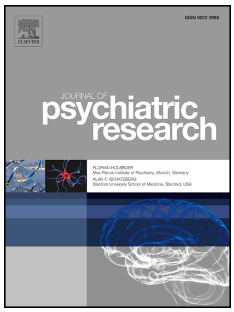

Functional benefits of co-occurring autistic symptoms in schizophrenia is delimited by symptom severity

Margherita Bechi, Ahmad Abu-Akel, Giulia Agostoni, Marta Bosia, Federica Cocchi, Marco Spangaro, Roberto Cavallaro

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Authors MBe, AA, GA and RC designed the study and wrote the study protocol.

Authors MBe and GA undertook the data analysis.

Author MBe, AA, and GA drafted the manuscript.

Authors GA, FC, MS, CG acquired the data.

Authors MBo and RC supervised the data analysis.

All authors contributed to data interpretation.

All authors critically revised the manuscript.

All authors contributed to and have approved the final manuscript.

Title: Functional benefits of co-occurring autistic symptoms in schizophrenia is delimited by symptom severity

Authors: Margherita Bechi [a§], Ahmad Abu-Akel [b§], Giulia Agostoni [c,a*], Marta Bosia [c,a] , Federica Cocchi [a], Marco Spangaro [a,c], Roberto Cavallaro [a,c].

§ Authors MB and AA should be considered joint first author.

[a] Schizophrenia Research and Clinical Unit, Department of Clinical Neurosciences, IRCCS San Raffaele Scientific Institute, Milan, Italy

[b] Institute of Psychology, University of Lausanne, Lausanne, Switzerland

[c] School of Psychology, Vita-Salute San Raffaele University, Milan, Italy

* Corresponding author:
Dr. Giulia Agostoni
Department of Clinical Neurosciences, San Raffaele Scientific Institute
Via Stamira d'Ancona 20, 20127, Milano, Italy.
Tel. +390226433418, Fax. +390226433265
Email: agostoni.giulia@hsr.it

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Abstract

Background: Impairments in daily functioning characterize both autism spectrum disorder and schizophrenia. Research has shown that a subsample of schizophrenia patients presents autistic symptoms, leading to the hypothesis that their co-occurrence would be associated with a 'double dose' of deficit. A growing body of research examined this hypothesis by looking at the joint effect of autistic and positive psychotic symptoms, and yielded contrasting results, ranging from benefits to adverse effects. We hypothesized that the interactive effect of autistic and positive symptoms on functioning in schizophrenia might depend on the patients' symptom severity.

Method: In 170 schizophrenia patients, a two-step cluster analysis identified two groups of patients with different levels of autistic and positive symptom severity. Using general linear models, we examined the interactions of groups, autistic and positive symptoms on functioning.

Results: Autistic and positive symptoms were interactively associated with better functioning, but only in the symptomatically less severe patients. In contrast, autistic and positive symptoms were independently associated with worse functioning in the symptomatically more severe patients. These associations were observed above and beyond the effects of I.Q. and illness duration.

Conclusions: The findings highlight the complex role played by co-occurring autistic symptoms in schizophrenia, whose beneficial effects on functioning appear to depend on patients' psychopathological severity. Our findings may help to reconcile the seemingly contrasting results from previous studies, and to understand the heterogeneity of behavior and functional outcomes in schizophrenia. This study underscores the potential utility of routinely assessing autism in schizophrenia, in order to better formulate individualized rehabilitative programs.

Key words: Psychosis; diametric model; functioning; psychopathology; autistic symptoms; positive symptoms

Introduction

Schizophrenia and autism spectrum disorder (ASD) are pervasive neuropsychiatric disorders, conceptualized as distinct disorders since the 1980s (APA, 1980). Despite their nosologic autonomy, accumulating evidence shows that schizophrenia presents high rates of co-occurrence with ASD at both the symptom and diagnostic levels (Hofvander et al., 2009; Rapoport et al., 2009; Davidson et al., 2014; Chisholm et al., 2015). According to a recent systematic review, the point prevalence rates for autistic-like traits in schizophrenia range from 9.6% to 61%, whilst the prevalence rates for diagnosed ASD range from <1% to 52% (Kincaid et al., 2017). Moreover, studies have reported similarities between schizophrenia and ASD in genetic, biological, clinical, (meta)cognitive and functional characteristics (Chisholm et al., 2015; Kinkaid et al., 2017; De Crescenzo et al., 2019). Elevated expressions of ASD symptoms in schizophrenia and apparent similarities between the disorders have led to increased interest in how ASD symptoms—characterized by a pattern of difficulties in social interactions, communication, emotion processing, and stereotypic behavior (Bastiaansen et al., 2011; Kastner et al., 2015)—might affect behavioral outcomes in schizophrenia, and social and functional impairments in particular. In this regard, it has been hypothesized that ASD symptoms could be present from childhood, affecting the development of social and daily functioning from infancy, and influencing post-onset functioning (Bechi et al., 2019). In this study, we examine the joint effect of ASD and schizophrenia on daily functioning to help determine whether these shared impairments are also similar or precipitated by disorder-specific pathways (Pinkham & Sasson, 2020), and to provide insight into the potential importance of autistic symptoms in characterizing the heterogeneity of schizophrenia patients.

Different theoretical models have tried to explain the association between ASD and schizophrenia, offering contrasting hypotheses (Chisholm et al., 2015). Most prominently are the multiple overlapping etiologies model (Craddock & Owen, 2010) and the diametric model (Crespi & Badcock, 2008). The multiple overlapping etiologies model suggests that ASD and schizophrenia share etiological pathways, whilst other causal pathways remain specific to one disorder or the other (Craddock & Owen, 2010; Chisholm et al., 2015). According to this model, both disorders are expected to have similar impairments on functioning, and that their co-occurrence would be associated with a 'double dose' of deficit. Support for this model are findings from both independent (Addington & Addington, 2007; Bechi et al., 2017; Bowie et al, 2006; Harvey et al., 2012; Horan et al 2006; Lai et al., 2014; Losh et al., 2009; Ventura et al., 2015) and comparative (Pinkam et al., 2020; Solomon et al., 2011; Spek and Wouters, 2010) studies showing that schizophrenia and ASD are similarly associated with significant social, personal and occupational dysfunctions, as well as overall poor quality of life. Consistent with this model are also studies reporting lower levels of social and sociocognitive functioning among schizophrenic patients presenting with high levels of autistic symptoms (Bechi et al., 2020; Deste et al., 2020; Deste et al., 2018) or autistic traits (Ziermans et al., 2020). These studies suggest that autistic symptoms could adversely influence functioning in schizophrenia, implying—as would be predicted by the overlapping model—that ASD and schizophrenia share similar pathways. However, this interpretation can be problematic since similar dysfunctions do not necessarily mean mechanistic similarities, not least because similar functional outcomes can also result from opposing biological causes (Crespi & Badcock, 2008).

The Diametric model (Crespi & Badcock, 2008), on the other hand, suggests that ASD and schizophrenia affect behavior in opposite directions, which are putatively precipitated by

reciprocal biological mechanisms. Individuals with both disorders are thus expected to benefit from the diametrical nature of the disorders, perhaps through the convergence of these contrasting mechanisms in a compensatory manner (Abu-Akel, 2018; Abu-Akel et al., 2018). This is consistent with genetic evidence suggesting that dosage-sensitive genes associated with ASD can reduce the risk for schizophrenia (Rees et al., 2014; Lin et al., 2017). A small, but emerging number of studies examining the concurrent effect of ASD and schizophrenia at both the diagnostic and symptom levels seem to support this prediction. At the diagnostic level, Sunwoo et al. (2019) reported the diagnosis of ASD in 3.7% of 544 individuals with First episode Psychosis (FEP). Compared to individuals with FEP without ASD, this comorbid group presented peculiar clinical and functional characteristics. While they were found to more likely experience difficulties in relationships, they were more engaged in work and education and less likely to have comorbid substance use issues. Moreover, the brain activations of adults with comorbid ASD and schizotypal personality disorder (SPD) during a social judgment task were generally indistinguishable from typically developing adults and fell intermediately between adults singly diagnosed with ASD or SPD (Stanfield et al., 2017). Dimensionally, Vaskinn and Abu-Akel (2019) reported better social and global functioning in patients with schizophrenia presenting with high levels of both autistic and positive psychotic symptoms. These studies provide tentative evidence suggesting that the co-presence of ASD in schizophrenia might, as predicted by the Diametric Model, confer functional benefits. However, the specific mechanism underlying the hypothesized normalizing effect of co-occurring ASD and schizophrenia is currently unknown.

Taken together, studies examining the effect of autistic symptoms on functioning in schizophrenia yield contrasting results, ranging from benefits (as would be predicted by the diametric model) to adverse effects (as would be predicted by the overlapping model). However, a close examination

of these two groups of studies suggests that these results could be confounded by the use of different assessment (self-report vs clinical) and statistical (categorical vs dimensional) approaches, as well as by the use of dissimilar samples (symptomatically less vs. more severe patients). First, Ziermans et al. (2020), for example, examined, in a mixed sample, consisting of patients with schizophrenia, psychotic and schizoaffective diagnoses, the association of social functioning with self-reported autistic traits, which may be of limited utility in clinical samples (Fusar-Poli et al., 2020). Second, the association of autistic symptoms with poor functioning in schizophrenia was found in studies that opted for a categorical group-based approach (low vs high level of severity)(Barlati et al., 2018; Bechi et al., 2020), whereas their association with better functioning was found in a study that examined their interaction with positive symptoms using a dimensional approach (Vaskinn and Abu-Akel, 2019). Third, the association of autistic symptoms with greater dysfunction in schizophrenia appears to be reported for symptomatically more severe patients. For example, the sample level of autistic symptoms reported in the study by Vaskinn and Abu-Akel (2019) was below the levels of autistic symptoms detected in other studies (Bechi et al., 2020; Deste et al., 2020). If so, it can be speculated that a determining factor in how autistic symptoms may affect functioning in patients with schizophrenia may depend on the patients' psychopathological severity. One potential reason as to why autistic symptoms may not confer benefits in the symptomatically more severe patients is because these patients tend to suffer from severe deterioration in brain mechanisms subtending functions important for daily functioning (Mathalon et al., 2001; Wood et al., 2011), which speculatively may prevent contrasting mechanisms associated with ASD and schizophrenia (Crespi & Badcock, 2008) from converging in a compensatory manner.

In an effort to add clarity to these contrasting results, and consistent with the need for more transdiagnostic research (Cuthbert, 2014), the use of the Research Domain Criteria framework (Insel et al., 2010), and the prioritization of improving functional outcome (Fleischhacker et al., 2014), we adopt a dimensional approach to examine the concurrent effect of autistic and positive symptom severity on daily functioning in patients with schizophrenia. Specifically, we examine how different levels of symptoms' severity may influence the impact of co-occurring autistic symptoms on functioning. On the assumption that functional impairments in ASD and schizophrenia might be precipitated by contrasting mechanisms (Crespi & Badcock, 2008), we predicted to observe functional benefits in the symptomatically less severe patients. This hypothesis draws on previous evidence showing that the risk for schizophrenia is reduced by risk factors for autism (Abu-Akel, 2018; Lin et al., 2017; Rees et al., 2014), which also seem to improve symptoms related to schizophrenia (Tseng et al., 2016; Yoshimura et al., 2007). In contrast, we predicted no benefit or even a worsening in functioning in the symptomatically more severe patients in whom, we speculate, brain mechanisms associated with daily functioning (Mathalon et al., 2001; Wood et al., 2011) may be too impaired to allow for contrasting mechanisms associated with ASD and schizophrenia to converge in a compensatory manner.

Methods

One hundred and seventy patients with schizophrenia, according to DSM 5 criteria (APA, 2013), were recruited at *[removed for blind peer review]*. Inclusion criteria were: 18-65 years of age; and treatment with a stable dose of the same antipsychotic therapy for at least 3 months. Exclusion criteria were: severe traumatic brain injury; neurological disorders; psychiatric comorbidities; alcohol or substance abuse in the past 6 months; and severe psychotic acutization in the past 3 months. The authors assert that all procedures contributing to this work comply with the ethical

standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the local Ethics Committee. Written informed consent was obtained from all patients.

Assessment

Patients were assessed for the severity of autistic and positive symptoms by trained psychiatrists. Trained psychologists evaluated intellectual level and functioning.

The *severity of positive symptoms* was assessed with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS)(Kay et al., 1987), a standardized measurement evaluating the severity of positive, negative, and general psychopathology. The measure of interest in this study was PANSS Positive Score (raw and standardized scores).

The severity of autistic symptoms were evaluated with the PANSS Autism Severity Score (PAUSS)(Kästner et al., 2015). The PAUSS is the only validated measure for the assessment of autistic symptoms in schizophrenia. Three scores, representing the three symptom domains of autism, are derived from specific PANSS items: 1) “Difficulties in Social Interaction” Score; 2) “Difficulties in Communication” Score; 3) “Stereotypies/Narrowed Interests” Score. The PAUSS Total Score is the sum of the subscales. A cut-off score of ≥ 30 identifies patients with autistic schizophrenia (Kästner et al., 2015). The measures of interest were: PAUSS subscores and Total Score (raw and standardize scores).

Intellectual level was assessed by means of the Wechsler Adult Intelligence Scale–Revised (WAIS-R, Italian Version)(Wechsler, 1997), a well-known battery estimating the intelligence quotient. The measure of interest was I.Q. Total Score.

Daily functioning was evaluated with the Quality of Life Scale (QLS) (Heinrichs et al., 1984). QLS is considered a measure of quality of life as well as daily functioning, since it includes subjective questions regarding life satisfaction and objective indicators of social and occupational role functioning (Bosia et al., 2017; Poletti et al., 2010). As in previous studies (Buonocore et al., 2017; Cavallaro et al., 2009), three domains of functioning were analyzed: 1) Interpersonal Relations; 2) Instrumental Role; 3) Personal Autonomy. A global index of functional status (i.e., QLS Total Score) is derived from the sum of QLS subscores. The measures of interest were: QLS subscores and Total Score.

Statistical analyses

A two-step cluster analysis, using Schwarz's Bayesian Criterion, was conducted to identify groups of patients characterized by different profiles of autistic symptoms and positive symptoms. PAUSS Total Score and PANSS Positive Score were considered as clustering variables. Differences between clusters in the PAUSS Total Score, in the PANSS Positive Score, and in the QLS (subscores and Total Score) were evaluated using Analyses of Variance (ANOVAs). Additionally, Spearman bivariate correlation analysis was performed to explore the relationship between QLS (subscores and Total Score) and both clinical and demographic variables (i.e., age, illness duration, and I.Q.) in the whole sample as well as in each cluster.

Next, several general linear models (GLMs) were conducted to estimate the association between Clusters, the standardized scores of PAUSS Total and PANSS Positive, with QLS Total and subscores. Variables with significant relationships with functioning, as revealed by the correlation analysis, were entered as covariates. First, a GLM was conducted in the whole sample, to estimate the association of the interaction between autistic and positive symptoms on functioning. Next, in order to test the association of the interaction between autistic and positive symptoms along different levels of clinical severity, we estimated the association of their three-way interaction (Clusters x PAUSS Score x PANSS Positive Score) with functioning (QLS Total and subscores).

Lastly, we performed moderation analyses in PROCESS macro for SPSS (Hayes, 2018) to probe the effect of significant interactions between autistic and positive symptoms on functioning. We used the Johnson–Neyman technique (Johnson & Neyman, 1936), whereby we first entered PANSS Positive as a predictor, functioning as a dependent variable, and PAUSS as a moderator. We then entered PAUSS as a predictor, functioning as a dependent variable, and PANSS Positive as a moderator. Parameters were set at 95% percentile-based confidence intervals (CIs).

Analyses were performed using the Statistical Package for the Social Sciences (IBM-SPSS for MAC, Version 25) and Statistica Software.

Results

Sample description

The sample consisted of 170 patients with schizophrenia, of which 100 males and 70 females, with a mean age of 42.51, mean duration of illness of 18.92. The mean PANSS Positive Score was 17.01 and the mean PAUSS Total Score was 25.93. The mean QLS Total Score was of 49.83. Details on

demographic, clinical, and functional characteristics of the study participants are presented in Table 1.

Cluster Analysis

The two-step cluster analysis, using PAUSS Total and PANSS Positive Scores as clustering variables, produced two clusters, with 90 and 80 members (see Table 1 for Clusters characteristics). Bayesian information criterion (BIC) value showed a maximum of 198.49, and a silhouette score of 0.5 (a measure of "cohesion and separation" of clusters) (Rousseeuw, 1987), suggesting a reasonable cluster structure (see Figure 1).

INSERT FIGURE 1

Clusters presented significantly different clinical and functional profiles, as confirmed by the ANOVAs (see Table 1). Cluster 1 (N=90) consisted of patients with the least severe clinical profile (mean PAUSS = 21.86, SD=5.77; mean PANSS Positive = 13.49, SD=3.45), and Cluster 2 (N=80) consisted of patients with a medium-severe clinical profile (mean PAUSS = 30.51, SD=9.35; mean PANSS Positive = 20.96, SD=3.45). Concerning functioning, Cluster 1 showed higher QLS scores compared to Cluster 2, except for the QLS Instrumental Role score.

INSERT TABLE 1

Correlation Analysis

Table 2 presents the results of the Spearman bivariate correlation analysis of QLS (Total and subscales) with age, illness duration and I.Q. for the overall sample and in each cluster. Variables with significant relationships with functioning were entered into the GLMs as covariates. We highlight that I.Q. was significantly positively correlated with QLS Interpersonal relations (in the

whole sample and in Cluster 1), Personal autonomy (in the whole sample), and Total score (in the whole sample and in Cluster 1).

INSERT TABLE 2

General Linear Model in the whole sample

QLS Total Score. The overall model was significant ($F(4,164)=15.51$, $p<.001$, $R^2Adj=.25$). Parameters estimates revealed significant positive association of IQ (β(SE)=0.18(0.07), $p=.010$), and significant negative associations of both PAUSS (β(SE)=-0.29 (0.07), $p<.001$) and PANSS Positive (β(SE)=-0.21(0.07), $p=.003$) with QLS Total Score. The two-way interaction of PAUSS x PANSS Positive was not significant (β(SE)=0.08(0.06), $p=.18$). This model revealed non-interactive, independent negative effects for autistic and positive symptoms on QLS Total Score.

General Linear Model with clusters

The overall model on QLS Total Score was significant ($F(7,162)=11.95$, $p<.001$, $R^2Adj=.31$). Parameters estimates revealed a significant positive association of I.Q. (β(SE)=0.19(0.07), $p=.008$), PAUSS x PANSS Positive interaction (β(SE)=0.37(0.12), $p=.004$), and Cluster x PANSS Positive interaction (β(SE)=-0.18(0.08), $p=.03$) with QLS Total Score. These two-way interactions were qualified by a significant negative three-way interaction of Cluster x PAUSS x PANSS Positive (β(SE)=-0.40(0.10), $p<.001$). This model revealed significant interaction between autistic and positive symptoms, as well as the interactive effects of symptoms and cluster on QLS Total Score, with Cluster 1 showing higher functioning compared to Cluster 2.

In order to explore this three-way interaction, we conducted separate GLMs in each Cluster. The overall models for Cluster 1 ($F(4,85)=12.92$, $p<.001$, $R^2Adj=.35$) and Cluster 2 ($F(3,76)=5.95$, $p=.001$, $R^2Adj=.16$) were significant (see Table 1S for complete models details).

For Cluster 1, parameters estimates revealed a significant positive association of I.Q. with QLS Total Score (β(SE)=0.28(0.09), $p=.003$). Importantly, the two-way interaction of PAUSS x PANSS Positive was significant and positively associated with QLS Total Score (β(SE)=0.53(0.18), $p=.006$). These results showed that the interaction between autistic and positive symptoms was associated with functional benefits (higher QLS total score) in patients with relatively less severe symptoms.

Concerning Cluster 2, parameters estimates revealed significant negative associations of both PAUSS (β(SE)=-0.33(0.14), $p=.02$) and PANSS Positive (β(SE)=-0.29(0.12), $p=.02$) with QLS Total Score. The two-way interaction of PAUSS x PANSS Positive was not significant (β(SE)=-0.03 (0.15), $p=.84$). Thus, the interaction between autistic and positive symptoms did not yield a positive effect on functioning in patients with more severe symptomatology.

Concerning GLMs on QLS subscores (i.e., of Interpersonal Relations, Instrumental Role, and Personal Autonomy), we found similar and consistent patterns of results: results showed significant negative associations between three-way interaction of Cluster x PAUSS x PANSS Positive and QLS subscores in the overall models, with patients belonging to Cluster 1 showing higher functional outcome compared to Cluster 2 patients. Moreover, we found positive associations between the two-way interaction of PAUSS x PANSS Positive and QLS subscores only in Cluster 1 (see Tables 2S, 3S, and 4S for further details), suggesting that the interaction between autistic and positive symptoms was associated with functional benefits (higher QLS subscores) in

patients with relatively less severe symptoms. These results confirm that the positive effect of the interaction between autistic and positive symptoms is present in the three functional domains of QLS, and only in patients with relatively less severe symptoms.

Moderation Analyses in Cluster 1

The results of the Johnson–Neyman technique (see also Table 5S) revealed that the negative association of PANSS positive with QLS Total Score decreases with increasing PAUSS scores, and becomes non-significant when PAUSS exceeded 22.48, above which 41.11% of all PAUSS scores lie (Figure 2A). Conversely, the negative association of PAUSS with the QLS Total Score decreases with increasing PANSS Positive scores and becomes non-significant when PANSS positive exceeded 14.61, above which 41.11% of all PANSS positive scores lie (Figure 2B). These analyses demonstrate the synergistic positive effect of autistic and positive symptoms on functioning.

The results of the moderation analyses for the QLS subscores in Cluster 1 are detailed in Tables 6S, 7S, and 8S, and Figure 1S.

INSERT FIGURE 2

Discussion

Accumulating evidence suggests that ASD can be ascertained in schizophrenia patients, both at the symptom and diagnostic levels (Chisholm et al., 2015; Kincaid et al., 2017; Rapoport et al., 2009; Sullivan et al., 2013). Studies investigating the effect of ASD on the social and daily functioning of patients with schizophrenia yielded contrasting results, ranging from adverse (Bechi et al., 2019; Deste et al., 2020, 2018; Ziermans et al., 2020) to beneficial (Stanfield et al., 2017; Sunwoo et al., 2019; Vaskinn and Abu-Akel, 2019) effects. We hypothesized that examining the

effect of autistic symptoms on the functioning of patients with schizophrenia at different levels of symptom severity may help reconcile discrepant findings in the literature. In patients with relatively less severe symptoms (Cluster 1), our results show that co-occurring autistic symptoms were associated with better overall daily functioning. In contrast, autistic symptoms were independently associated with worse daily functioning in the more severe patients (Clusters 2). These associations were observed above and beyond the effects of I.Q. and duration of illness. Our findings thus show that co-occurring autistic symptoms can confer functional benefits in schizophrenia, but this may be delimited by symptom severity.

The functional benefits we observed for the patients in Cluster 1 concord with the findings of previous research. Specifically, our findings are similar to those reported by Vaskinn and Abu-Akel (2019), who observed functional benefits for co-occurring autistic symptoms in schizophrenia patients. It is noteworthy that their patients are symptomatically similar to the patients in Cluster 1, although, we note, that our patients, one average, have lower I.Q. levels and longer duration of illness. Moreover, this result is consistent with the functional outcome of the individuals with comorbid FEP and ASD reported in Sunwoo et al. (2019), who, compared to the FEP-only group, were more likely to be engaged in employment or education at time of discharge from service. The co-morbid individuals in this study also appear to present with relatively non-severe symptom levels. Taken together, these findings lend support to the hypothesis the autistic symptoms may confer functional benefits in patients with schizophrenia who are symptomatically less severe.

The mechanism underlying the functional benefits of co-occurring autistic and positive psychotic symptoms is currently unknown, and should be the focus of future research. However, as illustrated in Figure 2, the adverse association of autistic symptoms with functioning is reduced

with increasing positive symptoms, and vice versa. This pattern of associations is consistent with the hypothesis of the Diametric Model, stating that social dysfunction in ASD and schizophrenia might be precipitated by contrasting mechanisms (Abu-Akel et al., 2015; Crespi and Badcock, 2008; Crespi and Go, 2015). According to the Diametric Model, ASD is associated with increased bias for mechanistic and non-social cognition (cognition focused on non-social, rule-based systems), whereas, schizophrenia is associated with increased bias for mentalistic, social cognition (cognition focused on sociality and self-other relations). Accordingly, it might thus be possible that these mechanisms converge in a compensatory manner in schizophrenia patients with co-occurring autistic symptoms. In support of this hypothesis, we leverage evidence indicating that risk factors for autism can reduce the risk for schizophrenia (Abu-Akel, 2018; Lin et al., 2017; Rees et al., 2014) and improve related symptoms (Tseng et al., 2016; Yoshimura et al., 2007) to further suggest that autistic symptoms may protect against the deleterious effects of positive psychotic symptoms on functioning, provided, we add, that patients are not too ill to benefit from such compensation.

In contrast to Cluster 1, patients in Cluster 2 showed high PAUSS scores (mean score ≥ 30, which is at or above the cut-off for autistic schizophrenia (Deste et al., 2020; Kästner et al., 2015)), a more severe positive symptomatology, and worse functioning. This finding is similar to the results from previous studies in which autistic symptoms were associated with impaired functioning (Barlati et al., 2018; Bechi et al., 2019; Deste et al., 2018; Ziermans et al., 2020). Interestingly, the symptom severity in those studies was similar to that of the patients in Clusters 2. Therefore, we hypothesize that, in schizophrenia patients in whom autistic symptoms are particularly severe, the balancing act between autistic and positive symptoms—observed in Cluster 1 (see Figures 1 and 1S)—is lost, thus negatively affecting functioning. This may coincide with the deterioration of

brain mechanisms subtending functions important for daily functioning that is typically observed in clinically more severe patients (Mathalon et al., 2001; Wood et al., 2011).

By considering the complexity and heterogeneity of symptoms in schizophrenia, our study highlights the interactive role played by autistic symptoms, whose beneficial effects appear to depend on the patient's psychopathological severity. Our findings thus may help to reconcile the seemingly contrasting results from previous studies, and to explain the heterogeneity of the disorder. At the clinical, translational level, this novel approach underscores the potential utility of implementing routine assessments of autistic symptoms in schizophrenia (Deste et al., 2018; Kästner et al., 2015; Maddox et al., 2017). Furthermore, studies showed that patients with high levels of autistic symptoms are characterized by specific cognitive and metacognitive profiles that could influence rehabilitation outcomes (Bechi et al., 2020). Thus, autistic symptoms should be taken into account in formulating individualized cognitive and metacognitive rehabilitative programs, with the final aim of promoting a full functional recovery.

The results of this study should be considered in light of some limitations. Functioning is a rather multifaceted construct, and future studies can, therefore, extend our research by evaluating the different facets of daily functioning (Bechi et al., 2017). Moreover, the patients had been followed for a long-time by psychiatric services, and thus they may not be fully representative of all patients with schizophrenia. Future research should also investigate the generalizability of our findings in individuals with ASD (Larson et al., 2017). Furthermore, the study would have benefited from the inclusion of treatment history and current antipsychotic therapy.

We hypothesized that the influence of co-occurring autistic symptoms in schizophrenia may be better clarified when examined at different levels of symptom severity. Our results show that co-occurring autistic and positive symptoms may confer functional benefits in symptomatically less severe patients (Sunwoo et al., 2019; Vaskinn and Abu-Akel, 2019), but not in patients with more severe symptomatology (Deste et al., 2018; Ziermans et al., 2020). The evidence presented in support of this hypothesis should promote the exploration of the potential benefits of autistic symptoms on the cognitive and socio-cognitive functioning of patients with schizophrenia. This new perspective on the effects of co-occurring autistic and positive symptoms in schizophrenia concurs with the need to build multidimensional models of psychopathology, and suggests that their predictive power of functional outcome may be delimited by symptom severity. Furthermore, future studies should focus on elucidating the mechanism underlying the normalizing effect of co-occurring autistic and positive psychotic symptoms, which is currently unknown.

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Table 1. Characteristics and functional measures of the patients overall and by cluster

	Group			Test		Effect size
	Overall (N= 170)	Cluster 1 (N=90)	Cluster 2 (N=80)	χ^2/F	*p*	*Cohen's d*
Gender (M:F)	100:70	48:42	52:28	2.38	.12	n/a
Age	42.51 (11.53)	42.45 (12.37)	42.85 (10.60)	.005	.94	0.03
Duration of illness	18.92 (10.49)	17.92 (10.64)	19.99 (10.28)	1.61	.20	0.19
I.Q.	82.52 (12.31)	85.59 (12.75)	79.06 (10.86)	12.72	**< .001**	0.55
PANSS						
Positive Score	17.01 (4.99)	13.49 (3.45)	20.96 (3.45)	215.12	**< .001**	2.16
PAUSS						
PAUSS Total Score	25.93 (8.79)	21.86 (5.77)	30.51 (9.35)	54.02	**< .001**	1.11
QLS						
Interpersonal Relations Score	19.48 (7.93)	21.33 (7.90)	17.37 (7.90)	11.50	**.001**	0.50
Instrumental Role Score	4.37 (5.88)	4.66 (6.33)	4.04 (5.34)	.46	.49	0.10
Personal Autonomy Score	25.98 (8.98)	28.60 (8.93)	23.00 (8.11)	18.01	**< .001**	0.65
QLS Total Score	49.83 (18.97)	54.59 (19.22)	44.41 (17.26)	12.97	**.001**	0.55

Data are given as mean and standard deviation (SD). ANOVAs and χ^2 examined differences between Cluster 1 and Cluster 2.

Bold values indicate a significant value (p set at .005 according to Bonferroni's correction)

Cluster 1 = patients with relatively less severe symptoms; Cluster 2 = patients with relatively more severe symptoms.

I.Q.= Intelligence quotients; PANSS= Positive and Negative Syndrome Scale for Schizophrenia; PAUSS= PANSS Autism Severity Score; QLS= Quality of Life Scale

Table 2. Correlation matrix of age, illness duration and IQ with functioning within the whole sample and clusters

		Whole sample			Cluster 1			Cluster 2		
		Age	**Illness Duration**	**I.Q.**	**Age**	**Illness Duration**	**I.Q.**	**Age**	**Illness Duration**	**I.Q.**
QLS Interpersonal Relations Score	Spearman's rho	-0.18	-0.21	0.24	-0.21	-0.17	0.35	-0.14	-0.21	0.04
	p-value	0.01	0.006	**0.002**	0.04	0.11	**0.001**	0.20	0.058	0.70
QLS Instrumental Role Score	Spearman's rho	-0.01	-0.07	0.06	-0.66	-0.13	0.13	0.04	-0.006	0.01
	p-value	0.88	0.34	0.38	0.54	0.20	0.19	0.66	0.96	0.93
QLS Personal Autonomy Score	Spearman's rho	-0.10	-0.18	0.27	-0.18	-0.27	0.29	-0.02	-0.07	0.18
	p-value	0.18	0.01	**< .001**	0.08	0.009	0.005	0.83	0.52	0.10
QLS Total Score	Spearman's rho	-0.12	-0.19	0.24	-0.20	-0.23	0.33	-0.05	-0.13	0.10
	p-value	0.09	0.01	**0.001**	0.06	0.03	**0.001**	0.60	0.26	0.33

I.Q.= Intelligence quotient; QLS= Quality of Life Scale

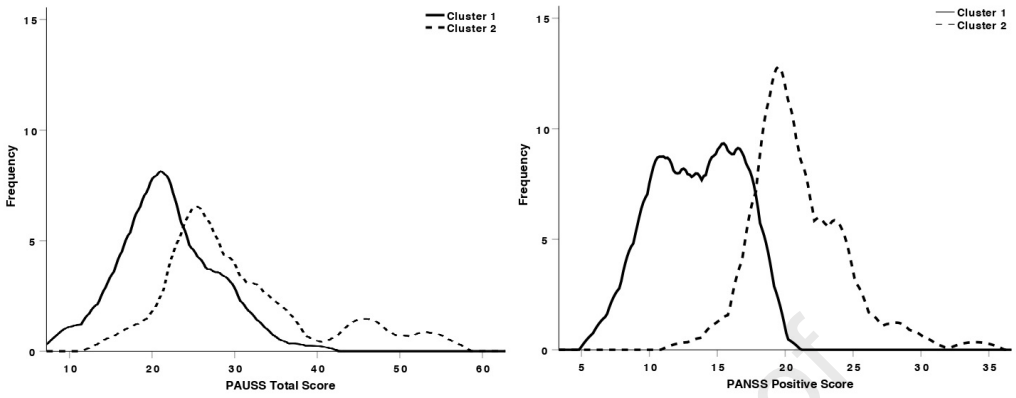
Bold values indicate a significant value (p set at .004 according to Bonferroni's correction)

Figure Legends

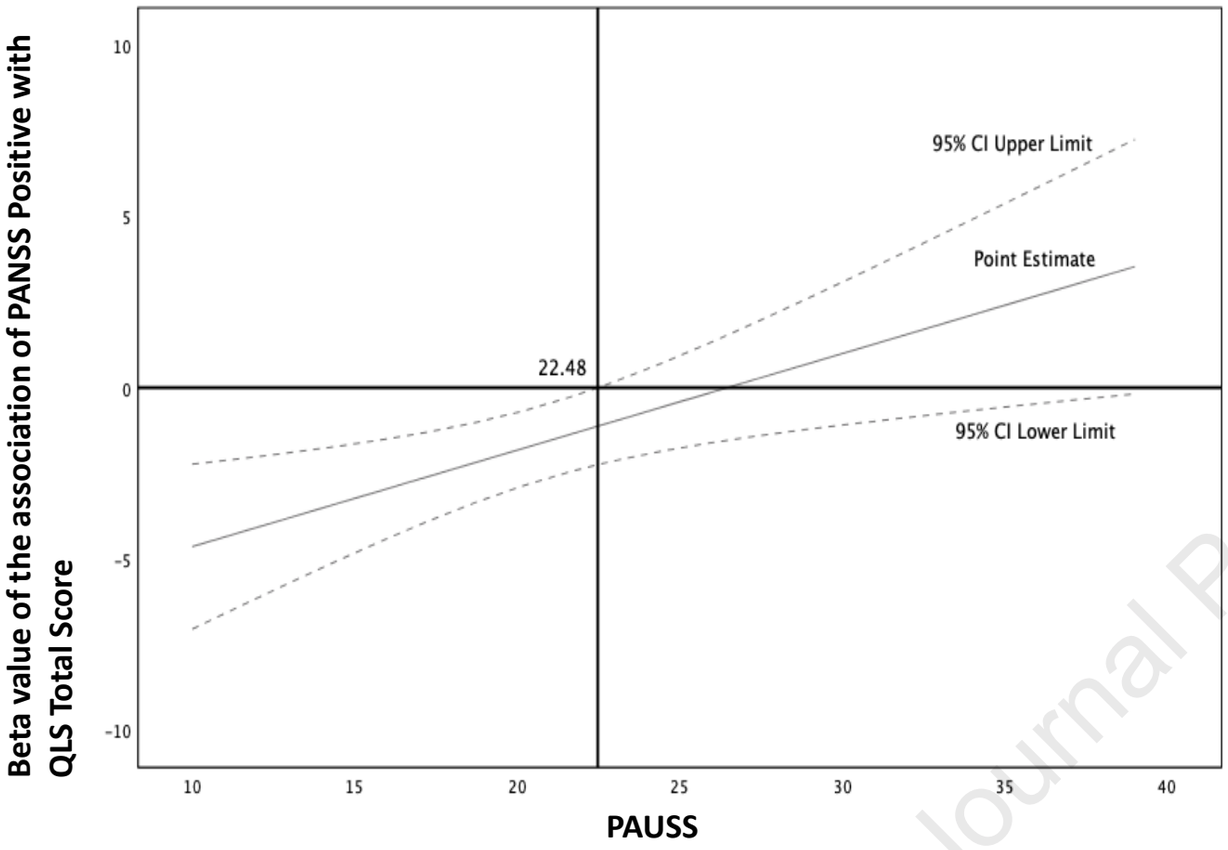
Figure 1. Density plots of the PANSS Autism Severity score (PAUSS) and the PANSS positive symptom scores for patients in Cluster 1 (solid line) and Cluster 2 (dashed line). The figure shows the significantly different psychopathological profiles of the two Clusters. Cluster 1 represents the profile of the relatively less severe patients (lower autistic and positive symptoms), and Cluster 2 represents the profile of the relatively more severe patients (higher autistic and positive symptoms).

Figure 2. Moderation analyses of autistic and positive symptoms on functioning with the Johnson-Neyman Technique. Panel **A** shows the moderating effect of PAUSS on the association between PANSS positive and the QLS Total scores, whereby the negative association of PANSS positive with QLS Total Score decreases with increasing PAUSS scores, becoming non-significant when PAUSS exceeded 22.48. Panel **B** shows the moderating effect of PANSS positive on the association between PAUSS and the QLS Total scores, whereby the negative association of PAUSS with the QLS Total Score decreases with increasing PANSS Positive scores, becoming non-significant when PANSS positive exceeded 14.61.

None.

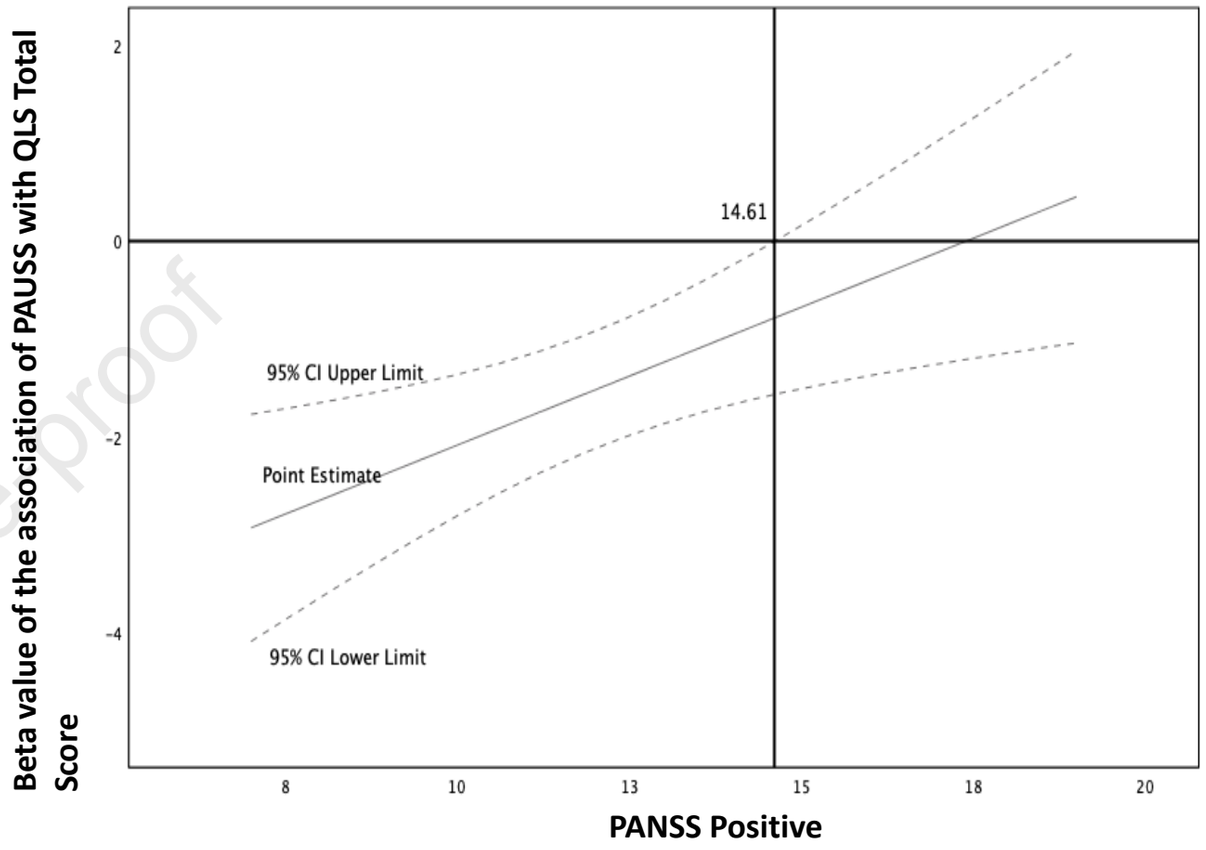


A.



Region of significance stands below the PAUSS cut-off of 22.48

B.



Region of significance stands below the PANSS POSITIVE cut-off of 14.61

- Co-occurring autistic and positive symptoms have beneficial effects on different aspects of functioning in symptomatically less severe patients
- This compensation mechanism can be explained by the Diametric Model
- The evaluation of autistic symptoms severity may help clinicians in the valuation of patients' prognosis and functional outcome

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None.