8 Supplementary Information

S0.1 Subject exclusions

	Chen et al., 2022 cohort (N = 2362)	Excluded Subjects (N = 468)	Included Subjects (N = 1894)
Biological Sex, N(%)			
Female	1265 (54)	247 (53)	876 (46)
Male	1096 (46)	220 (47)	1018 (54)
Age in months, Mean (SD)			
Female	119.9 (7.50)	120.08 (7.74)	120.50 (7.51)
Male	120.42 (7.50)	120.11 (7.44)	120.01 (7.44)
Family History of SUD N(%)			
FH+	534 (23)	83 (18)	451 (24)
FH-	1400 (59)	231 (49)	1169 (62)
FH+/-	319 (14)	45 (9)	274 (14)
Missing	109 (5)	109 (23)	0
Framewise Displacement, Mean (SD)			
Female	0.11 (0.07)	0.12 (0.07)	0.12 (0.08)
Male	0.12 (0.08)	0.13 (0.81)	0.11 (0.07)
MRI Scanner Model N(%)			
GE Discovery MR750	670 (28)	142 (30)	528 (28)
Siemens Prisma	823 (35)	132 (28)	691 (36)
Siemens Prisma Fit	867 (37)	192 (41)	675 (36)
Undefined	2 (0.08)	2 (0.4)	0
Household Income N(%)			
< $50,000	500 (21)	79 (17)	421 (22)
$50,000 - $100,000	666 (28)	97 (21)	569 (30)
$100,000+	1196 (51)	292 (62)	904 (48)
Parent Education N(%)			
> High School	68 (3)	19 (4)	49 (3)
High School/GED	160 (7)	33 (7)	127 (7)
Some College	251 (11)	67 (14)	284 (10)
Associates/Bachelor	1207 (51)	226 (48)	981 (52)
Postgraduate	673 (28)	120 (26)	553 (29)
Race/Ethnicity N(%)			
White	1412 (60)	218 (47)	1104 (63)
Black	203 (9)	62 (13)	141 (7)
Hispanic/Latinx	447 (18)	106 (23)	341 (18)
Asian	58 (3)	20 (4)	38 (0.2)
Other	241 (10)	61 (13)	180 (10)
In Utero Substance N(%)			
Yes	102 (4)	29 (6)	73(4)
No	2260 (96)	439 (94)	1821 (96)
Parent Mental Health N(%)			
Yes	1208 (51)	213 (45)	995 (53)
No	1034 (44)	135 (29)	899 (48)

Table S1. Demographic and characteristic data for the full cohort of subjects for whom we received rsfMRI data (134; 153), excluded subjects (via exclusion criteria and outlier global TE values) and all included subjects in our analyses.

S0.2 Choices in *k*-means clustering

S0.2.1 Choosing k

We performed 10 repetitions of k-means clustering for k=2 to k=14. We quantified the variance explained by clustering as the ratio of between-cluster variance to total variance in the data (47; 55; 157). We chose k by plotting the variance gained by increasing k, to observe where increasing k begins to provide diminishing returns in terms of variance explained. The elbow of the variance explained curve is k=4 to k=5. We also see that the gain in variance explained by increasing k to 4, the variance gained by increasing k falls below 1%, the threshold used previously for choosing k (Figure 1b) (47; 55). We therefore analyzed the results with k=4 and 5 and chose to include k=4 in the main analysis for ease of interpretation.

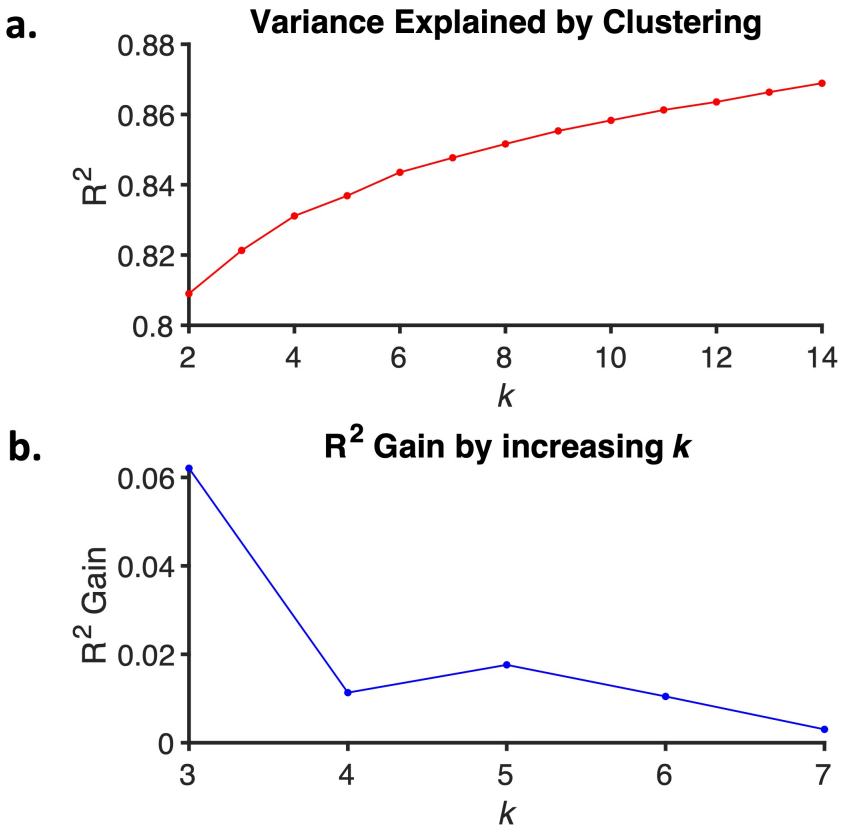

Figure S1. (a) Plot of the variance explained by clustering for each choice of k, showing an 'elbow' around 4-5. (b) Plot of the gained variance explained by increasing k.

S0.2.2 Assessing the stability of clustering

As mentioned in the main text, we performed 10 repetitions of k-means clustering, choosing the lowest error solution. To ensure this solution was a consistent global minimum, we repeated this entire process 10 times and compared the adjusted mutual information (AMI) shared between the 10 partitions. The partition that had the maximum sum of AMI scores with all other partitions was selected for analysis. More importantly, this process confirmed that k-means clustering was highly consistent and stable (AMI > 0.99).

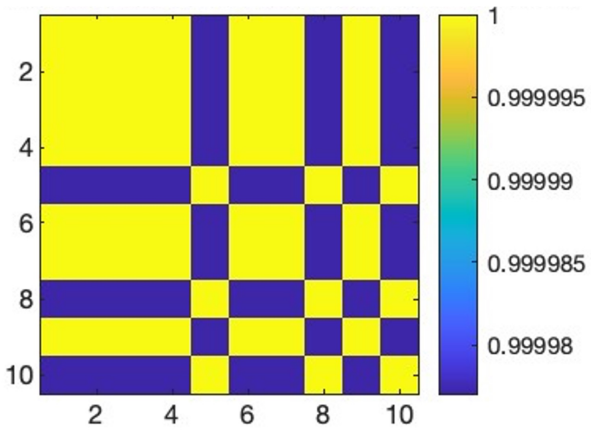

Figure S2. The adjusted mutual information (AMI) shared between 10 independently generated partitions of our data at *k*=4. Values can range from 0 to 1, with 1 indicating identical partitions. The AMI between all partitions was >0.99

S0.3 Pairwise regional transition energy: post hoc *t* tests.

S0.3.1 Post-hoc t-tests of pairwise regional transition energy in regions found to have significant effect of family history of SUD (across both sexes).

For each pair of brain states (*k*x*k*), we performed post hoc *t* tests for the pairwise regional TE in each of the seven regions found to be significant for family history of SUD (FH+ vs FH-).

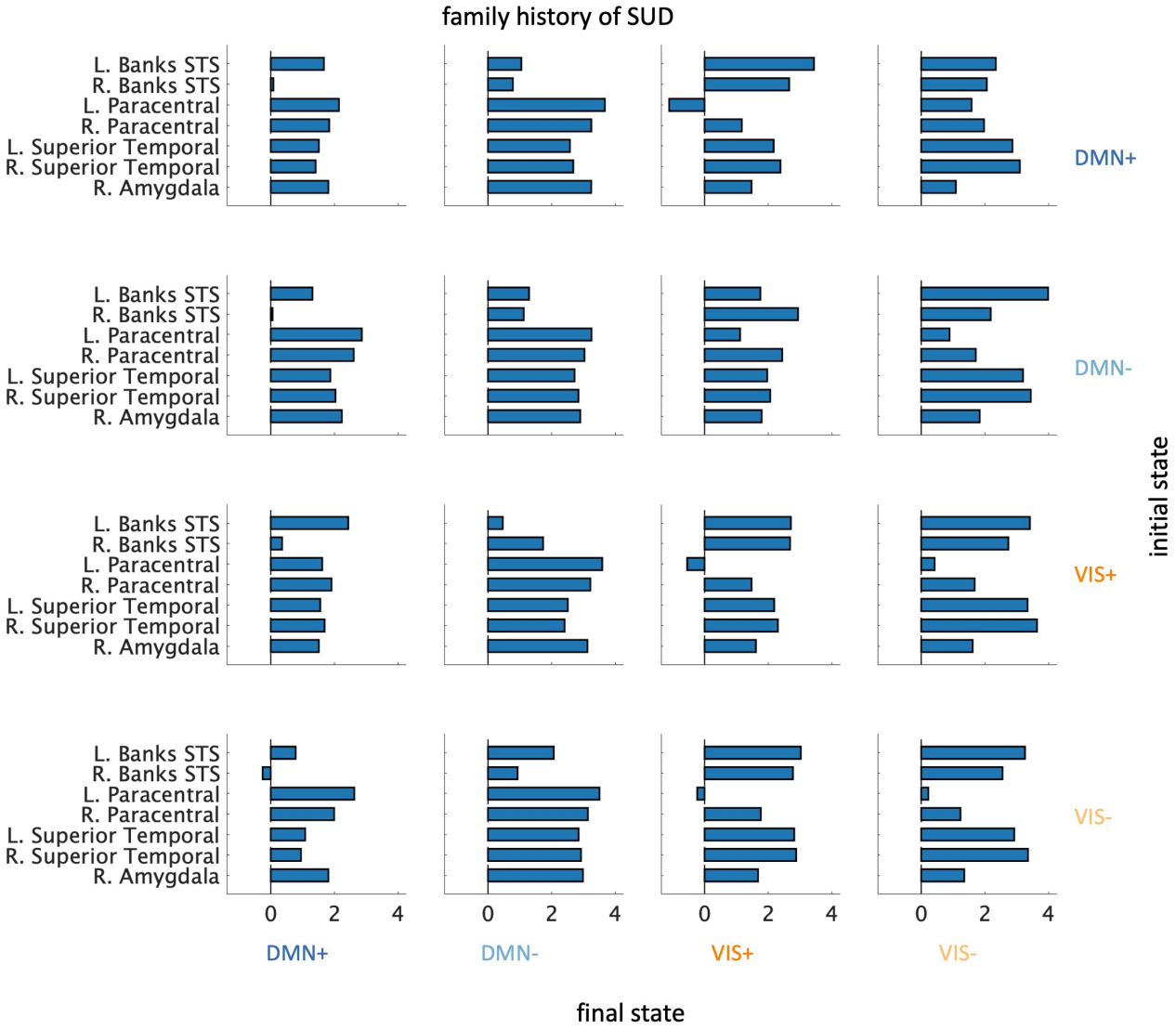

Figure S3. *T* test results for pairwise regional TE values for regions found to have a significant effect of family history of SUD.

S0.3.2 Post-hoc t-tests of pairwise regional transition energy in regions found to have significant effect of the interaction between sex and family history of SUD.

For each pair of brain states, we performed post hoc *t* tests for the pairwise regional TE in each of the eight regions found to be significant for the interaction of sex and family history of SUD (within-sex FH+ vs FH-).

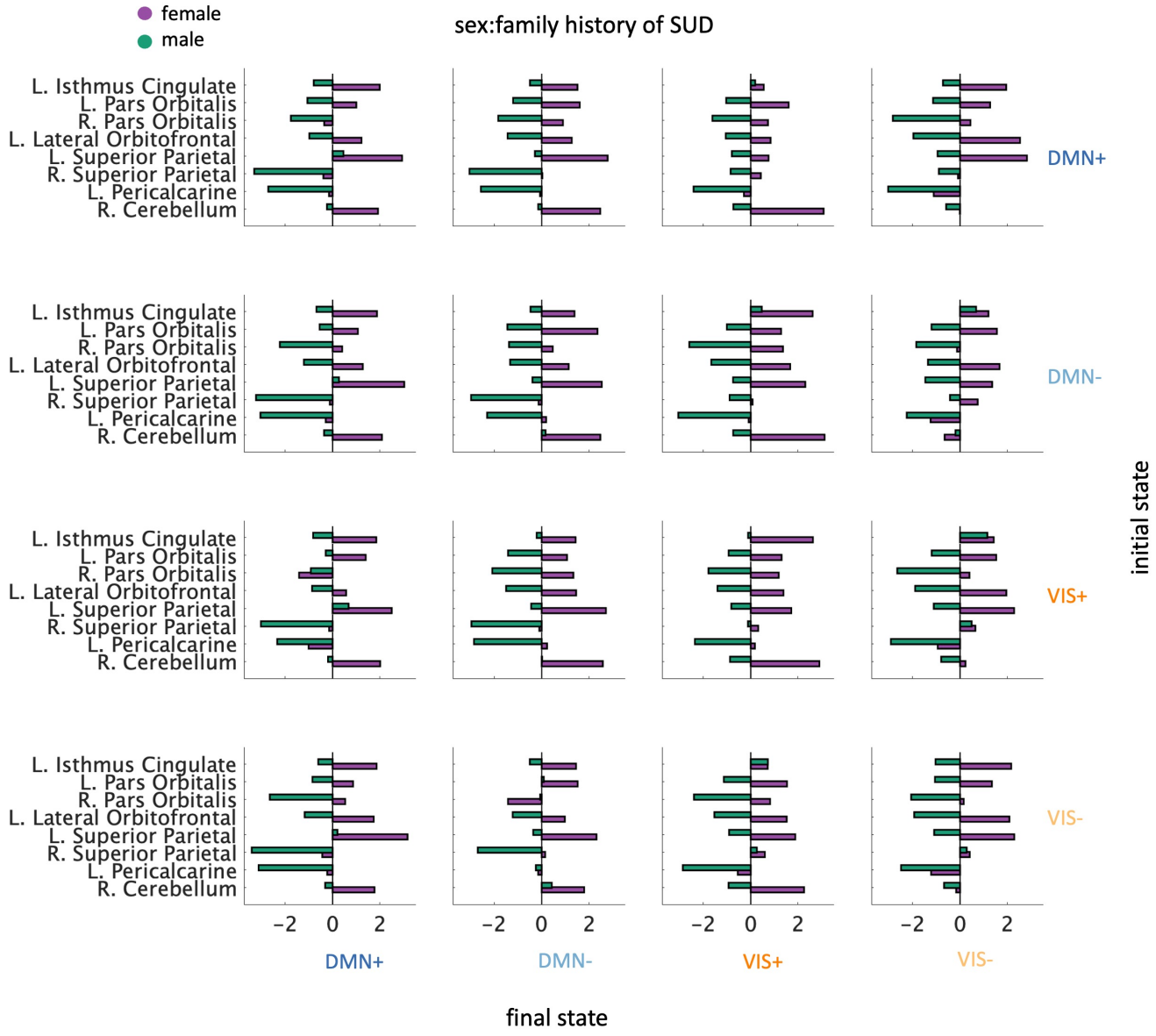

Figure S4. Within sex *t* test results for pairwise regional TE values for regions found to have a significant family history-by-sex effects.

S0.4 ANCOVA F Statistics for all included covariates.

S0.4.1 Network TE: ANCOVA F Statistics for all included covariates.

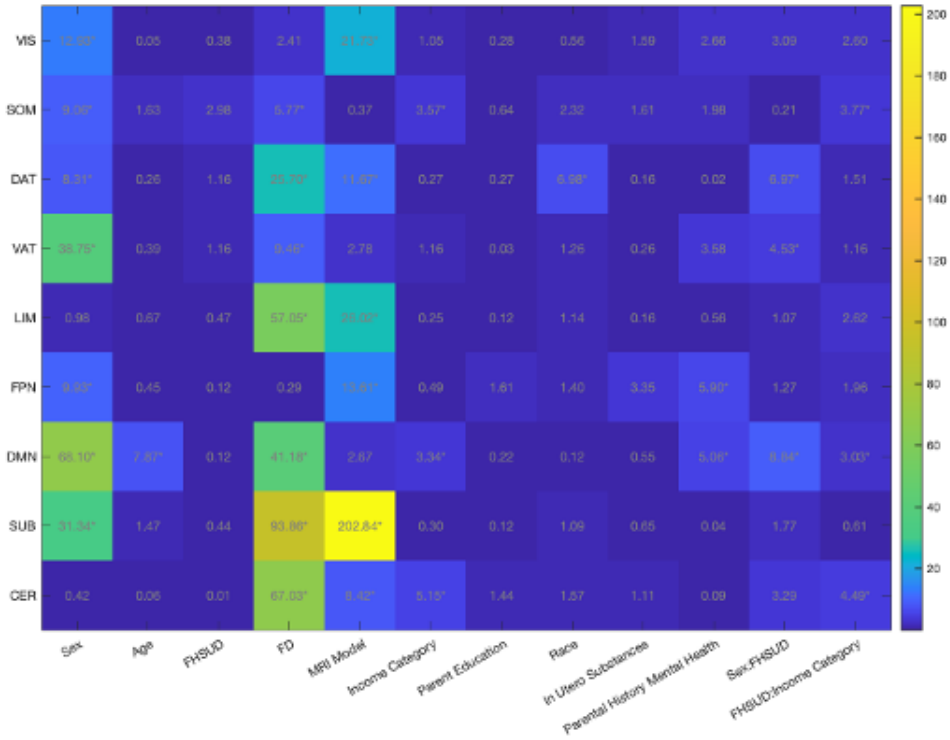

Figure S5. ANCOVA F-statistics for mean network TE values for all variables included in model.

S0.4.2 Regional TE: ANCOVA F Statistics for all included covariates.

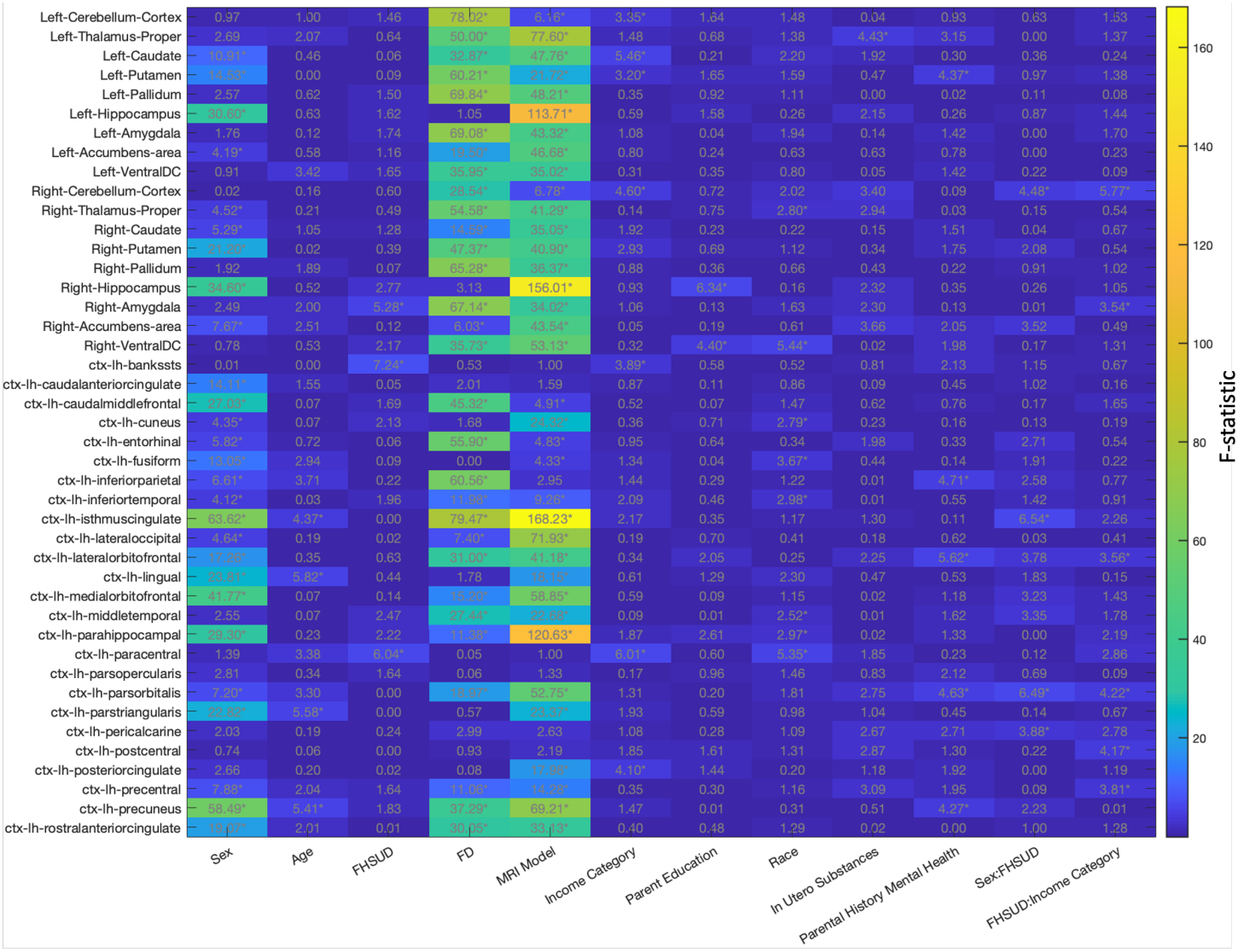

Figure S6. ANCOVA F-statistics for mean regional TE values for all variables included in model. Regions 1 to 43.

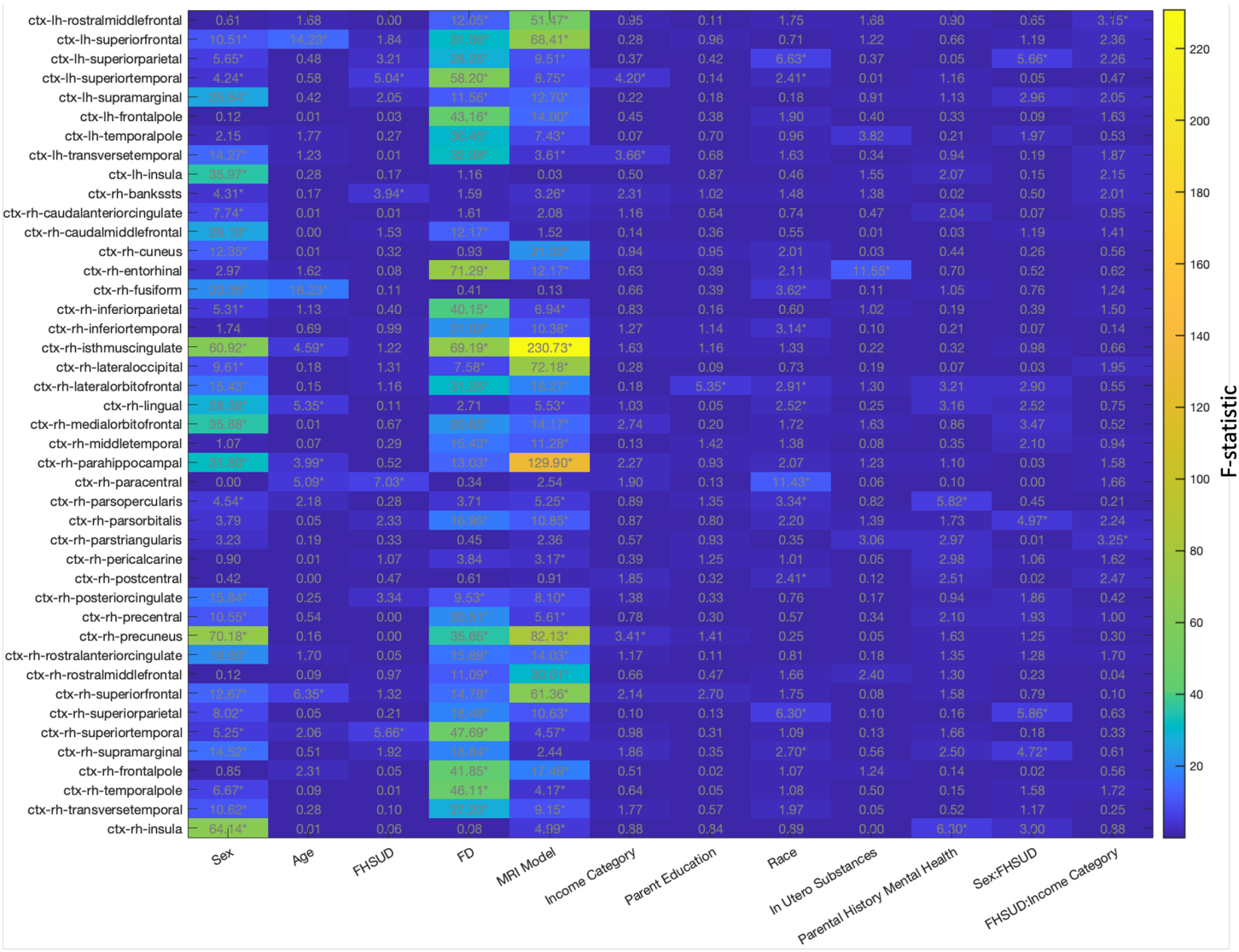

Figure S7. ANCOVA F-statistics for mean regional TE values for all variables included in model. Regions 44 to 86.

S0.5 Robustness analyses: replications

S0.5.1 Replication of main results with k = 5.

We replicate our main analysis with k=5 to demonstrate the robustness of our results. At k=5, the same four brain states as found in k=4 plus a state defined by positive amplitude activity in the limbic network (LIM+) were identified as brain states. All major results and trends hold.

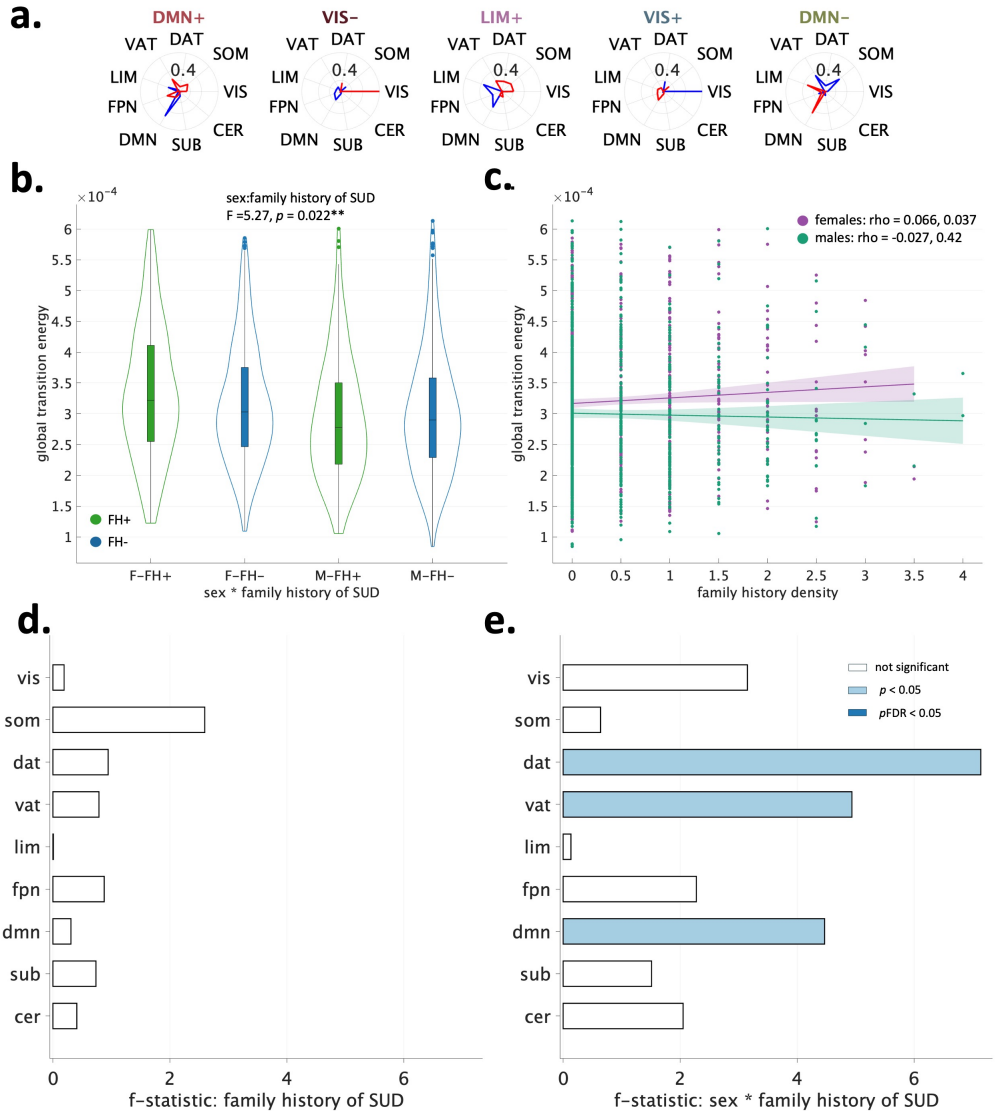

Figure S8. Replication of main analysis with k=5. For b-c, * = i<0.05, ** = pFDR < 0.5.

S0.5.2 Replication of global TE results in adolescents and young adults from the NCANDA dataset.

We replicated our results in a cohort of sex, age and in-scanner motion matched individuals from the NCANDA dataset (60). Baseline resting-state fMRI data were pre-processed using the publicly-available NCANDA pipeline (158), which consisted of motion correction, outlier-detection, detrending, physiological noise removal as well as temporal (low pass frequency: 0.1, high pass frequency: 0.01) and spatial smoothing. Frames in individual rsfMRI time series were labeled as outliers if framewise displacement >0.3 mm/TR. After removing scans with usable frames $<$ 7.8 min, each of the rs-fMRI images of the remaining 715 subjects (aged 12-21 years old, 52% female) were registered to the SRI24 atlas (159) and parcellated into 90 regions (80 cortical and 10 subcortical). The BOLD time series was normalized by the mean gray matter BOLD signal (pre-spatial and temporal filtering). We subsequently removed all censored frames, plus one frame before and two frames after, as well as uncensored segments of fewer than five contiguous frames. Using probabilistic tractography, structural connectomes (SC) were computed and parcellated into the same 90 regions.

Following the NCT analysis in the main text, we performed k-means clustering on BOLD time series data. Using a group-average SC, we calculated global and regional transition energies. We removed subjects whose global TE was +/- 3 scaled MAD. We excluded subjects who exceeded alcohol, tobacco, marijuana or other drug usage based on criteria from (60). Further, we limited our cohort to only subjects who aged 15.9 years or younger to better match our ABCD cohort and limit the range of substance exposure. We performed 500 iterations of a matching algorithm to pair each FH+ subject with a FH- subject of the same sex and identified the match with the smallest average difference in age and mean framewise displacement. Our final cohort consisted of N = 64 subjects. We ran an ANCOVA on global TE including sex, age, family history of SUD, race/ethnicity, in-scanner motion, SES, MRI scanner model (GE vs Siemens), and the interactions terms sex:age, sex:family history of SUD, and family history of SUD:SES.

As in our main results, we find FH+ females > FH- females, and FH+ males < FH - males in mean global TE (Figure S9. While family history of SUD had a very small effect size (F= 0.03, p = 0.863), the interaction of sex and family history of SUD trended towards significance (F = 3.15, p = 0.082). Family history density was weakly positively and negatively correlated with mean global TE in females and males, respectively, though the correlations were not significant. Across regional TE's, the majority of regions exhibited increased mean regional TE in FH+ versus FH- females, whereas the majority of regions had decreased TE in FH+ versus FH- males (Figure S10. We also replicated our previous result in the right pars orbitalis ("Frontal_Inf_Orb_R"), which was significant (pre-correction) for the interaction between sex and family history of SUD and exhibited the largest increase in TE of all regions in FH+ versus FH- females unpaired t tests. The bilateral middle occipital gyrus and the right precuneus (FH+ > FH- females, FH+ < FH- males) were also significant pre-correction for the interaction of sex and family history of SUD.

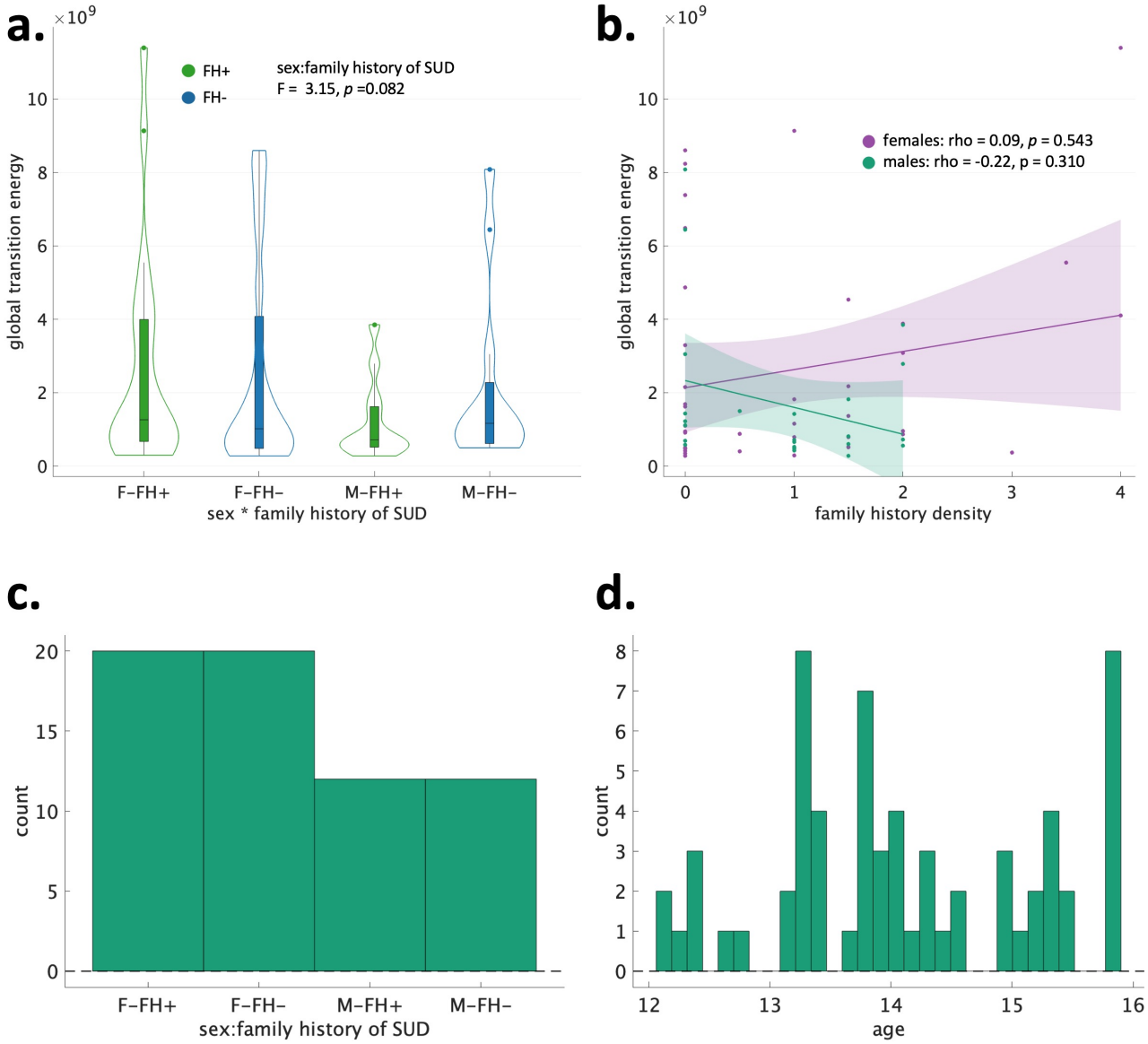

Figure S9. Replication of effect of interaction between sex and family history of SUD on global transition energy in external dataset (i.e., NCANDA).

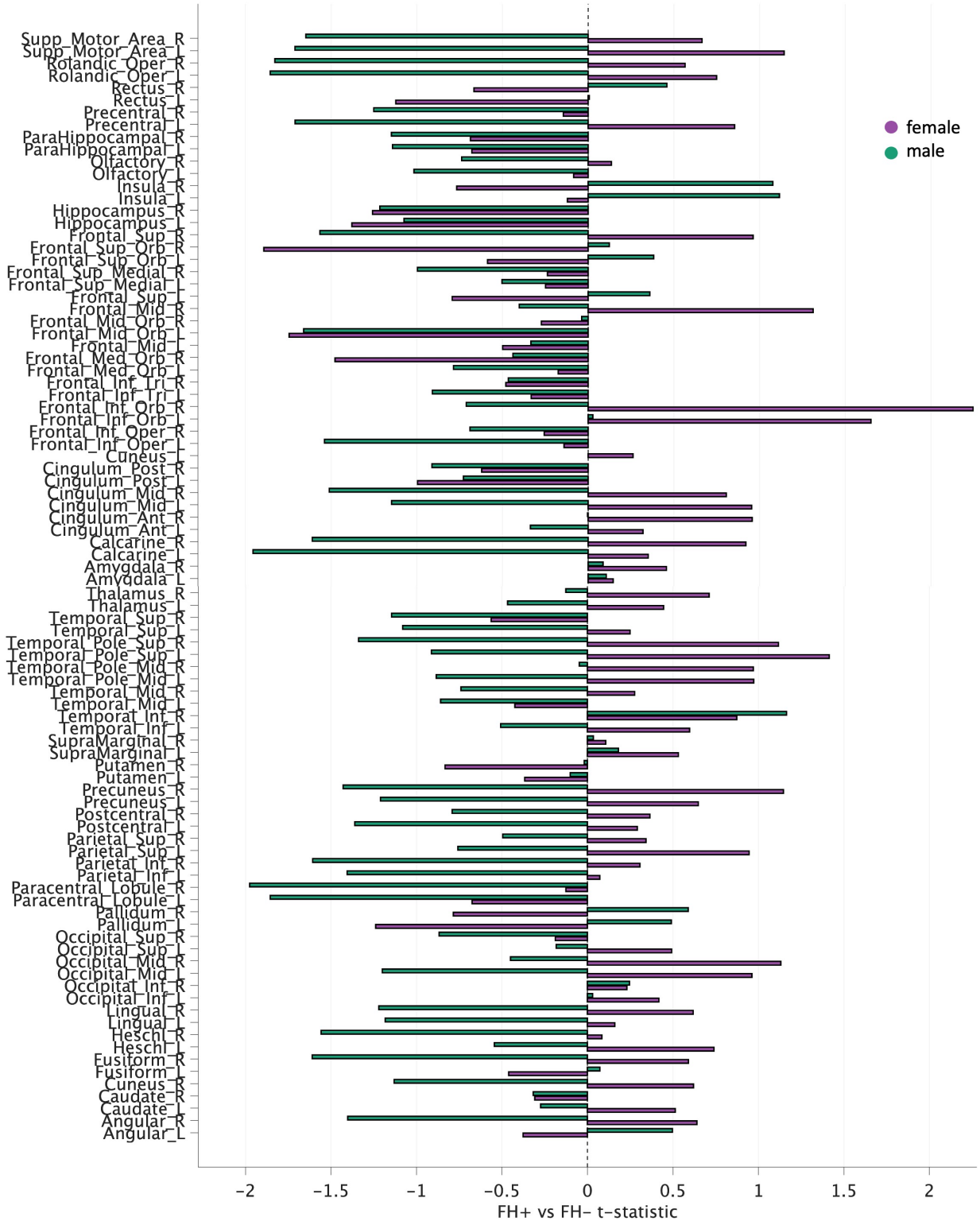

Figure S10. Replication of effect of interaction between sex and family history of SUD on regional transition energy in external dataset (i.e., NCANDA).

S0.5.3 Replication with individual structural connectomes in a cortex-only parcellation.

We replicated our main results using individual strucutral connectomes (SC) rather than a group-average in order to determine whether our results are a result of individual differences in structural connecitivty. Individual structural connectomes (SC) were available only in the Desikan-Killiany atlas (68 cortical regions; DK68) for a subset of subjects from the ABCD study (N = 2080). See main text for details. After using the same exclusions described in the main text, 1710 subjects were included in analyses. *K*-means clustering (k=4) was run on these subjects' regional resting-state functional MRI timeseries (DK68). Transition energies were calculated as described in the main text but with individual SCs (instead of a group-average SC) and only considering the seven Yeo Networks (59) in network-based analyses (not including subcortical or cerebellar networks). We find largely replicated results, except that family history-by-sex effects are significant in the VIS network is significant (pre-correction) and no longer significant in the VAT network. This effect in the VIS network was visible as a trend in group-average SC main analyses.

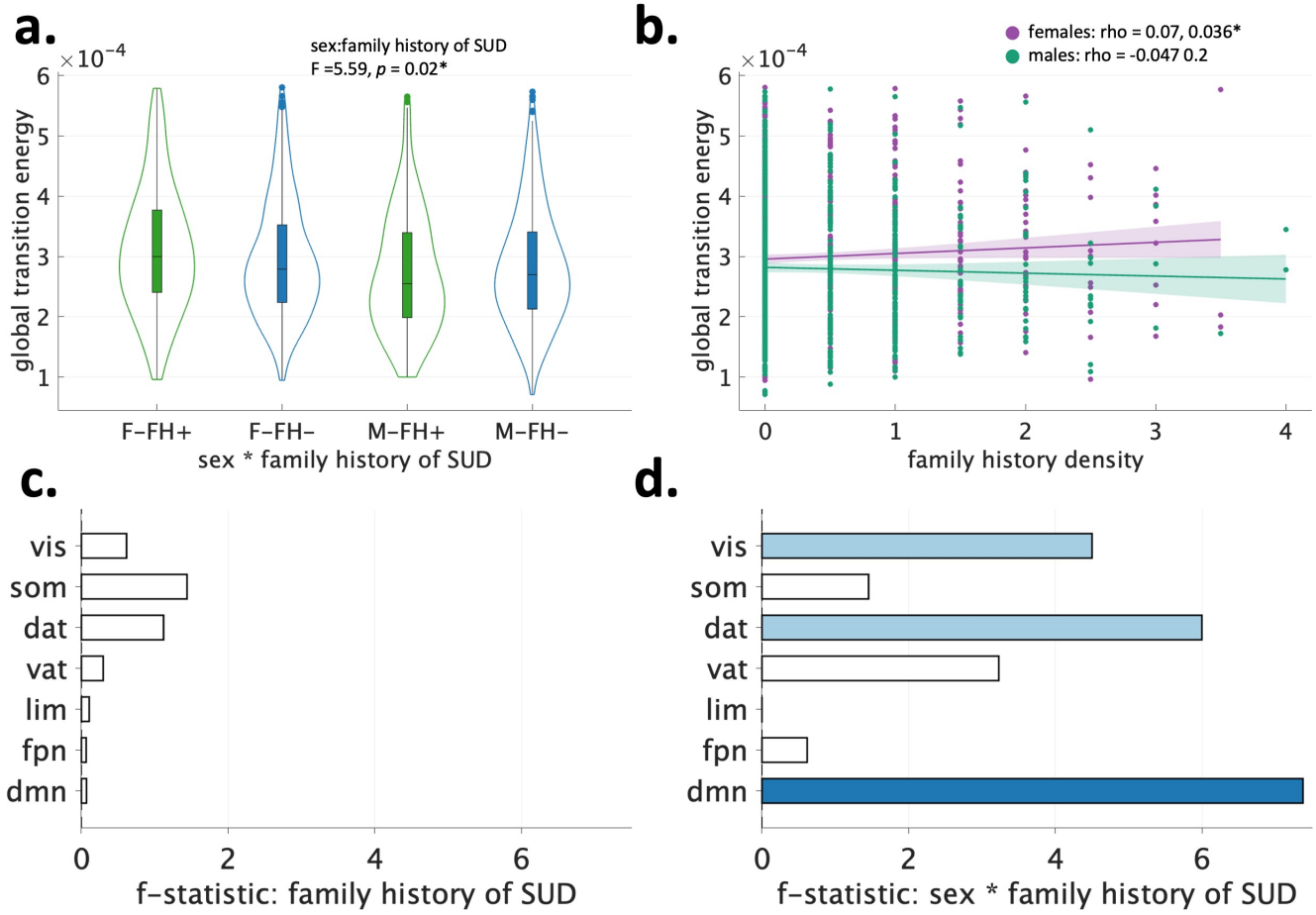

Figure S11. Global and network TE results are consistent with findings using group-average structural connectome, implicating functional dynamics in group differences.

S0.6 Robustness analyses: stratified by single site, MRI models, and income levels.

S0.6.1 Analysis within single-site.

To demonstrate our findings are not the result of site effects, we analyzed subjects from within a single site. Site 16 was chosen due to its large sample size (N = 292) and previous work has noted site 16 has having "high-quality data" and was chosen as a reference site in a site-harmonization study (160). Site 16 utilized a Siemens Prisma MRI scanner. Using TE calculations from the analysis in the main text of *k*-means clustering ($k = 4$) from the entire cohort, we ran ANCOVAs on global and network TE values from subjects from site 16 only. Despite a relatively low N for FH+ subjects of either sex, we replicated the trends in global TE such that FH+ > FH- and FH+ < FH- and found a significant effect of the interaction of sex and family history. In network TE, we found these group-sex effects in the DMN and CER networks only.

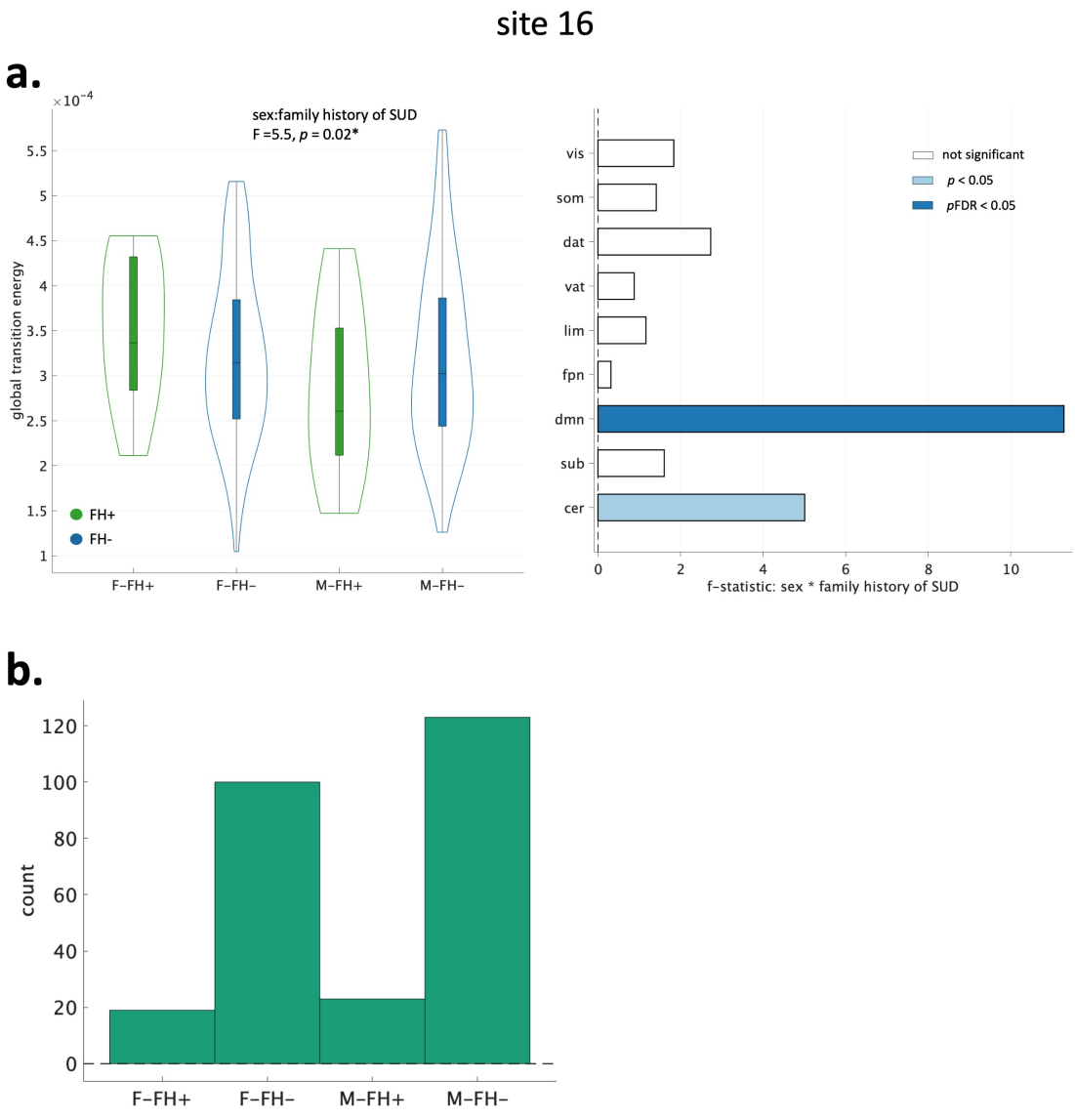

Figure S12

S0.6.2 Analyses within-MRI scanner models.

Given the high effect size of MRI model on our NCT metrics, we ran ANCOVAs separately on subjects scanned on each of the three scanner MRI models utilized in our cohort: Siemens Prisma, Siemens Prisma Fit, and GE Discovery MR750. We find that our main results from the main text are driven by subjects scanned on Prisma scanner models (Siemens). In both Siemens models (Prisma and Prisma fit), we find results in global TE consistent with our main results, such that FH+ > FH- in females and FH+ < FH- in males. Within GE scanner subjects, global TE was also FH+ > FH- females, but differed in males (FH+ > FH-). However, only Prisma scanners showed a significant family history of SUD-by-sex for global TE. At the network level, our main results are partially replicated in Prisma and Prisma Fit scanners. Prisma scanner subjects exhibit significant (post-correction) effects of family history of SUD-by-sex in DMN and DAT networks, and pre-correction significance in VIS, LIM, FPN and SUB networks. Subjects from Prisma Fit scanners exhibit pre-correction significance in the VAT network. No networks are exhibited significant family history of SUD-by-sex effects in subjects from GE scanners.

As discussed in the main text, GE scanners had the smallest number of subjects, made up of younger subjects with higher levels of framewise displacement, lower household income, and more racially/ethnically diverse compared to the other two scanner models. The lack of replication of the results from our main text in GE scanner subjects may thus reflect differences in demographics or age-related differences in the neurodevelopmental trajectory. See Table **??** for subject demographics by MRI model. Furthermore, previous ABCD analyses have GE scanners to have lower-quality data more confounds and lacking real-time motion monitoring ((61; 62; 63; 64) compared to Siemens.

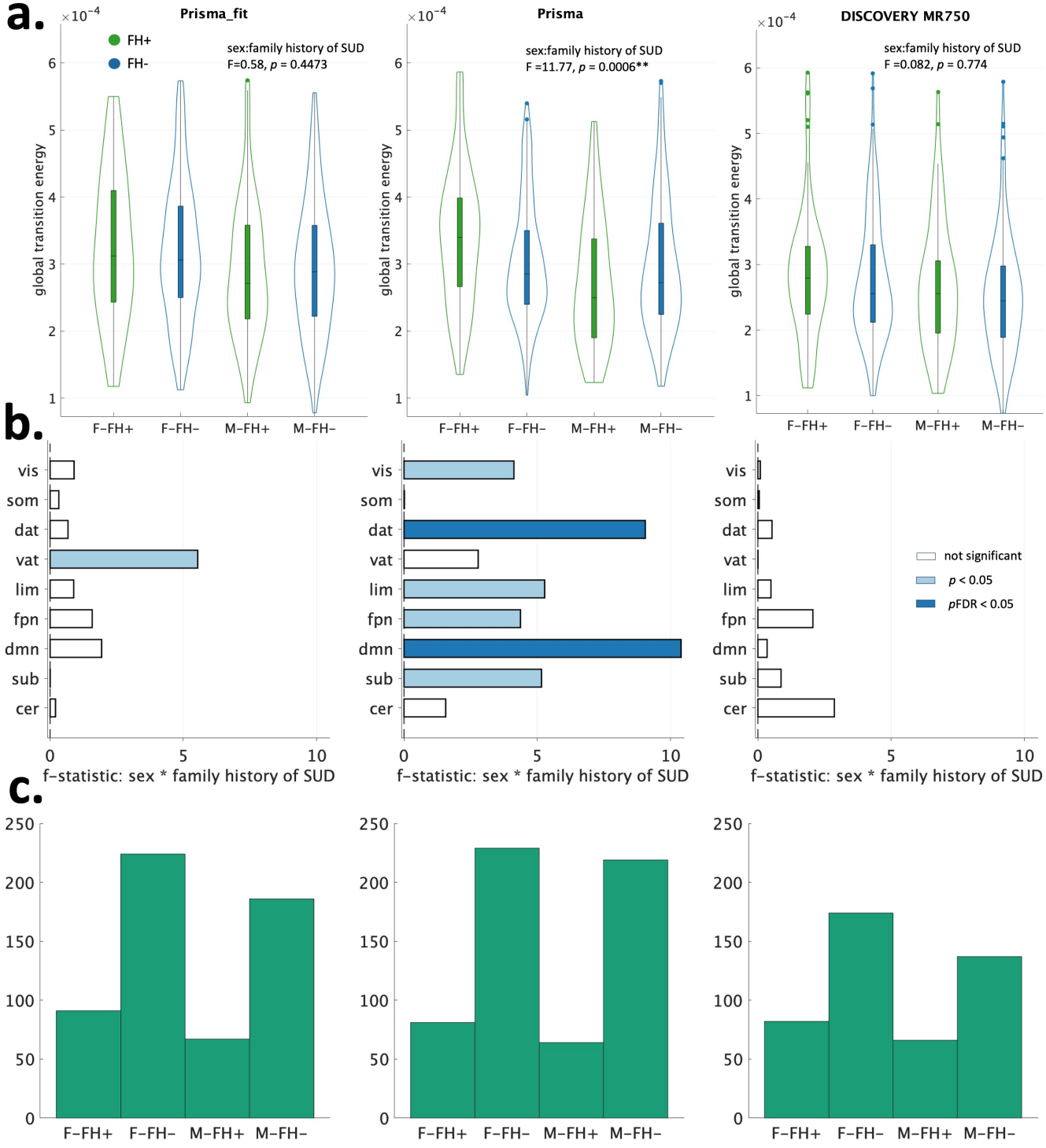

Figure S13

	DISCOVERY MR750 (n = 533)	Prisma_fit (n = 704)	Prisma (n = 710)
FH Status			
FH+	148 (27.77%)	161 (22.87%)	147 (20.70%)
FH-	314 (58.91%)	429 (60.94%)	462 (65.07%)
FH+/-	71 (13.32%)	114 (16.19%)	101 (14.23%)
Biological Sex, N(%)			
Male	239 (44.84%)	322 (45.74%)	339 (47.75%)
Female	294 (55.16%)	382 (54.26%)	371 (52.25%)
Age in months, Mean (SD)			
Male	119.33 (7.73)	120.64 (7.53)	121.02 (7.33)
Female	118.76 (7.40)	120.46 (7.19)	120.29 (7.70)
Framewise Displacement, Mean (SD)			
Male	0.133 (0.091)	0.130 (0.092)	0.115 (0.071)
Female	0.120 (0.077)	0.111 (0.062)	0.111 (0.067)
Household Income, N(%)			
$< 50,000$	151 (28.33%)	109 (15.48%)	170 (23.94%)
$50,000-100,000$	137 (25.70%)	205 (29.12%)	246 (34.65%)
$100,000+$	245 (45.97%)	390 (55.40%)	294 (41.41%)
Parent Education, N(%)			
> High School	4 (0.75%)	1 (0.14%)	4 (0.56%)
High School/GED	6 (1.13%)	2 (0.28%)	0 (0%)
Some College	523 (98.12%)	701 (99.57%)	706 (99.44%)
Associates/Bachelor	0 (0%)	0 (0%)	0 (0%)
Post-graduate	0 (0%)	0 (0%)	0 (0%)
Race/Ethnicity, N(%)			
White	292 (54.78%)	465 (66.05%)	476 (67.04%)
Black	34 (6.38%)	67 (9.52%)	44 (6.20%)
Hispanic/Latinx	117 (21.95%)	94 (13.35%)	135 (19.01%)
Asian	23 (4.32%)	14 (1.99%)	2 (0.28%)
Other	67 (12.57%)	64 (9.09%)	53 (7.46%)
In Utero Substance, N(%)			
Yes	20 (3.75%)	24 (3.41%)	31 (4.37%)
No	513 (96.25%)	680 (96.59%)	679 (95.63%)
Parent Mental Health, N(%)			
Yes	283 (53.10%)	360 (51.14%)	381 (53.66%)
No	250 (46.90%)	344 (48.86%)	329 (46.34%)

Table S2. Demographic and characteristic data of included subjects for the three MRI models (DISCOVERY MR750, Prisma_fit, and Prisma).

S0.6.3 Analyses within-income levels.

Given the significant interaction of family history of SUD and income category on global TE, we investigated whether our findings were consistent across all the three income levels: 1, 2, or 3 (low to high). After k-means clustering ($k = 4$) and calculating TE values across the entire cohort, we ran an ANCOVA on data from each income category and display the results here. From the same variables included in ANCOVAs as described in the main text, we removed household income, parental education and the interaction term of family history of SUD and household income. We find our main results are primarily driven by the largest group of subjects in the high-income category (income group 3), which replicate both global effects (FH+ > FH- females, FH+ < FH- males) and family history-by-sex effects in the DMN and DAT. Individuals in the income group 1 show the same effect in females (FH+ > FH-) global TE, but also an increase in males (FH+ > FH-). Individuals in income group 2 show decreased global TE in males (FH+ < FH-) but a slight decrease in females as well. Income levels 1 and 2 have do not show significant family history-by-sex effects in any network. Studies have shown that in the ABCD cohort, which is made up of a majority of those with higher income, individuals from higher income families have higher curiosity and availability to substances, and earlier substance use initiation (65; 66; 67).

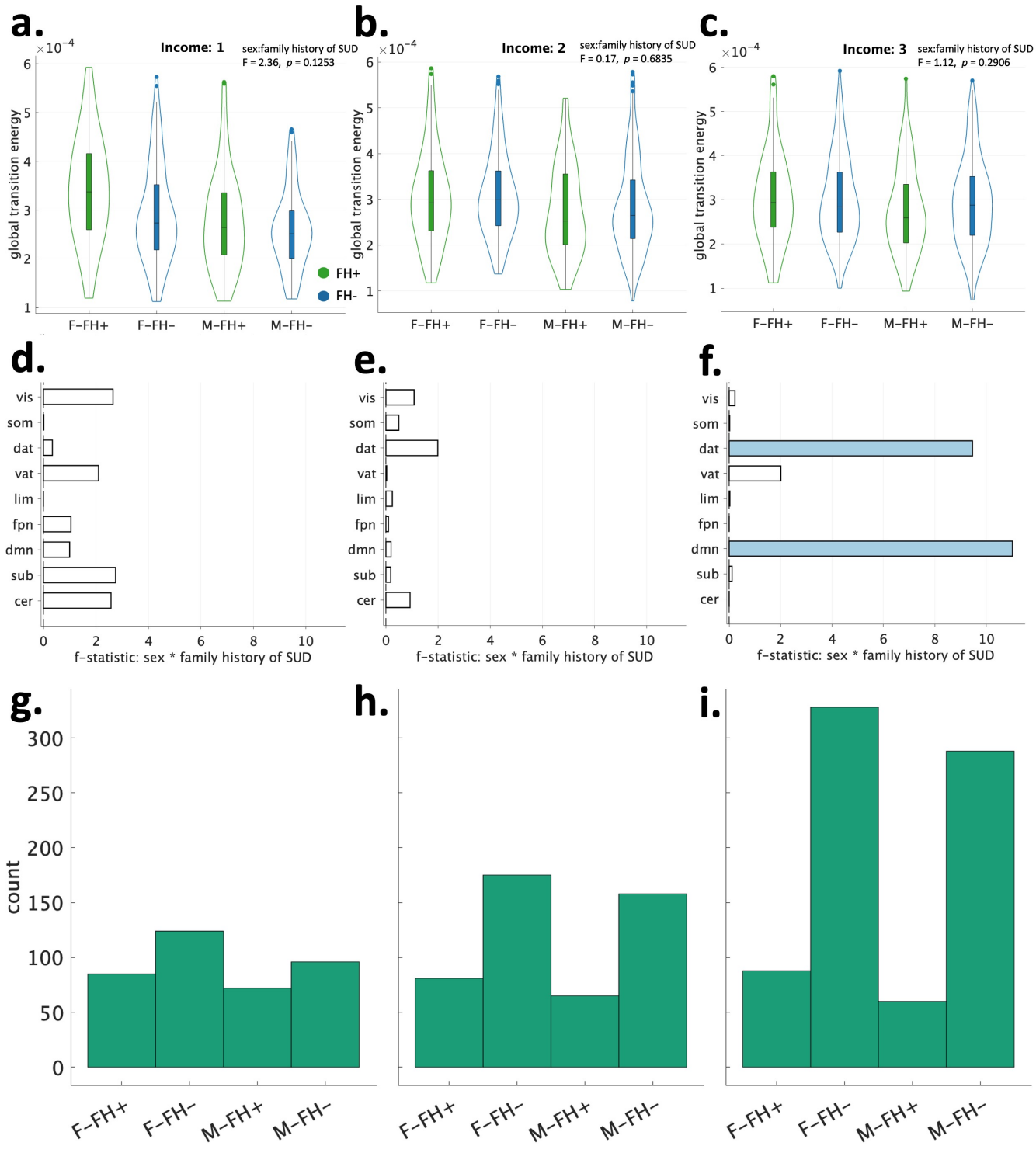

Figure S14