneliness in each cluster of patients. Thus, planning individualized treatment needs to consider both general levels of SC capacity and specific profiles of SC abilities in each patient.

While the current set of analyses was well-powered and included a wide range of measures, some limitations of the current design should be noted. First, the cross-sectional design limits the ability to infer which factors may be predictors or consequences of loneliness in persons with schizophrenia. As extensively discussed in Okruszek et al. (2021), the relationship between social cognitive capacity and social functioning is clearly bidirectional. While most of the studies with clinical studies usually include cognitive capacity among predictors of social functioning, the reverse relationship can also be considered e.g. chronic loneliness and associated social stress may produce neurotoxic effects and reduce social cognitive capacity. It is possible that negative findings in the SC-NP cluster may stem from the limited variability of the social cognitive performance in this cluster. As evidenced by the Table 1, higher performance variance was observed in the SC-IMP compared to SC-NP cluster. The post-hoc power analysis revealed that with 82 participants in the sample only correlations of r> = 0.3 in magnitude could have been observed in this sample with 80% power at the $p = .05$. Thus, it remains possible that similar, albeit weaker, effects may be observed in the SC-NP cluster with a sufficiently large sample. However, lack of such findings in our previous study with a larger cohort ($n = 252$) of non-clinical participants suggest that the negative findings in the SC-IMP cluster cannot be attributed purely to the lack of the statistical power in the current sample. Additionally, as both patient samples were recruited as part of larger projects, only clinically stable patients were included in the samples. Given the intensive testing schedule in both projects, only relatively high functioning patients without marked interference from symptoms could have been included in the sample, which may explain the relatively overall strong test performance and high prevalence of the NP cluster in the current study. This issue may limit the generalizability of the current findings to less clinically stable patients. At the same time, several recent studies which have utilized clustering methods, observed similar rates of patients without marked social cognitive impairments (e.g. ~65%, Hajdúk et al., 2018; 56%, Hajdúk et al., 2022) as the current study (56%). It is also worth noting that overlap between some of the tasks included in the SCOPE battery and constructs that they measure can be discussed. E.g. while primarily devised as a mentalizing task, RMET is believed to be a mixture of emotion recognition and theory of mind processes and due to its form, to entail both basic social cue processing and complex mental state inference (this issue has been discussed, e.g., in Mitchell & Phillips, 2015). RMET has also been heavily criticized for overly relying on a participant's vocabulary and educational attainment (Dodell-Feder et al., 2020), which confounds its assessment of mentalizing ability. In addition, in our recent study with a healthy population (Okruszek et al., 2021), despite our initial assumption, we had to include RMET among the indicators of 'lower-level processing of social cues'. We hypothesize that this effect may explain why tasks more clearly associated with the social cognitive constructs (Hinting task- mentalizing, PENN ER40 - emotion recognition) were found to be significantly associated with loneliness in the SC-IMP cluster, while RMET was not.

Furthermore, the effects observed in the current study can be due to some latent variable, which exacerbates both social cognitive deficits and loneliness in patients (e.g., objective social isolation). Second, because the current study merged data from two different sites, it is important to note that two different versions of the UCLA loneliness scale were administered in each study and shifting the response range by adding 20 points could bias the results in the UNC sample. Despite the consistency of findings across our samples which suggests robustness and replicability, future research with congruent methodology should be considered. Loneliness is also known to be a significant problem for patients with other psychotic disorders, so future studies should also extend their scope e.g., by including patients with depression with psychotic features or bipolar disorder. Furthermore, while we utilized an extensive battery to investigate SC capacity, future studies should also include assessment of factors linked to social motivation and cognitive biases which may also be of great importance for loneliness in individuals with schizophrenia (M. F. Green et al., 2018), especially given the fact that the SC predictors accounted only for 9% of loneliness variance in the SC-IMP cluster.

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