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Neurosteroid and White Matter Correlates of ADHD and Autism Symptoms in Children with ADHD

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Introduction
- Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder (NDD) characterized by inattentiveness, hyperactivity, and impulsivity.
- Autism spectrum disorder (ASD) is an NDD characterized by impaired social functioning and restricted interests and behaviors.
- Approximately 66% of individuals with ADHD exhibit traits of ASD, and up to 50% of people with ASD show traits of ADHD.
- Co-occurring symptoms of both is a risk factor for decreased quality of life in the NDD population.
- Individuals with ADHD, ASD, or both show differences in hormone levels and white matter (WM) connectivity.
- Better understanding of these differences in ADHD, and their relationship to both ASD and ADHD symptoms, would contribute to our understanding of the ASD-ADHD intersection.

Methods
- 4 groups of 121 children each (n=484) were comprised of boys with ADHD (ADHD (+)), boys without ADHD (ADHD (-)), girls with ADHD (ADHD (+)), and females without ADHD (ADHD (-)).
- Two cross-sectional observational design.
- Groups were matched by handedness, age, and Parent Pubertal Development Scale (PDMS) item sum.
- Dependent variables: salivary DHEA, salivary testosterone (T), ASD trait severity, # of ADHD symptoms endorsed by parents, and mean fractional anisotropy (FA) within each of the 23 WM tracts measured by ABCD with diffusion tensor imaging (DTI).
- Statistical analysis: two-way ANOVA, two-way t-test, and Pearson linear regression.

Results
- There were sex-by-diagnosis interaction effects on mean FA of the left cingulate gyrus cingulum (CGC) and the left inferior fronto-occipital fasciculus (IFOF). Males with ADHD exhibited higher FA and females with ADHD exhibited lower FA than their TD counterparts.
- Correlation of ADHD symptom severity with frontal right superior corticostriate (SCS) FA showed opposing trends between females with ADHD (+) and males with ADHD (-).
- Both ADHD and ASD symptom severity were negatively correlated with both DHEA and T among boys with ADHD.
- Left SCS FA was negatively correlated with DHEA in TD males, but not in males with ADHD (Figure 1).
- Forceps major FA was negatively correlated with T in females with ADHD, but positively correlated in TD females (Figure 2).

Conclusions
- Lower levels of DHEA and T may drive higher autistic trait severity in boys with ADHD.
- This reinforces the relationship between DHEA and ADHD symptom severity in boys, while highlighting that T may be a previously unknown correlate.
- Hormonal influence on ADHD symptom severity, but not autistic traits, may take place via regulation of the development of one or more specific WM tracts.
- Regulation of cortico-basal-ganglia communication development by DHEA may be disrupted in boys with ADHD.
- Regulation of interhemispheric communication development by T may be disrupted in girls with ADHD.
- The interaction effects found, as well as the differing trends by sex in ADHD symptoms over frontal right SCS FA, demonstrate sex differences in the WM changes that are present in ADHD.
- Limitations:
  - Cross-sectional design
  - Differences in medicated status
  - Sex assigned at birth used
- Future directions:
  - Inclusion of all gender identities
  - Inclusion of individuals with comorbid ASD
  - Longitudinal study

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References