Journal of Psychiatric Research 185 (2025) 119–129

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Severity of autism-related symptoms in treatment-resistant schizophrenia: associations with cognitive performance, psychosocial functioning, and neurological soft signs — Clinical evidence and ROC analysis

Licia Vellucci [a,b], Annarita Barone [a], Elisabetta Filomena Buonaguro [a,c], Mariateresa Ciccarelli [a], Giuseppe De Simone [a], Federica Iannotta [a], Marta Matrone [d,e], Benedetta Mazza [a], Roberto Vitelli [a], Andrea de Bartolomeis [a,f,*], Felice Iasevoli [a]

[a] Unit for Treatment-Resistant Psychoses, Section of Psychiatry, Department of Neuroscience, Reproductive Sciences and Dentistry - University of Naples "Federico II", Naples, Italy
[b] Department of Translational Medical Sciences, University of Naples "Federico II", Naples, Italy
[c] Unità Operativa di Salute Mentale Terzigno, ASL NAPOLI 3 SUD, Naples, Italy
[d] NESMOS (Neurosciences, Mental Health, and Sensory Organs) Department, Sapienza University of Rome, Faculty of Medicine and Psychology, Via di Grottarossa 1035-1039, 00189, Rome, Italy
[e] Department of Mental Health Protection and Promotion, Unit of Addiction Pathology, Via Salaria per Roma, 36, 02100, Rieti, Italy
[f] UNESCO Staff Chair on Health Education and Sustainable Development, University "Federico II", Naples, Italy

ARTICLE INFO

Keywords:
PAUSS
Schizophrenia
Autistic-related symptoms
Treatment-resistant schizophrenia
Antipsychotics
Clozapine
Machine learning

ABSTRACT

Treatment-resistant schizophrenia (TRS) occurs when symptoms persist despite adequate antipsychotic treatment in terms of both timing and dosage. This severe condition is often overlooked, despite the existence of guidelines, with an average delay of 4–9 years before the introduction of clozapine, the gold standard treatment. We hypothesized that schizophrenia patients with severe autistic symptoms are more prone to develop TRS. To test this, we administered the Positive and Negative Syndrome Scale for Schizophrenia Autism Severity Scale (PAUSS) to 117 patients diagnosed with schizophrenia. Our results revealed that both TRS and clozapine non-responder (CLZ-nR) groups had higher rates of autistic symptoms than non-TRS patients. A machine learning model was developed to examine the relationship between PAUSS scores and TRS, obtaining an accuracy of 0.65 and an AUC of 0.67. Specifically, PAUSS items N6 ("lack of spontaneity and flow of conversation") and N7 ("stereotypical thinking") emerged as the most significant factors in the model. In addition, PAUSS was correlated with cognitive and social functions, as well as soft neurological signs, in TRS patients. Autism-related symptoms were found to predict significant variance in motor coordination, verbal fluency, functional ability and soft neurological signs. These results suggest that autism-related symptoms in schizophrenia may define a distinct subgroup with unique neurobiological characteristics.

1. Introduction

Schizophrenia is conceptualized as a severe neurodevelopmental disorder of synaptic connections (McGrath et al., 2003), resulting in a brain-wide derangement of neural networks (Nath et al., 2021; van den Heuvel and Fornito, 2014; Zhou et al., 2015). Antipsychotics are the cornerstone of pharmacological treatment in schizophrenia; however, up to 30 % of patients exhibit an inadequate response to these drugs, defining a subset of patients known as treatment-resistant (Elkis, 2007; Howes et al., 2017; Kane et al., 1988). Clozapine stands as the sole pharmacological option with the specific indication for treatment-resistant schizophrenia (TRS) (de Leon et al., 2020); moreover up to 30 % of TRS patients are unresponsive even to this agent, constituting another subgroup termed as clozapine non-responder (CLZ-nR) (Siskind et al., 2017). TRS represents a major clinical challenge, particularly when addressing cognitive, social cognitive, and disorganization symptoms (Barone et al., 2022; de Bartolomeis et al., 2013; Frydecka et al., 2016; Iasevoli et al. 2016, 2018a; Joober et al.,

* Corresponding author. Laboratory of Translational and Molecular Psychiatry and Unit of Treatment– Psychosis, Department of Neuroscience, Reproductive Sciences and Dentistry University Medical School of Naples "Federico II", Via Pansini 5, 80131, Naples, Italy.
E-mail address: adebarto@unina.it (A. de Bartolomeis).

https://doi.org/10.1016/j.jpsychires.2025.03.040
Received 10 September 2024; Received in revised form 19 February 2025; Accepted 22 March 2025
Available online 27 March 2025

2002), which significantly impact the long-term course of the disease (Green, 2016; Javed and Charles, 2018; Pinkham, 2014). Notably, these symptoms - particularly those related to cognition, social cognition, and disorganization - could be conceptualized as transdiagnostic domains spanning schizophrenia and other neurodevelopmental disorders, including autism spectrum disorders (ASD) (Michelini et al., 2024; Nakata et al., 2020). Nakata and colleagues (Nakata et al., 2020), recently demonstrated an increased prevalence of ASD-like symptoms in TRS patients compared to schizophrenia patients in remission. These findings were supported by multiple validated assessment tools, including the Japanese version of the Autism-Spectrum Quotient (AQ) (Wakabayashi et al., 2004), the Autism Screening Questionnaire (ASQ) (Dairoku et al., 2016), and the Pervasive Developmental Disorder Assessment Rating Scales Text Revision (PARS-TR) (Adachi and Inoue, 2008). Interest in the co-occurrence of autistic-related symptoms - by some authors referred to as autistic features, autistic traits or autistic phenotypes (Deste et al., 2018; Kästner et al., 2015) - among individuals with schizophrenia is increasing, drawing from the historical perspective proposed by Eugen Bleuler, considering them as a pivotal feature of the most severe manifestations of schizophrenia (Bleuler, 1950; De Crescenzo et al., 2019; Kolvin, 1971; Ziermans et al., 2021). Subsequently, neuropsychological research profoundly reformulated the meaning of this term, characterizing it instead as a lack of unconscious symbolic life, a deficiency in the imaginative world, and including unusual features of language as well as deficits in relational communication and reciprocity (Evans, 2013). Given their divergent clinical profiles and natural histories, schizophrenia and ASD were finally conceptualized as two distinct nosological entities, albeit with discrete clinical and biological overlaps (Baribeau and Anagnostou, 2013; Khanzada et al., 2017; St Pourcain et al., 2018; Sugranyes et al., 2011). For instance, individuals diagnosed with both schizophrenia and ASD often display similar deficits in neurocognitive functions related to social cognition, exhibit comparable abnormalities in functional connectivity within large-scale brain networks (Chen et al., 2017; Eack et al., 2017; Park et al., 2018), and share genetic susceptibility with multiple genetic loci implicated in the etiology of both conditions (Lee et al., 2013; Sullivan et al., 2012). These findings suggest definite common phenotypic presentations extending beyond the diagnostic overshadowing of schizophrenia or unwarranted comorbidity diagnoses.

To explore these clinical similarities, a tool named Positive and Negative Syndrome Scale for Schizophrenia Autism Severity Scale (PAUSS) has been elaborated to capture the continuous nature of autistic-related phenotypes in schizophrenia patients (Kästner et al., 2015).

It has to be taken into account that the gold standard scales for the diagnosis of ASD in the general population are the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al. 1989, 1994). Although these instruments have high validity, they are difficult and lengthy to administer to evaluate autistic traits of schizophrenia subjects, especially in terms of reaching and interviewing with complex tools parents or caregivers of adults living with schizophrenia, which might not be considered feasible in clinical practice, and in some cases might not be possible at all (Nibbio et al., 2022). It is in this context that PAUSS was developed. Some early evidence demonstrated the effectiveness of the PAUSS in distinguishing between samples of ASD, schizophrenia, and other psychiatric disorders, with substantial correlation with the ADOS, as well as in identifying patients with concomitant ASD and schizophrenia (Deste et al., 2018). Recently, doubts have been raised about the use of PAUSS cut-offs for diagnostic purposes to identify autistic and non-autistic subjects, also considering the lack of long-term stability of this measure in study populations (Chisholm et al., 2023). Therefore, PAUSS is positioned as an instrument to be used preferentially on psychotic patients, capable of capturing state rather than trait symptomatology, and useful for the assessment of disease severity and the prediction of clinical outcomes. Lower PAUSS scores, together with younger age, higher premorbid intelligence quotient, and superior neurocognitive performance, have been found to predict better social cognitive outcomes in schizophrenia patients (Deste et al., 2020a). Further research within the Italian Network for Research on Psychoses corroborated these findings, demonstrating that higher PAUSS scores correlated with poorer performance across multiple Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) domains and lower global cognitive composite scores (Vita et al., 2020). Additionally, individuals with elevated PAUSS scores exhibited diminished functional capacity, impaired interpersonal relationships, and reduced participation in community activities, suggesting a link between autistic-related symptoms and severe, disabling forms of schizophrenia.

Recent clinical reports, based on the diametric conceptualization of schizophrenia and ASD, suggest that autistic traits may exert a compensatory effect on psychosocial functioning in schizophrenia patients with mild disease severity (Bechi et al., 2021; Vaskinn and Abu-Akel, 2019). This effect appears to arise from an interactive relationship between autistic and positive symptoms, which are thought to reflect opposing mentalizing tendencies (Bechi et al., 2021). However, these findings are primarily applicable to patients with mild clinical presentation. In patients with severe illness, autistic symptoms, as assessed by PAUSS, have been independently associated with worsening functional outcomes (Bechi et al., 2021), and poor premorbid adjustment, which reflects an individual's academic, occupational, social, and intellectual functioning prior to disease onset (Bechi et al., 2020; Cannon-Spoor et al., 1982). While previous studies highlighted the relevance of autism-like symptoms in schizophrenia, their role in TRS remains poorly understood. Given the substantial clinical and functional differences between schizophrenia subgroups, investigating these symptoms in TRS could provide valuable insights into disease trajectory and its treatment optimization.

The present study aimed to: i) determine whether the severity of autistic-related symptoms differs among TRS subgroups (CLZ-nR and CLZ-R), and non-TRS patients, given their distinct clinical profiles; ii) investigate which PAUSS item shows the strongest association with the TRS condition according to a machine learning approach; iii) define the association between PAUSS and cognitive functions, social skills, and neurodevelopmental outcomes, and examine the predictive role of PAUSS and Positive and Negative Syndrome Scale 5-factor (PANSS 5-factors) on these measures (van der Gaag et al., 2006).

Since this study is cross-sectional, it does not allow for inferences regarding the longitudinal progression of symptoms or causal relationships between autistic-related symptoms and schizophrenia severity. Instead, our findings provide a descriptive and exploratory analysis of symptom distribution across patient subgroups.

2. Materials and methods

2.1. Population

One hundred and seventeen patients meeting inclusion criteria were enrolled at the Outpatient Unit for Treatment-Resistant Psychosis, Section of Psychiatry, Department of Neuroscience, Reproductive Sciences and Dentistry, University "Federico II" of Naples. This cohort was derived from a pre-existing sample recruited for a previously published report and subjected to secondary analysis (Barone et al., 2022; de Bartolomeis et al., 2018). Enrolled patients were referred from community mental health services to our center, a tertiary care facility specializing in the assessment of suspected schizophrenia treatment non-response. Consequently, patients undergoing screening at our unit usually have active, moderate, or severe symptoms. All eligible patients underwent comprehensive assessments, including clinical, psychopathological, cognitive, and psychosocial evaluations.

Inclusion criteria were: i) age range 18–65 years; ii) diagnosis of schizophrenia; iii) stabilized symptoms (i.e., no requirement for changes in medication or dose, and no evidence of recent symptom exacerbation

within the last six months); iv) consent to participate in the study. Exclusion criteria were: i) presence or history of neurodevelopmental disorder, including ASD; ii) significant medical or psychiatric comorbidities; iii) concomitant substance use disorder; iv) conditions limiting the patient's ability to participate or provide informed consent.

The diagnosis of schizophrenia was performed by two trained psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria employing the Structured Clinical Interview for DSM-5 (SCID) (First et al., 2015).

Definitions of TRS and non-TRS were based on the American Psychiatric Association (APA) algorithm, later refined by the Treatment Response and Resistance in Psychosis (TRRIP) guidelines (Howes et al., 2017; Lehman et al., 2004). According to the TRRIP operational criteria, subjects were considered resistant following treatment failure with at least two different antipsychotic agents administered at an adequate dosage (≥ dose equivalent to 600 mg of chlorpromazine/day) for a minimum of six weeks (Howes et al., 2017), as observed during a prospective trial with an antipsychotics. TRS patients were prescribed clozapine unless clinical conditions contraindicated it. TRS patients who did not achieve a ≥25 % reduction in PANSS scores from baseline after an 8-week trial of clozapine administered at the target dose were categorized as CLZ-nR.

All research procedures were conducted in accordance with the ethical standards set by the national and institutional committees responsible for human experimentation, following the principles of the 1975 Declaration of Helsinki, revised in 2008. Experimental procedures involving patients were approved by our institutional review board, and all patients provided written informed consent before participation.

2.2. Demographic and clinical assessment

The following clinical and demographic data were gathered: age, sex, years of education, age of onset of psychotic symptoms, illness duration, number of hospitalizations, and current antipsychotic dosage in mg of chlorpromazine equivalents (CPZ) (Gardner et al., 2010). Psychotic symptoms were assessed by trained psychiatrists administering the PANSS (Kay et al., 1987), applying the 5-factor model that includes positive, negative, disorganization, excitement, and emotional distress factors (van der Gaag et al., 2006). Additionally, the PAUSS was computed to recognize autistic features in schizophrenia (Kästner et al., 2015). The PAUSS (ranging from 8 to 56) comprises items from PANSS covering the following diagnostic domains associated with ASD (Kästner et al., 2015):

- difficulties in social interaction: items 1 ('blunted affect'), 3 ('poor rapport'), and 4 ('social withdrawal') of the PANSS negative subscale (N1, N3, and N4);
- difficulties in communication: items 5 ('difficulties in abstract thinking') and 6 ('lack of spontaneity and flow of conversation') of PANSS negative subscale (N5 and N6);
- limited, repetitive, and stereotypic patterns of behavior: items 5 ('mannerism') and 15 ('preoccupation') of the PANSS general subscale and item 7 ('stereotyped thinking') of the PANSS negative subscale (G5, G15, and N7).

The Neurological Assessment Scale (NES) was used to measure neurological soft signs indicative of aberrant neurodevelopment (Buchanan and Heinrichs, 1989; Hirjak et al., 2019). The NES is a 30-item scale with score ranging from 0 to 2 (where 0 indicates absence, 1 presence with mild intensity, and 2 indicates presence with high intensity) for each item. The Italian version of the extended University of California, San Diego (UCSD) Performance-Based Skills Assessment (UPSA) was used to evaluate functional capacity (Iasevoli et al., 2018b). The UPSA is divided into five domains, generating a raw score ranging from 0 to 20 points. The total score, potentially ranging from 0 to 100 points, is calculated by summing the scores of each of the five domains, with higher scores indicating better performances (Heinrichs et al., 2006; Iasevoli et al., 2018b). Personal and social functioning were assessed using the Personal and Social Performance (PSP) scale (Morosini et al., 2000). This is a 100-point single-item rating scale subdivided into 10 equal intervals with the following scoring: 91 to 100, indicates more than adequate functioning; up to 70, indicates mild difficulties; 31 to 70, indicates various degrees of disabilities; and below 30, indicates poor functioning requiring intensive support or supervision (Morosini et al., 2000). The following tasks to assess cognitive performance were included: the category instances task for verbal fluency; the list learning task for working memory; the token motor task for motor coordination; the symbol coding task for processing speed; and, finally, the Tower of London task for problem solving (Keefe et al., 2004; Phillips et al., 2001).

2.3. Statistical analysis and machine learning approach

Statistical analyses were performed using IBM SPSS Statistics 28.0.1 and RStudio (RStudio, 2020). Descriptive statistics were used to examine clinical and demographic variables, and the Shapiro Wilk test was conducted to assess the normality of continuous variable. To evaluate potential differences between diagnostic groups (i.e. TRS vs. non-TRS), we performed either an independent-sample two-tailed Student's t-test or, for non-normally distributed variables, a Mann-Whitney test. The Chi-square test was used for dichotomous variables. Statistical significance threshold was set at $p < 0.05$. A one-way ANOVA with Tukey's HSD post-hoc test was employed to assess differences among non-TRS and TRS subgroups (CLZ-R, and CLZ-nR), while a Kruskal-Wallis test with Dunn-Bonferroni post-hoc correction was applied for non-normally distributed variables. A one-way ANCOVA was conducted to evaluate potential confounding effects on the PAUSS score. To examine the relationship between the PAUSS score and other clinical variables, we performed Pearson's for normally distributed variables and Spearman's correlations for non-normally distributed variables. The impact of PANSS factors, based on the five-factor model (van der Gaag et al., 2006), and PAUSS on cognitive, social and neurodevelopmental outcomes were explored by a multivariate forward stepwise linear regressions.

To investigate the association between PAUSS score and TRS, we constructed a multivariate logistic regression model using a machine-learning approach. The dichotomous variable TRS/nonTRS served as the dependent variable while the items comprised in the PAUSS as the independent variables. Nested cross-validation, a technique suitable for biomedical data with limited sample sizes and numerous variables, was employed. This approach maximized dataset utilization while maintaining a clear division between training and testing sets. By incorporating an inner loop for hyperparameter tuning and an outer loop for testing, nested cross-validation provides a more robust estimate of the model's performance. The number of inner and outer folds was set at ten. Performance metrics such as the area under the curve (AUC), accuracy, sensitivity, and specificity were computed. To assess the accuracy of probabilistic predictions, the Brier score was measured. All statistical analyses were conducted using the "nestedcv" package in RStudio, version 4.1.2. The variance and 95 % confidence intervals (95 % C.I.) of the AUC were calculated using the "pROC" package (Lewis et al., 2023; Robin et al., 2011; RStudio, 2020).

3. Results

We recruited 117 schizophrenia patients, 59 classified as TRS (51.28 %) and 58 as non-TRS (48.72 %) (Table 1). Within the TRS group, 23 patients were clozapine responder (CLZ-R), and 30 were CLZ-nR (Table 2). Six TRS patients were excluded from the subgroup analysis due to contraindications to clozapine. All participants were on antipsychotic treatment.

The independent samples two-tailed Student's t-test and non-

Table 1
Demographic and clinical characteristics of the sample splitting it in treatment responsive and treatment resistant schizophrenia. Values are given as mean ± standard deviation for continuous variables, rates for sex, and median (IQR) for non-continues variabels in non-TRS and TRS subjects. TRS, Treatment-Resistant Schizophrenia, non-TRS, non-Treatment-Resistant Schizophrenia; PANSS, Positive and Negative Syndrome Scale; CPZ, Chlorpromazine; UPSA, University of California, San Diego (UCSD) Performance-Based Skills Assessment; PSP, Personal and Social Performance; NES, Neurological Assessment Scale; VM, Verbal Memory; WM, Working Memory; CM, Motor Coordination; VF, Verbal fluency; PS: Processing speed; PSS, Problem solving; IQR, interquartile range. Significant results were given in bold ($p < 0.05$).

Demographic and clinical variables	Mean ± sd/Median(IQR)		p-value
	non-TRS (n = 58)	TRS (n = 59)	
Age	38.19 ± 11.92	35.76 ± 9.65	p > 0.05
Sex, male (%)[1]	41 (61.2 %)	33 (64.7 %)	p > 0.05
Years of schooling	13 (15–13)	13 (13–8)	p > 0.05
Age of onset	23 (28–20)	19 (25–16.5)	**p=0.049**
Illness duration	14.83 ± 10.17	15.45 ± 8.40	p > 0.05
CPZ equivalents	300 (450–200)	551 (662–417.2)	**p < 0.001**
PANSS Total score	84.59 ± 15.70	97.15 ± 16.62	**p < 0.001**
PANSS Positive score	18.42 ± 5.65	21.74 ± 4.82	**p < 0.001**
PANSS Negative score	22.36 ± 4.99	24.97 ± 5.78	**p =0.01**
PANSS General score	44.77 ± 9.38	50.09 ± 9.31	**p=0.003**
PANSS Disorganization Factor	28.42 ± 6.47	33.71 ± 7.55	**p < 0.001**
PANSS Positve Factor	21.37 ± 6.79	25.02 ± 6.38	**p=0.003**
PANSS Negative Factor	26 (29–22)	27 (31–22.5)	p > 0.05
PANSS Excitement Factor	19.53 ± 4.99	22.38 ± 5.17	**p=0.003**
PANSS Emotional distress Factors	24.93 ± 5.75	27.05 ± 6.08	p > 0.05
PANSS PAUSS Factor	24.17 ± 4.98	27.10 ± 5.71	**p=0.004**
UPSA total score	71 (83–52)	79 (87.5–43)	p > 0.05
PSP score	50 (65–44)	43 (60.50–31)	p > 0.05
NES score	14.88 ± 9.50	19.42 ± 11.03	p > 0.05
VM score	36.84 ± 11.69	35.12 ± 12.575	p > 0.05
WM score	16 (19–14)	15 (17–13)	p > 0.05
CM score	50.62 ± 16.68	45.86 ± 16.905	p > 0.05
VF score	32 (35–25)	36 (42–30)	p > 0.05
PS score	33.48 ± 11.73	29.10 ± 12.19	p > 0.05
PSS score	14 (16–13)	12 (16.5–9)	p > 0.05

parametric Mann-Whitney test for normally and non-normally distributed variables, respectively, revealed significantly higher PANSS total score, PANSS negative score, PANSS general psychopathology score, PANSS positive score, PANSS PAUSS factor, PANSS disorganization factor, PANSS positive factor, PANSS Excitement Factor, and CPZ-equivalent in TRS group compared to non-TRS group, consistent with evidence that TRS is a more severe clinical condition than drug-responsive forms of schizophrenia (Table 1). When we performed a one-way ANOVA with Tukey HSD post-hoc and non-parametric Kruskal-Wallis test with Dunn-Bonferroni post-hoc to investigate the differences among non-TRS, CLZ-R, and CLZ-nR groups, for normally and non-normally distributed variables, respectively, we found a significant increase in all PANSS subscales and factors in CLZ-nR group compared to non-TRS patients. Furthermore, we observed significantly higher values in PANSS total score, PANSS positive score, PANSS general score, and PANSS factors including disorganization, positive, and emotional distress factors, in CLZ-nR compared to CLZ-R group. According to the severity illness, we found significantly lower CPZ equivalent values in non-TRS patients compared to both CLZ-R and CLZ-nR groups. Additionally, UPSA total score, PSP score, and PS score also showed significant difference across patients' groups, as reported in Table 2.

3.1. Association between PAUSS score and antipsychotic response

The independent sample two-tailed Student's *t*-test compared PAUSS scores between TRS and non-TRS. As expected, TRS patients showed significantly higher PAUSS scores than non-TRS (95 % CI: −5,70 to −1,88; t(115,112) = −3,93, p = 0.004) (Fig. 1). A one-way ANCOVA was conducted to identify potential confounding effects, and the difference between TRS and non-TRS remained statistically significant after controlling for age, sex, level of education, age of onset, disease duration, and CPZ equivalents.

3.2. Autistic-related symptoms severity and clozapine response

PAUSS scores were significantly higher in CLZ-nR subjects compared to non-TRS (95 % CI: −6.58 to −1.05, mean difference = −3.82, p = 0.002) (Fig. 2). The difference between CLZ-nR and non-TRS remained statistically significant after controlling for age, sex, educational years, age of onset, disease duration, and CPZ equivalents.

3.3. Machine learning algorithm

We employed a machine learning multivariate logistic model to evaluate the classification performance of PAUSS items in predicting TRS diagnosis. Specifically, we included as independent variables the PANSS items that contribute to the PAUSS total score (N1, N3, N4, N5, N6, N7, G5, and G15). The primary objective was to determine their impact on accurately identifying the presence/absence of TRS diagnosis (dependent variable). The logistic model yielded an accuracy of 0.65, a sensitivity of 0.57, and a specificity of 0.75, with an AUC of 0.67 (95 %C. I. = 0.57, 0.77). The Brier score was 0.27. Notably, key contributors to the model included items N7 ('stereotyped thinking') and N6 ('lack of spontaneity and flow of conversation') (Intercept = −1.556; N7 = 0.431, N6 = 0.014) essential phenotypes to the clinical presentation of people with ASD. Final parameters: $\lambda = 0.06522$, $\alpha = 1.00000$. The Receiver Operating Characteristic (ROC) curves from outer and inner folds are depicted in Fig. 3.

3.4. Predictive value of PAUSS score on cognitive, social, and neurodevelopmental outcomes: insights from multivariate regression analysis

Since the PAUSS score was found to be significantly associated with more severe phenotypes, we explored whether it was predictive of worse cognitive performance, poorer social functioning, and more severe neurological soft signs, indicative of aberrant neurodevelopment. Pearson's correlations were performed to assess the relationship between the PAUSS score and other clinical variables in TRS and non-TRS subjects. The PAUSS score exhibited significant negative correlations with motor coordination and cognitive domains such as verbal fluency, processing speed, and problem solving, as well as PSP, and UPSA, while positively correlating with NES scores (Table 3).

Subsequently, we conducted multivariate stepwise linear regressions to determine which of the various PANSS factors, including PAUSS, were better predictors of cognitive performance, social functioning, and neurological soft signs. This analysis allowed us to identify the PAUSS score as the independent variable that accounted for most of the variance in cognitive and functioning scores. Infact, the PAUSS score was the only independent variable significantly predicting motor coordination, verbal fluency, UPSA score, and NES score (Table 3). The addition of other PANSS factors in the model did not contribute significantly to the variance of the aforementioned dependent variables (data not shown). Among the other dependent variables, problem solving variance was significantly explained by disorganization and positive symptom factors; processing speed variance was significantly predicted for the disorganization factor; PSP score was significantly accounted for the disorganization and emotional distress factors, and working memory score was significantly explained by positive symptoms (Table 4).

4. Discussion

Autistic-related phenotypes have consistently been described as part

Table 2
Demographic and clinical characteristics of the sample splitting TRS group into CLZ-R and CLZ-nR groups. Values are given as mean ± standard deviation for continuous variables, rates for sex, and median (IQR) for non-continues variabels in non-TRS, CLZ-R and CLZ-nR subjects. non-TRS, non-Treatment-Resistant Schizophrenia; CLZ-R, Clozapine responder, CLZ-nR, Clozapine non responders; PANSS, Positive and Negative Syndrome Scale; CPZ, Chlorpromazine; UPSA, University of California, San Diego (UCSD) Performance-Based Skills Assessment; PSP, Personal and Social Performance; NES, Neurological Assessment Scale: VM, Verbal Memory; WM, Working Memory; CM, Motor Coordination; VF, Verbal fluency; PS, Processing speed; PSS, Problem solving; ns, Non-Significant; IQR, interquartile range. Significant results were given in bold ($p < 0.05$).

Demographic and clinical variables	Mean ± sd/Median(IQR)			Tukey *post-hoc*/Dunn-Bonferroni *post-hoc*	p-value
	non-TRS (n = 58)	CLZ-R (n = 23)	CLZ-nR (n = 30)		
Age	38.19 ± 11.92	32.16 ± 74	37.94 ± 10.61	ns	p > 0.05
Sex, male (%)	41 (61.2 %)	15 (65 %)	18 (60 %)	ns	p > 0.05
Years of schooling	13 (15–13)	13 (13–13)	13 (13–8)	ns	p > 0.05
Age of onset	21 (28–20)	20 (25–16)	19 (25.75–16.5)	ns	p > 0.05
Illness duration	14.83 ± 10.17	13.09 ± 7.41	16.91 ± 8.57	ns	p > 0.05
CPZ equivalents	300 (450–200)	475 (810–400)	600 (656.25–488.75)	non-TRS < CLZ-R	**p=0.001**
				non-TRS < CLZ-nR	**p < 0.001**
PANSS Total score	84.59 ± 15.70	89.65 ± 15.70	101.49 ± 16.07	non-TRS < CLZ-nR	**p < 0.001**
				CLZ-R < CLZ-nR	**p=0.017**
PANSS Positive score	18.42 ± 5.65	19.65 ± 4.90	23.11 ± 4.30	non-TRS < CLZ-nR	**p < 0.001**
				CLZ-R < CLZ-nR	**p=0.036**
PANSS Negative score	22.36 ± 4.99	23.91 ± 6.04	25.657 ± 5.58	non-TRS < CLZ-nR	**p=0.013**
PANSS General score	44.78 ± 9.38	46.09 ± 7.91	52.71 ± 9.68	non-TRS < CLZ-nR	**p < 0.001**
				CLZ-R < CLZ-nR	**p=0.021**
PANSS Disorganization Factor	28.42 ± 6.47	31.00 ± 8.16	35.49 ± 6.67	non-TRS < CLZ-nR	**p < 0.001**
				CLZ-R < CLZ-nR	**p=0.044**
PANSS Positve Factor	21.37 ± 6.79	22.04 ± 5.34	26.97 ± 6.31	non-TRS < CLZ-nR	**p < 0.001**
				CLZ-R < CLZ-nR	**p=0.013**
PANSS Negative Factor	25 (29–22)	27 (28–18)	29 (33.25–26)	non-TRS < CLZ-nR	**p=0.015**
PANSS Excitement Factor	19.53 ± 4.99	21.30 ± 5.31	23.09 ± 5.03	non-TRS < CLZ-nR	**p=0.004**
PANSS Emotional distress Factors	24.93 ± 5.75	24.69 ± 5.04	28.60 ± 6.28	non-TRS < CLZ-nR	**p=0.010**
				CLZ-R < CLZ-nR	**p=0.035**
PANSS PAUSS Factor	24.93 ± 5.75	25.52 ± 6.01	28.142 ± 5.33	non-TRS < CLZ-nR	**p=0.002**
UPSA total score	78 (83–52)	75 (63.41–46)	63 (80.25–40)	CLZ-nR < CLZ-R	**p=0.001**
				CLZ-R< non-TRS	**p=0.029**
PSP score	50 (65–44)	55 (63.41–46)	35 (49.75–29.5)	CLZ-nR < non-TRS	**p=0.010**
				CLZ-nR < CLZ-R	**p=0.007**
NES score	14.88 ± 9.50	15.09 ± 6.670	20.41 ± 12.82	ns	p > 0.05
VM score	36.84 ± 11.69	38.08 ± 13.313	33.17 ± 11.855	ns	p > 0.05
WM score	16 (19–14)	14 (17–11)	15 (16.5–13)	ns	p > 0.05
CM score	50.62 ± 16.68	51.21 ± 16.87	42.47 ± 16.30	ns	p > 0.05
VF score	33.47 ± 10.81	33.60 ± 12.98	30.48 ± 8.71	ns	p > 0.05
PS score	33.48 ± 11.73	34.89 ± 11.50	25.43 ± 11.31	CLZ-nR < non-TRS	**p=0.009**
				CLZ-nR < CLZ-R	**p=0.017**
PSS score	14 (16–13)	11.39 (18–10)	12 (15–6.75	ns	p > 0.05

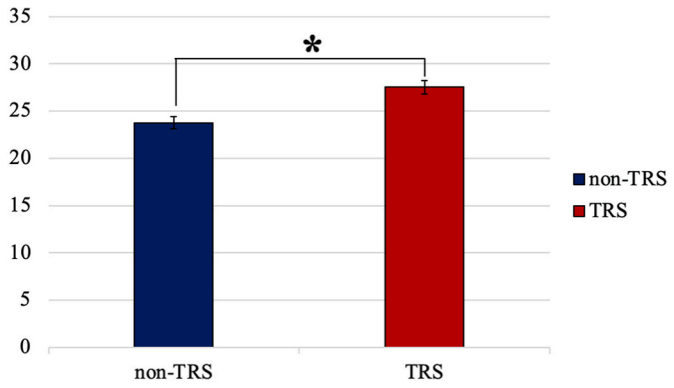

Fig. 1. Differences in PAUSS scores between TRS and non-TRS groups. The values are expressed as relative mean ± standard deviation – non-TRS (24.17 ± 4.98), TRS (27.10 ± 5.71). Asterisk indicates statistically significant difference between groups ($p < 0.05$). TRS, Treatment-Resistant Schizophrenia, non-TRS, non-Treatment-Resistant Schizophrenia; PAUSS, Positive and Negative Syndrome Scale for Schizophrenia Autism Severity Scale.

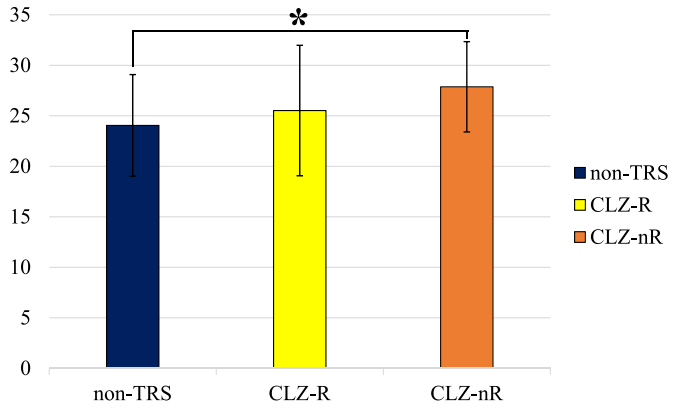

Fig. 2. Differences in PAUSS scores among non-TRS group and TRS groups divided into CLZ-R and CLZ-nR patients. The values are expressed as relative mean ± standard deviation - non-TRS (24.93 ± 5.75), CLZ-R (25.52 ± 6.01), CLZ-nR (28.142 ± 5.33). Asterisk indicates statistically significant difference between groups ($p < 0.05$). non-TRS, non-Treatment-Resistant Schizophrenia patients; TRS, Treatment-Resistant Schizophrenia; CLZ-R, Clozapine Responders; CLZ-nR, Clozapine non-responders; PAUSS, Positive and Negative Syndrome Scale for Schizophrenia Autism Severity Scale.

of the clinical profile of schizophrenia (Jutla et al., 2022). It has been suggested that more severe forms of schizophrenia could exhibit significant autistic-related symptoms (Deste et al., 2021). In the present study, we aimed to investigate the occurrence and severity of

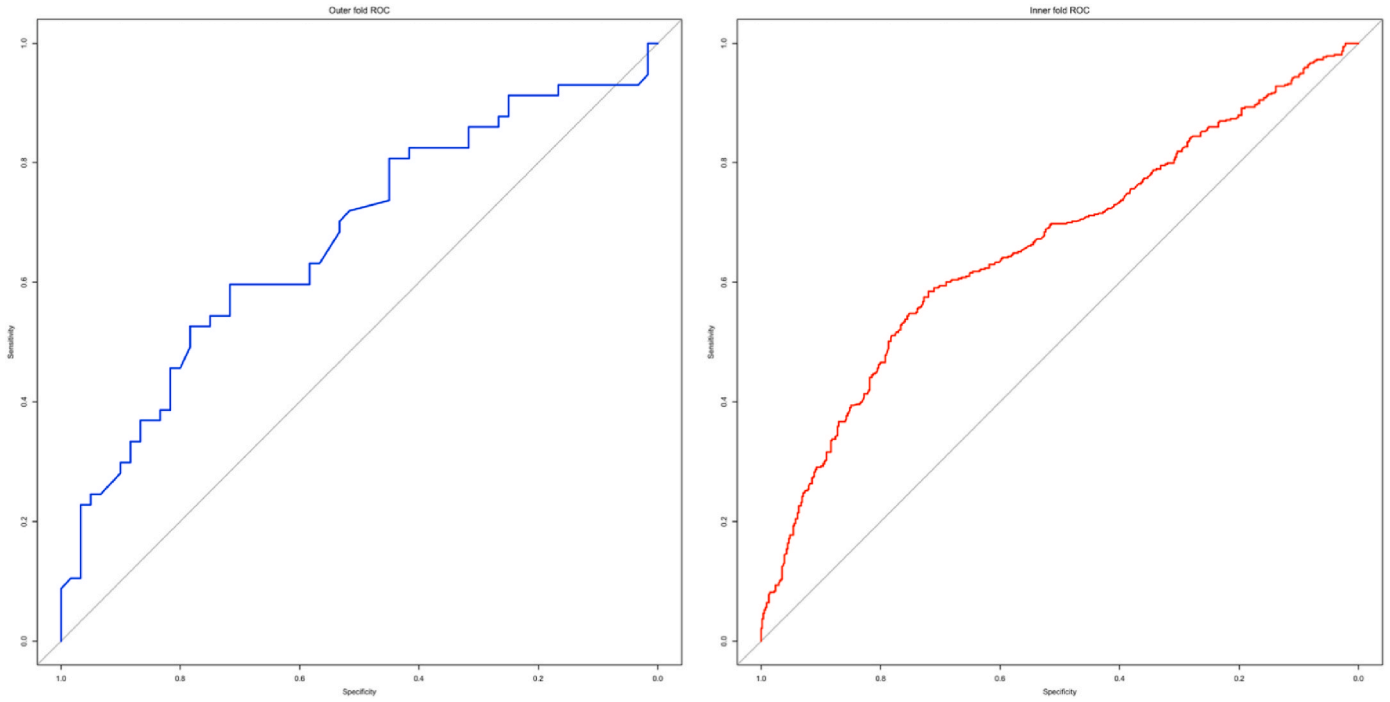

Fig. 3. Performance of the machine learning model explained by Operating Characteristic (ROC) curves. ROC curves were generated from both outer and inner folds. The independent variables comprised PAUSS items, while the outcome variable represented the condition of treatment resistance or responsiveness. The ROC curves visually illustrate the trade-off between sensitivity and specificity, providing insight into the performance characteristics of the logistic models in assessing the association between the presence or absence of treatment-resistant schizophrenia condition and the PAUSS items.

Table 3
Pearson's and Spearman's correlations between PAUSS score and cognitive measures in the two groups, respectively for normal and non-normal distributed variables. Statistically significant differences were given in bold ($p < 0.05$). TRS, Treatment-Resistant Schizophrenia, non-TRS, non-Treatment-Resistant Schizophrenia; PAUSS, Positive and Negative Syndrome Scale for Schizophrenia Autism Severity Scale; PSP, Personal and Social Performance; UPSA, University of California, San Diego (UCSD) Performance-Based Skills Assessment; NES, Neurological Soft Signs.

TRS										
		Motor coordination	Verbal Memory	Verbal fluency	Working memory	Processing speed	Problem solving	PSP	UPSA	NES
PAUSS	**Pearson's *r*/ Spearman's ρ**	−0.59	−0.156	−0.39	−0.82	−0,47	−0.405	−0.71	−0.573	0.49
	p-value	**<0.01**	>0.05	**<0.05**	>0.05	**<0.01**	**<0.05**	**<0.01**	**<0.001**	**<0.01**
non-TRS										
		Motor coordination	Verbal Memory	Verbal fluency	Working memory	Processing speed	Problem solving	PSP	UPSA	NES
PAUSS	**Pearson's *r*/ Spearman's ρ**	−0.03	−0.11	−0.23	0.03	−0.16	−0.08	−0.309	−0.09	0.042
	p-value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

autistic-related phenotypes in the group of TRS patients. We hypothesized that autistic-related symptoms could differ across schizophrenia groups with varying severity, namely non-TRS individuals, TRS patients, and the two TRS subgroups—CLZ-R TRS and CLZ-nR TRS patients. In recent years, the PAUSS scale has been proposed as a reliable tool to capture autism spectrum symptoms in patients diagnosed with schizophrenia (Kästner et al., 2015). Thus, we applied the PAUSS to our sample of schizophrenia patients categorized as non-TRS or TRS, with the latter subsequently split into CLZ-R and CLZ-nR subjects. Additionally, we aimed to explore the association between autistic-related symptoms and cognitive impairment, psychosocial dysfunctions, and aberrant neurodevelopment-related signs in the same sample.

We observed that TRS subjects exhibit significantly higher levels of autistic-related symptoms compared to non-TRS individuals. The significant difference was even more pronounced when comparing CLZ-nR to non-TRS subjects. The greater presence of autistic symptoms and disorganization (Barone et al., 2022) in TRS patients might be considered intuitively obvious, given that both of these symptom domains do not respond adequately to available antipsychotic agents, and thus their presence "selects" nonresponsive patients; on the other hand, their preponderance in a group of patients with schizophrenia can be understood as a marker of distinct neurobiological substrates, as already hypothesized (Gillespie et al., 2017; Iasevoli et al., 2023; Nucifora et al., 2019). Notably, in our previous study, we identified distinctive molecular signatures among non-TRS, TRS, and CLZ-nR subjects (Iasevoli et al., 2023), primarily implicating functional metabolism within the prefrontal cortex. On the other hand, multiple recent evidence reports frontotemporal dysconnectivity as a putative neurobiological substrate in this patients group (Chen et al., 2024; Molent et al., 2019). An aberrant functional connectome in TRS, and potentially CLZ-nR patients, may arise from altered cell programming and aberrant synaptic pruning processes during neurodevelopment (Eltokhi et al., 2020; Fox

Table 4
Selected predictive variables in the stepwise linear regression model. Statistically significant differences were given in bold ($p < 0.05$). PSP, Personal and Social Performance; UPSA, University of California, San Diego (UCSD) Performance-Based Skills Assessment; NES, Neurological Soft Signs. PAUSS, Positive and Negative Syndrome Scale for Schizophrenia Autism Severity Scale.

Dependent Variable	Whole Model				Stepwise		
	df	p	F	Adj R^2	Coefficient(s)	p	Standardized Beta
Motor Coordination	1,99	**<0.001**	11.9	0.098	PAUSS	**<0.001**	−0.328
Verbal Fluency	1115	**<0.001**	15.5	0.111	PAUSS	**<0.001**	−0.345
Verbal Memory	1115	**0.004**	8.5	0.061	Disorganization	**0.004**	−0.263
Processing Speed	1,98	**<0.001**	14.1	0.117	Disorganization	**<0.001**	−0.355
Problem Solving	2114	**<0.001**	16.6	0.212	Disorganization Positive Symptoms	**<0.001** **0.004**	−0.549 0.281
PSP Score	2.48	**<0.001**	19.5	0.426	Disorganization Emotional Distress	**<0.001** **0.023**	−0.457 −0.301
UPSA Score	1,49	**0.002**	11.1	0.168	PAUSS	**0.002**	−0.430
NES Score	1,56	**0.003**	9.6	0.131	PAUSS	**0.003**	0.382
Working memory	6,11	**0.031**	2.4	0.069	Positive Symptoms	**0.002**	0.404

et al., 2012; Lupu et al., 2012; Maccari et al., 2017). Notably, aberrant synaptic pruning has been implicated in the molecular mechanisms underlying both schizophrenia and ASD, although with fundamental qualitative distinctions (Howes and Onwordi, 2023; Tang et al., 2014; Zhang et al., 2021), and may represent a shared neurobiological substrate linking autistic-related symptoms to TRS. On the other hand, the lack of significant differences in PAUSS scores between non-TRS and CLZ-R groups may be attributed to the heterogeneity of TRS and its distinct neurobiological mechanisms. Given the broad spectrum of clozapine's efficacy on overall schizophrenia symptoms, it is plausible that TRS patients who receive and respond to clozapine may, after a certain duration, develop autistic-like symptoms that are not significantly different from those of patients who respond to other antipsychotics from the first exposure. In other words, the absence of a difference could, at least in part, be a consequence of clozapine treatment. Supporting this hypothesis, clozapine has been reported to improve symptoms in treatment-resistant autistic patients who failed to respond to other first-line treatments (Lambrey et al., 2010; Rabinowitz et al., 2013; Sahoo et al., 2017). The second main finding of our study was that discrete PAUSS items, particularly N6 and N7, performed with acceptable accuracy in predicting the TRS classification of patients. Indeed, the machine learning approach validated the association between PAUSS scores and TRS condition, highlighting the significance of 'lack of spontaneity and flow of conversation' and 'stereotyped thinking' as fundamental variables in shaping the model. Both these phenotypes are integral to the clinical presentation of individuals with ASD, suggesting that distinct schizophrenia symptoms, mainly negative ones, can overlap with core features of ASD. Indeed, in a recent study, scores on the PANSS negative subscale were found not to be significantly different between schizophrenia and ASD patients (Trevisan et al., 2020). 'Lack of spontaneity and flow of conversation' refers to the reduced or absent natural expression of thoughts, emotions, and behaviour, exemplified by decreased initiation of conversations, diminished emotional expression, and reduced engagement in activities (Marder and Galderisi, 2017). 'Stereotyped thinking' refers to a rigid, repetitive, and inflexible pattern of thinking, often seen in fixed beliefs, obsessions, or preoccupations (Marder and Galderisi, 2017). These behavioral phenotypes may stem from unique neurobiological alterations involving aberrant neurocircuitry due to synaptic plasticity processes, which cannot be targeted by current antipsychotics (Penzes et al., 2011).

The third finding of our study is that the PAUSS score significantly correlated with multiple measures of cognitive and psychosocial impairments (i.e., motor coordination, verbal fluency, UPSA score, and NES score) and was among the most predictive domains of outcome on several of these measures. Previous studies have consistently linked greater severity of autism symptoms in schizophrenia patients to poorer functional outcomes, diminished cognitive performance, decreased social abilities, and increased internalized stigma (Barlati et al., 2022; Deste et al., 2020a). Our results suggest a strong association between the behavioral phenotypes within the PAUSS construct and deficits in motor coordination, verbal fluency, performance-based social functioning, and clinical measures of aberrant neurodevelopment. These findings indicate an orthogonal effect of autism-related symptoms and disorganization in predicting these outcomes. High scores on the disorganization domain have been demonstrated to predict non-response to antipsychotics (Barone et al., 2022). It is noteworthy that idiosyncratic speech and thought, common in individuals with ASD, are often logical and should not be confused with formal thought disorders seen in schizophrenia patients (Lai and Baron-Cohen, 2015). Therefore, autistic-related symptoms individuated by PAUSS and phenotypes included into the disorganization domain should be clearly distinguished, consistent with the orthogonal effect observed in our study on cognitive and psychosocial measures, attributable to substantially divergent neurobiological bases. Each domain could define a discrete subgroup of TRS, putatively each one with its unique clinical presentation and neurobiological underpinnings, probably also influenced by other factors, such as tobacco smoking (Iasevoli et al., 2013).

In the present study, the PAUSS was used to detect autistic traits, providing a quantitative measure of autistic patterns, useful for tracking symptom severity and comparing outcomes across different patient populations. This aligns with a dimensional approach that conceptualizes ASD as at the severe end of a quantitative trait on a social behavior continuum. However, the literature does not unanimously support the presence of a continuous latent structure of ASD among the general population, relatives of ASD subjects, and other diagnostic groups, raising concerns that autistic symptoms may align more closely with a

categorical model, indicating a qualitatively distinct mode from typical functioning (Frazier et al., 2010). Chisholm and colleagues (Chisholm et al., 2023) have recently discouraged the use of PAUSS cut-offs to diagnose ASD as a qualitative or categorical trait. In agreement with this consideration, we avoided using the PAUSS for the diagnosis of ASD in patients suffering from schizophrenia. Instead, in the present study, we employed the PAUSS to quantitatively capture clinically relevant features of schizophrenia and to identify a subgroup of patients who are more challenging to treat. This lends support to the hypothesis that the severity of autistic symptoms may contribute to the overall severity of the illness (Deste et al. 2020a, 2020b, 2021).

This work has multiple limitations that need to be taken into account. The cross-sectional design does not allow for complete predictions, and the classification model should be tested in other independent samples for external validation. Despite our findings indicating a significant association between the presence of autistic-related clinical manifestations, as identified by PAUSS, and multiple treatment failures alongside severe cognitive impairment, the cross-sectional design precludes making inferences on the direction of these associations. As a further limitation, we acknowledge that we did not utilize specific screening tools (e.g., the ADOS) to exclude the diagnosis of ASD or other neurodevelopmental disorders in our sample, while relying on clinical evaluations performed by qualified psychiatrists. Considering that PAUSS includes several items from the PANSS negative subscale, we acknowledge the partial overlap between negative and autistic-related symptoms, which could lead to tautological findings. However, we also applied an alternative classification of TRS based exclusively on PANSS Positive Symptom subscale items (Rabinowitz et al., 2013) – data not shown – and our results remained significant ($p = 0.025$), further supporting the hypothesis that greater schizophrenia severity is associated with more pronounced autistic symptoms. On a molecular level, the partial overlap between PAUSS and PANSS negative subscale may reflect a shared biological basis that is not targeted by conventional antidopaminergic agents (Mandic-Maravic et al., 2021; Remington et al., 2011; Trevisan et al., 2020; Zheng et al., 2018).

In summary, our findings suggest that autistic traits in schizophrenia could be an indicator, among others, of disease severity and treatment response. Autistic symptoms should be considered when assessing the clinical profile of individuals with schizophrenia, as they may be associated with poorer outcomes. Future research should explore the neurobiological mechanisms underlying this relationship, with longitudinal studies needed to determine whether the progression of autistic traits reflects disease severity. This could guide clinical decision-making and facilitate the early identification of patients who might benefit from alternative treatments, such as clozapine. Moreover, the development of biomarkers for precise schizophrenia subtyping, particularly for patients with predominant autistic traits, will be essential for optimizing personalized treatments strategies.

5. Conclusion

Beyond limitations, the strength and novelty of the present study lie in the observation of worsening autistic traits in schizophrenia patients according to clinical severity. Our findings indicate that autistic traits in schizophrenia patients exhibit varying degrees of clinical relevance across different subgroups: significantly lower PAUSS scores in patients responsive to antipsychotic treatment (non-TRS) and significantly higher scores in those with the most severe clinical presentation (CLZ-nR). Moreover, we were the first to demonstrate that more severe autistic traits are linearly associated with defective cognitive performances, social dysfunctions, and impaired functional capacity.

In conclusion, we confirmed the presence of autistic-related symptoms within the spectrum of schizophrenia, with more severe forms of the disorder showing heightened levels of these symptoms. Our study offers preliminary evidence on the intricate relationship between pharmacological treatment response and autistic-related symptoms, revealing significant associations that could have implications for both clinical practice and future research.

CRediT authorship contribution statement

Licia Vellucci: Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis. **Annarita Barone:** Writing – review & editing, Validation, Investigation, Formal analysis. **Elisabetta Filomena Buonaguro:** Writing – review & editing, Investigation. **Mariateresa Ciccarelli:** Writing – review & editing, Investigation. **Giuseppe De Simone:** Writing – review & editing, Software, Formal analysis. **Federica Iannotta:** Writing – review & editing, Investigation. **Marta Matrone:** Writing – review & editing, Investigation. **Benedetta Mazza:** Writing – review & editing, Investigation. **Roberto Vitelli:** Writing – review & editing, Investigation. **Andrea de Bartolomeis:** Writing – review & editing, Supervision. **Felice Iasevoli:** Writing – review & editing, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Conceptualization.

Funding

Andrea de Bartolomeis MD PhD is a full-time employee at the University of Naples “Federico II”; Giuseppe de Simone MD is enrolled in the PhD Program in Neuroscience at the University of Naples “Federico II”; Licia Vellucci MD is enrolled in the PhD Program in Clinical and Experimental Medicine at the University of Naples “Federico II”; Federica Iannotta is enrolled in the PhD Program in Neuroscience at the University of Naples “Federico II”; Benedetta Mazza MD is enrolled in the Residency Program of Psychiatry at the University of Naples “Federico II”; Annarita Barone MD is a full-time employee at the University of Naples “Federico II”; Mariateresa Ciccarelli MD is Neuroscience PhD candidate at the Department of Neuroscience, University of Naples “Federico II”; Marta Matrone is full-time employee at the Department, Sapienza University of Rome, Faculty of Medicine and Psychology; Elisabetta Filomena Buonguro MD, PhD is a full-time employee at the ASL NAPOLI 3 SUD, Naples, Italy; Roberto Vitelli is a full-time employee at the University of Naples “Federico II”; Felice Iasevoli is a full-time employee at the University of Naples “Federico II”. The work of Andrea de Bartolomeis, Felice Iasevoli, Annarita Barone, and Giuseppe De Simone was supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022).

Declaration of competing interest

Authors declare they have no conflict of interest.

References

Adachi, J.Y.R., Inoue, M., 2008. Reliability and validity of short version of pervasive developmental disorders autism society Japan rating scale (PARS); a behavior checklist for people with PDD. Seishin Igaku 50, 431–438.

Baribeau, D.A., Anagnostou, E., 2013. A comparison of neuroimaging findings in childhood onset schizophrenia and autism spectrum disorder: a review of the literature. Front. Psychiatr. 4, 175. https://doi.org/10.3389/fpsyt.2013.00175.

Barlati, S., Morena, D., Nibbio, G., Cacciani, P., Corsini, P., Mosca, A., Deste, G., Accardo, V., Turrina, C., Valsecchi, P., Vita, A., 2022. Internalized stigma among people with schizophrenia: relationship with socio-demographic, clinical and medication-related features. Schizophr. Res. 243, 364–371. https://doi.org/10.1016/j.schres.2021.06.007.

Barone, A., De Prisco, M., Altavilla, B., Avagliano, C., Balletta, R., Buonaguro, E.F., Ciccarelli, M., D'Ambrosio, L., Giordano, S., Latte, G., Matrone, M., Milandri, F., Francesco, D.N., Vellucci, L., de Bartolomeis, A., 2022. Disorganization domain as a putative predictor of Treatment Resistant Schizophrenia (TRS) diagnosis: a machine learning approach. J. Psychiatr. Res. 155, 572–578. https://doi.org/10.1016/j.jpsychires.2022.09.044.

Bechi, M., Abu-Akel, A., Agostoni, G., Bosia, M., Cocchi, F., Spangaro, M., Cavallaro, R., 2021. Functional benefits of co-occurring autistic symptoms in schizophrenia is

delimited by symptom severity. J. Psychiatr. Res. 137, 48–54. https://doi.org/10.1016/j.jpsychires.2021.02.044.
Bechi, M., Agostoni, G., Buonocore, M., Bosinelli, F., Spangaro, M., Bianchi, L., Cocchi, F., Guglielmino, C., Cavallaro, R., Bosia, M., 2020. The influence of premorbid adjustment and autistic traits on social cognitive dysfunction in schizophrenia. J. Int. Neuropsychol. Soc. 26 (3), 276–285. https://doi.org/10.1017/s1355617719000961.
Bleuler, E., 1950. Dementia Praecox or the Group of Schizophrenias. International Universities Press.
Buchanan, R.W., Heinrichs, D.W., 1989. The neurological evaluation scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res. 27 (3), 335–350. https://doi.org/10.1016/0165-1781(89)90148-0.
Cannon-Spoor, H.E., Potkin, S.G., Wyatt, R.J., 1982. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr. Bull. 8 (3), 470–484. https://doi.org/10.1093/schbul/8.3.470.
Chen, H., Uddin, L.Q., Duan, X., Zheng, J., Long, Z., Zhang, Y., Guo, X., Zhang, Y., Zhao, J., Chen, H., 2017. Shared atypical default mode and salience network functional connectivity between autism and schizophrenia. Autism Res. 10 (11), 1776–1786. https://doi.org/10.1002/aur.1834.
Chen, Y., Liu, S., Zhang, B., Zhao, G., Zhang, Z., Li, S., Li, H., Yu, X., Deng, H., Cao, H., 2024. Baseline symptom-related white matter tracts predict individualized treatment response to 12-week antipsychotic monotherapies in first-episode schizophrenia. Transl. Psychiatry 14 (1), 23. https://doi.org/10.1038/s41398-023-02714-w.
Chisholm, K., Schirmbeck, F., Pinkham, A.E., Sasson, N.J., Simons, C.J.P., de Haan, L., Harvey, P.D., Penn, D.L., Ziermans, T., 2023. A cross-sectional conceptual replication and longitudinal evaluation of the PANSS-autism-severity-score measure suggests it does not capture autistic traits in individuals with psychosis. Schizophr. Bull. https://doi.org/10.1093/schbul/sbad161.
Dairoku, H.S.A., Hayashi, E., Toujyou, Y., Ichikawa, H., 2016. Kokuritu Tokusyu Kyouiku Sougou Kennkyuujyo Bunnsitu Ippan Kennkyu Houkokusyuo, vol. 3, pp. 19–34 vol. 3. 2016. Jiheisyou sukuriining situmonsi (ASQ) nihonngobann no kaihatu.
de Bartolomeis, A., Balletta, R., Giordano, S., Buonaguro, E.F., Latte, G., Iasevoli, F., 2013. Differential cognitive performances between schizophrenic responders and non-responders to antipsychotics: correlation with course of the illness, psychopathology, attitude to the treatment and antipsychotics doses. Psychiatry Res. 210 (2), 387–395. https://doi.org/10.1016/j.psychres.2013.06.042.
de Bartolomeis, A., Prinzivalli, E., Callovini, G., D'Ambrosio, L., Altavilla, B., Avagliano, C., Iasevoli, F., 2018. Treatment resistant schizophrenia and neurological soft signs may converge on the same pathology: evidence from explanatory analysis on clinical, psychopathological, and cognitive variables. Prog. Neuropsychopharmacol. Biol. Psychiatry 81, 356–366. https://doi.org/10.1016/j.pnpbp.2017.09.002.
De Crescenzo, F., Postorino, V., Siracusano, M., Riccioni, A., Armando, M., Curatolo, P., Mazzone, L., 2019. Autistic symptoms in schizophrenia spectrum disorders: a systematic review and meta-analysis. Front. Psychiatr. 10, 78. https://doi.org/10.3389/fpsyt.2019.00078.
de Leon, J., Ruan, C.J., Schoretsanitis, G., De Las Cuevas, C., 2020. A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology. Psychother. Psychosom. 89 (4), 200–214. https://doi.org/10.1159/000507638.
Deste, G., Barlati, S., Gregorelli, M., Lisoni, J., Turrina, C., Valsecchi, P., Vita, A., 2018. Looking through autistic features in schizophrenia using the PANSS Autism Severity Score (PAUSS). Psychiatry Res. 270, 764–768. https://doi.org/10.1016/j.psychres.2018.10.074.
Deste, G., Vita, A., Nibbio, G., Barlati, S., Penn, D.L., Pinkham, A.E., Harvey, P.D., 2021. Autistic symptoms in people with schizophrenia: neurocognitive, socio-cognitive, clinical and real-world functional characteristics of individuals without autistic features. Schizophr. Res. 236, 12–18. https://doi.org/10.1016/j.schres.2021.07.037.
Deste, G., Vita, A., Nibbio, G., Penn, D.L., Pinkham, A.E., Harvey, P.D., 2020b. Autistic symptoms and social cognition predict real-world outcomes in patients with schizophrenia. Front. Psychiatr. 11, 524. https://doi.org/10.3389/fpsyt.2020.00524.
Deste, G., Vita, A., Penn, D.L., Pinkham, A.E., Nibbio, G., Harvey, P.D., 2020a. Autistic symptoms predict social cognitive performance in patients with schizophrenia. Schizophr. Res. 215, 113–119. https://doi.org/10.1016/j.schres.2019.11.008.
Eack, S.M., Wojtalik, J.A., Keshavan, M.S., Minshew, N.J., 2017. Social-cognitive brain function and connectivity during visual perspective-taking in autism and schizophrenia. Schizophr. Res. 183, 102–109. https://doi.org/10.1016/j.schres.2017.03.009.
Elkis, H., 2007. Treatment-resistant schizophrenia. Psychiatr. Clin. 30 (3), 511–533. https://doi.org/10.1016/j.psc.2007.04.001.
Eltokhi, A., Janmaat, I.E., Genedi, M., Haarman, B.C.M., Sommer, I.E.C., 2020. Dysregulation of synaptic pruning as a possible link between intestinal microbiota dysbiosis and neuropsychiatric disorders. J. Neurosci. Res. 98 (7), 1335–1369. https://doi.org/10.1002/jnr.24616.
Evans, B., 2013. How autism became autism: the radical transformation of a central concept of child development in Britain. Hist. Hum. Sci. 26 (3), 3–31. https://doi.org/10.1177/0952695113484320.
First, M.B.W.J., Karg, R.S., Spitzer, R.L., 2015. User's Guide for the Structured Clinical Interview for DSM-5 Disorders, Research Version (SCID-5-RV). American Psychiatric Association, Arlington, VA, 2015.
Fox, D.A., Grandjean, P., de Groot, D., Paule, M.G., 2012. Developmental origins of adult diseases and neurotoxicity: epidemiological and experimental studies. Neurotoxicology 33 (4), 810–816. https://doi.org/10.1016/j.neuro.2011.12.016.
Frazier, T.W., Youngstrom, E.A., Sinclair, L., Kubu, C.S., Law, P., Rezai, A., Constantino, J.N., Eng, C., 2010. Autism spectrum disorders as a qualitatively distinct category from typical behavior in a large, clinically ascertained sample. Assessment 17 (3), 308–320. https://doi.org/10.1177/1073191109356534.
Frydecka, D., Beszłej, J.A., Gościmski, P., Kiejna, A., Misiak, B., 2016. Profiling cognitive impairment in treatment-resistant schizophrenia patients. Psychiatry Res. 235, 133–138. https://doi.org/10.1016/j.psychres.2015.11.028.
Gardner, D.M., Murphy, A.L., O'Donnell, H., Centorrino, F., Baldessarini, R.J., 2010. International consensus study of antipsychotic dosing. Am. J. Psychiatr. 167 (6), 686–693. https://doi.org/10.1176/appi.ajp.2009.09060802.
Gillespie, A.L., Samanaite, R., Mill, J., Egerton, A., MacCabe, J.H., 2017. Is treatment-resistant schizophrenia categorically distinct from treatment-responsive schizophrenia? a systematic review. BMC Psychiatry 17 (1), 12. https://doi.org/10.1186/s12888-016-1177-y.
Green, M.F., 2016. Impact of cognitive and social cognitive impairment on functional outcomes in patients with schizophrenia. J. Clin. Psychiatry 77 (Suppl. 2), 8–11. https://doi.org/10.4088/JCP.14074su1c.02.
Heinrichs, R.W., Statucka, M., Goldberg, J., McDermid Vaz, S., 2006. The university of California performance skills assessment (UPSA) in schizophrenia. Schizophr. Res. 88 (1–3), 135–141. https://doi.org/10.1016/j.schres.2006.07.026.
Hirjak, D., Rashidi, M., Fritze, S., Bertolino, A.L., Geiger, L.S., Zang, Z., Kubera, K.M., Schmitgen, M.M., Sambataro, F., Calhoun, V.D., Weisbrod, M., Tost, H., Wolf, R.C., 2019. Patterns of co-altered brain structure and function underlying neurological soft signs in schizophrenia spectrum disorders. Hum. Brain Mapp. 40 (17), 5029–5041. https://doi.org/10.1002/hbm.24755.
Howes, O.D., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N.J., Birnbaum, M.L., Bloomfield, M.A., Bressan, R.A., Buchanan, R.W., Carpenter, W.T., Castle, D.J., Citrome, L., Daskalakis, Z.J., Davidson, M., Drake, R.J., Dursun, S., Ebdrup, B.H., Elkis, H., Falkai, P., Fleischacker, W.W., Gadelha, A., Gaughran, F., Glenthøj, B.Y., Graff-Guerrero, A., Hallak, J.E., Honer, W.G., Kennedy, J., Kinon, B. J., Lawrie, S.M., Lee, J., Leweke, F.M., MacCabe, J.H., McNabb, C.B., Meltzer, H., Möller, H.J., Nakajima, S., Pantelis, C., Reis Marques, T., Remington, G., Rossell, S. L., Russell, B.R., Siu, C.O., Suzuki, T., Sommer, I.E., Taylor, D., Thomas, N., Üçok, A., Umbricht, D., Walters, J.T., Kane, J., Correll, C.U., 2017. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. Am. J. Psychiatr. 174 (3), 216–229. https://doi.org/10.1176/appi.ajp.2016.16050503.
Howes, O.D., Onwordi, E.C., 2023. The synaptic hypothesis of schizophrenia version III: a master mechanism. Mol. Psychiatr. 28 (5), 1843–1856. https://doi.org/10.1038/s41380-023-02043-w.
Iasevoli, F., Avagliano, C., Altavilla, B., Barone, A., Ciccarelli, M., D'Ambrosio, L., Notar Francesco, D., Razzino, E., Fornaro, M., de Bartolomeis, A., 2018a. Evaluation of a few discrete clinical markers may predict categorization of actively symptomatic non-acute schizophrenia patients as treatment resistant or responders: a study by ROC curve analysis and multivariate analyses. Psychiatry Res. 269, 481–493. https://doi.org/10.1016/j.psychres.2018.08.109.
Iasevoli, F., Balletta, R., Gilardi, V., Giordano, S., de Bartolomeis, A., 2013. Tobacco smoking in treatment-resistant schizophrenia patients is associated with impaired cognitive functioning, more severe negative symptoms, and poorer social adjustment. Neuropsychiatric Dis. Treat. 9, 1113–1120. https://doi.org/10.2147/ndt.S47571.
Iasevoli, F., D'Ambrosio, L., Ciccarelli, M., Barone, A., Gaudieri, V., Cocozza, S., Pontillo, G., Brunetti, A., Cuocolo, A., de Bartolomeis, A., Pappatà, S., 2023. Altered patterns of brain glucose metabolism involve more extensive and discrete cortical areas in treatment-resistant schizophrenia patients compared to responder patients and controls: results from a head-to-head 2-[18F]-FDG-PET study. Schizophr. Bull. 49 (2), 474–485. https://doi.org/10.1093/schbul/sbac147.
Iasevoli, F., D'Ambrosio, L., Notar Francesco, D., Razzino, E., Buonaguro, E.F., Giordano, S., Patterson, T.L., de Bartolomeis, A., 2018b. Clinical evaluation of functional capacity in treatment resistant schizophrenia patients: comparison and differences with non-resistant schizophrenia patients. Schizophr. Res. 202, 217–225. https://doi.org/10.1016/j.schres.2018.06.030.
Iasevoli, F., Giordano, S., Balletta, R., Latte, G., Formato, M.V., Prinzivalli, E., De Berardis, D., Tomasetti, C., de Bartolomeis, A., 2016. Treatment resistant schizophrenia is associated with the worst community functioning among severely-ill highly-disabling psychiatric conditions and is the most relevant predictor of poorer achievements in functional milestones. Prog. Neuropsychopharmacol. Biol. Psychiatry 65, 34–48. https://doi.org/10.1016/j.pnpbp.2015.08.010.
Javed, A., Charles, A., 2018. The importance of social cognition in improving functional outcomes in schizophrenia. Front. Psychiatr. 9, 157. https://doi.org/10.3389/fpsyt.2018.00157.
Joober, R., Rouleau, G.A., Lal, S., Dixon, M., O'Driscoll, G., Palmour, R., Annable, L., Bloom, D., Lalonde, P., Labelle, A., Benkelfat, C., 2002. Neuropsychological impairments in neuroleptic-responder vs. -nonresponder schizophrenic patients and healthy volunteers. Schizophr. Res. 53 (3), 229–238. https://doi.org/10.1016/s0920-9964(01)00279-1.
Jutla, A., Foss-Feig, J., Veenstra-VanderWeele, J., 2022. Autism spectrum disorder and schizophrenia: an updated conceptual review. Autism Res. 15 (3), 384–412. https://doi.org/10.1002/aur.2659.
Kane, J., Honigfeld, G., Singer, J., Meltzer, H., 1988. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch. Gen. Psychiatry 45 (9), 789–796. https://doi.org/10.1001/archpsyc.1988.01800330013001.
Kästner, A., Begemann, M., Michel, T.M., Everts, S., Stepniak, B., Bach, C., Poustka, L., Becker, J., Banaschewski, T., Dose, M., Ehrenreich, H., 2015. Autism beyond diagnostic categories: characterization of autistic phenotypes in schizophrenia. BMC Psychiatry 15, 115. https://doi.org/10.1186/s12888-015-0494-x.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative Syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276. https://doi.org/10.1093/schbul/13.2.261.

Keefe, R.S.E., Goldberg, T.E., Harvey, P.D., Gold, J.M., Poe, M.P., Coughenour, L., 2004. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr. Res. 68 (2), 283–297. https://doi.org/10.1016/j.schres.2003.09.011.

Khanzada, N.S., Butler, M.G., Manzardo, A.M., 2017. GeneAnalytics pathway analysis and genetic overlap among autism spectrum disorder, bipolar disorder and schizophrenia. Int. J. Mol. Sci. 18 (3). https://doi.org/10.3390/ijms18030527.

Kolvin, I., 1971. Studies in the childhood psychoses. I. Diagnostic criteria and classification. Br. J. Psychiatry 118 (545), 381–384. https://doi.org/10.1192/bjp.118.545.381.

Lai, M.C., Baron-Cohen, S., 2015. Identifying the lost generation of adults with autism spectrum conditions. Lancet Psychiatry 2 (11), 1013–1027. https://doi.org/10.1016/s2215-0366(15)00277-1.

Lambrey, S., Falissard, B., Martin-Barrero, M., Bonnefoy, C., Quilici, G., Rosier, A., Guillin, O., 2010. Effectiveness of clozapine for the treatment of aggression in an adolescent with autistic disorder. J. Child Adolesc. Psychopharmacol. 20 (1), 79–80. https://doi.org/10.1089/cap.2009.0057.

Lee, S.H., Ripke, S., Neale, B.M., Faraone, S.V., Purcell, S.M., Perlis, R.H., Mowry, B.J., Thapar, A., Goddard, M.E., Witte, J.S., Absher, D., Agartz, I., Akil, H., Amin, F., Andreassen, O.A., Anjorin, A., Anney, R., Anttila, V., Arking, D.E., Asherson, P., Azevedo, M.H., Backlund, L., Badner, J.A., Bailey, A.J., Banaschewski, T., Barchas, J. D., Barnes, M.R., Barrett, T.B., Bass, N., Battaglia, A., Bauer, M., Bayés, M., Bellivier, F., Bergen, S.E., Berrettini, W., Betancur, C., Bettecken, T., Biederman, J., Binder, E.B., Black, D.W., Blackwood, D.H., Bloss, C.S., Boehnke, M., Boomsma, D.I., Breen, G., Breuer, R., Bruggeman, R., Cormican, P., Buccola, N.G., Buitelaar, J.K., Bunney, W.E., Buxbaum, J.D., Byerley, W.F., Byrne, E.M., Caesar, S., Cahn, W., Cantor, R.M., Casas, M., Chakravarti, A., Chambert, K., Choudhury, K., Cichon, S., Cloninger, C.R., Collier, D.A., Cook, E.H., Coon, H., Cormand, B., Corvin, A., Coryell, W.H., Craig, D.W., Craig, I.W., Crosbie, J., Cuccaro, M.L., Curtis, D., Czamara, D., Datta, S., Dawson, G., Day, R., De Geus, E.J., Degenhardt, F., Djurovic, S., Donohoe, G.J., Doyle, A.E., Duan, J., Dudbridge, F., Duketis, E., Ebstein, R.P., Edenberg, H.J., Elia, J., Ennis, S., Etain, B., Fanous, A., Farmer, A.E., Ferrier, I.N., Flickinger, M., Fombonne, E., Foroud, T., Frank, J., Franke, B., Fraser, C., Freedman, R., Freimer, N.B., Freitag, C.M., Friedl, M., Frisén, L., Gallagher, L., Gejman, P.V., Georgieva, L., Gershon, E.S., Geschwind, D.H., Giegling, I., Gill, M., Gordon, S.D., Gordon-Smith, K., Green, E.K., Greenwood, T.A., Grice, D.E., Gross, M., Grozeva, D., Guan, W., Gurling, H., De Haan, L., Haines, J.L., Hakonarson, H., Hallmayer, J., Hamilton, S.P., Hamshere, M.L., Hansen, T.F., Hartmann, A.M., Hautzinger, M., Heath, A.C., Henders, A.K., Herms, S., Hickie, I.B., Hipolito, M., Hoefels, S., Holmans, P.A., Holsboer, F., Hoogendijk, W.J., Hottenga, J. J., Hultman, C.M., Hus, V., Ingason, A., Ising, M., Jamain, S., Jones, E.G., Jones, I., Jones, L., Tzeng, J.Y., Kähler, A.K., Kahn, R.S., Kandaswamy, R., Keller, M.C., Kennedy, J.L., Kenny, E., Kent, L., Kim, Y., Kirov, G.K., Klauck, S.M., Klei, L., Knowles, J.A., Kohli, M.A., Koller, D.L., Konte, B., Korszun, A., Krabbendam, L., Krasucki, R., Kuntsi, J., Kwan, P., Landén, M., Långström, N., Lathrop, M., Lawrence, J., Lawson, W.B., Leboyer, M., Ledbetter, D.H., Lee, P.H., Lencz, T., Lesch, K.P., Levinson, D.F., Lewis, C.M., Li, J., Lichtenstein, P., Lieberman, J.A., Lin, D.Y., Linszen, D.H., Liu, C., Lohoff, F.W., Loo, S.K., Lord, C., Lowe, J.K., Lucae, S., MacIntyre, D.J., Madden, P.A., Maestrini, E., Magnusson, P.K., Mahon, P. B., Maier, W., Malhotra, A.K., Mane, S.M., Martin, C.L., Martin, N.G., Mattheisen, M., Matthews, K., Mattingsdal, M., McCarroll, S.A., McGhee, K.A., McGough, J.J., McGrath, P.J., McGuffin, P., McInnis, M.G., McIntosh, A., McKinney, R., McLean, A. W., McMahon, F.J., McMahon, W.M., McQuillin, A., Medeiros, H., Medland, S.E., Meier, S., Melle, I., Meng, F., Meyer, J., Middeldorp, C.M., Middleton, L., Milanova, V., Miranda, A., Monaco, A.P., Montgomery, G.W., Moran, J.L., Moreno-De-Luca, D., Morken, G., Morris, D.W., Morrow, E.M., Moskvina, V., Muglia, P., Mühleisen, T.W., Muir, W.J., Müller-Myhsok, B., Murtha, M., Myers, R.M., Myin-Germeys, I., Neale, M.C., Nelson, S.F., Nievergelt, C.M., Nikolov, I., Nimgaonkar, V., Nolen, W.A., Nöthen, M.M., Nurnberger, J.I., Nwulia, E.A., Nyholt, D.R., O'Dushlaine, C., Oades, R.D., Olincy, A., Oliveira, G., Olsen, L., Ophoff, R.A., Osby, U., Owen, M.J., Palotie, A., Parr, J.R., Paterson, A.D., Pato, C.N., Pato, M.T., Penninx, B.W., Pergadia, M.L., Pericak-Vance, M.A., Pickard, B.S., Pimm, J., Piven, J., Posthuma, D., Potash, J.B., Poustka, F., Propping, P., Puri, V., Quested, D. J., Quinn, E.M., Ramos-Quiroga, J.A., Rasmussen, H.B., Raychaudhuri, S., Rehnström, K., Reif, A., Ribasés, M., Rice, J.P., Rietschel, M., Roeder, K., Roeyers, H., Rossin, L., Rothenberger, A., Rouleau, G., Ruderfer, D., Rujescu, D., Sanders, A.R., Sanders, S.J., Santangelo, S.L., Sergeant, J.A., Schachar, R., Schalling, M., Schatzberg, A.F., Scheftner, W.A., Schellenberg, G.D., Scherer, S.W., Schork, N.J., Schulze, T.G., Schumacher, J., Schwarz, M., Scolnick, E., Scott, L.J., Shi, J., Shilling, P.D., Shyn, S.I., Silverman, J.M., Slager, S.L., Smalley, S.L., Smit, J.H., Smith, E.N., Sonuga-Barke, E.J., St Clair, D., State, M., Steffens, M., Steinhausen, H. C., Strauss, J.S., Strohmaier, J., Stroup, T.S., Sutcliffe, J.S., Szatmari, P., Szelinger, S., Thirumalai, S., Thompson, R.C., Todorov, A.A., Tozzi, F., Treutlein, J., Uhr, M., van den Oord, E.J., Van Grootheest, G., Van Os, J., Vicente, A.M., Vieland, V.J., Vincent, J.B., Visscher, P.M., Walsh, C.A., Wassink, T.H., Watson, S.J., Weissman, M. M., Werge, T., Wienker, T.F., Wijsman, E.M., Willemsen, G., Williams, N., Willsey, A. J., Witt, S.H., Xu, W., Young, A.H., Yu, T.W., Zammit, S., Zandi, P.P., Zhang, P., Zitman, F.G., Zöllner, S., Devlin, B., Kelsoe, J.R., Sklar, P., Daly, M.J., O'Donovan, M. C., Craddock, N., Sullivan, P.F., Smoller, J.W., Kendler, K.S., Wray, N.R., 2013. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat. Genet. 45 (9), 984–994. https://doi.org/10.1038/ng.2711.

Lehman, A.F., Lieberman, J.A., Dixon, L.B., McGlashan, T.H., Miller, A.L., Perkins, D.O., Kreyenbuhl, J., 2004. Practice guideline for the treatment of patients with schizophrenia, second edition. Am. J. Psychiatr. 161 (2 Suppl. l), 1–56.

Lewis, M.J., Spiliopoulou, A., Goldmann, K., Pitzalis, C., McKeigue, P., Barnes, M.R., 2023. nestedcv: an R package for fast implementation of nested cross-validation with embedded feature selection designed for transcriptomics and high-dimensional data. Bioinform. Adv. 3 (1), vbad048. https://doi.org/10.1093/bioadv/vbad048.

Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., Schopler, E., 1989. Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. J. Autism Dev. Disord. 19 (2), 185–212. https://doi.org/10.1007/bf02211841.

Lord, C., Rutter, M., Le Couteur, A., 1994. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J. Autism Dev. Disord. 24 (5), 659–685. https://doi.org/10.1007/bf02172145.

Lupu, D.S., Tint, D., Niculescu, M.D., 2012. Perinatal epigenetic determinants of cognitive and metabolic disorders. Aging Dis. 3 (6), 444–453.

Maccari, S., Polese, D., Reynaert, M.L., Amici, T., Morley-Fletcher, S., Fagioli, F., 2017. Early-life experiences and the development of adult diseases with a focus on mental illness: the Human Birth Theory. Neuroscience 342, 232–251. https://doi.org/10.1016/j.neuroscience.2016.05.042.

Mandic-Maravic, V., Grujicic, R., Milutinovic, L., Munjiza-Jovanovic, A., Pejovic-Milovancevic, M., 2021. Dopamine in autism spectrum disorders-focus on D2/D3 partial agonists and their possible use in treatment. Front. Psychiatr. 12, 787097. https://doi.org/10.3389/fpsyt.2021.787097.

Marder, S.R., Galderisi, S., 2017. The current conceptualization of negative symptoms in schizophrenia. World Psychiatry 16 (1), 14–24. https://doi.org/10.1002/wps.20385.

McGrath, J.J., Féron, F.P., Burne, T.H., Mackay-Sim, A., Eyles, D.W., 2003. The neurodevelopmental hypothesis of schizophrenia: a review of recent developments. Ann. Med. 35 (2), 86–93. https://doi.org/10.1080/07853890310010005.

Michelini, G., Carlisi, C.O., Eaton, N.R., Elison, J.T., Haltigan, J.D., Kotov, R., Krueger, R. F., Latzman, R.D., Li, J.J., Levin-Aspenson, H.F., Salum, G.A., South, S.C., Stanton, K., Waldman, I.D., Wilson, S., 2024. Where do neurodevelopmental conditions fit in transdiagnostic psychiatric frameworks? Incorporating a new neurodevelopmental spectrum. World Psychiatry 23 (3), 333–357. https://doi.org/10.1002/wps.21225.

Molent, C., Olivo, D., Wolf, R.C., Balestrieri, M., Sambataro, F., 2019. Functional neuroimaging in treatment resistant schizophrenia: a systematic review. Neurosci. Biobehav. Rev. 104, 178–190. https://doi.org/10.1016/j.neubiorev.2019.07.001.

Morosini, P.L., Magliano, L., Brambilla, La, Ugolini, S., Rjaps, Pioli, 2000. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social funtioning, 101 (4), 323–329.

Nakata, Y., Kanahara, N., Kimura, A., Niitsu, T., Komatsu, H., Oda, Y., Ishikawa, M., Hasegawa, T., Kamata, Y., Yamauchi, A., Inazumi, K., Kimura, H., Iyo, M., 2020. Autistic traits and cognitive profiles of treatment-resistant schizophrenia. Schizophr. Res. Cogn. 22, 100186. https://doi.org/10.1016/j.scog.2020.100186.

Nath, M., Wong, T.P., Srivastava, L.K., 2021. Neurodevelopmental insights into circuit dysconnectivity in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 104, 110047. https://doi.org/10.1016/j.pnpbp.2020.110047.

Nibbio, G., Barlati, S., Calzavara-Pinton, I., Necchini, N., Invernizzi, E., Dell'Ovo, D., Lisoni, J., Deste, G., Vita, A., 2022. Assessment and correlates of autistic symptoms in schizophrenia spectrum disorders measured with the PANSS autism severity score: a systematic review. Front. Psychiatr. 13, 934005. https://doi.org/10.3389/fpsyt.2022.934005.

Nucifora Jr., F.C., Woznica, E., Lee, B.J., Cascella, N., Sawa, A., 2019. Treatment resistant schizophrenia: clinical, biological, and therapeutic perspectives. Neurobiol. Dis. 131, 104257. https://doi.org/10.1016/j.nbd.2018.08.016.

Park, M.T.M., Raznahan, A., Shaw, P., Gogtay, N., Lerch, J.P., Chakravarty, M.M., 2018. Neuroanatomical phenotypes in mental illness: identifying convergent and divergent cortical phenotypes across autism, ADHD and schizophrenia. J. Psychiatry Neurosci. 43 (2), 170094. https://doi.org/10.1503/jpn.170094.

Penzes, P., Cahill, M.E., Jones, K.A., VanLeeuwen, J.E., Woolfrey, K.M., 2011. Dendritic spine pathology in neuropsychiatric disorders. Nat. Neurosci. 14 (3), 285–293. https://doi.org/10.1038/nn.2741.

Phillips, L.H., Wynn, V., McPherson, S., KjtqjoEPSA, Gilhooly, 2001. Mental planning and the Tower of London task, 54 (2), 579–597.

Pinkham, A.E., 2014. Social cognition in schizophrenia. J. Clin. Psychiatry 75 (Suppl. 2), 14–19. https://doi.org/10.4088/JCP.13065su1.04.

Rabinowitz, J., Berardo, C.G., Bugarski-Kirola, D., Marder, S., 2013. Association of prominent positive and prominent negative symptoms and functional health, well-being, healthcare-related quality of life and family burden: a CATIE analysis. Schizophr. Res. 150 (2–3), 339–342. https://doi.org/10.1016/j.schres.2013.07.014.

Remington, G., Agid, O., Foussias, G., 2011. Schizophrenia as a disorder of too little dopamine: implications for symptoms and treatment. Expert Rev. Neurother. 11 (4), 589–607. https://doi.org/10.1586/ern.10.191.

Robin, X., Turck, N., Hainard, A., Tiberti, N., Lisacek, F., Sanchez, J.C., Müller, M., 2011. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinf. 12, 77. https://doi.org/10.1186/1471-2105-12-77.

RStudio T, 2020. Rstudio P, Boston, MA.

Sahoo, S., Padhy, S.K., Singla, N., Singh, A., 2017. Effectiveness of clozapine for the treatment of psychosis and disruptive behaviour in a child with Atypical Autism: a case report and a brief review of the evidence. Asian J. Psychiatr. 29, 194–195. https://doi.org/10.1016/j.ajp.2017.07.012.

Siskind, D., Siskind, V., Kisely, S., 2017. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. Can. J. Psychiatr. 62 (11), 772–777. https://doi.org/10.1177/0706743717718167.

St Pourcain, B., Robinson, E.B., Anttila, V., Sullivan, B.B., Maller, J., Golding, J., Skuse, D., Ring, S., Evans, D.M., Zammit, S., Fisher, S.E., Neale, B.M., Anney, R.J.L., Ripke, S., Hollegaard, M.V., Werge, T., Ronald, A., Grove, J., Hougaard, D.M., Børglum, A.D., Mortensen, P.B., Daly, M.J., Davey Smith, G., 2018. ASD and schizophrenia show distinct developmental profiles in common genetic overlap with population-based social communication difficulties. Mol. Psychiatr. 23 (2), 263–270. https://doi.org/10.1038/mp.2016.198.

Sugranyes, G., Kyriakopoulos, M., Corrigall, R., Taylor, E., Frangou, S., 2011. Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. PLoS One 6 (10), e25322. https://doi.org/10.1371/journal.pone.0025322.

Sullivan, P.F., Magnusson, C., Reichenberg, A., Boman, M., Dalman, C., Davidson, M., Fruchter, E., Hultman, C.M., Lundberg, M., Långström, N., Weiser, M., Svensson, A. C., Lichtenstein, P., 2012. Family history of schizophrenia and bipolar disorder as risk factors for autism. Arch. Gen. Psychiatry 69 (11), 1099–1103. https://doi.org/10.1001/archgenpsychiatry.2012.730.

Tang, G., Gudsnuk, K., Kuo, S.H., Cotrina, M.L., Rosoklija, G., Sosunov, A., Sonders, M.S., Kanter, E., Castagna, C., Yamamoto, A., Yue, Z., Arancio, O., Peterson, B.S., Champagne, F., Dwork, A.J., Goldman, J., Sulzer, D., 2014. Loss of mTOR-dependent macroautophagy causes autistic-like synaptic pruning deficits. Neuron 83 (5), 1131–1143. https://doi.org/10.1016/j.neuron.2014.07.040.

Trevisan, D.A., Foss-Feig, J.H., Naples, A.J., Srihari, V., Anticevic, A., McPartland, J.C., 2020. Autism spectrum disorder and schizophrenia are better differentiated by positive symptoms than negative symptoms. Front. Psychiatr. 11, 548. https://doi.org/10.3389/fpsyt.2020.00548.

van den Heuvel, M.P., Fornito, A., 2014. Brain networks in schizophrenia. Neuropsychol. Rev. 24 (1), 32–48. https://doi.org/10.1007/s11065-014-9248-7.

van der Gaag, M., Hoffman, T., Remijsen, M., Hijman, R., de Haan, L., van Meijel, B., van Harten, P.N., Valmaggia, L., de Hert, M., Cuijpers, A., Wiersma, D., 2006. The five-factor model of the Positive and Negative Syndrome Scale II: a ten-fold cross-validation of a revised model. Schizophr. Res. 85 (1–3), 280–287. https://doi.org/10.1016/j.schres.2006.03.021.

Vaskinn, A., Abu-Akel, A., 2019. The interactive effect of autism and psychosis severity on theory of mind and functioning in schizophrenia. Neuropsychology 33 (2), 195–202. https://doi.org/10.1037/neu0000499.

Vita, A., Barlati, S., Deste, G., Rocca, P., Rossi, A., Bertolino, A., Aguglia, E., Amore, M., Bellomo, A., Biondi, M., Carpiniello, B., Collantoni, E., Cuomo, A., D'Ambrosio, E., Dell' Osso, L., di Giannantonio, M., Giordano, G.M., Marchesi, C., Monteleone, P., Montemagni, C., Oldani, L., Pompili, M., Roncone, R., Rossi, R., Siracusano, A., Zeppegno, P., Nibbio, G., Galderisi, S., Maj, M., 2020. The influence of autistic symptoms on social and non-social cognition and on real-life functioning in people with schizophrenia: evidence from the Italian Network for Research on Psychoses multicenter study. Eur. Psychiatry 63 (1), e98. https://doi.org/10.1192/j.eurpsy.2020.99.

Wakabayashi, A., Tojo, Y., Baron-Cohen, S., Wheelwright, S., 2004. [The Autism-Spectrum Quotient (AQ) Japanese version: evidence from high-functioning clinical group and normal adults]. Shinrigaku Kenkyu 75 (1), 78–84. https://doi.org/10.4992/jjpsy.75.78.

Zhang, Y.Q., Lin, W.P., Huang, L.P., Zhao, B., Zhang, C.C., Yin, D.M., 2021. Dopamine D2 receptor regulates cortical synaptic pruning in rodents. Nat. Commun. 12 (1), 6444. https://doi.org/10.1038/s41467-021-26769-9.

Zheng, Z., Zheng, P., Zou, X., 2018. Association between schizophrenia and autism spectrum disorder: a systematic review and meta-analysis. Autism Res. 11 (8), 1110–1119. https://doi.org/10.1002/aur.1977.

Zhou, Y., Fan, L., Qiu, C., Jiang, T., 2015. Prefrontal cortex and the dysconnectivity hypothesis of schizophrenia. Neurosci. Bull. 31 (2), 207–219. https://doi.org/10.1007/s12264-014-1502-8.

Ziermans, T.B., Schirmbeck, F., Oosterwijk, F., Geurts, H.M., de Haan, L., 2021. Autistic traits in psychotic disorders: prevalence, familial risk, and impact on social functioning. Psychol. Med. 51 (10), 1704–1713. https://doi.org/10.1017/s0033291720000458.