



Abstract

Sensory modulation characteristics are now part of the DSM-5 Autism Spectrum Disorder (ASD) classification and defined as: "hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment" (DSM-5, p.50). We hypothesize that the sensory issues that affect individuals with ASD may also affect nuclear family members, but to a much lesser degree, not causing great inconvenience in daily living. These behaviors fit the characteristic profile of the Broad Autism Phenotype (BAP) and thus, might be used as behavioral phenotypes in family genetics studies.

One hundred sixteen (116) probands with ASD and 273 of their nuclear family members were rated on behaviors related to hypo- and hyper-reactivity. Rates of hypo- and hyper-reactivity were similar to what is reported in the literature with some probands showing evidence of both (55%-72%). Rates of hypo-reactivity in family members ranged from 8.3%-17.0% while rates of hyper-reactivity were higher, ranging from 20.8%-23.4%. There were no differences based on sex.

Genetic linkage was conducted on a subset of families and produced PPLs suggestive of linkage on Chromosomes 1 & 6 (38% and 39% respectively). Follow-up analyses are needed to include more comprehensive measures of sensory modulation that can lead to more distinct sensory phenotypes to be applied to family genetic data.

Background

Sensory reactivity is now part of the DSM-5 ASD diagnostic criteria. It includes aberrant behaviors that fall into three categories:

Hypo-reactivity	Unusual Interest	Hyper-reactivity
Intense stimulation is needed to produce a response to sensory stimulus	Excessive or unusual interest in sensory aspects of the environment	A sensory response is faster or more intense than expected

- Upwards of 90% of individuals with ASD experience some type of sensory issue (Schauder & Bennetto, 2016).
- **Broad Autism Phenotype (BAP):** presentation of sub-clinical manifestations of autistic traits (social and communication impairment, rigidity, and unusual personality characteristics) identified in family members of individuals with ASD (Gerds et al., 2013).

Hypothesis: In addition to the reactivity characteristics seen in ASD probands, other family members may also present with similar behaviors but to a lesser degree. These behaviors could be considered part of the BAP and thus, might be useful as a behavioral phenotype in family genetic studies of ASD.

Methods

The New Jersey Language and Autism Genetics Study (NJLAGS)

Families:

- Ascertained families with at least one family member with ASD and a language impairment (LI) and at least one other family member with LI with or without ASD.



Relevant Assessments from Battery:

- All participants received the Social Responsiveness Scale (SRS-2) (Constantino, 2012) as a part of the full NJLAGS testing battery.
- Participants with ASD received the Autism Diagnostic Interview-Revised (ADI-R) (Rutter & Le Couteur, 2003).

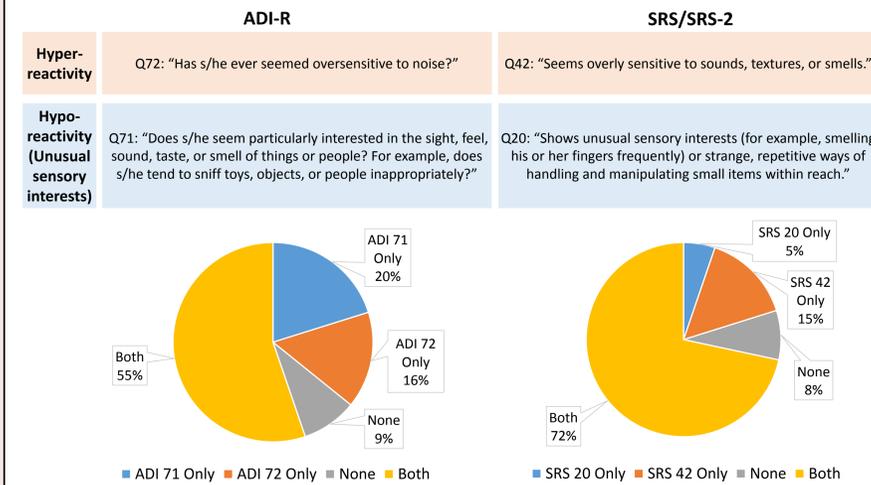
Genotyping:

- Collection of whole blood DNA stored in RUCDR
- Affymetrix Axiom or Illumina PsychArray genomewide microarrays
- Whole genome sequencing

Results

Sensory subtypes in ASD

Can we identify sensory subtypes using NJLAGS testing battery?



Compared responses to ADI-R and SRS sensory questions in 134 participants with ASD.

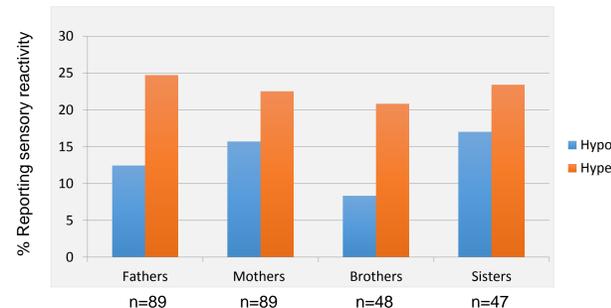
Rates of hypo- and hyper-reactivity based on the ADI-R and SRS-2 reveal that more than half of the ASD probands exhibited both types of sensory reactivity, and over 90% reported at least one (consistent with the literature).

There were no differences in rates of hypo- and hyper-reactivity for ASD probands by sex: $\chi^2(1, N=116) = 1.12, p = .290$.

Sensory subtypes as part of the BAP

Do family members without ASD also have sensory subtypes?

Unaffected family member responses to SRS sensory questions



Hypo-reactivity was determined by a score of >0 on SRS Q20, while hyper-reactivity was determined by a score of >0 on SRS Q42.

Pearson chi-square analysis revealed no difference in the rates of hypo- and hyper-reactivity based on family members and sex: HYPO- $\chi^2(2, N=273) = 537, p = .76$, HYPER- $\chi^2(2, N=273) = 204, p = .903$, as well as by sex: HYPO- $\chi^2(1, N=273) = 1.59, p = .21$, HYPER- $\chi^2(1, N=273) = 0.12, p = .91$.

More unaffected family members presented with hyper-reactivity than hypo-reactivity: $\chi^2(2, N=236) = 36.83, p < .001$.

Linkage analysis of sensory subtypes

Examined potential genetic markers across the entire genome for genetic linkage to these phenotypes using the Posterior Probability of Linkage Analysis (PPL) (Vieland, 1998).

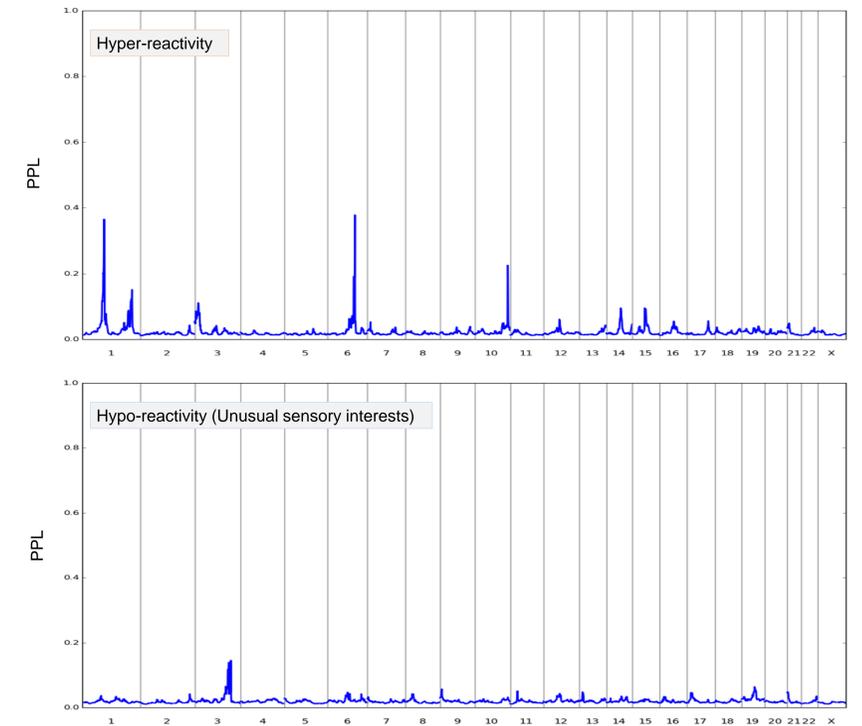
Initial prior probability of linkage is set at 0.02

PPL values < 2% represent evidence against linkage

PPL values > 2% represent evidence for linkage to that location

Linkage analysis was performed using the PPL on hypo- and hyper-reactivity. Based on the current sample, there was evidence of linkage on Chromosome 6 (39%) and Chromosome 1 (38%) for the hyper-reactivity phenotype. There was no evidence of linkage observed for hypo-sensitivity. Sequential updating will be performed when additional SNP and sequenced data are analyzed.

Results cont.



Conclusions

In this pilot study:

- ASD probands demonstrated high rates of hypo- and hyper-reactivity, with a majority demonstrating both forms of reactivity. These results support the inclusion of sensory modulation in the DSM-5 ASD diagnosis.
- Unaffected family members for ASD show some degree of hypo- and hyper-reactivity (range=8.3% to 24.7%) suggesting that these characteristics can be considered part of the BAP but should be explored as separate behavioral phenotype in family genetics studies such as ours.
- Preliminary linkage findings on Chromosomes 1 & 6 suggest that hyper-reactivity should be explored further in family genetics studies.

Limitations:

Although this is a pilot study with promising results, these phenotypes were based on only a few behavioral variables. More detailed sensory information must be collected on each subject to better define the phenotypic classifications. As additional families are genotyped, linkage findings can be updated.

Acknowledgements

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