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. Functionally impairing by definition, they are frequently the primary reason for treatment referral.
- However, children with STO commonly receive multiple diagnoses, including disruptive mood dysregulation disorder and oppositional defiant disorder [1]. Particularly, Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most prevalent comorbid syndromes that show increased risk in children with STO [2].
- The resulting trans-diagnostic 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 [3].
- Here we employed a data-driven Bayesian framework with the aim of extracting parsimonious structural substrates unique in children with STO. This model does not perform discrete clustering on the basis of a single pathological factor. Rather, it allows for the possibility that there are multiple latent factors which are expressed to varying degrees across individuals.
- We hypothesize that children with STO may exhibit multiple brain structural components as core pathological bases, which may collectively contribute to symptoms of explosive emotional dysregulation.

METHOD

- The final sample included 139 children (62 STO [with and without ADHD], 39 ADHD [without STO], 37 healthy comparisons).
- Latent Dirichlet allocation (LDA) [4] is a Bayesian generative model originally devised to infer latent topics from word pools of multiple text documents (corpus) in a fully unsupervised manner. In the context of the current clinical neuroimaging study, each subject with STO (and/or ADHD) can be thought of as a document in the corpus, each vertex as a word, and the potential pathological factors as latent topics. Then, a variational inference algorithm [5] can be utilized to optimize two sets of probabilities (**Fig 1A**):
  1. Pr(Vertex | Factor), which estimates how probable it would be for a given pathological factor to cause an abnormality in the thickness at that vertex,
  2. Pr(Factor | Subject), which indicates the probability that a given factor is expressed by a certain subject.
- Freesurfer-extracted cortical thickness values were z-scored against healthy comparisons and transformed into discrete word counts where higher z-scores resulted in higher word counts as input for LDA.
- To find the optimal number of latent topics, K, LDA models were systematically tested for a range of K = 2:5, using two independent criteria:
  1. *Accuracy*. A linear combination of each model's output [Pr(Topic | Document) * Pr(Word | Topic)] was correlated against the original z-score cortical thickness matrix.
  2. *Parsimony*. A higher the number of latent factors would allow the model to better predict the original thickness profiles, but it also increases the chance of overfitting. To address this issue, we penalized for the number of factors.

- The subject-wise factor loadings were then related to seven behavioral measures reflecting STO based on Partial Least Squares Correlation (PLS). This approach creates linear combinations of both the independent (structural LDA output) and dependent (behavioral) variables which maximize the covariance between the two sets.
- Bootstrapping was performed to test the stability and individual contribution of each variable.

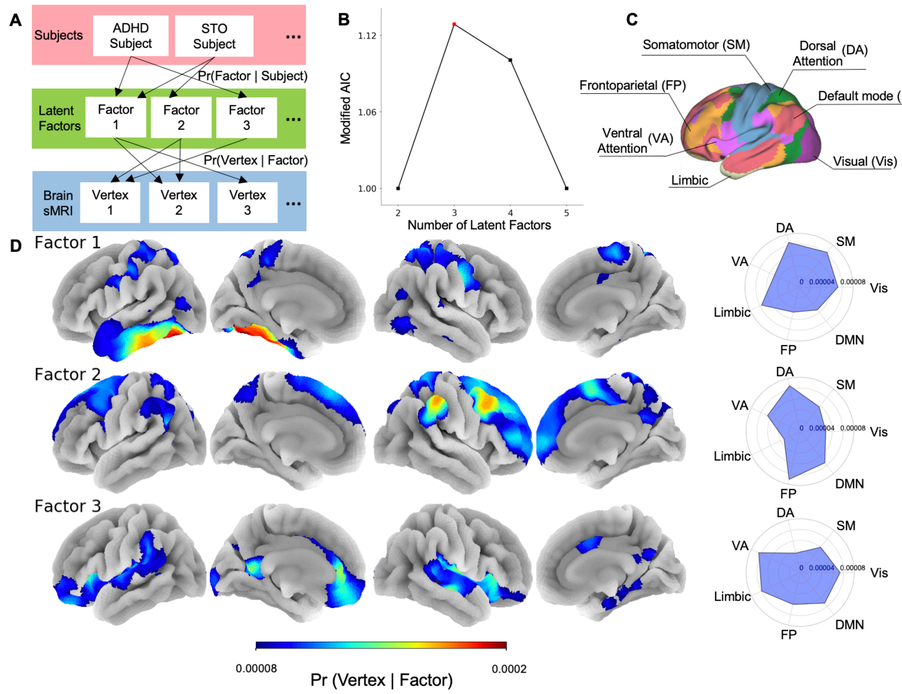

Figure 1. LDA-estimated pathological factor distributions. (A) Premise behind LDA which assumes that each subject expresses a combination of distinct yet possibly overlapping pathological factors. **(B)** Model selection scheme with 3-factor model highlighted as the best option. **(C)** Yeo Seven-Network parcellation. **(D)** Each estimated pathological factor visualized on cortical surface (left) and factors averaged across functional networks shown in **(C)** (right).

RESULTS

- The LDA model with 3 factors was found as the most optimal (**Fig 1B**). The distributions were each then averaged according to the Yeo Seven-Network parcellation **(Fig 1C)** [6]. These pathological factors span multiple brain networks **(Fig 1D)**, with the first factor focusing on the left inferior temporal and right postcentral central areas, the second on the bilateral frontoparietal and default mode networks (DMN), and the third one on bilateral salience networks and left DMN.
- Mapping the directions of z-score deviation at each vertex across all subjects (*i.e.* vertex-wise color-coding of increase/decrease/mixture, depending on the direction of changes that >60% of subjects show) demonstrated that most of latent factor areas have mixed cortical thickness changes (**Fig 2A**).
- A ternary plot displaying subjects' loadings onto each factor (**Fig 2B**) further confirms the heterogeneity of cortical thickness changes in both STO and ADHD groups.
- Through bootstrap resampling, the PLS analysis did not reveal any variables significantly contributing to the covarying latent space (**Fig 2C**).

DISCUSSION AND FUTURE DIRECTIONS

- This study represents a novel data-driven approach to identifying structural brain factors that may underlie severe temper outbursts in children.
- While three structural factors were identified, they failed to be associated with validated measures of emotion regulation.
- Failure of significance of the PLS model may be due to a lack of sensitivity of this LDA model to disentangle emotional from behavioral dysregulation or limitations in the parent-report measures used.
- Future analyses will examine factors based on increased and decreased cortical thickness to parse apart the heterogeneity that likely results from the use of a general deviation model. Psychometric evaluation of behavioral measures will be conducted to verify the best candidates for the PLS.

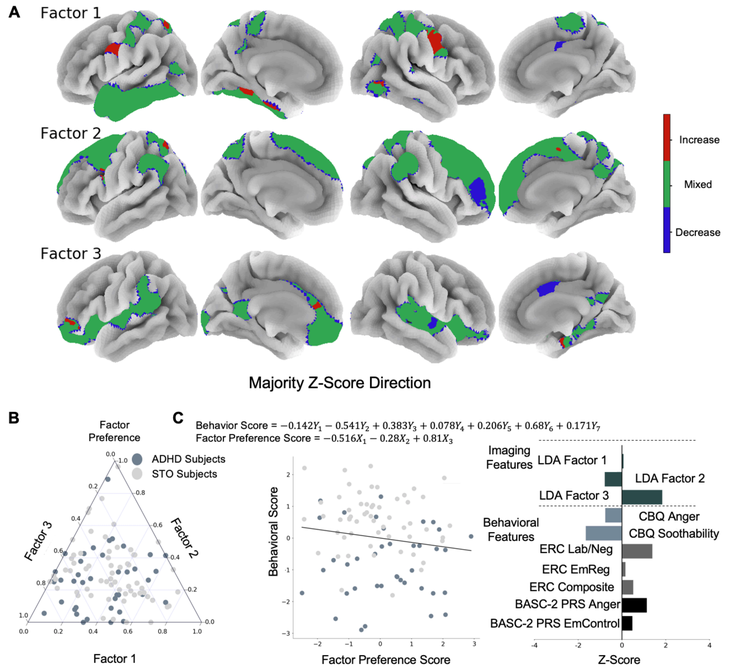

Figure 2. PLS analysis of subject-level pathological factor loadings and behavioral variables. (A) Majority z-score direction across subjects for vertices activated by pathological factors. **(B)** Subject-level pathological factor loadings stratified by subgroup. **(C)** Relationship of LDA-factors loadings and behavioral variables contributions onto maximally-covarying latent space spanned by first PLS component (left), and results of stability and individual contribution bootstrap testing (right).

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