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How to cite

RAFI, Halima. Mapping internally oriented attention in the brain across the continuum of attention difficulties: Findings from functional neuroimaging. Doctoral Thesis, 2023. doi: 10.13097/archive-ouverte/unige:187348

This publication URL: https://archive-ouverte.unige.ch/unige:187348
Publication DOI: 10.13097/archive-ouverte/unige:187348

UNIVERSITÉ
DE GENÈVE
FACULTÉ DE PSYCHOLOGIE
ET DES SCIENCES DE L'ÉDUCATION

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DOCTORAT EN NEUROSCIENCES
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UNIVERSITÉ DE GENÈVE FACULTÉ FPSE

Professeur Martin Debbané, directeur de thèse

MAPPING INTERNALLY ORIENTED ATTENTION IN THE BRAIN ACROSS THE CONTINUUM OF ATTENTION DIFFICULTIES: FINDINGS FROM FUNCTIONAL NEUROIMAGING

THÈSE

Présentée à la
Faculté de Psychologie et des Sciences de l'Éducation

de l'Université de Genève

pour obtenir le grade de
Docteure en Neurosciences

par

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de Lahore, Pakistan

Thèse N° 403

Genève

Editeur ou imprimeur : Université de Genève

2023

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Acknowledgements

I am deeply grateful to have had an enriching PhD experience. Over the past four and a half years, I have felt overwhelmingly supported and encouraged by mentors, peers, fellow scientists, friends, and family. I am indebted to everyone who has helped me, many of whom went out of their way to do so.

I would like to start by thanking my thesis director, Martin, for his encouragement and guidance. Thank you for being an available, supportive, and trusting advisor, and thank you for being an example of what it looks like to revel in ones' work. Your love and enthusiasm for research is contagious.

I would like to thank the members of my thesis committee, Prof. Maude Schneider and Prof. Daniel Schechter, for carefully reading my work and thoughtfully challenging me.

Thank you to my small équipe: Jessica, Juan, Vincent, Margaux and Mélissa. Thank you for being so easy to collaborate with, for educating me on clinical psychology, and for your endless patience with my French.

Thank you to the greater DIP lab, with whom I have shared many a Monday evening lab meeting, for sharing your interdisciplinary expertise with me. I am especially thankful to my fellow neuroscience PhD candidate and co-author, Farnaz Delavari: it is hard to overstate how much your strength as a scientist inspires and motivates me to do robust, creative research.

I would like to extend my sincere thanks to Dr. Camille Piguet and Dr. Ryan Murray for their collaboration, to Andrès Posada for helping with coding experimental tasks and to the FCBG MRI team (especially Loan Mattera) for being such wonderful company during MRI scans. I am also deeply thankful for the adolescents and families who participated in our research and generously gave us their time and mental energy.

To my loved ones: thank you for making me feel deeply loved and seen, and for giving me a full and wonderful life to anchor myself in.

To Ami, Baba, and my family: thank you for always supporting me, caring for me, and praying for me. Thank you for giving me every opportunity possible, for all your sacrifices, and for your belief in me. Thank you. I love you.

Lastly, this manuscript is dedicated to the memory of Prof. Rafi Ullah Khan (1920-2008). He was a history professor, an advocate for higher education, and my Dada Aba.

Abstract

Understanding ourselves and our connection to the world is a fundamental human endeavor. In pursuit of this, we spend time and cognitive resources to internally oriented activities like contemplation, reflection, and imagination. However, the neural foundations of internally oriented attention have received less scientific attention compared to externally oriented attention. This gap is especially salient in the literature devoted to individuals facing heightened attention difficulties such as attention deficit hyperactivity disorder (ADHD). The present thesis aimed to specifically address this gap in neuroscientific literature by investigating neural mechanisms of two types of internally oriented attention, namely controlled and automatic, in individuals along the continuum of attention problems.

In Chapter 1, we introduce the processes of controlled and automatic attention oriented towards our mental states. After discussing neural correlates of these processes, we shift focus towards characterizing attention difficulties. We argue for a continuum perspective on attention in which ADHD represents the extreme end of attention problems. We discuss neuroimaging findings to date that pertain to internally oriented attention within attention-related disorders and highlight critical gaps in the literature. Chapter 1 concludes by outlining the primary aims and hypotheses of this thesis, which were addressed through three scientific studies presented in Chapters 2-4, respectively. In Chapter 2, we present our first study which mapped neural correlates of controlled internal attention in young adults with and without ADHD. We demonstrated that adults with ADHD have aberrant activation in the right angular gyrus and within emotion regulation circuitry during internal attention, validating it as a topic of interest within the context of attentional difficulties. In our second study in Chapter 3, we transitioned from exploring neural correlates to investigating neural dynamics of automatic attention in neurotypical adolescents. We evaluate different methodologies for modeling brain functional network connectivity and show that time-varying methodologies can be used to detect subtle differences in neural dynamics as a function of attention difficulties. Finally, in Chapter 4 we present our final study on automatic attention in adolescents with and without ADHD. In this study we use dynamic and multivariate approaches to comprehensively characterize large-scale neural circuits involved in ADHD.

This thesis found atypical patterns of neural activity and connectivity among individuals with attention problems during both controlled and automatic internal attention processes. Our discussion in Chapter 5 notes that our results align closely with current literature, showing a critical role for salience network-centered functional connectivity in attention regulation. Our contributions can be summarized in three points. First, we establish that controlled internally oriented attention (as compared to externally oriented attention) is disrupted in individuals with ADHD. Second, we use a methodologically driven, neuroimaging approach to validate the neural dynamics related to the continuum of attention problems. Third, given the inconsistency of literature on automatic internal attention in ADHD, we stress the need to consider individual-specific variation when assessing brain-behavior relationships. On the methodological front, this means using nuanced, time-varying approaches to brain functional connectivity, which is dynamic by nature. On the clinical front, this means comprehensively characterizing individuals' behavior by assessing emotion dysregulation alongside experimental and self-reported measures of inattention, impulsivity, and hyperactivity. Taken together, this thesis contributes to the understanding of neural mechanisms of internally oriented mental processes in individuals with attention difficulties.

Resumé

La compréhension de nous-mêmes et de notre lien avec le monde est une entreprise humaine fondamentale. Pour y parvenir, nous consacrons du temps et des ressources cognitives à des activités orientées vers l'intérieur, telles que la contemplation, la réflexion et l'imagination. Cependant, les fondements neuronaux de l'attention orientée vers l'intérieur ont reçu moins d'attention scientifique que l'attention orientée vers l'extérieur. Cette lacune est particulièrement évidente dans la littérature consacrée aux personnes confrontées à des difficultés d'attention accrues telles que le trouble déficitaire de l'attention avec hyperactivité (TDAH). Cette thèse vise à combler cette lacune en étudiant les mécanismes neuronaux de deux types d'attention orientée vers l'intérieur : contrôlée et automatique, chez des individus situés dans le continuum des problèmes d'attention.

Dans le chapitre 1, nous présentons les processus de l'attention contrôlée et automatique orientée vers l'intérieur. Nous présentons les corrélats neuronaux de ces processus, puis nous nous concentrons sur la caractérisation des difficultés d'attention. Nous défendons une perspective de continuum de l'attention dans laquelle le TDAH représente l'extrémité des problèmes d'attention. Nous discutons des résultats de la neuro-imagerie sur l'attention orientée vers l'intérieur dans le cadre des troubles liés à l'attention et nous soulignons les lacunes critiques de la littérature. Le chapitre 1 conclut en exposant les principaux objectifs et hypothèses de cette thèse, qui ont été abordés dans le cadre de trois études scientifiques présentées dans les chapitres 2 à 4, respectivement

Dans le chapitre 2, nous présentons notre première étude qui a examiné les corrélats neuronaux de l'attention interne contrôlée chez les jeunes adultes avec et sans TDAH. Nous montrons que les adultes souffrant de TDAH présentent une activation aberrante dans le gyrus angulaire droit et dans les circuits de régulation des émotions pendant l'attention interne, ce qui valide le fait qu'il s'agit d'un sujet d'intérêt dans le contexte des difficultés attentionnelles. Dans notre deuxième étude du chapitre 3, nous passons de l'exploration des corrélats neuronaux à l'étude de la dynamique neuronale de l'attention automatique chez les adolescents neurotypiques. Nous évaluons différentes méthodologies de modélisation de la connectivité fonctionnelle et montrons que les méthodologies de variation temporelle peuvent être utilisées pour détecter des différences subtiles dans la dynamique neuronale en fonction des difficultés d'attention. Enfin, dans le chapitre 4, nous présentons notre dernière étude sur l'attention automatique chez les adolescents avec et sans TDAH. Dans cette étude, nous utilisons des approches dynamiques et multivariées pour caractériser de manière exhaustive les circuits neuronaux à grande échelle impliqués dans le TDAH.

Nos résultats s'alignent sur la littérature actuelle, montrant un rôle critique pour la connectivité fonctionnelle centrée sur le réseau de saillance dans la régulation de l'attention. Nos contributions peuvent être résumées en trois points. 1) Nous établissons que l'attention interne contrôlée (par rapport à l'attention externe) est perturbée chez les personnes atteintes de TDAH. 2) Nous utilisons une approche méthodologique de neuro-imagerie pour valider que les problèmes d'attention existent le long d'un continuum. 3) Étant donné l'incohérence de la littérature sur l'attention interne automatique dans le TDAH, nous soutenons qu'il est nécessaire de prendre en compte la variance individuelle lors de l'évaluation des relations entre le cerveau et le comportement. Sur le plan méthodologique, cela signifie utiliser des approches nuancées et variables dans le temps de la connectivité fonctionnelle du cerveau. Sur le plan clinique, cela signifie qu'il faut caractériser de manière exhaustive les individus à l'aide de mesures comportementales en évaluant la dysrégulation des émotions parallèlement à des mesures expérimentales et autodéclarées de l'inattention, de l'impulsivité et de l'hyperactivité. Globalement, cette thèse contribue à la compréhension scientifique des processus mentaux orientés vers l'intérieur chez les personnes souffrant de troubles de l'attention.

List of Acronyms

ADHD	Attention Deficit Hyperactivity Disorder
AI	Anterior insula
CEN/ECN	Central executive network / executive central network
CPT-3	Conners Continuous Performance Test-3
dACC	Dorsal anterior cingulate cortex
dlPFC	Dorso-lateral prefrontal cortex
DAN	Dorsal attention network
DMN	Default mode network
fMRI	Functional magnetic resonance imaging
FN	Functional network
FNC	Functional network connectivity
HF	Hippocampal formationn
lPFC	Lateral prefrontal cortex
mPFC	Medial prefrontal cortex
NAcc	Nucleus accumbens
PCC/PCu	Posterior parietal cortex/ precuneus
PLS-C	Partial least squares correlation
rs-fMRI	Resting state functional magnetic resonance imaging
SN	Salience network
TPJ	Temporal pareital junction
UPPS	Urgency-Premeditation-Perseverance-Sensation Seeking (UPPS) Impulsive Behavior Scale
VAN	Ventral attention network
vlPFC	Ventro-lateral prefrontal cortex
vmPFC	Ventro-medial prefrontal cortex
YSR	(Achenbach) Youth Self Report

As we take ... a general view of the wonderful stream of our consciousness, what strikes us first is this different pace of its parts. Like a bird's life, seems to be made of an alternation of flights and perchings ... The resting-places ... occupied by sensorial imaginations of some sort ...can be held before the mind for an indefinite time ... The places of flight ... obtain(ed) between the matters contemplated in the periods of comparative rest.

William James

Mind, 1884 & Principles of Psychology, 1890

Run your fingers through my soul. For once, just once, feel exactly what I feel, believe what I believe, perceive as I perceive, look, experience, examine, and for once; just once, understand.

Attributed to Oscar Wilde

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Chapter 1. Introduction

'Attention' is an umbrella term for describing numerous complex phenomena that are difficult to contort into a single coherent and exhaustive account. The objective of the present thesis was to investigate neural mechanisms of controlled and automatic attention processes that are oriented inwards (towards one's mental state) in individuals along the continuum of attention difficulties. This introduction is divided into five sections: the first section begins by outlining attention as a set of cognitive processes and mechanisms. We specifically focus on the distinction between controlled and automatic attentional processes, as well as between internally oriented and externally oriented attention. The second section introduces the continuum of attention difficulties and presents the neurodevelopmental disorder attention deficit hyperactivity disorder (ADHD) as occupying the extreme end of said continuum. This section then discusses the clinical and epidemiological underpinnings of ADHD. The third section discusses neuroimaging literature on the previous two sections, namely neuroscientific and psychological research related to attention difficulties during controlled and automatic attentional processes that are either internally or externally oriented. The fourth section presenting the aims and hypotheses of the three studies comprised in this thesis. The fifth and final section of this introduction summarizes each authors contribution to the studies included in this thesis.

1. Attention Processes

1.1. Definitions and scope

Cognitive neuroscience models attention as a collection of distinct psychological and neural mechanisms that process information and guide behavior in service of one's needs (Posner, 1980; Posner & Rothbart, 2007). Given the brain's limited information processing capacity (Lennie, 2003), humans struggle to attend to internal and external environments at the same time (Klinger, 1978; Uddin & Menon, 2010; Zabelina & Andrews-Hanna, 2016). This is further complicated by the fact that internally and externally oriented attention share common neural resources (Buckner et al., 2008; Verschooren, Liefooghe, et al., 2019; Verschooren, Schindler, et al., 2019; Zhou et al., 2022), despite having largely distinct neurophysiological mechanisms (Benedek et al., 2016; Dixon et al., 2014; Margulies et al., 2016). This section introduces psychological models of the interplay between internal and external attention and presents the key roles of bottom-up and top-down processes in attention. It then outlines the major neural mechanisms associated each attention orientation and brings attention to the imbalance in scientific literature, which has historically focused more on exploring externally oriented attention compared to internally oriented attention.

1.2. Attention Orientation

There are several types of attention and almost as many efforts to categorize and structure attention through models, theories, and taxonomies (Chun et al., 2011; Knudsen, 2007). To give a brief overview of its expansiveness, apart from its orientation, attention can manifest across single modalities, such as vision, or across multiple modalities, such as audio-visual experiences. It encompasses selective attention, where the focus hones in on specific information while filtering out distractions; sustained attention, which involves maintaining focus on a task for an extended duration; and divided attention, a scenario where cognitive resources are distributed across multiple stimuli at the same time. Moreover, attention can be overt, through conscious and deliberate shifts in focus that often involving eye movements, or covert, where mental focus shifts without accompanying eye movements. In regard to attention orientation, researchers hypothesize that the brain uses a dynamic, multilevel system to manage the constant interference and competition between internal and external attention (Chun et al., 2011; Narhi-Martinez et al., 2023). This system is believed to assign priority to stimuli generated both internally and externally by employing a system of weights and balances. As information moves from local to global levels, it competes at each stage with other information weighted by importance. Eventually information reaches a central processing stage, after which point the system decides what information will drive behavior (Narhi-Martinez et al., 2023). The (dys)regulation of this system and the dynamic interplay between internally and externally oriented attentional processes has consistently been implicated in various mental disorders (Mogg & Bradley, 2018; Williams et al., 1997).

Importantly, internally and externally oriented attention processes are subserved by the engagement and interaction of two critical cognitive processes: controlled, top-down attention and automatic, bottom-up attention (Carrasco, 2011; Chun et al., 2011; Corbetta & Shulman, 2002; Desimone & Duncan, 1995). The bottom-up system involves the involuntary reorientation of attention towards salient stimuli in the environment, prioritizing them over less relevant information. These stimuli can originate from either the external environment, for example when you hear the siren of an ambulance, or in one's internal environment, for example happy thoughts after hearing good news or nagging worries about an upcoming exam. In contrast, the process of top-down attention involves goal-directed mechanisms that assess whether to engage with incoming salient information. This determination hinges on an individual's motivation, goals, and the immediate situational demands. Consequently, top-down attention is not only essential for processes like sustained attention but also for higher-order cognitive functions like executive functioning and decision-making.

Externally oriented attention processes sensory and perceptual information stemming from outside the body. This information can be transmitted through specific sensory modalities, such as audition or vision, and may include information about different dimensions within that modality, such as frequency or spatial object features (for a review, see Chun et al., 2011). External attention, as compared to internal attention, is objectively easier to measure using experimental paradigms across different developmental and clinical populations. Research on external attention processes suggests a central role for at least two distinct neural networks: the dorsal attention network (DAN) and the ventral attention network (VAN) (Sridharan et al., 2007; Vossel et al., 2014). The DAN includes the intraparietal sulcus and the frontal eye fields and shows sustained activation when focusing attention on an object and is thought to be responsible for goal-directed, top-down processing of attention (Corbetta & Shulman, 2002). The VAN includes the temporoparietal junction (TPJ) and ventral frontal cortex, is dominant in the right hemisphere and is generally acts as a circuit-breaker when an unexpected event occurs, allowing one to shift attention from the current task (bottom-up processing).

As previously mentioned, neuroscientific research has disproportionately focused on characterizing external attention processing and its relationship to dysfunction (Mogg & Bradley, 2018; Van Bockstaele et al., 2014). As a result of this research bias, the role of internal attention in information processing and neuropsychiatric disorders has been largely understudied despite its enormous importance for daily functioning and well-being (Klinger, 1978; Zabelina & Andrews-Hanna, 2016). Intuitively, the capacity to, voluntarily or involuntarily, detach from external stimuli and attend to our internal world is fundamental to the human experience (Bulley et al., 2016; Suddendorf & Corballis, 2007; Waytz et al., 2015). Internally oriented attention allows us to partake in cognitive processes such as reflection, daydreaming (Benedek, 2018), imagination, planning (Spreng et al., 2010), creative thoughts

(Benedek, 2018; Ruby et al., 2013) as well as find meaning in our lived experiences (Waytz et al., 2015). Its momentous utility has become more of a topic of neuroscientific interest in recent years. The following section discusses two examples of internally oriented phenomena, namely, reflecting on and interpreting mental states and mind wandering. While innovative and insightful research on internally oriented phenomena such as thinking about the future (also known as mental time travel) and interoception (the perception of the body's internal state) have also been conducted over the last few decades, they are outside the scope of this thesis.

1.3. Controlled versus automatic attention

As previously mentioned, attention encompasses automatic and controlled attention processes and these processes have been disproportionately studied in external attention. The following section focuses on controlled and automatic attention processes within internally oriented attention. We first discuss prominent processes of controlled internal attention such as mentalization and their associated brain correlates, as identified through neuroimaging. We then focus on automatic internal attention and present the primary attention process: mind-wandering. We end this section by summarizing neural correlates of mind wandering.

1.3.1. Controlled, internally oriented attention

Controlled attention processes that are internally oriented typically involve interpreting and regulating one's mental state. Within the field of psychology, various theoretical frameworks have been developed to study these processes, with the most notable among them being mentalization and theory of mind. Theory of mind refers to the ability to understand and reflect on others' mental experiences through perspective- taking, reasoning, and interpreting affective cues (Premack & Woodruff, 1978). Mentalization, on the other hand, is the imaginative capacity to understand our own and others' mental states, include thoughts, feelings, beliefs, and intentions (Bateman & Fonagy, 2005). Although they come from distinct lines of scientific research, theory of mind and mentalization are related, metacognitive concepts that serve to help individuals make sense of the social world and their place in it. For the purposes of this thesis, we will employ the term "mentalizing" to refer to this overarching capacity and, given the focus on internally oriented processes, we will limit our scope to mentalizing about oneself (as opposed to others).

Mentalizing is deceptively simple concept; while our mental states are, in theory, always accessible to us, we often neglect them because we presume to already know who we are, how we feel and what we think (McLaren & Sharp, 2020). Consequently, the capacity to mentalize naturally varies between individuals (Sharp et al., 2006) and positively correlates with healthy social functioning (Slaughter et al., 2015). Mentalizing is strongly influenced by early life attachment and child-caregiver interactions (Fonagy et al., 2002; Bateman & Fonagy, 2016), which inform the ability to regulate emotions and develop adaptive attentional mechanisms. As put by Luyten and Fonagy, "*the capacity to reflect upon internal mental states represents a major leap in the individual's capacity to regulate his or her affect*" (Luyten & Fonagy, 2015). These capacities continue to grow as individuals are exposed to more social environments at school and, later, the workplace (Fonagy & Luyten, 2016). Difficulties with mentalizing can arise when parents and caretakers are consistently unable to accurately mentalize the child (Allen, 2018). This can lead to the child developing attachment trauma and decreased epistemic trust, meaning that they struggle to trust information coming from other or their own experience (Fonagy & Allison, 2014). Downstream consequences include the child struggling to self-regulate emotions and withdrawing from the mental world. In line with this, poor mentalizing skills have been identified in several psychiatric disorders, including ADHD, autism spectrum disorder, depression, and borderline personality disorder (Baron-

Cohen et al., 1997; Kerr et al., 2003; Sharp, 2008; Zobel et al., 2010; Moran et al., 2011; Sharp et al., 2011; Kronbichler et al., 2017).

1.3.1.1. Associated Neural Correlates

Researchers have used functional magnetic resonance imaging (fMRI) studies to identify distinct brain regions as well as functional networks (FNs) in the brain specialized for mentalizing. Various paradigms have been used that often require both mentalizing about oneself and others, including the false belief tasks (Mitchell, 2007; Tamnes et al., 2010), theory of mind cartoons, and self-referential knowledge tasks (Ochsner et al., 2005; Pfeifer et al., 2007). Convincing evidence for a mentalizing network in the brain comes from a recent meta-analysis that assessed functional connectivity patterns from different mentalizing tasks from 5,276 adults and 479 children (Fehlbaum et al., 2022). Fehlbaum and colleagues identified a mentalizing network in adults that comprised of the medial prefrontal cortex, middle/inferior frontal cortices, precuneus, TPJ and middle temporal gyri during mentalizing, which were functionally connected to the inferior/superior parietal lobule, thalamus, and striatum. This FN was relatively less well-defined in children, but common regions included the medial prefrontal cortex, precuneus and right TPJ. The authors argue that functional connectivity between these three regions form the foundation of the social brain, starting from childhood (Fehlbaum et al., 2022).

1.3.2. Automatic, internally oriented attention

Automatic attention, in the context of internally oriented attention, typically refer to the process of mind-wandering. During mind-wandering individuals detach from the attentional demands of their external environment and shift their attention towards task-unrelated and spontaneous thoughts (Smallwood & Schooler, 2006). Importantly, mind-wandering is distinguishable from rumination and intrusive thoughts, which are also internally oriented and task-unrelated, experiences seen in generalized anxiety disorder, major depressive disorder, and obsessive-compulsive disorder. The frequency of mind wandering is contingent upon factors such as the nature and cognitive demands of the current task; it is more common during repetitive and/or boring tasks that lack intrinsic motivation (Smallwood & Schooler, 2015). Experience-sampling studies estimate that humans spend roughly 50% of wakefulness time engaging in mind-wandering (Kane et al., 2007; Killingsworth & Gilbert, 2010; Klinger, 1978; Smallwood & Schooler, 2015). The tendency to mind wander is more pronounced in individuals who struggle with attentional focus, for example individuals with ADHD tend to experience mind wandering between 50–70% of wakefulness time (Bozhilova et al., 2020; Van den Driessche et al., 2017).

1.3.2.1. Associated Neural Correlates

Robust fMRI research associates mind-wandering with increased activation of the brain's default mode network (DMN). The DMN is a FN comprised of several intrinsically connected brain regions including the medial prefrontal cortex, the posterior cingulate cortex, and the medial temporal lobe (Andrews-Hanna et al., 2014; Andrews-Hanna, Reidler, Sepulcre, et al., 2010). The DMN was first believed to represent a baseline state of neural activity during periods of rest in which individuals were conscious and having thoughts unprovoked by external stimuli. While the conceptualization of the DMN continues to evolve, scientists now agree that this large-scale FN subserves several self-referential processes, such as reflecting on inner states, daydreaming as well as abstract, higher-level cognitive processing (Margulies et al., 2016). In their seminal paper, Margulies and colleagues provide an insightful framework for the association between structure and function in the DMN. They assessed large scale functional connectivity in humans and macaque monkeys to reveal a principal gradient that placed primary sensory and motor regions on one end and the DMN on the other. The authors argue that the DMN's hierarchical position in this principal gradient allows it to process trans-modal, cognitive information unrelated to immediate sensory inputs (Margulies et al., 2016).

In this section, we discussed how the phenomena of internal and external attention are processed in the brain. We summarized scientific literature on controlled and automatic attention processes, with a focus on the comparatively understudied processes of internal attention. This section ended by presenting major neural correlates of attention processes discovered through neuroimaging. The next section, Section 2, will explore what happens when these processes are disrupted, typically resulting in heightened attention problems. In accordance with this, Section 2 will comprehensively introduce the spectrum of attentional difficulties, which includes clinical disorders of attention.

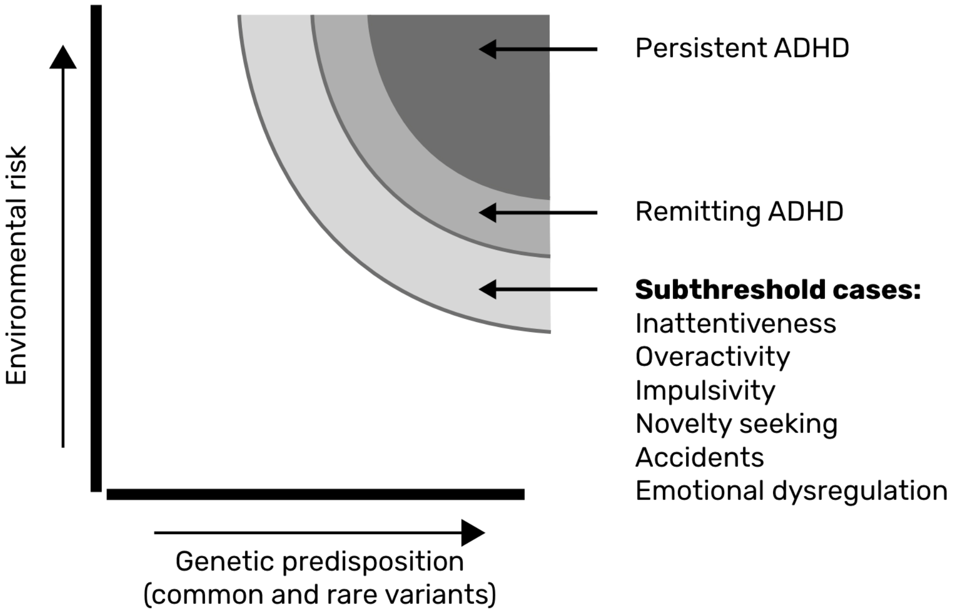
2. Attention: from processes to difficulties

This section focuses on prevalent difficulties seen in the attention processes previously described in Section 1. It begins by describing the continuum model of attentional difficulties and then positions ADHD as lying at the extreme end of this continuum. We briefly describe the history of ADHD, its associated functional impairments and burden on the individual and society. We then shift focus to the neural underpinnings of attention disorders. We present major findings from fMRI research, which has been widely employed to probe the neural mechanisms of attention processes and their dysfunction. Section 2 ends with a methodological section, which gives concise overview of fMRI principles before presenting a general theoretical framework that bridges together neural activity and general psychopathology known as the Triple Network Model of Psychopathology.

2.1. The continuum of attention difficulties

The capacity to pay attention varies continuously in the general population and this capacity is modulated by various biopsychosocial factors, including genetics and environmental influences ((Rohde et al., 2019); Fig. 1). This vast distribution of inter-individual differences in various attentional processes (including controlled and automatic attention processes) has led researchers to conceptualize attention as a continuum. Within this continuum, ADHD, a putatively neurodevelopmental disorder that typically emerges in childhood and is defined by age-inappropriate levels of inattention, hyperactivity, and impulsivity, represents an extreme end (Fair et al., 2012). This perspective posits that the same underlying neurobiological and cognitive mechanisms that contribute to variability in attentional abilities in the general population are also responsible for the attentional deficits observed in ADHD (Sonuga-Barke & Castellanos, 2007). In line with this, twin and family studies estimate the heritability of ADHD to be 74% (for a review see (Larsson et al., 2012). Studies on identical twins also demonstrate that when one twin has ADHD, the risk of the other twin having it is roughly 50%, suggesting a role of environmental factors. Meta-analyses have confirmed several environmental factors associated with attentional deficits, such as preterm birth, exposure to lead and psychosocial stressors such as family dysfunction and low social class (Bhutta et al., 2002; Goodlad et al., 2013).

FIGURE 1. Model of the etiology of ADHD showing the influence of the interaction of genetic predisposition and environmental risk on ADHD symptomology. Figure taken from Rohde, Buitelaar, Gerlach & Faraone, 2019, The World Federation of ADHD.



2.2. A psychiatric perspective on attention difficulties: ADHD

2.2.1. Examining the history of ADHD

The earliest known mention of an ADHD-like condition in scientific literature was in a German medical textbook by the physician Melchior Adam Weikart in the 1770s. In a chapter entitled “Mangel der Aufmerksamkeit” or Attention Deficit, Weikard described a mental disorder similar to the current diagnostic and statistical manual of mental disorders (DSM-V) (American

Psychiatric Association, 2013) characterization of the predominantly inattentive presentation of ADHD. Weikart wrote that mainly children suffered from a disorder of inattention, high distractibility and overly impulsive behavior and hypothesized this disorder was likely caused by a lack of discipline in early life and a dysregulated "sensibility of the nerves". Later in the 18th century, a Scottish physician called Alexander Crichton put forth a dimensional model of attention (Crichton, 1798). Crichton had noted attention problems in otherwise healthy individuals and argued that attention varied within a range both across and sometimes within individuals. Crichton described a medical condition in which attention problems co-occurred with increased restlessness and emotional reactivity, and noted that this condition was associated with other mental and physical disorders (Barkley, 2008). Like Weikard, Crichton reported that problems of heightened inattention and restlessness diminished with age. These early characterizations have been crucial in delineating the major pillars of ADHD, namely inattention, hyperactivity, and emotional dysregulation. These major components of ADHD have since been explored and expanded upon, resulting in a rich scientific literature on this clinical disorder.

2.2.2. Understanding functional impairments associated with ADHD

Over the past few decades, the work of clinicians and researchers like Russel A. Barkley has deepened understanding of ADHD and how it affects daily functioning. Barkley and colleagues argue ADHD is fundamentally a disorder of delayed and dysfunctional executive functioning. Executive functions are a set of higher-order mental processes that include self-awareness, inhibition, nonverbal and verbal working memory, emotional self-regulation, self-motivation, and planning/problem-solving.

In his work Barkley argues that 1) self-regulation is the self-direction of actions to modify behavior to ultimately diminish suffering from potential future consequences and 2) executive functions are those self-directed actions (Barkley, 1997, 2012, 2015, 2021, 2022). Barkley further characterizes ADHD as a disorder of mentally representing and preparing for the future by saying that future imagination requires having goals and plans (executive functioning) which guide behavior in the present (self-regulation). As individuals mature, they develop the self-control, deferred gratification, and goal-directed actions necessary to move towards an imagined future. In other words, a fundamental human experience is forgoing immediate desires for the sake of long-term goals and the ability to enact such goal-directed behavior is vital for overall health, social well-being and economic stability (De Ridder et al., 2012; Moffitt et al., 2011). In ADHD, the capacity to self-regulate is impaired which consequently places adaptive functioning in social, personal and economic domains at risk (Barkley, 2012, 2022).

Over time, the validity of ADHD as a disorder has been disputed (Honkasilta & Koutsoklenis, 2022; Quinn & Lynch, 2016; Tait, 2005). In response to this line of questioning, it is helpful refer to Jerome Wakefield's comprehensive definition of what constitutes a mental disorder: dysfunction in one or more evolved psychological abilities that are universal to the human species that lead to harm to the individual, including increased mortality, morbidity, and impairment (Faucher & Forest, 2021; Wakefield, 1997, 2006). This definition, and the description of ADHD in the DSM-V, is congruent with it being a disorder. Clinically-speaking, ADHD is defined as a putatively neurodevelopmental disorder with delays and impairments in two distinct, but related, dimensions of neuropsychological development: inattention and hyperactive-impulsive behavior (American Psychiatric Association & American Psychiatric Association, 2013; Table 1). The DSM-V proposes three presentations of ADHD: predominantly inattentive (the patient meets inattentive criterion, but not hyperactive/impulse criterion), predominantly hyperactive/impulsive (patient meets hyperactive/impulse criterion, but not inattentive criterion) and combined (patient meets both criteria). Despite the DSM-V's definition of ADHD as a binary condition, empirical research supports a continuum approach to attention (Levy et al., 1997; Lubke et al., 2009; McLennan, 2016). Through this lens, ADHD represents a developmental delay along a spectrum of the naturally varying traits in the population.

TABLE 1. DSM-V Criteria for a clinical diagnosis of ADHD in children. Symptoms need to have persisted over the past ≥ 6 months in ≥ 2 settings and impacted functioning. Symptoms must be present before age 12 and not better accounted for by a different psychiatric disorder. Patients aged < 17 years, need ≥ 6 symptoms for diagnosis; patients aged ≥ 17 years need ≥ 5 symptoms.

Diagnosis Criteria	Symptoms
Inattentive	• Displays poor listening skills
	• Loses and/or misplaces items needed to complete activities
	• Sidetracked by external or unimportant stimuli
	• Forgets daily activities
	• Diminished attention span
	• Lacks ability to complete assignments or to follow instructions
	• Avoids or is disinclined to begin homework or activities requiring concentration
	• Fails to focus on details and/or makes thoughtless mistakes in schoolwork or assignments
Hyperactive	• Squirms when seated or fidgets with feet/hands
	• Marked restlessness that is difficult to control
	• Appears to be driven by “a motor” or is often “on the go”
	• Lacks ability to play and engage in leisure activities in a quiet manner
	• Incapable of staying seated in class
	• Overly talkative
Impulsive	• Difficulty waiting turn
	• Interrupts or intrudes into conversations and activities of others
	• Impulsively blurts out answers before questions completed

2.2.3. Epidemiology and comorbidities of ADHD

While ADHD typically emerges in childhood, it often continues into adulthood: an estimated 65% of patients continue to experience symptoms as adults (Faraone et al., 2006) and approximately 4.4% of adults live with ADHD (Kessler et al., 2005). Research shows that ADHD can negatively impact quality of life throughout the lifespan (Manor et al., 2011): during childhood, ADHD is associated with getting bullied and rejected by peers (Holmberg & Hjern, 2008), and having fewer close friendships (Bagwell et al., 2001). These impairments are more likely to occur in girls than boys, and especially so for girls with a predominantly inattentive presentation of ADHD (Elkins et al., 2011). Children with ADHD are also more likely to struggle in academics compared to their typically developing peers and are less likely to graduate from high school (Birchwood & Daley, 2012; Galéra et al., 2009). They also tend to have decreased self-esteem and increased suicidal thoughts compared to typically developing peers (Hinshaw et al., 2012; Klassen et al., 2004; Manor et al., 2010). As adults, compared to typically developing peers, individuals with ADHD experience increased difficulty in romantic relationships (Biederman & Faraone, 2006; Moyá et al., 2014) and are less likely to sustain stable employment (Adamou et al., 2013; Barkley et al., 2006; Biederman & Faraone, 2006). Research shows mixed results on the meta-cognition of the impact ADHD imparts on peoples' lives. One study found that adults believed living with ADHD during childhood was the driving force behind their difficulties in school and significantly impacted the trajectory of their academic and professional lives (Brod et al., 2012) while another study revealed adults with ADHD tend to underestimate the extent of their ADHD-related impairments (Manor et al., 2012).

ADHD is also an exceptionally co-morbid disorder. Studies show that between 40-80% of individuals with ADHD have at least one other neuropsychiatric condition (Reale et al., 2017).

Neuropsychiatric comorbidities include autism spectrum disorder (65–80%), oppositional defiant disorder (50-60%), conduct disorders (40-50%), depression and anxiety (16–26%), bipolar disorders (11–75%) and substance abuse disorder (9-33%) (Gillberg et al., 2004; Jensen & Steinhausen, 2015; Jensen et al., 1997, 2001; Kessler et al., 2006; Luo & Levin, 2017; Martinez-Raga et al., 2013; Reimherr et al., 2017; Rommelse et al., 2010; Tannock, 2000). In line with this, individuals with ADHD are more likely to seek medical help with one study showing they are 10 times more likely to go to the doctor (Jacob et al., 2007; McGough et al., 2005) and 3 times more likely to go to the emergency room and/or be hospitalized (Kirino et al., 2015). A recent systematic review on the economic burden of ADHD in Europe and the United States of America estimated that the total costs associated with childhood ADHD ranged, per person, from 831.38 to 20,538 US dollars. National estimates ranged from 356 million to 20.27 billion US dollars in terms of direct costs (such as healthcare), indirect costs (such as productivity) as well as education and justice system costs (Chhibber et al., 2021).

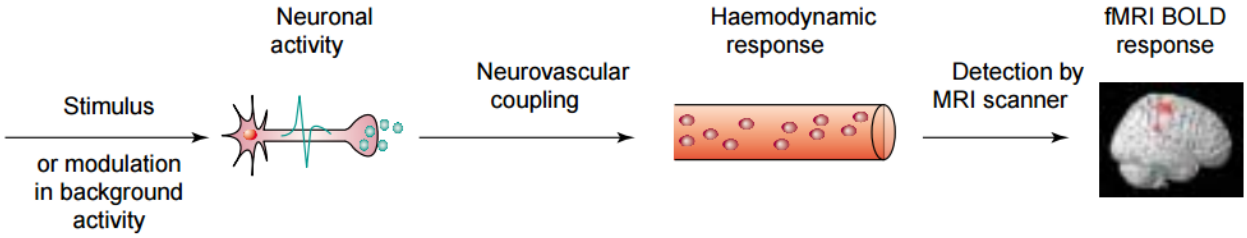
2.3. Methodologies for examining neurobiological bases of attention problems & ADHD

Despite the rich and ever-growing literature on ADHD, its heterogeneous nature consistently renders its neurobiology difficult to characterize. Contributions from subfields within neuroscience and psychology have helped develop understanding of ADHD's neural mechanisms, from fundamental to cognitive neuroscience. Research on the neurobiology and neurochemistry of ADHD has been especially helpful for situating the disorder within major brain regions that are often implicated in cognition and attention. While these fields are important to mention, in terms of methodology, the studies in this thesis focus on fMRI which has been a key tool for understanding how measurable neuronal activity in the human brain gives rise to the human mind. The following sections delve into the specifics of fMRI research and how it has been used to study attention difficulties.

2.3.1. Principles of Functional Magnetic Resonance Imaging

Researchers commonly use fMRI to characterize neural activity and identify neural correlates of cognitive functions. fMRI measures changes in the blood oxygen level-dependent (BOLD) signal induced by neural activity (Ogawa et al., 1990; Fig. 2). More precisely, as neural activity increases, so does local blood flow through a process known as neurovascular coupling. Blood flow encompasses both oxygenated and deoxygenated blood, which have different magnetic properties and the BOLD signal reflects changes in deoxyhemoglobin as a function of neural activity. These changes in the BOLD signal over time are modeled by the hemodynamic response function (HRF), a model that links neural activity to stimulus presentation (Hirano et al., 2011; Yeşilyurt et al., 2008).

FIGURE 2. A demonstration of the major psychological stages involved in detecting a BOLD response evoked by a stimulus, showing how fMRI allows for an indirect measure of brain activity. Figure taken from (Arthurs & Boniface, 2002).



There are two commonly used types of fMRI paradigms: the first uses an in-scanner cognitive task to evoke changes in neural activity (known as a task- or stimulus-driven paradigm) and the second assesses neural activity in the absence of cognitive task (known as a resting state fMRI paradigm or rs-fMRI). As its name suggests, task-based paradigms model changes in the BOLD signal in response to specific stimuli to infer which specific brain region or group of regions that task activates. These tasks typically require controlled, goal-oriented attention. Rs-fMRI paradigms measure spontaneous fluctuations in the BOLD signal when participants are not engaged in a specific, goal-oriented task i.e., when they are engaging in the automatic attention process of mind-wandering. Rs-fMRI is more recent than task-based fMRI and it has been instrumental in revealing insights into the brain's functional architecture. Perhaps the most important finding of rs-fMRI is the finding that the brain has intrinsic FNs comprised of functionally connected and spatially distinct brain regions (Fox & Raichle, 2007). Research shows that these FNs are remarkably preserved across different mental states (Jafri et al., 2008; Smith et al., 2009) even though their functional connectivity (FC) or its network analog functional network connectivity (FNC) varies as a function of state-dependent temporal and spatial modulation (Arbabshirani et al., 2013; Geerligs et al., 2015; Jafri et al., 2008). Rs-fMRI show that FNC between intrinsic networks use large amounts of the brain's metabolic budget during rest (Bressler & Menon, 2010; Raichle, 2010), sleep and sedation (Greicius et al., 2008; Horovitz et al., 2009) and cognitive tasks (Barrett & Satpute, 2013). Before getting into the specifics of neuroscientific literature on task- and resting state-fMRI in ADHD in the next section, we end Section 2 by presenting a critical fMRI-based model for understanding how neural activity relates to attention and psychopathology.

2.3.2. Triple Network Model of Psychopathology

As previously mentioned, fMRI has historically been used to identify individual neural correlates involved in cognitive tasks. More recently, fMRI research has aimed to identify neural networks, which are made up of multiple brain regions that appear functionally connected in that they increase or decrease activity in unison during cognitive tasks. The identification of activity patterns of neural correlates *and* neural networks are both critical to understanding how our brains intake and process information, as well as how we enact behavior. In this sub-section, we present the Triple Network Model of Psychopathology (Menon, 2011), an influential theoretical framework for understanding psychopathology and higher-order cognitive function through neural network activity in the brain. This theory argues that given the activity between default mode network (DMN), central executive network (CEN) and the salience network (SN) (Fig. 3) proportionately increases and decreases with cognitive demands in various tasks, this suggests that dynamic interactions between the DMN, CEN and SN substantially regulate attentional and cognitive control (Kelly et al., 2008).

We present this framework before delving into neuroimaging results on ADHD (which will follow in Section 3) for three reasons. First, this overarching theory helps to bridge findings from studies on the neural correlates and FC in ADHD populations. Second, the networks in this framework, namely the DMN, CEN and SN, are of particular relevance when it comes to attention disorders such as ADHD, specifically its predominantly inattentive presentation (Castellanos & Aoki, 2016). This sub-section will explain how these networks are vital for adaptive cognitive control and executive functioning. These psychological processes are impaired in individuals with attention difficulties and the majority of fMRI studies on ADHD, especially those on internally oriented attention, shows aberrant activation and functional connectivity in the major hubs of these three neural networks. Third, we previously discussed ADHD's high rate of comorbidity with other neuropsychiatric disorders. The Triple Network Model of Psychopathology is general framework that is heavily applicable, but not limited, to ADHD. Aberrant connectivity patterns between the neural networks of the Triple Network Model of Psychopathology have been robustly associated with various other psychiatric conditions that ADHD is highly co-morbid with, such as mood disorders (for a review see (Sandstrom et al., 2021)). We will now present this model in detail and then, in Section 3, we will present fMRI findings on internal and external attention processes in ADHD, many of which relate back to the networks in this framework.

The most well-researched neural network in attention disorders and in the triple network model is the DMN. Initially, the DMN was conceptualized as comprising the medial prefrontal cortex, the posterior cingulate cortex, the medial temporal lobe, and the angular gyrus (Gusnard & Raichle, 2001). These regions were first identified using independent components analysis and seed-based connectivity of rs-fMRI data. They were confirmed with multiple approaches including coactivation analysis and DTI studies showing a strong link between the medial PFC and posterior-medial nodes of the network (Greicius et al., 2008; Menon & D'Esposito, 2022). Presently, the DMN is understood to consist of a core network and at least two subsystems, each contributing differently to various cognitive functions (Andrews-Hanna, Reidler, Huang, et al., 2010; Corbetta et al., 2008). In their 2010 study, Andrews-Hanna and colleagues used hierarchical clustering analysis to reveal a core DMN network, comprised of the posterior cingulate cortex and the medial prefrontal cortex (referred to as DMN_{core}), a subnetwork in the medial temporal lobe (DMN_{MTL}) consisting of the parahippocampus, hippocampus, retrosplenial cortex, posterior inferior parietal lobe and ventromedial prefrontal cortex and a dorsal medial subnetwork (DMN_{DM}) comprising the dorsomedial prefrontal cortex, TPJ and temporal poles. A 2011 large-scale brain parcellation study on resting state fMRI data revealed a similar division of the DMN (Yeo et al., 2011) but with certain key differences; Yeo and colleagues found the vmPFC was better classified in the limbic network rather than the DMN_{MTL} and that the DMN_{core} included the angular gyrus and right anterior temporal lobe. It is generally understood that these two subnetworks of the DMN are strongly connected to the $DMN_{core,}$ allowing for information transfer within the FN (Corbetta et al., 2008).

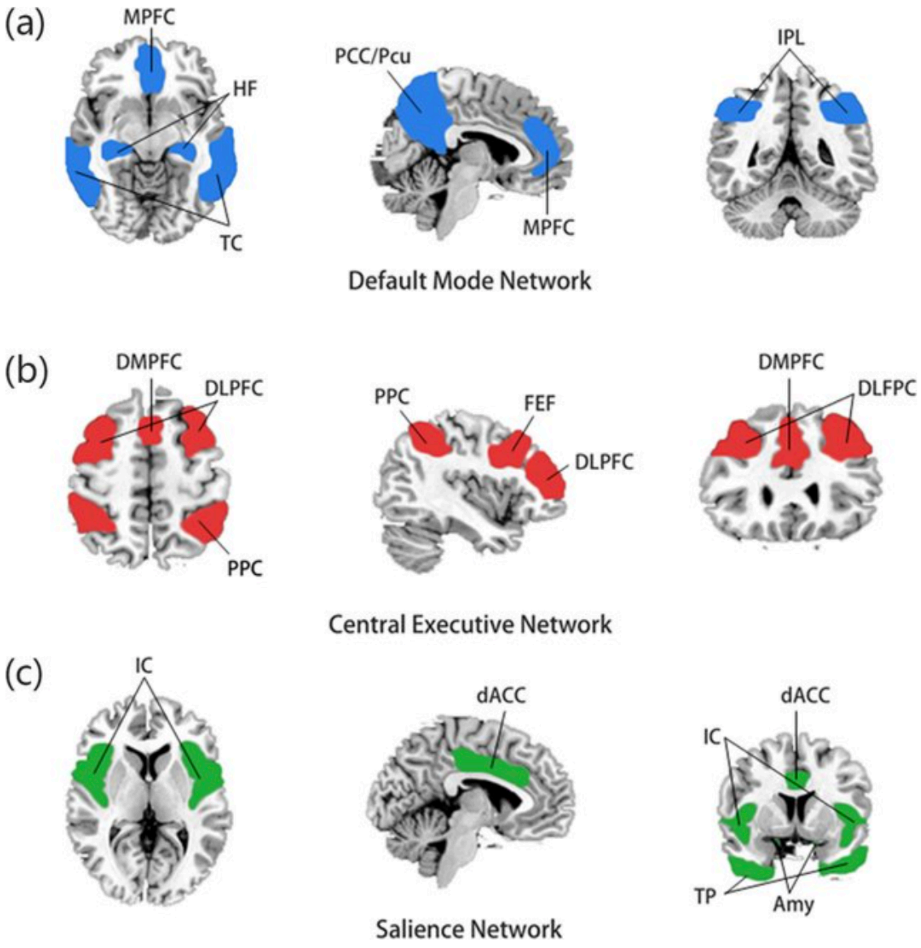


FIGURE 3. Components of the triple network model. (A) The default mode network (DMN) is mainly composed of the medial prefrontal cortex (mPFC) and posterior cingulate cortex/precuneus (PCC/PCu), and the temporal cortex (TC), hippocampus formation (HF) and inferior parietal lobule (IPL) are also closely related to this network. (B) The central executive network (CEN) is mainly composed of the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC), dorsolateral prefrontal cortex (DMPFC) and frontal eye field (FEF). (C) The salience network (SN) is composed of the insular cortex (IC), dorsal anterior cingulate cortex (dACC), temporal pole (TP) and amygdala (Amy). Figure taken from (Dai et al., 2019).

As previously mentioned, the DMN is robustly involved in internally directed cognitive tasks such as mind-wandering, autobiographical memory retrieval, imagining the present and the future, spatial planning and navigation and self-reflection and daydreaming. The DMN_{CORE} contributes to internally oriented cognition (Corbetta et al., 2008), the DMN_{MTL} is implicated in memory and constructive mental simulations (Andrews-Hanna et al., 2014; Buckner et al., 2008; Buckner & Carroll, 2007) and the DMN_{DM} subnetwork is linked to a wide range of functions, including mentalizing, conceptual processing, and emotional processing (Andrews-Hanna et al., 2014).

The remaining networks in the triple network model are the CEN and SN. The CEN (also referred to as the fronto-parietal network) is comprised of the dorsolateral and dorsomedial PFC, the supramarginal gyrus, posterior parietal cortex and subcortical regions including the dorsal caudate and anterior thalamus. The CEN is vital for externally directed cognitive control such as inhibition, decision-making, goal-directed behavior, and maintaining and manipulating information in working memory (Menon, 2011). Given its importance in top-down control, the CEN is also critical for emotion-regulation. Finally, the SN is comprised of nodes in the anterior insula, the fronto-insular cortex, and anterior cingulate cortex, and subcortical nodes in the amygdala, substantia nigra, ventral tegmental area, dorsomedial thalamus, hypothalamus, and periaqueductal gray (Seeley et al., 2007). The SN integrates and interprets salient external stimuli and interoceptive signals, and adjusts attention based on their relevance (Corbetta et al., 2008). It follows that the SN is critical for bottom-up, automatic attention processes described in Section 1. However, research indicates that this network is involved in a host of functions in addition to bottom-up attention allocation: nodes within the SN are engaged during various psychological states, including during emotion processing and empathy (Decety & Jackson, 2004; Fan et al., 2011) as well as language and executive function tasks (Nelson et al., 2010). As mentioned earlier in Section 2, these psychological capacities are often impaired in individuals with attention difficulties.

Effective attentional control requires dynamic interactions between the DMN, CEN and SN (Sonuga-Barke & Castellanos, 2007; Weissman et al., 2006). The triple network model postulates that the SN is vital for modulating the switching and/or reorienting of attention between internal and external cognitive processes subserved by the CEN and DMN (Corbetta et al., 2008; Uddin & Menon, 2010). In attentional disorders such as ADHD, it follows that aberrant SN-centered functional connectivity could lead to dysregulation of the DMN resulting in residual DMN activity during attention-demanding tasks which in turn has been associated with poorer performance (Fassbender et al., 2009; Weissman et al., 2006). In line with this, research using causal modeling analyses (such as Granger causality) within tasks (Chand & Dhamala, 2016) and when switching between externally-oriented tasks (Sidlauskaite et al., 2014) increasingly supports a causal role for the SN (Goulden et al., 2014; Sidlauskaite et al., 2014; Uddin, 2015). Most recently, Menon and colleagues conducted a feedforward optogenetic stimulation study that also supports the causal influence of the SN on the DMN and CEN; the researchers showed that optogenetic stimulation of neurons in the anterior insula suppressed activity of the DMN and decoupled functional connectivity between the SN and DMN (Menon et al., 2023).

3. Neuroimaging the continuum of attention difficulties

This section is dedicated to presenting major findings from functional neuroimaging literature investigating the neural underpinnings of the internal and external attentional processes (as presented in Section 1) across the continuum of attentional difficulties and disorders (as presented in Section 2). We begin by delving into fMRI literature on attention problems and ADHD from task-based and resting-state fMRI studies. We then discuss seminal methodologies used to analyze rs-fMRI, namely static and dynamic FNC analysis. This section concludes by summarizing the major neuroimaging findings in attention problems and ADHD, with a focus on the lack of consistency in rs-fMRI findings.

3.1. fMRI studies on controlled attention in ADHD

3.1.1. Internally oriented controlled attention

In these sub-sections, we focus on specific findings from fMRI studies on controlled and automatic attention in ADHD. Given the bias in cognitive research towards external attention (Driver, 2001), studies on internally oriented, controlled attention processes in ADHD are scarce. Behavioral studies on controlled, internally oriented attention suggest that children with ADHD have decreased theory of mind compared to controls (Mary et al., 2016) and that theory of mind capacities in children with ADHD are worse than in controls but better than in children with autism spectrum disorder (Demurie et al., 2011). Similarly, the first study to assess brain activations and FC associated with theory of mind in ADHD assessed adults with 1) ADHD, 2) autism spectrum disorder, 3) ADHD and autism spectrum disorder and 4) typically developing controls (Ilzarbe et al., 2020). The authors found that controls had theory of mind -related increases in activation in the right temporoparietal cortex, a key mentalizing region, but none of the three clinical groups did. Moreover, both the ADHD and the ADHD + autism spectrum disorder group had diminished connectivity between the medial prefrontal and left temporoparietal cortices compared to TD controls during theory of mind. While these results suggest ADHD populations may have specific pattern of neural activity that underlies their behavioral difficulties in internally oriented controlled attention processes, there is a clear need for more research and reproduced results when it comes to the neural correlates of controlled, internal attention in ADHD.

3.1.2. Externally oriented controlled attention

Most task-based fMRI studies on attention in ADHD focus on externally oriented attention using inhibitory control and working memory paradigms. While these studies have yet to produce reliably convergent results (Cortese et al., 2021; Cortese & Coghill, 2018; Samea et al., 2019), certain key differences between individuals with ADHD and typically developing controls have been identified. Largely in line with the Default Mode Interference Hypothesis of ADHD, which states that the DMN is not sufficiently inhibited during cognitive tasks in ADHD and that leads to poorer performance (Sonuga-Barke et al., 2008; Sonuga-Barke & Castellanos, 2007), meta-analyses show hypoactivation in the dorsolateral prefrontal cortex, insula and putamen during attention tasks (Hart et al., 2013) and inhibition tasks (Norman et al., 2016) in patients with ADHD relative to controls. ADHD population also tend to have lower activation of the CEN, SN, and fronto-striatal networks and higher activation of the DMN than controls (Cortese et al., 2012). One study assessing FNC between the DMN, CEN and SN during a Go/No-Go paradigm found that effective connectivity between hubs of the SN and CEN correlated with No-Go accuracy and inattention symptoms in children with ADHD (Cai et al., 2019). The authors argued that task-evoked connectivity between the SN and CEN was sufficiently different enough in children with ADHD compared to controls that it could potentially be used as a biological marker of ADHD.

3.2. fMRI studies on automatic internal attention in ADHD

The internally oriented, automatic attention process of mind-wandering has been well studied in individuals with attention problems and ADHD, with varying results. It is important to note that individuals with ADHD tend to mind wander more than those without (Franklin et al., 2017), is unclear whether mind wandering is associated with a specific presentation of ADHD. Studies have linked it with both the predominantly inattentive presentation of ADHD (Jonkman et al., 2017) as well as with all ADHD symptom domains (Arabacı & Parris, 2018). In terms of fMRI research, studies have looked generally focused combined subtypes when assessing how large-scale brain dynamics subserving mind-wandering.

Resting state studies consistently show altered FNC between nodes of major neural networks such as the DMN, CEN and SN in ADHD populations compared to controls. Most of these studies assessed time averaged FNC over the duration of the resting state scan and show lower FC within nodes of the DMN, both in children (Sun et al., 2012) and adults with ADHD as compared to controls (Uddin et al., 2008; Wang et al., 2013). These studies strongly suggest that the intrinsic architecture of the DMN is less efficient in ADHD compared to typically developing individuals.

Results from rs-fMRI also supports Barkley's previously mentioned theory of ADHD as a disorder of delayed and dysfunctional executive functioning. In a recent longitudinal resting state study on children between 9-14 years of age (ADHD sample *N*=91, controls *N*=84), researchers scanned children over three timepoints (Soman et al., 2023). They replicated results (see Christakou et al., 2011) showing FNC between major neurocognitive networks, namely the DMN, CEN SN, decreases over time in typically developing children. Soman and colleagues showed that children with ADHD had hypoconnectivity between the DMN, CEN and SN in late childhood but FNC normalized to the level of controls by adolescence, implying a maturational delay in ADHD. Another influential rs-fMRI study assessed time-averaged FNC across the seven Yeo-Krienen networks (Yeo et al., 2011) using 907 seeds in 276 children with ADHD and 481 controls (Sripada et al., 2014). The authors' main findings in relation to the ADHD group compared to controls were 1) diminished within-DMN FC, 2) diminished anti-correlation between the DMN and SN, and 3) lower FC between DMN and SN, CEN, and visual networks. In line with this, individuals with ADHD show diminished SN and CEN connectivity to the putamen, a well-connected striatal structure involved in motor function (Cai et al., 2014a; Di Martino et al., 2008), language processing (Booth et al., 2007) and working memory (Chang et al., 2007). A recent meta-analysis on rs-fMRI in ADHD focusing on the DMN, CEN, and affective network connectivity examined results from 21 resting state fMRI studies with a total of 700 ADHD cases and 580 controls (Gao et al., 2019). Gao and colleagues found that individuals with ADHD show reduced connectivity between the DMN and CEN compared to controls (Gao et al., 2019; Sutcubasi et al., 2020).

3.2.1. Time-Varying Functional Connectivity

FNC in the brain a multiscale, dynamic system and, in recent years, research methods have been developed to model the intrinsic fluctuations of FNC. These changes can be related to changes in behavior (Kucyi et al., 2013; Sadaghiani et al., 2015; Thomason et al., 2011) and symptoms of psychiatric disorders (Damaraju et al., 2014; Leonardi & Van De Ville, 2015; Sakoğlu et al., 2010). Regarding attention problems, dynamic FNC studies suggests that the associated cognitive deficits seen in individuals with ADHD are not only linked to the strength of the FNC between networks, but on how those connections vary over time. The first dynamic FNC resting state study on ADHD used permutation analysis in two cohorts to show children with ADHD moved between significantly more dynamic states, in a pattern that was more volatile and less persistent than typically developing children did (Cai et al., 2018a). In terms of dynamic brain connectivity, children with ADHD showed diminished SN-centered FNC with the DMN and CEN and this connectivity correlated strongly with symptoms of inattention across all participants. Since then, a growing literature has characterized the alterations in dynamic FNC between the DMN, CEN and SN in ADHD and its associations with symptoms of inattention (Abbas et al., 2019; De Lacy & Calhoun, 2019; Rolls et al., 2021; Shappell et al., 2021).

Interestingly, a central role for the SN has also been implicated in ADHD studies looking at the effects of methylphenidate, a dopamine reuptake-inhibitor widely used in ADHD treatment (McLennan, 2016). A resting state fMRI study in typically developing adults that also used positron emission tomography (PET) to assess dopamine synthesis capacity and dopamine release capacity found associations between the SN and the mesolimbic dopamine system. More specifically, researchers found that dopamine synthesis capacity was associated with greater SN connectivity while dopamine release capacity was associated with weaker SN connectivity (McCutcheon et al., 2019). A recent dynamic rs-fMRI study found that when children with ADHD took methylphenidate (as compared to a placebo), FNC between the SN-DMN and SN-CEN was remediated to the point that they were no longer distinguishable from controls (Mizuno et al., 2023). The authors argue that these observations suggest that amplification of dopamine signaling is a likely mechanism by which methylphenidate remediates aberrancies in SN-centered dynamics of cognitive control circuits in childhood ADHD.

3.3. Inconsistent results

It is crucial to stress the general lack of convergence in large-scale FNC in resting state studies on ADHD (Cortese et al., 2021). Cortese and colleagues conducted a large meta-analysis (1000+ ADHD patients and 800+ controls) on whole brain rs-fMRI and found no convergence of connectivity patterns in ADHD compared to controls. It is likely that differences in the rigor of quantitative analyses, and differences in protocols and data collection contribute to this. Further, the researchers suggested that given the heterogeneity of ADHD's phenotypes, there is also likely heterogeneity in the dysregulation and dysconnectivity patterns in the brain. In other words, rs-fMRI studies do not support the hypothesis of a single neurocognitive deficit in ADHD. Instead, it appears that multiple brain networks are likely involved, providing support of a neurobiological basis for the heterogeneity observed in ADHD presentation (Saad et al., 2020). In line with this, Cortese and colleagues also posited that ADHD-associated dysconnectivity could be broadly distributed across the whole brain. In this regard, individuals with ADHD may have many small alterations in functional connectivity in various FNs which, when taken together, vary with inattention and/or hyperactivity. This meta-analysis highlights the need for hypothesis driven research in ADHD, specifically within rs-fMRI and the importance of comprehensively assessing brain-behavior relationships.

4. Aims & hypotheses

Scientists have historically considered attention to be an externally oriented phenomenon. Accordingly, heightened attention problems such as those seen in ADHD have also been studied in relation to external attention. To date, it has been difficult to synthesize the various and, at times, contradictory findings on neural activations and dynamics associated with ADHD into a clear narrative. However, it is becoming increasingly clear that when we closely examine the phenological experience of attention in human beings, we have reason to believe that our default state of attending is oriented inwards, towards our thoughts, feelings, and beliefs, rather than outwards towards our physical environment. As humans we spend significant amounts our waking hours engaging in internally oriented attention processes (Kane et al., 2007; Killingsworth & Gilbert, 2010; Klinger, 1978; Smallwood & Schooler, 2015) and this tendency is even more pronounced if we struggle with attention problems (Bozhilova et al., 2020; Van den Driessche et al., 2017). It therefore appears not only logical but necessary to comprehensively assess neural mechanisms of internally oriented attention, which has yet to be done. The previous sections of this introduction have highlighted major gaps in attention literature, specifically a lack of research on mechanisms of controlled and automatic processes in internally oriented attention and how they relate to ADHD symptomology. To address this gap, this present thesis submits three fMRI studies on internally oriented attention in individuals across the continuum of attention difficulties. These studies and their primary research questions are as follows:

4.1. Neural Basis of Internal Attention in Adults with Pure and Comorbid ADHD

In this study, we contrasted internal and external controlled attention to map the neural correlates of internal attention in young adults and assess if and how neural activity differed between individuals with and without ADHD. As previously shown, individuals with ADHD show impairment in many aspects of internal attention yet fMRI literature has focused almost exclusively on characterizing externally oriented attention in ADHD. This study used a word-processing paradigm to assess neural responses to internally oriented attention in the form of self-mentalization cues in young adults with ADHD and in typically developing controls. We hypothesized that 1) individuals with ADHD show altered patterns of brain activity in regions associated with internally oriented attention when reflecting on their emotional state from controls and 2) this pattern of activity would relate to behavioral measures of ADHD symptomology. Finally, as a secondary analysis, we also examined whether our neuroimaging findings were driven by pure ADHD.

4.2. The continuum of attention dysfunction: Evidence from dynamic functional network connectivity analysis in neurotypical adolescents.

After establishing differences in the neural mechanisms of internally oriented attention processing in ADHD, this study shifted focus from neural correlates to neural dynamics. The continuum of attention dictates that a community sample of individuals will have varied levels of inattention difficulties ranging from mild to severe. Individual differences in inattention are likely accompanied by variations in the brain dynamics underpinning attention but this has never been testing in a typically developing sample. In this study, we used static, dynamic, and meta-state FNC analyses to assess relationships between FNC and attention problems in neurotypical adolescents. We hypothesized that dynamic FNC would explain more variance than static FNC, and this would allow us to uncover significant brain-behavior relationships between FNs associated with cognitive control and ADHD symptomology.

4.3. Attention and Emotion in Adolescents with ADHD; a Time-Varying Functional Connectivity Study

In this final study, we employed time-varying FNC analysis, which we previously validated as being more sensitive to a dimensional model of attention than static FNC, to adolescents with ADHD and age-matched controls. This study used multivariate analyses to assess brain-behavior relationships between the ADHD phenotype and network dynamics. Critically, this study aimed to comprehensively characterize ADHD using behavioral measures of inattention, impulsivity, as well as self-reported questionnaires to assess emotional dysregulation. In line with previous findings, we expected to find diminished SN-centered FNC in the ADHD group compared to controls. More generally, we hypothesized that by accounting for more ADHD symptomology and by using robust multivariate analyses, we would explain more neural and behavioral variation in the clinical ADHD group, allowing us to detect clearer brain-behavior relationships.

5. Summary of contribution to studies

The contribution of each author for each research article of this thesis is outlines below.

1. Rafi, H., Murray, R., Delavari, F., Perroud, N., Vuilleumier, P., Debbané, M., & Piguet, C. (2023). Neural Basis of Internal Attention in Adults with Pure and Comorbid ADHD. Journal of Attention Disorders, 10870547221147546.

Contribution: Conceptualization was done by CP, funding acquisition by CP, PV, data curation by CP, methodology by **HR**, RM, FD, formal analysis by **HR**, visualization by **HR**, supervision by CP, MD, writing (original draft) by **HR**, writing (review & editing) by all authors.

2. Rafi, H., Delavari, F., Perroud, N., Derome, M., & Debbané, M. (2023). The continuum of attention dysfunction: Evidence from dynamic functional network connectivity analysis in neurotypical adolescents. PloS one, 18(1), e0279260.

Contribution: Conceptualization was done by MD, funding acquisition by MD, data curation by **HR**, JLS, JB, EP, MG, methodology by **HR**, FD, formal analysis by **HR**, visualization by **HR**, supervision by MD, writing (original draft) by **HR**, writing (review & editing) by all authors.

3. Rafi H., Samson, J.L., Barrios, J., Poznyak E., Gauthey, M., Perroud, N., & Debbané, M. Attention and Emotion in Adolescents with ADHD; a Time-Varying Functional Connectivity Study (submitted).

Contribution: Conceptualization was done by MD, funding acquisition by MD, data curation by **HR**, JLS, JB, EP, MG, methodology by **HR**, formal analysis by **HR**, visualization by **HR**, supervision by MD, writing (original draft) by **HR**, writing (review & editing) by all authors.

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Chapter 2

This chapter was published in Journal of Attention Disorders in 2023

https://doi.org/10.1371/journal.pone.0279260

Neural Basis of Internal Attention in Adults with Pure and Comorbid ADHD

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Abstract

Objective: To examine whether putatively atypical neuronal activity during internal attention in ADHD yields insights into processes underlying emotion dysregulation. Methods: We used a word processing paradigm to assess neural activations in adults with ADHD (*N*=46) compared to controls (*N*=43). We measured effects of valence, applied partial-least squares correlation analysis to assess multivariate brain-behavior relationships and ran subgroup analyses to isolate results driven by pure ADHD (*N*=18). Results: During internal attention, ADHD, compared to controls, have 1) increased activation in the right angular gyrus (rAG), which appears driven by pure, not comorbid, ADHD and 2) diminished activation in the insula and fronto-striatal circuitry. Diminished activations were driven by negatively-valenced internal attention and negatively correlated with increased affective lability within the ADHD group. Conclusion: Internal attention in ADHD is associated with increased rAG activation, possibly reflecting difficulty converging external and internal information, and a diminished response within emotion regulation circuitry.

Introduction

Manifestations of attention-deficit/hyperactivity disorder (ADHD) evolve with age. In adults, ADHD primarily presents as difficulties in higher-order functions (Rösler et al., 2010; Wender, 1998), such as regulating attention, emotions and enacting goal-directed behaviors (Kessler et al., 2005). Impairments in such interconnected domains can lead to long-term dysfunctional professional and interpersonal relationships (Biederman & Faraone, 2006b; Faraone & Biederman, 2005), conveying a substantial lifetime burden on individuals with ADHD and society at large (Able et al., 2014). Questions about how specific brain regions and pathways are implicated in attention in ADHD can be researched through the broad lens of attention orientation, which can be defined as aligning attention with internal features of the self or with external sensory inputs (Posner, 1980). To date, few studies have examined differences in ADHD when attention is oriented inwards to sensations, emotions, and thoughts about the self (internal attention), in contrast to the more widely researched domain of outwardly oriented attention towards stimuli in the environment (external attention).

Internally oriented attention occupies much of our daily lives (Singer, 1966), and encompasses the higher-order function of self-mentalization. Self-mentalization is an interactive process between executive functions and imaginative capacities that allows us to attribute intentional mental states to ourselves and our behavior (Fonagy et al., 2002). The capacity to effectively self-mentalize is contingent upon adaptive attentional control and emotional self-regulation during early development. These abilities, in turn, allow for the self-governing necessary for adaptive social interactions (Barkley, 2015a; Cortese, Kelly, Chabernaud, Proal, Di Martino, Milham, & Xavier Castellanos, 2012; Durston et al., 2003). Emotional self-regulation is a core difficulty in ADHD (Barkley, 2015a) and is closely associated to cognitive processes contingent on internal attention, such as interoception (Craig, 2009; Critchley & Garfinkel, 2017; Tsakiris & Critchley, 2016). Interoception, the process of perceiving our body's physiological state (Craig, 2002), is crucial for maintaining physiological equilibrium. It allows us to recognize and experience embodied emotions and recent research links higher interoception to an increased capacity for feeling bodily states and regulating emotions (Zamariola et al., 2019). When it comes to ADHD, existing literature is mixed with studies showing both preserved interoception (Kutscheidt et al., 2019) and impaired interoception in adults with ADHD. In short, it is likely that ADHD's neurodevelopmental nature puts its population at risk for increased lifelong difficulties with various types of internal attention, like self-mentalization and interoception, but limited research exists on this topic (Perroud et al., 2017).

A rich literature on attention orientation in ADHD exists but most studies to date have focused on external, rather than internal, attention. Functional magnetic resonance imaging (fMRI) research on externally oriented attention shows a tendency in ADHD populations to be more distracted by salient stimuli (Forster & Lavie, 2016; Mason et al., 2005) and to have atypical activation in neural systems of executive functioning compared to healthy controls (HC) (Cortese, Kelly, Chabernaud, Proal, Di Martino, Milham, & Castellanos, 2012). Brain regions consistently hypoactive in ADHD compared to HC during executive functions-centered tasks include the striatum (Durston et al., 2003), the ACC (Konrad et al., 2006), the PFC (Rubia et al., 2005; Vaidya et al., 1998), and the inferior frontal gyrus (IFG) (Durston et al., 2006; Rubia et al., 2005). Interestingly, in addition to altered perceptual processing, literature has posited that the driving force behind increased susceptibility to external distractors in ADHD is the tendency for them to be disproportionately focused on internal states (Castellanos et al., 2006; Van den Driessche et al., 2017), leaving insufficient resources for attentional control. In terms of emotional effects, emotional external attention in ADHD has been well-studied, typically using temporal discounting and gambling tasks. Overall, studies show a tendency for ADHD populations to be hypersensitive to negatively valenced stimuli (López-Martín et al., 2013; Vetter et al., 2018; Wilbertz et al., 2017) and hyposensitive towards positively valenced stimuli (Conzelmann et al., 2009; Ibáñez et al., 2011). For example, a recent fMRI study showed that adolescents with ADHD had increased activation in the left AI and IFG during negatively valenced stimuli (Vetter et al., 2018). This finding was of special interest because insula is among the only brain regions with structural and functional abnormalities in children and adults with ADHD (Craig, 2009; Norman et al., 2017). It is a hub in both the ventral attention (Carretié, 2014; Norman et al., 2017) and salience networks (Barrett & Satpute, 2013b; Seeley et al., 2007b), which are responsible for detecting and reorienting attention towards salient stimuli. The authors argued their findings support altered salience processing of negative emotional distractors in ADHD; notably, this is also a putative mechanism in other psychiatric disorders, such as anxiety and depression disorders (Gotlib & Joormann, 2010; Joormann et al., 2011).

Generally speaking, fMRI research on internal attention suggests it is modulated by brain areas associated with memory processes, self-generated thought, and affective processing; regions include the precuneus, anterior insula (AI) and pre-supplementary motor area (pre-SMA) (Wade-Bohleber et al., 2019) and subgenual and dorsal anterior cingulate cortex (ACC) (Schilbach et al., 2014). Internal attention such as self-related thinking is also associated with increased default mode network (DMN) activation (Andrews-Hanna et al., 2014b). The DMN is a large-scale, functional brain network with hubs in the medial prefrontal cortex (mPFC) and the posterior cingulate cortex (PCC). It is typically activate when the mind is not directed towards a specific goal or object of thought (Andrews-Hanna, Reidler, Huang, et al., 2010b; Takeuchi et al., 2011). The notion that this distinct neural network underlies the human sense of self has been the subject of considerable empirical research; neuroimaging studies using self-referential cognitive (Harrison et al., 2008) and mind-wandering tasks (Mason et al., 2007) show patterns of activation like those seen in resting-state DMN. However, when it comes to the intersection of internal attention and emotion, the neural correlates of these complex processes are understudied in ADHD. Given that emotional dysregulation is increasingly considered a core symptom of ADHD (Corbisiero et al., 2013a; Retz et al., 2012), it is important to examine neural correlates of emotional internal attention. This line of research is relatively unexplored and may inform us on the pathways underlying difficulties with crucial abilities that pertain to the self, including both internal attention and emotional dysregulation in ADHD (Bateman & Fonagy, 2016; Perroud et al., 2017).

Importantly, ADHD shares high comorbidity rates with disorders such as major depressive disorder (up to 50% comorbidity rate (Angold et al., 1999)), anxiety disorders (up to 35% comorbidity rate (Busch et al., 2002; Jensen et al., 2001)) and externalizing disorders such as conduct disorder and oppositional defiance disorder (up to 50% comorbidity (Bird et al., 1988)). This poses a conundrum in scientific research, which is either conducted with "pure" ADHD samples, meaning patients with ADHD but without other diagnoses, or with samples having ADHD as well as other comorbid diagnoses. The first approach allows the isolation of behavioral and neural outcomes specific to ADHD, but at the cost of not being representative of ADHD in which comorbidities are the rule rather than the exception. The latter approach cannot disentangle which outcomes are related to comorbidities, and which are specific to ADHD itself.

The present fMRI study assessed patterns of brain activation related to internal attention and emotional valence in young adults with ADHD. Participants completed a word processing paradigm based on previously published paradigms (Davey et al., 2016; Kelley et al., 2002; Whitfield-Gabrieli et al., 2011) that required either internal or external attention to stimuli that were either positively or negatively valenced (for task details, please see Methods section 2.3.). Given previous fMRI literature on internal attention in HC as well as external attention in ADHD populations, we were especially interested in the brain activity of regions associated with self-processing, including the AI, operculum, IFG as well as regions consistently linked to emotion-processing such as the fronto-striatal circuitry. During internally oriented attention trials, we expected adults with ADHD compared to HC to show a) decreased activation of self- and emotion-processing regions for positively valenced stimuli and b) increased activation of self- and emotion-processing regions for negatively valenced stimuli. As a control measure, we also assessed brain activations to external positive and negative attention. To assess multivariate relationships between brain activity during internal attention and behaviors related to comorbid ADHD, we ran a partial-least squares correlation (PLS-C) analysis in the ADHD_{all} group. After running our primary analysis on how internal attention differed in ADHD compared to HC, we conducted a follow-up subgroup analysis to investigate whether observed differences were driven by ADHD alone rather than heterogeneity stemming from comorbidities. For the follow-up analysis, we selected a subgroup of participants with ADHD who did not have any comorbidities ($\text{ADHD}_{\text{pure}}$) and excluded patients with ADHD and comorbidities (ADHD_{com}). For clarity we refer to patients in our primary analysis as ADHD_{all} ($\text{ADHD}_{\text{all}} = \text{ADHD}_{\text{pure}} + \text{ADHD}_{\text{com}}$).

Method and Materials

2.1. Participants

We recruited 103 young adults, 55 of whom were patients with ADHD and 48 of whom were HC. Patients were recruited from the Emotion Regulation Disorders Unit at Geneva University Hospitals' Psychiatry Department; those with existing ADHD diagnoses were not re-diagnosed while the remaining patients were diagnosed with ADHD according to DSM-IV-TR criteria by trained psychologists using the DIGS (Diagnostic Interview for Genetic Studies) or the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS). Participants regularly taking medication with a half-life of longer than 24 hours were excluded, and the remaining participants were asked to stop all medication 24h before the scan. HC were adults without current psychiatric diagnoses and were matched for age, gender, and educational level. HC were recruited from Geneva and surrounding regions through web announcements. Five participants were excluded from the HC group, two for incomplete scans and three for excessive movement (>3mm) during the scan. Nine participants with ADHD were excluded (one for incomplete scans, two for excessive movement and six with comorbid ADHD who were taking medications with a half-life of longer than 24 hours). For more details on excluded participants, please refer to Supplementary Materials, Table A. The final analysis was conducted on 89 young adults, 46 of whom were patients with ADHD and 43 of whom were HC. In the follow-up subgroup analysis, we compared 18 patients who had ADHD but without comorbidities ($ADHD_{pure}$) to HC. Demographic data for all participants is shown in Table 1. All participants signed written informed consent in accordance with the approval of the Ethics Committee of the University of Geneva (CER 13-081).

Table 1. Demographic data

	ADHD_{all} (N = 46)	$\text{ADHD}_{\text{pure}}$ Subgroup (N = 18)	HC (N = 43)
Mean Age ± SD (years)	23.2 ± 3.5	23.1 ± 3	21.6 ± 3.1
Age Range (years)	17-30	20-29	17-29
No. of Females	24	12	23
Mean Education Level ± SD (years)	15.2 ± 3.0	15.2 ± 3.3	14.9 ± 3.1
Diagnostic Interview	DIGS (44) KSADS (2)	DIGS (18)	None
ADHD Presentations	18 Combined, 15 Predominantly Inattentive 5 Hyperactive-Impulsive 8 unspecified	6 Combined, 9 Predominantly Inattentive 3 unspecified	None
Comorbidities	Mood disorders (18) Generalized anxiety disorder (13) Drug abuse (12) Panic attack disorder (11) Social phobia (11) Post-traumatic stress disorder (7) Eating disorders (5) Panic disorders (2) Obsessive-compulsive disorder (2)	None	None
Medications (stopped 24h before scan)	Methylphenidate (12) Dexmethylphenidate (9) Asenapine (1) Trazodone (1) Albuterol (1) Lisdexamfetamine (2) Strattera (1) Fluticasone (1)	Methylphenidate (3) Dexmethylphenidate (4) Albuterol (1) Lisdexamfetamine (1) Fluticasone (1)	

DIGS=Diagnostic Interview for Genetic Studies; KSADS=the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)

2.2. Clinical Questionnaires

All participants filled out questionnaires assessing clinical metrics of inattention, hyperactivity, and emotional lability. Inattention and hyperactivity were measured using the World Health Organization's Adult ADHD Self-Report Scale (ASRS), which has two subscales: ASRS inattention (ASRSi) and ASRS hyperactivity (ASRShi). The ASRS is a reliable measure commonly used in clinical and research settings that is comprised of 18 questions on the recent frequency of ADHD symptoms, taken from the DSM-IV Criterion A for adult ADHD. Emotional lability was assessed using the Affective Lability Scales (ALS) (Harvey et al., 1989). The ALS is a validated, 54-item scale designed to assess self-reported affective changes from a normal mood to other affective states such as depression.

2.3. fMRI task

The attention task consisted of 112 trials requiring either internal or external attention to stimuli. The stimuli consisted of 28 positively valenced adjectives, 28 negatively valenced adjectives and 8 clinically relevant items (e.g., "stressed"). Stimuli were taken from the Profile of Mood State Questionnaire (POMS)(McNair et al., 1971) and each stimulus was presented once during internal trials and once during external trials. Stimuli were comparable for mean word length. The combinations of attention type and valence yielded four task conditions, which assessed differences between internal attention, as measured by internal positive (IntPos) and internal negative (IntNeg) and external attention, as measured by conditions external positive (ExtPos) and external negative (ExtNeg). The four task conditions were presented in a different randomized manner for each participant. This attention task has previously been used in other clinical populations in mood disorder research (Apazoglou et al., 2019).

Each trial began with an instruction screen of 2 seconds stating whether the upcoming stimulus required internal or external attention followed by stimulus presentation for 4 seconds. A numeric scale appeared at the bottom of each stimulus presentation screen that participants used to respond to the task (Fig. 1). During Internal trials, participants were asked to evaluate how much they currently felt the state indicated by the word using a numeric scale ranging from ≤ 3 (meaning they did not feel the state indicated, or they felt it a little bit), to 4-6 (meaning they did feel the state indicated to a moderate extent) to ≥ 7 (meaning they strongly felt the state indicated) (Joormann et al., 2011). Participants were instructed to respond as quickly as possible. The scale was designed to fit the external condition trials, where participants indicated the number of letters in the word using the same scale. A fixation-cross with a jittered duration between 500 to 1500 ms was shown after each trial and the overall task lasted for a total of 13 minutes. For more details about this paradigm, please refer to Supplementary Materials. This task was implemented using E-Prime 2.0 software (Psychology Software Tools Inc., USA). Reaction times and responses were recorded using an MRI-compatible button box (HH—1 × 4—CR, Current Designs Inc., USA).

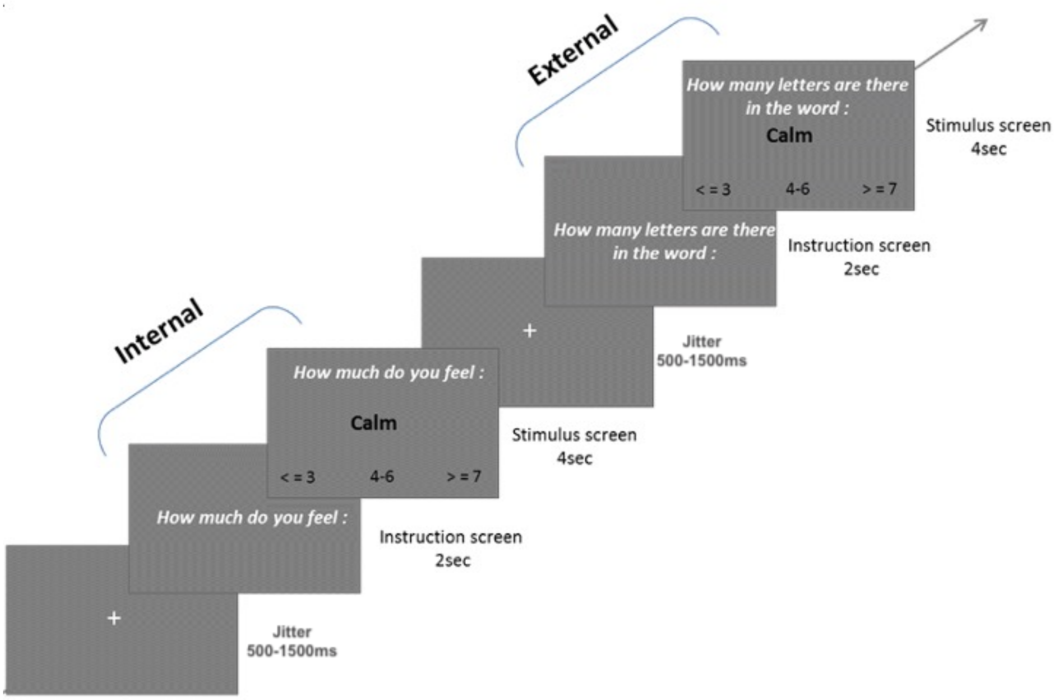

Fig. 1. Two trials in the attention task. The first trial demonstrates an example of the internal positive (IntPos) condition while the second demonstrates an external positive (ExtPos) condition.

2.4. Behavioral Analysis

For the primary analysis comparing the $ADHD_{all}$ group to HC, we first assessed group differences in age, years of education and questionnaire results using independent sample T-tests with Group ($ADHD_{all}$, HC) as the independent variable and age, years of education and questionnaire results as dependent variables. Group differences in reaction time data were analyzed using mixed model for repeated-measures using Group ($ADHD_{all}$, HC), Attention (Internal, External) and Valence (Positive, Negative) as fixed effects, participant ID as a random variable and reaction time as the dependent variable. The same methodology was used for subgroup analysis except for its Group variable consisted of $ADHD_{pure}$ and HC. Neither the

$ADHD_{all}$ group nor the $ADHD_{pure}$ subgroup (Supplementary Materials, Table B) differed in number of invalid trials, as compared to HC. Analyses were conducted using IBM SPSS Statistics, Version 26.0.

2.5. fMRI Acquisition & Processing

2.5.1. Acquisition

Functional brain images were acquired with a 3T Magnetom TIM Trio scanner (Siemens, Germany) and a 32-channel head coil using a standard echo-planar imaging sequence [36 transverse slices with 20% gap, 64 × 64 base resolution, voxel size: 3.2 mm × 3.2 mm × 3.2 mm, repetition time (TR): 2100 ms, echo time (TE): 30 ms, flip angle (FA): 80°, field of view (FOV): 192 mm]. Anatomical images were also acquired for precise localization and normalization to standard templates, using a T1-weighted 3D sequence (TR/TI/TE: 1900/900/2.32 ms, flip angle = 9°, field of view = 230 mm, PAT factor = 2, voxel dimensions: 1 mm, isotropic 256 × 256 × 192 voxel). One run of the attention task was acquired with a total of 380 scans.

2.5.2. Preprocessing

Image preprocessing was carried out using standard procedures implemented in SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Functional scans were manually reoriented to place the origin (0, 0, 0) at the anterior commissure and realigned using iterative rigid-body transformations that minimize the residual sum of square between the first and subsequent images and corrected for differences in acquisition time between slices. Participants with a rotation or translation of more than 3mm (1 voxel) were excluded from further analysis. The structural T1 image was co-registered and normalized with the mean image of the EPI series, and then the data was normalized to the MNI EPI template (2D spline, voxel size: 3 mm) and spatially smoothed with a Gaussian kernel with full width at half maximum (FWHM) of 6 mm.

2.5.3. Statistical Analysis

First level general linear models of blood oxygen-level dependent (BOLD) variation were modeled for each participant with a design matrix consisting of the four experimental task conditions (IntPos, IntNeg, ExtPos, ExtNeg) which were convolved with a canonical hemodynamic response function. Movement parameters estimated during realignment (x, y, z translations and pitch, roll, and yaw rotations) were included as regressors of no interest. In line with previous research using similar experimental paradigms, we analyzed correct trials only (Vetter et al., 2018) to assess group differences when both groups were engaging in the task at hand. There was no significant group difference between the number of incorrect responses during external trials (Supplementary Materials, Table B) and so we discarded the small number of incorrect trials from both groups. Mean framewise displacement as well as ExtPos and ExtNeg trials that were incorrectly answered were modeled as separate regressors of no interest. A high-pass filter with cut-off 128 s was applied to remove the low-frequency physiological noise and the default autoregressive AR(1) model was used to estimate residual temporal autocorrelation (Henson, 2006). Four contrasts of interest from the weighted beta-images (IntPos IntNeg, ExtPos & ExtNeg) were then fed into a whole-brain random-effects analysis to measure BOLD variation at the group-level with a 3x2x2 full factorial model. To use the same group-level model for the primary and subgroup analyses, we specified “Group” as the between-subject factor ($\text{ADHD}_{\text{pure}}$, ADHD_{com}, HC) and within-subject factors “Attention” (internal, external) and “Valence” (positive, negative). Importantly, during the primary analysis, we treated $\text{ADHD}_{\text{pure}}$ and ADHD_{com} as one group ($\text{ADHD}_{\text{all}} = \text{ADHD}_{\text{pure}} + \text{ADHD}_{\text{com}}$). Two manipulation checks assessing the main effect of attention (Internal>External and External>Internal) were conducted across all participants to verify the validity of the fMRI attention task (Supplementary Materials, Table C). We also assessed main effect of Group ($ADHD_{all}$>HC and HC>$ADHD_{all}$) (Supplementary Materials, Table D). Importantly, we performed statistical comparisons between groups during internal and external attention as well as during the four individual task conditions as planned comparisons of simple effects. Whole-brain results for the primary analysis, $ADHD_{all}$ compared to HC, are reported at a cluster-level threshold of p-FWE<.05. Brain regions were identified using the Harvard-Oxford atlas distributed with FSL (http://www.fmrib.ox.ac.uk/fsl/).

The methodology for the subgroup analysis was identical to that of the primary analysis. The same full factorial model created in the primary analysis was used to assess differences in brain activations between $ADHD_{pure}$ and HC. Results are reported at a corrected cluster-level threshold of p-FWE<.05 and with a cluster-forming threshold of voxel-level p<.001.

2.6. Partial Least Squares Correlation

To assess multivariate relationships between behavior and brain activations during internal and external attention, we ran a partial least squares correlation (PLS-C) analysis (Krishnan et al., 2011) in the $ADHD_{all}$ group. PLS-C is a well-established methodology used to assess brain-behavior relationships in various clinical populations (Delavari et al., 2022; Ziegler et al., 2013; Zöller et al., 2017) and we employed it using myPLS, a publicly available, Matlab-based toolbox (https://github.com/MIPLabCH/myPLS). To summarize the methodology used in PLS-C, we first computed correlations between matrix Y, which consisted of participants' behavioral scores (ASRSi, ASRShi and ALS), and matrix X, which consisted of voxel data per subject during the 4 task conditions (IntPos, IntNeg, ExtPos, ExtNeg). The resulting correlation matrices were concatenated into a common correlation matrix, $R=X^TY$. Matrix R then underwent singular value decomposition, resulting in latent variables or correlation components. Each correlation component is a combination of brain activations and behavior weights, which indicate how strongly each variable contributes to the multivariate brain-behavior correlation. These values can be interpreted similarly to correlation values. Significance of correlation components was determined by permutation testing (1000 permutations) and the stability of brain and behavior weights was ensured using bootstrapping (500 bootstrap samples). For more details on singular value decomposition and correlation components, please refer to previous publications using the myPLS toolbox (Zöller et al., 2017).

Results

3.1. Behavioral and Clinical Data

The primary analysis revealed no group difference between $\mathrm{ADHD}_{\mathrm{all}}$ and HC in average reaction times, nor age, gender, or education level. Regarding clinical measures of inattentiveness, the $\mathrm{ADHD}_{\mathrm{all}}$ group (mean = 22.8 ± 7.2) scored significantly higher ($t=7$, $df= 83$, $p<.001$) than HC (13.2 ± 5.6). For hyperactivity, $\mathrm{ADHD}_{\mathrm{all}}$ (mean = 17.5 ± 7.7) also scored significantly higher ($t=5.4$, $df= 83$, $p<.001$) than HC (9.9 ± 5.6). Finally, $\mathrm{ADHD}_{\mathrm{all}}$ (mean = 1.1 ± 0.6) also scored significantly higher ($t=4.5$, $df= 83$, $p<.001$) than HC (0.6 ± 0.3) in affective lability. Subgroup analysis revealed no differences between the $\mathrm{ADHD}_{\mathrm{pure}}$ subgroup and HC in reaction times, age, sex, nor educational level. The $\mathrm{ADHD}_{\mathrm{pure}}$ subgroup scored higher on inattentiveness ($\mathrm{ADHD}_{\mathrm{pure}} = 24 \pm 7.1$, $HC=13.2 \pm 5.6$, $t=5.7$, $df = 26$, $p<.001$) and on hyperactivity compared to HC ($\mathrm{ADHD}_{\mathrm{pure}} = 17.1 \pm 7.6$, $HC = 9.9 \pm 5.6$, $t=3.6$, $df = 25$, $p<.001$). No other differences were found.

3.2. fMRI Results

3.2.1. Manipulation Checks

To verify task validity, we ran two manipulation checks. The first contrasted Internal Attention > External Attention and revealed increased activations in regions including the inferior frontal gyrus, orbitofrontal cortex, and angular gyrus (Supplementary Materials, Table C). The second manipulation check contrasted External Attention > Internal Attention and revealed increased activation in regions including the occipital cortex, striatum, middle frontal gyrus, and thalamus (Supplementary Materials, Table C). Interaction contrasts between Group ($\mathrm{ADHD}_{\mathrm{all}}$ > HC and HC > $\mathrm{ADHD}_{\mathrm{all}}$) and Attention (Internal Attention > External Attention and External Attention > Internal Attention) revealed no significant effects.

3.2.2. Main Effects of Group, ADHD_{all} vs. HC

We assessed main effects of group, across all conditions (IntPos, IntNeg, ExtPos and ExtNeg). Results revealed that the ADHD_{all} group, as compared to HC, had increased activations in regions such as the angular gyrus and occipital fusiform gyrus (Supplementary Materials, Table D). The ADHD_{all} group, as compared to HC, had diminished activation in regions including the insular cortex, putamen, and precentral gyrus (Supplementary Materials, Table D).

3.2.3. Group Differences during Internal and External Attention

Next, we assessed simple effects of group during internal (IntPos + IntNeg trials) and external (ExtPos + ExtNeg trials) attention, as planned comparisons. Results for internal attention trials showed that, as compared to HC, the ADHD_{all} group had increased activity in the angular gyrus and middle temporal gyrus and diminished activity in the insular cortex and the fronto-striatal circuity, including the putamen, caudate and orbitofrontal cortex (Figure 2; Table 2). During external attention trials, the ADHD_{all} group had increased activity in the occipital cortex and diminished activity in regions including the superior frontal gyrus, supplementary motor cortex and paracingulate cortex (Figure 2c; Supplementary Materials, Table E). No other significant effects were found.

Table 2. Group differences during Internal Trials

Contrast	**Region**	**p**	**Cluster Size**	**T**	**MNI Coordinates**		
					x	y	z
ADHD$_{all}$ - HC (Internal)	Angular Gyrus	0	229	4.47	54	-51	21
				4.25	57	-60	15
				4.13	48	-57	33
	Middle Temporal Gyrus	0.029	92	4.36	-48	-51	6
				3.81	-60	-51	3
				3.41	-33	-51	-3
HC - ADHD$_{all}$ (Internal)	Superior Frontal Gyrus	0	327	7.57	-24	0	60
				6.17	-15	0	69
				5.71	-36	-18	60
	Paracingulate Gyrus	0	283	7.54	9	9	48
				6.42	-6	15	45
				6.23	-3	0	51
	Putamen	0	305	7.32	21	0	12
				7.16	57	9	18
				6.44	33	21	6
	Middle Frontal Gyrus	0	43	6.69	27	3	54
	Lateral Occipital Cortex	0	69	6.42	-18	-72	51
		0	174	6.2	-24	3	12
				6.12	-33	18	6
				6.07	-27	3	-9
	Lateral Occipital Cortex	0	23	5.89	18	-63	60
	Frontal Pole/ Inferior Parietal Gyrus	0	25	5.79	-42	45	6
				5.02	-45	39	15
	OrbitoFrontal Cortex	0.003	10	5.59	-30	18	-12
	Precentral Gyrus / Inferior Parietal Gyrus	0.009	5	5.41	-57	6	21
	Putamen	0.001	20	5.34	24	6	-12
	Paracingulate Gyrus	0.001	18	5.29	12	24	33
	Occipital Cortex	0.006	7	5.16	42	-81	6

p-FWE<.05 at the cluster-level.

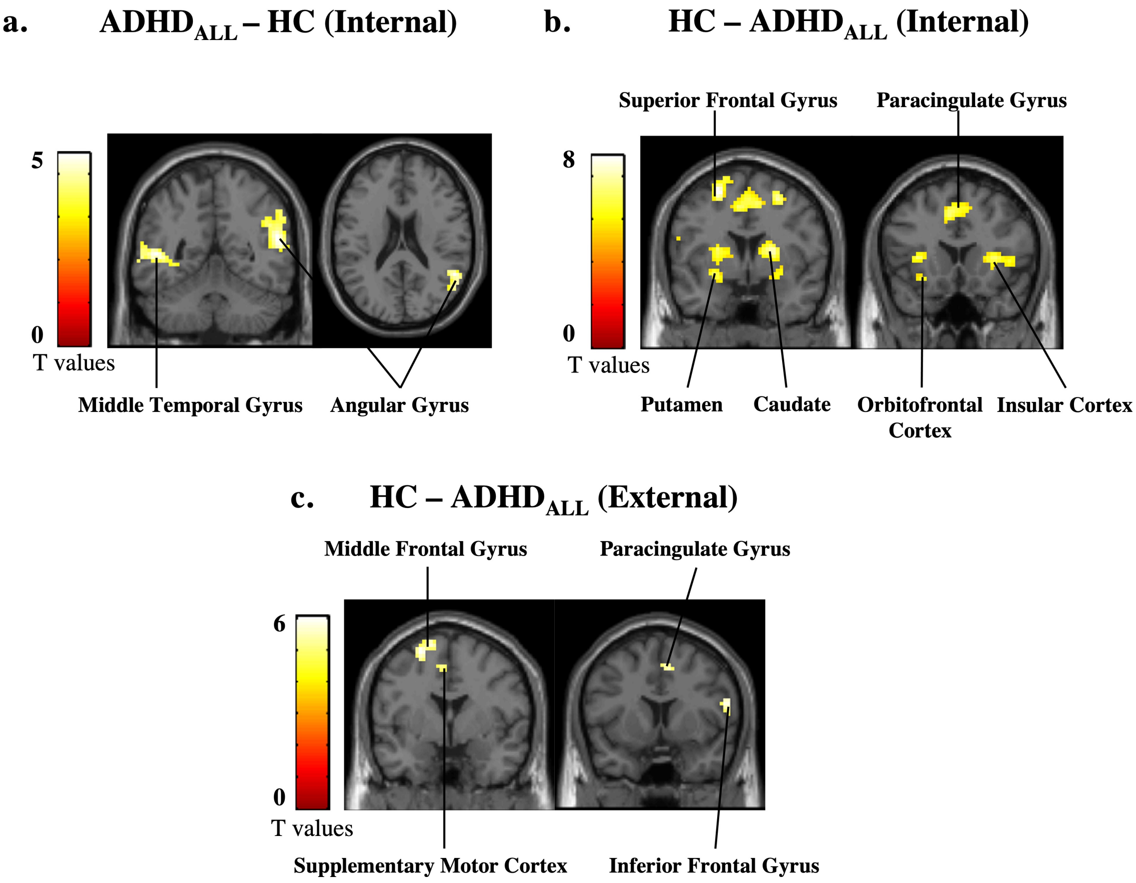

Fig. 2. Primary Analysis Results. a) Increases in activation in ADHD$_{all}$ compared to HC during internal attention, b) Decreases in activation in ADHD$_{all}$ compared to HC during internal attention and c) Decreases in activation in ADHD$_{all}$ compared to HC during external attention. Results are shown at a cluster-level threshold of *p*-FWE<.05.

The same simple effects analysis was conducted for ADHD$_{pure}$ subgroup analysis. During internal attention, the ADHD$_{pure}$ subgroup had increased activation in a cluster in the angular gyrus compared to HC (x=30, y=-42, z=42, kE=165, T=5.34, *p*=.0002). No other significant group differences were found.

3.2.4. Group Differences during Task Conditions

Next, we assessed whether group differences during internal attention and external attention were modulated by valence by looking within the four task conditions (IntPos, IntNeg, ExtPos and ExtNeg, respectively). Results revealed that during IntPos trials the ADHD_{all} group had diminished activation in the bilateral putamen, paracingulate gyrus and superior frontal gyrus compared to HC. During IntNeg trials, the ADHD_{all} group had diminished activation in regions including the insular cortex, paracingulate gyrus, caudate and IFG (Figure 3; Table 3). No other significant results were found. No significant results were found in the $\text{ADHD}_{\text{pure}}$ subgroup analysis.

Table 3. Group Differences During Individual Trial Conditions

Contrast	**Region**	**p**	**Cluster Size**	**T**	**MNI Coordinates**		
					x	y	z
HC - ADHD_{all} (Internal Positive)	Paracingulate Gyrus	0	28	5.64	9	9	48
	Superior Frontal Gyrus	0	26	5.56	-21	3	60
				4.87	-15	0	69
	Putamen	0	31	5.5	21	0	12
	Paracingulate Gyrus	0.008	6	4.9	-6	15	42
	Putamen	0.006	7	4.88	-24	3	12
HC - ADHD_{all} (Internal Negative)	Superior Frontal Gyrus	0	27	5.66	-24	0	60
	Precentral Gyrus / Inferior Frontal Gyrus	0.001	20	5.55	57	9	18
	Paracingulate Gyrus/ Supplementary Motor Cortex	0	24	5.53	6	9	51
	Putamen	0.001	18	5.31	21	0	12
	Middle Frontal Gyrus	0.008	6	5.25	27	3	54
	Insular Cortex	0.004	9	5.1	33	21	6
	Occipital cortex	0.005	8	5.01	-15	-72	51

p-FWE<.05 at the cluster-level.

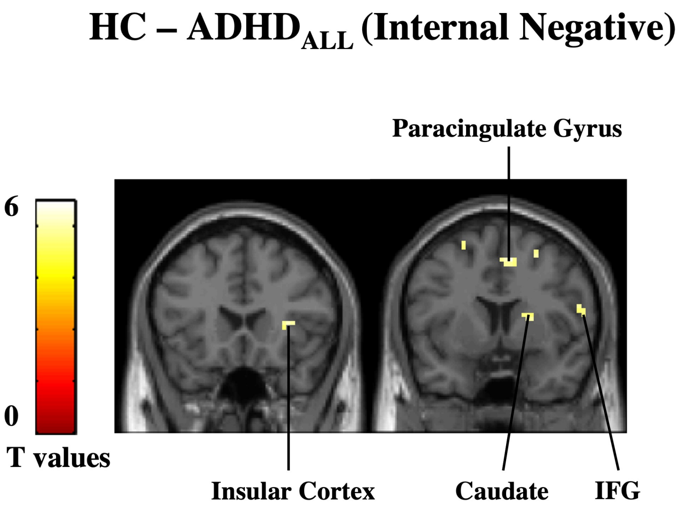

Fig. 3. Group Differences during IntNeg Trials. a) During negatively-valenced, internal attention trials, the ADHD$_{all}$ subgroup had diminished activation in the insular cortex, caudate, paracingulate gyrus and inferior frontal gyrus (IFG) compared to HC. Results are reported at a corrected cluster-level threshold of *p*-FWE<.05.

3.2.5. Partial Least Squares Correlation

PLS-C analysis resulted in one significant latent component (p<.05, r=0.59) that captured brain saliences representing voxels strongly correlated with affective lability and ADHD symptoms during IntPos and IntNeg trials but not during ExtPos and ExtNeg trials (Fig. 4a). Due to the high ALS loading, the corresponding pattern of brain salience bootstrap scores (Fig. 4b) contains the voxels where BOLD activation is strongly correlated with affective lability, moderately correlated to hyperactivity and weakly correlated to inattention in patients with ADHD. During internal attention, a similar pattern of activity is seen across IntPos and IntNeg trials in that the less affectively labile and symptomatic participants with ADHD were, the more activation they had in the orbitofrontal cortex, striatum, inferior frontal gyrus, supramarginal gyrus and cerebellum.

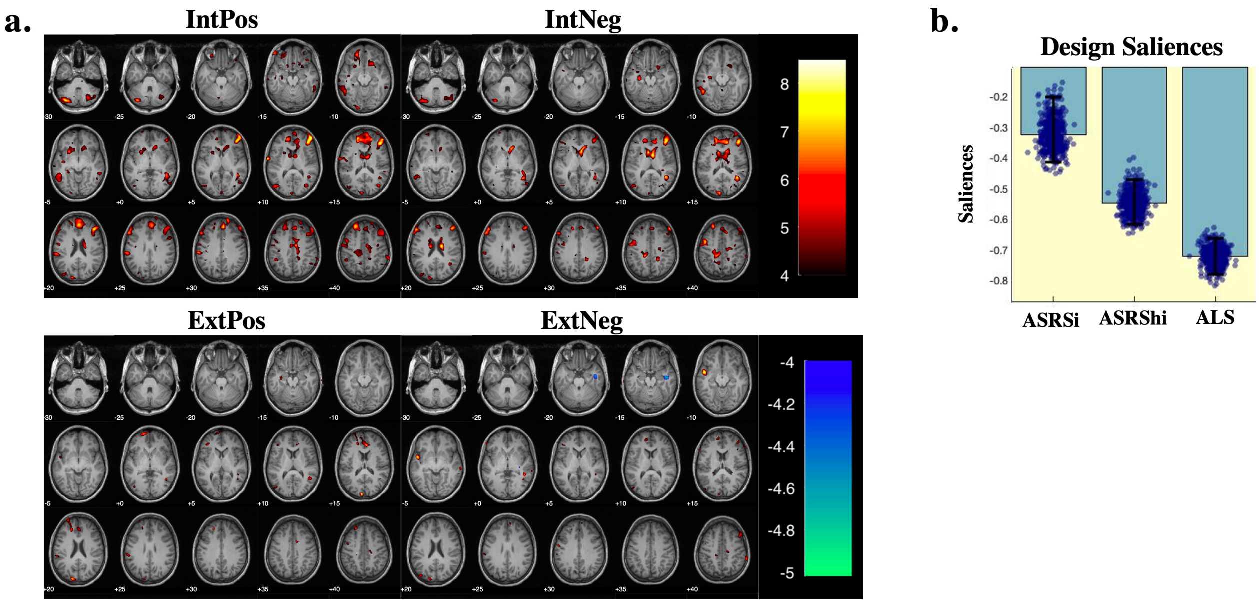

Fig. 4. Partial Least Squares - Correlation Results. a) Multivariate patterns reveal that the comorbid ADHD group had increased activations in the orbitofrontal cortex, striatum, and frontal gyri, including the inferior frontal gyrus (IFG), during IntPos and IntNeg trials but not during ExtPos and ExtNeg trials. b) Design saliences which show the loadings of our three behaviors of interest on the brain data. The pattern of neural activation was most strongly negatively correlated with affective lability (as measured by ALS scores), and moderately negatively correlated with ADHD symptomology (as measured by ASRS scores).

Discussion

The present study assessed how the neural bases of internally oriented attention differed in young adults with ADHD compared to controls, and how positive and negative valence modulated these processes. To this end, we employed a word processing fMRI task during which participants alternated between paying internal and external attention. This study revealed distinct patterns of brain activations associated with internal attention in our ADHD group, such that they have more activity in regions associated with mind-wandering and information integration and diminished activations in subcortical regions associated with self- and emotion-processing compared to controls.

When prompted to reflect upon internal states, the ADHD_{all} group had increased activation in the right angular gyrus (rAG) compared to controls. A recent meta-analysis on this region in the lateral parietal cortex characterized it as a dynamic, online buffer involved in combining internal and external information (Humphreys et al., 2021). Humphreys and colleagues state the rAG helps combine autobiographical experiences and conceptual knowledge structures in a manner necessary for higher-order, cognitive functions such as constructing internal models of the world (Hasson et al., 2008) or reconstructing autobiographical memories (Lerner et al., 2011). In the present study, increased rAG activation during internal attention may suggest it is more costly for ADHD populations to converge external information (such as the experimental setting and task at hand) with internal information (current internal state). It is possible that the information processing style in ADHD is less fluid than in controls, such that they get stuck in semantic and cognitive processing instead of integrating interoceptive information and activation brain regions involved in emotion regulation. Our results further indicate this difficulty is a property of ADHD itself; subgroup analyses revealed $\text{ADHD}_{\text{pure}}$

compared to controls also had increased activation of right rAG during internal attention suggesting that pure ADHD was driving increased rAG activation.

In terms of diminished activations during internal attention, the $\mathrm{ADHD}_{\mathrm{all}}$ group had decreased activity in self- and emotion-processing regions such as the insula, inferior frontal gyrus, and striatum compared to controls. Looking within individual task conditions revealed a similar pattern of activation during IntNeg trials suggesting that these activations were driven by a combination of internally oriented and negatively valenced emotional attention. These finding are reasonable given that the relationship between emotion and attention is intertwined, with the saliency needed for a stimulus to emerge from environmental noise being directly related to its emotional characteristics in terms of valence and arousal (Janak & Tye, 2015). Diminished activation during internal attention of the insula, which serves an important role in attention and converging internal bodily states to emotional experiences (Zaki et al., 2012), is consistent with the notion of adults with ADHD having a decreased capacity to reflect upon their internal state compared to controls (Perroud et al., 2017).

Interestingly, within internal attention trials, $\mathrm{ADHD}_{\mathrm{all}}$ showed diminished activation in the bilateral putamen during IntPos trials in compared to controls. This is in line with previous research showing a reduced capacity to process positive emotions in ADHD (Conzelmann et al., 2009; Ibáñez et al., 2011), which may reflect differences in ADHD populations in terms of reward processing and motivation (Scheres et al., 2007; Sonuga-Barke et al., 2008b). We also found decreased activation in the bilateral paracingulate cortex and going into the pre-supplementary motor area. The pre-supplementary motor area helps link the onset of movements with motivations (Rizzolatti & Luppino, 2001) and both animal models (Luppino et al., 1993) and human (Krolak-Salmon et al., 2006; Osaka et al., 2003) research have implicated it in processing positive emotions such as happiness.

The findings of the simple effects of group during IntPos and IntNeg trials help to contextualize the results of the PLS-C analysis in comorbid ADHD. The multivariate analysis revealed that a similar pattern of diminished activity seen in comorbid ADHD compared to HC during internal attention, correlated with increased affective lability and ADHD symptomology within the comorbid ADHD group. This result is notable for several reasons, the first being that, like the simple effects of group during internal and external attention, diminished activation in the frontal cortex and the striatum was specific to internal attention. Secondly, the PLS-C analysis revealed that behavior most correlated with brain activations was affective lability, not ADHD symptomology. Given that emotional dysregulation is increasingly seen as a core symptom of ADHD, this finding is not contrary to existing literature. More importantly however, it suggests that in comorbid ADHD such as the participants in the present study, emotional dysregulation comes to the forefront of ADHD symptoms.

During external attention trials we found diminished activation in the superior frontal gyrus, the bilateral paracingulate cortex and the operculum cortex. Previous research generally shows hyperresponsiveness toward emotional distractors in ADHD (controlling for other Axis I disorders) compared to controls: one study showed insula and inferior frontal gyrus hyperresponsiveness towards negatively valenced distractors (Vetter et al., 2018), while others showed that emotional distractors are associated with increased functional connectivity between the amygdala and emotion processing hubs (Posner et al., 2011) as well as striatal and occipital regions in ADHD compared to controls (Hwang et al., 2015). Other group differences seen during external attention include altered activation patterns in visual and motor planning cortices, which are largely in line with previous research (Brace et al., 2015; Lenz et al., 2010).

Our results should be contextualized regarding the study's limitations. First, our fMRI paradigm did not include a neutral valence condition, so we were not able to detect differences stemming from positive versus neutral and negative versus neutral stimuli. Second, we underline the preliminary nature of the subgroup analysis, given the small size of the pure ADHD subgroup. Finally, subject head motion is a well-known, major source of noise in fMRI; despite controlling for rotation and translation, as well as mean framewise displacement, it is possible that our results are influenced by noise related to movement (Friston et al., 1996).

The present study underlines the importance of studying effects of internal attention and emotion processes affected in ADHD, and suggests these processes involve altered rAG functioning in ADHD. In line with this, future studies with larger sample sizes of pure ADHD on internal emotional attention are needed to replicate the present results. More broadly, future fMRI studies researching if and how internal attention relates to executive dysfunction and emotion regulation capacities in ADHD populations would build upon current results and shed light on our current understanding of internal attention and emotion.

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Supplementary Materials

Table A. Independent Sample T-test assessing the No. of Invalid Trials per Group, Primary Analysis

	ADHD$_{\text{all}}$ (*N* = 52)	HC (*N* = 43)	df	*F*-Statistic	Sig. (*p*-value)
Mean No. of Invalid Trials ± Standard Deviation	7.8 ± 6.7	6.7± 3.8	93	5.8	0.50

Table B. Manipulation Checks, all participants.

Contrast	Region	p	k_E	T	MNI Coordinates (mm)		
					x	y	z
External > Internal	Putamen/ Caudate	0	349	8.24	18	9	-9
				8.16	21	12	0
	Putamen	0	284	7.91	-21	6	6
	Inferior Temporal Gyrus	0	328	6.68	-48	-63	-9
				5.97	-30	-90	-6
				5.82	-33	-87	12
	Cerebellum	0	44	5.58	-3	-75	-30
	Occipital Cortex	0	120	5.49	33	-84	-3
				5.47	15	-87	0
	Precentral Gyrus	0	32	5.47	42	3	24
	Caudate	0	29	5.46	-18	30	3
	Inferior Temporal Gyrus	0	25	5.37	51	-57	-12
	Middle Frontal Gyrus	0.007	7	5.11	33	-3	48
	Occipital Cortex	0.002	16	5	30	-69	30
	Thalamus	0.008	6	4.87	12	-15	9
	Cerebellum	0.01	5	4.78	27	-60	-24
Internal > External	Inferior Frontal Gyrus / Orbitofrontal Cortex	0	311	10.94	-51	27	3
				8.89	-45	27	-12
	Occipital Cortex	0	139	6.26	-48	-63	24
	Inferior Frontal Gyrus	0.001	22	6.08	54	30	3
	Middle Temporal Gyrus	0	28	5.87	-54	-6	-18
	Precuneus/ Posterior Cingulate Gyrus	0	39	5.61	-6	-57	21
				5.17	-6	-48	30
	Superior Frontal Gyrus	0.001	21	5.49	-9	54	21
	Middle Temporal Gyrus	0	44	5.36	-51	-36	-3
				4.98	-51	-21	-9
	Temporal Pole	0.006	8	4.91	51	9	-33

p<.05 FWE-corrected at the cluster-level

Table C. Group differences between ADHD$_{\text{all}}$ and HC during External Attention

Contrast	Region	p(*FWE*-corr)	k_E	T	MNI Coordinates (mm)		
					x	y	z
	Lingual Gyrus /	0	59	5.94	0	-81	-3

ADHD_{all} > HC	Occipital Gyrus			5.59	9	-84	-6
	Occipital Fusiform Gyrus	0.006	8	5.05	-21	-84	-15
HC > ADHD_{all}	Superior Frontal Gyrus / Postcentral Gyrus	0	298	6.81	-24	3	63
				5.97	-48	-27	48
				5.7	-33	-15	63
	Paracingulate Gyrus/ Supplementary Motor Cortex	0	174	6.13	6	9	51
				6.13	-6	15	45
				6.06	-6	-3	51
	Precentral Gyrus/Inferior Frontal Gyrus	0.001	17	5.88	60	9	18
	Occipital Cortex	0.001	21	5.69	18	-63	60
	Occipital Cortex	0	45	5.62	-18	-66	60
				5.2	-12	-75	48
	Frontal/Central Operculum/ Insular Cortex	0	66	5.48	-45	12	0
				5.11	-33	15	6
	Middle Frontal Gyrus	0.016	3	5.2	-39	24	27
	Frontal Pole/ Inferior Frontal Gyrus	0.013	4	5.1	-45	36	15
	Frontal Pole/Insular Cortex	0.016	3	4.86	-27	21	-9
	Heschl's Gyrus	0.008	6	4.72	-42	-24	15
	Insular Cortex	0.013	4	4.69	-30	0	12

p<.05 FWE-corrected at the cluster level

Table D. One-Way ANOVA assessing the No. of Invalid Trials per Group, Subgroup Analysis

	ADHD_{com} (*N* = 34)	$\text{ADHD}_{\text{pure}}$ (*N* = 18)	HC (*N* = 43)	df	F-Statistic	Sig. (*p*-value)
Mean No. of Invalid Trials ± Standard Deviation	7.2 ± 7.1	7.9 ± 5.9	6.7± 3.8	93	0.32	0.73

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Chapter 3

This chapter was published in PLOS ONE in 2023

DOI: https://doi.org/10.1371/journal.pone.0279260

The continuum of attention dysfunction: evidence from dynamic functional network connectivity analysis in neurotypical adolescents

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Abstract

The question of whether attention-related disorders such as attention-deficit/hyperactivity disorder (ADHD) are best understood as clinical categories or as extreme ends of a spectrum is an ongoing debate. Assessing individuals with varying degrees of attention problems and utilizing novel methodologies to assess relationships between attention and brain activity may provide key information to support the spectrum hypothesis. We scanned 91 neurotypical adolescents during rest using functional magnetic resonance imaging. We conducted static and dynamic functional network connectivity (FNC) analysis and correlated findings to behavioral metrics of ADHD, attention problems, and impulsivity. We found that dynamic FNC analysis detects significant differences in large-scale neural connectivity as a function of individual differences in attention and impulsivity that are obscured in static analysis. We show ADHD manifestations and attention problems are associated with diminished Salience Network-centered FNC and that ADHD manifestations and impulsivity are associated with prolonged periods of dynamically hyperconnected states. Importantly, our meta-state analysis results reveal a relationship between ADHD manifestations and exhibiting variable and volatile dynamic behavior such as changing meta-states more often and traveling over a greater dynamic range. These findings in non-clinical adolescents provide support for the continuum model of attention disorders.

Keywords: attention disorders, group independent component analysis, dynamic functional network connectivity, functional magnetic resonance imaging, adolescents

Introduction

Attention and impulsivity are continuously varying psychological processes influenced by individual differences in genetics, personality, as well as cognitive and affective processing(Brown et al., 2006; Hunt et al., 1989). Clinical evaluations of attention and impulsivity are designed to tease apart variation at the extreme end of said continuum, which is typically when attention disorders such as attention deficit hyperactivity disorder (ADHD) are diagnosed(Larsson et al., 2012). Adopting a strictly categorical lens comes with drawbacks: it ignores that typically developing (TD) individuals show important variation in attention and impulse-control that can lead to significant functional challenges(Fair et al., 2012). A categorically-truncated view of population variance decreases data reliability, validity and statistical power, making the identification of biomarkers for psychiatric conditions less probable(Markon et al., 2011; Van Der Sluis et al., 2013). In addition, attention disorders such as ADHD have high comorbidity rates with other psychiatric disorders, such as oppositional defiant disorders and anxiety disorders(Dwivedi & Banhatti, 2005; Gillberg et al., 2004). One way to side-step these confounding problems is to examine the variation of attention and impulsivity, and their associated neural mechanisms, within TD individuals. Similar to other fields of developmental psychopathology (Derome et al., 2018; Tanzer et al., 2020), the present study adopts a continuum approach towards attention-disorder related problems in order to contribute meaningful insights into the neural signature of attention disorders.

Spatially distributed and functionally linked brain networks can be reliably identified during adolescence(Thomason et al., 2011). Functional magnetic resonance imaging (fMRI) studies have increasingly used the triple network theory framework to research how complex interactions between these networks influence psychological processes in clinical populations(Cai et al., 2018a; Damaraju et al., 2014; Mennigen et al., 2019a). The triple network theory posits that atypical activity of three large-scale networks(Menon, 2011a), the default mode network (DMN), executive control network (ECN) and salience network (SN), underlies neurodevelopmental disorders. The DMN is arguably the most well-researched neural network, and is a task-negative network associated with mind-wandering and social cognition (for reviews, see(Mohan et al., 2016; Raichle, 2015)). It can be divided into the dorsal DMN (dDMN), including the anterior cingulate/medial prefrontal cortices, and the ventral DMN (vDMN), including the posterior cingulate cortex (PCC) and precuneus(Greicius et al., 2003; Greicius & Menon, 2004; Raichle, 2015). Attentional difficulties such as temporary lapses of attention(Weissman et al., 2006b) have long been associated with the DMN, so much so that ADHD was thought to be a disorder of the DMN(Broyd et al., 2009; Sonuga-Barke & Castellanos, 2007b; Uddin et al., 2008). This claim was partly supported by research showing ADHD populations have atypical functional network connectivity (FNC) within the DMN(Castellanos et al., 2008; Uddin et al., 2008), difficulty suppressing DMN activation when switching from rest to task-focused cognitive activity(Sonuga-Barke & Castellanos, 2007b), as well as abnormal functional connectivity between the DMN and cingulo-opercular and occipital regions(Barber et al., 2015; C. Sripada et al., 2014). However, current literature is inconsistent, with studies showing attention-related DMN hypo-connectivity(Castellanos et al., 2008; Fair et al., 2010; Uddin et al., 2008), hyper-connectivity(Tian et al., 2008; Yoo et al., 2018) as well as a combination of both(Franzen et al., 2013). The remaining networks of the triple network theory, the ECN and SN, are both task-positive networks involved in higher-order cognitive control; the ECN encompasses the dorsal lateral prefrontal cortex and helps integrate sensory and memory information, as well as regulate cognition, behavior and executive functions(Chan et al., 2008; Collette & Van Der Linden, 2002). The SN is anchored in the insular cortex and the anterior cingulate cortex (ACC), and responds to external events that are behaviorally salient(Uddin & Menon, 2010b).

Importantly, both networks are distinct from the dorsal attention network, which is comprised of the frontal eye fields and the intraparietal sulcus(Szczepanski et al., 2013).

Patterns of FNC between the DMN, ECN and SN at rest overlap with patterns seen during goal-directed behaviors(Berkes et al., 2011; Lewis et al., 2009; Sibley et al., 2012), suggesting this triad of networks is important for regulating attention, cognition and affect(Fox & Raichle, 2007). In particular, the SN is thought to allow for flexible cognitive control by regulating interactions between the DMN and ECN(Cai et al., 2018a; Sridharan et al., 2008). Subsequently, the failure to regulate DMN-ECN interactions is hypothesized to underlie task interference and downstream attention problems(Sun et al., 2012). Populations characterized by strong attention difficulties, such as ADHD, consistently show deficits in engaging and disengaging the SN, ECN and DMN compared to TD populations (for a meta-analysis, see(Cortese, Kelly, Chabernaud, Proal, Di Martino, Milham, & Castellanos, 2012)). Recent literature increasingly suggests that FNC centered around the SN, rather than the DMN, may represent a neural signature of childhood attention disorder symptoms(Di & Biswal, 2014; Sridharan et al., 2008; Uddin & Menon, 2010b).

Dynamic FNC analysis is a systems neuroscience approach to quantifying how neural networks interact over time (E. A. Allen et al., 2014a; Sakoğlu et al., 2010). This analysis identifies different dynamic states that represents a distinct, cross-network activation pattern that participants oscillate in and out of over time(E. A. Allen et al., 2014a). State-based metrics can be calculated from dynamic FNC analysis, such as mean dwell time, which is the time spent in a certain state before switching to another, fraction time, which reflects time spent in one state relative to the entire scan time and the number of transitions, which indicates how often a participant changed states(E. A. Allen et al., 2014a). Importantly, a novel measure of dynamism also derived from dynamic FNC analysis is meta-state analysis, which adopts a complex statistical approach and finer temporal resolution to calculate summary measures of brain dynamism. As compared to dynamic FNC analysis, meta-state analysis is better able to capture the dynamic fluidity and range of large-scale neural connectivity (Miller et al., 2016).

The first study to adopt a dynamic approach to FNC in ADHD reported diminished connectivity between the SN-DMN and the SN-ECN in young children with ADHD compared to controls, which correlated with the severity of inattention symptoms(Cai et al., 2018a). It also revealed that children with ADHD had less persistent brain states that lasted for shorter periods of time and fewer cross-network interactions as compared to controls. This hallmark study contributed to accumulating evidence that diminished SN-centered FNC plays a critical role in attention problems in children. It remains unknown whether this pattern of FNC continues to be associated with attention and impulse-control problems in later developmental stages such as adolescence. Adolescence is a formative developmental period with a unique mix of pubertal, social, and academic changes that influence neural and psychological maturation (Goddings et al., 2012). Despite their overall stability, large-scale brain networks undergo subtle reorganization during adolescence (for review see Grayson & Fair, 2017)) at the same time that attention-related functional impairments are often diagnosed. Given its unique window of analysis, dynamic FNC analysis may represent a key methodology for exploring the properties of time varying neural connectivity and its relationship to attention problems and impulsivity during adolescence.

Despite a long-standing debate on whether ADHD should be reclassified as a spectrum disorder, it is unknown whether ADHD symptomology correlates with FNC patterns in TD adolescents. To assess this, we scanned TD adolescents during rest and assessed both static and dynamic patterns of FNC. We followed a precedent set by a recent dynamic FNC study with a dimensional approach to clinical disorders(Espinoza et al., 2019) and assessed how FNC patterns related to ADHD manifestations, attention problems and impulsivity. We hypothesized that dynamic FNC would allow for the detection of activation patterns obscured in time-averaged FNC, namely that TD adolescents with greater attentional difficulties and impulsivity would show more variability in cross-network interactions as assessed by dynamic state metrics as well as meta-state features. In line with previous research in clinical populations(Cai et al., 2018a), we expected a continuation of diminished SN-centered connectivity in adolescents with higher up on the spectrum of attention-disorder related impairment.

Methods and Materials

Participants

We recruited 91 TD adolescents between the ages of 12 and 17 years (mean age = 15.4 ± 1.7 years, 42 females) from Geneva, Switzerland, and surrounding regions. Inclusion criteria included no previous psychiatric diagnosis, epilepsy, or neurological disorders, no intellectual impairments (based on the Cubes and vocabulary subtests of the Wechsler Scales of Intelligence for children (WISC-IV(Wechsler, 2003))) and normal or corrected-to-normal vision. Participants received financial compensation, and written consent was obtained from their parents or legal guardians under protocols approved by the local ethical commission (Commission Centrale d'éthique de la Recherche des Hôpitaux Universitaires de Genève) and in accordance with the Declaration of Helsinki. From the original sample, 9 participants were excluded for excessive movement, defined as a maximum displacement (rotation or translation) of more than 3.0 mm during the fMRI scan. An additional 2 participants were excluded for incomplete behavioral data, resulting in a final sample of 80 adolescents (average age = 15.6 ± 1.6 years, 38 females). There were no behavioral differences in terms of attention nor impulsivity between the 80 included participants and 9 excluded participants (S1 Table). Demographic and behavioral data for included participants can be found in Table 1.

Table 1. All participants demographic and behavioral data. Demographic data, means and standard deviations for all behavioral measures of interest for included and excluded participants.

	Group	**N**	**$N_{Females}$**	**Mean**	**Std. Deviation**
Age	Included	80	38	15.64	1.63
	Excluded	9	6	15.51	1.62
IQ (WISC-IV, Cubes Standardized Score)	Included	80	38	10.74	3.23
	Excluded	9	6	9.89	3.69
YSR Attention Problems	Included	80	38	57.19	6.85
	Excluded	9	6	61.27	12.17
YSR ADHD	Included	80	38	57.00	6.67
	Excluded	9	6	58.55	4.69
YSR Internalizing	Included	80	38	51.93	9.92
	Excluded	9	6	53.81	12.56
YSR Externalizing	Included	80	38	56.23	8.84
	Excluded	9	6	58.09	9.43
UPPS Urgency	Included	80	38	2.46	0.66
	Excluded	9	4	2.36	0.43
UPPS Lack of Premeditation	Included	80	38	2.21	0.63
	Excluded	9	4	2.38	0.75
UPPS Lack of Perseverance	Included	80	38	2.04	0.64
	Excluded	9	4	2.20	0.85
UPPS Sensation Seeking	Included	80	38	2.82	0.64
	Excluded	9	4	2.90	0.80

Questionnaires

Participants completed the Achenbach Youth Self Report(Achenbach, 1991) (YSR), which assesses behavioral problems in the previous 6 months using a 3-point scale (0= not true to 2= very true). Subscales include attention problems, attention deficit/hyperactivity, somatic complaints, social problems, thoughts problems, anxiety/depression, withdrawal/depression, rule-breaking behavior, and aggressive behavior. The attention deficit/hyperactivity subscale is one of the YSR's DSM-oriented subscales and while it was not designed to be a perfect equivalent of the DSM's ADHD criteria, it has nonetheless been found to be an accurate screener for ADHD. Due to the present study's focus on attentional difficulties, the two most relevant YSR subscales were selected from a version of the YSR validated for French-speakers(Wyss et al., 2003), namely attention problems and attention deficit/hyperactivity. Participants also completed the Urgency-Premeditation-Perseverance-Sensation Seeking (UPPS) Impulsive Behavior Scale(Whiteside & Lynam, 2001) a self-report questionnaire measuring four facets of impulsivity. The four facets are sensation seeking, lack of deliberation, lack of perseverance and urgency, all of which have been validated in diverse populations including TD children and adolescents(D'Acremont & Van Der Linden, 2005; Gunn & Smith, 2010; Zapolski et al., 2010), TD adults(Cyders et al., 2007; Magid & Colder, 2007) as well as various clinical populations(G. A. Jacob et al., 2010; Mobbs et al., 2010). Given the large age range of our sample, we controlled for developmental effects by correlating all behavioral measures with age. No significant results were found.

Data Acquisition

Anatomical and functional resting-state imaging data were acquired on a 3T Siemens Trio scanner. The T1-weighted sequence was collected with a 3D volumetric dimension using the following parameters: TR = 2500 ms, TE = 3 ms, flip angle = 8°, acquisition matrix = 256 x

256, field of view = 22 cm, slice thickness = 1.1 mm, 192 slices. An 8-minute resting state fMRI sequence was used during which subjects were asked to fixate their eyes on a white cross shown on a black screen, let their thoughts wander and refrain from falling asleep. We verified that participants kept their open during the scan using an in-scanner eye-monitor and, after the completion of the resting state scan, all participants were asked to describe their experience of the resting state scan and to disclose if they had fallen asleep at any point during the scan. Head movement was minimized with a vacuum cushion constraint. 200 BOLD images were acquired using the following parameters: TR = 2400 ms, TE =30 ms, 38 axial slices, slice thickness = 3.2 mm, flip angle = 85°, acquisition matrix = 94 x 128, field of view = 96 x 128.

Data Analysis

fMRI Data Preprocessing

For each participant, the first 10 functional volumes were discarded to control for equilibration effects of the T1 signal and functional volumes were manually reoriented to place the origin at the anterior commissure. fMRI data were preprocessed in a standardized manner using Data Processing Assistant for Resting-State fMRI (DPARSF) software (http://rfmri.org/DPARSF)(52) implemented using MATLAB(53). DPARSF is based on Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm) and the Resting-State fMRI Data Analysis Toolkit (http://www.restfmri.net)(54). More specifically, data were realigned, slice-timing corrected, co-registered to respective structural images of each subject and segmented. Six rigid body motion parameters, white matter and cerebrospinal fluid signal were regressed out. Images were normalized using Diffeomorphic Anatomical Registration using Exponential Lie algebra (DARTEL) to create a population-specific template, which was then spatially normalized to standard stereotaxic space based on the Montreal Neurological Institute (MNI) coordinate system. Spatial smoothing was applied using an isotropic Gaussian smoothing kernel with a full width at half maximum (FWHM) of 5mm to decrease noise and data was filtered using a temporal band-pass (0.01–0.08 Hz) to reduce the effect of low-frequency noise such as respiration, and high-frequency noise such as cardiac activity.

Group ICA Analysis

Preprocessed images were analyzed using the Group ICA of fMRI Toolbox (GIFT) software package (v4.0b; Medical Image Analysis Lab, University of New Mexico; http://icatb.sourceforge.net/groupica.htm). 29 independent components (ICs) were assumed, based on dimension estimation with minimum description length of the data. Group ICA was performed on fMRI data in three steps: data reduction, ICA, and back reconstruction. In the data reduction step, the data of each participant was reduced using principal component analysis (PCA). The data was then concatenated into a group and reduced again using PCA analysis. In the ICA step, the data underwent IC estimation. IC estimations were stabilized by repeating the ICA algorithm 20 times using ICASSO (http://research.ics.tkk.fi/ica/icasso). The Iq index from ICASSO was used to validate IC decomposition stability and only stable components with an index Iq value greater than 0.8 were retained. Finally, GIFT uses GICA1 back-reconstruction to create subject-specific time courses and spatial maps (78). For a schematic representation, please refer to Fig. 1.

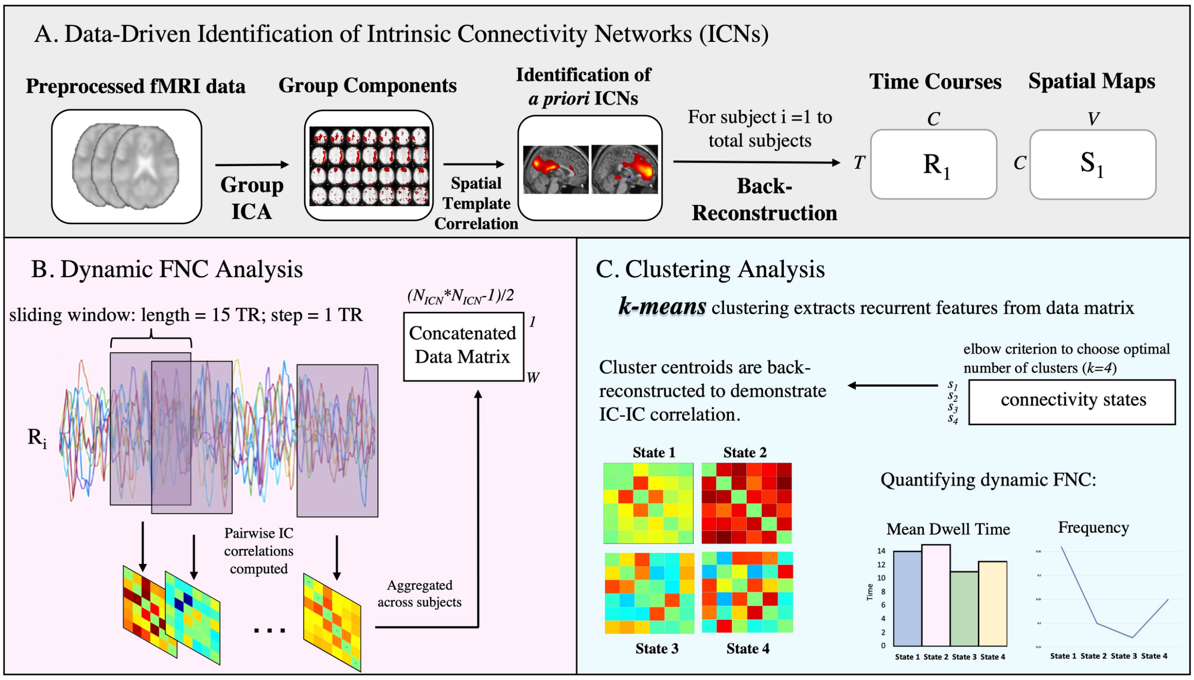

Figure 1. Illustration of major data analysis steps. A) Group ICA analysis was run on preprocessed subject data, resulting in 29 independent components ($C = 29$), 6 of which were identified as ICs in the DMN, ECN and SN. GICA1 back-reconstruction was used to estimate the time courses (R_i) and spatial maps (S_i) for each subject. B) The sliding window approach was used to estimate dynamic FNC as the series of correlation matrices from windowed portions (W) of R_i, resulting in a concatenated data matrix of all IC-IC paired correlation values over time. C) K-means was performed on the concatenated data matrix as outlined in Allen et al., 2014. The optimal cluster number was $k = 4$ and each windowed FNC was assigned to a cluster. Each cluster centroid (also known as state) is represented by a correlation matrix. Clustering analysis allows for quantifying dynamic FNC through measures such as Mean Dwell Time and Fraction Time. This figure was adapted from El-Baba and colleagues (El-Baba et al., 2019).

Identification of resting state networks

Valid networks of interest were identified by visual inspection and confirmed by spatial correlations with publicly-available functional network templates(Shirer et al., 2012) (http://findlab.stanford.edu/functional_ROIs.html). For each network of the triple network theory, the IC with the largest correlation coefficient was chosen (S3 Table). In accordance with our hypothesis, 6 ICs were chosen (ICs 22, 13, 7, 11, 14 & 27) that corresponded to the following 6 networks: dorsal DMN (dDMN), posterior ventral DMN (pvDMN), posterior dorsal DMN (pdDMN), right ECN (rECN), left ECN (lECN) and the SN (for a schematic representation, please refer to Fig. 1). Additional networks such as the basal ganglia, auditory, language, sensorimotor, visuo-spatial, and visual were also identified but not used in further analysis because they were outside the scope of the triple network theory.

Static FNC Analysis

Static FNC analysis was conducted using the MANCOVAN toolbox in GIFT (v4.0b; Medical Image Analysis Lab, University of New Mexico; http://icatb.sourceforge.net/groupica.htm). Analyses followed step-by-step procedures described in previous studies(Jafri et al., 2008): first, each subject's time course was detrended, de-spiked and filtered using a fifth-order Butterworth low-pass filter with a cutoff frequency of 0.15 Hz. Age, sex, frame-wise displacement and each subject's motion parameters (rp*txt) were included as nuisance covariates(Damaraju et al., 2014). For each participant, a correlation map was produced by computing the correlation coefficient *r* between the time series of each pair of ICs (the ICA algorithm assumes that the time courses of cortical areas within one component are synchronous(Calhoun et al., 2003)). Given that we had six networks of interest, a total of fifteen different pair-wise combinations of inter- and intra-network connectivity were obtained.

Static FNC Statistical Analysis

Before running statistical analysis on static FNC results, we transformed *r* values into z-scores using Fisher's transformation. We verified the data was normally distributed and used Pearson correlations to correlate each participant's measure of functional network connectivity with behavioral scores of attention problems and ADHD manifestations (as measured by the YSR subscale(Achenbach, 1991)) and impulsivity (as measured by the UPPS Impulsive Behavior Scale(Van Der Linden et al., 2006; Whiteside & Lynam, 2001). Correlation results were corrected for multiple comparisons for univariate analyses (for both number of IC pairs and number of behavioral questionnaires) using the false discovery rate (FDR; $p<0.05$). All statistical analyses were performed in RStudio (http://www.rstudio.com/).

Dynamic FNC Analysis

We conducted dynamic FNC analysis using the tapered sliding window approach (Allen et al., 2014a; Sakoğlu et al., 2010) to identify distinct, time-varying patterns of FNC. Critically, we chose to model our analysis based off of parameters used in recent dynamic FNC studies (Allen et al., 2014a; Damaraju et al., 2014; Mennigen et al., 2018), including one that also adopted a dimensional approach towards clinical disorders(Espinoza et al., 2019). In accordance with said studies, a rectangular window (width 15 TRs or 36 seconds) was convolved with a Gaussian of sigma 3 TRs and slid in steps of 1 TR across concatenated time courses, resulting in 160 time-windowed domains per subject. A separate FNC matrix was computed as the pairwise correlation between networks of interest (6 network x 6 networks) for each of the 160 time-windowed domains (per subject). In total, the dynamic FNC data was made up of 12800 windowed FNC matrices (80 participants * 160 windowed FNC). These windowed FNCs capture the changes in covariance between our 15 networks during the duration of the scan. Other important statistical measures included the graphical LASSO algorithm (Friedman et al., 2008), which was used to improve the estimation of correlations among time-courses with short time domains, as well as a penalty on the L1 norm of the precision matrix to increase sparsity. The regularization parameter was optimized for each subject by evaluating the log-likelihood of unseen data (subject's covariance matrices) in a cross-validation framework. For a schematic representation, please refer to Fig. 1.

Clustering Analysis

K-means clustering was applied to windowed FNCs for both dynamic FNC and meta-state analysis. For dynamic FNC, we used the k-means algorithm with the L1 distance (Manhattan distance) to run clustering analysis (Espinoza et al., 2019), a validated approach used to identify which FNC states had most commonly occurred during rest(E. A. Allen et al., 2014a; Calhoun et al., 2014). K-means was run on all subjects' dynamic FNC data with the number of clusters ranging from two to eight. Parameters for k-means included 10 cycles of clustering with a maximum of 200 iterations for reaching a solution. The elbow criterion was then applied to the resulting cluster index to estimate the optimal number of clusters, which was K=4. The four clusters, also referred to as FNC states, described the four connectivity patterns that subjects move between over time. Given that every subject’s trajectory between the four FNC states was different, it is important to note that not every subject entered every state. Based on the dynamic FNC states, three metrics characterizing each participant's dynamic behavior during the scan were calculated. These behavioral metrics include mean dwell time (MDT), which is the time spent in a certain state before switching to another one, fraction time (FT) which is the time spent in one state relative to the entire scan time and the number of transitions (NT), which represents how often participants changes between different dynamic states.

Meta-State Analysis

The difference between dynamic FNC analysis and meta-state analysis begins after the sliding window has dissected data into windowed FNC matrices. Rather than assigning each windowed FNC to one dynamic state as done in dynamic FNC analysis, meta-state analysis models each windowed FNC as weighted sums of maximally independent connectivity patterns (Miller et al., 2016). These connectivity patterns are then discretized using quartile discretization. The discretized connectivity pattern distance vectors are referred to as meta-states (Mennigen et al., 2019a). Four indices of connectivity dynamism can be calculated from meta-states, namely i) the number of distinct meta-states the subjects occupied during their scans (meta-state number); ii) the number of times that subjects switched from one meta-state to another (meta-state changes); iii) the largest distance between two meta-states that subjects occupied (meta-state span); and iv) the total distance traveled by each subject through the state space (meta-state total distance).

Dynamic FNC Statistical Analysis

Dynamic connectivity was assessed through three separate analyses, namely dynamic FNC, state-based metrics, and meta-state metrics. Statistical tests between each of these analyses and behaviors of interest (Attention Problems and ADHD Manifestations, as measured by the YSR (Achenbach, 1991), and impulsivity, as measured by the UPPS Impulsivity Scale (Van Der Linden et al., 2006; Whiteside & Lynam, 2001)), were computed using RStudio (http://www.rstudio.com/).

Dynamic FNC analysis output a matrix for each dynamic state, which consisted of correlation coefficients (r values) for each of the 15 IC-IC pairs, for each participant who entered that state. We stabilized variance by using the Fisher transformation to convert r values into z-scores. We then conducted Pearson correlations between the 15 IC-IC pairs and our 6 behavioral metrics of interest, for each of the four dynamic states. The results of this correlation analysis were corrected for multiple comparisons (360 comparisons) for univariate analyses using the false discovery rate (FDR; $p<0.05$).

We obtained 3 state-based metrics for each participant for each state (MDT, FT, and NT). We made one matrix with each participant's state-based metrics for all 4 states (MDT state 1, MDT state 2 etc.) and behavioral data and ran Pearson correlations and corrected for multiple comparisons (1440 comparisons) for univariate analyses (FDR; $p<0.05$).

We obtained 4 meta-analysis metrics (meta-state number, meta-state changes, meta-state span & meta-state total distance). We made one matrix with each participant's meta-state data and behavioral results ran Pearson correlations. The results of this correlation analysis were corrected for multiple comparisons (1920 comparisons) for univariate analyses (FDR; $p<0.05$).

Static FNC Results & Behavioral Correlations

During rest, the three ICs of the DMN (vDMN, pdDMN, and pvDMN) were most strongly correlated with themselves, as were the two ICs of the ECN (rECN and lECN) (Supplementary Materials, Figure S1). The posterior components of the DMN had weak positive correlations with both the SN and rECN. The ECN and SN were neither correlated nor anti-correlated with each other. No correlations between static FNC and behavioral measures survived multiple comparison correction.

Dynamic FNC Results

Dynamic FNC analysis revealed that time-varying FNC in our sample could be represented in 4 distinct states (Fig. 2) rather than a single, static state(Espinoza et al., 2019). State-1 was the most frequent, with an average fraction time of 37%, and represented a dynamic state in which posterior DMN and ECN were harmonically connected and segregated from the SN. ICs in State-1 shared weak positive correlations with each other, except for the posterior DMN, which was strongly correlated within itself (pdDMN-pvDMN) and with the right ECN (pdDMN-rECN). 74 out of the 80 participants spent time State-1. State-2 was the second most frequent state with an average fraction time of 24%. It displayed patterns of resting state activation typically seen in time-averaged FNC, with strong positive correlations within nodes of the DMN and the ECN, respectively, anti-correlations between the DMN-ECN and moderately strong correlations between the DMN-SN. 66 out of 80 participants spent time in State-2. State-3 had an average fraction time of 20% and showed positive connectivity between all networks. 54 out of 80 participants spend time in State-3. Finally, State-4 had an average fraction time of 19% and can be defined by a strong and isolated synchronization between the pvDMN-SN; both the pvDMN and SN were either not correlated or anti-corrected with the remaining ICs namely the dDMN, pdDMN and ECN, which were, in turn, positively correlated amongst themselves correlated with each other. 50 out of 80 participants spend time in State-4. Importantly, to confirm our results were not majorly driven by motion difference among the participants. we calculated Pearson correlations between the rate of occurrence of each dynamic state and mean framewise displacement of our participants. We found no significant correlation (S3 Table).

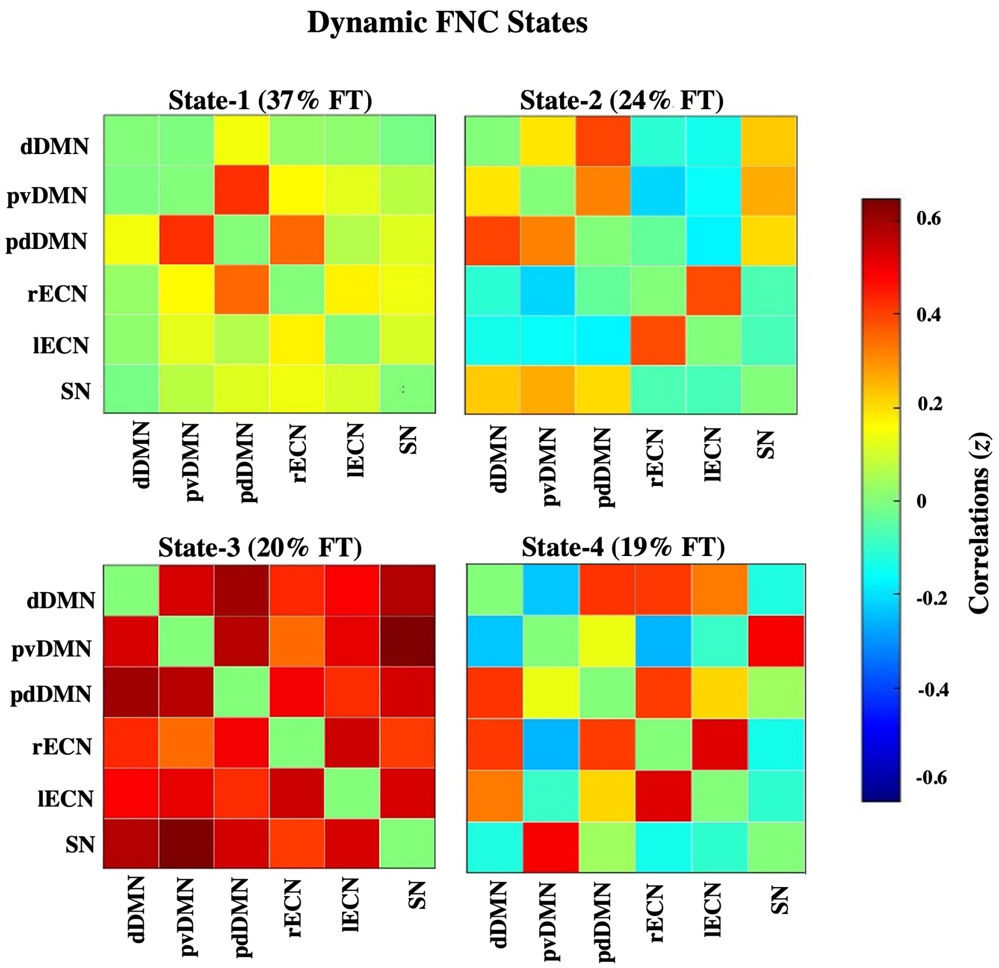

Figure 2. Dynamic FNC Results. Correlation matrices showing the fraction time and pattern of cross-network functional connectivity (represented using z-scores) of each of the four dynamic FNC states. 74 participants entered State-1, 66 participants entered State-2, 54 participants entered State-3, and 50 participants entered State-4. dDMN = dorsal default

mode network; pvDMN= posterior ventral default mode network; pdDMN = posterior dorsal default mode network; rECN = right executive control network; lECN = left executive control network; SN = salience network.

Associations between Dynamic FNC, State-Based Metrics and Behavior

To assess relationships between dynamic FNC and behavior, we computed Pearson correlations between each dynamic state (State-1, State-2, State-3 and State-4) and behaviors of interest, namely, Attention Problems & Manifestations of ADHD (as measured by the YSR(Achenbach, 1991)) and impulsivity (as measured by the UPPS Impulsivity Scale(Van Der Linden et al., 2006; Whiteside & Lynam, 2001). Results revealed that, unlike the static connectome, dynamic connectivity patterns did correlate with variations seen in behavior. This was illustrated by two behavioral scores that correlated with diminished SN-lECN functional connectivity during State-1: first, Manifestations of ADHD correlated with diminished FNC between the SN and the lECN (p=.02, r=-.38) and second, Attention Problems also correlated with diminished FNC between the SN and the lECN (p=.01, r=-.39) (Fig. 3). No other correlations survived correction for multiple comparisons (FDR; p<0.05).

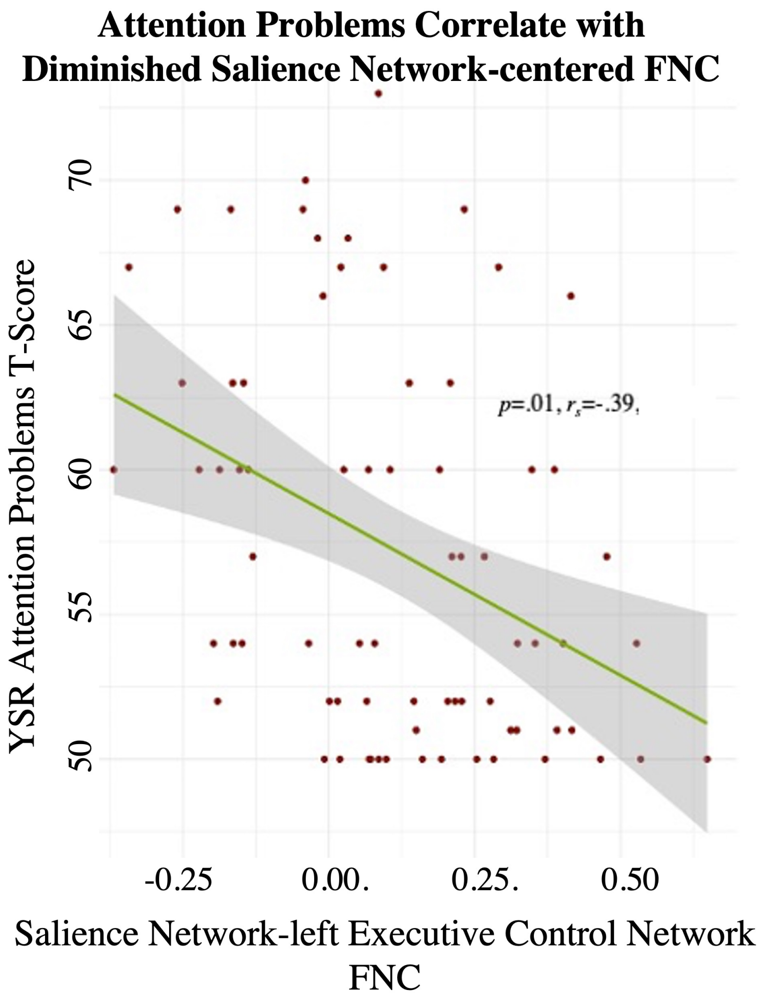

Figure 3. Association between FNC in Dynamic State-1 and Attention Problems. Pearson correlations revealed that participants' T-Scores for Attention Problems (as measured by the YSR) correlated with diminished functional connectivity between the Salience Network and the left Executive Control Network during Dynamic State-1 (No other correlations survived correction for multiple comparisons (FDR; p<0.05).

We also assessed relationships between state-based metrics and behavior. Results revealed that mean dwell time in State-3 correlated with both ADHD manifestations, as measured by the YSR(Achenbach, 1991) (*p*=.03, *r*=.30), and impulsivity, as assessed by the Lack of Perseverance subscale of the UPPS-S(Van Der Linden et al., 2006; Whiteside & Lynam, 2001) (*p*=.02, *r*=.33). No other correlations survived correction for multiple comparisons (FDR; p<0.05).

Associations between Meta-States and Behavior

Meta-state analysis revealed positive associations between ADHD manifestations, as measured by the YSR(Achenbach, 1991) and the number of times participants changed meta-states (*p*=.04, *r*=.24) as well as the total distance (*p*<.01, *r*=.35). No other correlations survived correction for multiple comparisons (FDR; p<0.05).

Discussion

This study assessed whether dynamic FNC analysis could detect meaningful relationships between large-scale brain networks and ADHD manifestations, attention problems and impulsivity in TD adolescents, that were obscured in static FNC. Only one study to date has used the triple-network model of cognitive control to test the hypothesis that SN-centered interactions are impaired in ADHD(Cai et al., 2018a) and no study has assessed how time-varying interactions relate to attention disorder-related symptoms in TD adolescents.

Overall, our results suggest that dynamic FNC is a sensitive approach to underpinning fine alterations in large-scale neural circuits and their behavioral correlates in non-clinical populations. We found no significant relationship between behaviors associated with attention disorders and static FNC patterns in TD adolescents. Static FNC analysis is a well-known methodology that has been linked to behaviors associated with clinically diagnosed attention disorders(Cai et al., 2018a), the present lack of findings suggests our sample size of TD adolescents may not have been adequately large enough to detect what may be relatively small effects. To assess whether a different approach would yield results, we conducted dynamic FNC analysis which revealed 1) that network interactions between the DMN, ECN and SN in our sample could be optimally represented through four dynamic states (Fig. 2) and 2) that there is enough variation within TD populations to allow for detection of relationships between large-scale networks and behaviors associated with attention disorders.

Most participants entered and spent the most time in State-1, which showed strong connectivity within the posterior DMN and between the DMN-ECN along with a complete absence of SN-centered connectivity. Remarkably, within this dynamic state, we were able to observe lower FNC between the SN-ECN in participants with higher scores for attention problems. This lends additional evidence that SN-centered connectivity contributes to clinical manifestations of attentional disorders (see recent review(Harikumar et al., 2021)). The anterior insula, a hub within the SN(Uddin & Menon, 2010b), is believed to play a crucial role in mediating switching between the ECN and the DMN. The SN-ECN connectivity specifically is thought to signify the detection of salient stimuli by the anterior insula and subsequent signaling to the ECN to recruit recourses necessary for attentionally demanding tasks(Cai et al., 2014; Uddin & Menon, 2010b). Previous research has linked aberrant activation the SN, including the anterior insula, to ADHD(Orinstein & Stevens, 2014). In the present study, the similarity of diminished SN-centered connectivity to behavioral measures of both ADHD and Attention Problems may suggest that the former is being driven by the latter. Moreover, the fact that we can observe attention-related impairments in the SN-ECN in TD populations suggests that this circuit may be most relevant to attention problems in ADHD and could potentially be influenced by aberrant structural connectivity between the SN-ECN. We also find results relevant to impulse-control/hyperactivity seen in ADHD: in our sample, participants higher up on the spectrum of both ADHD manifestations and impulsivity problems spent longer in the hyperconnected State-3 before switching to another state. This finding uncovered by dynamic FNC analysis suggests two things: first, that while all TD adolescents may enter and leave hyperconnected states during rest, such states are more stable in adolescents with increased ADHD manifestations. Second, given that State-3's mean dwell time also correlated with increased impulsivity, having prolonged periods of time where large-scale neural networks are hyperconnected to each other may be specific to the hyperactive manifestations of ADHD.

Critically, we present evidence of enhanced global dynamic activity over an extended dynamic range, reflected by increasingly volatile meta-states that change more often and travel a greater total distance, in adolescents with increased ADHD manifestations. Meta-state analysis aims to account for as much information within each windowed FNC as possible by creating a vector representing the distance of each windowed FNC to each dynamic state(Miller et al., 2016) and, in doing so, circumvents issues with the more conservative dynamic state-based metrics, which assign every windowed FNC to its most highly correlated state. If dynamic FNC analysis is viewed as a more comprehensive, process-focused extension of static FNC analysis, meta-state analysis can be viewed as a similar continuation of dynamic FNC. Assessing the number of unique meta-states and other meta-state metrics may allow for the detection of subtle relationships between attention and FNC that state-based dynamic metrics, which are comparatively more conservative, only capture in clinical samples. Here, we present results indicating the continuation of that same finding in TD adolescents. In other words, previous dynamic FNC studies have shown that children with ADHD oscillate between a greater number of dynamic FNC states and have more variable network interactions than TD children(Cai et al., 2018a). In the present study, we present evidence that this phenomenon is not restricted to categorically defined, clinical ADHD, but that non-clinical adolescents higher up on the *spectrum* of attention dysfunction also follow volatile patterns of changing meta-states more often and trending towards oscillating between a greater number of meta-states than adolescents lower down on the same continuum. We also show that the total distance traveled by each subject through the state space (the sum of the L1 distances between successive meta-states, i.e., meta-state total distance) was greater for participants higher up on the attention problem continuum. When taken with our previous findings, we show that as ADHD manifestations increase, adolescents tended to spend more time in a state of hyperconnectivity while also traveling over an increased dynamic range, once again supporting the pattern of increased volatility associated with attention disorders.

We acknowledge the present study has several limitations. Future studies should aim to include behavioral instruments measuring attention problems and impulsivity that are less dependent on participant self-report. This is particularly the case for ADHD populations(Smith et al., 2000), for whom it is important to include performance tasks sensitive to attentional disturbances such as the continuous performance test (CPT)(Riccio et al., 2002). Future studies should also aim to include measures of hyperactivity, a core symptom in attention-related disorders, especially during adolescence. In terms of task validity, we instructed participants to let their mind wander without falling asleep during the scan. We used an in-scanner eye monitor to ensure they did not close their eyes but did not include questionnaires about thoughts or cognitions afterwards to get an indication of their scan experience, which could have influences static and dynamic connectivity(Kucyi & Davis, 2014). It is important to underline that we did not directly compare static to dynamic FNC and therefore cannot state that dynamic FNC is better suited to uncovering trends in non-clinical populations. In terms of the applicability of the present results, it is of high importance to repeat these analyses in populations with and without clinical ADHD and to do so longitudinally. Pursuing such analyses will bring further insights into the clinical states of ADHD and its presentations, and into common clinical and theoretical challenges such as comorbidity in ADHD and functional outcomes along development. While out of the scope of the present study, another interesting avenue for future research would be using dynamic FNC to assess heterogeneous presentations of attention disorders such as ADHD.

Overall, our results add to accumulating evidence that we, as individuals, all fall somewhere on a spectrum ranging from highly attentive/motor-impulse controlled to highly inattentive/hyperactive-impulsive(Borsboom et al., 2016; Coghill & Sonuga-Barke, 2012). We show dynamic FNC analysis yields a process-focused understanding of large-scale neural connectivity and its association to attention problems and impulsivity. Our results in TD adolescents are consistent with clinical ADHD literature, underlying the importance of re-evaluating attention disorders like ADHD as being best conceptualized as extreme ends of a spectrum rather than categorically defined disorders.

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Supplementary Materials

S1 Table. Independent sample t-tests between included and excluded participants. Independent sample T-tests revealed no significant differences between included and excluded participants for age nor behavioral measures of interest.

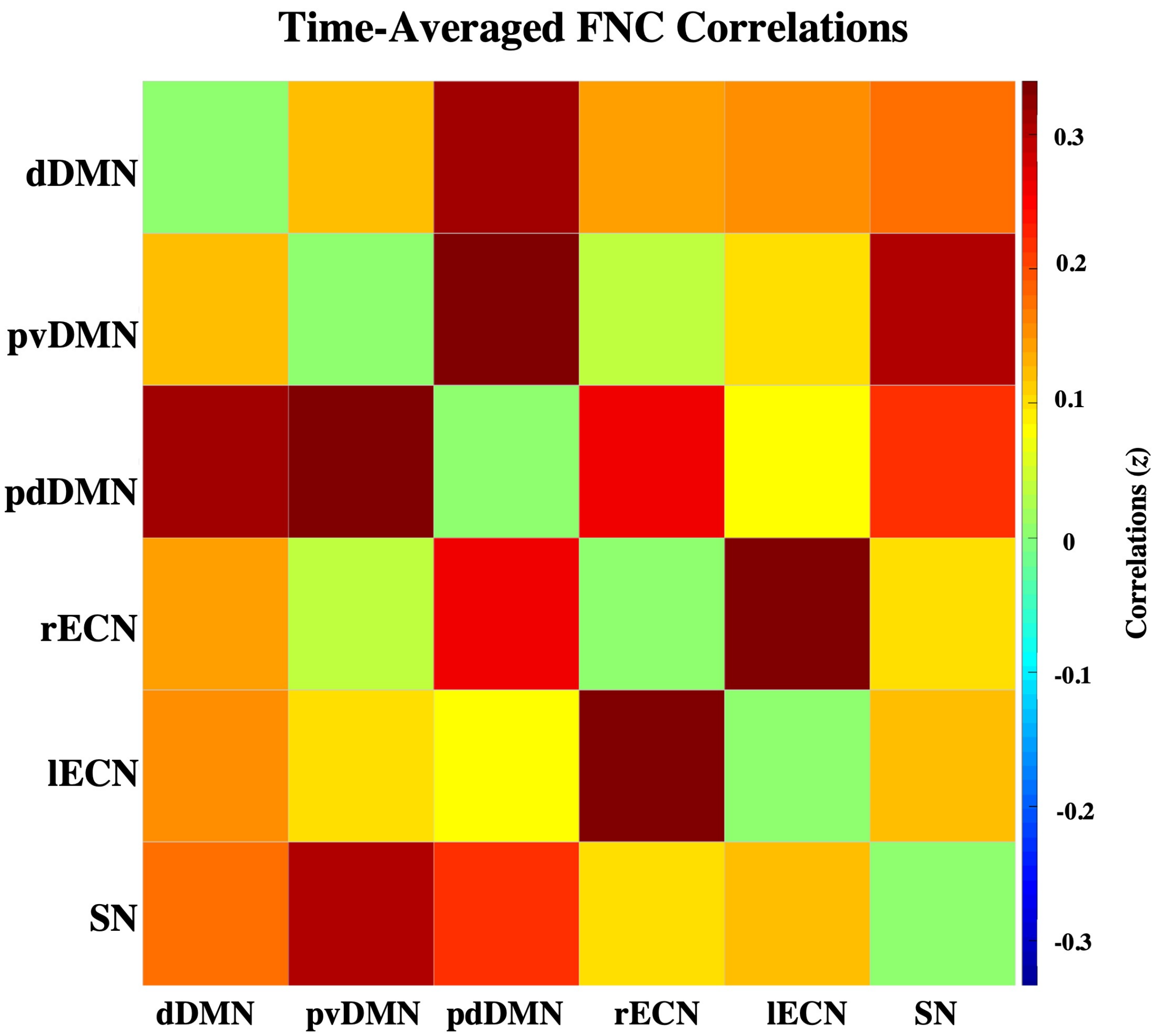
	t	**df**	**Sig.**	**95% Confidence Interval**	
				Lower	Upper
Age	0.23	87	0.82	-0.92	1.16
IQ (WISC-IV, Cubes Standardized Score)	0.737	87	0.46	-1.44	3.14
YSR Attention Problems	-1.66	87	0.10	-8.96	0.79
YSR ADHD	-0.75	87	0.45	-5.71	2.57
YSR Internalizing	-0.57	87	0.57	-8.43	4.67
YSR Externalizing	-0.65	87	0.52	-7.55	3.82
UPPS Urgency	0.63	87	0.53	-0.22	0.41
UPPS Lack of Premeditation	-0.72	87	0.48	-0.69	0.34
UPPS Lack of Perseverance	-0.60	87	0.55	-0.74	0.42
UPPS Sensation Seeking	-0.34	87	0.73	-0.63	0.46

S2 Table. Spatial correlations results. Spatial correlation coefficients between ICs of interest with functional network templates (http://findlab.stanford.edu/functional_ROIs.html).

Template	**Most Correlated IC**	**Correlation Coefficient**
dDMN	22	0.46
pvDMN	13	0.33
pdDMN	7	0.63
rECN	11	0.40
lECN	14	0.34
SN	27	0.35

S3 Table. Correlations between dynamic states and framewise displacement. Pearson correlations coefficients between the mean framewise displacement and the occurrence of each dynamic FNC state per participant.

	Coefficient	***p*-value**
State 1	-0.1551717	0.16931917
State 2	-0.0033445	0.97651084
State 3	0.15495473	0.16992346
State 4	0.02312143	0.83868425



S4 Figure. Static FNC Results. Correlation matrix showing Static FNC results between ICs of Interest. dDMN = dorsal default mode network; pvDMN= posterior ventral default mode network; pdDMN = posterior dorsal default mode network; rECN = right executive control network; lECN = left executive control network; SN = salience network.

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Chapter 4

This chapter was submitted for publication in October 2023

Attention and Emotion in Adolescents with ADHD; a Time-Varying Functional Connectivity Study

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Abstract

Background

The objective of this study was to comprehensively assess brain-behavior relationships between time-varying FNC and an integrated attention-deficit/hyperactivity disorder (ADHD) phenotype, including measures of inattention, hyperacuity and emotional dysregulation. While emotion dysregulation is a common clinical feature of ADHD, neuroimaging studies on ADHD rarely assess its impact on large-scale functional network connectivity (FNC).

Methods

We conducted resting-state functional magnetic resonance imaging in 78 adolescents (34 with ADHD) and obtained experimental and self-report measures of inattention, hyperactivity, and emotional reactivity. We used time varying FNC analysis and multivariate analysis to evaluate group differences in large-scale, dynamic FNC and ADHD symptomology.

Results

Multivariate analysis revealed two significant group*behavior differences. Dynamic FNC analysis revealed the ADHD group, compared to controls, had diminished salience network centered FNC that was driven by a comprehensive ADHD phenotype ($p<.004$, $r=0.57$). Meta-state analysis revealed ADHD group had more volatile patterns of global connectivity that were driven by increased emotional reactivity, compared to controls ($p<.002$, $r=0.63$).

Conclusions

Atypical patterns of dynamic FNC in adolescents with ADHD are associated with the affective and cognitive components of ADHD symptomology.

Introduction

A rich neuroimaging literature exists on brain systems underlying the neurodevelopmental condition attention-deficit/hyperactivity disorder (ADHD). The neural correlates of ADHD, which is defined by age-inappropriate levels of inattention and hyperactivity (American Psychiatric Association & American Psychiatric Association, 2013), have yet to be fully characterized despite decades of neuroimaging research using task-based functional magnetic resonance imaging (fMRI) paradigms. Importantly, research consistently shows that heightened emotion dysregulation, in addition to inattention and hyperactivity, is a core symptom of ADHD (Barkley, 2015a; Corbisiero et al., 2013; Shaw et al., 2014). In recent years, researchers have started using task-free paradigms, otherwise known as resting-state fMRI (rs-fMRI), to assess ADHD's neural underpinnings. Rs-fMRI measures spontaneous neuronal activity that occurs when individuals let their mind freely wander for the duration of the MRI scan. This spontaneous activity organizes itself into reliable and reproducible functional networks (FNs) composed of functionally connected brain regions (for a review, see (Grayson & Fair, 2017)). Connectivity within and between large-scale, neurocognitive FNs in individuals with ADHD has typically been studied using time-averaged approaches which have largely resulted in inconsistent and contradictory findings (Cortese et al., 2021). In recent years, to better characterize temporal variations in FN connectivity (FNC) over time and how they may relate to ADHD symptomology, researchers have started adopting dynamic approaches to rs-fMRI (Calhoun & Adali, 2012; Erhardt et al., 2011).

A commonly used framework to assess neural systems implicated in cognitive control and psychopathology is the Triple Network Model (Menon, 2011). This parsimonious model focuses on the interplay between three major neuro-cognitive networks during rest, namely, the salience network (SN), the central executive network (CEN) and default mode network

(DMN) (Menon, 2011; Uddin & Menon, 2010). These networks can be derived from rs-FMRI using mathematical modeling, such as independent component analysis (ICA) which characterizes networks as distinct independent components (ICs) comprised of spatial maps and time-courses of functional activity. A static approach to functional connectivity assumes it remains constant over time (Jafri et al., 2008; Allen et al., 2011). The majority of studies on functional connectivity adopt this approach but as demonstrated by a recent systematic review on rs-fMRI in ADHD, there has been no spatial convergence of ADHD-related hyperconnectivity or hypoconnectivity across static FNC studies (Cortese et al., 2021). The authors suggest this lack of convergence may be due to several factors such as heterogeneity of study participants' characteristics (such as age, sex, and comorbidities) as well as heterogeneity of ADHD symptomology (such as severity and type of symptoms). Another likely reason is that the nature of brain functional connectivity is intrinsically multi-scale and dynamic over time.

In recent years there has been a sustained increase in dynamic FNC research because it can capture fluctuations in brain networks that might not be apparent in static connectivity analyses (Allen et al., 2014a). The increased sensitivity of a dynamic compared to static approach allows it to assess variations in the strength of interregional coupling over time (Calhoun & Adali, 2012; Erhardt et al., 2011). This allows for a more fine-grained evaluation of the relationship between functional connectivity and cognition related to phenotypic traits of ADHD (Lurie et al., 2020). There are various methods of assessing time varying FNC between large-scale neural networks. One approach uses a 'hard-clustering' method in which the time-course of each FN is segregated into short time windows and each window is attributed to one of a few repeating, stable connectivity states (Allen et al., 2014a). Another approach is meta-state analysis, which assumes dynamic states can overlap in time. Meta-state analysis creates a vector representing each time window's correlation to each connectivity state, allowing for a more nuanced measure of dynamic fluidity and range of whole-brain connectivity (Miller et al., 2016). Literature shows that ADHD populations generally have increased variability in global dynamic FNC (De Lacy & Calhoun, 2019), as well as within-network FNC (Mowinckel et al., 2017) and between the DMN, SN, and CEN (Cai et al., 2018; Tottenham et al., 2012). A recent study used multivariate regression analysis to assess how brain dynamics relate to distinct behavioral and cognitive dimensions of ADHD (Luo et al., 2023). Luo and colleagues found distinct dynamic FNC states that corresponded differently to ADHD symptomology: the inattention/hyperactivity dimension was positively associated with dynamic FNC within the default mode network (DMN) and negatively associated with dynamic FNC between DMN and the sensorimotor network (SMN); the inhibition and flexibility dimension, and fluency and memory dimensions were both positively associated with dynamic FNC within DMN and between DMN and SMN, and negatively associated with dynamic FNC between DMN and the CEN. This promising study used a multivariate approach, but interestingly did not find associations between the SN and inattention or hyperactivity/impulsivity, which previous studies have (Cai et al., 2018).

Dynamic FNC analysis may help tease out some of the current challenges in understanding the variety of functional impairments in ADHD. Indeed, clinical research consistently shows that inattention and hyperactivity alone cannot adequately explain the severity of ADHD nor its associated functional impairments (Anastopoulos et al., 2011; Skirrow et al., 2014). To allow for a more comprehensive characterization of ADHD, difficulties with emotion regulation and reactivity have been proposed as the fourth tenet of ADHD (Barkley, 2015a; Corbisiero et al., 2013; Shaw et al., 2014). Emotion regulation refers to how we manage the experience and expression of our emotions (Gross 1998), and emotion reactivity refers to the degree to which emotions arouse our physiological state (Dennis 2006). Individuals with ADHD present with difficulties in both emotion regulation and reactivity (Anastopoulos et al., 2011; Biederman, Spencer, Lomedico, et al., 2012; Biederman, Spencer, Petty, et al., 2012; Graziano & Garcia, 2016; Skirrow et al., 2014; Sobanski et al., 2010). These difficulties are highly persistent (Biederman, Spencer, Petty, et al., 2012), associated with significant functional impairments (Barkley & Fischer, 2010; Brocki et al., 2019) and appear specific to ADHD in that they not better explained by comorbidities (Barkley & Fischer, 2010; Skirrow et al., 2014; Sobanski et al., 2010). However, rs-fMRI studies rarely include emotion regulation difficulties when assessing how altered FNC may relate to behavioral presentations of ADHD. This may result in a truncated understanding of brain-behavior relationships in ADHD, as in the study of Luo and colleagues (Luo et al., 2023). It therefore important to continue using robust, multivariate approaches in dynamic FNC while also comprehensively assessing ADHD symptomology.

The present study aimed to characterize differences in large-scale FNC between adolescents with and without ADHD using both hard-clustering and meta-state dynamic FNC analyses. It used multivariate approaches to relate dynamic FNC patterns to core ADHD symptomology, namely, inattention, impulsivity, and emotion dysregulation. We hypothesized that, compared to their typically developing peers, adolescents with ADHD would have increased behavioral difficulties with attention and emotion, and more volatile patterns of dynamic FNC during rest. We anticipated that we would find group differences in brain-behavior relationships that were driven by ADHD symptomology of inattention, hyperactivity and/or a combination. Finally, we hypothesized we would find group differences in brain-behavior relationships that were driven by comprehensive ADHD including heightened emotional dysregulation.

Methods and Materials

Participants

We recruited 78 adolescents between the ages of 12 and 17 years, 34 of whom were diagnosed with ADHD (mean age = 15.18 ± 1.94 years, 16 females) and 44 of whom were TD (mean age = 16.01 ± 1.64 years, 24 females) from Geneva, Switzerland, and surrounding regions. Patients were recruited from local medical clinics specialized in child psychiatry. Patients were diagnosed with ADHD by psychologists (JRB and JLS) using the ADHD Child Evaluation (ACE). The ACE is a semi-structured clinical interview used to evaluate the presence of ADHD in children and was developed to directly map onto the DSM-V's diagnostic criteria for ADHD. 8 participants were regularly taking medication with a half-life of less than 24 hours and were asked to stop all medication 24h before the scan. TD controls were adolescents matched for age and gender. Inclusion criteria included no previous psychiatric diagnosis, epilepsy, or neurological disorders, no intellectual impairments (based on the Cubes and vocabulary subtests of the Wechsler Scales of Intelligence for children (WISC-IV(Wechsler, 2003)) and normal or corrected-to-normal vision. Participants received financial compensation, and written consent was obtained from their parents or legal guardians under protocols approved by the local ethical commission (Commission Centrale d'éthique de la Recherche des Hôpitaux Universitaires de Genève) and in accordance with the Declaration of Helsinki. Four participants were excluded from the TD group, three for excessive movement (>2mm) during the scan and one for incomplete behavioral data. Four participants were excluded from the ADHD group (two for incomplete scans, two for excessive movement during the scan). The final analysis was conducted on 70 adolescents, 30 of whom were patients with ADHD and 40 of whom were TD controls (Table 1).

Measures of Attention & Emotional Reactivity

To evaluate ADHD's heterogenous symptomology, we assessed facets of inattention, impulsivity, and emotional reactivity. All participants completed the Conners Continuous Performance Test-3 (CPT-3), a computer-based neuropsychological test for individuals aged 8 and over that utilizes a go-no go paradigm and assesses the ability to discriminate between target and non-target stimuli presented in a continuous and repetitive manner. The CPT-3's measurements (Supplementary Materials, Table 1) assess inattentiveness, impulsivity, sustained attention, and vigilance. Increased inattentiveness is indicated by poor Detectability (d'), a slow Hit Reaction Time (HRT), high rates of Omissions, Commissions, and high inconsistency in response speed (HRT's Standard Deviation (HRT SD). Increased impulsivity is indicated by a faster HRT and higher rates of Commissions and/or Perseverations. Problems with sustained attention are indicated by an atypical slowing in the respondent's HRT over time (measured by the HRT Block Change variable), and high rates of Omissions and Commissions in later blocks of the administration. Finally, vigilance is ability to maintain performance level at varying levels of stimulus frequency (inter-stimulus intervals; ISIs). Vigilance is indicated by the variable HRT ISI Change, and patterns of Omissions and Commissions at different ISIs.

In addition to inattention and impulsivity/hyperactivity, decades of scientific research has established emotion dysregulation as the third central tenet of ADHD (Barkley, 2015b). Characterization of integrative ADHD symptomology would be incomplete without assessing the ability to process and regulate emotions. To this end, subjects also completed the Emotion Reactivity Scale (ERS) (Nock et al., 2008), a validated self-report questionnaire measuring three facets of emotional reactivity: sensitivity, persistence, and intensity. Emotion reactivity refers to the extent to which an individual experiences emotion (a) in response to a wide array of stimuli (i.e., emotion sensitivity), (b) strongly or intensely (i.e., emotion intensity), and (c) for a prolonged period before returning to baseline level of arousal (i.e., emotion persistence).

Data Acquisition

Anatomical and functional resting-state imaging data were acquired on a 3T Siemens Trio scanner. The T1-weighted sequence was collected with a 3D volumetric dimension using the following parameters: Voxel size: 1.0×1.0×1.0 mm, TR = 2200 ms, TE = 2.96 ms, flip angle = 9°, acquisition matrix = 256 x 256, field of view = 256 mm, slice thickness = 1 mm. An 8-minute resting state fMRI sequence was used during which subjects were asked to fixate their eyes on a white cross shown on a black screen, let their thoughts wander and refrain from falling asleep. We verified that participants kept their open during the scan using an in-scanner eye-monitor. Head movement was minimized with a vacuum cushion constraint. 480 BOLD images were acquired using the following parameters: voxel size: 1.0×1.0×1.0 mm, TR = 1000 ms, TE =32 ms, 66 axial slices, slice thickness = 2 mm, flip angle = 50°, acquisition matrix = 94 x 128, field of view = 224 mm x 132 mm.

Data Analysis

fMRI Data Preprocessing & Group ICA Analysis

For each participant, the first 10 functional volumes were discarded to control for equilibration effects of the T1 signal and functional volumes were manually reoriented to place the origin at the anterior commissure. fMRI data were preprocessed in a standardized manner using Data Processing Assistant for Resting-State fMRI (DPARSF) software (http://rfmri.org/DPARSF) implemented using MATLAB. DPARSF is based on Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm) and the Resting-State fMRI Data Analysis Toolkit (http://www.restfmri.net). Preprocessed images were analyzed using the Group ICA of fMRI

Toolbox (GIFT) software package (v4.0b; Medical Image Analysis Lab, University of New Mexico; http://icatb.sourceforge.net/groupica.htm). The estimated number of independent components (ICs) was 34 based on dimension estimation with minimum description length of the data. For specific details on fMRI data preprocessing and group ICA analysis, please refer to our previous publications on this methodology (Rafi et al., 2023).

Identification of resting state networks

First, we visually identified ICNs of interest and then confirmed them using spatial correlations with publicly-available functional network templates (Shirer et al., 2012; http://findlab.stanford.edu/functional_ROIs.html). We modeled the triple network model by choosing five ICs (for correlation results, please see Supplementary Materials, Table 2) to model the following five networks: dorsal DMN (dDMN), ventral DMN (vDMN), right ECN (rECN), left ECN (lECN) and the salience network (SN).

Dynamic FNC Analysis

We used a tapered sliding window approach to conduct dynamic FNC analysis (Allen et al., 2014b; Sakoğlu et al., 2010). Previous research has demonstrated that window sizes between 30-60 seconds (Allen et al., 2014; Hutchison et al., 2013) are effective at capturing fluctuations in functional connectivity strength over time. We chose a sliding window length of 40 TR (40 seconds), convolved with a Gaussian of sigma 3 TRs and slide step of 1 TR across concatenated time courses, resulting in 390 time-windowed domains per subject. For each subject, we removed variance associated with rotation and translation movement parameters (using their respective rp files) from their time-course and added subject age and gender as covariates of no interest. An FNC matrix was computed as the pairwise correlation between networks of interest (5 networks x 5 networks) for each of the 390 time-windowed domains (per subject).

In total, the dynamic FNC data was made up of 27300 windowed FNC matrices (80 participants * 160 windowed FNC). Windowed correlation matrices were regularized with the graphical LASSO method (Varoquaux, Gramfort, Poline, & Thirion, 2010) to minimize within-window noise. The graphical LASSO method estimates functional connectivity by applying L1 regularization to the inverse covariance matrix, optimizing the lambda parameter separately for each subject (Allen et al., 2014; Damaraju et al., 2014; Nomi et al., 2016; Yang et al., 2014).

K-means

To identify distinct FNC states, we applied k-means clustering was applied to windowed FNC with the L1 distance (Allen et al., 2014b; Calhoun et al., 2014). K-means was run with the number of clusters ranging from two to eight with 10 cycles of clustering with a maximum of 200 iterations for reaching a solution. The elbow criterion was applied to the resulting cluster index to estimate the optimal number of clusters, which was four (k=4). We derived three metrics characterizing each participant's dynamic behavior namely their mean dwell time (MDT), which is the time spent in a certain state before switching to another one, fraction time (FT) which is the time spent in one state relative to the entire scan time and the number of transitions (NT), which represents how often they changed between different dynamic states. K-means clustering was also used for meta-state analysis. This methodology captures nuances in variance by modeling each windowed FNC as weighted sums of maximally independent connectivity patterns (Miller et al., 2016). Connectivity patterns are discretized using quartile discretization and their distance vectors are referred to as meta-states (Mennigen et al., 2019a). The four indices of connectivity dynamism are the number of distinct meta-states the subjects occupied during their scans (meta-state number), the number of times that subjects switched from one meta-state to another (meta-state changes), the largest distance between two meta-states that subjects occupied (meta-state span) and the total distance traveled by each subject through the state space (meta-state total distance).

Univariate Analyses

To assess for group differences in the output metrics of dynamic FNC analysis (such as mean dwell time, number of transitions from one state to another and fraction time spend in each state), we ran two-sample t-tests in a univariate manner. All results were corrected for multiple comparisons using the false discovery rate (FDR; p<.05).

Multivariate Analyses

To assess how behavioral metrics of ADHD affected brain activations in the ADHD group compared to controls rest, we ran partial least squares correlation (PLS-C) analyses (Krishnan et al., 2011) using myPLS, a publicly available, Matlab-based toolbox (https://github.com/MIPLabCH/myPLS). PLS-C has been used to assess brain-behavior relationships in many clinical populations (Delavari et al., 2022; Ziegler et al., 2013; Zöller et al., 2017) and is especially appropriate for the present study because of the collinearity of the CPT and ERS measures.

To conduct PLS-C analysis, we first computed correlations between matrix Y, which consisted of participants' behavioral scores (nine CPT measures and three ERS subscales per participant), and matrix X, which consisted of voxel data per subject during the 4 dynamic states. The resulting correlation matrices were concatenated into a common correlation matrix, $R=X^TY$. Matrix R underwent singular value decomposition, resulting in latent variables. For more details on singular value decomposition and correlation components, please refer to previous publications using the myPLS toolbox (Zöller et al., 2017). Each latent variable is a combination of brain activations and behavior weights, which indicate how strongly each variable contributes to the multivariate brain-behavior correlation. These values can be interpreted similarly to correlation values. Significance of correlation components was determined by permutation testing (1000 permutations) and the stability of brain and behavior weights was ensured using bootstrapping (500 bootstrap samples). The same analysis was repeated for state-based and meta-state metrics. We applied a Bonferroni correction for multiple comparisons while testing for the 6 PLS-C. A latent component was considered significant if it survived a correction of $p<.008$.

In summary, we used PLS-C to assess the following questions: how do brain-behavior relationships differ between the ADHD compared to TD group 1) within each of the four dynamic FNC states, 2) in terms of dynamic state-based behavior (such as mean dwell time) and 3) in terms of meta-state behavior (such as the number of meta-states changes)? To answer the first question, we derived the analysis correlation coefficient matrix between each of the 15 IC-IC pairs for each participant who entered that state. We stabilized variance by using the Fisher transformation to convert *r* values into z-scores. We conducted PLS-C on each of the 4 dynamic states by using the z-score matrices as matrix X and the respective participants behavioral scores as matrix Y. To answer the second and third question, we repeated a similar analysis except this time we used each participant's state-based metrics (for question 2) and each participants meta-analysis metrics (for question 3) as matrix X and each participants behavioral scores as matrix Y.

Results

Behavioral Results

There was no difference in age (p>.05) or sex (X^2 = 12.86, df = 1, p = 0.58) between the ADHD and TD group. Behavioral data results from the CPT-3 and the ERS questionnaire were not normally distributed, we therefore conducted non-parametric independent samples Mann-Whitney U tests to assess group differences in CPT-3 variables and ERS subscales. We controlled for multiple comparisons by using a false discovery rate (FDR; p<.05). All group differences are reported in Table 1.

Table 1. Group comparisons on CPT measures and ERS subscales. Results that survived multiple comparison correction are marked with *.

	Group	**Mean ± SD**	**Mann-Whitney U**	***p*-value**
CPT Commissions	ADHD	48.366 ± 8.273	632.5	0.704
	HC	48.675 ± 9.517		
CPT d'	ADHD	51.366 ± 10.626	747.0	0.138
	HC	48.250 ± 12.069		
CPT HRT block change	ADHD	55.300 ± 8.296	792.0	0.057
	HC	49.850 ± 11.118		
CPT HRT ISI change	ADHD	62.433 ± 12.546	854.0	0.021*
	HC	54.025 ± 8.942		
CPT HRT SD	ADHD	61.500 ± 12.408	834.5	0.022*
	HC	54.950 ± 9.999		
CPT HRT SD Var	ADHD	56.103 ± 11.920	736.5	0.141
	HC	51.871 ± 9.849		

CPT HRT	ADHD	50.433 ± 13.082	846.5	0.020*
	HC	42.950 ± 7.649		
CPT omissions	ADHD	51.766 ± 11.406	779.5	0.064
	HC	50.200 ± 12.512		
CPT perseverance	ADHD	58.333 ± 17.778	689.5	0.312
	HC	55.400 ± 15.145		
ERS intensity	ADHD	14.866 ± 7.655	790.5	0.057
	HC	10.425 ± 6.694		
ERS persistence	ADHD	8.233 ± 3.501	693.5	0.313
	HC	7.175 ± 3.802		
ERS sensitivity	ADHD	22.033 ± 10.578	742.5	0.137
	HC	17.300 ± 8.653		

Dynamic FNC Results

Dynamic FNC analysis revealed four connectivity patterns that subjects move between over time (Fig.1). Every subject's trajectory between the four FNC states was different, and not every subject entered every state.

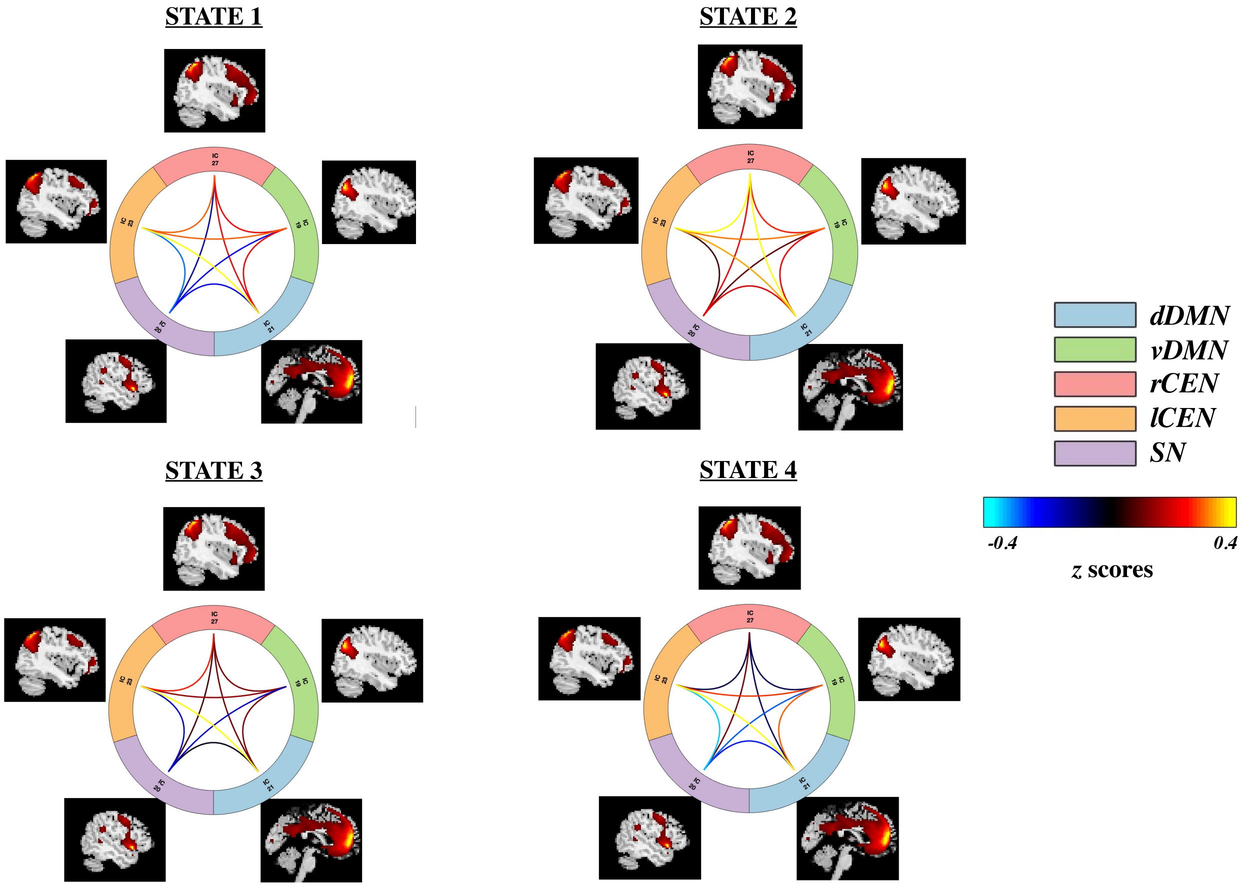

Figure 1. Dynamic FNC Results. Connectograms showing the patterns of functional network connectivity in the four dynamic FNC states. dDMN = dorsal default mode network; vDMN= ventral default mode network; rCEN = right executive control network; lCEN = left executive control network; SN = salience network.

In State 1 (average fraction time of 22%), the SN was effectively isolated with strong anti-correlations between it and all other ICs, while the DMN and CEN were positively correlated with each other. State-2 (average fraction time of 15%), was a state of hyperconnectivity, with the ICs of the DMN and CEN being strongly correlated with each other and moderately correlated with the SN. State-3 (average fraction time of 42%) was the most common state and was characterized by largely isolated ICs. Correlation z-scores ranged between 0.1 and -0.1 between all ICs of the triple network model, except for the lCEN which was moderately positively correlated with the dDMN. Finally, state-4 (average fraction time of 19%) was characterized by a near isolation of the rCEN, which weakly correlated (between 0.1 and -0.1) with all other ICs. Meanwhile the hubs of the DMN were strongly synchronized with each other and the lCEN, and anti-correlated with the SN. To confirm our results were not driven by motion difference among the subjects, we calculated Pearson correlations between the rate of occurrence of each dynamic state and mean framewise displacement of our participants. We found no significant relationship ($p>.05$). There was no significant difference in the number of TD and ADHD who entered each state (Table 2; $p<.05$). Two-sample t-tests showed no difference in the fraction time nor mean dwell time spend in any dynamic state between the ADHD and TD groups.

Table 2. Number of participants from the ADHD and TD groups in each dynamic state.

	State 1	**State 2**	**State 3**	**State 4**
No. of ADHD	23 (76.7%)	22 (73%)	29 (97%)	25 (83.3%)
No. of TD	31 (77.5%)	26 (65%)	39 (97.5%)	30 (75%)

Multivariate Associations between Behavior and Dynamic FNC Results

In State 2, PLS-C analysis resulted in one significant latent component ($p<.004$, $r=0.57$) that captured brain loadings representing voxels strongly correlated with ADHD symptomology more so in the ADHD group compared to the TD group, when the SN was increasingly isolated from the DMN and CEN (Fig. 2). Fig. 2a shows State-2's average FNC connectivity matrix in which all ICs are hyper-correlated with each other except for the SN, which is weakly correlated to all other ICs. Fig. 2b and Fig 2c shows the imaging loadings and the design loadings, respectively, for Latent Component 1. The yellow columns indicate the most robust results over bootstrapping while the salience loading on the Y axis indicate which connectivity patterns are driving the results in the latent component. Fig 2b shows a pattern of diminished BOLD activation in the voxels of the SN (dDMN-SN, vDMN-SN, rCEN-SN) as well as in the voxels of the DMN hubs (dDMN-vDMN). Given that the SN's correlations to the other ICs in state two were already moderate-to-weak, this pattern of imaging loadings would mean the SN would be effectively disconnected from the remaining ICs and the hubs of the DMN would be weakly correlated with each other. At the same time, we see increases in the connectivity between the CEN and DMN (dDMN-lCEN) and between the CEN hubs (rCEN-lCEN), strengthening the connectivity that already exist between these connections in State 2. In Fig. 2c, the design loadings for latent component 1 reveal that a comprehensive ADHD phenotype is driving the results, from inattention (i.e., omission rate), impulsivity (i.e., commissions rate) and emotional reactivity (i.e., ERS intensity). The most influential loadings are positive and for behavior*group contrasts (TD>ADHD). For visualization purposes, we plotted the brain salience loadings' bootstrap scores and the behavioral scores for participants in State-2 (Fig. 2d). We can see that the TD have a relatively flat slope while the ADHD group appears to be driving the results. None of the remaining results of PLS-C analysis survived multiple comparisons.

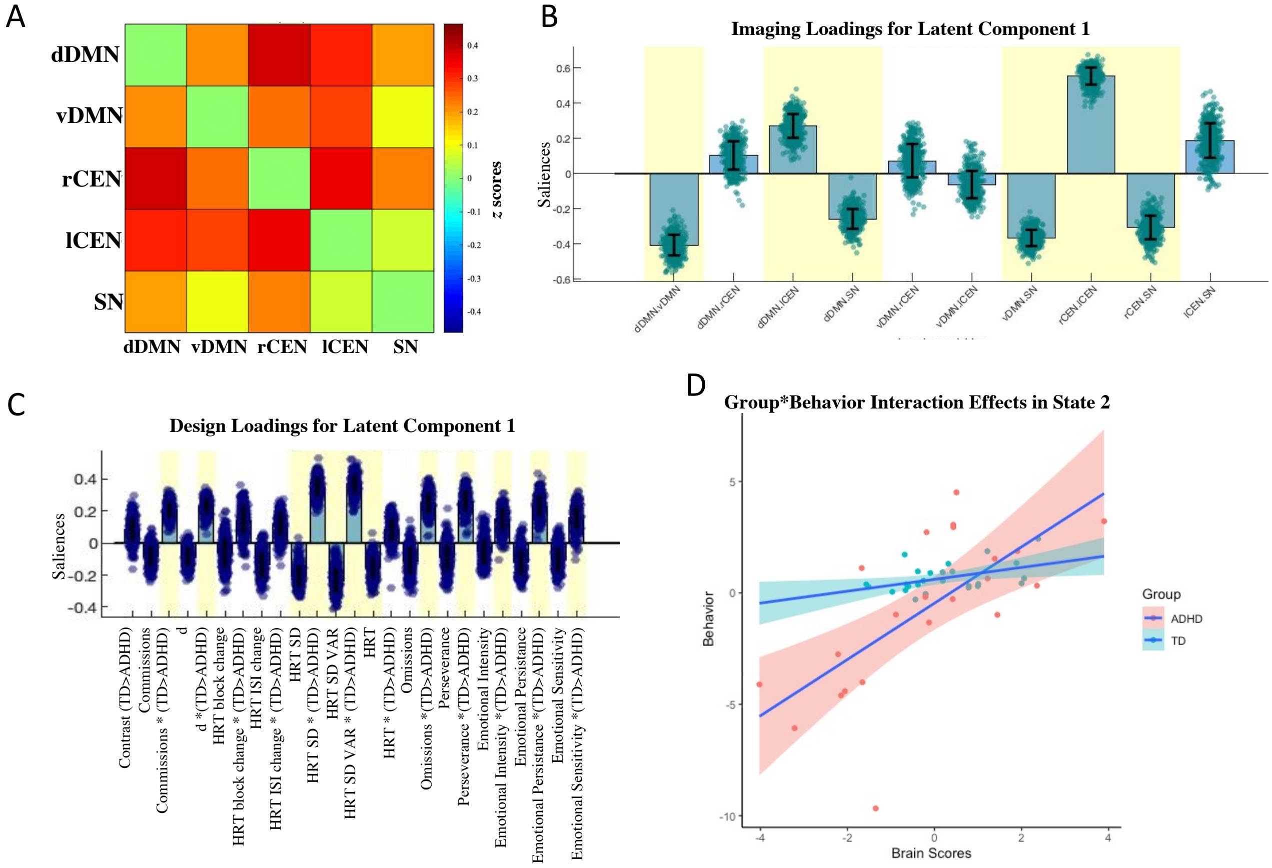

Fig. 2. Results of PLS-C in State 2. Fig. 2a shows a functional connectivity matrix between networks of interest in State 2. Fig. 2b shows the imaging loadings for Latent Component 1, which reveal a general pattern of diminished BOLD activation in the SN and DMN and increased BOLD activation in the CEN. Fig. 2c shows the design loadings for Latent Component 1, which reveal that a comprehensive ADHD phenotype (including measures of inattention, hyperactivity, and emotional reactivity) were driving the results. Fig. 2d shows the group interaction between behavior and brain scores in State-2, revealing that the group effect was driven by the ADHD group given that the TD group's behavioral scores were fairly stable over their brain scores.

Multivariate Associations between Meta-States and Behavior

We assessed if and how the ADHD and TD groups differed in their relationship between meta-states and ADHD symptomology. PLS-C analysis revealed one significant latent component (p<.002, r=0.63) that captured brain loadings representing voxels strongly correlated with emotional reactivity, more so in the ADHD group compared to the TD group (Fig. 3). Fig. 3a shows the imaging loadings for Latent Component 1 and indicates that all meta-state variables were robust over bootstrapping and had strong loadings on Latent Component 1. Fig. 3b shows the design loadings which revealed two important findings: first, the HRT block change, ERS Intensity, ERS, perseverance and ERS sensitivity (across all subjects in the ADHD and TD groups) were associated with Latent Component 1. Second, we see a group effect for emotional intensity and emotional sensitivity, which indicates that the ADHD group was driving this result more so than the TD group. We confirm this inference in the Fig. 3c, which shows that the brain scores for the TD group were relatively unaffected by emotional dysregulation whereas the ADHD group had a strong positive correlation between behavior (namely emotional intensity and emotional sensitivity) and brain scores. No other significant results were found.

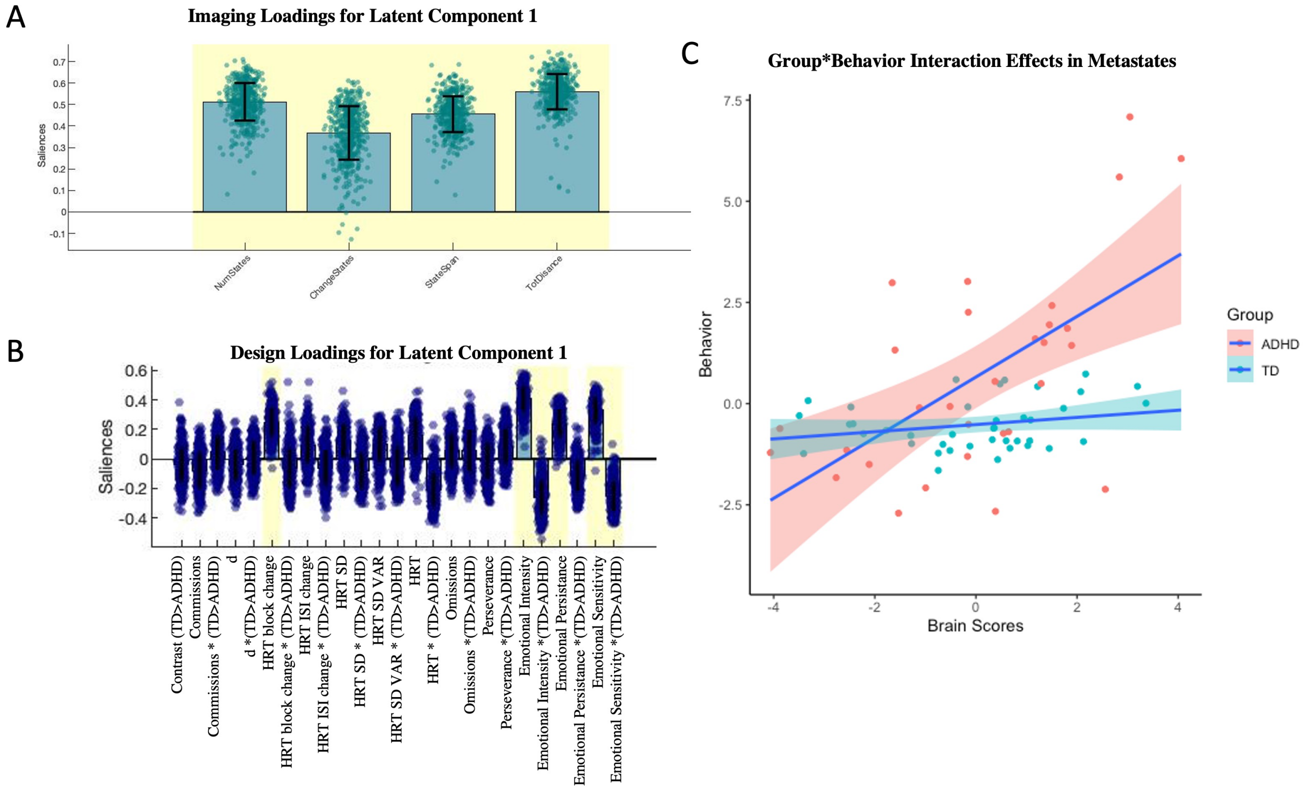

Fig. 3. Results of PLS-C on meta-states and ADHD symptomology. Fig. 3A shows the imaging loadings, which reveal that all meta-state metrics were loading onto the significant Latent Component. Fig. 3B shows the design loadings, which reveal that the behavioral measures of HRT block change, ERS Intensity, ERS, perseverance and ERS sensitivity were robustly associated with this Latent Component and there was a group difference. Fig. 3C shows a correlation plot of the brain salience loadings' bootstrap scores and the behavioral scores for participants, revealing that that the ADHD group was driving this group difference. No other significant results were found.

Discussion

This study used multivariate analyses to characterize brain-behavior relationships between large-scale dynamic FNC and ADHD symptomology in adolescents. We comprehensively characterized ADHD by including measures of inattention, impulsivity/hyperactivity, *and* emotion dysregulation. We then assessed 1) whether adolescents with ADHD showed more volatile patterns of dynamic FNC compared to controls, 2) whether group differences in dynamic FNC related to ADHD symptomology of inattention and/or hyperactivity and 3) whether group differences in dynamic FNC related to increased emotional dysregulation in the ADHD group. We used two methods to assess FNC; a hard-clustering approach which allowed us to assess group differences in FNC between specific pairs of ICs, and a meta-state approach that assessed overall brain fluidity rather than differences in IC-IC pair connectivity (Miller et al., 2016).

There are two major findings in the present study. First, in dynamic State-2 we found a specific pattern of FNC between the DMN, CEN and SN that was a) stronger in the ADHD compared to control group and b) driven by a comprehensive ADHD phenotype, including impaired emotion regulation. Second, our meta-state analysis results show increased volatile connectivity in the ADHD group compared to controls, and this dynamic behavior was driven by heightened emotional reactivity.

The FNC pattern in dynamic State-2, which 73% of ADHD and 65% of controls entered, showed the SN being effectively isolated from the DMN and CEN, which were positively correlated with each other. This pattern was largely driven by the ADHD group and associated with increased inattention, impulsivity, and emotional regulation problems. Unlike Luo and colleagues (2023), multivariate analyses did not reveal associations between distinct dimensions of ADHD phenotypes and dynamic states. Instead, we present a specific pattern of brain-behavior relationships in aberrant SN-centered FNC that differs between ADHD and controls and is driven by a comprehensive ADHD phenotype. The importance of this finding is twofold: first, it accounts for the potential influence of emotion dysregulation in ADHD. Despite the centrality of emotion dysregulation in this disorder, it often gets overlooked in studies on brain-behavior relationships because it is not a part of the diagnostic criteria for ADHD. Second, it replicates previous studies showing altered SN-centered connectivity in clinical ADHD (Cai et al., 2018; Sripada et al., 2014). Theoretical models propose that inattention is regulated by continuous interactions between task-positive networks, especially the SN, and the task-negative DMN (Castellanos & Proal, 2012; Sonuga-Barke & Castellanos, 2007). While directionality of this relationship remains unknown, recent advances in animals models suggest the SN may causally inhibit the DMN (Menon et al., 2023). Recent work suggests that SN-DMN connectivity in may strengthen as attentional problems increase to maintain normal functioning to a certain degree, which, when bypassed, results in a loss of FNC between the SN and DMN. This loss of FNC is related to ADHD symptomology and dysfunction (Guo et al., 2020). Our results are in line with these findings and suggest increased isolation of the SN from the DMN is associated with not only inattention but the holistic ADHD phenotype.

Our meta-state results demonstrate how dynamic fluidity and range of whole-brain functional connectivity differ between groups. We observe that the ADHD group has increased global dynamic fluidity with a higher number of occupied meta-states and number of changes from one meta-state to another which operate over a larger dynamic range (as indicated by increased meta-state total distance travelled between meta-states) compared to controls. Importantly, PLS-C analysis revealed this pattern of whole brain functioning across different temporal scales is driven by increased emotional intensity and sensitivity indicating a relationship between meta-state behavior and under-regulated emotion in children with ADHD compared to controls. Given the present study used the Triple Network Model of Psychopathology framework, we only assessed network dynamics between the SN, DMN, and CEN and not affective/limbic circuitry. Yet, still we find a strong association between brain dynamics and behavior reinforces the value of including measures of brain fluidity, rather than individual structures, when researching complex, multi-level complex processes such as emotion reactivity and regulation. Nuanced methodologies like meta-state analyses are especially useful for characterizing brain dynamics and psychopathology symptoms that extend beyond clinical diagnostic criteria (Clark et al., 2017; Van Os et al., 2009). Taken together, our results are consistent with ADHD being a neurodevelopmental and affective disorder.

We acknowledge several limitations of study. We did not find significant differences in the number of ADHD and controls entering in each dynamic state. Previous dynamic FC studies have found this and perhaps this could be attributed to our sample size. Another potential limitation of our sample size is that we did not replicate findings of distinct dimensions of ADHD symptomology relating to specific patterns of FNC (Guo et al., 2020). It is also important to note that our study only assessed behavior and dynamic FNC; future research might benefit from incorporating more multi-modal methods, such as genomics to more comprehensively study the brain-behavior mechanisms implicated in the present study (Kim et al., 2018).

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Supplementary Materials

S1 Table. CPT-3 variables & their interpretations

CPT Variable Type	**CPT Measure**	**Interpretation**
Detectability	d'	Differentiate targets from non-targets
Error Type	Omissions	Failure to respond to targets
	Commissions	Incorrect responses given to non-target
	Perseverance	Rate of random, repetitive, or anticipatory responses
Reaction Time Statistics	Hit Response Rate (HRT)	Mean response speed
	HRT standard deviation (SD)	Consistency in reaction times
	Variability	Similar to HRT SD but is a within-subject measure
	HRT Block Change	Ability to sustain or increase response speed in later block
	HRT Inter-Stimulus Interval (ISI) Change	Ability to sustain or increase response speed at longer ISIs

S2 Table. Spatial correlation results between ICNs of interest and publicly-available functional network templates (Shirer et al., 2012; http://findlab.stanford.edu/functional_ROIs.html).

Functional Network	**Correlation *r***
dorsal DMN (Independent Component 21)	0.59
ventral DMN (Independent Component 19)	0.45
right CEN (Independent Component 27)	0.47
left CEN (Independent Component 23)	0.54
SN (Independent Component 20)	0.47

Abbreviations: DMN= Default Mode Network, CEN = Central Executive Network, SN = Salience Network

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To show compassion for an individual without showing concern for the structures of society that make him an object of compassion is to be sentimental rather than loving.

William Sloane Coffin, Jr.

Chapter 5. Discussion

The aim of this thesis was to examine the neural dynamics of internally oriented attention along the continuum of attention difficulties. Studies 1-3 assessed relationships between ADHD symptomology and patterns of neural activity in major neurocognitive networks during the internally oriented processes of self-mentalizing and mind wandering. This discussion is organized into three sections, the first of which summarizes the main findings of Studies 1-3 and discusses how they relate to existing literature. The second section examines a framework of internally oriented mental states and associated brain dynamics as thought moves from more constrained paradigms to free-flowing thought. We situate Studies 1-3 within that framework, discuss how impairments in this framework lead to symptoms of ADHD and discuss the framework with respect to the Triple Network Model of Psychopathology. The last section of this discussion focuses on limitations of the present thesis and explores future research ideas.

Summary of main findings

To the best of our knowledge, few studies have used task-based fMRI to investigate controlled internally oriented attention in ADHD, making it empirically understudied. The first study in this thesis identified neural correlates of emotional self-referential thought and demonstrated how their activations differed in individuals with ADHD compared to typically developing controls. Specifically, this study demonstrated a key role for the right angular gyrus in individuals with ADHD. The angular gyrus, along with other cortical regions associated with mind-wandering, was more activated and subcortical regions associated with self- and emotion-processing were less activated in the ADHD group compared to controls when reflecting on internal states. The angular gyrus is a part of the core DMN network, which integrates internal and external stimuli as well as information coming from other DMN subnetworks and acts as a 'sense-making' network (Yeshurun et al., 2021). In other words, to comprehend the world around us, we need to pay attention to, and contextualize, extrinsic stimuli using our intrinsic schemas and prior knowledge of preceding moments. We then need to meld that information with our concept of the self (our beliefs, emotions, and long-term memories) in order to comprehend our place in the world. These complex processes are likely subserved in large part by the DMN and its subnetworks (Yeshurun et al., 2021). Taken as a whole, Study 1 demonstrates that the processes of internally oriented attention may function differently in the brains of individuals with ADHD. More specifically, Study 1 suggests that, when reflecting on our internal emotional states, the mechanism that appears disrupted (or less effective) in individuals with ADHD is integrating external and internal information with a sense of self. This is consistent with behavioral research on adults with ADHD demonstrating a positive correlation between mentalizing impairments and the severity of ADHD symptoms (Perroud et al., 2017). Furthermore, a less efficient DMN is also in line with resting state studies that repeatedly show decreased functional connectivity within the DMN in ADHD (Wang et al. 2009; Sun et al. 2012, Zhang et al., 2020). Taken together with the results of Study 1, this suggests that one of the consequences of atypical functional connectivity within the DMN in ADHD may be increased difficulty in cohesively understanding the relationship between the world and themselves. For future studies it would be important to delve more specifically into the processes of self-mentalizing; while the task in study one partially encompassed mentalizing, it was not designed to purely assess mentalizing. It therefore cannot be considered a mentalizing task. Future studies should try to characterize patterns of angular gyrus activity during self-mentalizing tasks in comorbid and pure ADHD.

The process of mind-wandering is a well-researched domain of internally oriented attention. Despite the richness of the literature, resting state studies show conflicting results and no convergence in potential functional imaging biomarkers of ADHD (Cortese et al., 2021). This inconsistency is well known amongst researchers who often cite the extreme heterogeneity of ADHD as the reason why characterizing its neural signature is so difficult. Given that it is both a common and exceptionally comorbid disorder, the ADHD phenotype is strongly influenced by individual differences. Despite this, neuroimaging research rarely assesses ADHD through a dimensional lens. In keeping with an emphasis on individual differences, Study 2 aimed to validate ADHD as existing on a continuum using a dynamic FNC approach. It used three types of analyses that got progressively more nuanced in terms of the variance they capture: static FNC analysis, dynamic FNC analysis and meta-state analysis. Brain-behavior relationships were found using dynamic FNC analysis (diminished SN-centered functional connectivity correlated with increased attention problems, hyperconnectivity as well as longer dwell times in hyperconnected states and increased ADHD manifestations and trait impulsivity) and meta-state analysis (increased number of meta-states changes in and increased ADHD manifestations) but not in static FNC analysis. As noted in its discussion, Study 2's brain connectivity results are consistent with the model of ADHD put forth by Alexander Crichton in 1789, and innumerous psychological studies since showing that ADHD is best conceptualized as an extreme end of a spectrum rather than categorically defined disorder. Our findings support the view that a paradigm shift is required in how the medical and scientific communities' approach mental health classification and treatment. Despite empirical evidence that many conditions, particularly neurodevelopmental disorders, lay on a continuum between normality and pathology, the DSM-V categorizes disorders into groups. Medical and psychological treatment is based on this diagnostic method, which is related to insurance corporations and wider, capitalistic social systems. As more scientific studies advocate for the need for dimensional classification system, the more likely that such a system might develop to complement the DSM-V.

In addition to taking individual differences into account, there is a need for neuroimaging research pursuing robust brain-behavior relationships in ADHD to better characterize the ADHD phenotype. Study 3 built on the results of Study 2 by including a clinical sample of adolescents with ADHD and using a sustained attention task, the CPT, to experimentally obtain measures of impulsivity and inattention. Critically, Study 3 acknowledged overwhelming literature showing that emotional dysregulation is the third core ADHD symptom and included measures of emotional reactivity. Study 3 then used multivariate approaches to account for as much data variance as possible to understand brain-behavior relationships. Critically, both studies 2 and 3 adopted a hypothesis driven approach to FNC, which was appropriate given the large body of existing literature on resting state in ADHD and the sample sizes of both studies. Study 3's findings revealed a pattern of FNC with diminished SN-centered connectivity and increased DMN-CEN that was stronger in the ADHD compared to control group and driven by a comprehensive ADHD phenotype (inattention, impulsivity, and emotion dysregulation). The meta-state analysis showed increased volatile connectivity in the ADHD group compared to controls, and this dynamic behavior was driven by heightened emotional reactivity. When taken together, Studies 2 and 3 both support adolescents with increased ADHD symptoms having atypical SN-centered FNC and more volatile patterns of dynamic FNC. Going forward, it is possible that by accounting for more individual variance in the core symptoms of ADHD (inattention, impulsivity, and emotional dysregulation) when assessing brain-behavior relationships during rest in individuals with ADHD may lead to consistent and replicable findings.

A framework for internally oriented mental states

In their seminal 2016 paper, Christoff and colleagues introduced a dynamic framework for understanding different types of internal phenomena through the type and strength of constraints exerted on them (Christoff et al., 2016). In this framework, internally oriented attention spans from spontaneous thought to goal-oriented thought, the latter of which is comprised of mental states that occur freely in the absence of any constraints on their contents or transitions from one state to another (Christoff et al., 2016; Figure 4). The first kind of constraint is deliberate/top-down, such as when one intentionally brings attention to, or back to, a tedious task. The second type of constraint is automatic/bottom-up, which includes salient stimuli that serve as distractors as well as affective, sensory, and perceptual biases (Christoff et al., 2016; Irving, 2016). This framework predicts that the strength and type of constraints naturally fluctuate as we engage in different kinds of internally oriented activities, such as daydreaming or creative thought. Variations in constraints are subserved by corresponding variations in the activity of large-scale brain networks, which largely overlap with the major neurocognitive networks implicated in Menon's Triple Network Theory of Psychopathology (2011), namely the DMN, CEN, SN, as well as the dorsal attention network. Deliberate constraints are associated with executive functions and control networks while automatic constraints are presumably supported by diverse brain correlates given that they are more varied in nature.

This framework is valuable for understanding how changes in one's internal experiences can be maladaptive. In other words, persistent and significant shifts in the constraints on internally focused thought can lead to substantial functional impairment. For example, excessive constraints could sharply reduce the dynamic, free flow of thought. If chronic, they could result in increased rumination and obsessive thinking, both of which are symptoms of impaired mental health. Likewise, diminishment in both deliberate and automatic constraints could lead to increased variability in spontaneous thought which, in turn, would make it difficult to establish a sense of continuity and coherence in one's thought. Regarding the studies in the present thesis, Study 1 assessed internally oriented attention, through self-mentalizing, during a task-based paradigm. This falls on the deliberately constrained, goal-directed end of the framework. Studies 2 and 3 were on mind-wandering, which tends to be relatively less-deliberately constrained than goal-oriented thought such as planning but more constrained than other types of spontaneous thought such as dreaming.

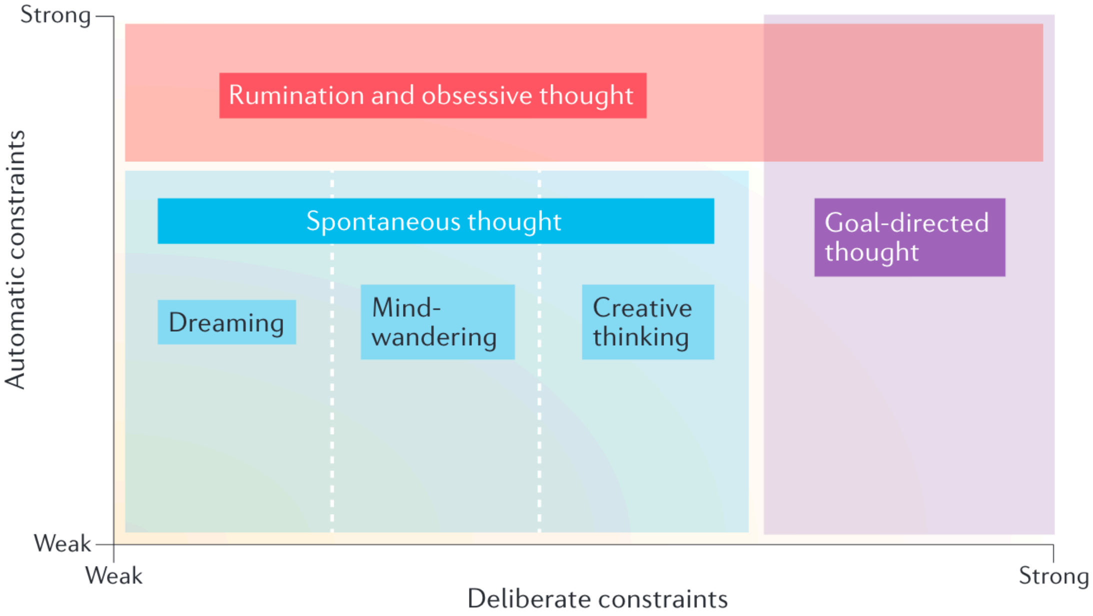

FIGURE 4. Conceptual space relating different types of thought. Deliberate and automatic constraints serve to limit the contents of thought and how these contents change over time. Deliberate constraints are implemented through cognitive control, whereas automatic constraints can be considered as a family of mechanisms that operate outside of cognitive control, including sensory or affective salience. Figure taken from (Christoff et al., 2016).

Within this framework, ADHD is a disorder defined by a general reduction in constraints which leads to increased variability, spontaneity, and volatility in thought (Christoff et al., 2016). This view is consistent with Barkley's view of ADHD as a disorder of self-regulation and delayed maturation of cognitive control (Barkley, 2013) as well as with research on externally oriented attention in ADHD, with studies showing increased variability in attention and a lack of focus in individuals with ADHD during cognitive tasks (Karalunas et al., 2012; Kuntsi & Klein, 2012). It is also consistent with mind-wandering research; a recent EEG study showed adults with ADHD experience more off-task thought than those without, but also engaged in a greater proportion of freely moving off-task thought than controls (Alperin et al., 2021). In terms of internal attention, there are several potential consequences of struggling to produce stable thoughts fixated on a specific topic. For example, going back to Narhi-Martinez and colleagues' model of attention in which it attention is a system of weights and balances in which information "competes" at local and global levels to reach a central processing stage which decides what and how the information will drive behavior (Narhi-Martinez et al., 2023). It is plausible that if individuals with ADHD have increasingly disjointed and free flowing thought, they would have more competing information at the local level to begin with, which could increase the processing load for all subsequent "competitions". This would make the later processes of information integration more difficult and cause them to struggle to form a coherent mental narrative to guide behavior. This could possibly be what increased activation of the angular gyrus reflects in Study 1.

In this context of this framework, it is likely that the SN and, to a lesser degree, the CEN are the main sources of deliberate constraints on internally oriented attention. The CEN contributes to executive control: it is robustly associated with the ability to flexibly allocate attentional resources to internal and external information and then integrate the relevant information in service of both immediate and long-term goals (Spreng et al., 2013; Vincent et al., 2008). The anterior insula, a hub of the SN, has been identified as a crucial intermediary for switching between the DMN and the CEN, during cognitive tasks (Cai et al., 2019; Supekar et al., 2019). This relationship makes SN-mediated, dynamic interactions between the DMN, CEN and SN essential for attention and flexible cognitive control (Braun et al., 2015; Cai et al., 2014b, p. 201; Goulden et al., 2014; Supekar & Menon, 2012; Taghia et al., 2018). As previously noted, the first resting state study to use dynamic FNC analysis in ADHD research showed aberrant SN-centered FNC in children with ADHD in two independent cohorts (Cai et al., 2018b). Both studies 2 and 3 in the present thesis also show aberrant SN-centered FNC in adolescents with increased ADHD symptomology, which correlate with measures of inattention. While these results are in accordance with diminished constraints by way of SN-centered FNC, they are only correlational. However, new evidence is emerging in animal studies that supports that the SN plays a causal role in suppressing activation of the DMN, thereby potentially acting as a constraint on internally generated thought (Menon et al., 2023). In their recent paper using feedforward optogenetic stimulation, Menon and colleagues showed that stimulating anterior insula neurons suppressed activation of the DMN and dynamically decoupled the SN and DMN. These results are consistent with previous human fMRI studies implicating the SN in network switching (Goulden et al., 2014; Sidlauskaite et al., 2014; Uddin, 2015). Given the complexity of neural dynamics, it is likely that deliberate constraints operate on several levels, both between and within neural networks. For example, in their 2014 paper Anderson and colleagues applied a positively constrained version of ICA called non-negative matrix factorization to multimodal ADHD data containing fMRI, MRI, phenotypic and behavioral measurements (Anderson et al., 2014). They found a pattern that was significantly different between individuals with a predominantly inattentive presentation of ADHD compared to controls, in which there was increased connectivity within the DMN_{MTL} and decreased connectivity within the $\mathrm{DMN}_{\mathrm{core}}$. This result is consistent with decreased constraints in the $\mathrm{DMN}_{\mathrm{MTL}}$ and, given the association of the medial temporal lobe with episodic memory used while generating self-referential thought, this could contribute to the generation of mental content in ADHD. Meanwhile the decreased constraints on the $\mathrm{DMN}_{\mathrm{core}}$ could result in difficulties integrating disparate conceptual information when computing the overarching significance or importance of a particular thought (Andrews-Hanna et al., 2014; Margulies et al., 2016).

In summary, this thesis has detailed two psychological frameworks that have independently conceptualized ADHD: the internal cognition framework defines ADHD as a disorder of diminished deliberate and automatic constraints and Barkley defines ADHD as a disorder of delayed executive function and self-regulation. Both theorems are consistent with the Triple Network Model of Psychopathology and general neuroimaging results that consistently show aberrant activation of control networks, especially SN-centered FNC, in individuals with ADHD. Both frameworks recognize how attention oriented towards one's thoughts, feelings, and beliefs, become vulnerable as ADHD symptomology increases in severity. In other words, given the accordance between distinct frameworks that define ADHD as a disorder of delayed executive functioning and self-regulation (Barkley and colleagues), define internally oriented thought by varying levels of deliberate and automatic constraints (Christoff and colleagues) and the Triple Network Model of Psychopathology (Menon), this thesis supports the view of ADHD being a disorder of altered internally oriented attention that is largely subserved by variable and volatile patterns of FNC between nodes of large-scale neural networks such as the DMN, CEN and SN. Going forward clinical and theoretical frameworks are critical for guiding neuroimaging research on the complex and heterogenous continuum of attention problems and ADHD.

Limitations and future directions

On a macroscale, major limitations of neuroimaging research on internally oriented attention in ADHD are as follows: few fMRI studies have used task-based paradigms and, while there are countless resting state studies, there has been limited spatial convergence in terms of the brain dynamics underlying ADHD symptomology. The studies in present thesis attempted to respond to these concerns by exploring task-based internal attention in ADHD and controlling for variations by prioritizing individual differences and a comprehensive ADHD phenotype that included emotional dysregulation. These studies themselves had important limitations, as noted in their respective discussion sections. There rests an overwhelming need to address methodological and conceptual limitations for fMRI research on ADHD to yield robust and definitive conclusions.

A major methodological limitation is the relatively small sample size used in Studies 1-3. There is a clear replication crisis in psychological sciences, and this is especially the case for fMRI studies (Open Science Collaboration, 2015). It is now largely understood that sample sizes commonly used in task fMRI studies of roughly 30 participants is insufficient for obtaining reproducible brain-behavior correlations, regardless of the analytic approach (Grady et al., 2021). Future resting state studies on internally oriented attention in ADHD should make use of large, collaborative, open-source datasets such as the Adolescent Brain Cognitive Development or ABCD study (Casey et al., 2018). Such databases collect resting state data from multiple research centers in the world using harmonized MRI acquisition protocols. Another important limitation is that studies 1-3 were all cross-sectional. More longitudinal neuroimaging studies in ADHD are needed given its nature as a neurodevelopmental disorder.

Longitudinal analyses evaluating how structural and functional connectivity mature over time are necessary to develop the maturational delay hypothesis of ADHD.

To the best of our knowledge, researchers have yet to develop a standardized procedure for qualitatively measuring internally oriented attention, whether it be spontaneous, automatically constrained, or goal-directed thought. Neurophenomenological techniques (Fazelpour & Thompson, 2015) that combines online experience sampling or fine-grained first-person reports of moment-to-moment variability in attention, metacognition, emotion, bodily sensation, and memory with measures of brain activity may be especially helpful for future research on internal attention. Acquiring data on subjective experiences (e.g., thoughts and feelings) happening in close temporal proximity to changes in brain dynamics could help researchers better understand and categorize brain-behavior relationships. In general, it is likely that the more alterations in functional connectivity can be connected to variances in ADHD symptom profiles, neuropsychological deficits, and behaviors such as internal attention towards off-task thoughts, the more homogenous the results will be. This is exemplified by the dynamic approach to functional connectivity adopted in Studies 2 and 3, which showed clear advantages over static analyses.

Future studies should also adopt an integrative perspective towards the relationship between the dopaminergic system and activity of cognitive control networks in ADHD. Recent findings in a randomized controlled trial shows that the dopamine re-uptake inhibitors methylphenidate increases spontaneous neural activity in the SN, DMN and nucleus accumbens (Mizuno et al., 2023). Furthermore, methylphenidate-induced changes in the DMN correlated with improvements in omission errors, mean response time, and intraindividual response variability during a sustained attention task. Given that methylphenidate appears to be acting upon hubs in the SN and DMN, it is also likely impacting internally oriented cognition. The relationship between internally oriented attention the dopaminergic system has yet to be explored in ADHD.

Finally, returning to Christoff and colleagues' dynamic thought frame, research has overwhelmingly focused on deliberate constraints on internal attention. Little is known about the relationship between automatic constraints and spontaneous thought. Future studies assessing neural patterns underlying automatic constraints such as habits of attention, affective salience, and sensory salience that likely depend on the interactions between various neural correlates in cortico–thalamic–striatal circuits are likely to be of theoretical and clinical significance. Understanding the neural mechanisms of automatic constraints could help pinpoint how to restrict their automatization when they start resulting in functional impairment, as seen in ADHD.

Historically, neuroscientists, psychiatrists and psychologists have noticed disruptions in behavior and/or functional impairments and have attempted to find the corresponding change/impairment in the brain that caused it, as exemplified in the classic case of Phineas Gage. For Phineas Gage, the profound changes in his behavior after he suffered abrupt, physical trauma to the frontal lobe suggested a link between specific brain regions and personality. The assumption that cognitive activities can be attributed to the functioning of specific and singular brain areas has given way in modern neuroscience. However, the goal of understanding brain-behavior relationships persists. As our understanding of human behavior becomes richer and more complex, scientists work to refine hypotheses about corresponding brain dynamics and develop more complex and nuanced methodologies for uncovering said dynamics. In the case of neurodevelopmental disorders such as ADHD, there is growing understanding about the complex interplay between of genetic predisposition, early life development and effects of the current environment. Going forward, it is crucial to account for as much variation as possible in both the clinical evaluations, neuroimaging methodologies and mathematical analyses to yield replicable and robust conclusions.

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