Reduced white matter microstructure is associated with escalating depressive symptoms in female adolescents

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Background

- More than 13% of adolescents in the U.S. are diagnosed with at least one major depressive episode (MDE) in a given year[1]
- Depressive symptoms during adolescence are a risk factor for adverse outcomes in adulthood, including chronic/recurring depression, and higher rates of suicidality[2]
- Sex differences in prevalence emerge during puberty, with females being twice as likely to experience depression[3]
- Fronto-limbic dysregulation has been implicated in manifest depression, but few studies have looked at neural precursors of sex differences in sub-clinical symptoms

Research Aims

1) Identify premorbid white matter microstructural features that relate to escalating depressive symptoms in adolescence
2) Examine sex differences in any potential neural risk features

Methods

PARTICIPANTS

- Selected from the National Consortium on Alcohol and Neurodevelopment in Adolescence (N-CANDA) study (N = 831 participants, ages 12-21)
- 177 adolescents (n = 81 females), between the ages of 14-16 at baseline, who had none/minimal depressive symptoms at baseline (CES-D score ≤ 16), and demonstrated an increase in depressive symptoms during 3 years of follow-up
- No psychiatric diagnoses or major medical conditions at baseline

IMAGE ACQUISITION & PROCESSING

- DTI (diffusion tensor imaging) scans acquired on 3T Siemens Tim Trio (UPMC and OHSU) or 3T GE MR750 (SRI, Duke and UCSD); outcome measure = FA (fractional anisotropy)
- 2D axial spin echo, EPI sequence with gradient-encoding pulses in 60 directions (b = 1,000 s/mm²) and two b=0 s/mm² images, as well as a reverse-phase sequence for distortion correction
- TR = 8,000 ms; TE = 89 ms (UPMC and OHSU) or 79 ms (SRI, Duke, and UCSD); slices = 64; slice thickness = 2.5 mm; resolution = 2.5 x 2.5 x 2.5
- Standard processing using FSL included: correction for susceptibility-induced distortions, eddy current effects, magnetic field inhomogeneities and head motion, followed by calculation of diffusion tensors with dtifit, and registration to MNI space with ANTs
- Visual quality inspection (scans excluded if ≥12 volumes contained artifact)

	Boys	Girls	
Total Participants (N = 177)	96 (54.2%)	81 (45.8%)	
Caucasian/White	77 (80.2%)	60 (74.1%)	
BASELINE			
Age	15.64 ± 0.89	15.48 ± 0.90	
PDS Score[1]	2.69 ± 0.44	3.49 ± 0.41	*
Median Household Income	$100,000 through $199,000	$100,000 through $199,000	
Median Parental Education	1 year of graduate/ professional school	4 years of college	
CES-D Score[2]	4.02 ± 2.96	5.35 ± 3.73	*
FOLLOW-UP			
Experience MDE[3]	12 (12.5%)	20 (24.7%)	*
Maximum Increase in CES-D Score[2]	5.75 ± 5.47	9.30 ± 7.27	*
Lifetime Alcohol Use (drinks)[4]	196.19 ± 1144.56	52.77 ± 160.46	
Lifetime Marijuana Use (days)[4]	61.70 ± 154.00	31.10 ± 118.00	

[1]Pubertal Development Scale
[2]Center for Epidemiologic Studies Depression Scale
[3]Major Depressive Episode assessed with Semi-Structured Assessment for the Genetics of Alcoholism
[4]Assessed using the Customary Drinking and Drug Use Record
* p < 0.05

MEASURES

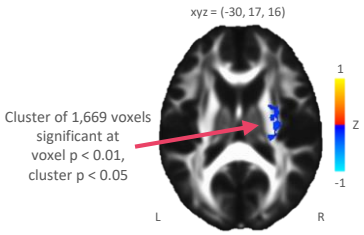
- Center for Epidemiologic Studies Depression Scale (CES-D)[4], self-report measure of depressive symptoms in the past 2 weeks
- Peak increase in CES-D score from baseline

ANALYTIC STRATEGY

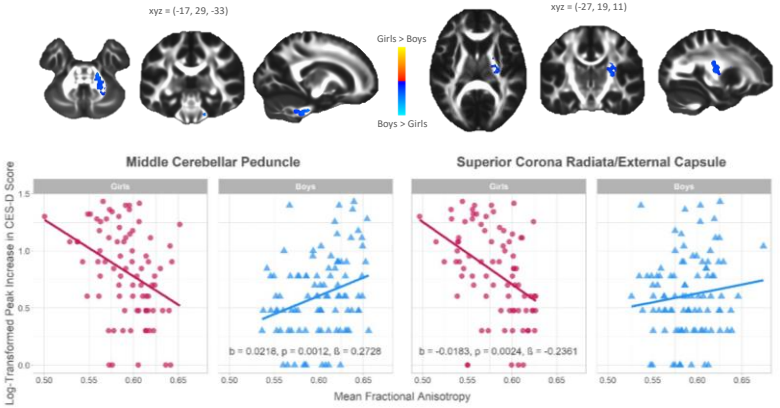
- White matter mask including all voxels where mean FA ≥ 0.3, global scaling factor of 0.916 applied to GE scans[5]
- Multivariate ANOVA with AFNI's 3dttest++ to examine the relationship between whole-brain FA and peak increase in CES-D score (non-parametric permutation testing to correct for multiple comparisons)
- Voxel p < 0.01, cluster p < 0.05 (size > 1,362 voxels)

Results

When collapsing across sex,
lower FA at baseline is generally associated with later escalations in depressive symptoms
in the right superior corona radiata (SCR) and external capsule (EC)



When examining the sex-by-depressive symptom interaction,
adolescent girls and boys exhibit different patterns
For girls, lower FA is associated with escalating depressive symptoms, but for boys higher FA is associated with escalating symptoms



Conclusions

For adolescent girls, **lower FA** in the SCR and EC is associated with later escalations in depressive symptoms

Adolescent boys show a different pattern, where **higher FA** in the middle cerebellar peduncle predicts greater depressive symptoms

- These alterations in white matter microstructure may represent sex-specific risk profiles for adolescent depression
- Future studies should examine how these phenotypes persist or remit through development, and whether or not they are specific to depression

References & Acknowledgments

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