**Introduction**

- Anxiety disorders (ADs) emerge in childhood, and, with the onset of puberty, females are twice as likely as males to have ADs.1
- Considerable research has implicated alterations in the white matter (WM) microstructure of prefrontal-limbic tracts, as well as other WM regions, in the pathophysiology of ADs.2,3,4
- These findings are of interest because WM consists primarily of myelinated axons, and myelin plays an important role in mediating optimal neuronal communication.
- Few studies have examined AD-related WM alterations in youth and in relation to sex.
- To further examine associations between childhood ADs, WM microstructural integrity, and sex, we analyzed diffusion tensor imaging (DTI) data from 295 preadolescent youth with and without ADs.

**Methods**

- Across 3 studies, preadolescent youth with ADs (social, generalized, and/or separation AD) and healthy controls were enrolled between the ages of 8-12 at 2 study sites (UW-Madison and NIMH) and completed a DTI scan on a 3T-scanner.
- The final sample (n=295; 201 F, 94 M) included 163 children with ADs and 132 healthy controls.
- Using a mega-analytic approach, tractography-based and voxelwise analyses examined the main effect of ADs, as well as the AD-by-sex interaction, in relation to 4 WM metrics (fractional anisotropy [FA], radial diffusivity [RD], mean diffusivity [MD], and axial diffusivity [AD]) in 7 bilateral tracts of interest and in WM across the whole brain.

**Results**

- Tract-based and voxelwise results demonstrated widespread AD-related alterations in DTI metrics across multiple WM regions.
- Critically, AD-related effects demonstrated a significant interaction with sex, such that FA reductions and RD increases were observed exclusively in boys and not in girls, indicating anxiety-related WM alterations may be more robust in males than in females.
- Preadolescent boys with ADs exhibited exhibited decreased FA and elevated RD relative to healthy control boys (P<0.05, corrected) across various WM regions across the brain, in association (UF, EC, IFO, SLF, ST, ILF), commissural (CC), projection (CR, IC), and brainstem (CST, CP, ML) tracts; no group differences were seen in girls.

**Discussion**

- This study constitutes the largest cross-sectional DTI study of childhood anxiety to date.
- Results show that childhood ADs are associated with broadly distributed alterations in WM microstructure and, importantly, this relationship appears more robust or prominent in boys.
- The findings – particularly the combination of reduced FA and increased RD – point to the possibility that altered myelination processes are associated with childhood ADs.
- While sex-related hormone levels did not account for the sexually dimorphic effect, in vitro evidence suggests differential sensitivity to stress in male vs. female OPCs.5,6
- Future work should investigate the extent to which these findings may play a causal role that would further support targeting WM microstructure, especially in boys with ADs.

**Acknowledgments**

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**Tract-Based Analyses – Sex-Specific AD-Related Reductions in WM FA – P-values**

**Voxelwise Analyses – Sex-Specific AD Effects on WM FA and RD**

**Proposed theoretical framework for explaining the sexually dimorphic WM-anxiety associations**

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**Sample and Analysis**

**Demographics/Clinical Characteristics**

**Group x Sex**

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**Effects of Age, Sex, and Site on Tract-Based FA Results**

**Group-by-Sex FA Interactions in 7 Bilateral WM Tracts**

**Voxelwise RD Results – Group and Group-by-Sex Effects**