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Multivariate associations between cortical morphometry and dimensions of the adolescent psychosis spectrum

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Background

- The psychosis spectrum (PS) includes subclinical psychotic-like experiences that are present in the general population and are most prevalent in youth, a time of dynamic cortical maturation[1]
- PS youth show abnormalities in various cortical measures compared to healthy controls,[2,3] but changes to the coordinated variation of multiple morphometric features remain unclear
- Data-driven psychopathology dimensions in youth show dissociable links with altered structure in cortical thickness covariance networks[4]
- Distinct dimensions of symptoms have been suggested to underpin the PS,[5] but remain poorly characterized neuroanatomically

Objective: To identify latent symptom dimensions of the PS and evaluate how they map to abnormalities in interrelated cortical morphometric features during development.

Results A: Latent dimensions of PS symptoms

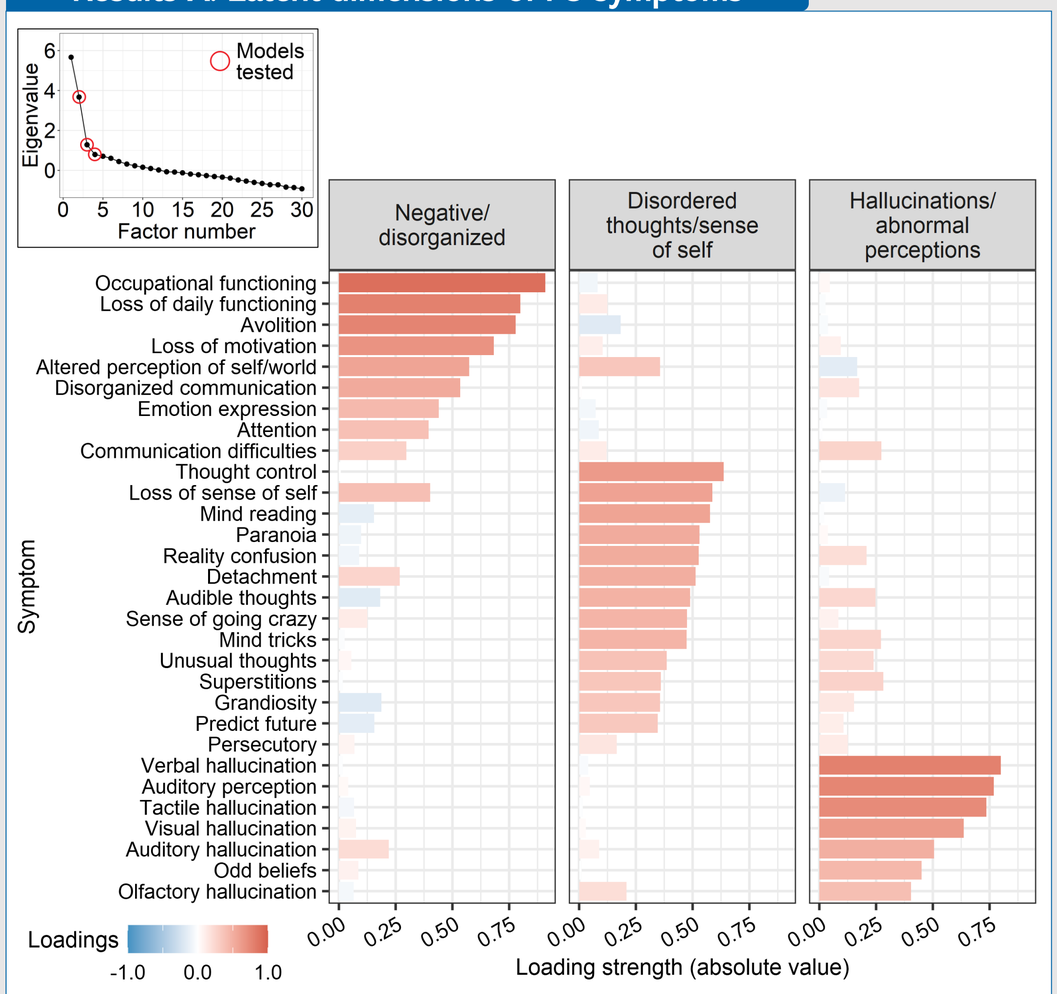

Fig. 2. The 3-factor factor analysis solution, corresponding to the "elbow" in the scree plot (inset), was optimal, having no salient cross-loadings (cutoff = 0.35) of symptom items[8] yet highly interpretable symptom groupings. The model revealed a **negative/disorganized symptom** factor, a sub-psychotic factor determined by **disordered thinking/a disordered sense of self**, and a **hallucinations/abnormal perceptions** factor.

Results B: Morphometric covariance patterns

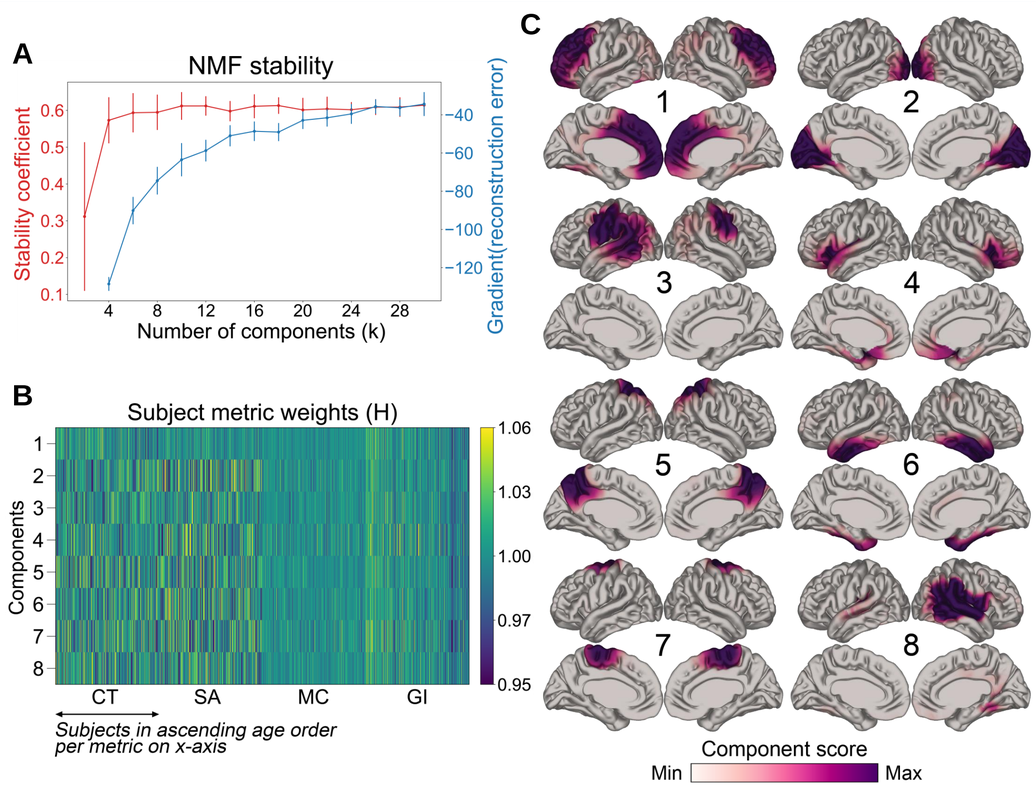

Fig. 3. a) Results of split-half stability and reconstruction error analyses for 2-30 component NMF decompositions. To balance stability (red curve) with capturing major changes in the gain in accuracy (blue curve), k=8 was chosen for further analysis. **b)** Subject-level relative contribution of each metric to each component in the k=8 solution. **c)** Spatial patterns of the 8 extracted components of morphometric covariance. **Note:** The NMF input matrix contained metrics residualized for mean CT and total SA to avoid deriving components driven by global mean differences in CT/SA.

[1] Calkins ME, et al. *World Psychiatry*. 2014;13(3):296-305. doi:10.1002/wps.20152 [2] Jalbrzikowski M, et al. *J Am Acad Child Adolesc Psychiatry*. 2019;58(11):1079-1091. doi:10.1016/j.jaac.2018.11.012 [3] Meller T, et al. *Psychol Med*. 2020;1-10. doi:10.1017/S0033291720002044 [4] Kaczkurkin AN, et al. *Am J Psychiatry*. 2019;176(12):1000-1009. doi:10.1176/appi.ajp.2019.18070835. [5] Calkins ME, et al. *J Child Psychol Psychiatry*. 2015;56(12):1356-1369. doi:10.1111/jcpp.12416 [6] Satterthwaite TD, et al. *Neuroimage*. 2014;86:544-553. doi:10.1016/j.neuroimage.2013.07.064 [7] Patel R. *Neuroimage*. 2020;207:116348. doi:10.1016/j.neuroimage.2019.116348 [8] Rosenblad A. *Int Stat Rev*. 2009;77(3):476-476. doi:10.1111/j.1751-5823.2009.00095_13.x

Methods

Subjects: 266 youth (mean age 15.8; range 8-23; 117 males) from the Philadelphia Neurodevelopmental Cohort (PNC)[6] who endorsed PS criteria, i.e. extreme scores (≥ 2 SDs above than age-matched peers or rating of extreme agreement on ≥ 1 symptoms) on screens for positive sub-psychosis, positive psychosis, and negative/disorganized symptoms in the GOASSESS interview.[1] As the PNC is a community-based rather than clinical cohort, our sample offers a window into the earliest emergence of PS symptoms.
Measures: Subject responses to the 30 item-level PS symptoms (summarized in Fig. 2 y-axis labels); vertex-wise cortical thickness (CT), surface area (SA), mean curvature (MC), and gyrification index (GI) quantified using T1-weighted (T1) structural MRI.

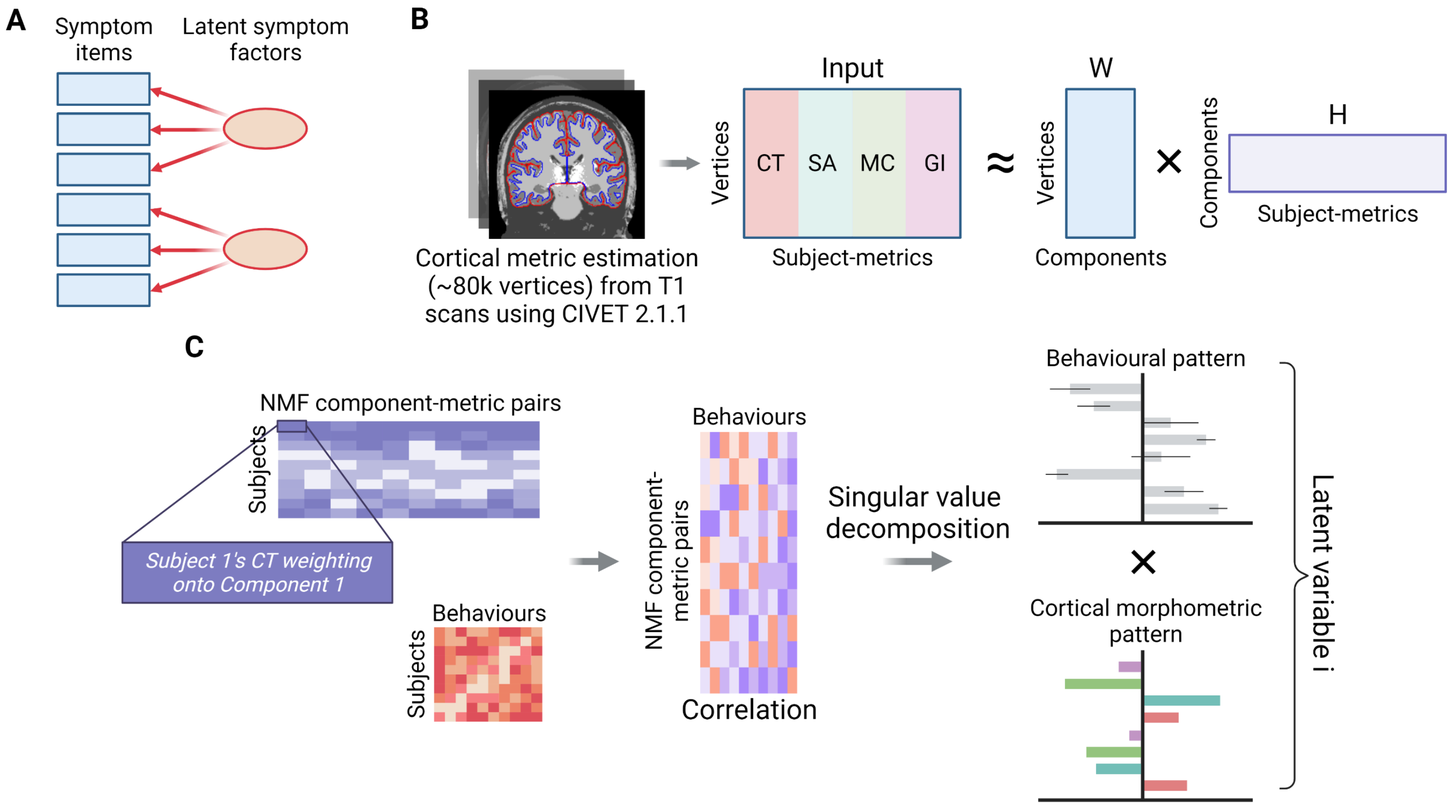

Fig. 1. Workflow. a) We performed factor analysis on the 30 PS symptom items to estimate the major underlying symptom dimensions. **b)** Non-negative matrix factorization (NMF) decomposed the matrix of concatenated cortical metrics into component (W) and weight (H) matrices *(see Fig. 3 note)*. W contains vertex-wise component scores, describing vertex clusters sharing a morphometric covariance pattern; H contains subject weightings describing the morphometric variation of an individual within each spatial component.[7] **c)** Partial least squares (PLS) related subject-specific component-metric weights to demographic measures and scores on each symptom factor. PLS finds maximally covarying patterns of the brain and behavioural data as latent variables (LVs). Significance of LVs was assessed with permutation testing; bootstrap resampling assessed contributions of brain variables to each LV.

Results C: Morphometry-behaviour relationships

PLS detected 2 LVs (ps < 0.05), which revealed: **LV 1 (left):** younger age and African American (AA) race were correlated with, and European American race negatively correlated with, widespread ↑GI and localized, heterogeneous CT and SA changes; **LV 2 (right):** younger age, female sex, non-AA race, and lower scores on the 'disordered thoughts/sense of self' factor correlated with ↓CT, ↑GI in prefrontal cortical components (1,4); ↑CT, ↓SA in a sensorimotor-like component (3); and localized ↑SA, ↑MC.

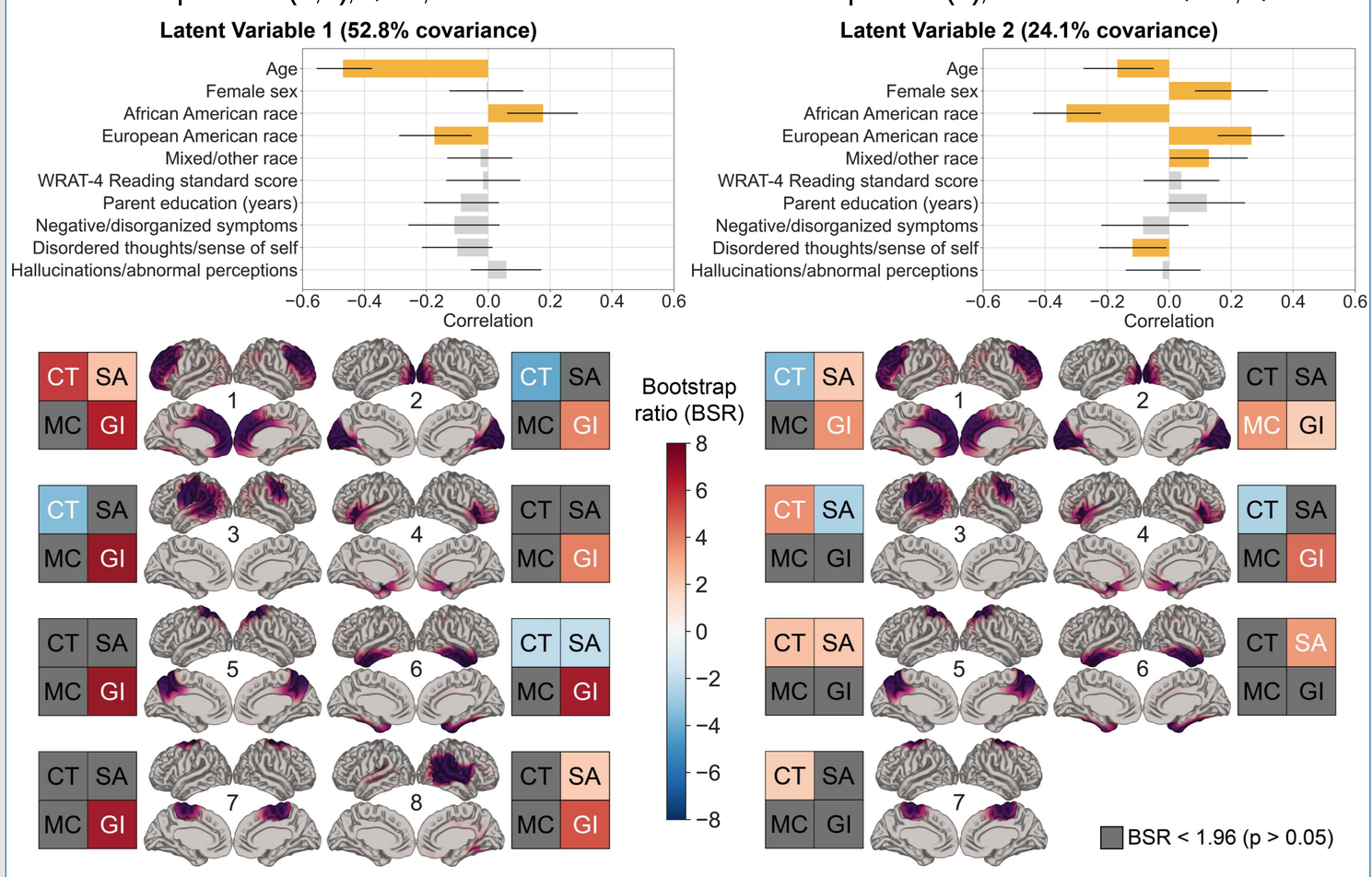

Fig. 4. Top row: Correlations of demographic measures, Wide Range Achievement Test (WRAT) 4 Reading score (IQ estimate), and the 3 latent symptom factors with each LV. Variables with 95% confidence intervals not overlapping zero (yellow bars) contributed to the LV. **Bottom row:** Cortical maps of components in which ≥ 1 metric contributed to the LV (ps < 0.05). Corresponding 2×2 plots summarize the morphometric pattern correlated with the behavioural pattern for the LV, within each component.

Discussion

- We identified 3 dimensions of the PS in youth that underpin both interpretable and distinct symptom clusters compared to conventional symptom screening categories
- Using four metrics indexing different aspects of cortical maturation, we delineated 8 data-driven components of morphometric covariance that were largely bilateral and spatially contiguous
- Profiles of metrics within morphometric covariance patterns were age-, race-, and sex-specific
- Youth scoring lower on measures of 'disordered thoughts/sense of self' tended to display distributed increases in cortical metrics and circumscribed decreases in CT and SA

Our results refine previous case-control characterizations of the PS and provide evidence that subclinical symptom dimensions of the PS have distinct brain morphometric signatures in youth.