Increased Reaction Time Variability in ADHD: A Novel Approach to Detect Inattention

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Motivating questions

- **What are the neurobiological mechanisms behind increased Reaction Time Variability (RTV) in ADHD?**
- **Is RTV a suitable metric for detecting inattention?**

Attention-Deficit/Hyperactivity Disorder

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common mental condition among U.S. children (Fig 1).[1] Usual symptoms of ADHD are impulsivity, hyperactivity, and inattention.

The current system to diagnose ADHD lacks efficiency and is based on potentially biased parental and teacher observations of children's behavior.

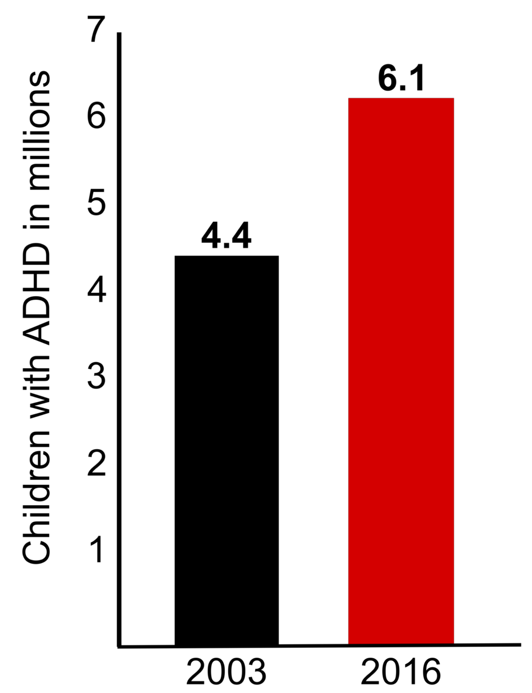
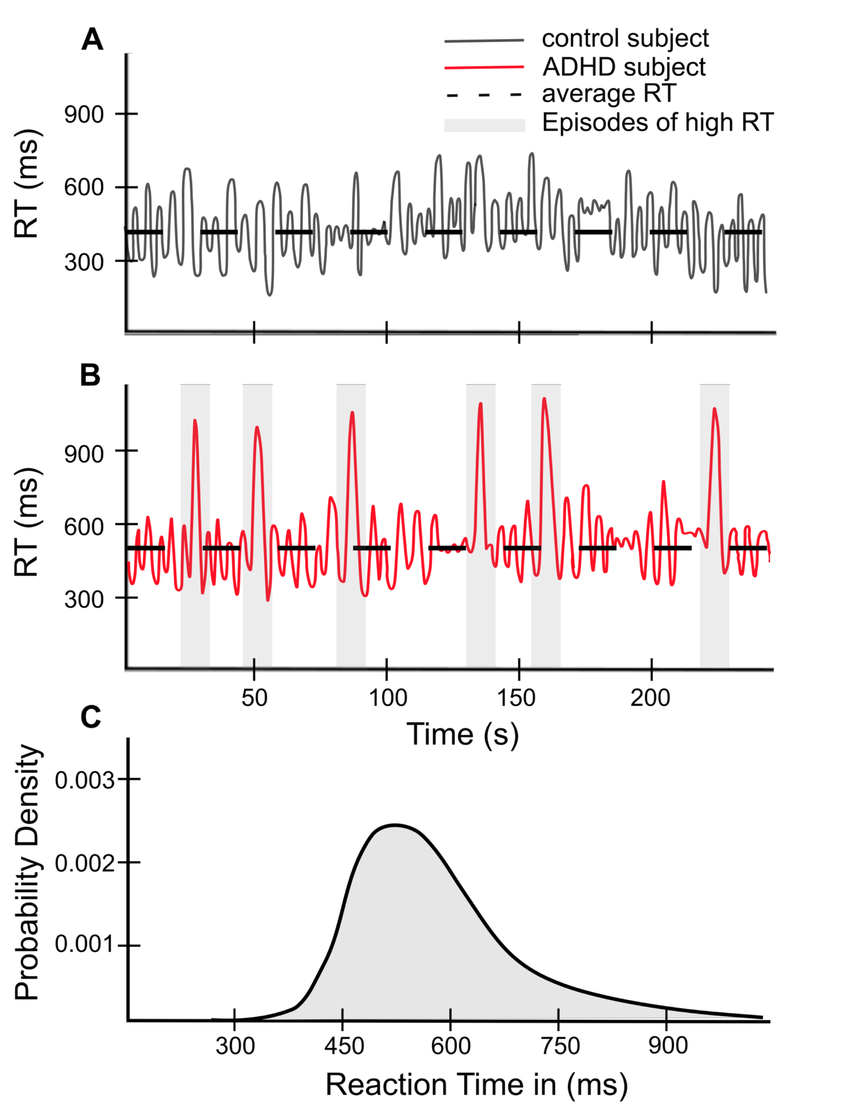


Figure 1: Estimated Number of children with ADHD in the USA based on the 2003 and 2016 National Survey of Children's Health administered by the Center for Disease Control and Prevention. From 2003 to 2016, the number of children with ADHD increased by approximately 1.7 million, or 23%, exceeding the rate of population growth (10%) during the same period.

Reaction Time and Reaction Time Variability

In experimental tasks, the reaction times (RT) of individuals with ADHD fluctuate more compared to healthy subjects (Fig 2A/B).[2] RTV, measured as the standard deviation of RT, is a metric to quantify these fluctuations.[3] We believe that high RTV can be used to detect inattention.



- Increased RTV is primarily the result of abnormally slow responses, which result in a right-skewed RT distribution (Fig 2C).[2]
- High RTV is not unique to ADHD. Numerous studies have linked elevated RTV with Alzheimer's Disease, bipolar disorder, autism spectrum disorder (ASD), and traumatic brain injury.[3]
- RTV has a genetic component and is heritable.[2] Studies have shown that the siblings of children with ADHD likewise express high RTV, even though they may not have the disorder.[2,3]

Figure 2: Schematic to visualize RT fluctuations in ADHD. A) RTs of a healthy subject while performing an experimental task. B) RTs of an individual with ADHD over task performance. Grey rectangles indicate sudden increases in RT and, hence, episodes of increased RTV. Overall the average RTs in A and B are similar, yet the RTs of the ADHD subject fluctuate more compared to the healthy subject. C) Distribution of the RTs of an ADHD subject. Right-skewed distribution with a long-tail resulting from the abnormally slow responses in figure 2 B. Developed based on data from Castellanos et al., 2005.

The Default Mode Network

The Default Mode Network (DMN) is a functional brain system that is responsible for internal mentation and self-referential tasks (Fig.3).[4,5] The DMN is deactivated during active states and is most active when not engaged in focus-requiring tasks.[5]

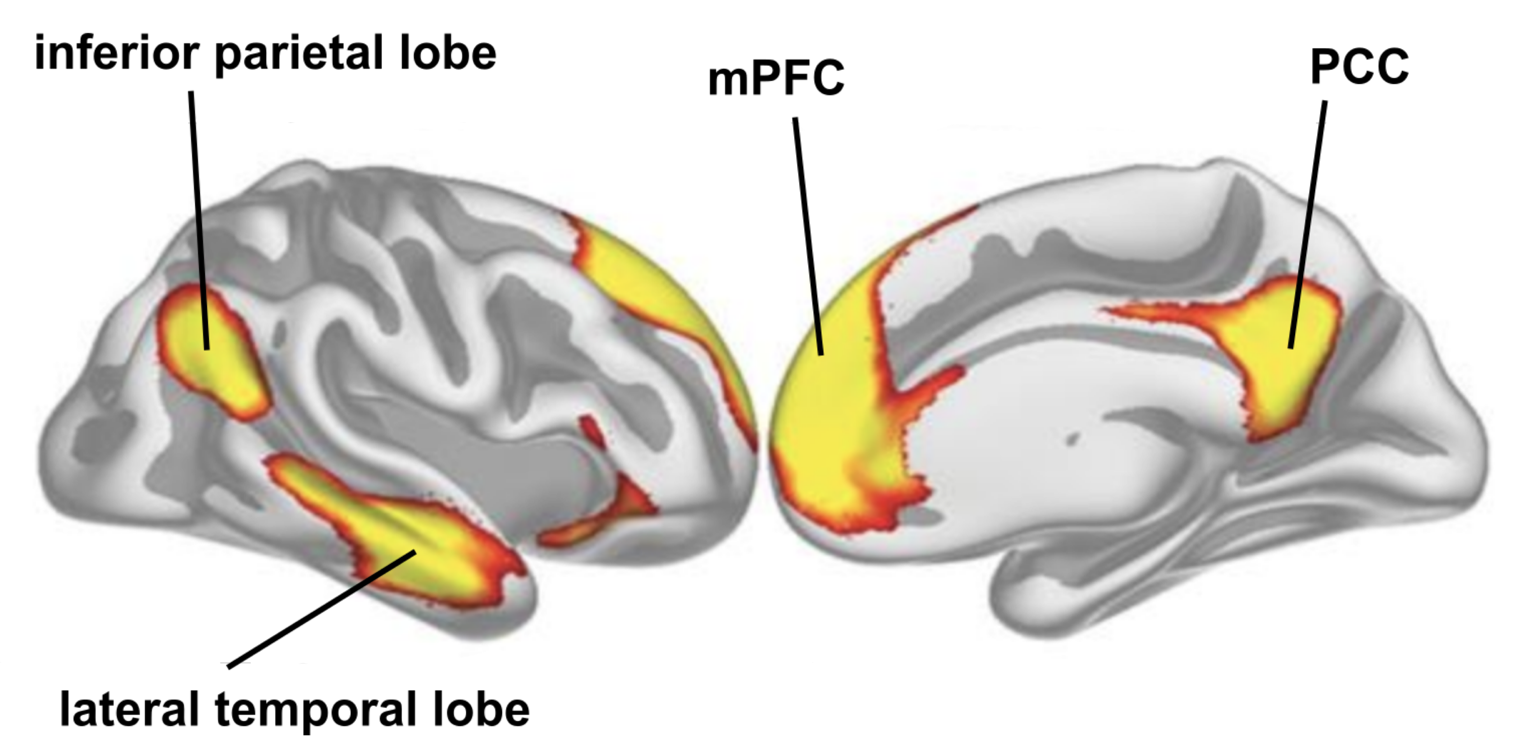


Figure 3: Regions of the DMN delineated on an expanded brain. Color scale indicates the probability of each region to be part of the DMN from red (lest likely) to yellow (most likely). Adapted from Fjell et al., 2014.

Predicted Model

Activation of the DMN may cause inattention and lead to increased RTV. We expect a positive correlation between increased RTV and DMN activation. DMN activation will be increased during periods of high RTV compared to episodes of stable RTV.

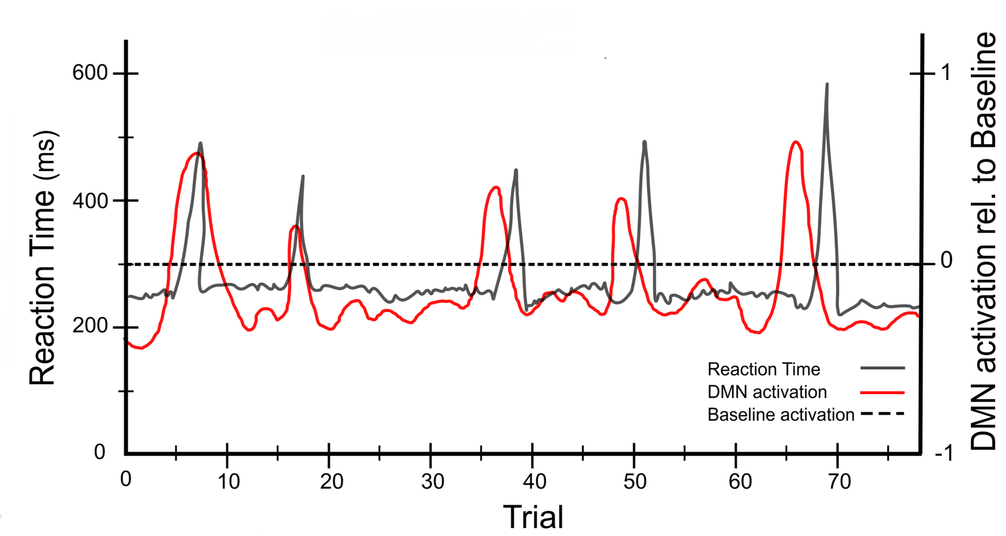
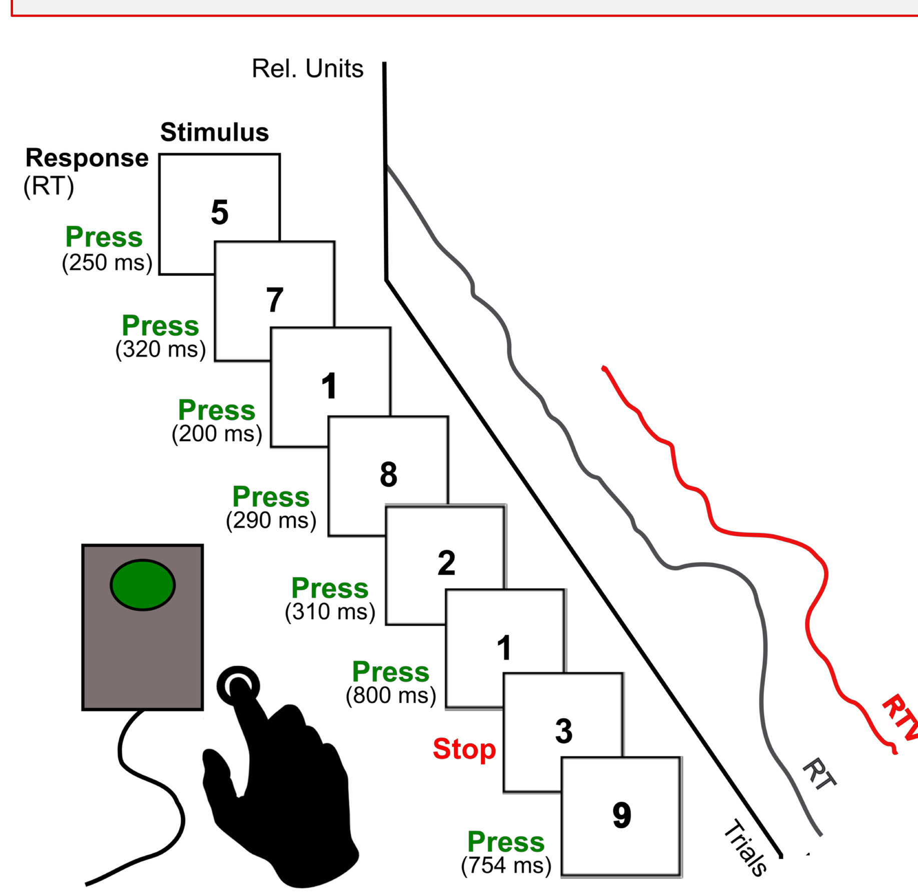


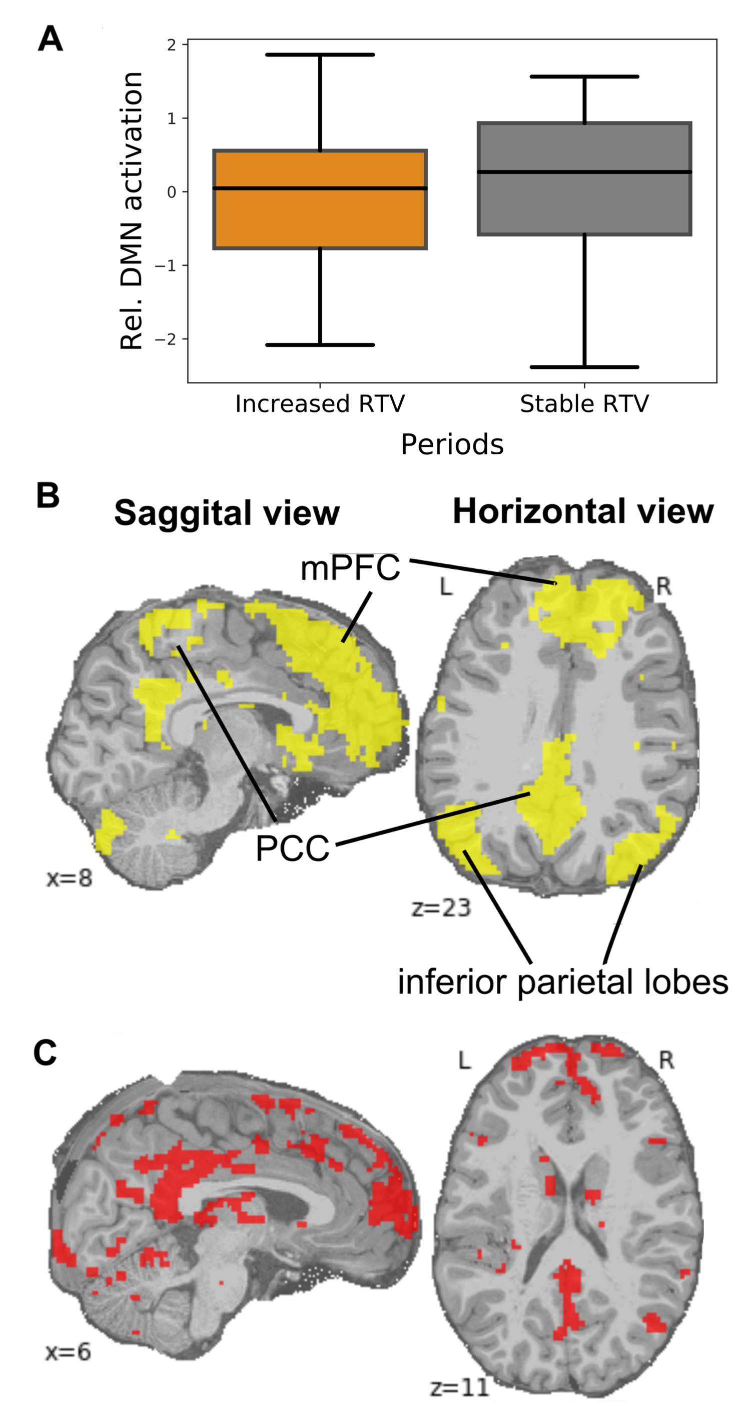
Figure 4: Schematic predicting the association between DMN activation and episodes of increased RT and RTV. Throughout task performance, the DMN is expected to be suppressed below the reference activation defined through a resting state scan (baseline activation). DMN activation increases will precede surges in RT and RTV.

Methods



- 17 subjects (8-12 years old), performed 4 runs each.
- Sustained attention to response task (SART): Subjects press a button for every number (1-9) displayed on a screen except for the number 3. RTs are recorded, RTV is calculated.
- Blood oxygen-level dependent (BOLD) magnetic resonance imaging (MRI) is used to identify the DMN and record neural activation.

Results



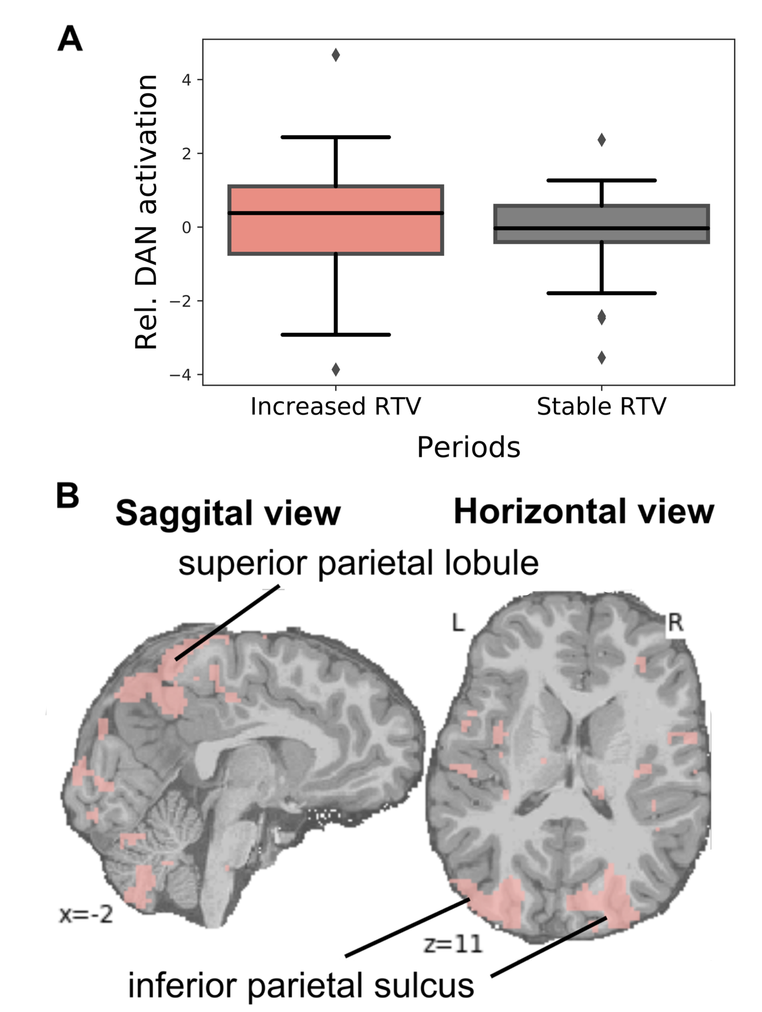


Figure 7: Dorsal Attention Network (DAN) activation across all subjects during periods of increased vs. stable RTV expressed in relative units with reference to the baseline activation obtained during a resting scan. A) DAN activation was not decreased during periods of increased RTV (p=0.29). B) Representative DAN mask that captures the inferior parietal sulcus but misses crucial regions, such as the frontal eye fields.

Figure 6: DMN activation across all subjects during periods of increased vs. stable RTV expressed in relative units with reference to the baseline activation obtained during a resting scan. A) DMN activation was not significantly increased during periods of high RTV (p=0.79). B) Representative mask that meets quality control criteria and captures the DMN adequately. Regions of the DMN are marked yellow. Any yellow segment that is not labeled is erroneously captured as part of the DMN mask and must be extracted for further analyses. C) Representative DMN mask that does not meet quality control criteria. Regions identified as part of the DMN are marked red and appear to be dispersed across the cerebral cortex. The mPFC, the PCC and the inferior parietal lobes are not captured sufficiently.

Discussion

- Even though previous studies have ascertained an association between increased RTV and DMN activation, our data do not support this relationship.
- Capturing the subjects' DMN with enhanced masks will be the key for extracting DMN activation data exclusively. Findings from the DAN suggest that our data might be "noisy."
- Our masks include a significant number of brain regions that are not part of the networks of interest. Activation during periods of high RTV is reduced by suppression of other brain regions so that the overall activation is balanced out.

Future Directions

- Develop code to enhance the DMN and DAN mask.
- Compare DMN activation in ADHD subjects to activation in control subjects during episodes of increased vs. stable RTV (Between-group analysis).

References

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