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Autistic symptoms in people with schizophrenia: Neurocognitive, socio-cognitive, clinical and real-world functional characteristics of individuals without autistic features

Giacomo Deste [a,*], Antonio Vita [a,b], Gabriele Nibbio [b], Stefano Barlati [a,b], David L. Penn [c,d], Amy E. Pinkham [e,f], Philip D. Harvey [g,h]

[a] Department of Mental Health and Addiction Services, ASST Spedali Civili of Brescia, Brescia, Italy
[b] Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
[c] Department of Psychology, University of North Carolina, Chapel Hill, NC, United States of America
[d] School of Psychology, Australian Catholic University, Melbourne, VIC, Australia
[e] School of Behavioral and Brain Sciences, The University of Texas at Dallas, Richardson, TX, United States of America
[f] Department of Psychiatry, University of Texas Southwestern Medical School, Dallas, TX, United States of America
[g] Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, United States of America
[h] Research Service, Miami VA Healthcare System, United States of America

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ABSTRACT

Objective: Autism spectrum disorders (ASD) symptoms are frequent in people living with schizophrenia spectrum disorders (SSD) and have a relevant impact on their daily life. However, current literature is mostly focused on investigating correlates of high levels of ASD symptoms, leaving largely unexplored the clinical, neurocognitive, socio-cognitive and functional characterization of individuals with minimal or absent ASD symptoms, which may represent a peculiar sub-population.

Methods: A total of 361 patients (mean age 41.7 years; 117 females) included in the SCOPE study were assessed with clinical, neurocognitive, socio-cognitive, functional capacity, social skills and real-world functioning measures. The severity of ASD symptoms was assessed with the PANSS Autism Severity Scale (PAUSS): individuals with a PAUSS score < 10 were considered without significant ASD symptoms.

Results: Seventy-two (19.95%) participants had no significant ASD symptoms and presented a less severe clinical status, as well as a better cognitive and socio-cognitive performance and functional profile. Lower non-autistic SSD symptoms severity and better social skills, functional capacity, global cognitive and Theory of Mind/Mental State Attribution (as measured by the Hinting task) performance and real-world social relationships emerged as predictors of non-ASD symptoms status in the logistic regression analyses.

Conclusion: Individuals without ASD symptoms represent a minority of people diagnosed with SSD that appears to be characterized by specific correlates, resulting in a less severe situation and more positive outcomes. As these factors could have a relevant impact on treatment response, assessing the severity of ASD symptoms could be an important step required to define a personalized treatment.

1. Introduction

1.1. Background

Autism spectrum disorders (ASDs) and schizophrenia spectrum disorders (SSDs) are considered separate entities in current nosological classifications as their symptoms emerge at different developmental periods and each spectrum is characterized by specific and distinctive features (American Psychiatric Association, 2013). However, autistic features were described by Eugen Bleuler as a central element of schizophrenia in one of the earliest conceptualizations of the disorder (Bleuler, 1911), and the dichotomic separation between the two spectra

* Corresponding author.
E-mail addresses: giacomodeste@mac.com (G. Deste), antonio.vita@unibs.it (A. Vita), dpenn@ad.unc.edu (D.L. Penn), amy.pinkham@utdallas.edu (A.E. Pinkham), pharvey@miami.edu (P.D. Harvey).

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has been called into question in recent years on the basis of a growing body of scientific literature (Barlati et al., 2016; Hommer and Swedo, 2015; King and Lord, 2011).

Social cognition deficits represent a central feature of both ASD and SSD (Harvey and Penn, 2010; Lai et al., 2014; Pinkham, 2014; Sasson et al., 2020), and the severity of these impairments appears to be similar across the two spectra (Boada et al., 2020; Eack et al., 2013; Oliver et al., 2020; Pinkham et al., 2019). According to a recent meta-analysis, non-social cognitive profiles of subjects diagnosed with SSD and ASD show small differences in working memory and language performance and a substantial overlap in processing speed and verbal comprehension domains, albeit presenting relevant differences in visuospatial perception and reasoning and problem solving (Kuo and Eack, 2020). Moreover, several brain imaging and genetic studies suggest that, although some essential differences can be found, ASD and SSD likely share several similarities at a neurobiological, pathophysiological and etiopathogenetic level (Barlati et al., 2020; Carroll and Owen, 2009; Eack et al., 2017; Sugranyes et al., 2011).

ASD symptoms are frequent in subjects diagnosed with SSD and have important clinical implications (Barlati et al., 2019; Bechi et al., 2020; Crescenzo et al., 2019; Kincaid et al., 2017; Ziermans et al., 2020). More severe ASD symptoms represent an individual predictor of worse socio-cognitive performance (Deste et al., 2020b) and poorer real-world social functioning (Deste et al., 2020a), and are correlated with greater impairments in the ability to self-evaluate the quality of everyday functioning (Harvey et al., 2019) and with higher levels of internalized stigma (Komatsu et al., 2020). ASD features might also be linked to poorer response to antipsychotic treatment (Downs et al., 2017; Nakata et al., 2020).

Recently, a large multicenter study, conducted on a comprehensive sample of people diagnosed with schizophrenia, found that subjects with higher levels of ASD symptoms show poorer performance on most neurocognitive domains and in social cognition, as well as poorer functional capacity, real-world interpersonal relationships and participation in community-living activities, but better social acceptability (Vita et al., 2020).

However, the role of ASD symptoms in SSD is still debated, as a positive impact on theory of mind performance and psychosocial function of co-occurring high levels of ASD and positive symptoms has been observed in another recent study (Vaskinn and Abu-Akel, 2018).

Moreover, although evidence assessing the role of ASD symptoms in SSD is recently emerging, current literature is mostly focused on subjects diagnosed with schizophrenia and with prominent or high levels of ASD symptoms, leaving the assessment of subjects with low or absent ASD symptoms largely unexplored. The majority of subjects diagnosed with schizophrenia, in fact, present some degree of ASD symptoms (Vita et al., 2020), and it is possible that individuals diagnosed with SSD and without ASD features might be characterized by specific clinical and cognitive correlates. In particular, they may show peculiar traits that could go beyond a lower level of impairment in the domains that are influenced by high levels of ASD symptoms. Investigating the features that characterize people diagnosed with SSD without ASD features could be potentially useful not only with the purpose of better defining their clinical condition, but also in the perspective of providing a personalized treatment and implementing individualized psychosocial interventions (Maj et al., 2021).

1.2. Aims

The aim of the present study was to investigate the clinical, cognitive and real-world functional characteristics of individuals diagnosed with SSD without ASD symptoms, compared with subjects presenting ASD symptoms, in a large sample of clinically stable outpatients living in the community. The amount of variance accounted for by clinical, cognitive, and real-world functioning in the absence of ASD symptoms will also be assessed.

Our primary hypothesis is that subjects diagnosed with SSD and without ASD features might represent a sub-population characterized by specific correlates, including better performance in some socio-cognitive domains such as Emotion Recognition and Theory of Mind/Attribution of Mental State and better real-world psychosocial functioning.

2. Materials and methods

2.1. Participants

Data analyzed in the present study were obtained by merging the datasets gathered for the third and the fifth phase of the Social Cognition Psychometric Evaluation (SCOPE) research project, a multi-center study assessing clinical, cognitive and functional characteristics of people diagnosed with SSD and focusing on subjects' performance in different domains of social cognition.

The SCOPE Phase 3 study (Pinkham et al., 2016) included a total of 179 subjects recruited at 2 sites, the Southern Methodist University and the Miami Miller School of Medicine, while the SCOPE Phase 5 study (Pinkham et al., 2018) included a total of 218 subjects recruited at 3 sites, the University of Texas at Dallas, the University of Miami Miller School of Medicine, and the University of North Carolina at Chapel Hill. As 36 subjects participated in both phases, their duplicate entries were removed in the final database, and a total of 361 participants were included in the present analysis.

Inclusion and exclusion criteria were identical across the two studies.

Inclusion criteria were: (I) diagnosis of Schizophrenia or Schizoaffective Disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994), confirmed with the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) and the Structured Clinical Interview for DSM Disorders Psychosis Module (First et al., 2002), (II) clinical stability, defined as the absence of any hospitalization occurring in the previous two months, the absence of any change in the medication regimen in the previous 6 weeks, and the absence of any medication dosage change in the previous 2 weeks.

Exclusion criteria were: (I) presence or history of pervasive developmental disorder, including ASD, or of mental retardation with an IQ < 70, as defined by the diagnostic criteria reported in the DSM-IV, (II) presence or history of any medical or neurological illness that could have a negative impact on the functioning of the central nervous system, such as epilepsy, seizures, neoplasms of the central nervous system structures, inflammatory or autoimmune disorders affecting the central nervous system, (III) presence of visual or hearing impairment that could limit the assessment, (IV) no or very limited proficiency with English language, (V) presence of substance abuse in the past month, (VI) presence of active substance dependence in the past six months.

2.2. Measures

2.2.1. Clinical assessment

Socio-demographic characteristics such as age, gender and years of education were collected for each participant. Premorbid IQ was also taken into account, and was assessed with the Wide Range Achievement Test- 3 Reading subscale (WRAT-3) (Weickert et al., 2000).

All participants were assessed with the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987) to evaluate SSD symptoms severity.

Functional capacity was assessed with the UCSD Performance-Based Skills Assessment, Brief (UPSA-B) (Mausbach et al., 2007), while social competence was assessed with the Social Skills Performance Assessment (SSPA) (Patterson et al., 2001).

2.2.2. Cognitive assessment

The neurocognitive assessment was composed of a subset of tests from the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein

et al., 2008): Trail Making Test - Part A (TMT-A); BACS Symbol Coding; Category Fluency (Animal Naming); Letter-Number Span; and Hopkins Verbal Learning Test - Revised (HVLT-R). Following the recommendation of the developers of the battery, a global composite score was calculated by averaging the t-scores of all the tests (Nuechterlein and Green, 2006).

Assessment of social cognition included the Bell Lysaker Emotion Recognition Task (BLERT) (Bryson et al., 1997) and the Penn Emotion Recognition Text (ER-40) (Kohler et al., 2003) for the Emotion Processing domain and the Reading the Mind in the Eyes Test (Eyes) (Baron-Cohen et al., 2001), The Awareness of Social Inferences Test, Part 3 (TASIT) (McDonald et al., 2003) and the Hinting Task (Hinting) (Corcoran et al., 1995) for the Theory of Mind/Attribution of Mental State domain.

2.2.3. Real-world outcomes assessment

Real-world functional outcomes were assessed with the Specific Level of Functioning Scale (SLOF) (Schneider and Struening, 1983) including three informant-rated subscales: interpersonal relationships, participation in activities and work skills. Informants were trained study personnel who utilized all-sources of information to generate judgments including patient self-reports, community informants, and interaction with study staff.

The SLOF represents a reliable and valid tool for the assessment of real-world outcome in subjects diagnosed with schizophrenia, with good construct validity and high internal consistency (Harvey et al., 2011; Mucci et al., 2014).

2.2.4. ASD symptoms assessment

ASD symptoms were assessed with the PANSS Autism Severity Score (PAUSS) (Kästner et al., 2015), a scale designed to measure ASD symptoms in subjects diagnosed with SSD and derived from the PANSS.

The validity of the PAUSS has been compared to that of more established but time -consuming diagnostic tools for the assessment of ASD, such as the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989) and the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994), and shows adequate sensitivity in detecting ASD symptoms in people with SSD (Deste et al., 2018; Pina-Camacho et al., 2020).

It has also been used in genetic (Ehrenreich et al., 2018; Stepniak et al., 2015) and neuroimaging studies (Oliveira et al., 2018; Parellada et al., 2017) analyzing neurobiological correlates of ASD features.

According to the cut-off scores identified by the scale Authors in the original validation study of the PAUSS (Kästner et al., 2015), participants were divided into two different groups: subjects without ASD symptoms, also defined as "non-autistic schizophrenia" (PAUSS $\leq$10), and subjects presenting ASD symptoms, or with "moderate ASD symptoms" and "autistic schizophrenia" (PAUSS >11). This cut-off represents the first percentile in the distribution of ASD symptoms in the original validation study, requiring that all items have a score of 1 ("absent") with at most two having a score of 2 ("minimal") or one a score of 3 ("mild"). Therefore, individuals fulfilling this criterion are defined as an "extreme group" by the scale Authors, characterized by the substantial absence of ASD symptoms.

2.3. Statistical analyses

Subjects with and without ASD symptoms, identified with the PAUSS cut-off score, were compared on demographic, clinical, cognitive, and real-world outcomes measures using Pearson's χ^2 test for dichotomous variables and *t*-test for continuous variables. Parametric tests were adopted regardless of the distribution of the data due to the large size of the investigated sample and in order to avoid false negatives (or type II errors) (Elliott and Woodward, 2007; Ghasemi and Zahediasl, 2012).

Variables emerging as significant in the between-groups univariate analyses were introduced as potential predictors in three multivariate forward logistical regression analyses, one for socio-demographic and clinical characteristics, one for cognitive performance assessments and one for real-world functional outcomes, in order to investigate individual predictors of ASD symptom absence. The number of potential predictors in each model was lower than one for every twenty observed subjects so the number of the included predictors was considered appropriate (Austin and Steyerberg, 2015; Schmidt, 1971). Of note, PANSSminusPAUSS score was included in the regression model for clinical characteristics. PANSSminusPAUSS includes all PANSS items that are not components of the PAUSS, and accurately assesses the severity of non-autistic symptoms, avoiding potential collinearity with the PAUSS. This approach has been previously validated in other studies conducted on a large sample of participants diagnosed with SSD (Deste et al., 2020b; Vita et al., 2020).

Statistical analyses were performed using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA), and p-values <0.05 (2 tailed) were considered significant.

3. Results

3.1. Univariate analyses

Of the 361 subjects included in the study, 72 (19.95%) had a PAUSS score $\leq$ 10 and were considered without ASD symptoms, while 289 (80.05%) had a PAUSS score > 10 and were considered with ASD symptoms.

Results of between-groups comparisons are reported in Table 1.

No between-group difference emerged as regards gender distribution (chi-square 0.220, p = 0.639).

Patients without ASD symptoms showed higher premorbid IQ, less severe non-autistic SSD symptoms, better functional capacity and better social skills.

As regards cognitive assessment, patients without ASD symptoms

Table 1
Differences between patients without ASD symptoms (Non-ASDS, PAUSS $\leq$10, n = 72) and patients with ASD symptoms (ASDS, PAUSS >10, n = 289) (*t*-tests).

Variable	Non-ASDS (PAUSS $\leq$ 10) (mean ± SD)	ASDS (PAUSS > 10) (mean ± SD)	*t*-Test p	Cohen's d
Age	39.68 ± 11.35	42.23 ± 12.15	0.107	0.216
Education years	13.11 ± 1.96	12.84 ± 2.43	0.323	0.122
WRAT-3 Standard Score (Premorbid IQ)	97.88 ± 15.39	93.64 ± 15.08	**0.034**	0.278
Neurocog (Global Cognition)	41.53 ± 5.84	37.48 ± 7.23	**<0.001**	0.616
PANSS (Symptoms Severity)	48.45 ± 10.29	65.27 ± 14.44	**<0.001**	1.34
PANSSminusPAUSS (Non-autistic SSD Symptoms Severity)	39.22 ± 10.28	48.40 ± 11.74	**<0.001**	0.801
UPSA-B (Functional Capacity)	77.27 ± 11.19	67.92 ± 14.26	**<0.001**	0.729
SSPA (Social skills)	4.39 ± 0.42	4.04 ± 0.53	**<0.001**	0.731
BLERT (Social Cognition, Emotion processing)	14.44 ± 3.62	13.28 ± 4.07	**0.028**	0.301
ER-40 (Social Cognition, Emotion processing)	31.38 ± 4.32	29.94 ± 5.32	**0.017**	0.297
EYES (Social Cognition, Theory of Mind)	22.47 ± 4.93	20.25 ± 5.52	**0.002**	0.424
HINTING (Social Cognition, Theory of Mind)	14.75 ± 3.01	13.00 ± 3.92	**<0.001**	0.500
TASIT (Social Cognition, Theory of Mind)	47.61 ± 7.29	43.82 ± 7.48	**<0.001**	0.513
SLOF: Interpersonal Relationship	3.83 ± 0.75	3.20 ± 0.84	**<0.001**	0.791
SLOF: Activities	4.78 ± 0.75	4.44 ± 0.81	**0.001**	0.435
SLOF: Work	4.00 ± 0.69	3.66 ± 0.84	**0.001**	0.442

had better cognitive performance in global cognition and in each of the social cognition tasks.

Finally, patients without ASD symptoms had better real-world functional outcomes in interpersonal relationships, participation in community activities and work skills.

3.2. Regression analyses

Results of the regression analysis investigating socio-demographic and clinical predictors of ASD symptoms absence are reported in Table 2.

Lower non-autistic SSD symptoms severity, better social skills and better functional capacity emerged as significant individual predictors of the absence of ASD symptoms.

As concerns the results of the analysis including performance in cognitive tasks as potential predictors, results are reported in Table 3.

Better global cognitive performance and better Theory of Mind/Mental State Attribution, as measured by the Hinting task emerged as significant individual predictors of belonging to the "non autistic schizophrenia" group.

Results of the analysis concerning real-world functional outcomes are reported in Table 4: only better real-world social relationships emerged as significant individual predictor of the absence of ASD symptoms.

4. Discussion

Results of the current study show that individuals with some measure of ASD symptoms represented the vast majority of the sample, while those without ASD symptoms were a minority. This finding is line with previous literature, confirming that various degrees of ASD symptoms are a common feature in people with SSD (Crescenzo et al., 2019; Stanghellini et al., 2014; Ziermans et al., 2020).

Individuals diagnosed with SSD that had few or no autistic features were significantly different from other SSD subjects in a number of clinical, cognitive and real-world functional characteristics, with a clinically less severe presentation of the disorder.

In fact, subjects without ASD symptoms showed lower non-autistic SSD symptoms severity, better social skills and better functional capacity, and well as better cognitive performance both in social and non-social cognition. Real world social functioning was the only everyday functioning variable discriminating the groups, in line with the idea that ASD have substantial social impacts.

Among the different validated measures of social cognition included in the present study, measuring the domains of emotion recognition and Theory of Mind/mental state attribution, only the Hinting Task emerged as a significant predictor in the multivariate regression analysis. This finding, beside confirming the usefulness of the Hinting Task in both research and clinical settings, suggests that individuals diagnosed with SSD and without ASD symptoms show better social cognitive skills, and in particular better higher level inferential processing, which are closely related to social functioning (Buck et al., 2016).

To the best of our knowledge, this represents the first study to specifically evaluate clinical, cognitive and real-world outcomes of subjects with a well-defined SSD diagnosis showing no ASD symptoms. However, our results in a way reflect those of studies evaluating features of subjects with high levels of ASD symptoms that show a more severe clinical picture and more severe impairment in those with greater ASD symptoms (Vita et al., 2020).

Taken together, these findings confirm the results of previous studies reporting that ASD symptoms have a relevant and negative impact on the clinical situation and on real-world outcomes of individuals diagnosed with SSD (Deste et al., 2020a, 2020b; Harvey et al., 2019), and suggest that individuals diagnosed with SSD without ASD symptoms might represent a group of subjects characterized by specific clinical, cognitive and functional features, in particular those related to social interactions.

In the perspective of better characterizing the clinical profile of each patient and personalizing treatment, which represents an essential goal in the management of SSD (Hamburg and Collins, 2010; Jones and Harvey, 2020; Maj et al., 2021), assessing the severity of ASD symptoms might represent an important step, especially due to their direct impact on real-world outcomes. In the context of everyday clinical practice, the PAUSS might represent a quick and valid tool for the investigation of ASD features patients with SSD.

In particular, individuals diagnosed with SSD and without ASD symptoms might show differences in treatment response, as recent evidence suggests that ASD features are related to antipsychotic treatment resistance (Downs et al., 2017; Nakata et al., 2020). Furthermore, since better cognitive performance represents a predictor of functional recovery (Santesteban-Echarri et al., 2017), these individuals could also be

Table 2
Clinical predictors of absence of ASD Symptoms (Non-ASDS, PAUSS ≤10).

Dependent variables	Individual predictors	B	Exp (B)	p
Non-ASDS PAUSS ≤ 10	PANSSminusPAUSS	−0.064	1.066	<0.001
	SSPA	1.225	0.285	0.001
	UPSA-B	0.040	0.961	0.002
	Model: $Chi^2 = 64.713$			<0.001
	Cox-Snell $R^2 = 0.172$, Nagelkerke $R^2 = 0.270$			
	Variables not included in the model	**Score**		**p**
	WRAT-3	0.927		0.336

Potential predictors: PANSSminusPAUSS (Symptoms Severity), UPSA-B (Functional Capacity), SSPA (Social Skills), WRAT 3 Standard Score (premorbid IQ). Forward Stepwise.

Table 3
Cognitive and social cognitive predictors of absence of ASD Symptoms (Non-ASDS, PAUSS ≤10).

Dependent variables	Individual predictors	B	Exp (B)	p
Non-ASDS PAUSS ≤ 10	Neurocog	0.065	0.937	0.002
	HINTING	0.113	0.893	0.014
	Model: $Chi^2 = 27.764$			<0.001
	Cox-Snell $R^2 = 0.069$, Nagelkerke $R^2 = 0.110$			
	Variables not included in the model	**Score**		**p**
	BLERT	0.002		0.965
	ER-40	0.208		0.648
	EYES	0.237		0.627
	TASIT	2.787		0.095

Potential predictors: Neurocog (Global Cognition), BLERT (Social cognition, Emotion processing), ER-40 (Social cognition, Emotion processing), EYES (Social cognition, Theory of Mind), HINTING (Social cognition, Theory of Mind), TASIT (Social cognition, Theory of Mind). Forward Stepwise.

Table 4
Real-world outcome predictors of absence of ASD Symptoms (Non-ASDS, PAUSS ≤10).

Dependent variables	Individual predictors	B	Exp (B)	p
Non-ASDS PAUSS ≤ 10	SLOF: Interpersonal Relationships	0.905	0.405	<0.001
	Model: $Chi^2 = 31.496$			<0.001
	Cox-Snell $R^2 = 0.084$, Nagelkerke $R^2 = 0.199$			
	Variables not included in the model	**Score**		**p**
	SLOF: Activities	3.758		0.053
	SLOF: Work	0.519		0.471

Potential predictors: SLOF: Interpersonal Relationships, SLOF: Activities, SLOF: Work. Forward Stepwise.

identified as valid candidates for evidence-based psychiatric rehabilitation interventions (Nibbio et al., 2020; Vita et al., 2021; Vita and Barlati, 2019). These hypotheses, however, remain to be adequately verified by methodologically accurate studies.

This study has some limitations. As some items of the PANSS negative subscale are included in the PAUSS, it could be argued that a measure of overlap between negative and ASD symptom might be observed with this tool. However, the independent validity of the PAUSS was previously assessed in large samples of SSD patients (Deste et al., 2018; Kästner et al., 2015). Moreover, the PANSSminusPAUSS score was included in the regression model evaluating clinical characteristics; therefore, the relative impact of SSD symptoms on other clinical parameters was taken into account.

The SCOPE project, from which the databases analyzed in this study were obtained, was not designed to specifically investigate the role of ASD symptoms in SSD and their impact on real-world functioning. For this reason, some aspects of global real-world functioning, such as physical functioning or self-care skills were not included in the assessment.

Beyond these limitations, the findings of the present study confirm the relevant role of ASD symptoms in the clinical, cognitive and, most importantly, real-world functional situation of people living with SSD. Subjects without ASD symptoms might represent a minority of individuals with SSD that might be characterized by specific correlates, resulting in a less severe situation and more positive outcomes.

Future studies should include longitudinal observations of SSD subjects with various degrees of ASD symptoms severity, to better assess the role of these features on various outcomes and to better establish if ASD symptoms represent a trait or a state variable in SSD patients. More research is also warranted in order to evaluate neurobiological and molecular aspects of ASD features in subjects with SSD, as neuroimaging characteristics of SSD subjects with no ASD symptoms, intermediate ASD symptoms and prominent ASD symptoms remain to be separately evaluated and compared.

Finally, evaluating if different levels of ASD symptoms severity could have an impact on the response to pharmacological treatment or to specific psychosocial interventions remains an important clinical issue that requires further exploration.

Data availability statement

The datasets used in this study are available upon reasonable request from Dr. Philip Harvey at the following e-mail address: pharvey@miami.edu.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics Committees at the University of Miami, University of Texas at Dallas, and the University of North Carolina at Chapel Hill. The University of Miami IRB has agreed the current analyses are exempt from review as human subjects because of the de-identified nature of the data. The patients/participants provided their written informed consent to participate in this study.

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CRediT authorship contribution statement

AP, DP, and PH participated in the design of the study and edited the paper. PH also reviewed and discussed the data and statistical analyses and the final version of the paper. GN prepared the database and participated in the analyses. GD and SB participated in the analyses and wrote the paper. AV participated in the design of the project and discussion of the data and manuscript. All authors contributed to and approved the final manuscript.

Declaration of competing interest

In the last year PH has received consulting fees or travel reimbursements from Acadia Pharma, Alkermes, Bio Excel, Boehringer Ingelheim, Minerva Pharma, Regeneron Pharma, and Sunovion Pharma during the past year. He has signed contracts but received no compensation to date from Karuna Pharma and Takeda Pharma. He receives royalties from the Brief Assessment of Cognition in Schizophrenia (Owned by Verasci, Inc.). He is chief scientific officer of i-Function, Inc. He had a research grant from Takeda and from the Stanley Medical Research Foundation.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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All authors who contributed to this paper are listed as authors. No professional medical writer was involved in any portion of the preparation of the manuscript.

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