Altered brain state dynamics in children with a family history of substance use disorder vary by sex.

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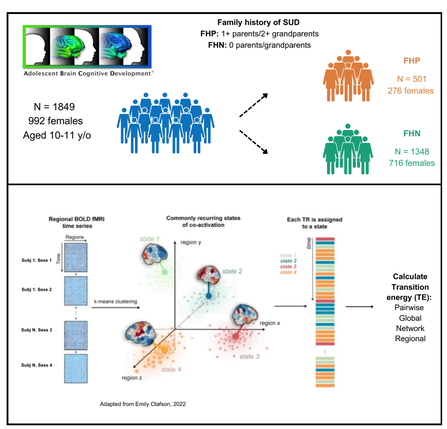
Background

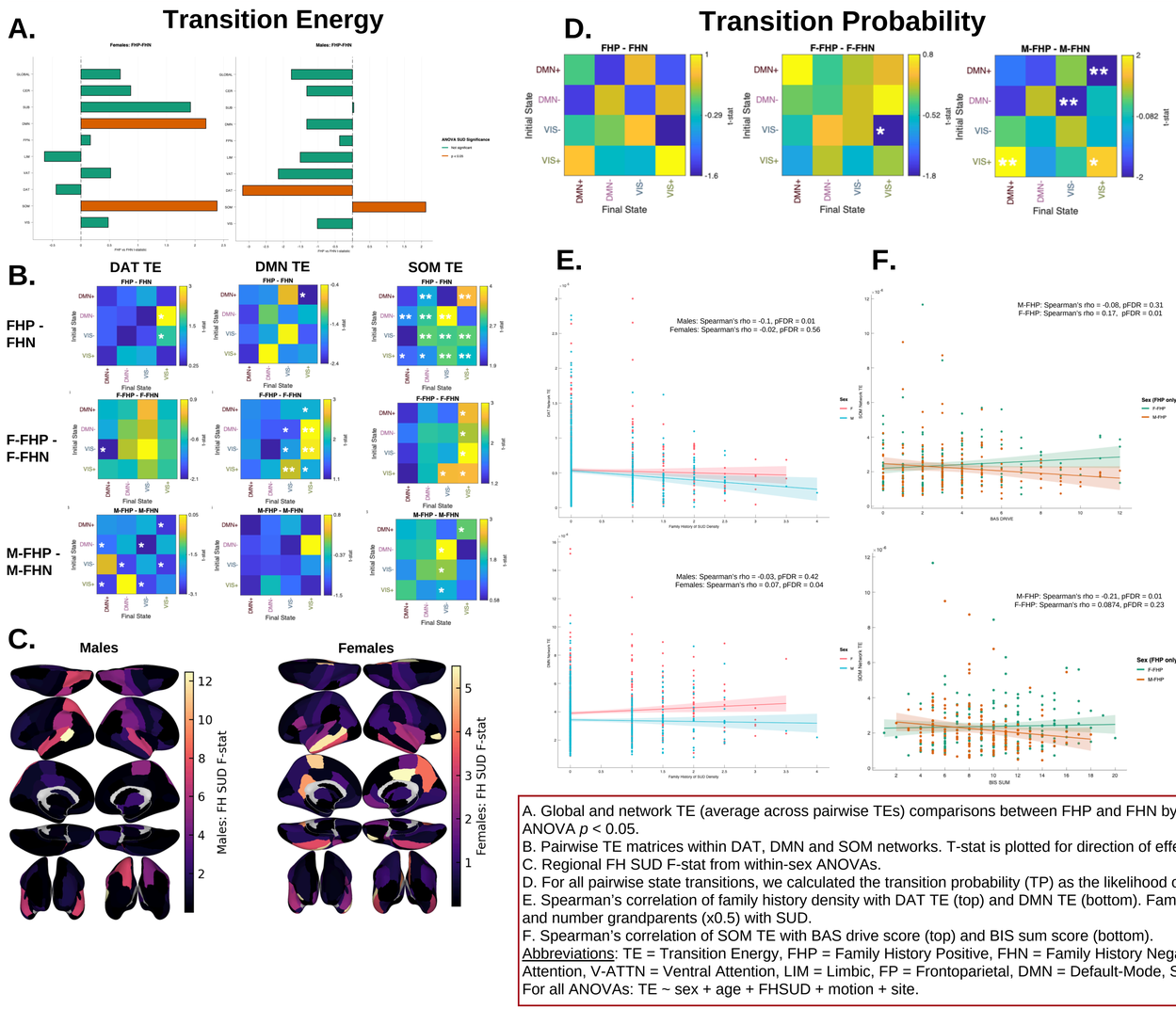
While chronic substance use increases an individual's chances of developing a substance use disorder (SUD), not everyone makes this transition. As such, elucidating the neurobiology of SUD risk is crucial to addressing the escalating rates of the disorder. An individual's risk of SUD is shaped by a complex interplay of biosocial factors, with genetics being particularly potent (Hatoum et al., 2023). As such, a family history of SUD is a strong predictor of an individual's susceptibility (Bogdan et al., 2023). Current developmental models describe individual vulnerability to SUD as being due to an aberrant reward system, reduced inhibitory control, or a combination of these (Heitzeg et al., 2015). Further, recent findings suggests both structural and functional brain alterations are associated with risk of SUD (Zilverstand et al., 2018 & Tervo-Clemmens et al., 2020). Yet, few studies have explored how family history affects brain function and structure prior to substance exposure. Herein, we used a network control theory (NCT) approach to quantify sex-specific differences in brain state dynamics in N=1403 substance-naïve youth with (FHP) and without (FHN) a family history of SUD.

Methods

We analyzed a subset of 1403 pre-adolescents (768 females, aged 9-11) from the baseline sample of the ABCD study. Parent-reported family history of SUD was used to categorize subjects as FHP (1+ parent and/or 2+ grandparents with SUD) or FHN (no parental nor grandparental SUD). Individual rs-fMRI data and a group average (N=149) structural connectome (via diffusion-weighted imaging and tractography) were pre-processed by Chen et al. (2022) in the FS86 parcellation (68 cortical + 18 subcortical regions). Using a network control theory framework, we investigated the energetic requirements of the brain as it progresses through various states over time. Following previous work (Cornblath et al., 2020), we performed *k*-means clustering of brain activity into recurring brain "states". After determining the optimal *k*=4, we calculated transition probabilities and transition energies (TEs) for each pair-wise state transition. Across all transitions, we then calculated average global, network and regional-level TEs for each individual.



Results



Averaged across all pairwise transitions, global TE was not significantly different between FHP and FHN individuals of either sex. M-FHP individuals had decreased DAT TE compared to M-FHN (A), which correlated with family history density in males (E). This lower energetic requirement of DAT regions was true across a diverse range of pairwise transitions (C).

Increased average DMN TE in FHP females compared to FHN females (A), which correlated with family history density (E), was primarily driven by transitions to or persistence within the VIS meta-state (VIS+/-; B).

FHP individuals of both sexes exhibited increased SOM TE compared to FHN (A). However, each sex exhibited unique patterns of SOM TE in pairwise transitions – where SOM TE was primarily increased in transitions to the VIS+ network in FHP females and to the VIS- in FHP males (B). Further, SOM TE correlated with low behavioral inhibition in FHP males but not females and with increased behavioral drive in FHP females but not males (F).

M-FHP youth exhibit decreased probability of transitioning from DMN+ to VIS+ and DMN- to VIS-, and an increased probability from VIS+ to DMN+ and VIS+ to VIS+ compared to FHN males. FHP females exhibited a lesser likelihood of transitioning from VIS- to VIS+ compared to FHN females (D).

In females, the effect of FH of SUD on regional TE was significant (ANOVA p <0.05) in the left isthmus cingulate, left middle temporal, left para-central, right pars orbitalis, and right posterior cingulate. Within males, the left banks STS, left superior parietal, left superior temporal, left supra-marginal, right para-central, right superior parietal, right superior temporal and right supra-marginal were significant (C).

A. Global and network TE (average across pairwise TEs) comparisons between FHP and FHN by sex. T-stat is plotted for direction of effect and color designates ANOVA $p < 0.05$.
B. Pairwise TE matrices within DAT, DMN and SOM networks. T-stat is plotted for direction of effect with color designating ANOVA $p < 0.05$.
C. Regional FH SUD F-stat from within-sex ANOVAs.
D. For all pairwise state transitions, we calculated the transition probability (TP) as the likelihood of transitioning from a given state to every other state.
E. Spearman's correlation of family history density with DAT TE (top) and DMN TE (bottom). Family history density was calculated as the number of parents (x1) and number grandparents (x0.5) with SUD.
F. Spearman's correlation of SOM TE with BAS drive score (top) and BIS sum score (bottom).
Abbreviations: TE = Transition Energy, FHP = Family History Positive, FHN = Family History Negative. VIS = Visual, SM = Somato-motor, D-ATTN = Dorsal Attention, V-ATTN = Ventral Attention, LIM = Limbic, FP = Frontoparietal, DMN = Default-Mode, SUB = Subcortical, and CER = Cerebellar.
For all ANOVAs: TE ~ sex + age + FHSUD + motion + site.

Conclusions

These findings suggest the effect of family history of SUD on brain function and structure is modulated by biological sex. Lower energetic demand in the DAT network in FHP males and higher energetic demand in the DMN network in females may interact differently with and/or contribute to the higher energetic demands in the SOM network, perhaps leading to reduced behavioral inhibition in males and stronger behavioral drive in females – both of which are thought to increase one's predisposition to SUD.

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