Early Substance Use and Co-Morbid Risk Factors on Developmental Trajectories of Brain and Cognitive Measures

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Introduction

Early Substance Use (ESU) of alcohol, nicotine, and marijuana before age 14 increases risks for substance use disorders and adverse social, health, and behavioral outcomes.[1-4] However, it remains unclear whether abnormalities in brain morphometry and cognition observed in adolescents with ESU are due to premorbid risk factors or ESU.

Aim: To prospectively examine brain and neurocognitive measures between youths with and without ESU, to examine its impact on brain structure and its potential role in abnormal or delayed cognitive development.

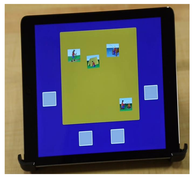
Methods

Participants From 11,875 youths aged 108-120 months (9-10 yrs.) at baseline, 669 who reported ESU at the 4th year follow-up were matched by sex, age, and race with 669 youths without ESU. Among the 669 ESU children, 33 had reported ESU at the 4th-year follow-up but 636 had not started using substances at baseline. All participants included in the study had complete cognitive and brain morphometric datasets (from baseline through to the 4th-year follow-up).

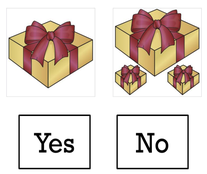
Imaging: Structural MRIs were acquired from 22 ABCD Sites using 3T MRI scanners. The MRIs were processed by the ABCD-Data Analysis and Informatics Center using Freesurfer version 7.1.1, and the Desikan-Killiany atlas, yielding cortical volumes and thickness in 34 regions per hemisphere, and volumes in 10 subcortical regions.

Cognitive Testing: Six neurocognitive measures were collected at each MRI-scan visit years using the NIH Toolbox® Cognitive Battery.

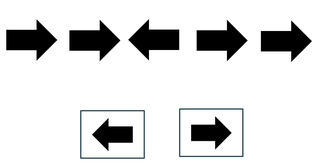
Picture Sequence Memory (PSM)



Pattern comparison Processing Speed



Flanker Inhibitory control and Attention Test



Statistical Analyses: Children with and without ESU were matched by age and race using propensity score matching, set at the 4th-year follow-up. Linear Mixed Models were used to assess if children with ESU exhibit abnormal longitudinal brain and cognitive developmental trajectories, adjusting for age, race, family income, visit type (e.g., in-person, hybrid, or remote for cognitive measures), and intracranial volume (for volumetric brain measures) as fixed effects, with ABCD site and MRI scanner ID as random effects. Significance was established at p<0.05, corrected for false discovery rate (FDR).

References

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Results

Figure 1: Lesser Cognitive Performance Improvements with Age in ESU-Children Relative to Controls

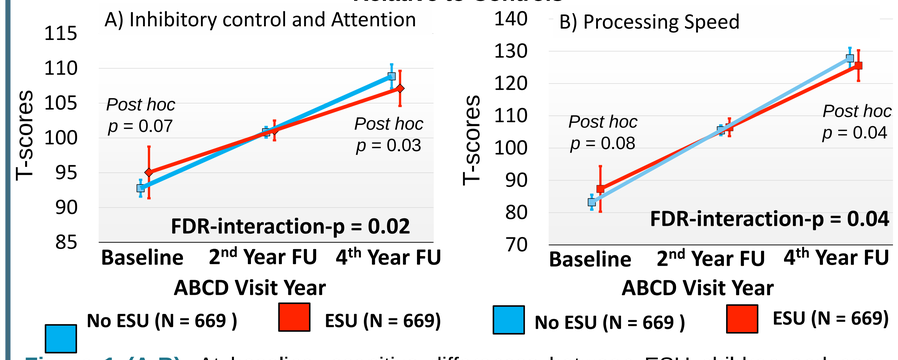
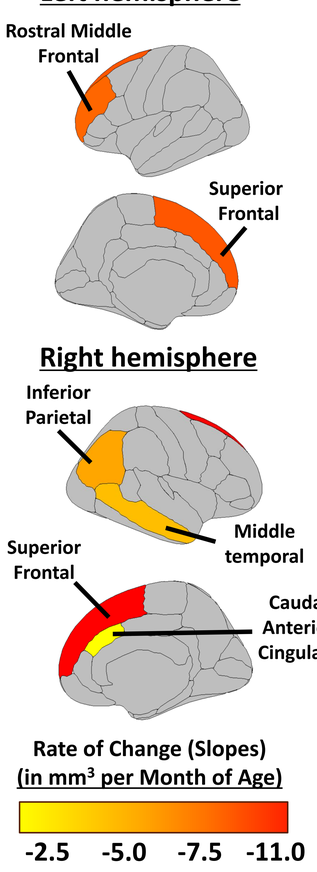


Figure 1 (A-B). At baseline, cognitive differences between ESU children and non-users were not significant. However, by the 4th year, ESU children demonstrated lesser improvements in NIHTB scores compared to non-users, especially in tasks related to inhibitory control and attention (**1A**; FDR-interaction-p-values = 0.02) and processing speed (**1B**; FDR-interaction-p-values = 0.04).

Figure 2. Children with ESU had a steeper decline in cortical volumes (mm3) with increasing age (months) compared to controls.

A) Significant estimates of the age and ESU interaction by region



B) Estimated marginal means between ESU-children and Controls over time

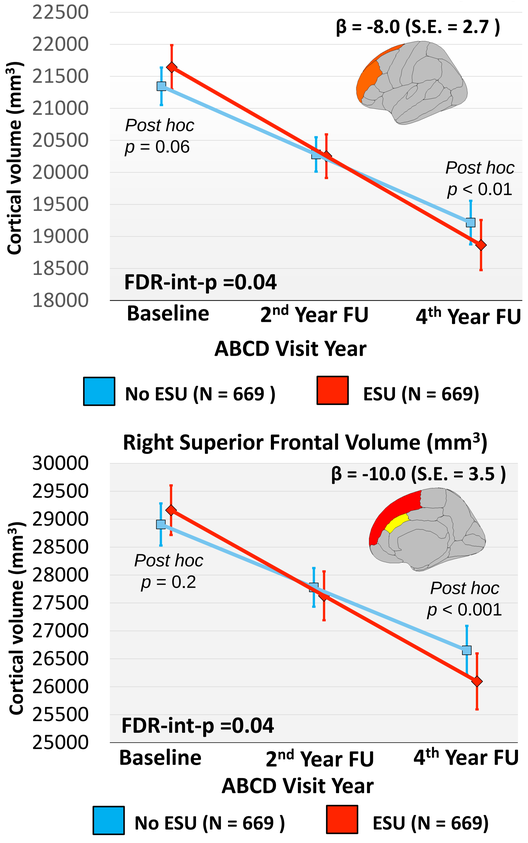
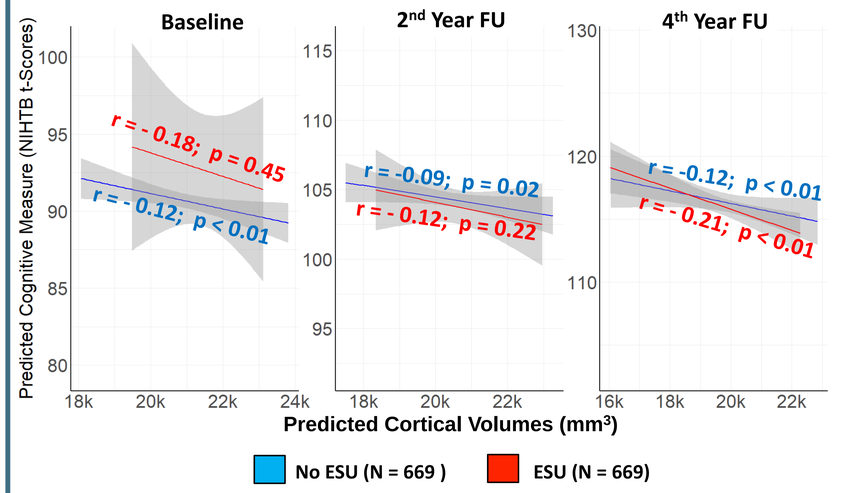


Figure 2 (A-B). **A)** youths with ESU had smaller cortical volumes in multiple brain regions compared to non-ESU peers. **B**) These group differences in cortical volumes became more pronounced over time, particularly in the rostral middle (Slope: β = -8.0 mm³/month) and superior frontal gyri (Slope: β = -9.9 mm³/month), both with FDR-adjusted p-values of 0.04.

Figure 3. ESU effects associated with smaller cortical volumes (in mm³) predicted lesser improvements in cognitive performance (NIHTB scores) over time.

A) Processing Speed Scores and Volumes of the Left Rostral Middle Frontal Gyrus



B) Processing Speed Scores and Volumes of the Left Superior Frontal Gyrus

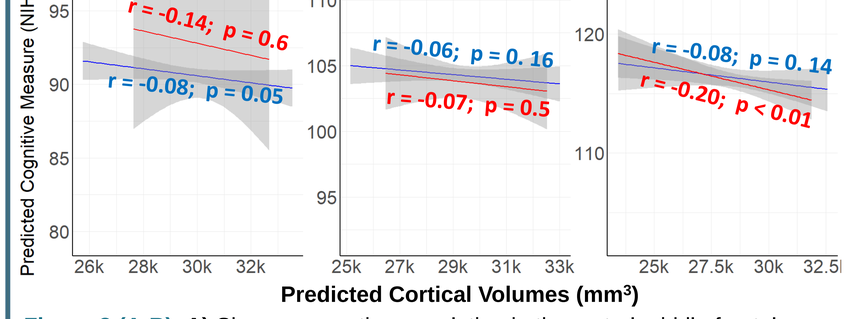


Figure 3 (A-B). **A)** Shows a negative correlation in the rostral middle frontal gyrus over successive time points, observed in both ESU and non-ESU groups. Notably, a significant negative correlation emerges for the ESU group at the 4th-year follow-up (Pearson's r = -0.21; p = 0.03). As shown in **B**, we found that, within the superior frontal gyrus, the negative correlation between cortical volume and processing speed in the ESU group becomes more pronounced with time, achieving significance by the 4th year (Pearson's r = -0.2; p < 0.01).

Discussion

- Our findings support previous neuroimaging studies showing ESU is associated with:
  - Smaller cortical grey matter volumes[5-6]
  - Poorer attention[7-8] and executive function[8-9]
- A novel finding from the current study is that ESU effects on developmental trajectories in cortical volumes may be associated with poorer cognitive development
- The limitations of the current study include: the self-reported substance use and the need for additional know comorbid risk factors , which cannot determine casual relationships.
- Future analysis will longitudinally evaluate the potential effects of ESU on the neurodevelopmental trajectories of functional brain measures in this population, as well as the inclusion of important comorbid risk factors..