



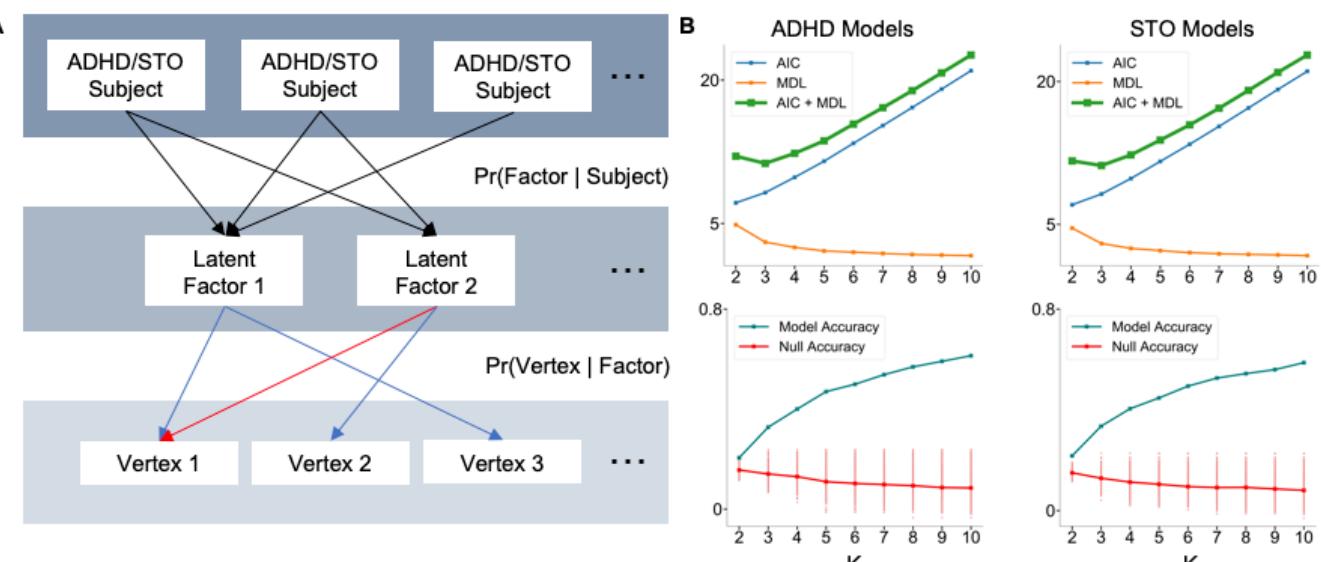
# Mapping latent neuroanatomical substrates underlying severe temper outbursts in children

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## INTRODUCTION

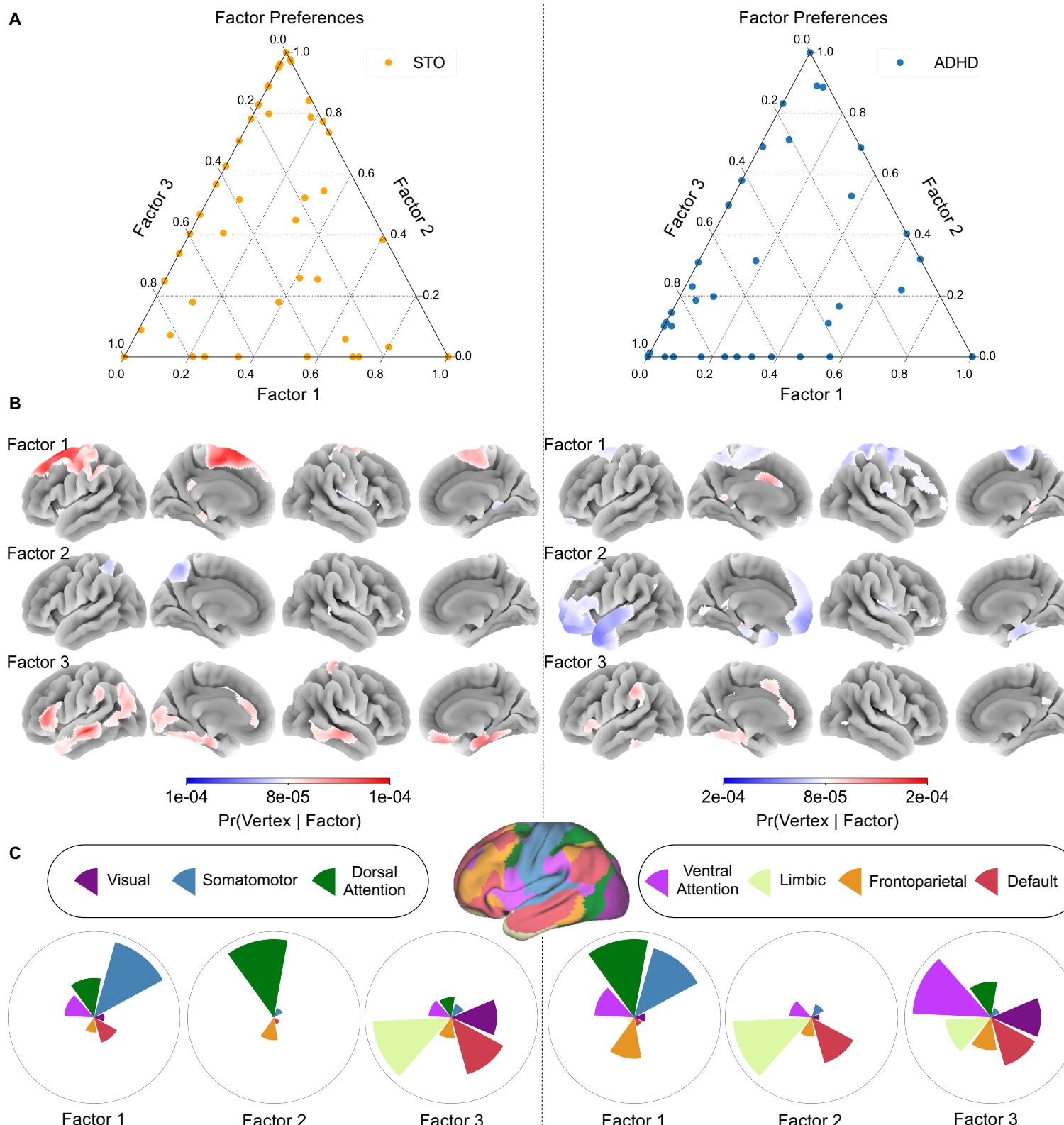
- Severe temper outbursts (STO) in young children are a significant source of concern in child psychiatry.
- Children with STO commonly receive multiple diagnoses, with Attention-Deficit/Hyperactivity Disorder (ADHD), disruptive mood dysregulation disorder, and oppositional defiant disorder being main comorbid syndromes [1].
- Resulting transdiagnostic nature of STO has led to conflicting conceptualizations of these behaviors as symptoms of mania, oppositional and defiant behaviors, and manifestations of poor emotion regulation [2].
- This challenge highlights the need for parsing out the heterogeneity in the neurobiological underpinnings of STO.
- To this end, we employed Latent Dirichlet Allocation (LDA) [3], a fully unsupervised Bayesian framework which effectively summarizes the original data with multiple parsimonious latent factors.
- The clinical use of this model allows for describing underlying heterogeneous pathological sources as a mixture of latent factor memberships, instead of attributing them to single isolated causes.
- We assessed a hypothesis that children with STO would exhibit multiple distinct pathological substrates, which may collectively contribute to the manifestation of their heterogeneous atypical neuroanatomy.



**Figure 1.** Polar LDA and model selection. **A)** Diagram of polar LDA. This model assumes that each subject's cortical thickness deviations arise due to varying contributions of multiple latent pathological factors which, in turn, underlie the behavioral symptoms in children with STO. **B)** (Top) Combination of two separate model selection metrics for ADHD and STO respectively. (Bottom) Estimated latent pathological profiles correlated to cortical thickness profiles; model significance evaluated by correlating to shuffled thickness profiles

## METHODS

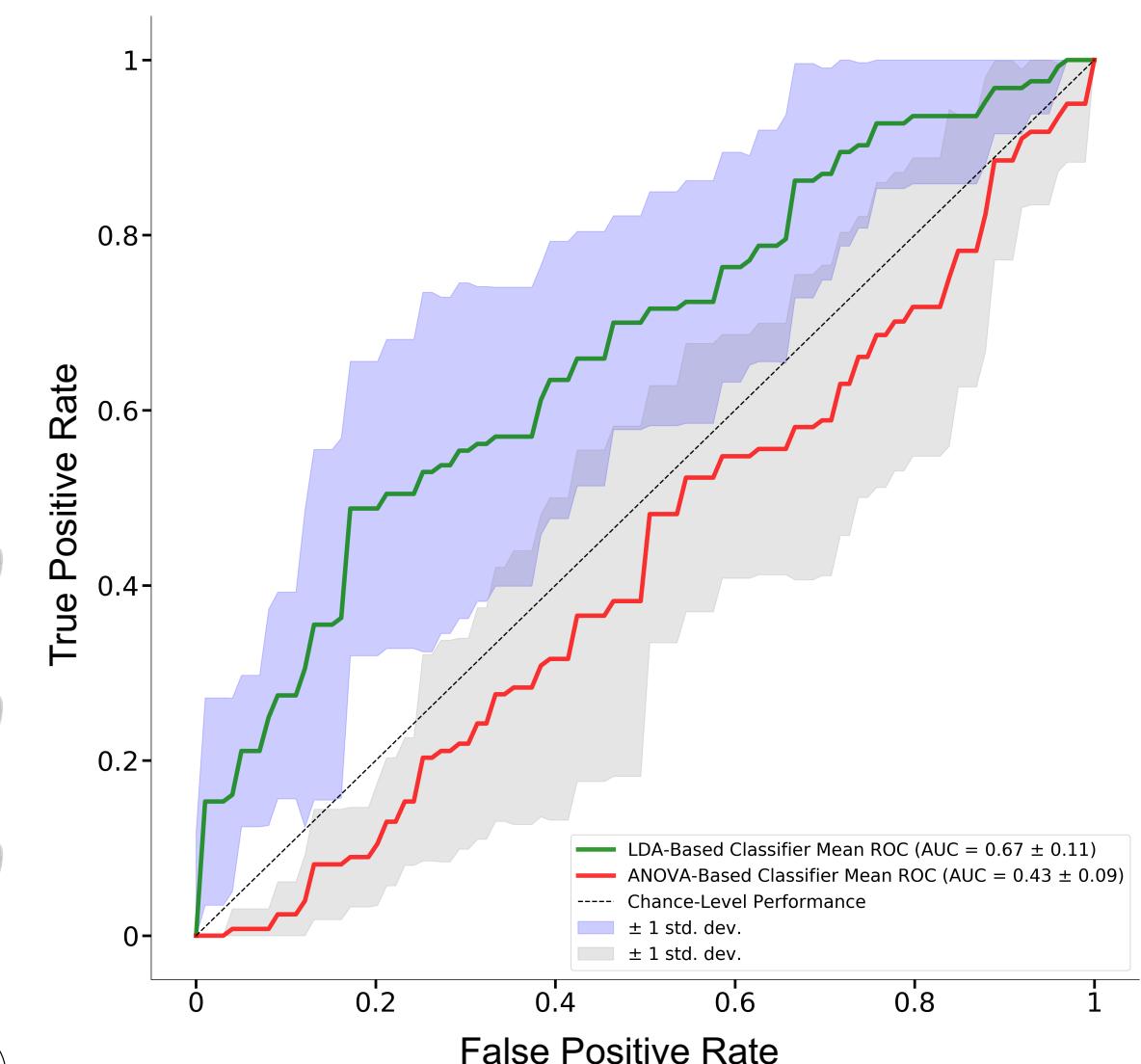
- Cortical thickness obtained from 123 T1w MRI scans (47 STO with ADHD, 39 ADHD, 37 healthy controls) using FreeSurfer.
- Since cortical thickness of clinical samples (i.e., ADHD and STO) can deviate bidirectionally compared to healthy controls (either thicker or thinner), we used a modified polar LDA model, [4] (Figure 1A) which extends the original model via a vertex-wise directional distribution to estimate probability of cortical thickening/thinning.
- Thickness values were z-scored relative to the healthy controls, thresholded at  $|z| > 0.1$ , and discretized as input into polar LDA models.
- Separate models were estimated for STO and pure-ADHD groups to parse heterogeneities specific to each group.
- Running across a range of factors ( $K=2:10$ ), the model significance was assessed based on a null distribution. Optimal  $K$  was chosen by balancing between model goodness-of-fit and complexity based on two statistical criteria—Akaike Information Criterion and Minimum Description Length (Figure 1B).
- Using identified latent factor models from the STO and ADHD groups, a support-vector machine (SVM) algorithm was employed to classify amongst the three groups using factor-specific average cortical thickness.



**Figure 2.** Polar LDA output visualization. **A)** Ternary plots visualizing  $\text{Pr}(\text{Factor} | \text{Subject})$ . The distribution of individual dots recapitulate how heterogeneous the anatomical substrates of children with STO and ADHD are and show both commonalities and discrepancies between the two conditions. **B)**  $\text{Pr}(\text{Vertex} | \text{Factor})$  visualized with estimated direction (increased or decreased thickness) encoded at each vertex; vertices with a corresponding positive deviation estimation are shown on the red colormap while negative deviations are on the blue colormap. **C)** LDA output parcellated into Yeo-Krienen functional seven networks.

## RESULTS

- $K=3$  was chosen at an optimal solution for both STO and pure-ADHD groups (Figure 1B).
- Visualizing each subject's factor probabilities highlights the heterogeneity in factor memberships (Figure 2A).
- Stratifying vertex-wise probabilities according to the Yeo-Krienen 7 brain networks [5] highlights a unique involvement of specific functional systems at each factor.
- STO-group model highlights concentration in thickening of somatomotor, limbic, and default mode networks and thinning in dorsal attention network.
- ADHD-group model highlights concentration in thickening of ventral attention and default mode networks and thinning in somatomotor, limbic, and dorsal attention network (Figure 2C).
- Average thickness of vertices in each factor stratified by deviation direction used as features in SVM-based group classification task achieved 55% accuracy (chance=33%) and receiving operating characteristic curve area under the curve (ROC AUC) of 0.67; simple ANOVA-based clustering approach (utilizing SurfStat toolbox [6]) achieved only 32% accuracy and ROC AUC of 0.43.



**Figure 3.** Receiver operating characteristic (ROC) curves of SVM classifiers utilizing both LDA- and ANOVA-based structural clusters.

## DISCUSSION

- This study provides a novel avenue to decompose the heterogeneous neuroanatomical signatures of children with severe temper outbursts by harnessing advanced latent factor analyses.
- Our models revealed that there are indeed multiple latent pathological substrates influencing cortical thickness abnormalities, which may potentially aid more precise clinical diagnosis in children with STO.
- Although the direction of changes is different, the area showing deviated cortical thickness from the healthy controls show some level of commonalities between ADHD and STO groups, for instance in the factors 1 and 2, while they also present distinct patterns which may explain differential behavioral symptoms between the two conditions.

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