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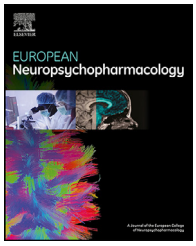

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Theory of Mind and social functioning among neuropsychiatric disorders: A transdiagnostic study

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Abstract
Social dysfunction is commonly present in neuropsychiatric disorders of schizophrenia (SZ) and Alzheimer's disease (AD). Theory of Mind (ToM) deficits have been linked to social dysfunction in disease-specific studies. Nevertheless, it remains unclear how ToM is related to social functioning across these disorders, and which factors contribute to this relationship. We investigated transdiagnostic associations between ToM and social functioning among SZ/AD patients and healthy controls, and explored to what extent these associations relate to information processing speed or facial emotion recognition capacity. A total of 163 participants were included (SZ: n=56, AD: n=50 and age-matched controls: n=57). Social functioning was assessed with the Social Functioning Scale (SFS) and the De Jong-Gierveld Loneliness Scale (LON). ToM was measured with the Hinting Task. Information processing speed was measured by the Digit Symbol Substitution Test (DSST) and facial emotion recognition capacity by the facial emotion recognition task (FERT). Case-control deficits in Hinting Task performance were larger in AD (r_{rb} = -0.57) compared to SZ (r_{rb} = -0.35). Poorer Hinting Task performance was transdiagnostically associated with the SFS ($\beta_{\text{Hinting-Task}}$ = 1.20, $p<0.01$) and LON ($\beta_{\text{Hinting-Task}}$ = -0.27, $p<0.05$). DSST, but not FERT, reduced the association between the SFS and Hinting Task performance, however the association remained significant ($\beta_{\text{Hinting-Task}}$ = 0.95, $p<0.05$). DSST and FERT performances did not change the association between LON and Hinting Task performance. Taken together, ToM deficits are transdiagnostically associated with social dysfunction and this is partly related to reduced information processing speed.

1. Introduction

Social dysfunction is broadly defined as a reduced capacity of integrating behavioural, cognitive and affective skills that are important for social interactions, which subsequently lead to behaviour that within the social context is judged by others as inflexible, rude or inappropriate (Porcelli et al., 2019). Social dysfunction is often observed as an early common symptom in various neuropsychiatric disorders, including – but not limited to - schizophrenia (SZ) and Alzheimer's disease (AD) (Porcelli et al., 2019; Saris et al., 2022). From a clinical point of view, identifying individuals with social dysfunction is of paramount importance since it greatly influences their quality of life and mortality risk, and it also places a large burden on caregivers (Hawkley & Cacioppo, 2010; Holt-Lunstad et al., 2010; Dickerson, 2015). However, despite the large burden of social dysfunction on patients and their caregivers, potential driving forces behind social dysfunction in neuropsychiatric disorders have not been examined extensively.

While SZ and AD patients differ in clinical symptoms, there may be groups of patients with similar social dysfunction across SZ and AD (Saris et al., 2022). Examining which mechanisms contribute to or increase the risk of social dysfunction may result in useful new transdiagnostic insights (Kas et al., 2019). In recent years, it has become clear that the diagnostic categories based on clinical consensus fail to cover the clinical heterogeneity within and across disorders and in most cases do not reflect underlying disease mechanisms (Insel et al., 2010; Kas et al., 2019). The Research Domain criteria (RDoC) framework presents a new paradigm which advocates an understanding of clinical phenomena and their neurobiobehavioural basis that may span multiple disorders (Insel et al., 2010). In the end, this may improve precision medicine by classifying mental disorders based on the pathophysiology (Insel et al., 2010). In view of the RDoC framework, the Psychiatric Ratings using Intermediate Stratified Markers (PRISM) consortium focuses on the shared and unique biological basis of social dysfunction in two diverse neuropsychiatric disorders - SZ and AD - to ultimately accelerate the discovery and development of novel treatments for these disorders (Kas et al., 2019).

One of the driving forces behind social dysfunction are impairments in social cognition. This could be defined as the set of cognitive processes, such as Theory of Mind (ToM), that are essential for social interactions (Porcelli et al., 2019). ToM is the ability to notice and interpret one's own, as well as other's intentions, emotions and beliefs, and may be impaired in both SZ and AD (Green et al., 2015; Moreau et al., 2016; Lucena et al., 2020; Kessels et al., 2021). Some studies have linked ToM deficits to social dysfunction in either SZ or AD (Roncone et al., 2002; Bora et al., 2006; Brown et al., 2014; Dodell-Feder et al., 2014a; Dodell-Feder et al., 2014b; El Haj et al., 2015). However, how ToM deficits are related to social dysfunction across these disorders has not been investigated. ToM can be measured with a large variety of instruments that assesses different parts of the concept. One of the most widely used instruments to assess ToM is the Hinting Task, which has been linked to so-

cial functioning in SZ (Corcoran et al., 1995; Bora et al., 2006; Brown et al., 2014; Eddy, 2019). The Hinting Task measures the ability to infer intent from indirect speech requests and, therefore, assesses the more cognitive aspects of ToM ('reading between the lines') (Corcoran et al., 1995).

How could ToM impact social functioning? There are at least two important processes involved: information processing speed and facial emotion recognition capacity. Adequate social functioning requires real time perception of social information from speech, body language or facial expressions, for which basic general cognitive functioning including information processing speed must be intact and, more particularly, visual recognition of facial emotions must be adequate (Adolphs, 2009; Charlton et al., 2009; Ayesa-Arriola et al., 2016). Information processing speed, which is reduced in both SZ and AD, has a tight association with higher order cognitive processes such as social functioning (Nestor et al., 1991; van Hooren et al., 2008; Ayesa-Arriola et al., 2016; Haworth et al., 2016; Deckler et al., 2018; Lindgren et al., 2018; Sjolie et al., 2020). Additionally, facial emotion recognition capacity is often observed to be reduced in both SZ and AD (Green et al., 2015; Jani & Kasparek, 2018; Torres Mendonca De Melo Fadel et al., 2019; Lee et al., 2020; de la Torre-Luque et al., 2021). Previously, our consortium showed that facial emotion recognition capacity was associated with social dysfunction across SZ and AD (de la Torre-Luque et al., 2021). As facial emotion recognition capacity is important for the perception of social information, it is possible that it may also play a role in potential associations between ToM and social functioning (Adolphs, 2009).

The current study aimed to investigate the transdiagnostic relationship between ToM and social functioning among SZ/AD patients and healthy controls. We set out to explore to what extent these potential associations between ToM and social functioning relate to information processing speed or facial emotion recognition capacity. We hypothesize that ToM is transdiagnostically associated with social functioning and that these associations are partly dependent on information processing speed and facial emotion recognition capacity. This study will contribute to the understanding of the factors that are related to social dysfunction across neuropsychiatric disorders.

2. Experimental procedures

2.1. Participants

Data for the current study were derived from the EU-funded PRISM Project, which examines the transdiagnostic value of social dysfunction and its biological and behavioural correlates among individuals with SZ (n=56), probable AD (n=52), and two age-matched healthy control groups ($SZ_{controls}$: n=29, $AD_{controls}$: n=28) (Kas et al., 2019). All data used were collected at Assessment visit 1 of the PRISM study. Two participants (AD patients) did not complete social functioning questionnaires, leaving 163 participants for analyses.

Participants were recruited between July 2017 and March 2019 from five different recruiting sites in Spain (Hospital General Universitario Gregorio Marañón and Hospital Universitario de La Princesa) and the Netherlands (University Medical Center Utrecht, VU University Medical Center Amsterdam and Leiden University Medical Center). The study was approved by the Ethics Review Board of corresponding countries and by local review boards of all participating centers. All participants provided verbal and written informed consent. Rationale and implementation for the PRISM study is described in depth elsewhere (Bilderbeck et al., 2019; Kas et al., 2019; van der Wee et al., 2019).

2.2. In- and exclusion criteria

SZ patients were eligible if they had a) a diagnosis of SZ (confirmed using the Mini-International Neuropsychiatric Interview (MINI)), b) a maximum of 15-year disease duration since diagnosis, c) an age between 18-45 years, and d) a score of $\leq$22 on the 7-item positive subscale of the positive and negative syndrome scale (PANSS) to rule out an active psychotic episode hampering adequate study participation (Kay et al., 1987; Bilderbeck et al., 2019). SZ patients were excluded when they were a danger to themselves or others, as judged by the clinician.

AD patients were eligible if they had: a) a diagnosis of probable AD (meeting the National Institute on Aging and the Alzheimer's Association criteria), b) a Mini-Mental State Examination (MMSE) score between 20-26 (indicating mild AD), and c) an age between 50-80 years (Folstein et al., 1975; Tombaugh & McIntyre, 1992; Jack et al., 2018). Multiple strokes, either based on clinical judgement, medical history or imaging results were exclusion criteria for the AD patient group.

For both the SZ and AD patient groups, additional exclusion criteria were: a) a diagnosis of a current severe Major Depressive Disorder DSM-IV diagnosis (as assessed with the MINI and with a Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR) $\geq$16), b) a diagnosis of any other *primary* psychiatric diagnosis that required intervention, c) alcohol or drug abuse/dependence within the previous 3 years (as assessed with the MINI), d) severe Parkinsonism as a consequence of antipsychotic medication (as assessed with a score $\geq$4 on the Extrapyramidal Symptom Rating Scale), e) unstable comorbid somatic disorders potentially affecting the central nervous system (CNS), and f) unstable use of medication that could affect the CNS (e.g. started or changed dosage within last 8 weeks) (Sheehan et al., 1998; Rush et al., 2003).

The $SZ_{controls}$ and $AD_{controls}$ were matched on sex and age with the SZ (between 18-45 years) and AD (between 50-80 years) groups, respectively. Exclusion criteria for the control groups were: a) a history of psychiatric Axis-I disorder (as confirmed by the MINI) or neurological disease associated with cognitive impairment, b) mild or more severe depression (score >5 on the QIDS-SR), and c) current or prior use of antidepressant or anxiolytic medication including benzodiazepines, or other prescribed medication in the last 6 weeks that may affect the CNS.

2.3. Demographics and clinical characteristics

A semi-structured interview on sociodemographic and medical data was conducted (i.e., age, sex, years of education). Cognitive dysfunction was estimated in AD patients using the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-cog) which includes 13 tasks involving both subject-completed test and observer-based assessments such as word recall, naming objects, and orientation (Rosen et al., 1984). Current states of positive and negative symptoms in SZ patients were measured using the PANSS (Kay et al., 1987).

2.4. Social dysfunction indicators

Different instruments were used to measure social dysfunction. The Social Functioning Scale (SFS) (Birchwood et al., 1990) is a self-rated questionnaire consisting of seven subscales; social withdrawal, interpersonal functioning, independence-competence, independence-performance, recreational activities, prosocial activities, and employment. The subscale 'employment' was excluded, since most participants were retired in the AD and $AD_{controls}$ group introducing a bias as confirmed by the significant association with age and in line with reporting in a previous study (Morejon & G-Boveda, 2000). The total SFS score was used as the outcome measure in the analyses. A lower SFS score indicates more social dysfunction. Additionally, perceived loneliness was assessed with the 11-item de Jong-Gierveld Loneliness Scale (LON) (de Jong-Gierveld, 1987). A higher score indicates more perceived loneliness.

2.5. Theory of mind (ToM)

ToM was measured using the Hinting Task, a pen-and-paper dialogue based interview that measures higher-order social cognition (Corcoran et al., 1995). Ten short stories were told in which one subtle and implicit message (a 'hint') is expressed by one person to another in each story. The subject had to identify the indirect message when first asked. If the answer was correct, 2 points were given. However, if the answer was wrong, a cue was given and the subject was asked a second question for half the points compared to the unaided question. Therefore, a total score can range from 0 to 20. A lower score implicates a decreased capability in mentalising and thus a lower ToM. The Hinting Task has strong psychometric properties and links to functional outcomes in SZ, but has not been investigated in AD (Pinkham et al., 2016).

2.6. Information processing speed and facial emotion recognition

Information processing speed was measured using the digital version of the Digit Symbol Substitution Test (DSST) which involves matching symbols to numbers according to a certain key (Jaeger, 2018). The used outcome score is constructed by adding the number of correctly coded symbols within 90 seconds. DSST performance links to the ability to perform activities of daily living (Jaeger, 2018).

The facial emotion recognition task (FERT) is a computer-generated task that requires participants to interpret and categorise briefly displayed (500 ms) emotional expressions (happiness, sadness, fear, disgust, surprise, anger, or neutral) (Montagne et al., 2007). The emotions are displayed at 10 different intensities (10% to 100% in steps of 10%). The endpoint of the FERT task was the accuracy rate (expressed as a percentage) for all emotions. The FERT task has effectively been administered in various clinical samples, including SZ and AD, and is able to detect subtle differences between healthy subjects, showing the robustness of this task (Montagne et al., 2005; Montagne et al., 2007; Catalan et al., 2016; Uhlmann et al., 2018; Kessels et al., 2021).

2.7. Statistical analyses

General demographic and clinical characteristics of the four study groups (SZ, AD, $SZ_{controls}$, $AD_{controls}$) were described using χ^2 for dichotomous variables and Student's t-tests for continuous variables, or in case of violating assumptions of parametric testing, the Mann-Whitney U test. Effect sizes were estimated by calculation rank-biserial correlation coefficients (r_{rb}), comparing Hinting Task performance in patient groups to their matched controls.

Linear regression analyses were conducted to study the transdiagnostic relationship between Hinting Task performance (the independent variable) and SFS or LON scores (the dependent variables) among SZ/AD patients and healthy controls, while adjusting for age, sex, years of education and country. Here a model rationale was followed by first assessing whether the potential associations between Hinting Task performance and SFS or LON scores were dependent on disease status or patient status. Disease status and patient status were dummy variables (coded: disease status: SZ/AD=0, $SZ_{controls}$/$AD_{controls}$=1 & patient status: SZ=0, AD=1) that were included as interaction-effect terms with Hinting Task performance. These dummy variables were excluded from the models if associations between Hinting Task performance and SFS or LON scores did not depend on disease status and patient status. A post hoc sensitivity analysis was performed to examine whether the potential association between Hinting Task performance and SFS score was not driven by a specific SFS subscale.

We further explored to what extent the potential associations between Hinting Task performance and SFS or LON scores were independent of DSST or FERT. Firstly, Spearman correlations described associations between these measures in the overall sample. Subsequently, we included DSST and FERT as independent variables in the models that described the transdiagnostic relationship between Hinting Task performance and the total SFS score and LON.

All analyses were conducted using RStudio 1.1.463, and a two-tailed significance level of $p < 0.05$ was considered statistically significant.

3. Results

Table 1 shows the demographics and clinical characteristics of the study participants. The patient groups were age- and sex matched to their respective controls. The majority of SZ patients used antipsychotics (89.3%), with some also using an antidepressant (19.6%). Nearly half (46%) of the AD patients used AD-specific medication (e.g. acetylcholinesterase and/or NMDA receptor antagonist), while some also used an antidepressant (16.0%). SZ and AD patients had less years of education compared to $SZ_{controls}$. In SZ, the mean current positive and negative symptoms measured with the PANSS were, respectively, 11.0 (SD $\pm$ 3.4) and 14.6 (SD $\pm$ 6.2), indicating mild clinical symptoms. Moreover, the AD group had a mean ADAS-cog of 26.9 (SD $\pm$7.2), which indicates mild dementia symptomatology. SZ patients had lower total SFS scores and higher LON scores compared to all other groups. Furthermore, AD patients had lower total SFS scores compared to the control groups, while their LON scores were similar to $AD_{controls}$. Performance on the Hinting Task, DSST and FERT was lower in the patient groups compared to their controls and lower in AD compared to SZ. Fig. 1 shows the distribution of Hinting Task performance in each study group and the effect sizes for the differences between patient groups and controls. The effect size comparing patient groups and controls was larger in AD (r_{rb} = -0.57) compared to SZ (r_{rb} = -0.35).

To investigate whether Hinting Task performance was transdiagnostically associated with SFS and LON scores in our sample, we first investigated whether these associations differed by disease or patient status. Table 2 shows the as-

Table 1 Baseline characteristics by study group.

	Schizophrenia patients (SZ) n=56	Younger healthy controls (SZc) n=29	Alzheimer's disease patients (AD) n=50	Older healthy controls (ADc) n=28	Pairwise differences
Demographics					
Age, median years (Q1-Q3)	29.5 (26.0 - 36.0)	28.0 (22.0 - 33.0)	69.5 (64.0 - 73.0)	67.0 (63.0 - 73.0)	
Sex, (% female)	28.6%	41.4%	44.0%	46.4%	
Education, median years (Q1-Q3)	15.0 (12.8 - 16.3)	17.0 (16.0 -19.0)	15.5 (10.3 - 19.8)	16.5 (14.0 - 20.0)	SZc > SZ & AD
Country (% Spain)	39.3%	48.3%	42.0%	25.0%	
Psychotropic medication					
Antipsychotic (%)	89.3%	0.0%	4.0%	0.0%	
Antidepressant (%)	19.6%	0.0%	16.0%	0.0%	
Acetylcholinesterase inhibitor and/or NDMA receptor antagonist (%)	0.0%	0.0%	46.0%	0.0%	
Disease characteristics					
Positive symptoms, mean PANSS (SD)	11.0 (3.4)	NA	NA	NA	
Negative symptoms, mean PANSS (SD)	14.6 (6.2)	NA	NA	NA	
AD severity, mean ADAS-cog (SD)	NA	NA	26.9 (7.2)	NA	
Social functioning					
Total SFS score, median (Q1-Q3)	110 (103 - 116)	126 (123 - 128)	118 (112 - 122)	126 (123 - 130)	SZ < all other groups; AD < ADc & SZc
LON, median (Q1-Q3)	4.50 (1.00 - 8.00)	0 (0 - 1.00)	1.00 (0 - 3.00)	0 (0 - 2.25)	SZ > all other groups; AD > SZc
Cognitive performance					
Theory of Mind, median Hinting Task (Q1-Q3)	18.0 (17.0 - 20.0)	20.0 (19.0 - 20.0)	17.0 (15.0 - 18.0)	19.0 (18.0 - 20.0)	SZc > SZ & ADc; SZ & ADc > AD
Information processing speed, median DSST (Q1-Q3)	34.0 (30.8 - 38.0)	42.0 (38.0 - 47.0)	14.5 (9.0 - 18.0)	24.0 (21.0 - 32.0)	SZc > SZ > ADc > AD
Facial emotion recognition accuracy, median FERT (Q1-Q3)	56.8 (48.9 - 66.8)	66.5 (61.4 - 68.9)	35.9 (24.1 - 44.3)	51.5 (44.9 - 57.9)	SZc > SZ > ADc > AD

PANSS = Positive and Negative Syndrome Scale, ADAS-cog = Alzheimer's Disease Assessment Scale – Cognitive subscale, SFS = Social Functioning Scale, LON = de Jong-Gierveld Loneliness Scale, DSST = Digit Symbol Substitution Test. Pairwise comparisons were performed using the Student's t-test or Mann-Whitney U test for continuous variables or χ^2 for binary outcomes. Group sample sizes of facial emotion recognition accuracy measured with the facial emotion recognition task were SZ: n=55, SZc: n=28, AD: n=46 and ADc: n=28. A two-tailed significance level of $p < 0.05$ was considered statistically significant.

Table 2 Associations between Hinting Task performance and social functioning indicators with and without including disease status or patient status (n = 163).

	Total SFS score		LON	
	B	*SE*	B	*SE*
Overall model, not adjusting for disease or patient status				
Hinting Task	**1.20****	0.38	**-0.27***	0.13
Including disease status				
Interaction effect (Hinting Task x disease status)	0.92	0.94	-0.28	0.37
Including patient status				
Interaction effect (Hinting Task x patient status)	0.54	0.84	-0.16	0.32

Adjusted for age, sex, years of education and country. Disease status was a dummy variable coded SZ/AD = 0 and $SZ_{controls}/AD_{controls} = 1$. Patient status was a dummy variable coded SZ = 0 and AD = 1. SFS = Social Functioning Scale, LON = de Jong-Gierveld Loneliness Scale. * p-value < 0.05, ** p-value < 0.01.

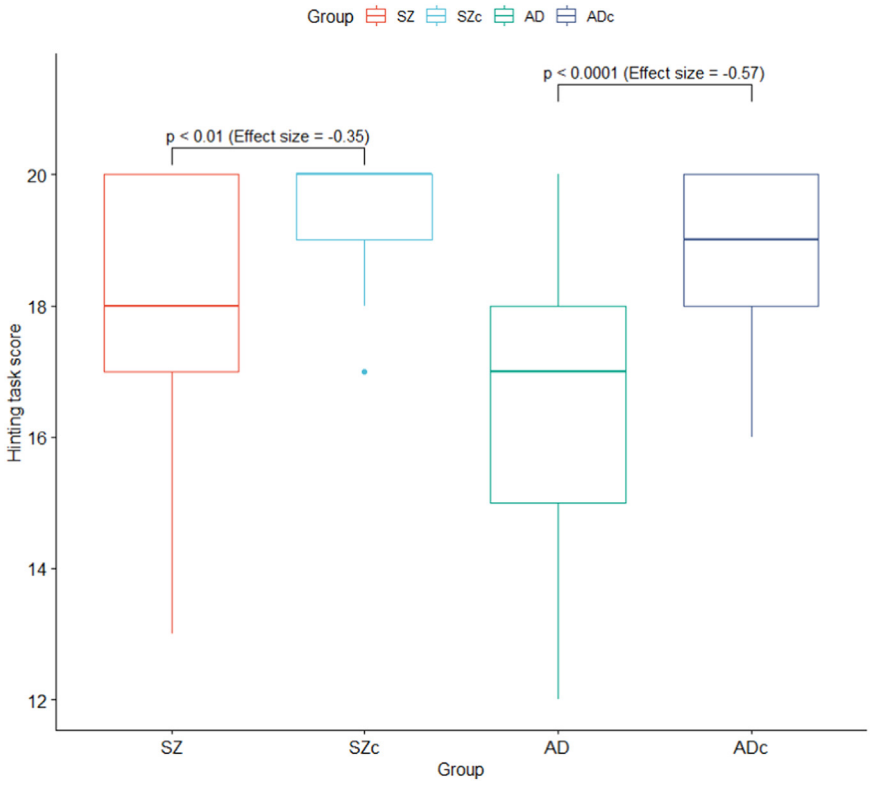

Fig. 1 Boxplots of Hinting Task scores of the four study groups.
Red line = Schizophrenia (SZ), Blue line = Schizophrenia healthy controls (SZc), Green line = Alzheimer's disease (AD), Purple line = Alzheimer's disease healthy controls (ADc). Effect sizes were calculated following rank-biserial correlation for estimated differences between patient groups and controls.

sociations between Hinting Task performance and SFS and LON scores with and without including interaction-effect terms of disease status and patient status in the linear regression models. These interaction-effect terms were not significant in the models (Table 2). Thus, the potential associations between Hinting Task performance and SFS and LON scores did not depend on disease status or patient status. Therefore, we chose to further examine the transdiagnostic associations in the overall sample. Hinting Task performance was associated with SFS (β = 1.20, p<0.01) and LON scores (β = -0.27, p<0.05). The association between Hinting Task performance and the total SFS score was not driven by a specific subscale, as Hinting Task performance showed a significant positive loading on multiple SFS subscales (Interpersonal functioning, independence-competence, independence-performance and recreational activities) (sTable 1).

We further explored whether the transdiagnostic associations between Hinting Task performance and the total SFS score and LON were independent of DSST and FERT. Table 3 shows the intercorrelation matrix of these measures in the overall sample. The total SFS score was weakly correlated with DSST (ρ = 0.10, p<0.01) and FERT (ρ = 0.11, p<0.01). LON was not correlated with either DSST or FERT. Furthermore, DSST and FERT were strongly intercorrelated (ρ = 0.64, p<0.001) and were both moderately correlated with the Hinting Task (ρ = 0.38 and ρ = 0.47, p <0.001, respectively).

Table 3 Spearman correlations between social functioning indicators and cognitive performance in the overall sample.

	Total SFS	LON	Hinting task	DSST	FERT
Total SFS	1	-	-	-	-
LON	-0.55***	1	-	-	-
Hinting Task	0.23***	-0.10**	1	-	-
DSST	0.10**	0.05	0.38***	1	-
FERT	0.11**	-0.02	0.47***	0.64***	1

Correlations are corrected for age, sex, years of education and country. SFS = Social Functioning Scale, LON = de Jong-Gierveld Loneliness Scale, DSST = Digit Symbol Substitution Test, FERT = facial emotion recognition task. * p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001. Overall sample size is n=163 and FERT sample size is n=158.

Finally, we included DSST and FERT as independent variables in the models that described the transdiagnostic association between Hinting task performance and SFS and LON scores. In this multivariate model, DSST, but not FERT, remained to show a positive association with SFS score (β = 0.23, p<0.01) and its inclusion reduced the coefficient of Hinting Task performance from β = 1.20 (p<0.01) to β = 0.95 (p<0.05) (Table 4). FERT and DSST were not significantly associated with LON in the multivariate model and did not change the coefficient of Hinting Task performance with LON (Table 4).

Table 4 Association between social functioning indicators and Hinting Task performance after controlling for information processing speed or facial emotion recognition capacity.

	Total SFS		LON	
	B	*SE*	B	*SE*
Basic model				
Hinting Task	**1.20****	0.38	**-0.27***	0.13
Additionally including DSST				
Hinting Task	**0.95***	0.39	**-0.27***	0.14
DSST	**0.23****	0.08	0.01	0.03
Additionally including FERT				
Hinting Task	**1.13***	0.44	**-0.30***	0.15
FERT	0.03	0.04	0.01	0.01

Adjusted for age, sex, years of education and country. SFS = Social Functioning Scale, LON = de Jong-Gierveld Loneliness Scale, DSST = Digit Symbol Substitution Test, FERT = facial emotion recognition test. * p-value < 0.05, ** p-value < 0.01.

4. Discussion

In the current study, we investigated whether ToM is transdiagnostically associated with social functioning among SZ/AD patients and healthy controls, and to what extent these associations related to information processing speed or facial emotion recognition capacity. We found that higher ToM performance is associated with better social functioning across groups. Information processing speed and facial emotion recognition capacity were both weakly correlated with social function and moderately correlated to ToM. The association between ToM performance and social functioning was partly dependent of information processing speed, but independent of facial emotion recognition capacity. Our findings indicate a role for cognitive aspects of ToM in social functioning independent of diagnostic status and facial emotion recognition capacity, but partly dependent of information processing speed.

Our study clearly shows that ToM deficits are associated with social dysfunction. Interaction effects of disease status and patient status with ToM were not observed, indicating that these associations were generally present in our sample and not specific for one disease group. To our knowledge, no prior study has examined transdiagnostic ToM associations with social functioning within a sample of neuropsychiatric patients and healthy controls. Nevertheless, prior studies have found associations between ToM and social functioning in either SZ or AD (Roncone et al., 2002; Bora et al., 2006; Brown et al., 2014; Dodell-Feder et al., 2014a; Dodell-Feder et al., 2014b; El Haj et al., 2015). The instruments used to assess ToM and social functioning were, however, different across these studies (Roncone et al., 2002; Bora et al., 2006; Brown et al., 2014; Dodell-Feder et al., 2014a; Dodell-Feder et al., 2014b; El Haj et al., 2015). In light of this, we show that ToM deficits, measured with the widely-used Hinting Task, is also related to social dysfunction across these disorders by using two social functioning indicators (SFS and LON). These social functioning indicators were moderately correlated, suggesting that they assess partly different aspects of social functioning (Saris et al., 2022). Therefore, ToM seems important both in the more behavioural aspects of social functioning (measured with the SFS) and the more subjective experience of social functioning (i.e. loneliness as measured with LON). Additionally, post-hoc sensitivity analyses showed that ToM associations with social functioning were not driven by specific subscales of the SFS, as ToM was found to be associated with multiple SFS subscales. Besides, it is worth mentioning that our consortium previously showed that disease severity was not associated with the total SFS score in SZ and AD patients, while LON scores were only weakly correlated with positive SZ symptoms (Saris et al., 2022). This indicates that disease severity might not have impacted the association between ToM and social functioning. Furthermore, the majority of the patients in the current study were on psychotropic drug treatment. A recent systematic review found that compared to controls, SZ patients performed less well on social cognition tasks, whether or not they were on antipsychotics (Haime et al., 2021). Moreover, their research showed inconclusive results on the effect of psychotropic medication on social cognition/functioning (Haime et al., 2021). Therefore, it may be unlikely that medication could have played an important role in the association found between ToM deficits and social dysfunction within the current study. Future research is needed to confirm and generalize the initial cross-disorder findings by including other aspects of social functioning, such as social anhedonia and social anxiety, and including other disorders characterized by severe social dysfunction (e.g. major depressive disorder).

We found that the relationship between ToM and social functioning (measured with the SFS) across SZ/AD patients and healthy controls partly depends on information processing speed. Information processing speed was also associated with ToM in the overall sample. In line with this, a prior study showed that age-related ToM deficits are fully mediated by cognitive functioning including information processing speed, which altogether may indicate that lower scores on the Hinting Task may be at least partly explained by the task's cognitive demands rather than mentalising impairments (Charlton et al., 2009). Thus, it may be possible that information processing speed mediated a part of the relationship between ToM and social functioning in our study. However, whether other aspects of cognitive function are also relevant in this relationship remains unknown. Findings from prior studies suggest that working memory may also be an important aspect (Bowie et al., 2008; Charlton et al., 2009; Couture et al., 2011; McQuade et al., 2013; Spunt & Lieberman, 2013; Porcelli et al., 2019). Nevertheless, the mentalising aspect of the Hinting Task still seems to be important in the relationship between ToM and social functioning, since information processing speed only explained a part of this relationship. Future research could examine which brain networks are involved in this relationship to support our results and to further clarify the role of mentalising capacity and cognitive function in social dysfunction across neuropsychiatric disorders.

Contrary to our expectations, we observed that facial emotion recognition capacity did not change the association between cognitive aspects of ToM and social functioning. Nevertheless, prior studies have implicated facial emotion recognition capacity as a key factor for the perception of social information (Adolphs, 2009). Furthermore, our consortium previously showed that social withdrawal was associ-

ated with better facial emotion recognition capacity across SZ and AD, indicating a hypervigilance to social threat in these patients (de la Torre-Luque et al., 2021). Taken together, while facial emotion recognition capacity and cognitive aspects of ToM are correlated and are both part of social cognition, they may potentially act differently on social functioning. This assumption might be addressed in future studies by examining potential associations between facial emotion recognition/ ToM and social functioning using a wider variety of instruments to assess these broad concepts. Additionally, while investigating a potential hypervigilance to social threat in neuropsychiatric patients was beyond the scope of the current study, it would be interesting to examine whether higher ToM performance is associated with more social withdrawal in these neuropsychiatric patients specifically. These associations might then be mediated by insight of the negative social consequences of their illness, as higher clinical insight is linked to higher ToM in SZ (Bora, 2017).

By focusing on the shared biological basis of social dysfunction in SZ and AD, it is possible to gain new insights into social dysfunction across these disorders, which may accelerate the discovery and development of new treatments for these disorders. Previously, our consortium showed that social dysfunction represents a transdiagnostic domain of SZ and AD (Saris et al., 2022). By showing that this domain is associated with ToM deficits, we may provide directions for future personalized treatment irrespective of diagnostic status (Kas et al., 2019). Some interventions to improve ToM performance are already available, of which some might also have an effect on social functioning outcomes, ranging from targeted ToM interventions (e.g. imitation treatment) to broad based non-ToM interventions (e.g. family-assisted Social Cognition Interaction Training) (Mazza et al., 2010; Tas et al., 2012; Vass et al., 2018; d'Arma et al., 2021). However, despite our findings and their implications, our study had some limitations that need to be discussed. First, our analyses were cross-sectional, thereby not allowing causal inferences. Future studies should aim to examine whether decreased ToM results in social dysfunction over time across neuropsychiatric disorders. Second, our consortium previously showed that AD patients may underreport their perceived social disability, as they self-reported their social abilities equal to their matched controls, even though their close-relatives rated the patients social abilities to be severely impaired (Saris et al., 2022). To overcome potential self-evaluation bias, more objective methods to quantify social functioning may be used in the future. For example, BeHapp smartphone technology may objectively measure social functioning by passively monitoring social explorations and communications (Eskes et al., 2016; Jongs et al., 2020; Jongs et al., 2022). Third, while the instruments to assess social functioning and ToM are easily accessible, reliable and have proven importance in neuropsychiatric disorders, they are simplifications of complex domains (de Jong-Gierveld, 1987; Birchwood et al., 1990; Corcoran et al., 1995; Bora et al., 2006; Brown et al., 2014; Pinkham et al., 2016; Jaeger, 2018; Uhlmann et al., 2018; Eddy, 2019; Kessels et al., 2021). Fourth, as the Hinting task measures the more cognitive aspects of ToM, it cannot be excluded that facial emotion recognition could influence potential associations between perceptual emotional aspects of ToM and social function (Corcoran et al., 1995). Fifth, the Hinting Task showed ceiling effects, especially in the control groups, and variation in Hinting Task and SFS/LON scores was lower in subgroups compared to the overall sample. While this should not have affected our main findings, it might have resulted in less power to find interaction effects of disease status and patient status. Finally, Hinting Task performance depends heavily on verbal cognition, hence potential deficits in verbal cognition may have contributed to the transdiagnostic association between ToM and social functioning (Corcoran et al., 1995). Future research should address the role of verbal skills in social functioning across neuropsychiatric disorders, for example by the use of speech elicitation tasks (Petti et al., 2020).

In summary, the current study shows that ToM is transdiagnostically associated with social functioning among SZ/AD patients and healthy controls and this partly depends on information processing speed. These findings could serve as a point of departure for interventions that improve social dysfunction irrespective of diagnosis by targeting ToM abilities, while taking cognitive deficits into account.

5. Contributors

SB performed the analyses. SB and WK wrote the main manuscript. SB, TS, WK, YALP and BP conceived the study and interpreted the data. LMR, IMJS and AVC conducted the study protocols. YALP, NVW, ACB, GRD, IWVR, CA, MJK and BP were involved in study supervision. All the authors reviewed the final manuscript.

Conflicts of Interest

G.R. Dawson is co-owner and employee of P1vital LTD who provide the FERT and the digital version of the DSST for this study.

A. Bilderbeck is an employee of P1vital LTD who provide the FERT and the digital version of the DSST for this study.

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All other authors declare that they have no conflicts of interest.

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Supplementary materials

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References

Adolphs, R., 2009. The social brain: neural basis of social knowledge. Annu. Rev. Psychol. 60, 693–716.

Ayesa-Arriola, R., Setien-Suero, E., Neergaard, K.D., Ferro, A., Fatjo-Vilas, M., Rios-Lago, M., Otero, S., Rodriguez-Sanchez, J.M., Crespo-Facorro, B., 2016. Evidence for trait related theory of mind impairment in first episode psychosis patients and its relationship with processing speed: a 3 year follow-up study. Front. Psychol. 7, 592.

Bilderbeck, A.C., Penninx, B., Arango, C., van der Wee, N., Kahn, R., Winter-van Rossum, I., Hayen, A., Kas, M.J., Post, A., Dawson, G.R., 2019. Overview of the clinical implementation of a study exploring social withdrawal in patients with schizophrenia and Alzheimer's disease. Neurosci. Biobehav. Rev. 97, 87–93.

Birchwood, M., Smith, J., Cochrane, R., Wetton, S., Copestake, S., 1990. The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. Br. J. Psychiatry 157, 853–859.

Bora, E., 2017. Relationship between insight and theory of mind in schizophrenia: A meta-analysis. Schizophrenia Res. 190, 11–17.

Bora, E., Eryavuz, A., Kayahan, B., Sungu, G., 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.

Bowie, C.R., Leung, W.W., Reichenberg, A., McClure, M.M., Patterson, T.L., Heaton, R.K., Harvey, P.D., 2008. Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. Biol. Psychiatry 63, 505–511.

Brown, E.C., Tas, C., Can, H., Esen-Danaci, A., Brune, M., 2014. A closer look at the relationship between the subdomains of social functioning, social cognition and symptomatology in clinically stable patients with schizophrenia. Compr. Psychiat. 55, 25–32.

Catalan, A., de Artaza, M.G., Bustamante, S., Orgaz, P., Osa, L., Angosto, V., Valverde, C., Bilbao, A., Madrazo, A., van Os, J., Gonzalez-Torres, M.A., 2016. Differences in facial emotion recognition between first episode psychosis, borderline personality disorder and healthy controls. PLoS One 11.

Charlton, R.A., Barrick, T.R., Markus, H.S., Morris, R.G., 2009. Theory of mind associations with other cognitive functions and brain imaging in normal aging. Psychol. Aging 24, 338–348.

Corcoran, R., Mercer, G., Frith, C.D., 1995. Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. Schizophr. Res. 17, 5–13.

Couture, S.M., Granholm, E.L., Fish, S.C., 2011. A path model investigation of neurocognition, theory of mind, social competence, negative symptoms and real-world functioning in schizophrenia. Schizophr. Res. 125, 152–160.

d'Arma, A., Isernia, S., Di Tella, S., Rovaris, M., Valle, A., Baglio, F., Marchetti, A., 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.

de Jong-Gierveld, J., 1987. Developing and testing a model of loneliness. J. Pers. Soc. Psychol. 53, 119–128.

de la Torre-Luque, A., Viera-Campos, A., Bilderbeck, A.C., Carreras, M.T., Vivancos, J., Diaz-Caneja, C.M., Aghajani, M., Saris, I.M.J., Raslescu, A., Malik, A., Clark, J., Penninx, B., van der Wee, N., Rossum, I.W., Sommer, B., Marston, H., Dawson, G.R., Kas, M.J., Ayuso-Mateos, J.L., Arango, C., 2021. Relationships between social withdrawal and facial emotion recognition in neuropsychiatric disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 113, 110463.

Deckler, E., Hodgins, G.E., Pinkham, A.E., Penn, D.L., Harvey, P.D., 2018. Social Cognition and neurocognition in schizophrenia and healthy controls: intercorrelations of performance and effects of manipulations aimed at increasing task difficulty. Front. Psychiatry 9.

Dickerson, B.C., 2015. Dysfunction of social cognition and behavior. Continuum (Minneap Minn) 21, 660–677.

Dodell-Feder, D., DeLisi, L.E., Hooker, C.I., 2014a. Neural disruption to theory of mind predicts daily social functioning in individuals at familial high-risk for schizophrenia. Soc. Cogn. Affect. Neurosci. 9, 1914–1925.

Dodell-Feder, D., Tully, L.M., Lincoln, S.H., Hooker, C.I., 2014b. The neural basis of theory of mind and its relationship to social functioning and social anhedonia in individuals with schizophrenia. Neuroimage Clin. 4, 154–163.

Eddy, C.M., 2019. What do you have in mind? Measures to assess mental state reasoning in neuropsychiatric populations. Front. Psychiatry 10.

El Haj, M., Gely-Nargeot, M.C., Raffard, S., 2015. Destination memory and cognitive theory of mind in Alzheimer's disease. J. Alzheimers Dis. 48, 529–536.

Eskes, P., Spruit, M., Brinkkemper, S., Vorstman, J., Kas, M.J., 2016. The sociability score: app-based social profiling from a healthcare perspective. Comput. Hum. Behav. 59, 39–48.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.

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

Haime, Z., Watson, A.J., Crellin, N., Marston, L., Joyce, E., Moncrieff, J., 2021. A systematic review of the effects of psychiatric medications on social cognition. BMC Psychiatry 21.

Hawkley, L.C., Cacioppo, J.T., 2010. Loneliness matters: a theoretical and empirical review of consequences and mechanisms. Ann. Behav. Med. 40, 218–227.

Haworth, J., Phillips, M., Newson, M., Rogers, P.J., Torrens-Burton, A., Tales, A., 2016. Measuring information processing speed in mild cognitive impairment: clinical versus research dichotomy. J. Alzheimers Dis. 51, 263–275.

Holt-Lunstad, J., Smith, T.B., Layton, J.B., 2010. Social relationships and mortality risk: a meta-analytic review. PLoS Med. 7, e1000316.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am. J. Psychiatry 167, 748–751.

Jack Jr., C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R., 2018. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 14, 535–562.

Jaeger, J., 2018. Digit symbol substitution test: the case for sensitivity over specificity in neuropsychological testing. J. Clin. Psychopharm. 38, 513–519.

Jani, M., Kasparek, T., 2018. Emotion recognition and theory of mind in schizophrenia: a meta-analysis of neuroimaging studies. World J. Biol. Psychiatry 19, S86–S96.

Jongs, N., Jagesar, R., van Haren, N.E.M., Penninx, B., Reus, L., Visser, P.J., van der Wee, N.J.A., Koning, I.M., Arango, C., Sommer, I.E.C., Eijkemans, M.J.C., Vorstman, J.A., Kas, M.J., 2020. A framework for assessing neuropsychiatric phenotypes by using smartphone-based location data. Transl. Psychiatry 10, 211.

Jongs, N., Penninx, B., Arango, C., Ayuso-Mateos, J.L., van der Wee, N., Winter-van Rossum, I., Saris, I.M.J., van Echteld, A., Koops, S., Bilderbeck, A.C., Raslescu, A., Dawson, G.R., Sommer, B., Marston, H., Vorstman, J.A., Eijkemans, M.J.C., Kas, M.J., 2022. Effect of disease related biases on the subjective assessment of social functioning in Alzheimer's disease and schizophrenia patients. J. Psychiatric Res. 145, 302–308.

Kas, M.J., Penninx, B., Sommer, B., Serretti, A., Arango, C., Marston, H., 2019. A quantitative approach to neuropsychiatry: the why and the how. Neurosci. Biobehav. Rev. 97, 3–9.

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

Kessels, R.P.C., Waanders-Oude Elferink, M., van Tilborg, I, 2021. Social cognition and social functioning in patients with amnestic mild cognitive impairment or Alzheimer's dementia. J Neuropsychol 15, 186–203.

Lee, S.C., Liu, C.C., Kuo, C.J., Hsueh, I.P., Hsieh, C.L., 2020. Sensitivity and specificity of a facial emotion recognition test in classifying patients with schizophrenia. J. Affect. Disord. 275, 224–229.

Lindgren, M., Torniainen-Holm, M., Heiskanen, I., Voutilainen, G., Pulkkinen, U., Mehtala, T., Jokela, M., Kieseppa, T., Suvisaari, J., Therman, S., 2018. Theory of mind in a first-episode psychosis population using the Hinting Task. Psychiat. Res. 263, 185–192.

Lucena, A.T., Bhalla, R.K., Belfort Almeida Dos Santos, T.T., Dourado, M.C.N, 2020. The relationship between theory of mind and cognition in Alzheimer's disease: A systematic review. J. Clin. Exp. Neuropsychol. 42, 223–239.

Mazza, M., Lucci, G., Pacitti, F., Pino, M.C., Mariano, M., Casacchia, M., Roncone, R., 2010. Could schizophrenic subjects improve their social cognition abilities only with observation and imitation of social situations? Neuropsychol. Rehabil. 20, 675–703.

McQuade, J.D., Murray-Close, D., Shoulberg, E.K., Hoza, B., 2013. Working memory and social functioning in children. J. Exp. Child. Psychol. 115, 422–435.

Montagne, B., Kessels, R.P., De Haan, E.H., Perrett, D.I., 2007. The Emotion Recognition Task: a paradigm to measure the perception of facial emotional expressions at different intensities. Percept. Mot. Skills 104, 589–598.

Montagne, B., Kessels, R.P., Frigerio, E., de Haan, E.H., Perrett, D.I., 2005. Sex differences in the perception of affective facial expressions: do men really lack emotional sensitivity? Cogn Process 6, 136–141.

Moreau, N., Rauzy, S., Viallet, F., Champagne-Lavau, M., 2016. Theory of mind in alzheimer disease: evidence of authentic impairment during social interaction. Neuropsychology 30, 312–321.

Morejon, A.J.V., G-Boveda, R.J, 2000. Social Functioning Scale: new contributions concerning its psychometric characteristics in a Spanish adaptation. Psychiat. Res. 93, 247–256.

Nestor, P.G., Parasuraman, R., Haxby, J.V., 1991. Speed of information-processing and attention in early Alzheimers dementia. Develop. Neuropsychol. 7, 243–256.

Petti, U., Baker, S., Korhonen, A., 2020. A systematic literature review of automatic Alzheimer's disease detection from speech and language. J. Am. Med. Inform. Assn. 27, 1784–1797.

Pinkham, A.E., Penn, D.L., Green, M.F., Harvey, P.D., 2016. Social cognition psychometric evaluation: results of the initial psychometric study. Schizophr. Bull. 42, 494–504.

Porcelli, S., Van Der Wee, N., van der Werff, S., Aghajani, M., Glennon, J.C., van Heukelum, S., Mogavero, F., Lobo, A., Olivera, F.J., Lobo, E., Posadas, M., Dukart, J., Kozak, R., Arce, E., Ikram, A., Vorstman, J., Bilderbeck, A., Saris, I., Kas, M.J., Serretti, A., 2019. Social brain, social dysfunction and social withdrawal. Neurosci. Biobehav. Rev. 97, 10–33.

Roncone, R., Falloon, I.R., Mazza, M., De Risio, A., Pollice, R., Necozione, S., Morosini, P., Casacchia, M., 2002. Is theory of mind in schizophrenia more strongly associated with clinical and social functioning than with neurocognitive deficits? Psychopathology 35, 280–288.

Rosen, W.G., Mohs, R.C., Davis, K.L., 1984. A new rating scale for Alzheimer's disease. Am. J. Psychiatry 141, 1356–1364.

Rush, A.J., Trivedi, M.H., Ibrahim, H.M., Carmody, T.J., Arnow, B., Klein, D.N., Markowitz, J.C., Ninan, P.T., Kornstein, S., Manber, R., Thase, M.E., Kocsis, J.H., Keller, M.B., 2003. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol. Psychiatry 54, 573–583.

Saris, I.M.J., Aghajani, M., Jongs, N., Reus, L.M., van der Wee, N.J.A., Bilderbeck, A.C., Winter-van Rossum, I., Arrango, C., de la Torre-Luque, A., Malik, A., Raslescu, A., Dawson, G.R., Ayuso-Mateos, J.L., Kas, M.J., Penninx, B., 2022. Cross-disorder and disorder-specific deficits in social functioning among schizophrenia and Alzheimer's disease patients. PLoS One **Accepted for publication**.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 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 **Suppl 20**quiz 34–57.

Sjolie, C., Meyn, E.K., Raudeberg, R., Andreassen, O.A., Vaskinn, A., 2020. Nonsocial cognitive underpinnings of theory of mind in schizophrenia. Psychiat Res 289.

Spunt, R.P., Lieberman, M.D., 2013. The busy social brain: evidence for automaticity and control in the neural systems supporting social cognition and action understanding. Psychol. Sci. 24, 80–86.

Tas, C., Danaci, A.E., Cubukcuoglu, Z., Brune, M., 2012. Impact of family involvement on social cognition training in clinically stable outpatients with schizophrenia – a randomized pilot study. Psychiatry Res. 195, 32–38.

Tombaugh, T.N., McIntyre, N.J., 1992. The mini-mental state examination: a comprehensive review. J. Am. Geriatr. Soc. 40, 922–935.

Torres Mendonca De Melo Fadel, B., Santos De Carvalho, R.L., Belfort Almeida Dos Santos, T.T., Dourado, M.C.N, 2019. Facial expression recognition in Alzheimer's disease: a systematic review. J. Clin. Exp. Neuropsychol. 41, 192–203.

Uhlmann, A., Ipser, J.C., Wilson, D., Stein, D.J., 2018. Social cognition and aggression in methamphetamine dependence with and without a history of psychosis. Metab. Brain Dis. 33, 559–568.

van der Wee, N.J.A., Bilderbeck, A.C., Cabello, M., Ayuso-Mateos, J.L., Saris, I.M.J., Giltay, E.J., Penninx, B., Arango, C., Post, A., Porcelli, S., 2019. Working definitions, subjective and objective assessments and experimental paradigms in a study exploring social withdrawal in schizophrenia and Alzheimer's disease. Neurosci. Biobehav. Rev. 97, 38–46.

van Hooren, S., Versmissen, D., Janssen, I., Myin-Germeys, I., Campo, J.A., Mengelers, R., van Os, J., Krabbendam, L., 2008. Social cognition and neurocognition as independent domains in psychosis. Schizophrenia Res. 103, 257–265.

Vass, E., Fekete, Z., Simon, V., Simon, L., 2018. Interventions for the treatment of theory of mind deficits in schizophrenia: systematic literature review. Psychiatry Res. 267, 37–47.