Multidimensional Approaches in the Study of Autistic Traits using Behavioral and Imaging Data

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Introduction

- Autism spectrum disorder (ASD) is a complex array of neurodevelopmental conditions, typically characterized by social interaction and communication impairments, and restricted and repetitive behaviors[1].
- Patients exhibit widespread heterogeneity in behavior, biological phenotypes, and genetics.
- Scientific literature has reported gross neuroanatomical inconsistencies, possibly due to classically adopted case-control approaches lumping together these heterogeneities.
- We propose a gradual shift toward experimental designs focused on subtyping ASD before further case-control investigations.
- **Objective:** Uncover ASD cortical phenotypes after subgrouping autistic traits by A) age, and B) behavioral phenotypes.

Results

Part 1: Score Distribution

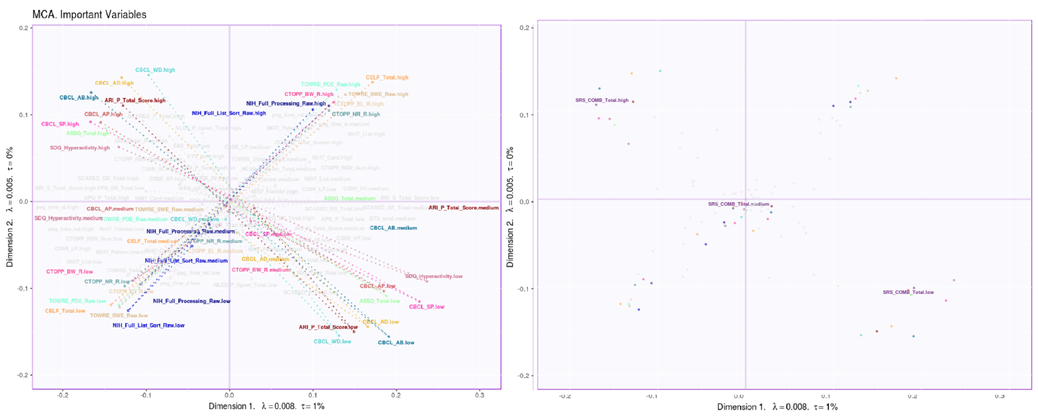

Figure 1: MCA plot. Correlation between several behavioral and cognitive scores (left). To better interpret correlation with SRS, score labels removed and only SRS projected onto plot (right). Showed SRS closely correlates with scores representing aggression, hyperactivity, attention deficits, depression, reactivity, and anxiety.

Part 2: Cortical Structures in Children and Adults

> 12 years old

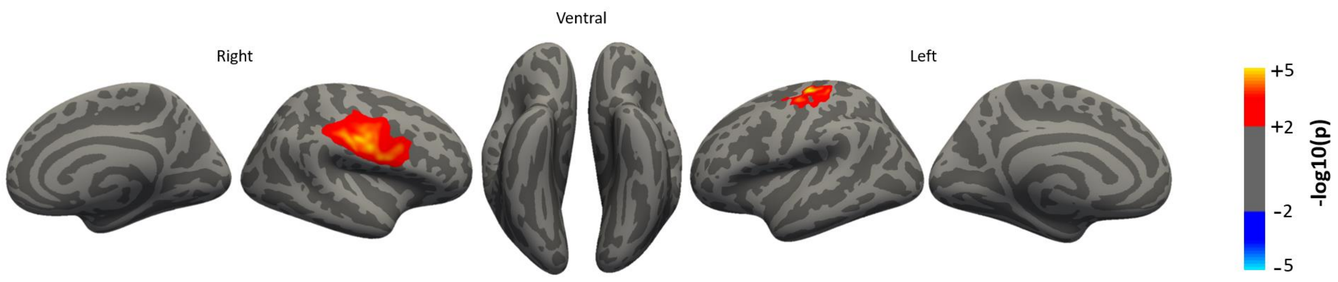

Figure 2: Age Effect in Cortical Structure. Comparing high vs. low autistic traits in adults yielded bilateral increases in gyrification in precentral and frontal regions of right hemisphere (p<0.01), and in precentral region of left hemisphere (p<0.01). Same contrast run in children (below 12 years old) with no results.

Part 3: Cortical Comparisons in Behavioral Subgroups

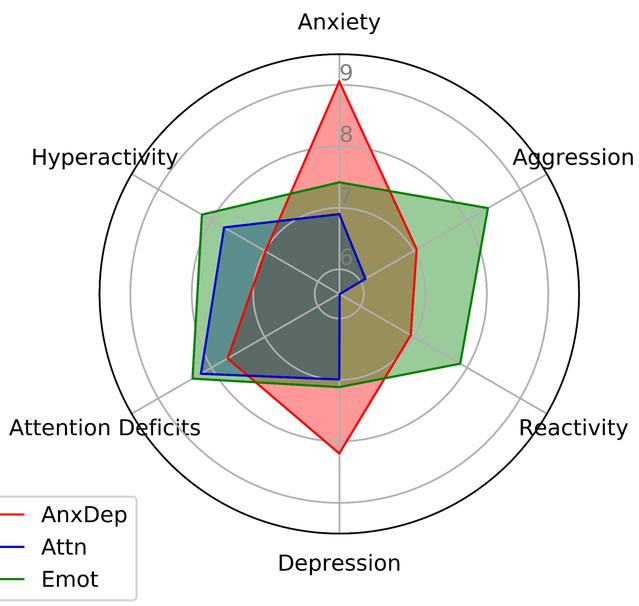

Figure 3: Radar Plot of High Autistic Traits Subgroups. Clustering analysis yielded 9 subgroups varying in behavioral composition. From these, 3 exhibited high SRS. First subgroup (AnxDep) exhibited high levels of anxiety and depression, second (Attn) showed ADHD-like tendencies, and third (Emot) had ADHD-like tendencies with strong emotional dysregulation (high aggression and reactivity levels).

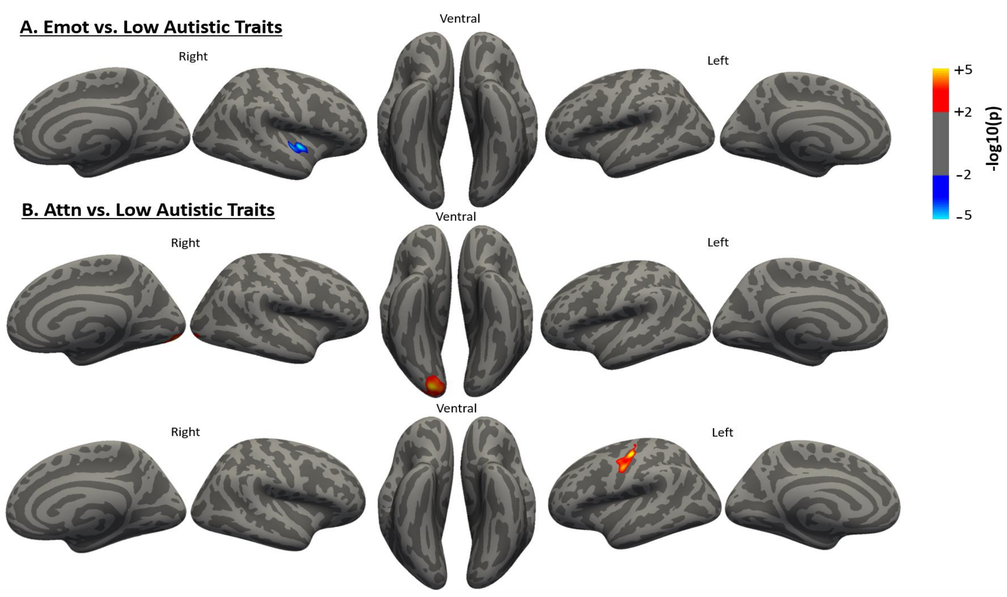

Figure 4: Comparing Surface Features Between each Subgroup and Clinical Controls. A) Comparing Emot subgroup against control group yielded decreases in cortical thickness in right insula (p<0.005). B) Comparisons between Attn subgroup and controls showed increases in gyrification in right lateraloccipital (p<0.005), and in surface area in left precentral region (p<0.005). AnxDep showed no results.

Methods and Materials

Cohort

- Used the Healthy Brain Network (HBN) cohort[2] comprised of children and youth that are either diagnosed or at risk for psychiatric illnesses.
- Contains wide variety of clinical scores, neuroimaging data, and genetics.
- Age range: 5-21 years old, n = 1753, M:F ratio = 1111:642

Part 1: Score Distribution

- Conducted a Multiple Correspondence Analysis[3] (MCA) to determine variance of the Social Responsiveness Scale[4] (SRS) among behavioral scores.

Part 2: Cortical Structure in Children and Adults

- Intersection between high and low SRS groups, QC images, IQ>70, yielded n= 319 (age 5-18; 58% males).
- First compared participants with high SRS to those with low SRS, then further divided into two age groups: children (below 12; n=195, 61% males) and adults (above 12; n=120, 55% males) and compared high vs. low SRS again within each age group.
- Scans quality checked manually and with euler metric[5].
- FreeSurfer pipeline[6] and vertex-wise analysis to look at cortical thickness, gyrification, and surface area by running a GLM at each vertex. Covariates considered: age, gender, IQ, and site.

Part 3: Cortical Comparisons in Behavioral Subgroups

- 1092 subjects (aged 5-18, m=11.1 | M:F = 681:411) based on score availabilities in **social impairment, anxiety, reactivity, hyperactivity, aggression, attention deficits** and **depression**.
- Conducted k-means clustering analysis on behavioral scores to find high autistic traits subgroups based on **high SRS**. BIC method suggested a k=9 optimal cluster level.
- 549 subjects had good quality T1 scans.
- First, ran cortical morphology comparison between all subgroups combined (one heterogeneous high autistic traits group) and controls. Second, compared each autistic trait subgroup to controls.
- FreeSurfer pipeline[6] and vertex-wise analysis to look at cortical thickness, gyrification, and surface area by running a GLM at each vertex. Covariates considered: age, gender, IQ, and site.

Conclusions

- Wide range of data in the HBN cohort allowed to observe autistic traits correlation to several behaviors by means of MCA analysis (**Part 1**)(*Fig. 1*).
- Could also finely investigate structural differences in 2 conditions: high vs. low autistic traits in children and in adults (**Part 2**), and differences between behaviorally distinct subgroups and controls (**Part 3**).
- Presence of surface structure signatures in adults, but not in children (*Fig. 2*).
- Showed that behavioral traits distribute differently thereby isolating autistic traits subgroups (*Fig. 3*). Affected brain regions in each subgroup are associated to functions spanning ASD[7,8,9] (*Fig. 4*).
- **Perspectives**: To emphasize the importance of ASD stratification in the search of biological phenotypes. We demonstrated that though subtypes (age, behavior, etc.) show cortical signatures, **combining them into one collective and heterogeneous autistic traits group does not reveal structural brain differences**.

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