Replicable functional connectivity patterns associated with sensory over-responsivity in children

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Background

- Sensory over-responsivity (SOR) is a behavioral pattern characterized by strong negative responses to innocuous sensory stimuli, affecting 15-20% of typically developing children.[1-3]
- While SOR has been recognized for its association with ASD[4], a recent meta-analysis across more than 15,000 children suggests that SOR as a transdiagnostic latent trait associated with higher likelihood for both autism and anxiety[5].
- Mild SOR is particularly common in the general population. Recent neurobiological investigations have begun identifying neural correlates of severe SOR[6], though less is known about the neurobiological signatures of mild SOR.

- **Aim**: Characterize the underlying functional connectivity (FC) patterns associated with mild SOR.

Participants

- 8841 participants (8-9yrs, mean=9.94) from ABCD Study®[7] with usable resting state fMRI data for first-pass analysis.
- Subjects from the **no and mild SOR groups** were split into **2 independent (Exploratory-S1, Replication S2) subsamples** matched on SOR prevalence, demographic information, and clinical symptoms

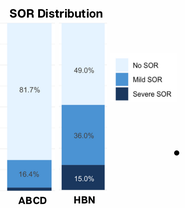
- 356 participant (8-9yrs, mean=9.47) from Healthy Brain Network Biobank[8] (HBN) with distinct sample characteristics were included in the secondary analysis to test for generalizability

Method

Measurements

SOR Severity:
- Social Responsiveness Scale item-42 producing 3 levels (no, mild, severe) of SOR.

Psychiatric Symptom Scores:
- Child Behavior Checklist DSM-5 Oriented subscales



Functional Connectivity Analysis

- **Exploratory analysis** was conducted in **422** FC pairs between 12 cortical networks[9] and 10 subcortical structures[10] were fitted with three hierarchical multilevel linear models

3 Linear Mixed-Effects Models

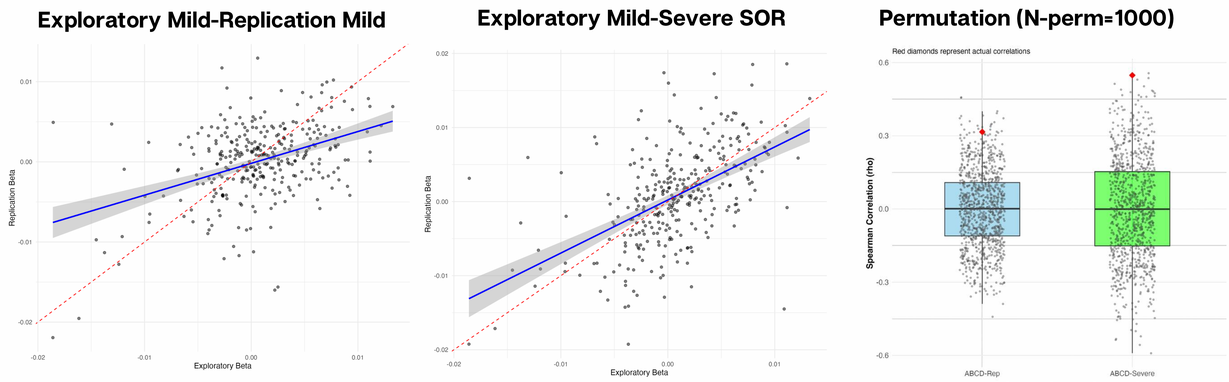
Note: Study site was included as a level 2 random effect variable

Model 1	Model 2	Model 3
SOR	SOR *Age, Sex* *Economic disadvantage* *Framewise Displacement*	SOR Age, Sex Economic disadvantage Framewise Displacement *Internalizing & Externalizing, Autism*

- **Brain wide FC associated with SOR:** Replicability of whole-brain FC patterns associated with mild SOR was assessed by correlating standardized beta coefficients from multilevel models between Exploratory (S1) and Replication (S2) and S1 to Severe Samples. Additionally, S1 patterns were validated against the Severe SOR group using permutation tests.
- **Replication analysis:** FC pairs identified as candidate associations with mild SOR *(p<0.05 in Model 1 and 2)* in the exploratory subgroup were advanced for testing in the replication and severe subset. Pairs with successful replication were then tested in HBN dataset for extension

SOR is Associated with Specific, Replicable Brain-wide FC Patterns

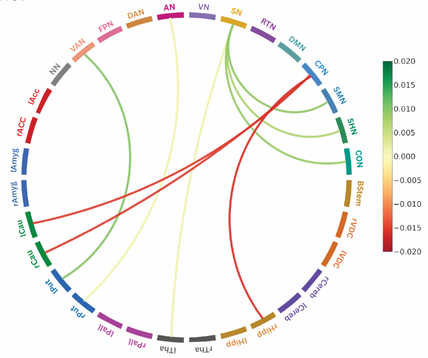
- The functional connectivity patterns associated with mild SOR in the exploratory sample show a moderate correlation with the replication sample (ρ≈0.31, p<0.001) and an even stronger correlation with the severe SOR sample (ρ≈0.55, p<0.001).

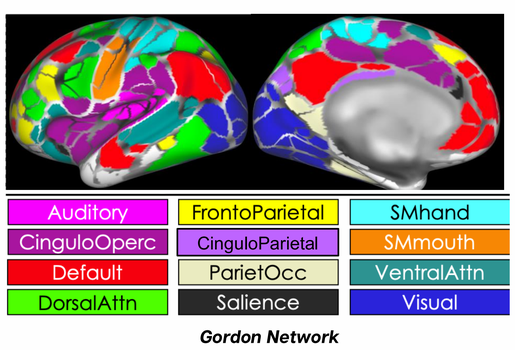


- Both actual correlations were significantly higher than their respective permutation distributions (n=1000), suggesting a common functional connectivity pattern linked specifically to SOR.

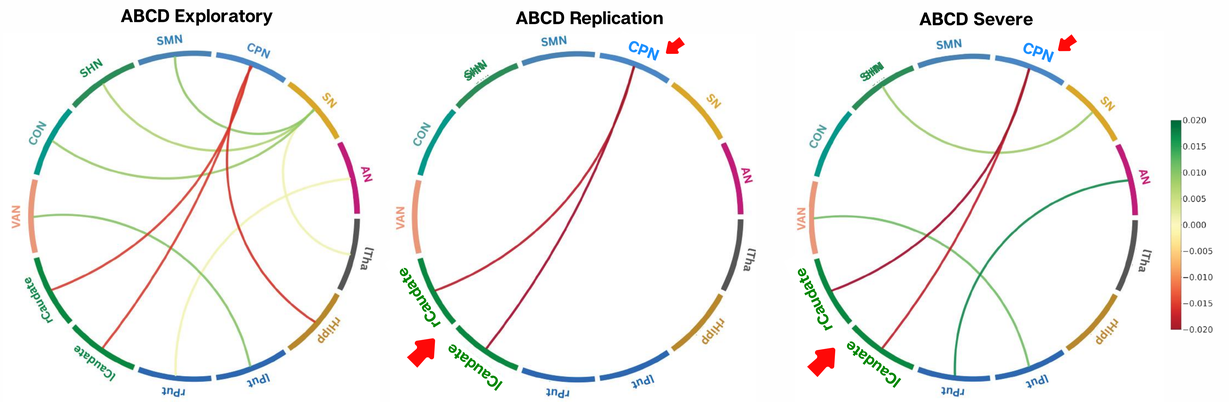
SOR is Associated with Reduced FC between Cingulo-parietal Network and Bilateral Caudate Nucleus

- 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.



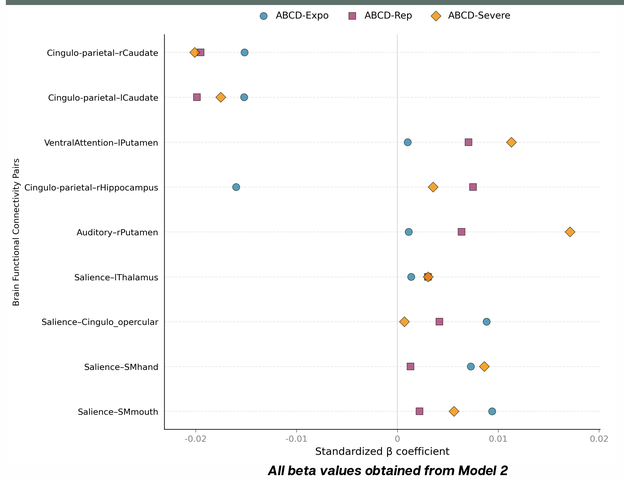


- Upon replication testing, we identified **mild SOR** is consistently associated reduced functional connectivity between the **cingulo-parietal network and left and right caudate.** This result further extends to severe SOR, and also enhanced FC in somatomotor hand-salience, auditory network-right putamen, and ventral attention to left putamen.



- None of the FC effects identified in ABCD sample were significantly associated with SOR in the smaller HBN sample (N=356, NoSOR=175, AnySOR=181). However, these effects were also not significant when tested in a subset of ABCD subjects (N=356, NoSOR=175, AnySOR=181) with matched demographics and clinical profiles with HBN.

Standardized Beta Coefficients from FC Pairs Identified from Exploratory Analysis



All beta values obtained from Model 2

- 8 out of 9 FC pairs detected from the exploratory analysis shares show the same direction of effect in the replication of mild SOR and extension of severe SOR.

Discussion

- We identified specific, replicable brain-wide patterns associated with SOR, particularly negative associations between cingulo-parietal network and bilateral caudate.
- This result is the first to identify cingulo-parietal network (also know as parietal memory network) in relation to SOR, revealing reduced connectivity with striatal regions involved in action initiation and sensory-motor integration
- Recent precision imaging suggests the cingulo-parietal network may unify with the salience network; thus, reduced CPM-caudate FC could impair filtering and prioritization of sensory inputs (via disrupted salience detection and gating), leading to SOR.
- The small effect sizes may reflect neurobiological heterogeneity, where multiple distinct pathways can each produce SOR phenotype, diluting associations between any single neural feature and the overall phenotype–a pattern observed broadly in psychiatric FC research.

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