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DMN Activation May Not Be Related To Increased RTV In ADHD

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder and one of the most common mental conditions in U.S. children, affecting more than 6.1 million individuals between the ages of 2-17 years. Defined by two behavioral features - inattention and hyperactivity - identifying and studying ADHD, especially related periods of inattention, a defining feature, poses an important limitation. Recent studies have identified elevated reaction time variability (RTV) as a reliable feature of ADHD, which may be related to periods of inattention. However, the neural mechanisms behind RTV, and thereby inattention, are not well understood. The default mode network (DMN) is a functional brain system responsible for internally-directed mental processes, that is active when not engaged in cognitively demanding externally directed tasks. Activation of the DMN during active states, thus, could disrupt externally directed behavior and related neurobiological mechanisms – perhaps acting as an internal distraction. We predicted that activation in the DMN during an externally directed task will be elevated during periods of increased RTV. Further, we anticipated DMN activation to precede abnormally slow responses. We used blood-oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) while participants with and without ADHD performed a standard sustained attention to response (SART) task. We then examined the activation of the DMN during episodes of aberrant RTV, defined as reaction times more than two standard deviations from the preceding measure of variability, to ascertain the nature of the aforementioned association. Based on a preliminary analysis of DMN activation in 17 subjects, we found no evidence that DMN activation is increased during periods of elevated RTV. The neurobiological mechanisms that are related to the attention-deficit in ADHD must be better understood to aid in diagnosis and treatment. This study aims to be the first to provide comprehensive evidence of the neural underpinnings behind increased RTV and thereby inattention in individuals with ADHD.

Keywords: Attention-deficit/hyperactivity disorder, Default Mode Network, Reaction Time Variability

1. Introduction

1.1. A Brief Overview of ADHD

Attention is a pivotal component of goal-directed behaviors. When attention is impaired, the consequences can be disastrous. Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental chronic mental conditions affecting U.S. children [1]. Based on the National Survey of Children's Health (NSCH), the Center for Disease Control and Prevention (CDC) estimates that 9.4% of all children between the ages of 2-17 years, so a total of 6.1 million individuals, have been diagnosed with the disorder [2]. The primary symptoms of ADHD in children are inattention, a lack of sustained attention, hyperactivity, and impulsivity [3]. The American Psychological Association (APA) outlines three subtypes of ADHD to maintain a degree of accuracy regarding the comparative prevalence of potential symptoms of the disorder in individuals [4]. Accordingly, individuals may be diagnosed with the *predominantly hyperactive-impulsive, the predominantly inattentive*, or the *combined subtype*.

ADHD negatively impacts the lives of affected individuals on multiple layers. Several studies over past decades have linked ADHD with lower educational attainment, impaired social interactions, and lower economic achievements [5]. Given this wide range of negative impairments associated with ADHD, it is paramount to diagnose and treat ADHD efficiently in children to attenuate the harm cause by the disorder as much as possible. Yet, several deficiencies exist in the treatment and diagnosis of the disorder.

The diagnostic process for ADHD in children is subjective and time-consuming. Pediatricians, psychiatrists, and child psychologists diagnose ADHD based on behavioral observations by parents, legal guardians, and teachers [6]. These behavioral observations, however, may be biased. In order to diagnose the disorder in children, the symptoms associated with the given subtype must have endured for at least for six consecutive months [7]. Currently, there are no metrics to detect inattention reliably.

ADHD in children is treated with a variety of non-pharmacological and pharmacological approaches neither of which "heals" the disorder. Psychotherapy, often used synonymous with behavioral therapy, is an umbrella term for numerous types of interventions that target children's behavior, including social skills and parent training [8]. Psychotherapy is not a cure. The interventions mentioned above allow children with ADHD to control the symptoms of the disorder, but they do not heal the mental condition, and it is hard to quantify their success objectively. Further, studies indicate that more efficient treatment outcomes are accomplished when behavioral therapy is combined with medication compared to behavioral therapy alone [9].

Medication is the most common treatment for ADHD in children [10]. The two most frequently prescribed drugs for ADHD are norepinephrine reuptake inhibitors and stimulants [11]. Atomoxetine is the most frequently prescribed norepinephrine reuptake inhibitor, blocking the presynaptic reuptake of norepinephrine in the brain [12]. Most commonly, the intake of atomoxetine is associated with nausea gastrointestinal distress, drowsiness, and sleep disturbances [13]. Stimulants, such as methylphenidate are globally the most frequently used drugs to treat ADHD [14]. Methylphenidate causes elevated stimulation of dopaminergic cell groups of the brain and among other consequences increases alertness [15]. The efficiency of methylphenidate has been revealed by numerous studies, yet stimulants are associated with significant side-effects [16]. Common side effects of methylphenidate consumption include loss of appetite, sleep disturbances, dizziness and headaches, a variety of gastrointestinal symptoms, increased blood pressure and heart rate, and growth restrictions [17]. Further, recent findings suggest that the risk of suffering from Parkinson's disease or related diseases of the basal ganglia and cerebellum increases more than 8-fold for patients who regularly take stimulant medication [18]. The deficiencies in the diagnosis and treatment of ADHD suggest that more research is needed. Recent findings concerning reaction time variability (RTV) in ADHD may pave the path towards more efficient treatment and diagnosis of the disorder.

1.2. Elevated Reaction Time Variability in ADHD

The reaction times of individuals are variable. Reaction time has been used as a metric to evaluate an individual's performance in cognitive tasks for decades [19]. In experimental tasks, reaction time variability (RTV) refers to fluctuations in an individual's response time measured in seconds or milliseconds [20].

RTV has been linked to numerous mental conditions. Compared to healthy control subjects, individuals with ADHD show greater variation in their response times throughout task-performance (Fig. 1) [21]. In addition to ADHD, RTV has been observed among individuals with schizophrenia, autism spectrum disorder (ASD), bipolar disorder, traumatic brain injury, and Alzheimer's Disease [22]. A commonality associated with all conditions listed above is inattention, which hints at the potential neurobiological connection between elevated RTV and attention-deficit [23]. Because the neural mechanisms behind increased RTV are not well understood and due to its occurrence in an array of mental conditions, it is currently controversial whether high RTV is a behavioral phenotype for ADHD. By enhancing our understanding of RTV in ADHD, our work aims to contribute to resolving the question at hand.

There is no standard method for quantifying RTV [24]. The most commonly used statistical approach is the standard deviation (SD) of the reaction time because it is fairly simple to compute [25]. Other common statistical approaches are the coefficient of variation (CV) and the parameter tau in ex-Gaussian distributions [26].

Reaction time distributions are not normally distributed and follow an ex-Gaussian pattern [27]. Elevated RTV is related to higher tau values, which are indicative of distributions with a larger right-skewed tail [28]. Thus, increased RTV is primarily driven by abnormally slow responses, which are believed to be related to sudden lapses in attention [29].

The neurobiological mechanisms behind increased RTV in ADHD are not well understood. Several different neurobiological hypotheses aim to explain the brain processes behind this phenomenon. Two popular explanations focus on insufficient deactivation of the default mode network (DMN) of the brain and decreased activation of the PFC in individuals with ADHD during task performance [30]. Understanding the neural underpinnings behind elevated RTV in ADHD is vital, as it may allow us to understand the disorder better, and ultimately develop more effective

treatments and diagnostic standards for affected individuals. Up to this date, experts are questioning both of the hypotheses mentioned above so that more research must be conducted to find a valid and persuasive scientific hypothesis explaining increased RTV in ADHD.

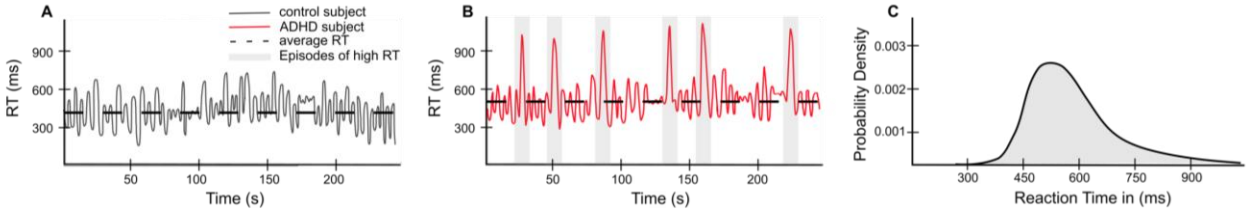

Figure 1: Schematic to visualize RT fluctuations in ADHD. A) RTs of a healthy subject while performing an experimental task. B) RTs of an individual with ADHD over task performance. Grey rectangles indicate sudden increases in RT and, hence, episodes of increased RTV. Overall the average RTs in A and 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 from Castellanos et al., 2005

1.3 The Default Mode Network

The DMN is a functional brain system responsible for internally-directed mental processes [31]. It has long been known that individuals are involved in internally directed tasks [32]. DMN activation is believed to be responsible for directing passive mental processes, including self-reflection, mind-wandering, reflections about the past, and imaginations of the future [33]. Consequently, the DMN is mainly activated during passive states when individuals are not engaging in goal-directed behaviors [34]. During task-performance when individuals are in active states, the DMN is mainly deactivated [35].

The anatomy of the DMN can be broken down into several subsystems. Regions of the hippocampal formation, the dorsal medial prefrontal cortex (dmPFC), the ventral medial prefrontal cortex (vmPFC), the lateral temporal lobe, the inferior parietal lobe, and the posterior cingulate/retrosplenial cortex (PCC) constitute the human DMN (Fig. 2) [36].

The DMN plays a vital role in an array of mental disorders. Abnormal DMN activation patterns have been linked with autism spectrum disorder, schizophrenia, and Alzheimer's disease [37]. Further, increased DMN activation during active states has been identified as a critical indicator for ADHD [38]. Because the DMN plays a central role in numerous impactful mental disorders, understanding the pathological mechanisms involving the DMN is paramount. The dorsal attention network (DAN) comprises task-positive regions of the dorsolateral prefrontal cortex, the frontal eye fields, the inferior precentral sulcus, the superior occipital gyrus, the middle temporal motion complex, and the superior parietal lobule [39]. The DAN directs top-down executive processes to maintain individuals' attention during task performance [40]. Sustained performance relies on activation of the DAN. During experimental tasks, activation of the DAN is associated with enhanced task performance [41]. The activation patterns of the DAN and the DMN are anti-correlated [42]. Studies have shown that the higher the magnitude of DAN activation, relative to the suppression of the DMN, the better the subject's performance of the task [43].

Insufficient recruitment of top-down executive processes may underlie attention-deficit. Activation of the DAN during task performance has been linked with sustained attention and enhanced task performance [44]. However, the role of DAN activation in ADHD is currently not well understood. While the functional connectivity between the DAN and the DMN has been established, it remains unclear whether insufficient DAN activation mediates a mechanism for elevated RTV, indicating at lapses of attention [45].

Do episodes of high RTV represents periods of reduced attention? Is there sufficient evidence to reliably classify RTV as a behavioral marker of ADHD? What neurobiological mechanisms mediate increased RTV in ADHD and how can we intervene? In this work, we used fMRI to look at DMN and DAN activation in children with ADHD during an experimental task. We believe that activation of the DMN of the brain is an internal distraction that leads to an increase in RTV. Activation of the DMN during task performance could comprise a neural mechanism explaining the attention-deficit in ADHD. Therefore, we hypothesized that DMN activation (relative to a resting-state baseline) may be higher during episodes of increased compared to stable RTV during an experimental Sustained Attention to Response Task (SART). Further, because there is evidence that DAN and DMN activation are anti-correlated, we

predicted DAN activation to be increased during periods of stable RTV. This work was a preliminary analysis that was used to validate our approach and to obtain an oversight of the first quarter of our data. Based on this preliminary analysis of the experimental data, no significant difference was found between DMN and DAN activation during periods of increase vs. stable RTV. Further, several analytical deficiencies were identified with regard to our DMN and DAN masks.

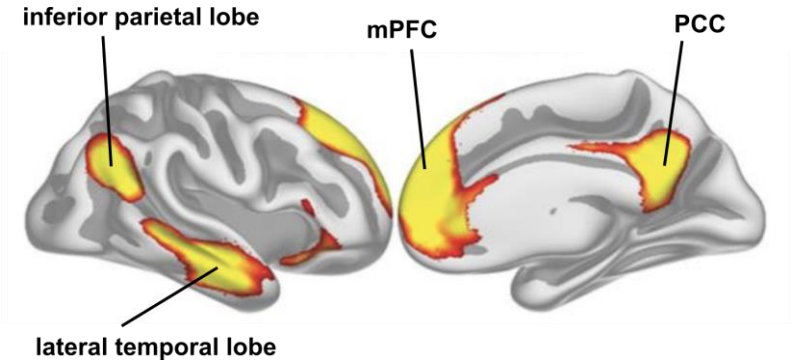

Figure 2: Inflated brain regions displaying the DMN. The scale indicates the likelihood that a region will be part of the DMN from yellow (most likely) over red (less likely) to grey (unlikely). Adapted from Fjell et al., 2014

2. Methods

Participants. This project was part of the broad study which is still ongoing and in the process of recruiting participants. A total of 90 children (60 with ADHD and 30 healthy individuals) between the ages of 8-12 years will be recruited to participate in the overall study over two years. The data will be incrementally reanalyzed as participants gradually participate in the project. The analyses shown in this work were derived from a subset of 17 participants, which were recruited according to the protocol of the broad study (12 typically developing and 5 ADHD subjects).

Recruitment and Compensation. ADHD participants were recruited from the Summer Treatment Program (STP) at FIU's Center for Children and Families. Participants without ADHD were recruited from the Miami-Dade community through flyers, word-of-mouth, and active outreach efforts in the school system. To incentivize participation in this study, participants received a $90 gift card upon completion of the scanning session. Further, parents received a summary of their child's intellectual abilities, academic attainment, and neurocognitive functioning.

Inclusion/Exclusion criteria. Participants were between 8 and 12 years old, had an IQ above 80, were right-handed, had a normal or corrected-to-normal vision, and spoke English fluently. Further, participants fulfilled all criteria for being able to obtain magnetic resonance imaging (MRI) scans (e.g., do not have pacemakers or any metallic medical devices such as prosthesis). Participants in the ADHD group were additionally diagnosed with ADHD (any subtype) based on the DSM-V criteria (refer to introduction). Individuals did not participate in this study if they were currently receiving or had received psychotropic medication in the past six months for mental conditions other than ADHD. ADHD participants who were at the time of the study taking stimulant medications withholded their dose 24 hours before their MRI scan session. Further, children with comorbid mental diseases (e.g. bipolar disorder, psychosis, or ASD) were not recruited for this study. These inclusion and exclusion criteria aimed to create comparable participant groups (ADHD and control), in which the subject's behavior was as similar as possible.

Clinical/Neurocognitive Intake. Participants who were eligible for the study first completed a clinical/neurocognitive intake session. During this session the following measures were collected: Wechsler Intelligence Scale for Children (WISC) [46], Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) semi-structured interview [47], Disruptive Behavior Disorders (DBD) checklist for parents and teachers, the Child Behavior Checklist (CBCL), and the Wechsler Individual Achievement Test (WIAT) [48].

FMRI Task. Before performing the experimental task, participants briefly practiced the experiment in a "mock scanner" to minimize ambiguities and train participants on the scanning procedures. Each participant performed four runs of an fMRI adapted sustained attention to response (SART) task, during which numbers between 1 and 9 were

displayed on a screen every 1000 ms in a pseudo-random order (Fig. 3). Participants were instructed to press a button for every number ("Go-stimulus") except for the number 3 ("Stop-stimulus"). 90% of the trials displayed a Go-stimulus, while 10% were Stop-trials. The time interval between each trial was randomly varied and was either 1200, 1600, or 2000 ms long.

Structural and functional MRI imaging. Participants were scanned on a Siemens Prisma 3.0T Magnetic Resonance (MR) scanner at FIU's Center for Imaging Sciences. A typical scanning session was approximately one hour long and consisted of one structural and five functional scans. The data acquisition was led by the principal investigator and graduate as well as undergraduate students who assisted in the process. Structural imaging consisted of a T1-weighted (TR/TE = 2500/2.88 ms) scan. Structural images allowed us to develop an individualized map for each subjects' brain. These anatomical maps were the foundation for the analysis of functional data. The purpose of functional imaging was to monitor neural activation. Functional images were T2* blood-oxygen level dependent (BOLD) fMRI (TR/TE = 800/30 ms) scans. The first functional scan was a resting scan during which subjects saw a fixation cross on a screen. The neural activation data obtained in this scan served as a frame of reference (baseline) for activation during the task performance. The neural activity below the baseline was referred to as suppression while neural activity above the reference was termed activation. After the functional resting scan, the participants performed four runs of the experimental task. We used the BOLD signal to monitor subjects' neural activation during task performance.

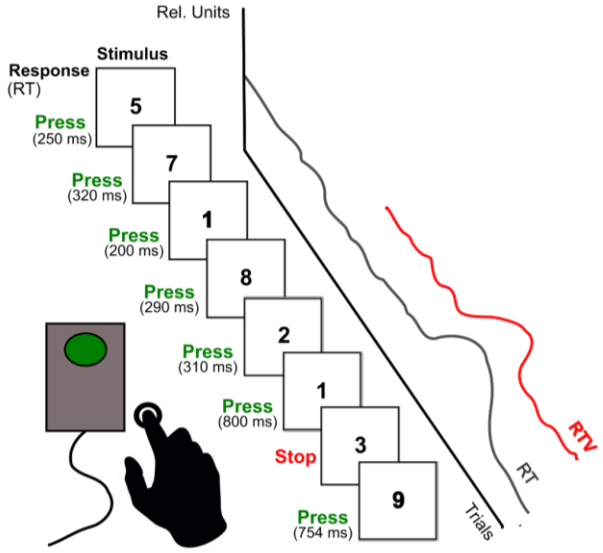

Figure 3: Experimental task. Numbers between 1 and 9 are depicted on a white screen successively. Subjects press a button for every number except for the number 3. The reaction time is measured in milliseconds and RTV is calculated as the standard deviation of 4 successive trials. Interpolations are used to account for trials in which no response is rendered.

Identifying the Default Mode Network. The resting-state scan (fixation-cross eyes open) preceding the task was used to identify the regions that make up the DMN. To identify the regions corresponding to a subjects DMN, we extracted an averaged time series from the posterior cingulate (PCC) and medial prefrontal (mPFC) cortices during the resting-state scan (seed regions). A correlation analysis was then conducted to identify which voxels displayed similar activation patterns to the averaged activations from the PCC and mPFC during the resting-state scan. Voxels exhibiting a high correlation with the PCC and mPFC were classified as a subjects DMN. Subject-specific region of interest (ROI) brain masks were developed, so that neural activation data could be extracted from the ROIs. Previous publications provided a detailed frame of reference for potential brain regions of interest: We expected to identify voxels within subjects' hippocampal formation, dorsal medial prefrontal cortex, lateral temporal cortex, inferior parietal lobe, posterior cingulate/retrosplenial cortex, and the ventral medial prefrontal cortex [49].

Identifying Periods of Elevated Reaction Time Variability. The reaction time, as well as a measure of variability in reaction time (standard deviation), were monitored to identify episodes of increased reaction time and reaction time variability. Reaction time variability was defined as the standard deviation of four trials preceding the response period of a trial throughout task performance. If RTs were missing from specific trials (e.g. omission errors on go-trials or

correctly withholding responses on stop trials), the missing RTs were replaced by interpolated values derived from the adjacent trials. Trials with inconsistent reaction time variabilities, defined as deviations beyond two standard deviations of the reaction time were marked as deviant and used to evaluate the DMN and DAN activation during these times.

Examining DMN and DAN activation patterns. Periods of deviant reaction time variability were identified and marked prior to this analysis. The average DMN and DAN activation was calculated for defined periods throughout task performance. For this project, t-tests ($\alpha = 0.05$) were performed to test the significance of the mean DMN and DAN activation during the selected periods across all subjects. For the overall study, DMN and DAN activation will in addition be compared between the ADHD and control group.

3. Results

We found no significant difference in DMN activation during periods of increased vs. stable RTV across all subjects (Fig 4). Further, the DMN does not appear to display changes in activation during task performance compared to the reference resting state. In relative units, activation of the DMN during both periods, increased and stable RTV was around 0. However, upon closer examination DMN activation across subjects was quite variable. As indicated by the variability bars, the DMN activation overall displayed a large spread. During both periods, no pattern was observed for the relative DMN activation as the DMN appears to have been measurably activated for some (positive values) but significantly suppressed (negative valued) for other subjects during either period.

The mean DAN activation was stable during task performance. No significant difference was detected when comparing DAN activation during periods of increased vs. stable RTV (Fig. 4). Further, compared to the resting state, the DAN was neither activated nor suppressed throughout periods of increased and stable RTV. The relative mean DAN activation during both periods was around 0, which represent the mean DAN activation during the resting state. The variability in DAN activation across subjects was reminiscent of the DMN activation. Overall, DAN activation was more variable during periods of increased compared to periods of stable RTV. During periods of increased RTV, the DAN activation of some subjects was measurably increased (positive values), while the DAN of other subjects was suppressed (negative values). Two outliers were detected during periods of increased and three outliers were detected during periods of stable RTV.

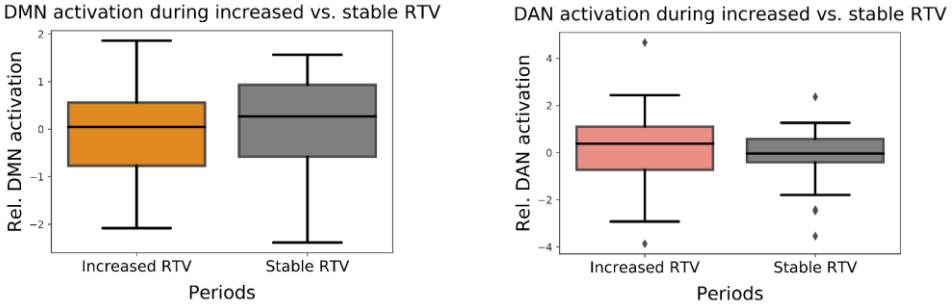

Figure 4: *DMN and DAN activation across all subjects during periods of increased vs. stable RTV*. Activation is expressed in relative units with reference to the baseline activation obtained during a resting scan. DMN activation was not significantly increased during periods of high RTV (p=0.79). DAN activation was not decreased during periods of increased RTV (p=0.29).

4. Discussion

Our current findings suggest that there is no evidence that DMN activation leads to an increase in RTV. Across all 17 subjects, activation of the DMN was stable during periods of increased and stable RTV, which ostensibly suggests that the activation of the DMN does not fluctuate throughout task performance. Considering the unexpected variability in DMN activation, it is consequential that average DMN activation across all subjects appears stable. During both

periods, the DMN deactivation of some subjects counterbalances the activation of others, so that in sum no net activation is observed.

Multiple explanations could be behind this observation: First, DMN activation may be unrelated to RTV. If there is no neurobiological link between DMN activation and RTV, one would expect DMN activation to be random during episodes of increased and stable RTV. In this case, the role of the DMN during task performance would be independent of RTV and therefore comparing DMN activation during periods of increased vs. stable RTV would not capture episodes in which differences in DMN activation are expected. Essentially in this scenario, we would be monitoring the activation of a neural network during two randomly selected episodes throughout the experiment that do not capture the event or stimulus that is associated with activation changes of the network of interest. This would also explain the unusual variability that we observed, as in the randomly selected episodes a variety of neurobiological processes not accounted for in our hypothesis could cause activation changes in the DMN.

Further, our methodology may be erroneous. As expressed above, the analysis of fMRI data is associated with numerous obstacles that are challenging to overcome. During the preprocessing of fMRI data, noise filters are applied that remove selected signal frequencies from the BOLD signal [50]. The removed frequencies ideally represent physiological noise caused by heartbeats and respiration [51]. The threshold frequencies are not individualized but are derived from previously conducted large-sample experiments. Considering that the sample size for the current analyses was less than one-fifth of the desired sample of the RTV study, small irregularities in the noise filtration of the data might exert a large observable effect. The great variability in the data suggests that physiological noise may not have been sufficiently removed so that the BOLD signal used to measure activation in the selected brain regions was not capturing neural activation exclusively. To correct for this effect, the thresholds for the noise filters must be adjusted and, potentially, individualized filters may be developed for each subject, although this approach would not reflect the contemporary practice and poses unique challenges that would add multiple layers of complexity to this study.

The most likely cause behind the great variability in DMN activation across subjects are neural masks that do not capture individuals DMN well (Fig. 5). Because each individual's brain is unique, as highlighted in the methodology section, neural masks must be developed to identify brain regions that correspond to an individual's DMN. These DMN masks are obtained with correlation analyses that are conducted during the resting scan. Upon close examination of all 17 DMN masks, it must be pointed out that a significant number simply does not capture the subject's DMN well (Fig. 5B). As a result, the average activation that is obtained for the DMN during the selected episodes most likely includes data from other brain regions as well, significantly affecting the accuracy of the DMN activation we hoped to measure. The more brain regions are erroneously captured in a neural mask, the greater the likelihood of observing no activation changes, as activation of some and deactivation of other brain regions tend to balance each other out. As shown in mask 5B the brain regions that were in some cases classified as part of the DMN were in many

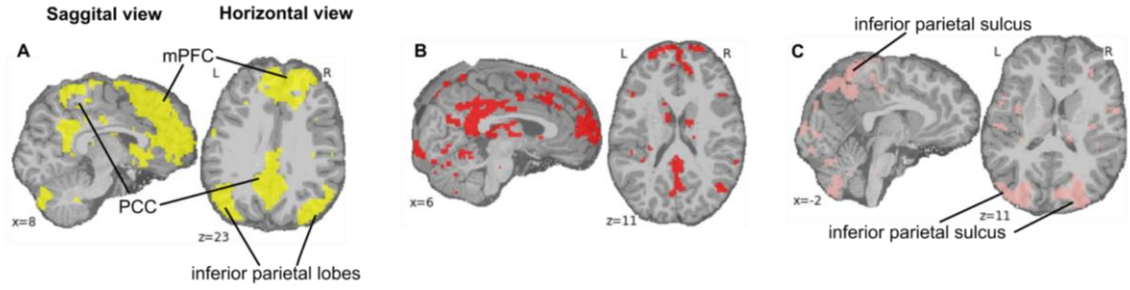

Figure 5: Representative masks. A) Representative DMN mask that meets quality control criteria and captures the DMN adequately. Any yellow segment that is not labeled is erroneously captured as part of the DMN mask and must be extracted for further analyses. B) Representative DMN mask that does not meet quality control criteria. Regions identified as part of the DMN appear to be dispersed across the cerebral cortex. The mPFC, the PCC and the inferior parietal lobes are not captured sufficiently. C) Representative DAN mask that is inadequate and does not capture the frontal eye fields.

cases dispersed across the brain. This spatial variety of brain regions that were included again tends to diminish the activation changes that we aimed to measure. Further, critical regions, such as the PCC and the mPFC were in many cases not captured sufficiently.

Similar irregularities may have affected the unexpected outcome of the DAN activation pattern during the task performance. As explained above, the DAN is often characterized as the counterplayer of the DMN, so that the activation patterns of DAN and DMN were expected to anti-correlate during the task performance. Accordingly, we expected the DAN to be activated during periods of stable and deactivated during periods increased RTV. Several studies in the past have ascertained the DAN's role in attention-requiring tasks [52]. If periods of increased RTV are indicative of lapses of attention, one would, therefore, expect the DAN to be deactivated during these periods. However, our results suggest that DAN activation was stable during the task. Upon close examination of the individualized DAN masks, we observed that a variety of brain regions not part of the DAN were captured erroneously (Fig. 5C). Most likely, the activation in these regions across the brain balanced each other out so that no net activation was measured in the DAN.

It is important to note that both analyses, DAN and DMN activation during periods of increased vs. stable RTV, were sensitive to errors. Due to the small sample size, minor errors that might have persisted in the data processing of individual subjects were given relatively more weight in the entirety of the analyses. In the prospective sample size of 90 subjects, these minor irregularities will most likely have a minor effect on the outcome of the findings, however, the smaller the sample size, the more weight is given to the data of each subject which makes the entire analyses more sensitive to errors.

Given the limitations that were discussed above the analyses that we conducted must, to our disappointment, be classified as unsatisfactory. With regard to the future of this study, two major challenges must be overcome: First and foremost, a larger sample must be collected so that the data is less prone errors and effect sizes are accounted for. Second, the accuracy of our DMN and DAN masks must be significantly improved so that we can exclusively focus on and extract data from the regions of interest. On the one hand, this could be accomplished by using a higher correlation coefficient for the correlation analysis that is conducted during the resting state. By using a higher correlation coefficient, we would set a higher bar for each selected voxel (spatial unit of the brain) to be classified as part of the DMN or DAN. This would most likely eliminate erroneously selected region and at the same time reduce the size of the regions from which data is extracted. On the other hand, we could rely on DMN and DAN masks that have been developed through previous studies. This process would be less time-consuming, however, most DMN and DAN studies in the past have been conducted on adults whose brains anatomically differs from children's. As a result, translation matrices must be developed to transform "adult DMN and DAN coordinates" to "children DMN and DAN coordinates." This process will inevitably be prone to errors and adds complexity to our study. Ultimately, this will reduce the credibility and comprehensibility of our approach and, therefore, the former method of obtaining more accurate DMN and DAN must should be given preference.

To understand the association between increased RTV and lapses in attention, it will be inevitable to conduct analyses that incorporate response accuracy. Provided that in the future we can link DMN activation to increased RTV the next step will be to find a connection between elevated RTV and inattention. If DMN activation accounts for the inattention in ADHD on a neurobiological level, a connection between DMN activation and increased RTV will be insufficient. Therefore, no conclusions should be drawn before all six proposed analyses are conducted on larger sample sizes.

The potential benefits of understanding the neurobiological nature of the attention-deficit in ADHD, as highlighted in the introduction of this work, are crucial to providing better diagnosis and treatment for affected individuals. Science is humanities most potent tool in enabling us to understand and treat diseases more effectively. The moment we accept temporary failure and reject to enhance our scientific methodologies at the expense of comfort is the moment when we give up our most significant agency for fighting diseases. Our duty to fight for the health of millions of children affected by ADHD will, therefore, not stop with this work but only intensify in the weeks and months to come.

5. Conclusion

In this work, we proposed a novel approach to detect inattention in ADHD and attempted to explain the neurobiological mechanisms that lead to attention-deficit. Based on the findings of previous studies, we predicted that DMN activation would lead to an increase in RTV and, therefore, we expected the DMN to be more active during episodes of elevated RTV. Likewise, because accumulating evidence suggests that the DAN acts as the counterplayer of the DMN, we expected DAN activation to be decreased during periods of increased RTV. 17 individuals (12 typically developing and 5 ADHD subjects) performed the experimental task, and the fMRI BOLD signal was used

to monitor activation in the brain regions of interest. Based on two preliminary analyses, both DMN and DAN activation were stable during task performance, so that our hypothesis cannot be supported at this stage. However, significant variability was observed in subjects DMN and DAN activation during both periods of increased and stable RTV. Upon close examination of individualized DMN and DAN masks, it was concluded that the masks failed to capture the regions of interest exclusively and included a variety of other brain regions. Multiple proposals were provided on how to increase the accuracy of the neural masks, and ultimately it was concluded that a higher correlation coefficient should be used during the resting state scan to identify subjects DMN and DAN. Further, the sample size must be increased and additional analyses that incorporate between-group comparisons, as well as response accuracy as a metric, must be included to expand the findings of this work. By understanding the nature of attention-deficit in ADHD, future iterations of this study have the potential to provide a path towards enhancing the diagnosis and treatment of the disorder. This will, potentially, reduce the health care costs of affected individuals and increase their overall life quality, as ADHD has been liked to lower academic attainment and a variety of social hardships [53].

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