Replicable, Transdiagnostic Behavioral and Neural Correlates of Sensory Over-responsivity

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Abstract

Sensory over-responsivity (SOR), characterized by strong negative reactions to typically innocuous stimuli, is considered a symptom of autism spectrum disorder. However, SOR also affects 15-20% of children overall, including a majority of children with common psychiatric conditions. Despite its prevalence, the clinical specificity and neurobiological bases of SOR remain poorly understood. Our study aims to determine the specific clinical significance of SOR across diverse child samples and establish whether SOR is associated with distinct patterns of functional connectivity (FC). We analyzed data from 15,728 children (ages 6-17.9 years) across five datasets: three community samples, including the Adolescent Brain Cognitive Development [ABCD] and Healthy Brain Network [HBN] studies, and two autism-enriched samples. Bivariate and multivariate models examined associations between SOR and symptoms of anxiety, attention-deficit/hyperactivity disorder, depression, conduct disorder, and oppositional defiant disorder, as well as autistic traits. Analysis of resting-state functional MRI (fMRI) data from the ABCD study tested brain-wide and circuit-specific FC correlates of mild SOR, replication of effects in an independent ABCD subsample, as well as extension to severe SOR in ABCD and to SOR in the HBN sample. Multivariate analyses revealed that SOR is associated with a remarkably consistent transdiagnostic profile: greater levels of both autistic traits and anxiety symptoms and, in community samples, lower levels of conduct disorder symptoms. Across samples, SOR is not reliably associated with symptoms of any other analyzed psychiatric conditions. Resting state fMRI analyses reveal that SOR is associated with both brain-wide and circuit-specific functional connectivity (FC) patterns in networks related to tactile processing (somatomotor-hippocampal) and error detection (cingulo opercular-ventral diencephalon) that replicate in independent subsamples. Our results demonstrate that SOR may constitute a transdiagnostic latent trait with both specific clinical risk and protection, and with replicable

neural correlates that implicate specific cortico-subcortical circuits. These findings advance our understanding of the neurobiology and clinical relevance of SOR. They may also inform clinical practice and future research aimed at understanding and supporting individuals with sensory challenges.

Introduction

Sensory over-responsivity (SOR) is a behavioral pattern characterized by strong, negative responses to sensory stimuli that are typically considered innocuous, such as traffic noise or tactile stimulation from clothing. SOR affects approximately 15 to 20% of children[1–4] and is associated with psychiatric problems and significant functional impairment, including sleep and gastrointestinal problems.[5–8] Neuroimaging studies linking SOR to altered activation of sensory areas have provided early clues that SOR may reflect differences in sensory processing and habituation.[3,9–11] Parallel work from animal models shows that neonatal transgenic mice with autism-associated mutations exhibit peripheral and central sensory dysfunction that, in turn, triggers a developmental cascade to long-term anxiety-like behaviors and social deficits.[12–19] Interventions to mitigate this dysfunction in early life rescue mice from anxiety-like behavior and reduce social impairments later in development, demonstrating a causal role for sensory dysfunction in long-term behavioral and social challenges.[20]

SOR has long been recognized for its association with autistic traits and was added to the diagnostic criteria for autism spectrum disorder (ASD) in The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[21,22] However, SOR is also over-represented among children across psychiatric disorders extending beyond autism, including anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), tic disorders, and obsessive-compulsive disorder (OCD), and is understood to reflect risk for emerging psychopathology.[2,23–28] Because SOR tends to manifest in early childhood,[4,29,30] before the onset of most psychiatric conditions, and is readily observed by caregivers, it may be a useful marker for identifying high-risk children who would benefit from psychiatric screening. However, its associations with diverse conditions raise an important question: is SOR a universal correlate of psychiatric conditions, or does it provide more specific information about clinical symptoms and risk?

Existing research linking SOR to psychiatric conditions has largely taken a bivariate analytic approach by examining the relation of SOR with symptom burden or diagnostic status for a single condition. However, interpretation of results from this research is limited by the considerable comorbidity and subclinical symptom associations of common conditions of childhood, such as autism, anxiety, and ADHD.[8,31–34] Given this overlap, a multivariate approach is needed to determine whether SOR indicates universal versus specific psychiatric problems. We previously applied this multivariate approach to data from a large, community sample of preadolescents and found significant SOR-symptom relationships in both positive (anxiety, depression, oppositional-defiant disorder) and negative (conduct disorder) directions.[3] Yet due to

the extreme size (N>11,000) of the sample, even small (i.e., clinically insignificant) effects can achieve statistical significance. Moreover, those effects may be specific to that sample's clinical or demographic characteristics, including its restricted age range (10-11 years). A multi-sample approach is therefore needed to determine whether robust, specific SOR-symptom associations exist for conditions other than autism.

Like many behavioral phenotypes associated with psychiatric conditions, SOR is a dimensional trait that exhibits a continuum of severity and associated functional impairment across the population. Whereas severe SOR has received more clinical and research attention, mild SOR appears to be more prevalent in the general population, constituting approximately two-thirds of children with SOR.[3] Consequently, it is important to investigate the clinical significance and biological bases of both severe and mild SOR in childhood. Our recent analysis of functional magnetic resonance imaging (fMRI) data from the Adolescent Brain Cognitive Development (ABCD) dataset provided insights into the neural correlates of severe SOR, including identifying differences in functional connectivity (FC) patterns in the brains of children with severe SOR, relative to children without SOR.[3,11,35] These differences included decreased FC within somatosensory networks and between the medial somatosensory network and left hippocampus, highlighting candidate alterations in neural circuitry that may contribute to severe SOR. However, our prior work only examined a subset of subcortical regions and did not test whether FC patterns replicate across independent samples of children. Moreover, despite the prevalence of mild SOR in the general population, it remains unknown whether children with mild SOR exhibit FC differences, and if so, whether these patterns resemble those found in children with severe SOR.

The current study analyzed 15,698 children across 5 diverse datasets to 1) determine the specific clinical significance of SOR across diverse pediatric samples; and 2) establish whether mild SOR, a prevalent trait in the population, is associated with distinct, replicable FC patterns. To address the first aim, we conducted parallel analyses of SOR and psychiatric symptoms across multiple community and autism-enriched samples and computed pooled effect sizes to identify effects that were robust and generalizable. To address the second aim, we capitalized on the large number of children ages 9-10 years with mild SOR in the ABCD dataset to identify candidate associations between FC and mild SOR in an exploratory subset of the sample and then test replication of these associations in an independent set of children. Given that many brain-behavior associations exhibit small effect sizes[23] and that psychiatric symptoms often result from numerous small, distributed alterations in FC patterns throughout the brain, we first examined whether mild SOR is associated with replicable brain-wide FC patterns across the exploratory and replication subsamples. To provide clues about circuit-specific differences, we additionally identified specific SOR-FC associations in the exploratory subsample and tested replication of these associations in the independent subsample. Candidate FC-SOR associations identified in the exploratory subsample were also tested for extension to a substantially smaller dataset with

distinct sample characteristics. Findings from this work provide valuable information about childhood SOR that could prove clinically useful for early risk identification and screening.

Method

Samples for Symptom Analyses

To identify SOR-symptom associations that are robust across sample characteristics, data were obtained from five independent datasets (total *N*=15,728; ages 6-17.9 years, Table S1) that vary dramatically in psychiatric symptoms, autistic traits, and rates of SOR. These datasets include community samples, clinical samples, and samples enriched for psychopathology. Specific sample sizes vary by analysis depending on data availability.

The Human Connectome Project-Development Study (HCP-D). HCP-D is a cross-sectional community study of children recruited to represent normative development across diverse demographic backgrounds while excluding individuals with serious medical conditions.[49] Given the breadth of ages in this study and the low numbers of children under the age of 8, analyses for the current study were restricted to *N*=302 participants ages 8-15 years with all required measures collected.

The Healthy Brain Network Study (HBN). HBN is a cross-sectional, multi-site study enriched for children with transdiagnostic symptoms and behavioral problems.[50] The current study analyzed data from *N*=3,635 HBN participants ages 8-14 with all required measures collected.

The Simons Simplex Collection (SSC). The SSC is a core project of the Simons Foundation Autism Research Initiative that collected data from families with a child affected by autism.[51] Data from *N*=2,109 children ages 6-18.9 years with autism diagnoses and all required measures were included in the current analyses.

The Brain Gene Registry (BGR). BGR is a national repository of information on individuals with variants in genes related to intellectual and developmental disabilities.[52] Behavioral and symptom information is additionally collected and stored in the repository when possible. Data from the *N*=162 participants aged 6-18.9 years (mean: 10.6 years) with available measures were analyzed for the current study.

Adolescent Brain Cognitive Development ^{SM} *Study* (ABCD Study®). ABCD study is a longitudinal, multi-site community study of adolescents recruited through a school-based strategy designed to maximize sample representativeness, beginning at ages 9-10 years.[53,54] Analyses were restricted to children with all required measures from the baseline and Year 1 timepoints (*N*=11,218). ABCD study recruitment neither excluded nor enriched based on psychiatric conditions or autism. However, children with conditions that required special schooling were not recruited. We reported results of related analyses from this dataset

previously.[55] Reanalysis was performed to provide consistency in modeling approach and permit pooling of effect-size estimates across datasets in the current study.

Assessments

To maximize the interpretability of results across datasets, we restricted analyses to the same core set of standardized parent-report measures collected from all included samples. Additional details about these measures are provided in the Supplement.

Social Responsiveness Scale, Second Edition (SRS-2): Parent report of child SOR was obtained from the SRS-2, a parent-report instrument used to identify the presence and severity of social impairment and autistic traits.[56] Analyses were limited to the 11 items from the SRS-2 that were administered in all five datasets. As described previously,[3] responses on one item from SRS-2 (*My child seems overly sensitive to sounds, textures, or smells)* were used to assign each participant to a SOR category. Item responses were given on a four-point scale: "Not True" (0), "Sometimes True" (1), "Often True" (2), or "Almost Always True" (3). Based on responses, children were categorized into three SOR groups: No SOR (0), Mild SOR (1), and Severe SOR (2 or 3).

A dimensional measure of autism traits excluding SOR was derived from the sum of the remaining 10 items that were administered across all five studies. The summed raw scores were converted to standardized T-scores for cross-sample comparison and statistical analysis. A supplementary analysis confirmed that our single-item measure of SOR correlates well with a multi-item measure of SOR obtained with an established questionnaire assessing sensory behaviors (see Supplement).

Child Behavior Checklist (CBCL 6-18): The CBCL 6-18 is a Likert-style, norm-referenced caregiver-completed rating scale that assesses children's functioning (ages 6-18) during the previous six months.[57] For each item, parents/guardians respond using a 3-point Likert scale: "Not True" (0), "Somewhat or Sometimes True" (1), and "Very True or Often True" (2).

For modeling of SOR-symptom associations, we analyzed the raw scores from DSM-oriented subscales of the CBCL, which have demonstrated strong validity for assessing specific psychiatric symptoms.[57,58] These subscales comprised depressive problems, anxiety problems, attention-deficit/hyperactivity problems, oppositional defiant problems, and conduct problems. Models for FC analyses based on the neuroimaging data included the broader internalizing and externalizing problem subscales, which represent higher-order dimensions of psychopathology.[57] The CBCL scales have shown robust psychometric properties across diverse populations and clinical settings.[59,60]

Participants for Neuroimaging Analyses

Functional MRI analyses were conducted on data from two of the five datasets: the ABCD Study and the Healthy Brain Network (HBN). Primary analyses investigating FC associations with mild SOR were conducted using the ABCD dataset, given the large number of participants with mild (*n*=1,069) or no SOR (*n*=7,306) in this sample, as defined above. To meet best practices of replication and reproducibility, we randomly divided ABCD participants with mild or no SOR into two independent groups matched by their demographic, psychiatric, and SOR characteristics (see full details in Tables S2, S3). After excluding participants missing functional data, we retained *N*=4,195 for the exploratory group and *N*=4,190 for the replication group. Each group was comprised of approximately 13% participants with mild SOR (*n*=554 and *n*=525, respectively) and the remaining 87% of participants with no SOR. We additionally tested whether FC-SOR effects found for mild vs no SOR in the exploratory sample extended to *n*=457 children with severe SOR in ABCD and to children with mild or severe SOR in *n*=181 from the independent HBN dataset (see Supplement for full details).

Neuroimaging Data Acquisition and Preprocessing

ABCD acquisition and processing: Resting-state functional MRI (rs-fMRI) data were collected using 3T scanners across 21 ABCD sites at the baseline timepoint, adhering to detailed protocols published previously.[53] Children underwent high-resolution (2.4-mm isotropic, repetition time = 800 ms) multiband (factor = 6) scanning during rs-fMRI acquisition. Scan sessions typically included three or four 5-minute runs of rs-fMRI, with slices acquired in the axial plane.

Standardized preprocessing of rs-fMRI data was performed, encompassing registration, distortion correction, and normalization. Post-processing for resting-state FC involved several steps: regression of 24 temporally filtered motion parameters, exclusion of outlier frames with framewise displacement >0.2 mm, and regression of signals from white matter, cerebrospinal fluid, and the whole brain. Cortical parcels were delineated and assigned to one of 13 functional networks according to the Gordon–Laumann parcellation scheme,[61] whereas subcortical regions of interest were identified using the ASEG FreeSurfer subcortical segmentation scheme.[62] Mean pairwise blood oxygen level–dependent (BOLD) signal correlations between cortical parcels, as well as between cortical parcels and subcortical regions, were computed, Fisher-transformed, and averaged by cortical network (422 total FC pairs: 103 cortical-cortical network pairs and 319 cortical-hemisphere-specific subcortical pairs). Analyses were limited to data from participants recommended for inclusion based on ABCD study's recommendations for data quality control.[63]

HBN acquisition and processing: fMRI data were collected with a 64-channel head coil during rest and movie-watching from two locations: CitiGroup Cornell Brain Imaging Center using a Siemens 3T Prisma scanner and Rutgers University Brain Imaging Center using a Siemens 3T Trio scanner. The fMRI data underwent initial minimal processing using the Human Connectome Project minimal processing pipeline.[64] We conducted further preprocessing utilizing Python 3.8 for both resting-state and movie-watching fMRI data as follows. Raw functional data

were denoised using a residual threshold of 0.3 and temporally filtered. To minimize motion-related artifacts, we applied motion correction using framewise displacement (FD), with temporal censoring of volumes exceeding 0.2 mm displacement. The preprocessed data were parcellated according to the Gordon333 atlas and ASEG FreeSurfer subcortical segmentation scheme.[61] For participants with both resting-state and movie-watching scans, data were initially processed separately and later concatenated into a single time series.

Main Analysis

SOR-Symptom Analyses: We examined the relationship between SOR and psychiatric symptoms across five datasets, encompassing 15,728 participants ages 6-18 years. For large, cross-sectional datasets (HBN and SSC) with broader age ranges, we further subdivided participants into specific age groups (see Table S4 for details of subgroups) to allow for developmental variations, resulting in 9 separate subsamples of participants. For each subsample, we conducted separate hierarchical mixed-effects models comparing no SOR with SOR (either mild or severe). We separately computed effect-size estimates from conventional bivariate approaches and from our multivariate approach that accounts for common comorbidity/symptom co-occurrence. For bivariate analyses, we tested each psychiatric symptom individually (anxiety, depression, ADHD, ODD, conduct disorder, and autism). In the multivariate analysis, we tested all six psychiatric symptoms together in a single mixed-effects linear model with SOR. In all models, the dependent variable was binary SOR group, with psychiatric symptoms scores entered as continuous predictors. For datasets that included site information (ABCD, HCP-D, and HBN), we incorporated data collection site as a second-order random-effects variable in the models to account for site-specific variations in our analyses.

Given that SOR is considered a symptom of autism, its clinical significance might differ for autistic and community samples. We therefore grouped studies into community (ABCD, HCP-D, HBN) or autism (SSC, BGR) datasets based on their study recruitment objectives and severity of autistic traits in the sample. Odds ratios from bivariate and multivariate models were pooled separately across community and autism samples to assess the overall strength and consistency of SOR-symptom associations within these distinct populations. To confirm that the pattern of results was not contingent on SOR grouping, we also performed the analyses separately for mild versus no SOR and for severe versus no SOR (see Supplement for details). Analyses were carried out using the *nlme* and meta packages available in R (version 4.3.2).[65]

Functional Connectivity Analyses: We adopted a two-stage approach to FC analyses. First, we analyzed FC patterns across the whole brain to determine whether these global patterns are associated with mild SOR. We then tested whether specific FC pairs demonstrate robust, replicable associations with mild SOR, providing insight into circuit-specific differences. For

both analytic approaches, we used independent subsamples to identify and replicate FC-SOR associations and additionally tested their extension to severe SOR.

We evaluated associations between mild SOR and FC in the exploratory, replication, and severe subgroups of the ABCD dataset using hierarchical linear mixed-effects models of FC that accounted for scanner-related variance across multiple study sites as a second-level random-effects variable. We tested for associations with SOR by modeling pairwise (network-network or network-subcortical structure) FC for all FC pairs (see Supplement for a complete list of regions tested). In addition to the second-order variable of scanner, the model contained key covariates, including sex, age, economic disadvantage, framewise displacement, psychiatric symptoms scales (standardized CBCL-Internalizing, CBCL-Externalizing raw scores) and autistic traits (adjusted S-SRS score excluding SOR item) as first-order variables. This comprehensive approach allowed us to disentangle the specific contribution of SOR from related demographic, clinical, and methodological factors, thereby isolating its unique effect on functional connectivity while controlling for potential confounding variables.

Tabulated resting state functional connectivity, SOR, and all covariates were mean-centered and transformed into standardized scores, and then winsorized using the interquartile method. Economic disadvantage was operationalized using distinct but comparable measures that were available in ABCD and HBN datasets (see Supplement for details).

Brain-wide Functional Connectivity Pattern Analysis: From each dataset, we extracted standardized beta coefficients from multilevel models (MLMs) representing the magnitude and direction of the relationship between SOR and FC pairs. These coefficients were organized into symmetric matrices where both rows and columns represented the 32 brain regions of interest (13 cortical networks and 19 subcortical structures). Each cell (i,j) in the matrix contained the beta coefficient reflecting the SOR-related FC between regions i and j.

To quantify the similarity of SOR-related FC patterns across exploratory and replication subsamples, we calculated Spearman rank correlations (ρ) between the beta coefficient matrices. Two key comparisons were performed: ABCD Exploratory vs. ABCD Replication and ABCD Exploratory vs. ABCD Severe. To examine generalizability, we additionally computed the correlation between ABCD Exploratory vs. HBN and compared with an ABCD subset matched to the HBN sample (see Supplement).

To assess the statistical significance of cross-sample beta correlations, we implemented a permutation testing approach by creating 1,000 permuted versions of the exploratory ABCD subsample in which the SOR variable was randomly shuffled while preserving the original distribution. For each permutation, we generated new beta coefficient matrices using the same MLM model, then calculated Spearman correlations between these permuted matrices and the original matrices from comparison datasets (ABCD Replication, ABCD Severe, and HBN). The

p-value for each cross-dataset comparison was calculated as the proportion of permuted correlations that were greater than or equal to the actual observed correlation.

Identifying Specific Candidate FC Pairs Associated with SOR: To identify robust, SOR-specific candidate brain regions in the exploratory subsample, we applied a MLM to each pairwise FC variable using a primary SOR+Demographics model that included SOR, demographic variables (sex, age, economic disadvantage), and mean framewise displacement (FD) to control for motion effects. To ensure that findings are robust to model selection, we additionally computed basic models (Minimal Model: SOR only) and models with additional psychiatric covariates (Symptom Model: SOR+Demographics+FD+Symptoms model that included internalizing/externalizing behaviors and autistic traits; see Supplement). Identifying a given candidate FC pair in the exploratory subsample or determining that it replicated in the replication subsample required statistical significance ($p<.01$) of SOR effect in both the minimal model and the primary SOR+Demographics model.

Testing Extension of Results to Severe SOR in ABCD and to HBN: Although prior work investigated FC associations with severe SOR in ABCD, those analyses did not test effects from all pairwise FC variables or assess replication in a sample of independent participants.[3] The current investigation of FC associations with mild SOR included exhaustive pairwise exploratory analyses and independent replication. To determine if FC associations with mild SOR identified in the current exploratory analyses extend to severe SOR, we therefore applied the same MLM models to a subset of the ABCD sample comprising children with severe SOR and the participants with no SOR from the replication subsample. In addition, we tested whether the results from ABCD generalize to a small, separate study with distinct characteristics (i.e., sample age range, sample psychopathology, sample size, and task during data collection) from HBN participants 8-11 years of age (N=356) with high-quality fMRI data and SOR measures. Given the relatively small sample size and continuity between effects observed for mild and severe SOR in ABCD, we grouped HBN participants into SOR- (no SOR, n=175) and SOR+ (mild or severe SOR, n=181) groups, rather than analyzing mild and severe SOR separately.

Results

SOR and psychiatric symptoms by dataset

SOR rates varied substantially across samples (Figure 1A). Rates of SOR (combined mild and severe) in community samples were 19.2% in the HCP-D dataset, 18.3% in the ABCD dataset, and 51.0% in the HBN dataset. In samples enriched for autism, rates were 87.3% in the SSC dataset and 66.9% in the BGR dataset. Profiles of dimensional clinical symptoms also varied dramatically across samples (Figure S1). As expected, we observed positive associations among all dimensional scores of psychiatric symptoms (anxiety, depression, conduct disorder [CD],

attention-deficit/hyperactivity disorder [ADHD], oppositional defiant disorder [ODD], and autism spectrum disorder [ASD]) within samples (See Figure 1B, Figure S2).

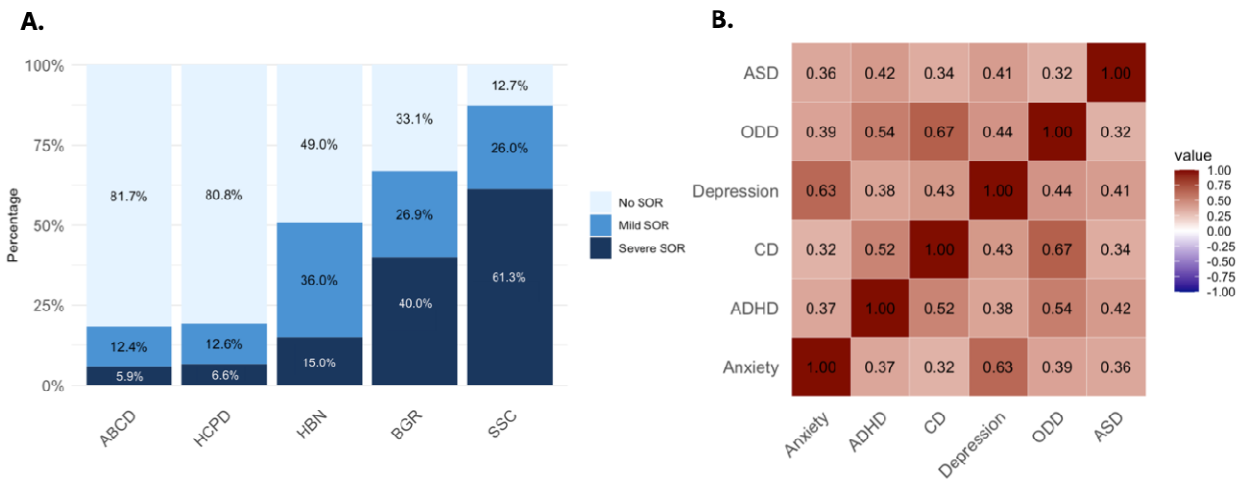

Figure 1: SOR and psychiatric symptoms measures in 5 independent datasets. A. Rates of SOR group by dataset. B. Matrix of correlations computed between clinical symptom scores within datasets and then averaged across datasets.

SOR-Symptom Associations

Results from conventional bivariate analyses show indiscriminate positive associations between SOR and all psychiatric measures (all pooled ORs >1.2, $p < 0.05$; Figures S3 and S4). However, the multivariate models that simultaneously incorporate all symptom variables revealed a striking pattern: specific, independent associations of both anxiety symptoms and autistic traits with SOR. Notably, anxiety is significantly associated SOR (pooled OR = 1.50, 95% CI [1.42, 1.58]; Figure 2) with mild heterogeneity (I^2= 33.2%) in effect pooled across all subsamples. Results are similar when pooled by sample type (community samples: pooled OR = 1.48, 95% CI [1.40, 1.57], I^2 = 0%, and autism samples: pooled OR=1.93, 95% CI: [1.56, 2.40], I^2 = 1.7%), indicating highly stable effect sizes across different studies and age groups (Table 1). The confidence intervals for pooled effect size estimates of anxiety-SOR associations by SOR severity overlapped in community and autism samples, indicating no significant difference in the strength of anxiety-SOR associations across these two types of samples. We note that odds ratios from these multivariate models reflect the size of effects in terms of unshared variance and will therefore be smaller than odds ratios from bivariate models.

Multivariate analyses also supported the expected positive relation of SOR with other autistic traits (pooled OR across all subsamples = 1.92, 95% CI [1.60, 2.31])), but with high heterogeneity (I^2= 86.1%). Intriguingly, the association between SOR and autistic traits was larger in the community samples (pooled OR=2.17, 95% CI: [2.00, 2.35], I^2 = 28.3%) than in the

autism samples (pooled OR=1.48, 95% CI: [1.32, 1.65], I^2 = 5.4%). The multivariate analyses also replicated and extended published findings from the ABCD dataset[3] that SOR is negatively associated with conduct disorder symptoms in models that account for co-occurring psychiatric symptoms (pooled OR across all subsamples= 0.79, 95% CI [0.67, 0.94], I^2 = 65.8%; Figure 2A). Separate pooling by sample type indicates that this association is specific to community samples (pooled OR = 0.74, 95% CI [0.67, 0.82], I^2 = 25%), whereas CD symptoms are not significantly associated with SOR in pooled analyses from autism samples (see Table 1 for full results). Separate post hoc analyses for mild SOR and severe SOR (relative to no SOR) yielded a highly similar pattern of results (Figures S5 and S6). Any significant associations between SOR and psychiatric symptom other than anxiety or autism in the community samples were of small effect size. No other symptom scales beyond anxiety and autism were significantly associated with SOR in the autism samples. This pattern of results demonstrates a *specific relationship between SOR and anxiety symptoms* that is consistent across 9 subsamples varying in age, autism diagnostic status, and enrichment for other psychiatric symptoms.

SOR / Symptom	Pooled OR	I^2
ASD		
Community Sample	2.17 [2.00; 2.35]***	28.3%, p-0.23
ASD Sample	1.48 [1.32; 1.65] ***	5.4%, p=0.36
Anxiety		
Community Sample	1.49 [1.41; 1.58]***	0%, p=0.57
ASD Sample	1.84 [1.56; 2.41]***	0%, p=0.52
Conduct Disorder		
Community Sample	0.76 [0.67; 0.82]***	0%, p=0.25
ASD Sample	0.97 [0.83, 1.13]	1.7%, p=0.38
ADHD		
Community Sample	1.17 [1.10, 1.25]***	0%, p=0.90
ASD Sample	1.09 [0.96, 1.24]	0%, p=0.61
Depression		
Community Sample	1.08 [0.98; 1.19]	37.7%, p=0.17
ASD Sample	1.07 [0.94, 1.22]	0%, p=0.89
ODD		
Community Sample	1.17 [1.04; 1.32]**	0%, p=0.21
ASD Sample	1.07 [0.94; 1.22]	0%, p=0.89

Table 1. Pooled effect sizes for associations of psychiatric symptoms with SOR in multivariate models computed across all nine subsamples. Confidence intervals shown in square brackets. I^2 indicates heterogeneity. Significant associations (where the 95% CI does not include 1.0) are indicated [**p < 0.01, ***p < 0.001]. Community samples include HBN, ABCD, and HCP-D studies. Autism samples include SSC and BGR studies.

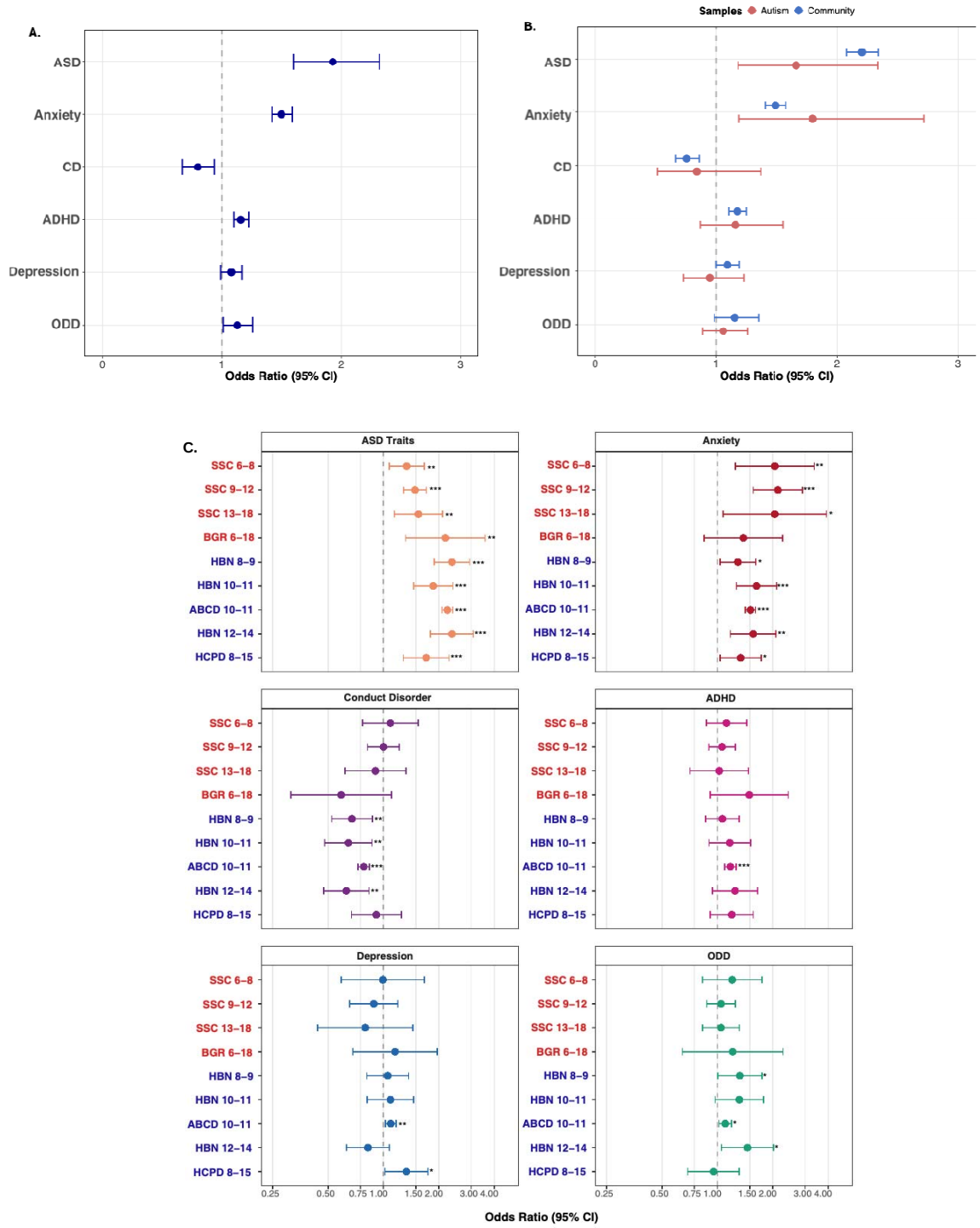

Figure 2. SOR is consistently associated with both anxiety and autism. A. Multivariate associations between SOR and psychiatric symptoms pooled across all subsamples. B. Multivariate associations between SOR and psychiatric symptoms by community and ASD samples. C. Age-specific multivariate associations of SOR with all modeled symptoms. Community samples are indicated in blue font, autism samples in red font. Labels include subsample age ranges (in years) [**p < 0.01, ***p < 0.001.].

SOR and functional connectivity

The second aim of the current study is to advance neurobiological models of SOR by identifying neural differences in FC that are replicably associated with mild SOR, a common trait in children. Multilevel models were used to derive beta weights for associations of brain-wide, pairwise network-level FC with mild SOR in an exploratory subset of children in the ABCD study and, separately, in a matched, non-overlapping replication subset of children in the study mild SOR. The pattern of brain-wide FC-SOR betas replicated across these independent samples, as indicated by permutation testing (ρ=0.31, p_{perm}=0.021; brain-wide FC-SOR effect: ρ=0.31, p<0.001; see Figure 3 and Figure S7). Analyses limited to the largest FC-SOR effects (top 10% of the absolute value of beta coefficients) in the exploratory sample yielded a higher correlation (ρ=0.61, p<0.001, Figure S8). FC-SOR effects from the exploratory sample for mild SOR also extended to severe SOR in an independent subset of children (ρ=0.55, p_{perm}<0.001; brain wide FC-SOR effect: ρ =0.55, p<0.001; top 10%: ρ =0.65, p<0.001), indicating that FC effects are shared across levels of SOR severity (mild vs severe). This pattern did not extend to a substantially smaller sample from the HBN study (ρ=0.025, p_{perm}=0.419; brain wide FC-SOR effect: ρ=0.025, p=0.54; top 10% effect: ρ=0.16, p=0.38; Figure S7 and S9). A comparison analysis with ABCD participants matched to the HBN sample in sample size and clinical profile also failed to reach significance, indicating that larger sample sizes are needed to observe these brain-wide effects (Figure S9)

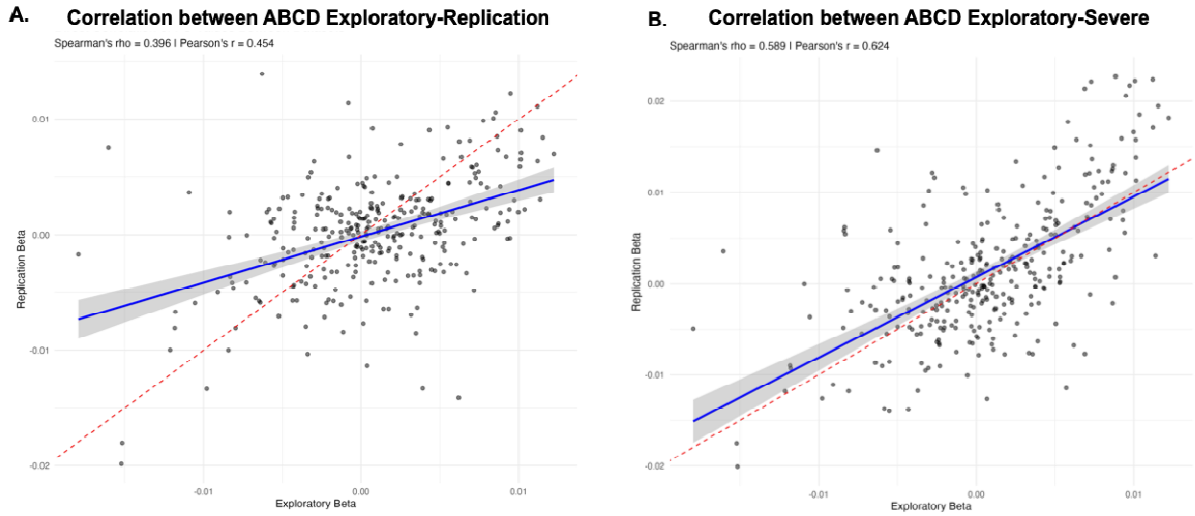

Figure 3. Brainwide patterns of FC-SOR associations replicate across independent subsamples. A. Spearman correlations of functional connectivity pattern associated with SOR between ABCD exploratory-ABCD replication subsets. B. Spearman correlations of functional connectivity pattern associated with SOR between ABCD exploratory-ABCD Severe subsets.

Next, we utilized the exploratory and replication samples from the ABCD dataset to test whether we could identify specific FC pairs that demonstrate replicable associations with mild SOR. Identification of such pairs can inform circuit-specific understanding of neural basis of SOR. Among the 422 FC pairs tested in the exploratory ABCD sample, 9 met criteria for selection to be tested for replication in the replication sample (Figure 4A; Table S5). Of these FC pairs, two met the stringent replication criteria for replication (see Methods): mild SOR was associated with reduced FC between the cingulo-opercular network and left ventral diencephalon, and reduced FC between the sensorimotor hand network and left hippocampus (Fig.4B). Of the 9 FC pairs identified in the exploratory sample, five met criteria for extension to the severe SOR subsample (Fig.4B; Table S5); these included the two FC pairs mentioned above. Notably, three of these FC pairs included the somatomotor hand network that subserves bodily tactile processing.

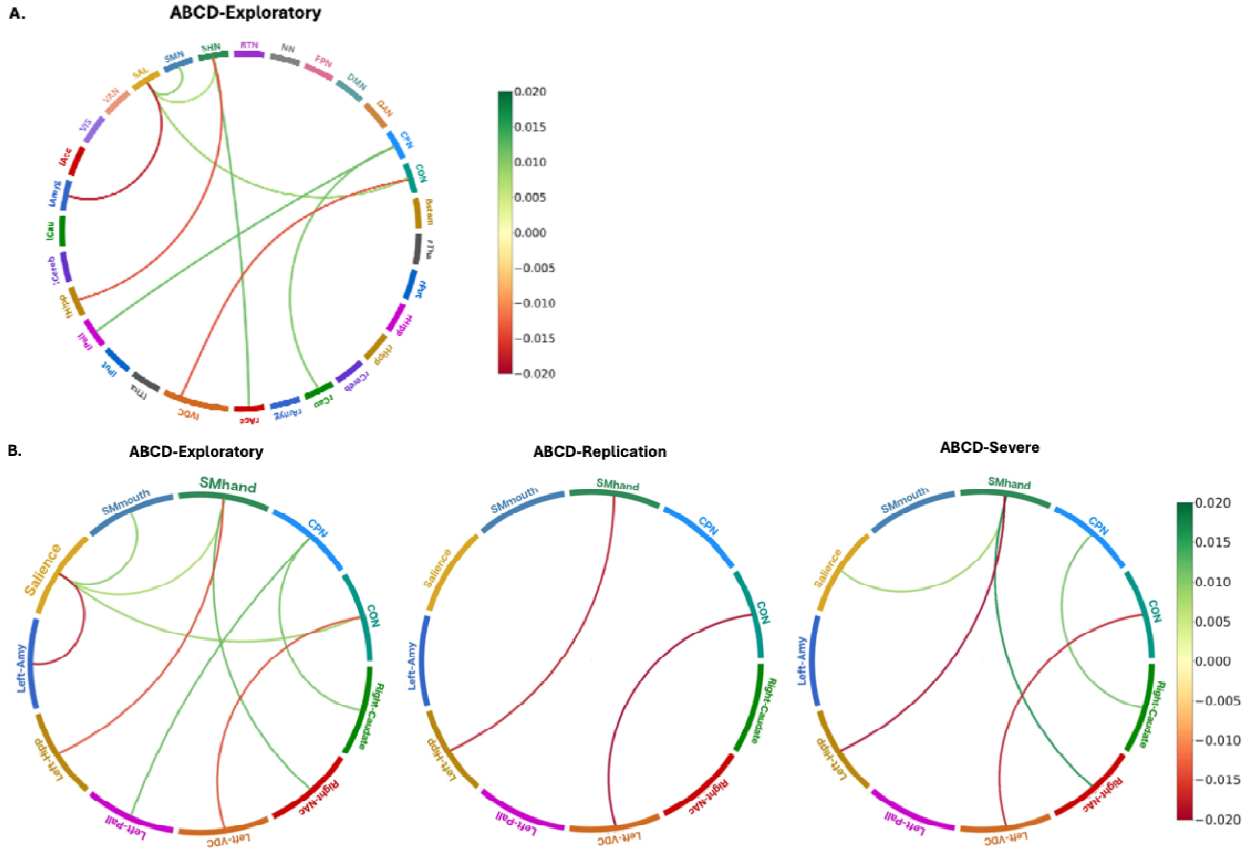

Figure 4. Specific, replicable FC differences associated with SOR. A. Change in functional connectivity associated with mild SOR from ABCD-exploratory SOR-demographics model. B. Replication test for functional connectivity pairs associated with SOR: Mild SOR (ABCD-Exploratory and Replication) and Severe SOR (ABCD-Severe) results from the SOR-demographics model

Finally, we tested whether the specific SOR-FC associations identified in the ABCD sample extend to the smaller HBN sample mentioned above. Although neither cingulo-opercular-left ventral diencephalon nor somatomotor hand-left hippocampus FC were significantly associated

with SOR in the smaller HBN sample (beta=-0.006, p=0.57; beta=0.004, p=0.72, respectively; Table S6), the direction and size of the cingulo-opercular-left ventral diencephalon FC-SOR association was consistent across samples (Figure 5 and Figure S10), according to a Fisher's r-to-z transformation test (z=0.003, see Supplement).

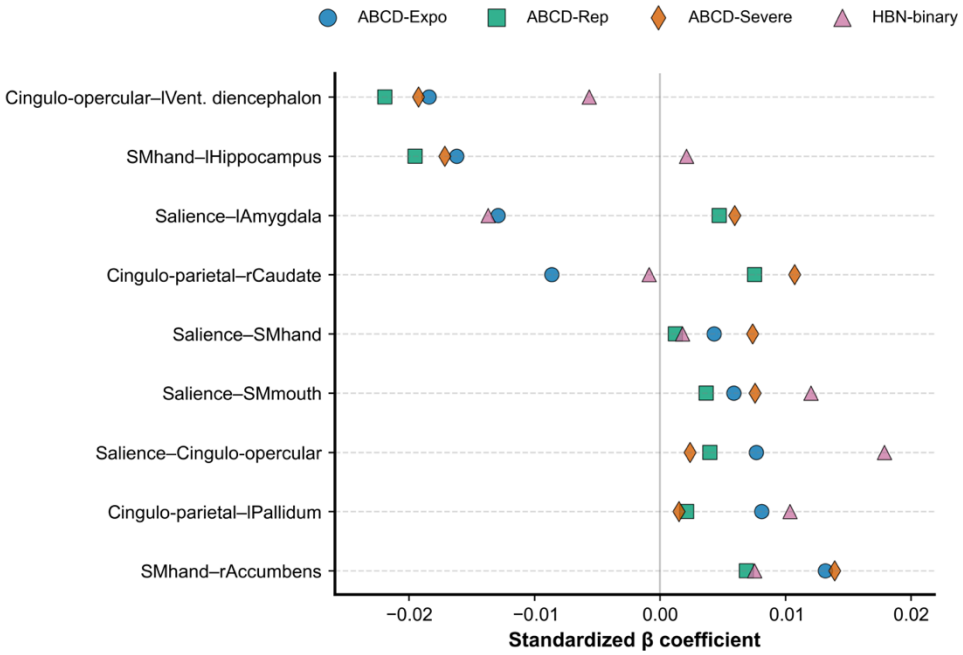

Figure 5: Summary of Beta Weights Across ABCD and HBN samples. Beta weights correlate with SOR for the 9 functional connectivity pairs tested across three samples: ABCD-exploratory, ABCD-replication, ABCD-severe, HBN-Binary SOR

Discussion

Based on data from more than 15,728 children across five independent datasets, this study provides a comprehensive account of clinical associations with SOR in childhood, demonstrating specific, consistent links between SOR, ASD and anxiety that transcend study design and population characteristics. Functional neuroimaging analyses of data from 9,197 children additionally identified and independently replicated whole-brain FC differences associated with both mild and severe SOR, while the pairwise FC analysis implicated cingulo-opercular and somatomotor networks, hippocampus, and structures of the ventral diencephalon as candidate regions in the neurobiology of childhood SOR.

By clarifying the specific clinical relevance of SOR, the current findings inform our understanding of SOR and raise new questions. Given that SOR is neither universally associated with psychopathology nor uniquely associated with a single diagnosis, we might conceptualize SOR as a transdiagnostic latent trait associated with higher likelihood for both autism and anxiety. A key outstanding question is exactly how SOR relates to these conditions. Are they causal relationships, and if so, what is the directionality of these effects? A few early findings

suggest that SOR and associated sensory gating impairments may precede and promote emerging anxiety symptoms in development. These include correlational evidence from longitudinal studies showing that SOR unidirectionally predicts anxiety in children[2,9,10,36,37] and experimental evidence that sensory gating disruptions in early development promote social impairments and anxiety-like behavior in transgenic mouse models of autism.[14,17,20,38] Additional studies in humans and animal models are needed to resolve the nature, causality, and directionality of relationships between SOR and both autism and anxiety.

The present analysis of clinical symptoms demonstrates the importance of accounting for co-morbidities and co-occurring symptoms in pediatric psychiatry. Whereas bivariate analyses yield non-specific positive associations between SOR and symptoms of all psychiatric conditions analyzed, multivariate analyses reveal robust, specific associations between SOR and anxiety symptoms in both autistic and community samples. Multivariate models also uphold expected positive associations between SOR and autistic traits in most samples and support prior findings that conduct disorder symptoms are *negatively* associated with SOR in community samples when accounting for co-occurring symptoms.[3] Although prior studies have documented higher rates of SOR among children with ADHD,[23,39,40] the current results suggest that such findings primarily stem from the high comorbidity and symptom co-occurrence of ADHD with both anxiety disorders and autism.[32–34,40–43]

Results of the neuroimaging results indicate that mild SOR is associated with brain-wide differences in functional neuroarchitecture and specific network-level differences that replicate across independent samples and generalize to children with severe SOR. Prior analysis of FC effects associated with severe SOR yielded a greater number of robust effects;[3] this difference may reflect neurobiological differences associated with SOR severity or methodological differences (i.e., requiring replication in an independent subsample of children). In particular, the current study finds that mild and severe SOR are associated with reduced FC between regions of the somatomotor hand cortical network and the left hippocampus – an effect that was also identified in relation to severe SOR in our prior analyses[3] and may reflect differences related to sensory prediction.[44] The current analysis, which provided a more comprehensive coverage of subcortical structures, also identified a novel association with functional connectivity between the cingulo-opercular cortical network and the left ventral diencephalon, a subcortical area that encompasses several anatomical structures related to arousal and low-level sensory processing, including the hypothalamus, mamillary bodies, and lateral and medial geniculate nuclei of the thalamus. These associations were robust to model selection, replicated in an independent set of participants, and generalized across SOR severity level; Interestingly, a separate exploratory investigation of volumetry effects in the ABCD study found that mild SOR is specifically associated with larger relative volumes of both left and right ventral diencephalon.[45]

Strengths of the current work include its large total sample size, analysis of effect consistency across several datasets differing in demographic and clinical sample characteristics, a data-driven,

whole-brain investigation of FC correlates of SOR, and replication of identified FC effects in independent data. To harmonize cross-sample comparisons, we used parent-report measures common to these datasets. Future work should seek to replicate these findings using gold-standard clinical measures and more comprehensive sensory assessments.

We also note that although the FC-SOR associations identified in this study replicated in an independent dataset, effect sizes were small, and most available datasets would be underpowered to reliably detect them. Effect sizes are affected by a variety of factors, including heterogeneity of underlying neural signatures. Specifically, if heterogeneous neurobiological effects converge in affecting adaptive sensory modulation and producing the behavioral phenotype we know as SOR, then any specific neural difference would account for only a fraction of the cases of SOR, resulting in small overall effect sizes. Similar considerations are believed to affect FC associations with psychiatric symptoms more broadly.[46–48] In light of this, replication of individual FC associations in the current study are noteworthy and specify a potential subset of the neural correlates of SOR, which can inform future research.

Our study provides evidence for the clinical and neurobiological significance of SOR in diverse populations through comprehensive analyses and replication across multiple datasets. The consistency in both clinical and neural signals suggests that SOR represents a unique, clinically relevant phenotype with distinct neural correlates. These insights can inform both clinical practice and future research aimed at understanding and supporting individuals with sensory processing differences.

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Disclosure: We declare that one of the authors, John Constantino, receives royalties for the commercial distribution of the Social Responsiveness Scale we have used in our main analysis. The remaining authors declare no conflicts of interest.

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