

The interactive effect of autism and psychosis severity on theory of mind and functioning in schizophrenia

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Abstract

Objective: Autism and schizophrenia are characterized by impairments in social cognition and functioning. They can co-occur at both the trait/symptom and diagnostic levels. We investigated the concurrent effect of autism and psychotic symptom severity on social cognition and functioning in schizophrenia.

Method: Eighty-one individuals (thirty-two females) with schizophrenia or schizoaffective disorder were included. Symptoms were measured with the Positive and Negative Syndrome Scale using the positive subscale (PANSSpos) and the PANSS Autism Severity Score (PAUSS). Theory of mind (ToM) was assessed with the Movie for the Assessment of Social Cognition (MASC) which yields scores for three error types: overmentalizing, undermentalizing and no-mentalizing. Functioning was assessed with the Global Assessment of Functioning (GAF-f) and the Social Functioning Scale (SFS). The sample was bimodally distributed and therefore divided into low and high PAUSS groups. Generalized linear models examined the effect of PANSSpos, PAUSS and their interaction on GAF-f, SFS and MASC scores.

Results: For the entire cohort, the PANSSpos x PAUSS interaction was significantly associated with better GAF-f ($p=0.005$), SFS ($p=0.029$), and overall ToM ($p=0.035$), and, for the high PAUSS group, with reduced overmentalizing errors ($p=0.002$), resulting in better overall ToM.

Conclusions: Concurrent elevated levels of autism and positive psychotic symptoms seem to benefit functioning and social cognition in schizophrenia. The results are consistent with the diametric model which posits that autism and schizophrenia are characterized by opposing patterns in mentalizing, and promote the radical idea that the presence of both disorders may be associated with attenuated impairments.

Keywords

social cognition, mentalizing, mind-reading, social functioning, diametric model

Public health significance

Autism co-occurs with schizophrenia at both the diagnostic and symptom levels at more than the expected rate in the general population. In this study, we found that autism symptom levels moderated social cognition and functioning difficulties in individuals with schizophrenia. Intriguingly, in individuals with elevated expressions

of both autism and positive symptoms, these difficulties were attenuated. Our findings underscore the need to routinely assess autism in schizophrenia.

Introduction

The association between autism and schizophrenia spectrum disorders and their impact on outcome measures is an area of growing interest and debate. Historically, autism and schizophrenia had a close association. Bleuler (1911/1950) originally used the term autism to describe the social withdrawal observed in individuals with what he labeled "the schizophrenias". Kanner (1943) and Asperger (1944) later used the term to describe children with limited social interest and abilities. Only with the introduction of the third edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-III; APA, 1980) were autism and schizophrenia conceptualized as separate diagnostic entities. This distinction was motivated, in part, by the observation that these conditions occurred in different families (Rutter, 1972) and followed different developmental trajectories with the onset of autism in childhood, and of schizophrenia during adolescence-early adulthood (Kolvin, 1971). Precipitated by this distinction, these conditions were largely studied independent of one another.

However, an absolute form of distinction has been challenged in light of recent evidence for significant areas of overlap (King & Lord, 2001; Chisholm, Li, Abu-Akel, & Wood, 2015; Rutkowski et al., 2017). Notably, autism and schizophrenia are characterized by considerable impairments in both social cognition and functioning (Sasson, Pinkham, Carpenter, & Belger, 2011; Stone & Iguchi, 2011; Pina-Camacho, Parellada, & Kyriakopoulos, 2016). Intriguingly, accumulating evidence also suggests that autism and schizophrenia can co-occur within the individual at both the trait/symptom and diagnostic levels. Several models have been proposed to explain such co-occurrence (Chisholm et al., 2015; Larson et al., 2016; Kincaid, Doris, Shannon, & Mulholland, 2017). In their review, Chisholm et al. (2015) reported that,

on average, autism-schizophrenia comorbidity was found in 13.8 % of individuals with autism, and in 24.1 % of individuals with schizophrenia. Despite this evidence, no studies to date have examined the impact that diagnostic or symptom-level co-occurrence could have on social cognition or functioning in either clinical population. The current study examines, in individuals with schizophrenia, the concurrent effect of positive psychotic and autism symptom severity on impairments in social cognition and functioning – defining features of both disorders.

According to the DSM-5 (APA, 2013) schizophrenia presents with positive psychotic symptoms and is associated with impaired functioning in major areas of life, such as interpersonal relations. Further, the disorder is characterized by deficits in all domains of social cognition (Savla, Vella, Armstrong, Penn, & Twamley, 2013), which include emotion processing, theory of mind (ToM, also referred to as mentalizing), social perception/social knowledge and attributional style (Green et al., 2008). Social cognitive impairments are important predictors of functional outcome in schizophrenia (Couture, Penn, & Roberts, 2006), mediating the association between non-social cognition and outcome (Schmidt, Mueller, & Roder, 2011). ToM, the ability to attribute mental states to others, is an especially strong predictor of functional outcome (Bae, Lee, Park, Hyun, & Yoon, 2010; Fett et al., 2011).

Similarly, autism spectrum disorders are associated with persistent social deficits and repetitive patterns of behaviors, interests, or activities. The social impairments include lack of social reciprocity, deficits in non-verbal communication, as well as difficulties with social relationships. These deficits are thought to stem from impairments in social cognition, particularly in ToM abilities (Baron-Cohen, 2001; Frith, 2001).

While autism and schizophrenia are seemingly characterized by similar impairments in social cognition and social functioning, the impairments may stem from different underlying abnormalities within the social brain network (Sasson et al., 2011; Eack, Wojtalik, Keshavan & Minshew, 2017; Mitelman et al., 2017, Stanfield et al., 2017). It has been suggested that these impairments may be linked to biases for mentalistic cognition (dealing with social entities) in schizophrenia and mechanistic cognition (dealing with objects and systems) in autism (Abu-Akel & Bailey, 2000; Crespi & Badcock, 2008). These contrastive cognitive styles have been respectively associated with hyper-mentalism (or overmentalizing; erroneously over-attributing mental states) in schizophrenia, and hypo-mentalism (or undermentalizing; diminution in the ability to understand and attribute mental states) in autism (Abu-Akel & Bailey, 2000; Crespi & Badcock, 2008), although it is notable that both hypo- and hyper-mentalism has been reported in schizophrenia spectrum disorders (Fretland et al., 2015; Bliksted et al., 2018). Accordingly, both hypo- and hyper-mentalism can have equally deleterious effects on overall mentalizing abilities and on social functioning. This has been referred to as the diametric model (Abu-Akel & Bailey, 2000; Crespi & Badcock, 2008), which posits that autism and schizophrenia are affected by reciprocal causes, and that they are placed at the extreme ends of a mentalizing continuum. These contrasting social cognitive styles in autism and schizophrenia have recently been linked to opposed neural signatures in key regions of the social brain (Ciaramidaro et al., 2015). However, the nature of the relationship of these phenotypes within an individual with schizophrenia remains unexplored.

In departure from analyses that investigated the independent effect of autism and psychosis on social cognition and functioning, nascent research has explored their concurrent effect in non-schizophrenia populations. Research within non-clinical populations showed that co-occurring autistic traits and positive psychotic experiences interactively reduced difficulties with perspective-taking (Abu-Akel, Wood, Hansen, & Apperly, 2015), improved social functioning (Shi et al., 2017), and modulated activity of the temporoparietal junction, a key region within the social brain network, during a social competitive game (Abu-Akel, Apperly, Wood, & Hansen, 2017a). Within clinical populations, the interaction of autism and positive schizotypal traits was associated with better global functioning during the worst depressive episode experienced by individuals with bipolar I disorder (Abu-Akel et al., 2017b). Further, better social pragmatic skills were observed in children with a dual diagnosis of autism and schizotypal disorder compared to children with either disorder alone (Abu-Akel et al., 2018). Consistent with this finding, adults with comorbid autism and schizotypal personality disorder activated social brain regions similarly to healthy controls during a social judgment task, and were intermediate to the groups with either disorder alone (Stanfield et al., 2017). This is intriguing as the comorbid group, in this study, presented higher negative and positive symptom levels compared to both the autism and the schizotypal personality disorder groups. In all of these studies, the co-occurrence of autism and psychosis (proneness or symptoms) had beneficial effects.

Using a dimensional approach, we examine for the first time, the concurrent effect of autism and psychotic symptom severity on ToM/mentalizing ability and functioning of individuals with schizophrenia. ToM abilities were assessed with the Movie for the

Assessment of Social Cognition (MASC; Dziobek et al., 2006), a naturalistic well-validated task that distinguishes between three types of erroneous mentalizing: overmentalizing, undermentalizing, and no-mentalizing errors. This task has been shown to be sensitive to variation in ToM abilities in both autism (Dziobek et al., 2006) and schizophrenia (Fretland et al., 2015). Functioning was assessed with two clinically validated instruments: the Global Assessment of Functioning (GAF; Pedersen, Hagtvet, & Karterud, 2007) and the Social Functioning Scale (SFS; Birchwood et al., 1994). Based on previous research showing that elevated expressions of autism and psychosis were associated with better social cognition and functioning, and in line with the diametric model, we predicted attenuated ToM impairments and better functioning in individuals with schizophrenia scoring high on both autism and positive psychotic symptoms.

Methods

Participants

Eighty-one individuals (49 males, 32 females) with a DSM-IV (APA, 2000) diagnosis of schizophrenia ($n = 61$) or schizoaffective disorder ($n = 20$) were recruited from both inpatient and outpatient units at hospitals in an urban area and assessed in a clinically stable state. Diagnostic assessments were completed with the SCID interview (First, Spitzer, Gibbon, & Williams, 1996) by clinical psychologists or medical doctors/psychiatrists who had completed the general training and reliability checks for the study protocol, using the UCLA programme (Ventura et al., 1998). Both for the training videos and for a randomly drawn subset of actual study participants, the mean k was 0.77 (95 % confidence interval 0.60-0.94). All participants had an $IQ \geq 70$ as assessed with the Wechsler Abbreviated Scale of

Intelligence (WASI; Wechsler, 2007). The study was approved by the regional committee for medical research ethics and was completed in accordance with the Helsinki Declaration. All participants signed informed consent after receiving oral and written information.

Measures

Clinical measures

Autism and psychosis were assessed with the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987). The PANSS consists of 30 items grouped into a positive symptoms subscale (7 items), a negative symptoms subscale (7 items) and one subscale for general symptoms (16 items). Each item receives a score from 1 (= symptom not present) to 7 (= present to an extreme degree, severe interference with functioning and communication). For the current study, positive psychotic symptoms were indexed by the original PANSS positive subscale (7 items: PANSSpos). Autism symptoms were assessed using the PANSS Autism Severity Score (PAUSS) (Kästner et al., 2015). The PAUSS is a newly developed dimensional measure of autism symptoms that was constructed by selecting PANSS items indicative of autistic behavior (Kästner et al., 2015). The following 8 PANSS items are included in the PAUSS: N1 (blunted affect), N3 (poor rapport), N4 (social withdrawal), N5 (difficulties in abstract thinking), N6 (lack of spontaneity and flow of conversation), N7 (stereotyped thinking), G5 (mannerisms), and G15 (preoccupation). These items cover the three symptom domains of autism according to the DSM-IV: difficulties in social interaction (items N1, N3, N4), difficulties in communication (items N5, N6), and limited, repetitive and stereotypic patterns of behavior (items N7, G5, G15) (see Fig. 1S). The PAUSS was developed in a large schizophrenia sample (n = 1156) and

validated in a high-functioning autism spectrum disorder sample ($n = 165$) (Kästner et al., 2015). The PAUSS had high internal consistency (Cronbach's $\alpha = 0.857$), showed convergent validity through substantial correlations with an established measure of autism pathology ($r = 0.763$), and discriminated between individuals with and without autism. Recently, the PAUSS has been shown to be a sensitive measure of autism symptom severity in young people with first-episode psychosis (Parellada et al., 2017). The range (min-max) for the PANSS positive scale is 7-49, and 8-56 for the PAUSS. These are raw scores.

Cognitive measures

IQ was assessed with the 2-subtest version of the WASI, consisting of the Vocabulary and Matrix Reasoning subtests (Wechsler, 2007). The MASC (Dziobek et al., 2006) was used to measure ToM. The MASC is a 15-minute movie of four people interacting in real-life situations. The movie is paused 45 times. Each time a question regarding the characters' thoughts, emotions and intentions is posed. The test has a multiple-choice response format with four response categories. The correct response category reflects that the respondent adequately perceives the character's mental state. The three other response categories correspond to three different types of mentalizing errors, yielding information about the process underlying impaired mentalizing. These include overmentalizing, undermentalizing and no-mentalizing errors.

Overmentalizing errors consist of over-interpretive responses where too much is read into the situation; undermentalizing errors reflect situations where too little is read into the situation such that the participant's answers are under-interpretive of the character's mental state and do not pick up all relevant information of the event; and no-mentalizing errors reflect situations where the participant's answers suggest a lack

of understanding the character's thoughts, emotions or intentions. The range for all scores is 0-45, and these are raw scores. The MASC differentiates between healthy control participants and individuals with schizophrenia (Montag et al., 2011; Andreou et al., 2015; Vaskinn et al., 2015; Vaskinn et al., 2018), who make both over- and undermentalizing errors (Montag et al., 2011; Andreou et al., 2015; Fretland et al., 2015; Vaskinn et al., 2018).

Measures of functioning

Global functioning was measured with the function subscale of the GAF, split version which has been shown to have adequate reliability (GAF-f; Pedersen et al., 2007), whereas social functioning was assessed with SFS (Birchwood et al., 1994). The SFS is a self-report questionnaire that yields seven subscale scores which for the current study were combined to one overall score. Higher scores on both scales indicate better functioning. GAF scores range from 0-100, whereas for the SFS the mean standardized score in a schizophrenia sample is 100 with a standard deviation of 15. The SFS is an instrument commonly used to assess social functioning in studies on severe mental disorders and has been found suitable for use in both schizophrenia and bipolar disorder (Hellvin et al, 2010).

Statistical analyses

Analyses were done using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 24.0, IBM Corp, Armonk, NY) and R, version 3.2.4.

First, we examined the distribution of the PAUSS and PANSSpos scores, using Hartigan's Dip Test function in R (Hartigan & Hartigan, 1985). A Monte-Carlo

simulation of 1000 replicates found that the distribution of the PAUSS deviated significantly from a unimodal distribution (Hartigan's Dip = 0.055, $p = 0.045$), suggesting the existence of two or more subgroups (see Fig. 1). We, therefore, conducted in SPSS a two-step auto-cluster analysis, using Schwarz's Bayesian Criterion. The analysis revealed two subgroups that primarily clustered along the PAUSS dimension: a Low (LPAUSS) and a High PAUSS (HPAUSS) group. The HPAUSS group ($n = 29$) had a mean PAUSS score of 20.4 ($SD = 3.0$) and a mean PANSSpos score of 14.9 ($SD = 5.4$). The mean PAUSS score of the LPAUSS group ($n = 52$) was 12.2 ($SD = 2.1$), and the mean PANSSpos score was 13.3 ($SD = 5.4$).

Next, using Spearman's ρ , we examined, the bivariate correlations between the outcome measures (functioning: GAF-f, SFS; ToM: MASC total correct responses, MASC overmentalizing errors, MASC undermentalizing errors, MASC non-mentalizing errors) and demographic and clinical background variables (age, IQ, illness duration). We also examined sex differences in study variables using independent samples t -tests. Variables with significant effects were included as covariates in Generalized Linear Models (GLMs) that factorially examined the association of the standardized scores of PANSSpos, PAUSS, and Group (LPAUSS or HPAUSS) with functioning and ToM. The GLMs were conducted with robust estimations. Effect sizes for the GLMs were calculated in terms of Pseudo R^2 using the following formula: $= 1 - \frac{Deviance}{Null\ Deviance}$. For outcome variables where the 3-way interaction (PANSSpos x PAUSS x group) was significant, analyses were repeated in the LPAUSS and HPAUSS groups, separately. Moreover, all significant effects are reported, but not interpreted if subsumed under higher order interactions. Finally, to adjust for false discovery rate (FDR) across the six GLMs, we applied the Benjamini-

Hochberg procedure (Benjamini & Hochberg, 1995) with an FDR rate of 5%. This procedure involves ranking the p-values from the significance tests from 1 (smallest) to, in our case, 6 (largest). The rank number is i . The number of significance tests is m . Q is the chosen FDR (in our case 0.05). The formula $(i/m)Q$ yields a Benjamini-Hochberg critical value. The p-values are compared to these critical values, and the largest p-value, which is smaller than its Benjamini-Hochberg critical value, is significant, as are all the other smaller p-values. We report both whether the p-value remained significant when compared to the Benjamini-Hochberg critical values, and the Benjamini-Hochberg p-values, which were calculated using the spreadsheet at www.biostathandbook.com/multiplecomparisons.html

Results

Table 1 presents the sample's demographic and clinical information and performance on the MASC test.

Insert Table 1 about here

The results of the correlation analyses (see Table 2) show that WASI IQ was significantly and positively associated with GAF-f, MASC total correct responses, and negatively with both MASC over- and undermentalizing errors. There were no significant associations between age or illness duration, and any of the outcome variables. Therefore, only WASI IQ was included as a covariate in the GLMs examining the association of PAUSS, PANSSpos, Group and their interaction with functioning and ToM scores, except for the GLMs examining SFS and MASC no-mentalizing errors.

Insert Table 2 about here

The independent samples *t*-tests (Bonferroni corrected for multiple comparisons: p -value = $0.05/11 = 0.005$) yielded statistically significant sex differences only for the PAUSS score ($t = 3.43$, $p = 0.001$) (Cohen's $d = 0.75$) where females had lower scores (13.3 ± 3.8) than males (16.5 ± 4.7). Importantly, as there were no differences between males and females in the outcome measures (i.e. functioning and ToM: t s = $0.07 - 1.86$, p s = $0.066 - 0.945$), sex was not included as a covariate in the GLMs (Miller & Chapman, 2001).

In what follows, we report the results of the GLMs for the functioning and ToM measures. Full details of models and parameter estimates are reported in supplementary material Table 1S-6S.

Functioning

The overall model for GAF-f was significant (omnibus test: $\chi^2 = 32.23$, $df = 8$, $p < 0.001$, Pseudo $R^2 = 0.34$). The p -value remained significant after applying the Benjamini-Hochberg procedure (Benjamini-Hochberg p -value = 0.003). Parameter estimates (see Table 1S) revealed a significant positive effect for WASI IQ (β (se) = $0.161(0.068)$, Wald $\chi^2 = 5.61$, $p = 0.018$), and negative effects for PAUSS (β (se) = $-3.567(1.804)$, Wald $\chi^2 = 3.91$, $p = 0.048$) and PANSSpos (β (se) = $-7.740(1.961)$, Wald $\chi^2 = 15.57$, $p < 0.001$). Results also revealed significant positive 2-way interactions between PAUSS x PANSSpos (β (se) = $3.060(1.091)$, Wald $\chi^2 = 7.88$, $p = 0.005$) and between PANSSpos x Group (β (se) = $11.197(3.371)$, Wald $\chi^2 = 11.03$, $p =$

0.001). However, these 2-way interactions were qualified by a positive 3-way PAUSS x PANSSpos x Group interaction at the threshold for significance ($\beta(\text{se}) = 7.267(3.711)$, Wald $\chi^2 = 3.84$, $p = 0.050$). To probe the 3-way interaction, two separate follow-up GLMs were conducted, in the LPAUSS and HPAUSS groups (see Table 1S). The overall models were significant for both groups (LPAUSS: $\chi^2 = 16.51$, $df = 4$, $p = 0.002$, Pseudo $R^2 = 0.27$; HPAUSS: $\chi^2 = 16.26$, $df = 4$, $p = 0.003$, Pseudo $R^2 = 0.45$). For the LPAUSS group, parameter estimates revealed a significant and positive PAUSS x PANSSpos interaction effect on GAF-f scores ($\beta(\text{se}) = 10.092(3.577)$, Wald $\chi^2 = 7.96$, $p = 0.005$). For the HPAUSS group, there was a positive significant effect for WASI IQ ($\beta(\text{se}) = 0.294(0.118)$, Wald $\chi^2 = 6.22$, $p = 0.013$), and negative significant effects for both PAUSS ($\beta(\text{se}) = -3.786(1.765)$, Wald $\chi^2 = 4.60$, $p = 0.032$) and PANSSpos ($\beta(\text{se}) = -7.037(1.904)$, Wald $\chi^2 = 13.66$, $p < 0.001$). Importantly, the effects of PAUSS and PANSSpos were qualified with a significant positive PAUSS x PANSSpos interaction effect on GAF-f scores ($\beta(\text{se}) = 2.521(1.071)$, Wald $\chi^2 = 5.54$, $p = 0.019$).

For SFS, the overall model was significant ($\chi^2 = 17.13$, $df = 7$, $p = 0.017$, Pseudo $R^2 = 0.19$). The p-value remained significant after applying the Benjamini-Hochberg procedure (Benjamini-Hochberg p-value = 0.025). Parameter estimates (Table 2S) revealed a significant negative main effect of PAUSS ($\beta(\text{se}) = -3.741(1.629)$, Wald $\chi^2 = 5.27$, $p = 0.022$). However, the effect of PAUSS was qualified with a significant positive 2-way interaction with PANSSpos ($\beta(\text{se}) = 3.293(1.509)$, Wald $\chi^2 = 4.76$, $p = 0.029$).

Theory of mind

MASC total correct responses: The overall model was significant ($x^2 = 28.92$, $df = 8$, $p < 0.001$, Pseudo $R^2 = 0.30$). This p-value was significant also after FDR adjustment with the Benjamini-Hochberg procedure (Benjamini-Hochberg p-value = 0.003).

Parameter estimates (Table 3S) revealed a significant positive effect of WASI IQ ($\beta(se) = 0.144(0.051)$, Wald $x^2 = 7.99$, $p = 0.005$), and a significant negative effect of PANSSpos ($\beta(se) = -7.725(3.073)$, Wald $x^2 = 6.32$, $p = 0.012$). However, the effect of PANSSpos was qualified with significant positive 2-way interactions with Group ($\beta(se) = 7.015(3.191)$, Wald $x^2 = 4.83$, $p = 0.028$) and, importantly, with PAUSS ($\beta(se) = 4.273(2.029)$, Wald $x^2 = 4.43$, $p = 0.035$).

MASC overmentalizing errors: The overall model was significant ($x^2 = 18.84$, $df = 8$, $p = 0.016$, Pseudo $R^2 = 0.21$), also after FDR correction with the Benjamini-Hochberg procedure (Benjamini-Hochberg p-value = 0.025). As can be seen from the parameter estimates in Table 4S, there was a significant positive effect of PANSSpos ($\beta(se) = 3.731(0.998)$, Wald $x^2 = 13.99$, $p < 0.001$). The effect of PANSSpos on overmentalizing errors was qualified with a significant negative 2-way interaction with PAUSS ($\beta(se) = -2.248(0.654)$, Wald $x^2 = 11.81$, $p = 0.001$), which was further qualified with Group in a significant positive 3-way interaction ($\beta(se) = 2.462(1.202)$, Wald $x^2 = 4.20$, $p = 0.041$). This 3-way interaction was investigated further by two separate follow-up GLMs in the LPAUSS and HPAUSS groups (Table 4S). The overall model was significant only for the HPAUSS group ($x^2 = 18.63$, $df = 4$, $p = 0.001$, Pseudo $R^2 = 0.47$). Parameter estimates showed a significant negative effect for WASI IQ ($\beta(se) = -0.151(0.045)$, Wald $x^2 = 11.23$, $p = 0.001$), and a positive effect for PANSSpos ($\beta(se) = 3.134(0.866)$, Wald $x^2 = 13.11$, $p < 0.001$).

Importantly, the effect of PANSSpos was qualified with a significant negative interaction with PAUSS ($\beta(\text{se}) = -1.848(0.597)$, Wald $\chi^2 = 9.58$, $p = 0.002$).

MASC undermentalizing errors: The overall model was at trend-level ($\chi^2 = 15.45$, $df = 8$, $p = 0.051$, Pseudo $R^2 = 0.17$; see Table 5S). The p-value was non-significant after Benjamini-Hochberg FDR adjustment (Benjamini-Hochberg p-value = 0.061).

MASC no-mentalizing errors: Finally, the overall model for MASC no-mentalizing errors was non-significant ($\chi^2 = 12.21$, $df = 7$, $p = 0.094$, Pseudo $R^2 = 0.14$; see Table 6S).

Discussion

This study sought to assess the concurrent effect of autism and psychotic symptom severity on ToM/mentalizing and functioning of individuals with schizophrenia. Our study shows that the concurrent presence of high levels of autism and positive psychotic symptoms in individuals with schizophrenia is associated with better functioning, across two measures, and better ToM, independent of IQ. Specifically, the effects of autism and psychosis were greatest when both symptoms were high rather than when both were low. Moreover, the overall improvement in ToM seems to be driven by a reduction in overmentalizing tendencies in participants with high levels of autism severity. Thus, if a person with schizophrenia experiences high psychotic symptom load, it appears that the presence of high levels of autism symptoms to some extent protect against functional impairment and social cognitive deficits.

These findings corroborate the results of previous studies. Our findings regarding functioning are consistent with earlier studies where concurrent high levels of autistic and positive schizotypal traits were associated with better global functioning during the worst depressive episode in individuals with bipolar I disorder (Abu-Akel et al., 2017b), and with better social functioning in healthy individuals (Shi et al., 2017). Further, children with comorbid autism and schizotypal disorder were found to have better executive functioning and social skills than children with either autism or schizotypal disorder (Abu-Akel et al., 2018). Similar findings were also observed in adults with comorbid autism and schizotypal personality disorder, activating social brain regions similarly to healthy controls during a social judgment task, and intermediately to groups with either disorder alone (Stanfield et al., 2017). Moreover, our findings regarding social cognition are consistent with a study showing that healthy adults, high on both autism traits and psychosis proneness, had better perspective-taking performance than healthy adults with either high levels of autism or high levels of psychosis (Abu-Akel et al., 2015). This concordance of results in healthy versus clinical populations, suggests that explorations of subclinical expression in healthy populations can inform investigations within clinical populations.

The mechanism underlying the normalizing effect of high levels of co-occurring autism and positive psychotic symptoms on functioning and mentalizing is currently unknown, and should be the focus of future research. Nonetheless, our findings are consistent with the diametric model (Abu-Akel & Bailey, 2000; Crespi & Badcock, 2008) which posits that psychosis is associated with overmentalizing, and autism with undermentalizing. Accordingly, it is reasonable to assume that when both autism and

psychosis are present, the overmentalizing style associated with psychosis will be attenuated by the undermentalizing style of autism, resulting in a balance (normalization) of mentalizing tendencies and thus a better overall ToM. Consistent with the predictions of the diametric model, our results revealed, for the first time, that high levels of co-occurring autism and positive psychotic symptoms improved mentalizing abilities in schizophrenia by reducing overmentalizing errors. The notion that high levels of autism symptoms in individuals with schizophrenia may protect against any deleterious effects of positive psychotic symptoms on functioning and social cognitive abilities is consistent with genetic evidence suggesting that dosage-sensitive genes associated with autism can reduce the risk for schizophrenia (Rees et al., 2014; Lin et al., 2017). The diametric model is also supported by evidence that autism and schizophrenia are associated with opposed neural responses and connectivity patterns during mentalizing (Ciaramidaro et al., 2015), as well as with evidence showing that the socio-cognitive component of the temporoparietal junction was diametrically modulated by autistic and positive schizotypal traits in neurotypical adults (Abu-Akel et al., 2017a).

The strength of this study is the use of multiple clinical measures for the assessment of functioning, as well as the use of a naturalistic task for the assessment of mentalizing that distinguishes between different types of mentalizing errors. Importantly, by analyzing different mentalizing scores, the MASC can provide an insight into the mechanisms of social cognitive impairment in schizophrenia.

A limitation of the study is the lack of clinical measures for the assessment of autism spectrum disorder. However, it is not clear that the use of the Autism Diagnostic

Observation Schedule (ADOS; Lord et al., 1989), for example, in schizophrenia would yield different assessments from the PAUSS, particularly due to the high correlation of the ADOS with negative symptoms (Bastiaansen et al., 2011; Kästner et al., 2015, Fig 1S). While the PAUSS is the only measure known to us that has been validated for the assessment of autism symptom severity in schizophrenia, we realize that some researchers may be critical of this measure, since it assumes concordance between autism and negative symptoms. However, a growing body of research, which suggests that autism symptoms co-vary with negative symptoms (Sheitman, Kraus, Bodfish, & Carmel, 2004), and that they share common genetic mechanisms (Searles Quick, Davis, Olincy, & Sikela, 2015; Taylor et al., 2015), may support such a convergence. Moving beyond such controversies, and in order to move the field forward, there is an urgent need for the validation and development of instruments suited for the diagnosis of autism in adult clinical populations, and particularly those with psychosis (Maddox et al., 2017). In fact, the bimodal distribution of PAUSS scores in our sample suggests the existence of subgroups within the schizophrenia population. The presence or absence of autism pathology in individuals with schizophrenia may help explain some of the heterogeneity of the disorder.

Positive psychotic symptoms receive much clinical attention and are the main target of both psychopharmacological and psychotherapeutic interventions. Clinical efforts that seek to reduce the negative consequences of distressing psychotic symptoms such as malevolent voices or frightening delusions are paramount. Our findings, which suggest that concurrent high levels of psychotic symptoms and autism symptoms appear to be associated with improved functioning and social understanding, highlight the importance of assessing ongoing symptomatology in persons who receive

treatment for schizophrenia, beyond their positive psychotic symptoms. A further implication of our results is that future research is needed in various domains, beyond social cognition and functioning, in order to optimize clinical interventions for individuals with concurrent high levels of psychosis and autism. A thorough clinical evaluation, where a multidimensional assessment of symptomatology and cognition is included along with the individuals' subjective wishes and aims, could pinpoint relevant treatment targets.

The study revealed that concurrent elevated levels of autism and positive psychotic symptoms benefit functioning and social cognition in persons with schizophrenia. This finding underscores the importance of assessing autism symptom severity in individuals with schizophrenia, particularly in the light of the increased recognition of the co-occurrence of these conditions and the need to build multidimensional models of psychopathology (Wood, 2017). Coming full circle, revisiting the historical link between the terms “autism” and “schizophrenia” may, in fact, usher a new way of thinking about the treatment of individuals with either condition.

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Table 1. Demographic and clinical information and ToM performance in participants with schizophrenia (n = 81)

	Mean	SD	Range
Age	28.6	8.3	18-51
Gender (males/females)	49/32 (n)	61/39 (%)	-
Years of education	12.0	2.4	7-23
WASI IQ	100.4	13.2	70-125
Illness duration (years) ¹	6.4	6.4	0-29
PAUSS	15.1	4.7	8-30
PANSS positive symptoms	13.9	4.8	7-29
GAF-f ²	44.9	11.0	28-80
SFS total score	105.3	9.1	83.6-127.4
MASC total errors	15.7	7.0	6-36
MASC overmentalizing errors	5.3	3.7	0-20
MASC undermentalizing errors	6.6	3.6	0-10
MASC no- mentalizing errors	3.8	2.6	0-10

¹ n = 75 due to missing data, ² n = 79 due to missing data

Table 2. Bivariate associations (Spearman's rho) in participants with schizophrenia (n = 81)

	Age	WASI IQ	Illness duration
GAF-f	-0.06 ¹ p = 0.610	0.26¹ p = 0.019	0.07 ² p = 0.526
SFS total	0.03 p = 0.820	-0.06 p = 0.614	0.18 ² p = 0.118
MASC total errors	0.17 p = 0.139	-0.34 p = 0.002	0.07 ² p = 0.547
MASC overmentalizing errors	0.01 p = 0.914	-0.32 p = 0.003	0.12 ² p = 0.297
MASC undermentalizing errors	0.17 p = 0.121	-0.23 p = 0.044	0.03 ² p = 0.811
MASC no-mentalizing errors	0.20 p = 0.073	-0.18 p = 0.100	0.05 ² p = 0.673

¹ n = 79 due to missing data

² n = 75 due to missing data

Figure 1.

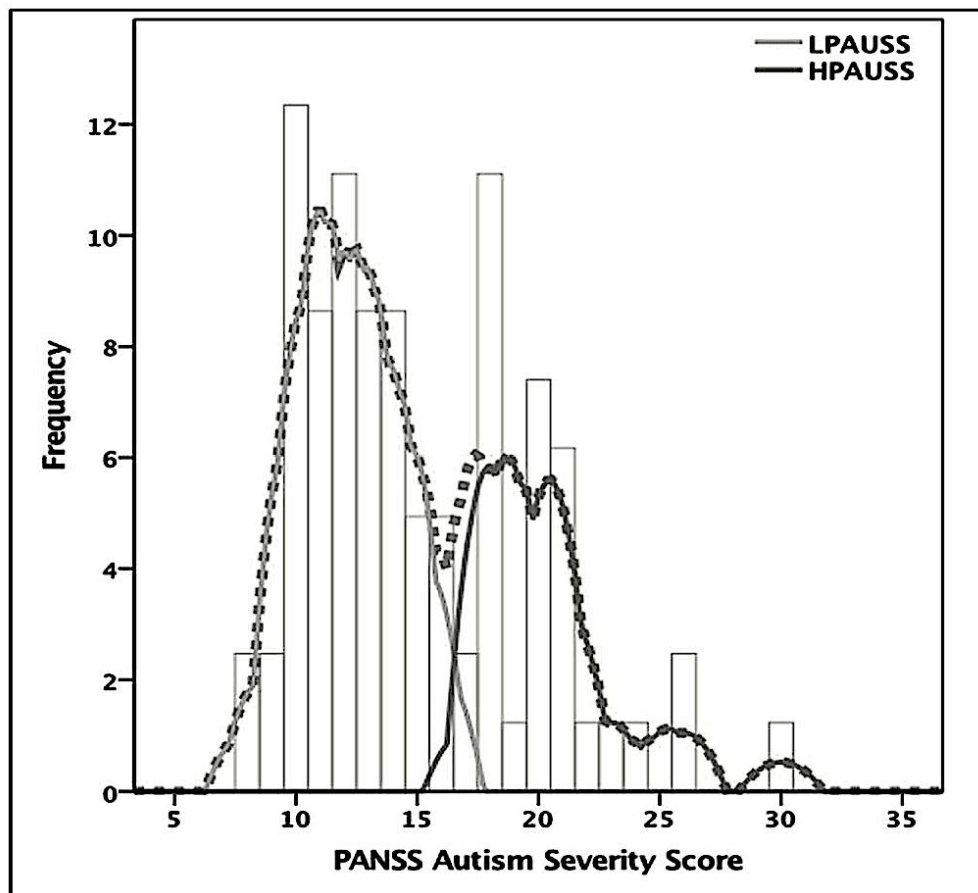


Figure legends

Figure 1.

A histogram of the PANSS Autism Severity Scores (PAUSS) and kernel density estimations of the overall data (red dotted line), the low PAUSS group (LPAUSS, grey line) and the high PAUSS group (HPAUSS, black line).