How anxiety and depression relate to brain structure **depends on ADHD subtype and Anxiety and Depression symptom level.**

ADHD Symptom Dimensions Show Distinct Nonlinear Regional Volume Responses to Anxiety/Depression

Rafaela Goveia, Jennifer Crosbie, Elizabeth Kelly, Julia Frei, Jason Lerch, Evdokia Anagnostou, and Jacob Ellegood.

Introduction

- ADHD-I (inattentive) and ADHD-C (combined) show distinct structural profiles: ADHD-I linked to frontal and default-mode differences; ADHD-C to striatal and frontoparietal alterations
- Anxiety and depressive symptoms co-occur at high rates across subtypes and reflect added regulatory loadon fronto-limbic and executive networks
- Most neuroimaging studies model relationships as fixed linear effects, unlikely to hold across the full severity range or across presentations with different neural baselines

Research Question

Across ADHD subtypes, how does anxiety/depression severity relate to regional volume and hemispheric asymmetry, and is that relationship non-linear and subtype-specific?

Methods

Sample

- 359 children and adolescents (ages 3–27; mean 12.8; 292 male, 87 female) from the Province of Ontario Neurodevelopmental Network (POND)
- Grouped into ADHD-I (n=109), ADHD-C (n=138), and Non-ADHD (n=112) using SWAN (Strengths and Weaknesses of ADHD Symptoms and Normal Behavior) scale cut-offs

Measures

- Anxiety and depression severity measured with the RCADS (Revised Children's Anxiety and Depression Scale) ANXDEP (Anxiety and Depression) T-score (continuous, adjusted for age and sex)
- Structural MRI (MPRAGE) run through POND's standardized pipeline, giving harmonized volumes for 79 paired left/right cortical and subcortical ROIs (Regions of Interest)
- Hemispheric asymmetry index computed per region:

$$Asymmetry\ Index = \frac{Left\ - Right}{Left + Right}\ x\ 100$$

Analysis

- For each ROI, the shape of the ANXDEP effect (linear, quadratic, or natural cubic spline; df=3) was chosen by AICc, with 5-fold cross-validated RMSE
- Final models tested the ADHD subtype x ANXDEP interaction, controlling for age, sex, and ASD diagnosis
- Effect sizes reported as Cohen's f^2; p-values corrected with Benjamini-Hochberg FDR within each term family
- Symptom-related structural variation summarized as the peak-to-trough range of predicted values across the 5^{th}-95^{th} ANXDEP percentile

Relevance to Holland Bloorview

- Backs a symptom-dimension approach over diagnostic labels, fitting Holland Bloorview's transdiagnostic, individualized care.
- Anxiety and depression track brain structure differently by ADHD profile, so they warrant attention as modifiers of neurodevelopment, not generic comorbidities.
- Continuous, flexible modeling captures child-level heterogeneity that group comparisons miss, and points to which systems may matter for whom, attention-related in ADHD-I, reward-related in ADHD-C.

Results

Right NAcc and Right Postcommissural Putamen

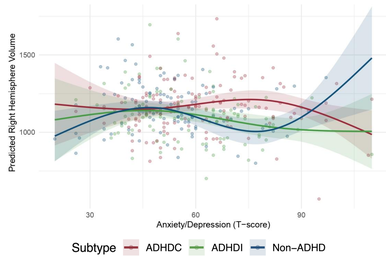

Figure 1. Right Nucleus Accumbens Ventral Striatum (Nacc).

Striatal subtypes differed in spline timing rather than curvature: ADHD-C declined early (U-shaped) then recovered, non-ADHD the inverse, ADHD-I a single high-severity inverted-U, right-lateralized. ADHD-C spanned the full severity range while ADHD-I was restricted to high severity, implicating the hyperactive-impulsive dimension in striatal sensitivity to internalizing load.

Left SMG, Posterior Cingulate Cortex, and Postcentral Gyrus

ADHD-I and ADHD-C followed inverted-U trajectories and non-ADHD a U-shape

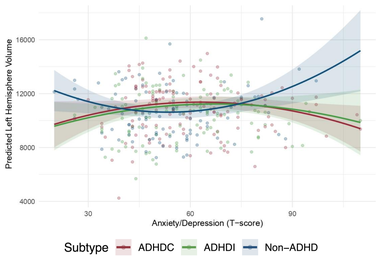

Figure 2. Left Supramarginal Gyrus (SMG)

Asymmetry Middle Frontal Gyrus

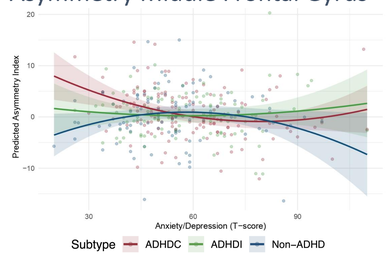

Figure 3. Asymmetry Index Middle Frontal Gyrus (MFG)

In ADHD-C, asymmetry followed a U-shape, rightward lateralization peaking at moderate severity,

Curvature amplitude and trajectory direction across ROIs and subtypes

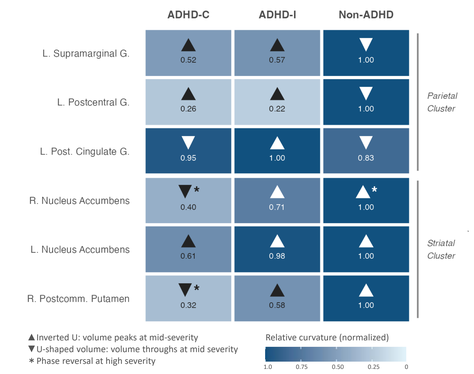

Figure 4. Curvature amplitude and trajectory direction across ANXDEP

Non-ADHD showed the greatest curvature amplitude across most regions, ADHD-I intermediate, and ADHD-C the lowest, with trajectory direction differing by subtype and cluster.

Conclusion

- Anxiety/depression severity organizes brain structure across parietal, striatal, and frontal systems in a subtype-specific, non-linear way, through trajectory shape, timing, and phase reversals rather than uniform volume differences.
- These features are invisible to case-control designs and emerge only when severity is modeled continuously.
- ADHD-I and ADHD-C engage distinct systems at different points on the internalizing spectrum, parietal for ADHD-I, striatal for ADHD-C, arguing against a single severity continuum.
- Cross-sectional design, unmeasured medication, and a merged anxiety–depression score limit inference.
- Next: longitudinal follow-up, separated RCADS subscales, medication-stratified analyses.

Holland Bloorview Kids Rehabilitation Hospital

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