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Schizophrenia Following Early Adolescence Prodrome: A Neurodevelopmental Subtype With Autism-like Sensorimotor and Social Cognition Deficits

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Anton Iftimovici and Gilles Martinez are considered co-first authors of this work.

***Background and Hypothesis*: While age at onset in schizophrenia (SCZ) is usually defined by age at onset of psychosis, the illness actually occurs earlier, with a prodrome often starting in childhood or adolescence. We postulated that SCZ with early-adolescence prodromes (SCZ-eaP) presents with social cognition deficits and sensorimotor impairments more similar to autism spectrum disorders (ASD) than SCZ with late-adolescence prodromes (SCZ-laP).**

***Study Design*: The movie for the assessment of social cognition and neurological soft signs (NSS) were compared between four groups, ASD, SCZ-eaP (<15 years), SCZ-laP (>15 years), and controls ($N = 119$), while accounting for age, sex, intelligence quotient, education level, and medication effect. Mediation analyses tested the effect of NSS on social cognition, across groups, and local gyrification indices were used to test whether NSS reflected deviations in early neurodevelopmental trajectories.**

***Study Results*: For social cognition and NSS, subjects with ASD were not different from SCZ-eaP, while they differed from SCZ-laP. Age at onset of prodrome correlated with NSS ($r = -0.34$, $P = .018$), and social cognition ($r = 0.28$, $P = .048$). Neurological soft signs mediated social cognition impairment across diagnoses ($\beta = -1.24$, $P < 1e^{-6}$), and was explained by hypergyrification in the right fusiform gyrus, right frontal pole gyrus, and left postcentral gyrus.**

***Conclusions*: Earlier age of prodrome in SCZ is associated with impaired social cognition, mediated by neurodevelopmentally-related sensorimotor impairments along the ASD-SCZ spectrum. It suggests age of prodrome, rather than the age at psychosis onset, should be considered to define more homogeneous subgroups in SCZ.**

Key words: psychosis; prodrome; neurological soft signs; neuroimaging.

Introduction

Schizophrenia (SCZ) classically begins in late adolescence or young adulthood. But it is now well established that prodromal signs precede the onset of full-blown SCZ and could reflect the actual onset of illness. Since puberty and the subsequent maturation processes correspond to a timeframe of both social and biological transformations that affect the last stages of brain maturation[1] and the risk of psychosis,[2] a disease onset before or during this period may reflect a higher developmental vulnerability than a disease starting after puberty. Supporting this view, the rare childhood- or early-onset SCZ (before 13 years of age) are known to have a stronger biological overlap with autism spectrum disorders (ASDs) than adolescence- and adult-onset SCZ.[3,4]

Deficits in social cognition are core features both to SCZ and ASD, and they lead to poor functional outcomes and severe daily-life disability.[5,6] This multidimensional construct is defined by the progressive acquisition of several dimensions during development: basic social cognition (eg, emotional processing) in early childhood, and more complex social abilities relating to mentalization and the perception of social cues later on.[7–9] Social cognition can be measured using the Movie for the Assessment of Social Cognition (MASC),[10] previously shown to accurately distinguish between young adults with SCZ and those with ASD, who displayed the most difficulties.[11]

Sensorimotor anomalies, assessed by neurological soft signs (NSS), correspond to subtle neurological abnormalities in motor coordination and integration, and in sensory integration. While they are common in neurotypical children and reflect brain immaturity, NSS are strongly associated with cognition,[12] and their persistence into adulthood is considered an indicator of neurodevelopmental burden.[13–15] They are an established vulnerability marker in SCZ,[16] where they may translate diffuse brain structural changes.[17] Like social cognition, NSS are an important predictor of long-term functional[18] and clinical outcomes in SCZ,[19] as well as early treatment response.[20]

While both social cognition and NSS are linked to neurodevelopment, there is little data on their interaction, despite growing evidence of relationships between social cognition and sensorimotor systems. Clinically, social and sensorimotor deficits are strongly intertwined in neurodevelopmental disorders such as ASD or Attention-Deficit/Hyperactivity disorder.[21] In the general population, lateralization anomalies reflecting sensorimotor biases have been found to be significantly associated with self-reported social difficulties.[22] From a neuroanatomic perspective, there is an overlap in brain networks involved in social cognition and sensorimotricity, supporting the idea of embodied social cognition.[23] This paradigm maintains that inference of other individuals' intentions relies in part on social mirroring, based on the interpretation of their goal-directed actions through the understanding of their movements, known as motor resonance.[9] This is supported by literature implicating the posterior cerebellum,[24,25] and, more recently, by the demonstration that spatial coding of observed actions depends on others' social relevance.[26]

In this context, quantification of cortical gyrification in structural neuroimaging further provides a means of transdiagnostically assessing whether NSS observed during adulthood is linked to early neurodevelopment. Indeed, the organization of (convex) gyri and (concave) sulci starts in utero during the third fetal trimester[27] and culminates during toddlerhood.[28] Its destabilization by genetic factors or early environmental exposures may result in decreases or increases in gyrification, quantified by the local gyrification index (LGI),[29] which constitutes a marker of early life events that are less affected by age, specific psychiatric pathophysiology, and psychotropic drugs than the gray matter volume.[30]

Here, we explore the hypothesis that SCZ with prodromes starting before the age of 15 (SCZ-eaP) has a higher neurodevelopmental burden resulting in a profile closer to ASD than SCZ with late-adolescence prodromes (SCZ-laP) in terms of social cognition, sensorimotor anomalies, and their underlying gyrification correlates in structural neuroimaging. We then test how the sensorimotor dimensions mediate social cognition variation transdiagnostically, before evaluating the relevance of using NSS as a neurodevelopmental proxy by correlating them with brain gyrification.

Methods

Participants

Young adult participants ($N = 119$, 18-30 years old) were prospectively recruited in the study "From Autism to Schizophrenia" (AUSZ), from April 2012 to February 2017 in Sainte-Anne's Hospital (GHU Paris Psychiatrie and Neurosciences, Paris, France). Four groups were defined: (1) 30 subjects with ASD without intellectual deficit (high-functioning autism or Asperger syndrome), (2) 25 subjects with adult-onset SCZ after an early-adolescence prodromal phase that began before age 15 (SCZ-eaP), (3) 34 subjects with adult-onset SCZ after a late-adolescence prodromal phase that began after age 15 (SCZ-laP), and (4) 30 healthy controls (CTRL) matched for age and sex. Autism spectrum disorder subjects were diagnosed using the Autism Diagnostic Interview—Revised[31] and the Diagnostic and Statistical Manual of Mental Disorders revised fourth edition (DSM-IV-TR criteria). The Diagnostic Interview for Genetic Studies 3.0 (DIGS) was used to ascertain the diagnosis of SCZ (DSM-IV-TR criteria) and to exclude any comorbidity in ASD or Axis 1 disorder in controls.[32] The nature and duration of the prodromal phase of SCZ were assessed with the Comprehensive Assessment of At-Risk Mental States,[33] by psychiatrists trained in the administration of this semi-structured psychometric scale. The participants were all French native speakers, educated in France. The main exclusion criteria were: Intelligence quotient (IQ) <70, neurological or any severe medical condition, recent substance abuse or history of dependence >5 years (except for smoking), schizo-affective disorder, current mood disorder, suicidal risk, use of benzodiazepines, antidepressant medication initiated during the last 3 weeks and, for ASD, an additional diagnosis of SCZ. Additional exclusion criteria for CTRL were a history of Axis 1 disorder, a family history of psychosis or developmental disorders (up to the second degree), and any psychotropic medication. All subjects, patients, and controls, underwent several assessments: (i) a clinical evaluation, for positive, negative, and general symptomatology with the Positive and Negative Symptoms Scale (PANSS)[34]; (2) a general cognitive evaluation of IQ with the WAIS-III scale; (3) an assessment of the years of education; and (4) an evaluation of antipsychotic medication, computed in chlorpromazine equivalence.

Social Cognition Evaluation

All participants were assessed with the French version of the MASC, previously validated in ASD, SCZ. and CTRL.[10,11,35] The MASC is a 15-minute film depicting 4 characters who meet for a party. The first slides describe the test and introduce the characters. Subjects are asked to imagine what the characters are thinking or feeling at the very moment the film is stopped. Then, the movie is presented and stopped at various points, and questions are asked. Through these 45 questions, subjects are asked about the mental states of the characters (epistemic, emotional, and volitional). One answer is to be picked among 4 options: (1) the correct one, (2) "under-mentalizing," (3) lack of mental state attribution, and (4) "over-mentalizing." Six additional control questions assess the subject's non-social inference abilities. There is no time limitation. Administration of the test takes 30-45 minutes. The MASC provides a sum score for all mental state decoding questions (maximum 45) and 3 scores for errors related to lack of mental state attribution, under-mentalizing, and over-mentalizing.

Sensorimotor Examination

Neurological soft signs examination comprised 23 items divided into 3 factors (motor integration, motor coordination, and sensory integration) investigating gait and balance, coordination precision on various praxis tasks, speed and dysrhythmia in rapid alternating movements, stereognosis and graphesthesia, lateral preference and right/left discrimination.[36] For every item, the rating ranges from 0 to 3, with an explicit definition and descriptive anchors. This scale showed good Internal consistency (Cronbach's $\alpha = .85$) and inter-rater reliability (score of 0.82) in a previous study.[36] In addition, Parkinsonism, akathisia, and dyskinesia were assessed, respectively, with the Simpson Angus scale,[37] the Barnes Akathisia Rating Scale (BARS),[38] and the Abnormal Involuntary Movement Scale (AIMS).[39]

MRI Features Extraction

Magnetic resonance imaging (MRI) was acquired on the same site at Sainte-Anne Hospital, GHU Paris Psychiatrie & Neurosciences, using a 3D T1-weighted spoiled gradient-recalled echo sequence (excitation time 2.2 ms, inversion time 450 ms, flip angle 15°, bandpass 11.90 kHz, field of view 24 cm, slicing window 1.2 mm, matrix 256 × 256, 1 excitation, and 124 axial slices). Regions of interest (ROI) measurements were obtained using Freesurfer, Stable v7.1.1 (http://surfer.nmr.mgh.harvard.edu/), from which 68 LGIs were computed.

Statistical Analysis

For descriptive statistics between the groups, we applied Chi-square and one-way analysisi of variance (ANOVA) tests, with pairwise post-hoc Tukey tests, and a Bonferroni correction for 14 comparisons (corrected *P*-value set to .003). In order to test the main hypothesis of the effect of the diagnostic group on social cognition or NSS, we used analysis of covariance (ANCOVA) includes NSS or MASC as dependent variables, diagnosis as the explanatory "between" variable and medication, and level of education as covariates, to account for their previously identified significant variation between groups. For this analysis, we used a Bonferroni correction threshold set at 0.006 to account for the 8 tests done related to the main hypothesis (differences of NSS, MASC, and their subscales). Post-hoc Tukey tests were also corrected for the 6 pairwise tests for each ANOVA/ANCOVA, with a threshold set at 0.008. We further assessed the correlation between NSS and MASC totals using Pearson's correlation coefficient. Causal mediation analysis was used to test whether NSS mediated the variation of total MASC scores across diagnoses while controlling for education level and medication. This was done with the bias-corrected non-parametric bootstrap method provided in Python by the Pingouin package.[40,41] Finally, for each of the 68 local gyrification indices, we applied a linear regression to test whether it could explain NSS variation, after controlling for age, sex, and medication effect. We report the coefficient of the regression slopes, after a stringent Bonferroni correction for 68 tests set to 0.0007.

Results

Sociodemographic and Clinical Comparisons

There were no differences between SCZ-eaP, SCZ-laP, ASD, and CTRL for age, sex ratio, and total IQ. Education level was slightly higher in CTRL compared to SCZ-eaP, SCZ-laP, and ASD, yet similar among the three groups of patients. As predefined by a threshold set at 15 years, SCZ-eaP had a lower average age of onset of prodromal symptoms (10.9 ± 3.7 years) than SCZ-laP (17.5 ± 3.0 years), while both SCZ groups were diagnosed at similar ages, around 20 years. Clinically, SCZ patients were relatively stabilized under medication with PANSS scores in the lower range, with only SCZ-eaP having significantly higher positive symptoms than ASD, and no difference between all groups for negative symptoms. There was no significant clinical difference in the PANSS between SCZ-eaP and SCZ-laP. Both SCZ groups were under significantly more antipsychotic medication than the ASD group where only 7 patients were treated with antipsychotics. Nevertheless, there was no significant difference in akathisic or dyskinetic symptoms between the groups. There was no difference in medication between SCZ-eaP and SCZ-laP, but ASD had nonetheless more extrapyramidal symptoms than SCZ-eaP (**Table 1**).

Social Cognition and NSS Across Diagnostic Groups

Even when controlling for the effect of antipsychotic medication and level of education, the ANCOVA found

Table 1. Sociodemographic and Clinical Characteristics

	Diagnostic groups				ANOVA tests		Post-hoc Tukey tests					
	CTRL	SCZ-laP	SCZ-eaP	ASD	$F(X^2)$	P	ASD vs CTRL	ASD vs SCZ-laP	ASD vs SCZ-eaP	CTRL vs SCZ-laP	CTRL vs SCZ-eaP	SCZ-laP vs SCZ-eaP
Sociodemographic characteristics												
Number of subjects	30	34	25	30								
Age at inclusion	22.77 ± 3.09	23.0 ± 3.3	22.8 ± 3.3	22.3 ± 3.3	0.25	0.86						
Age of onset of prodrome		17.5 ± 3.0	10.9 ± 3.7		27.02	**<1e^{-6}**						
Age of onset of schizophrenia		20.4 ± 2.6	19.0 ± 3.4		1.57	0.21						
Sex (F/M)	6/24	6/28	5/20	6/24	0.06	0.99						
Years of education	14.3 ± 2.2	12.2 ± 2.2	11.6 ± 2.5	12.2 ± 2.5	6.85	**3e^{-4}**	**0.006**	0.99	1	**0.006**	**3e^{-4}**	0.70
Total intellectual quotient	102.5 ± 24.2	96.3 ± 24.5	91.1 ± 12.1	98.1 ± 17.4	1.25	0.30	0.86	0.99	1	0.68	0.23	0.81
Positive and negative syndrome scale (PANSS)												
Positive		12.9 ± 4.8	15.9 ± 4.7	10.1 ± 3.8	91.96	**<1e^{-6}**		**0.023**	**1e^{-6}**			**0.020**
Negative		17.8 ± 7.3	22.8 ± 6.5	19.8 ± 9.0	69.19	**<1e^{-6}**		0.63	0.34			**0.026**
General Psychopathology		30.4 ± 8.6	37.8 ± 11.8	33.0 ± 12.6	95.24	**<1e^{-6}**		0.71	0.25			**0.021**
Total		61.2 ± 17.6	76.5 ± 21.2	62.9 ± 22.4	109.6	**<1e^{-6}**		0.98	0.026			**0.007**
Medication and side effects												
Proportion on medication (%)	0%	97% (33/34)	96% (24/25)	23% (7/30)								
Olanzapine equivalent (mg)		14.1 ± 20.0	15.2 ± 15.2	3.4 ± 10.3	9.0	**2e^{-5}**		**0.013**	**<1e^{-6}**			0.99
Extrapyramidal symptoms	0.52 ± 0.94	3.50 ± 3.94	3.30 ± 3.57	4.81 ± 2.93	9.47	**1e^{-5}**	**8e^{-6}**	0.41	**<1e^{-6}**	**0.003**	**0.013**	1
Akathisia	0.15 ± 0.53	0.55 ± 1.38	3.64 ± 6.67	1.92 ± 4.44	4.04	0.009	0.34	0.55	**<1e^{-6}**	0.98	**0.011**	**0.028**
Dyskinesia	0.08 ± 0.39	0.46 ± 1.75	3.73 ± 8.13	4.08 ± 5.87	4.76	0.004	**0.020**	**0.038**	1	0.99	0.054	0.094

Bonferroni significance threshold for the 8 ANOVA tests set to 0.003. Bonferroni significance threshold for the 6 subsequent pairwise post-hoc Tukey tests was set at 0.008 (significant p-values under this threshold in bold). Current medication in chlorpromazine equivalent (mg; all medicated patients received atypical antipsychotics); extrapyramidal side effects, akathisia, and dyskinesia were assessed respectively with the Simpson Angus scale, the Barnes Akathisia Rating Scale and the Abnormal Involuntary Movement Scale (AIMS).

Abbreviations: ASD, autism spectrum disorder; CTRL, healthy controls; SCZ-eaP, schizophrenia with early adolescent prodrome (<15 yo); SCZ-laP, schizophrenia with late-adolescence prodrome (>15 yo); yo, years old.

Table 2. Social Cognition and Neurological Soft Signs.

	Diagnostic groups				ANCOVA tests		Post-hoc Tukey tests				
	CTRL	SCZ-laP	SCZ-eaP	ASD	*F*	*P*	ASD vs CTRL	ASD vs SCZ-laP	ASD vs SCZ-eaP	CTRL vs SCZ-laP	CTRL vs SCZ-eaP	SCZ-laP vs SCZ-eaP
Social cognition (MASC)												
Total	33.1 ± 2.9	29.0 ± 4.9	25.8 ± 4.9	24.4 ± 6.15	13.98	**<1e^{-6}**	**<1e^{-6}**	**0.002**	0.77	**0.005**	**<1e^{-6}**	0.09
No mental state attribution	1.50 ± 1.31	2.67 ± 1.78	2.65 ± 1.81	3.30 ± 2.71	3.96	**0.01**	**0.004**	0.60	0.68	0.09	0.18	1
Under-mentalizing	5.80 ± 2.14	7.52 ± 4.00	8.35 ± 3.60	9.59 ± 4.10	5.16	**0.002**	**6e^{-4}**	0.11	0.63	0.23	0.07	0.84
Over-mentalizing	4.57 ± 2.27	5.79 ± 3.14	8.20 ± 2.95	7.67 ± 2.35	6.45	**5e^{-4}**	**2e^{-4}**	**0.041**	0.91	0.28	**1e^{-4}**	**0.011**
Neurological soft signs												
Total	5.2 ± 3.6	9.9 ± 5.3	12.3 ± 8.5	17.3 ± 6.0	15.41	**1e^{-6}**	**<1e^{-6}**	**1e^{-4}**	**0.024**	**0.021**	**4e^{-3}**	0.49
Motor coordination	3.3 ± 2.6	5.5 ± 3.6	6.4 ± 4.7	8.4 ± 3.8	7.29	**2e^{-4}**	**<1e^{-6}**	**0.021**	0.26	0.13	**0.021**	0.80
Motor integration	0.82 ± 0.8	1.2 ± 1.1	2.2 ± 2.3	3.5 ± 1.9	13.12	**<1e^{-6}**	**<1e^{-6}**	**<1e^{-6}**	**0.04**	0.80	**0.016**	0.13
Sensory integration	1.0 ± 1.1	2.3 ± 1.7	2.8 ± 1.9	3.4 ± 2.1	6.20	**7e^{-4}**	**<1e^{-6}**	0.11	0.63	**0.027**	**0.003**	0.78

Abbreviations: ASD, autism spectrum disorder; CTRL, healthy controls; MASC, movie assessment of social cognition; NSS, neurological soft signs; SCZ-eaP, schizophrenia with early adolescent prodrome (<15 yo); SCZ-laP, schizophrenia with late-adolescence prodrome (>15 yo); yo, years old.
ANCOVA using medication (olanzapine equivalents) and level of education as covariates. Bonferroni significance threshold for 8 ANCOVA tests was set to 0.006. Bonferroni significance threshold for the 6 subsequent pairwise post-hoc Tukey tests was set at 0.008 (significant p-values under this threshold in bold).

significant differences between the 4 groups in social cognition ($F = 13.98$, $p < 1e^{-6}$), and NSS ($F = 15.41$, $P < 1e^{-6}$) (**Table 2**, **Figure 1**).

Regarding Social Cognition. Autism spectrum disorder was not significantly different from SCZ-eaP, but differed from SCZ-laP, with an overall decreasing performance from CTRL to SCZ-laP, then SCZ-eaP, and finally ASD. This difference was driven by the over-mentalizing subscore of the MASC, while there was no difference between groups for under-mentalizing or lack of mental state attribution.

Regarding NSS. Autism spectrum disorder was not significantly different from SCZ-eaP, but differed from SCZ-laP, with an overall increasing impairment from CTRL, to SCZ-laP, SCZ-eaP, and then ASD. Considering the NSS subscales, there was no difference in motor coordination and sensory integration between ASD and SCZ groups; motor integration impairment was higher in ASD compared to SCZ-laP than SCZ-eaP. Schizophrenia with late-adolescence prodromes did not significantly differ on the NSS subscales from controls, while SCZ-eaP was significantly more impaired than controls for total NSS and sensory integration (**Table 2**).

Dyskinesia was correlated with NSS across all groups ($r = 0.66$, $P = 1e{-}13$), although the level of dyskinesia remains rather low: less than 16% of subjects of the cohort ($N = 19$) had an AIMS score ≥3.

Relationship Between Social Cognition and Sensorimotor Dimensions

Social cognition performance on the MASC test was strongly inversely correlated with sensorimotor impairment ($R = -0.62$, p-value = $7e^{-13}$) (**Figure 2A**). Moreover, age at onset of prodrome was negatively correlated with NSS ($r = -0.34$, $P = .018$), and positively with social cognition performance ($r = 0.28$, $P = .048$). In order to test a possible mediating effect of NSS on the increase of social cognition deficits across diagnoses, from healthy controls to SCZ-laP, -eaP, and then ASD, we used a causal mediation analysis. The total effect of diagnosis on social cognition was very significant, with decreasing MASC scores from CTRL to SCZ-laP, SCZ-eaP, and ASD ($\beta = -2.76$, $P < 1e^{-6}$). A direct effect of diagnosis on social cognition ($\beta = -1.52$, $P = .0002$) and an indirect effect through causal mediation by NSS score ($\beta = -1.24$, $P < 1e^{-6}$) was also significant (**Figure 2B**).

Relationship Between the Sensorimotor Dimensions and Local Gyrification

Across diagnostic groups and after correction for multiple testing, the increase in 3 local gyrification indices significantly explained the increase of NSS in this

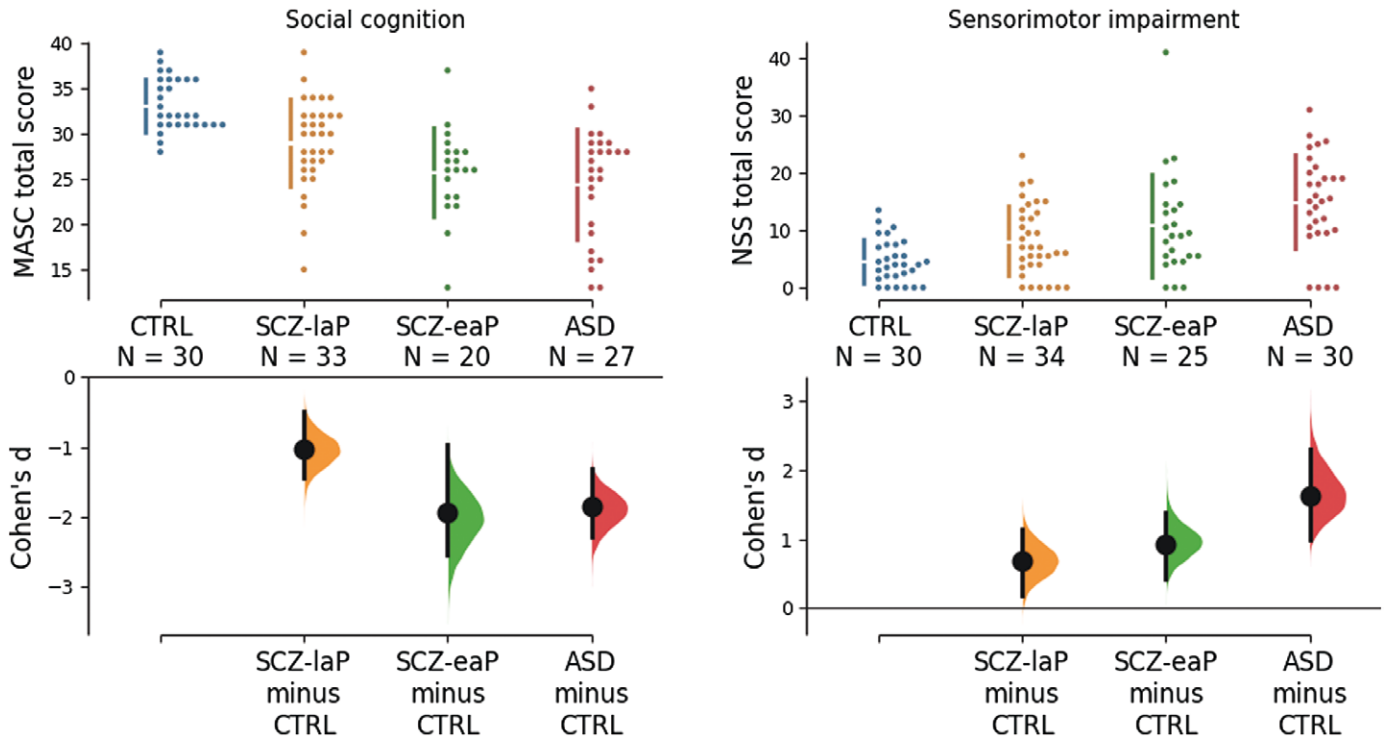

Figure 1. Differences Between Healthy Controls (CTRL) and Schizophrenia with Late-Adolescence Prodromes (SCZ-laP), Schizophrenia with Early Adolescence Prodromes (SCZ-eaP), Autism Spectrum Disorder (ASD), in Terms of Social Cognition (with the Movie Assessment for Social Cognition—MASC) and Neurodevelopmental Burden (with Neurological Soft Signs—NSS)

population: the right fusiform gyrus (β = .34, $P = 3e^{-5}$), the right frontal pole gyrus (β = 1.19, $P = 3e^{-4}$), and the left postcentral gyrus (β = .21, $P = 5e^{-4}$) (**Figure 3**).

Discussion

In this study, we introduced a distinction among patients with SCZ based on age at prodrome onset. We hypothesized that subjects with prodromes starting in early adolescence (SCZ-eaP) had social cognition deficits and sensorimotor impairments similar to subjects with autism, contrary to individuals with SCZ with prodromes starting in late adolescence (SCZ-laP). Confirming our hypothesis, we found that for both social cognition and NSS, subjects with ASD were not different from those with SCZ-eaP while they differed from SCZ-laP. Drawing on the most recent meta-analysis directly comparing social cognition in ASD and SCZ, which found similar levels of impairment between the groups but high intragroup heterogeneity,[42] we propose age at onset of prodrome as a way of sub-phenotyping SCZ that allows to characterize more homogeneous SCZ groups with and without social cognition deficits. Interestingly, this difference in social cognition was observed in the context of relatively small clinical differences between the groups on the PANSS symptomatic scales, as patients with SCZ were stabilized under treatment and only differed from ASD for positive symptoms, but not for negative ones or general psychopathology. This confirms that, in SCZ, social cognition measured by the MASC test captures a dimension more specific to autism than negative symptoms. While negative symptoms have historically been associated with the autism-SCZ continuum, they may increase in both conditions for different reasons (eg, amotivation/avolition in SCZ versus anxiety-related social motivation deficits in autism).[43]

The social cognition deficits associated with overmentalization were greater in SCZ-eaP than in SCZ-lap, as in the case of ASD, which extends our previous analysis in a subset of the same cohort[11] and is in line with another study that found better social cognition in patients with SCZ with a later age of onset.[44] Nevertheless, interpreting the association between age at onset and social cognition deficit remains challenging, since effects are probably bidirectional. On the one hand, the onset of disease might disrupt the development of social cognition abilities when occurring during adolescence. On the other hand, pre-existing social cognition deficits may constitute a vulnerability for psychosis, consistent with the finding that hyper theory-of-mind in children could be a risk factor for psychotic experiences.[45] Regardless of effect directionality, distinguishing between early and late prodromes may be important for prognosis, since the presence of the prodrome itself has been associated with a higher risk of not adhering to treatment[46] and poorer global outcomes.[47] It was further shown that early

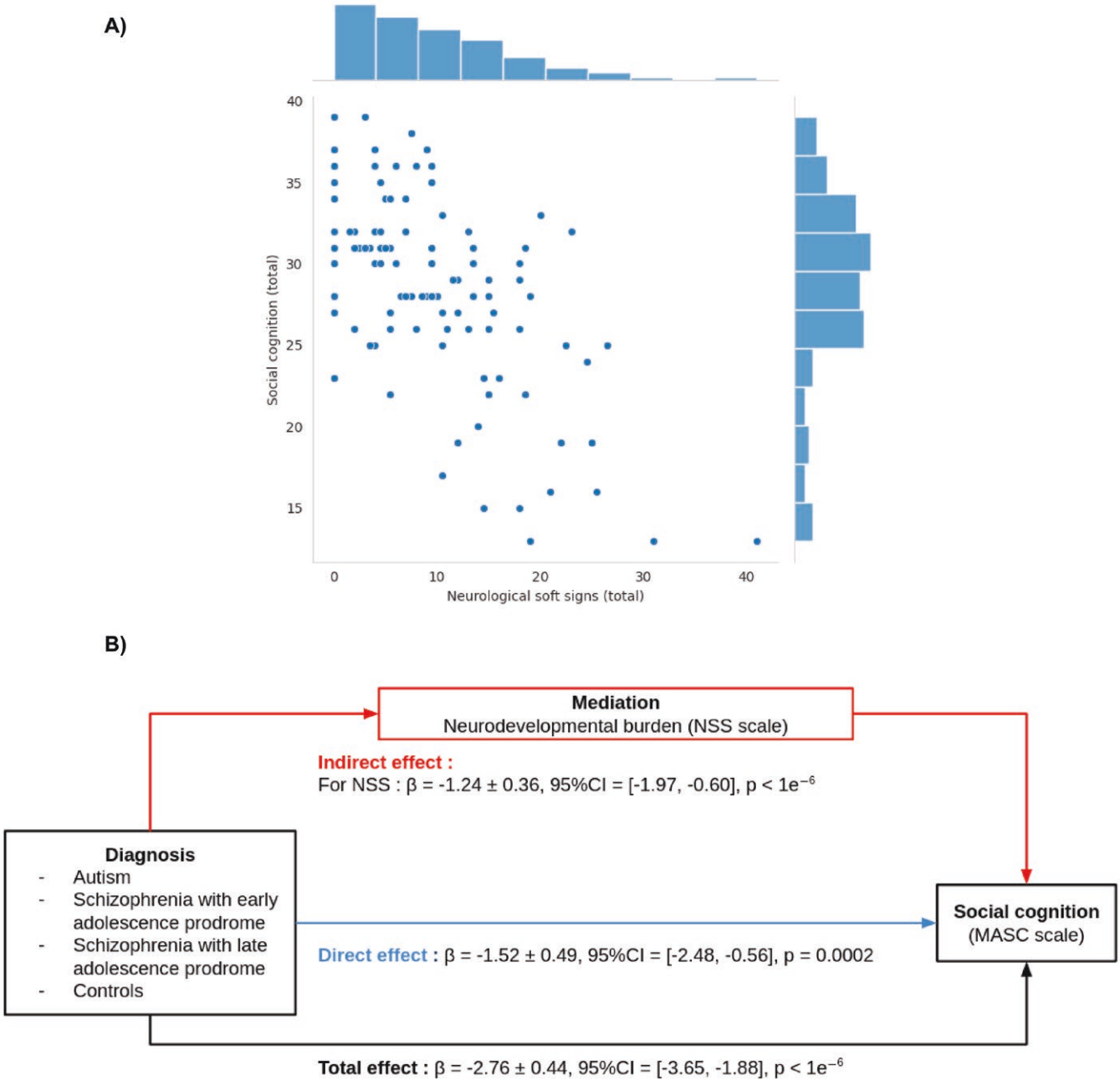

Figure 2. (A) Correlation Between Social Cognition and NSS. (B) Causal Mediation Analysis. The Place on the Schizophrenia-Autism Spectrum (Diagnosis) had an Effect on Social Cognition (Total Effect), But This Effect was Mediated in Part by Neurodevelopmental Burden (Indirect Effect), in Addition to a Direct Effect of Diagnosis on Cognition. NSS, Neurological Soft Signs

prodromal age at the beginning of adolescence, in relationship with high NSS scores, was predictive of poor initial response to antipsychotics.[20] Considering that compensation for social skills impairment is possible in ASD, targeting social cognitive deficits in children and adolescents with prodromal psychotic symptoms should therefore be an essential part of early intervention in psychosis, as cognitive behavioral therapy has already proven efficient in reducing symptoms and transition risk.[48]

The diagnostic-related decrease in social cognition was mirrored by a symmetrical increase in sensorimotor anomalies, from CTRL to SCZ groups, and finally ASD, with a very significant inverse correlation between NSS and age at the onset of prodrome, and between NSS and social cognition performance. Concordant results were found in the only other study, to our knowledge, that compared these three groups.[49] Both total NSS and its motor integration subscale were significantly higher in ASD compared to SCZ-laP, while there was no difference between ASD and SCZ-eaP. Importantly, our causal mediation analysis revealed that the impact of one's position on the autism-SCZ continuum in relation

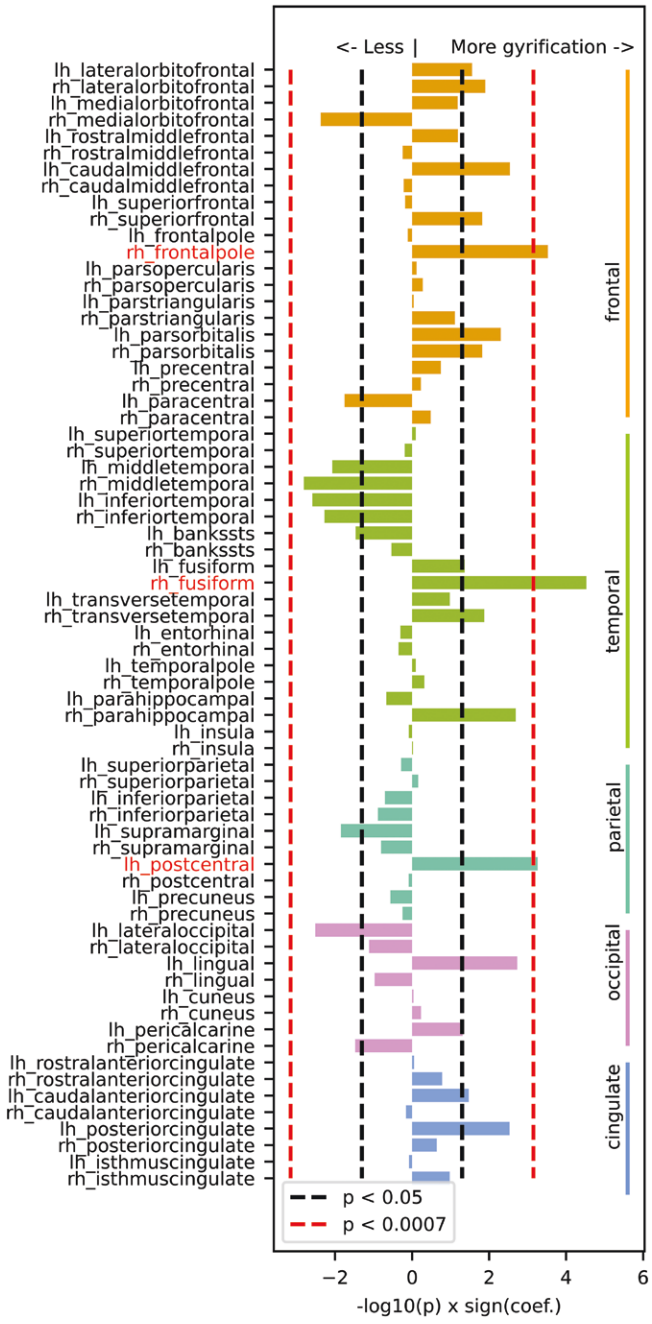

Figure 3. Association Between NSS and Local Gyrification Indices (LGI). Linear Regression of NSS ~ LGI + Age + Sex + Antipsychotic Medication, for 68 LGI. X-Axis Represents the Direction of the LGI Coefficient Weighted by Its Statistical Significance. LGI highlighted in red and represented on the cortical surface are significant. After a Stringent Bonferroni Correction for 68 Tests Set to 0.0007. NSS, Neurological Soft Signs. lh, left hemisphere. rh, right hemisphere.

to social cognition deficits may be partially mediated by sensorimotor impairment, independently of medication and education level. To our knowledge, only two previous studies explored the relationship between NSS and social cognition in SCZ, reporting correlations between motor symptoms and theory-of-mind deficits, through core tasks such as false-belief understanding,[50] "reading the mind in the eye" and picture sequencing tasks.[51] Our results extend and strengthen these previous studies by using a higher-level social cognition task and demonstrating the correlation between NSS and social cognition not only in SCZ and healthy controls but also across a spectrum ranging from healthy subjects to those with ASD.

The relationship between sensorimotor and social cognition functions is consistent with the growing evidence of a unified psychomotor dysregulation in psychiatric disorders, including catatonia, where motor and non-motor networks are strongly intertwined.[52] For instance, cerebellar dysfunctions have been associated with social cognitive impairment through functional neuroimaging and in vivo neurophysiology.[53,54] Here we show that the psychomotor paradigm extends to a range of presentations on the SCZ-autism continuum. Its explanatory model strongly relies on the neurodevelopmental dimensional framework,[21] where both social and motor domains may progressively develop in a dynamic interaction across time,[55] determined by the maturation of brain connectivity.[1] Notably, this connectivity depends on a balance between excitatory and inhibitory populations of neurons, essential to normal oscillatory activity and impaired both in SCZ and autism.[56,57] Decreases in oscillatory phase coherence have thus been suggested to be at the basis of temporal imprecision in psychosis, which may be key to predictive coding impairments, themselves associated both with motor and cognitive deficits.[58]

Finally, given that we used NSS as a marker of neurodevelopment, but that it is also known that NSS can increase under the effect of antipsychotic drugs,[59] we tested whether the variation in NSS that we observed in our population could itself be explained by a strong marker of early development, such as local gyrification of the cortex, which is one of the quantitative markers of the brain least affected by late environmental factors, diseases and medication trajectories.[30] We found that 3 local gyrification indices could significantly explain NSS variation transdiagnostically: the right fusiform gyrus, the right frontal pole gyrus, and the left postcentral gyrus. While the association of fronto-parietal areas with NSS could be explained by their role in executive functions, the increased right fusiform gyrus LGI is intriguing in the neurodevelopmental context, as it is a region implicated in emotion regulation,[60] face perception,[61] and gyrification of its contralateral left fusiform gyrus was associated with increased general psychopathology on the PANSS in drug-naive first-episode SCZ.[62] Overall, these increases replicate observations in first-episode SCZ patients with similar age ranges.[63] However, a recent study of antipsychotic-naive first-episode SCZ reports the opposite patterns of widespread hypogyrification,[64] suggesting that in spite of our corrections, we can not exclude that the gyrification increases are related to antipsychotic

medication. Further strategies could therefore take advantage of gyrification markers that are more stable in time, such as abnormalities in their spatial organization.[65]

Other strengths and limitations of our study are as follows. First, a major strength was the match for age, sex, IQ, for all groups, and education level in the groups of patients, which permitted control for important biases in this transdiagnostic design, in a young population with SCZ and ASD that are rarely compared. The main limitations concern the sample size. A possible influence of antipsychotics on NSS could also be discussed, as sensorimotor anomalies can be an interplay between genetic vulnerability and environmental effects such as medication. Dyskinesia was correlated with NSS across all groups but it remained low, below 3, which is the threshold used for tardive dyskinesia.[66] Moreover, there were no significant differences in dyskinesia between the groups, nor in akathisia. It is noteworthy that participants with ASD had the highest score of dyskinesia and Parkinsonism but were minimally treated, indicating that extrapyramidal symptoms reflect a pre-existing alteration of the basal ganglia circuits and/or a specific sensitivity to antipsychotics. Moreover, low doses of antipsychotics were used, with a short overall duration of treatment, and extrapyramidal scales were not different between groups. Likewise, despite the fact that most ASD patients had no antipsychotic medication, they still had the highest NSS score, supporting the notion that NSS reflects a neurodevelopmental burden, independent of medication. This is in line with previous reports of increased NSS in unmedicated offspring of individuals with SCZ,[67] and in antipsychotic-naIve subjects with SCZ.[36] Another limitation is that this cross-sectional design does not offer the possibility to dynamically study the developmental relationship between social cognition and sensorimotor impairment, which would require a longitudinal approach.

In conclusion, our results support an impairment in social cognition that is mediated by neurodevelopmental burden along the ASD-SCZ spectrum. Using age-at-prodrome as the onset of disease may help identify more homogeneous subgroups in the SCZ spectrum disorders, the ones with earlier prodromes presenting with autism-like social cognition and sensorimotor impairments that could be relevant predictors of clinical trajectories.

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Conflicts of interest

None declared.

References

1. Marín OD. Timing and critical windows for the treatment of psychiatric disorders. *Nat Med.* 2016;22:1229–1238.
2. Patel PK, Leathem LD, Currin DL, Karlsgodt KH. Adolescent neurodevelopment and vulnerability to psychosis. *Biol Psychiatry.* 2021;89:184–193. https://doi.org/10.1016/j.biopsych.2020.06.028
3. Driver DI. Childhood-onset schizophrenia and early-onset schizophrenia spectrum disorders. *Child Adolesc Psychiatr Clin N Am.* 2020;29:71–90.
4. Rapoport J, Chavez A, Greenstein D, Addington A, Gogtay N. Autism spectrum disorders and childhood-onset schizophrenia: clinical and biological contributions to a relation revisited. *J Am Acad Child Adolesc Psychiatry.* 2009;48:10–18.
5. Green MF, Horan WP, Lee J. Nonsocial and social cognition in schizophrenia: current evidence and future directions. *World Psychiatry.* 2019;18:146–161.
6. Isaksson J, Van't Westeinde A, Cauvet E, et al. Social cognition in autism and other neurodevelopmental disorders: a co-twin control study. *J Autism Dev Disord.* 2019;49:2838–2848.
7. Davidson CA, Piskulic D, Addington J, et al. Age-related trajectories of social cognition in youth at clinical high risk for psychosis: an exploratory study. *Schizophr Res.* 2018;201:130–136.
8. Sasson NJ, Pinkham AE, Carpenter KLH, Belger A. The benefit of directly comparing autism and schizophrenia for revealing mechanisms of social cognitive impairment. *J Neurodev Disord.* 2011;3:87–100.
9. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. *Nat Rev Neurosci.* 2015;16:620–631.

10. Dziobek I, Fleck S, Kalbe E, et al. Introducing MASC: a movie for the assessment of social cognition. *J Autism Dev Disord.* 2006;36:623–636.
11. Martinez G, Alexandre C, Mam-Lam-Fook C, et al. Phenotypic continuum between autism and schizophrenia: evidence from the Movie for the Assessment of Social Cognition (MASC). *Schizophr Res.* 2017;185:161–166.
12. Alamiri B, Nelson C, Fitzmaurice GM, Murphy JM, Gilman SE. Neurological soft signs and cognitive performance in early childhood. *Dev Psychol.* 2018;54:2043–2052.
13. D'Agati E, Pitzianti M, Curatolo P, Pasini A. Scientific evidence for the evaluation of neurological soft signs as atypical neurodevelopment markers in childhood neuropsychiatric disorders. *J Psychiatr Pract.* 2018;24:230–238.
14. Gay O, Plaze M, Oppenheim C, et al. Cognitive control deficit in patients with first-episode schizophrenia is associated with complex deviations of early brain development. *J Psychiatry Neurosci.* 2017;42:87–94.
15. Gay O, Plaze M, Oppenheim C, et al. Cortex morphology in first-episode psychosis patients with neurological soft signs. *Schizophr Bull.* 2013;39:820–829.
16. Chan RCK, Gottesman II. Neurological soft signs as candidate endophenotypes for schizophrenia: a shooting star or a Northern star? *Neurosci Biobehav Rev.* 2008;32:957–971.
17. Mouchet-Mages S, Rodrigo S, Cachia A, et al. Correlations of cerebello-thalamo-prefrontal structure and neurological soft signs in patients with first-episode psychosis: cerebello-thalamo-prefrontal structure and neurological soft signs. *Acta Psychiatr Scand.* 2011;123:451–458.
18. Peralta V, García de Jalón E, Moreno-Izco L, et al; SEGPEPs Group. Long-term outcomes of first-admission psychosis: a naturalistic 21-year follow-up study of symptomatic, functional and personal recovery and their baseline predictors. *Schizophr Bull.* 2022;48:631–642.
19. Ferruccio NP, Tosato S, Lappin JM, et al. Neurological signs at the first psychotic episode as correlates of long-term outcome: results from the AESOP-10 study. *Schizophr Bull.* 2021;47:118–127.
20. Iftimovici A, Krebs E, Dalfin W, et al. Neurodevelopmental predictors of treatment response in schizophrenia and bipolar disorder. *Psychol Med.* 2024;54:1–12. https://doi.org/10.1017/S0033291724001776
21. Michelini G, Carlisi CO, Eaton NR, et al. Where do neurodevelopmental conditions fit in transdiagnostic psychiatric frameworks? Incorporating a new neurodevelopmental spectrum. *World Psychiatry.* 2024;23:333–357.
22. Donati G, Edginton T, Bardo A, et al. Motor-sensory biases are associated with cognitive and social abilities in humans. *Sci Rep.* 2024;14:14724.
23. Wang Y, Metoki A, Alm KH, Olson IR. White matter pathways and social cognition. *Neurosci Biobehav Rev.* 2018;90:350–370.
24. Van Overwalle F, D'aes T, Mariën P. Social cognition and the cerebellum: a meta-analytic connectivity analysis. *Hum Brain Mapp.* 2015;36:5137–5154.
25. Van Overwalle F, Manto M, Cattaneo Z, et al. Consensus paper: cerebellum and social cognition. *Cerebellum (London, England).* 2020;19:833–868.
26. Ninomiya T, Isoda M. Dynamic spatial representation of self and others' actions in the macaque frontal cortex. *Proc Natl Acad Sci USA.* 2024;121:e2403445121.
27. Chi JG, Dooling EC, Gilles FH. Gyral development of the human brain. *Ann Neurol.* 1977;1:86–93.
28. Raznahan A, Shaw P, Lalonde F, et al. How does your cortex grow? *J Neurosci.* 2011;31:7174–7177.
29. Jalil Razavi M, Zhang T, Liu T, Wang X. Cortical folding pattern and its consistency induced by biological growth. *Sci Rep.* 2015;5:14477.
30. Joo SW, Jo YT, Kim Y, Lee WH, Chung Y-C, Lee J. Structural variability of the cerebral cortex in schizophrenia and its association with clinical symptoms. *Psychol Med.* 2024;54:399–408.
31. Lord C, Rutter M, Le Couteur A. Autism diagnostic interview-revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord.* 1994;24:659–685.
32. Nurnberger JI, Blehar MC, Kaufmann CA, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psychiatry.* 1994;51:849–59; discussion 863.
33. Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Aust N Z J Psychiatry.* 2005;39:964–971.
34. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13:261–276.
35. Montag C, Dziobek I, Richter IS, et al. Different aspects of theory of mind in paranoid schizophrenia: evidence from a video-based assessment. *Psychiatry Res.* 2011;186:203–209.
36. Krebs MO, Gut-Fayand A, Bourdel M, Dischamp J, Olié J. Validation and factorial structure of a standardized neurological examination assessing neurological soft signs in schizophrenia. *Schizophr Res.* 2000;45:245–260.
37. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl.* 1970;212:11–19.
38. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry.* 1989;154:672–676.
39. Munetz MR, Benjamin S. How to examine patients using the abnormal involuntary movement scale. *Hosp Community Psychiatry.* 1988;39:1172–1177.
40. Vallat R. Pingouin: statistics in Python. *J Open Source Softw.* 2018;3:1026.
41. Hayes AF, Rockwood NJ. Regression-based statistical mediation and moderation analysis in clinical research: observations, recommendations, and implementation. *Behav Res Ther.* 2017;98:39–57.
42. Oliver LD, Moxon-Emre I, Lai M-C, Grennan L, Voineskos AN, Ameis SH. Social cognitive performance in schizophrenia spectrum disorders compared with autism spectrum disorder: a systematic review, meta-analysis, and meta-regression. *JAMA Psychiatry.* 2021;78:281–292.
43. Corbera S, Wexler BE, Bell MD, et al. Disentangling negative and positive symptoms in schizophrenia and autism spectrum disorder. *Schizophr Res.* 2024;271:1–8.
44. Linke M, Jankowski KS, Ciołkiewicz A, et al. Age or age at onset? Which of them really matters for neuro and social cognition in schizophrenia? *Psychiatry Res.* 2015;225:197–201.
45. Clemmensen L, van Os J, Drukker M, et al. Psychotic experiences and hyper-theory-of-mind in preadolescence—a birth cohort study. *Psychol Med.* 2016;46:87–101.
46. Daneault J-G, Maraj A, Lepage M, et al. Medication adherence in first episode psychosis: the role of pre-onset subthreshold symptoms. *Acta Psychiatr Scand.* 2019;139:336–347.
47. Rosengard RJ, Malla A, Mustafa S, et al. Association of pre-onset subthreshold psychotic symptoms with longitudinal

outcomes during treatment of a first episode of psychosis. *JAMA Psychiatry.* 2019;76:61–70.

48. Zheng Y, Xu T, Zhu Y, et al. Cognitive behavioral therapy for prodromal stage of psychosis—outcomes for transition, functioning, distress, and quality of life: a systematic review and meta-analysis. *Schizophr Bull.* 2022;48:8–19.
49. Hirjak D, Wolf RC, Paternoga I, et al. Neuroanatomical markers of neurological soft signs in recent-onset schizophrenia and Asperger-syndrome. *Brain Topogr.* 2016;29:382–394.
50. Romeo S, Chiandetti A, Siracusano A, Troisi A. An exploratory study of the relationship between neurological soft signs and theory of mind deficits in schizophrenia. *Psychiatry Res.* 2014;218:7–11.
51. Herold CJ, Duval CZ, Lässer MM, Schröder J. Neurological soft signs (NSS) and cognitive impairment in chronic schizophrenia. *Schizophr Res Cogn.* 2019;16:17–24.
52. Northoff G, Hirjak D, Wolf RC, Magioncalda P, Martino M. All roads lead to the motor cortex: psychomotor mechanisms and their biochemical modulation in psychiatric disorders. *Mol Psychiatry.* 2021;26:92–102.
53. Hur SW, Safaryan K, Yang L, et al. Correlated signatures of social behavior in cerebellum and anterior cingulate cortex. *eLife.* 2024;12:RP88439.
54. Kong Y, Roser M, Bègue I, et al. Cerebellum and social abilities: a structural and functional connectivity study in a transdiagnostic sample. *Hum Brain Mapp.* 2024;45:e26749.
55. Casey BJ, Oliveri ME, Insel T. A neurodevelopmental perspective on the Research Domain Criteria (RDoC) framework. *Biol Psychiatry.* 2014;76:350–353.
56. Hirano Y, Uhlhaas PJ. Current findings and perspectives on aberrant neural oscillations in schizophrenia. *Psychiatry Clin Neurosci.* 2021;75:358–368.
57. Bellato A, Norman L, Idrees I, et al. A systematic review and meta-analysis of altered electrophysiological markers of performance monitoring in Obsessive-Compulsive Disorder (OCD), Gilles de la Tourette Syndrome (GTS), Attention-Deficit/Hyperactivity disorder (ADHD) and Autism. *Neurosci Biobehav Rev.* 2021;131:964–987.
58. Wolff A, Northoff G. Temporal imprecision of phase coherence in schizophrenia and psychosis—dynamic mechanisms and diagnostic marker. *Mol Psychiatry.* 2024;29:425–438.
59. Lui SSY, Yip SSL, Wang Y, et al. Different trajectories of neurological soft signs progression between treatment-responsive and treatment-resistant schizophrenia patients. *J Psychiatr Res.* 2021;138:607–614.
60. Geckeler KC, Barch DM, Karcher NR. Associations between social behaviors and experiences with neural correlates of implicit emotion regulation in middle childhood. *Neuropsychopharmacology.* 2022;47:1169–1179.
61. Sellal F. Anatomical and neurophysiological basis of face recognition. *Rev Neurol (Paris).* 2021;178:649–653, S0035-3787(21)00764-5. https://doi.org/10.1016/j.neurol.2021.11.002
62. Zhou H, Wang D, Wang J, Xu H, Cao B, Zhang X. Association of altered cortical gyrification and psychopathological symptoms in patients with first-episode drug-naïve schizophrenia. *Asian J Psychiatry.* 2021;64:102749.
63. Sasabayashi D, Takayanagi Y, Takahashi T, et al. Increased brain gyrification in the schizophrenia spectrum. *Psychiatry Clin Neurosci.* 2020;74:70–76.
64. Gao X, Yao L, Li F, et al. The cortical hypogyrification pattern in antipsychotic-naive first-episode schizophrenia. *Cereb Cortex.* 2023;33:7619–7626.
65. Cachia A, Borst G, Jardri R, et al. Towards deciphering the fetal foundation of normal cognition and cognitive symptoms from Sulcation of the cortex. *Front Neuroanat.* 2021;15:712862.
66. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. *Arch Gen Psychiatry.* 1982;39:486–487.
67. Sugranyes G, de la Serna E, Borras R, et al. Clinical, cognitive, and neuroimaging evidence of a neurodevelopmental continuum in offspring of Probands with schizophrenia and bipolar disorder. *Schizophr Bull.* 2017;43:1208–1219.