

Irritability in Adolescent ADHD: Relations with Functional Connectivity and Subsequent Degree of ADHD Symptoms

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Introduction

- Attention deficit/ hyperactivity disorder (ADHD) is the most prevalent childhood behavioral neurodevelopmental disorder
- A significant number of children retain symptoms throughout adolescence and adulthood
- Irritability is increasingly recognized as an important symptom in ADHD as it may escalate risk for social problems, comorbid psychiatric disorders and suicidality in ADHD
- Relatively little is known about the neural underpinnings of irritability in adolescent and young adult (AYA) ADHD
- Adolescence is a dynamic period of emotional development as well as shifts in ADHD symptoms; an important goal is to identify youth at risk of increasing or persisting symptoms
- We present two analyses on ADHD and irritability: Study 1 aimed to investigate the functional connectivity networks of the amygdala and the nucleus accumbens in relation to irritability symptoms in AYA ADHD; Study 2 applied a dimensional approach to examine changes over time in irritability, inattentive, hyperactive/impulsive symptoms

Methods

Study 1 - rsfMRI

Participants

n = 34 ADHD; M = 17 years (22 male, age range 12-23 years)
n = 34 typically-developing participants (TD) – demographically matched to ADHD on sex, age, head motion and IQ

Methods

Participants underwent resting state fMRI. We examined whole-brain functional connectivity of amygdala and nucleus accumbens seeds in relation to parent-rated measures of irritability from items on the Conners' Parent Rating Scale – 3 and the Conners' Adult ADHD Rating Scale (Observer form – parent ratings). All reported clusters were significant at a false discovery rate (FDR) cluster-corrected threshold of $p < .05$. Seed-to-voxel group analyses were performed using a group by irritability interaction controlling for hyperactive-impulsive symptoms. Significant interactions were decomposed followed-up by one-sample t-tests for irritability associations within the ADHD and TD group only.

Study 2 – Longitudinal changes in irritability and ADHD Ratings

Participants

Time 1 (T1): 108 12-16-year-olds (M = 14.21 years, SD = 1.44 years; 72 males)

- 64 met criteria for ADHD

Time 2 (T2): 80 returned ~1 year later (M = 15.03 years, SD = 1.42)

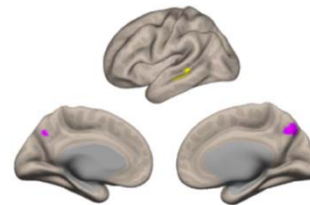
Methods

Using path models and a dimensional approach we examined changes over time in parent-reported irritability, inattentive, hyperactive/impulsive symptoms

Results

Study 1 - Results rsfMRI analysis

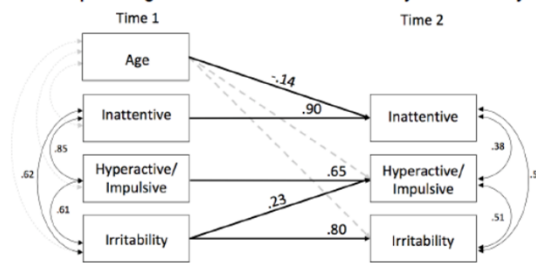
Main effect of irritability in ADHD: connectivity between left nucleus accumbens and middle temporal gyrus (-58 -26 -12 k=155), positively associated with irritability symptoms. In contrast irritability symptoms, negatively correlated with connectivity between left nucleus accumbens and precuneus (+10 -64 +40 k=238). No significant irritability TD group association with left nucleus accumbens. Significant group x irritability interaction for right nucleus accumbens and connectivity with left cerebellum (Cereb 8) (-30 -48 -62 k=137). Irritability in TD group only positively associated with connectivity between right NAcc and left cerebellum (-16 -56 -60 k=231).



Study 2 - Results Longitudinal analysis of irritability, inattention, Hyperactive/impulsive symptoms

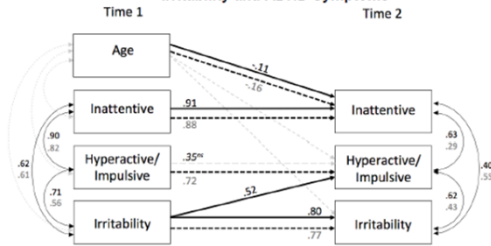
Longitudinal path analysis revealed that irritability at Time 1 predicted higher relative hyperactive/impulsive symptoms at Time 2, but not inattentive symptoms, after controlling for age and longitudinal stability in all variables (below, left panel). A multiple-group analysis examining moderation by sex/gender revealed that this association was significant only for females (below, right panel). These results suggest that irritability may play a key role in the persistence and worsening of hyperactive/impulsive symptoms across adolescence for females, with potential implications for the diagnosis and treatment of females with ADHD.

Full sample: Longitudinal Links between Irritability and ADHD Symptoms



Standardized estimates shown. All depicted values are significant at $p < .05$; non-significant paths retained in the model are depicted by a grey dashed line.

Gender effects: Multiple Group Analysis of Longitudinal Links between Irritability and ADHD Symptoms



Effects for females depicted by solid black lines, black font, and top values. Effects for males depicted by dashed black lines, grey font, and bottom values. Standardized estimates shown. All depicted values are significant at $p < .05$ unless noted, non-significant paths retained in the model are depicted by a grey dashed line.
ns non-significant

Discussion

The rsfMRI analyses in Study 1 suggest irritability in ADHD is associated with alterations in reward/emotion neural systems and may predict the course of future expression of ADHD symptoms, but also the comorbidity that frequently develops in adults with ADHD. Future, larger data sets should also examine the potential for sex differences, based on our longitudinal, path analysis of symptoms.

Our rating scale data in Study 2 demonstrated that for adolescent females, irritability was a clear predictor of increasing or persisting hyperactive/impulsive symptoms. In contrast, for males, earlier executive function problems played a larger role in predicting the development of both types of ADHD symptoms. These gender differences may impact the screening, diagnosis, and even treatment for adolescent females with ADHD, a population that is currently under-recognized⁵ and is at high risk for negative outcomes.