Deviations in neural activity and network integration underpinning the co-occurrence of emotion dysregulation and attention-deficit/hyperactivity disorder: Analyses of fMRI task activations and functional brain network topology

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Deviations in neural activity and network integration underpinning the co-occurrence of emotion dysregulation and attention-deficit/hyperactivity disorder: Analyses of fMRI task activations and functional brain network topology

Tammo Constantin Viering

Summary

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by inattention, hyperactivity-impulsivity, or a combination of both. Emotion dysregulation is a common problem in ADHD that is associated with significant impairment in the quality of life. Emotion regulation can be defined as the adjustment of contextually inappropriate emotions to align them with individual goals. While the prevalence of ADHD decreases with age, the prevalence of emotion dysregulation appears to increase in the ADHD population. Research does not yet provide a unified model to explain the co-occurrence of emotion dysregulation and ADHD. The neural changes that may underlie the deficits in emotion regulation in ADHD appear to be multifaceted and extend to different neural networks.

The aim of the present work was to improve our understanding of the relationship between ADHD and emotion dysregulation and the underlying neural activity. Three research articles examine specific aspects of the relationship between ADHD and emotion dysregulation, namely the perception of emotional stimuli, the association between functional brain topology and emotion dysregulation in different ADHD presentations, and emotion dysregulation-related neurobiological and phenotypical predictors of the course of ADHD. All three articles are based on functional magnetic resonance imaging (fMRI) data.

In the first article (chapter 2), neural activity during the processing of angry and fearful facial stimuli and visuospatial control stimuli was investigated. For this purpose, individuals with ADHD and healthy control subjects completed a matching task with emotional face and control stimuli. In addition, data were collected for emotion dysregulation, ADHD presentation, and age. Individuals with ADHD were compared with healthy control subjects. Individuals with ADHD had higher scores on emotion dysregulation than control subjects. They also responded more slowly and inaccurately to emotional but not to visuospatial control stimuli. Neural response differences in processing the different stimuli were significantly smaller in the subjects with ADHD, especially in the left amygdala. While coupling between the right amygdala and bilateral ventromedial prefrontal cortex was stronger for emotional stimuli than for visuospatial stimuli in the control subjects, the coupling in the subjects with ADHD did not differ significantly between trial types. Neither emotion dysregulation data nor ADHD presentation or age were related to response behavior or neural processing during the emotional mapping task.

In the second article (chapter 3), I used a combination of graph analysis and structural equation modeling (SEM) to examine resting-state functional connectivity (measured via resting-state fMRI) in young adults with ADHD and age-matched healthy controls. Emotion dysregulation was measured with four

questionnaire subscales and operationalized by a latent variable of the SEM. The latent emotion dysregulation variable was characterized by subscales that captured emotional problems, behavioral problems, and emotional lability. Graph analysis was applied to the resting-state fMRI data, and region-specific measures of network topology were calculated. The measures were then analyzed with SEM models to identify brain regions in which the association between local network integration and connectivity, on the one hand, and emotion dysregulation, on the other, depended on the ADHD presentation. In subjects with ADHD characterized by hyperactivity-impulsivity, the latent variable of emotion dysregulation was associated with increased clustering coefficients and local efficiency of the right insula. Neither healthy control subjects nor subjects with ADHD exhibiting only symptoms of inattention showed a similar pattern.

The third article (chapter 4) examined whether emotion dysregulation and the integration of emotion-related functional brain networks are associated with interindividual change in ADHD severity. ADHD severity and resting-state fMRI data were measured in individuals with ADHD and healthy controls at two points in time in late adolescence and young adulthood. Bivariate latent change score models were applied to examine whether emotion dysregulation and network integration during adolescence are associated with changes in ADHD severity. Emotion dysregulation was measured using questionnaire subscales for behavioral problems, emotional problems, and emotional lability. Better emotion regulation was associated with better ADHD outcome. Using graph analysis, we identified network integration of emotion-related functional brain networks. Network integration was measured by nodal efficiency, which is the average inverse path distance from one brain region to all other brain regions in the network. A pattern of low nodal efficiency in brain regions associated with basic emotional processes and high nodal efficiency in regions of implicit emotion regulation predicted a less severe course of ADHD. In addition, greater nodal efficiency in the right orbitofrontal cortex was associated with a better course of ADHD.

The articles provide evidence that neural activity and functional connectivity between brain structures affecting emotion may be related to the co-occurrence of emotion dysregulation and ADHD. ADHD and the common co-occurring emotional problems should not be attributed to single, isolated systems, e.g., for executive functions and cognitive control. The neurobiological roots appear to be complex and heterogeneous, involving the interplay of different brain networks that are at least partly emotion-related. The present findings are consistent with literature that does not attempt to explain ADHD via monocausal models but emphasizes the complexity of ADHD and describes heterogeneous profiles with different deficits and neurobiological abnormalities. It is important to assess each ADHD case individually,

considering deficits, ADHD symptoms, co-occurring (emotional) problems and comorbidities, and potential strengths. Only in this way can optimal support be provided.

Deutsche Zusammenfassung

Aufmerksamkeitsdefizits-/Hyperaktivitätsstörung (ADHS) ist eine häufig auftretende Entwicklungsstörung, die durch Unaufmerksamkeit, Hyperaktivität-Impulsivität oder eine Kombination aus beidem gekennzeichnet ist. Die Dysregulation von Emotionen ist ein häufiges Problem bei ADHS, das mit einer erheblichen Beeinträchtigung der Lebensqualität verbunden ist. Emotionsregulation kann definiert werden als die Anpassung von kontextuell unangemessenen Emotionen, um sie mit individuellen Zielen in Einklang zu bringen. Während die Prävalenz von ADHS mit dem Alter abnimmt, scheint die Prävalenz von Emotionsdysregulation in der ADHS-Population zuzunehmen. Die Forschung liefert noch kein einheitliches Modell zur Erklärung des gemeinsamen Auftretens von Emotionsdysregulation und ADHS. Die neuronalen Veränderungen, die den Defiziten bei der Emotionsregulation bei ADHS zugrunde liegen könnten, scheinen vielfältig zu sein und sich auf verschiedene neuronale Netzwerke zu erstrecken.

Ziel der vorliegenden Arbeit war es, unser Verständnis der Beziehung zwischen ADHS und Emotionsdysregulation sowie der zugrundeliegenden neuronalen Aktivität zu verbessern. In drei Forschungsartikeln werden spezifische Aspekte des Zusammenhangs zwischen ADHS und Emotionsdysregulation untersucht, nämlich die Wahrnehmung emotionaler Stimuli, die Assoziation zwischen funktioneller Hirntopologie und Emotionsdysregulation bei verschiedenen ADHS-Präsentationen sowie mit Emotionsdysregulation zusammenhängende neurobiologische und phänotypische Prädiktoren für den Verlauf von ADHS. Alle drei Artikel beruhen auf Daten der funktionellen Magnetresonanztomographie (fMRT).

Im ersten Artikel (Kapitel 2) wurde die neuronale Aktivität bei der Verarbeitung von wütenden und ängstlichen Gesichtsstimuli und visuell-räumlichen Kontrollstimuli untersucht. Hierzu absolvierten Individuen mit ADHS und gesunde Kontrollprobanden eine Zuordnungsaufgabe mit emotionalen Gesichts- und Kontrollstimuli. Zusätzlich wurden Daten für Emotionsdysregulation, ADHS-Präsentation und Alter erhoben. Personen mit ADHS wurden mit gesunden Kontrollpersonen verglichen. Personen mit ADHS wiesen höhere Werte bei der Emotionsdysregulation auf als die Kontrollprobanden. Außerdem reagierten sie langsamer und ungenauer auf emotionale, aber nicht auf visuell-räumliche Kontrollstimuli. Die neuronalen Reaktionsunterschiede bei der Bearbeitung der unterschiedlichen Stimuli waren bei den Personen mit ADHD deutlich geringer, insbesondere in der linken Amygdala. Während die Kopplung zwischen der rechten Amygdala und dem bilateralen ventromedialen präfrontalen Kortex bei den Kontrollpersonen bei emotionalen Stimuli stärker war als bei visuell-räumlichen Stimuli, unterschieden sich die Werte der Kopplung bei den Personen mit ADHS nicht signifikant zwischen den Versuchsarten.

Weder Emotionsdysregulationsdaten noch ADHS-Präsentation oder Alter standen in Zusammenhang mit dem Antwortverhalten oder der neuronalen Verarbeitung während der emotionalen Zuordnungsaufgabe.

Im zweiten Artikel (Kapitel 3) untersuchte ich mit einer Kombination aus Graphenanalyse und Strukturgleichungsmodellen (SEM) die funktionelle Konnektivität im Ruhezustand (gemessen via „Resting-State"-fMRT) bei jungen Erwachsenen mit ADHS und altersentsprechenden gesunden Kontrollpersonen. Die Emotionsdysregulation wurde mit vier Skalen aus Fragebögen gemessen und durch eine latente Variable des SEM operationalisiert. Die latente Emotionsdysregulationsvariable wurde durch Skalen charakterisiert, die emotionalen Probleme, Verhaltensprobleme und emotionale Labilität erfassten. Graphenanalyse wurde auf die „Resting-State"-fMRT Daten angewandt und regionenspezifische Maße für die Netzwerktopologie wurden berechnet. Die Maße wurden anschließend mit SEM-Modellen analysiert, um Hirnregionen zu identifizieren, bei denen die Assoziation zwischen lokaler Netzintegration und Konnektivität einerseits und Emotionsdysregulation andererseits von der ADHS-Präsentation abhängt. Bei Personen mit ADHS, die durch Hyperaktivität-Impulsivität gekennzeichnet sind, war die latente Variable der Emotionsdysregulation mit einem erhöhten Cluster-Koeffizienten und lokaler Effizienz der rechten Insula assoziiert. Weder bei gesunden Kontrollprobanden noch bei Personen mit ADHD, die nur Symptome der Unaufmerksamkeit aufweisen, zeigte sich ein ähnliches Muster.

Im dritten Artikel (Kapitel 4) wurde untersucht, ob Emotionsdysregulation und die Integration emotionsbezogener funktioneller Hirnnetzwerke mit der interindividuellen Veränderung des ADHS-Schweregrads in Zusammenhang stehen. Der Schweregrad von ADHS und „Resting-State"-fMRT Daten wurden bei Personen mit ADHS und gesunden Kontrollpersonen zu zwei Zeitpunkten in der späten Jugend und im jungen Erwachsenenalter gemessen. Es wurden bivariate latente Change-Score-Modelle angewandt, um zu untersuchen, ob Emotionsdysregulation und Netzwerkintegration während der Adoleszenz mit Veränderungen des ADHS-Schweregrads im Zusammenhang stehen. Die Dysregulation von Emotionen wurde anhand von Fragebogen-Subskalen für Verhaltensprobleme, emotionale Probleme und emotionale Labilität gemessen. Eine bessere Emotionsregulation war mit einem besseren Verlauf von ADHS assoziiert. Mithilfe der Graphenanalyse identifizierten wir die Netzwerkintegration emotionsbezogener funktioneller Gehirnnetzwerke. Die Netzwerkintegration wurde anhand der nodalen Effizienz gemessen, d. h. der durchschnittlichen inversen Pfaddistanz von einer Hirnregion zu allen anderen Hirnregionen des Netzwerkes. Ein Muster aus niedriger nodaler Effizienz in Hirnregionen, die mit grundlegenden emotionalen Prozessen in Verbindung gebracht werden, und hoher nodaler Effizienz in Regionen der impliziten Emotionsregulation sagte einen weniger schweren Verlauf von ADHS voraus.

Außerdem stand eine größere nodale Effizienz des rechten orbitofrontalen Kortex in Zusammenhang mit einem besseren Verlauf der ADHS.

Die Artikel liefern Hinweise darauf, dass die neuronale Aktivität und die funktionelle Konnektivität zwischen Emotionen betreffenden Hirnstrukturen mit dem gemeinsamen Auftreten von Emotionsdysregulation und ADHS zusammenhängen könnten. ADHS und die häufig gemeinsam auftretenden emotionalen Probleme sollten nicht auf einzelne, isolierte Systeme, z. B. für exekutive Funktionen und kognitive Kontrolle, zurückgeführt werden. Die neurobiologischen Wurzeln scheinen komplex und heterogen zu sein und das Zusammenspiel verschiedener, zumindest teilweise emotionsbezogener Gehirnnetzwerke zu beinhalten. Die vorliegenden Ergebnisse stehen im Einklang mit Literatur, die nicht versucht ADHS über monokausalen Modelle zu erklären, sondern die Komplexität von ADHS betont und heterogene Profile mit unterschiedlichen Defiziten und neurobiologischen Anomalien beschreibt. Es ist wichtig, jeden ADHS-Fall individuell zu beurteilen und die Defizite, einschließlich der ADHS-Symptome, der gleichzeitig auftretenden (emotionalen) Probleme und der Komorbiditäten sowie der potenziellen Stärken zu berücksichtigen. Nur auf diese Weise kann eine optimale Unterstützung gewährleistet werden.

Nederlandse samenvatting

Aandachtsdeficiëntie-/hyperactiviteitsstoornis (ADHD) is een veel voorkomende ontwikkelingsstoornis die wordt gekenmerkt door onoplettendheid, hyperactiviteit-impulsiviteit of een combinatie van beide. Emotiedysregulatie is een veelvoorkomend probleem bij ADHD dat gepaard gaat met een aanzienlijke vermindering van de kwaliteit van leven. Emotieregulatie kan worden gedefinieerd als de aanpassing van contextueel onaangepaste emoties om ze in overeenstemming te brengen met individuele doelen. Terwijl de prevalentie van ADHD afneemt met de leeftijd, lijkt de prevalentie van emotiedysregulatie toe te nemen binnen de ADHD-populatie. Onderzoek heeft nog geen eenduidig model opgeleverd om het samen voorkomen van emotiedysregulatie en ADHD te verklaren. De neurale veranderingen die ten grondslag kunnen liggen aan de moeilijkheden met emotieregulatie bij ADHD lijken divers te zijn en zich uit te strekken tot verschillende neurale netwerken.

Het doel van dit proefschrift was om een beter inzicht te krijgen in de relatie tussen ADHD en emotiedysregulatie en de onderliggende neurale activiteit. Als beschreven in drie onderzoeksartikelen onderzocht ik specifieke aspecten van de relatie tussen ADHD en emotiedysregulatie, namelijk de perceptie van emotionele stimuli, de associatie tussen functionele hersentopologie en emotiedysregulatie bij verschillende ADHD presentaties, en emotiedysregulatie-gerelateerde neurobiologische en fenotypische voorspellers van ADHD progressie. Alle drie de artikelen zijn gebaseerd op gegevens van functionele magnetische resonantiebeeldvorming (fMRI).

In het eerste artikel (hoofdstuk 2) werd de neurale activiteit tijdens de verwerking van boze en angstige gezichtsstimuli en visuospatiale controle stimuli onderzocht. Voor dit doel hebben mensen met ADHD en gezonde controlepersonen een matching taak uitgevoerd met emotionele gezichts- en controlestimuli. Bovendien werden gegevens verzameld over emotiedysregulatie, ADHD-presentatie en leeftijd. Individuen met ADHD werden vergeleken met gezonde controlepersonen. Individuen met ADHD hadden hogere scores op emotiedysregulatie dan de controlepersonen. Zij reageerden ook trager en minder accuraat op emotionele, maar niet op visuospatiale controlestimuli. De neurale responsverschillen bij het verwerken van de verschillende stimuli waren significant kleiner bij de proefpersonen met ADHD, vooral in de linker amygdala. Terwijl de koppeling tussen de rechter amygdala en de bilaterale ventromediale prefrontale cortex sterker was voor emotionele stimuli dan voor visuospatiale stimuli bij de controlepersonen, verschilden de waarden van koppeling bij de proefpersonen met ADHD niet significant tussen de experimentele typen. Noch emotiedysregulatiegegevens, noch ADHD-presentatie of leeftijd waren gerelateerd aan het responsgedrag of de neurale verwerking tijdens de emotionele mapping taak.

In het tweede artikel (hoofdstuk 3) heb ik een combinatie van grafiekanalyse en structurele vergelijkingsmodellering (SEM) gebruikt om de functionele connectiviteit in rusttoestand (gemeten via rusttoestand fMRI) te onderzoeken bij jongvolwassenen met ADHD en bij leeftijdsgenoten die gezonde controles hebben. Emotiedysregulatie werd gemeten met vier schalen uit vragenlijsten en geoperationaliseerd door een latente variabele van de SEM. De latente emotiedysregulatievariabele werd gekarakteriseerd door schalen voor emotionele problemen, gedragsproblemen en emotionele labiliteit. Grafiekanalyse werd toegepast op de fMRI-gegevens in rusttoestand en regiospecifieke maten van netwerktopologie werden berekend. De metingen werden vervolgens geanalyseerd met SEM modellen om hersengebieden te identificeren waarin de associatie tussen lokale netwerkintegratie en connectiviteit enerzijds, en emotiedysregulatie anderzijds, afhing van de presentatie van ADHD. Bij proefpersonen met ADHD gekenmerkt door hyperactiviteit-impulsiviteit, was de latente variabele van emotiedysregulatie geassocieerd met een verhoogde clustercoëfficiënt en lokale efficiëntie van de rechter insula. Noch bij gezonde controlepersonen, noch bij personen met ADHD, die alleen symptomen van onoplettendheid vertonen, kwam een soortgelijk patroon naar voren.

In het derde artikel (hoofdstuk 4) onderzocht ik of emotiedysregulatie en de integratie van emotie-gerelateerde functionele hersennetwerken geassocieerd zijn met interindividuele veranderingen in ADHD ernst. De ernst van ADHD en fMRI-gegevens in "rusttoestand" werden gemeten bij personen met ADHD en gezonde controles op twee tijdstippen in de late adolescentie en de jongvolwassenheid. Bivariate latente change score modellen werden toegepast om te onderzoeken of emotiedysregulatie en netwerkintegratie tijdens de adolescentie geassocieerd zijn met veranderingen in ADHD ernst. Emotiedysregulatie werd gemeten met behulp van subschalen voor gedragsproblemen, emotionele problemen en emotionele labiliteit in de vragenlijst. Betere emotieregulatie werd geassocieerd met een beter resultaat bij ADHD. Met behulp van grafiekanalyse, identificeerden we netwerkintegratie van emotie-gerelateerde functionele hersennetwerken. De netwerkintegratie werd gemeten aan de hand van de knooppuntefficiëntie, d.w.z. de gemiddelde inverse padafstand van een hersengebied naar alle andere hersengebieden in het netwerk. Een patroon van lage nodale efficiëntie in hersengebieden die geassocieerd worden met basale emotionele processen en hoge nodale efficiëntie in gebieden van impliciete emotieregulatie voorspelde een minder ernstig beloop van ADHD. Bovendien werd een grotere nodale efficiëntie in de rechter orbitofrontale cortex geassocieerd met een beter beloop van ADHD.

De artikelen leveren bewijs dat neurale activiteit en functionele connectiviteit tussen emotie-gerelateerde hersenstructuren gerelateerd kunnen zijn aan het samen voorkomen van emotiedysregulatie en ADHD. ADHD en de vaak voorkomende gelijktijdige emotionele problemen mogen niet worden toegeschreven

aan afzonderlijke, geïsoleerde systemen, bij voorbeeld voor executieve functies en cognitieve controle. De neurobiologische wortels blijken complex en heterogeen te zijn, waarbij sprake is van een samenspel van verschillende hersennetwerken die op zijn minst gedeeltelijk met emotie te maken hebben. De huidige bevindingen zijn in overeenstemming met literatuur die ADHD niet probeert te verklaren via monocausale modellen, maar de complexiteit van ADHD benadrukt en heterogene profielen beschrijft met verschillende stoornissen en neurobiologische afwijkingen. Het is belangrijk om elk geval van ADHD individueel te beoordelen, rekening houdend met de gebreken, waaronder ADHD-symptomen, bijkomende (emotionele) problemen en comorbiditeiten, alsook met potentiële sterke punten. Alleen op die manier kan een optimale ondersteuning worden gewaarborgd.

Table of content

Chapter 1

General introduction

The focus of the present doctoral thesis is on emotion dysregulation in attention-deficit/hyperactivity disorder (ADHD) and its underlying neural processes. Emotion dysregulation is a common problem in individuals with ADHD that is associated with significant reductions in the quality of life. While the prevalence of ADHD decreases with age, the prevalence of emotion dysregulation appears to increase with age in individuals with ADHD. Research does not yet provide a unified model to explain the co-occurrence of emotion dysregulation and ADHD. Neural alterations that may underlie emotion regulation deficits in ADHD appear to be diverse and span across different neural networks.

The purpose of the studies described in this thesis was to increase our understanding of the relationship of ADHD with emotion dysregulation, specifically in relation to the perception of emotional stimuli, different ADHD presentations, and the course of ADHD. Functional magnetic resonance imaging (fMRI) was used to investigate underlying alterations of brain activity during task performance and at rest. Neuroimaging data were analyzed using classical methods such as general linear modeling and psychophysiological interaction analysis on the one hand, and a novel combination of graph theory analysis and structural equation modeling (SEM) on the other hand.

This chapter first introduces the topics of ADHD and emotion dysregulation and provides an overview of the current state of research. In doing so, it emphasizes the importance of a better understanding of the relationship between ADHD and emotion dysregulation. This will be followed by an overview of the methods used in this thesis to analyze the neuroimaging data. A special focus is on the application of graph theory methods and SEM in the field of neuroimaging. Finally, the study design of the thesis is presented, its aims are summarized and an outline of the following chapters is given.

Attention-deficit/hyperactivity disorder and emotion dysregulation

Attention-deficit/hyperactivity disorder

ADHD is a frequently occurring neurodevelopmental disorder characterized by inattention, hyperactivity-impulsivity, or a combination of both (Faraone et al., 2015). Based on the DSM-5 criteria, a prevalence of 11.4% in primary school children and a prevalence of 5% in adults is assumed (American Psychiatric Association, 2013). While in childhood most cases show both, hyperactive-impulsive as well as inattentive

symptoms, predominantly inattentive cases are more common in adults (Willcutt, 2012). ADHD is thought to be causally related to different risk factors that in combination lead to changes in functional and structural brain networks. It has been shown that genetic disposition plays a prominent role in the etiology of the disorder. While genome-wide association studies frequently did not identify specific ADHD-related genes, a recent GWAS meta-analysis identified 12 loci with genetic variants significantly associated with ADHD. Each of them, however, only captured a tiny fraction of the common variant risk for ADHD. These loci were located in or at genes associated with neurodevelopmental processes (Demontis et al., 2019). Further, meta-analysis show that particularly gene variants associated with monoamine neurotransmitter systems, i.e., involving dopamine, serotonin, and noradrenaline, may be relevant (Faraone et al., 2015). Environmental risk factors range from pre- and perinatal factors such as maternal drug use to psychosocial factors such as adverse family circumstances and neglect, or negative peer influences (Faraone et al., 2015). The individual symptom profiles of ADHD are similarly heterogeneous as the underlying risk factors. This refers not only to the distinctions of the three diagnosable presentations, i.e. predominantly inattentive, predominantly hyperactive-impulsive, and combined, but also to associated impairments and accompanying comorbidities. Only a minority of affected individuals do not have comorbidities, many have several. ADHD often co-occurs with other psychiatric disorders, such as depression, bipolar disorder, autism spectrum disorders, anxiety disorders, oppositional defiant disorder, conduct disorder, eating disorder, and substance use disorder (Bernardi et al., 2012; Q. Chen et al., 2018), as well as non-psychiatric problems, such as obesity, diabetes, and sleep disorder (Q. Chen et al., 2018; Kapellen, Reimann, Kiess, & Kostev, 2016; Sedky, Bennett, & Carvalho, 2014). The course of ADHD and outcomes in later life, i.e., persistent or remitting ADHD, have been associated with several predictive markers. Genetic factors as well as cognitive performance may be relevant. However, other clinical features such as symptom severity, depression, behavioral problems, and emotion dysregulation in childhood have also been linked to the course of the disorder and adult-age outcomes (Shaw & Sudre, 2021). In any case, quality of life can be severely affected by ADHD on multiple levels. Physical impairments, such as obesity, hypertension, and even premature death, social disabilities with poor family or peer relationships, psychological dysfunctions, especially emotion dysregulation, lacking motivation or suicidal tendencies, risky behaviors, and academic and occupational underperformance were reported (Dalsgaard, Ostergaard, Leckman, Mortensen, & Pedersen, 2015; Faraone et al., 2015).

Despite the steadily improving methodological capabilities in the field of imaging research and the ever growing and diversifying ADHD literature, the underlying pathophysiological mechanisms of ADHD remain only partially understood (Cortese et al., 2012). Earlier research particularly emphasized the importance

of frontostriatal circuits (e.g. Sonuga-Barke, 2003). These pathways connect prefrontal regions to the basal ganglia and are categorized into different main circuits. Connections to the dorsolateral prefrontal cortex are associated with executive control and cognitive processes, whereas circuits including the orbitofrontal and anterior cingulate regions are associated with emotional and behavioral inhibition on the one hand and motivational and reward processes on the other (Tekin & Cummings, 2002). The multifaceted nature of the frontostriatal circuits inspired neurocognitive models that postulate that the heterogeneity of ADHD is due to alterations in different areas of the circuits. Inattentive Symptoms have been postulated to arise from disturbances in executive circuits and resulting executive dysfunction, whereas predominantly hyperactive-impulsive symptoms have been postulated to originate from disturbances in the emotional and reward circuits (Sonuga-Barke, 2003). While these dual-pathway models try to account for the heterogeneity in ADHD, they certainly cannot explain ADHD in its entirety, especially considering that different ADHD presentations may change across the lifespan. In ADHD, pharmacological intervention is primarily achieved through the administration of stimulants that act at the catecholaminergic, thus dopaminergic and noradrenergic, receptors and have an impact on the prefrontal cortex and basal ganglia function (Bachmann et al., 2017).

A variety of cortical and subcortical structures as well as neurotransmitter systems, each associated with different sets of functions, may play a role in ADHD (Faraone et al., 2015). Children with ADHD have a slightly reduced total cortical area. They have been found to have reduced cortical thickness, especially in the frontal, cingulate, and temporal regions. Moreover, reduced volume of subcortical regions, namely basal ganglia, amygdala, hippocampus can also be observed (Hoogman et al., 2019). Diffusion tensor imaging can most robustly find ADHD-specific abnormalities in sections of the corpus callous, indicating problems with connections between the two hemispheres in the posterior parieto-temporal attention regions (L. Chen et al., 2016). Promising findings have emerged in studies of intrinsic functional connectivity and associated brain networks. In networks associated with goal-directed executive control and reorientation of attention to salient and behaviorally relevant stimuli, i.e. the frontoparietal and ventral attention network, individuals with ADHD appear to show hypoactivity. Hyperactivity was shown in regions attributed to the default mode network, which is associated with emotional and social evaluation, as well as self-referential processes (Cortese et al., 2012). The commonly observed inverse correlation between the default mode and frontoparietal network appears to be less pronounced in ADHD (Posner, Park, & Wang, 2014). Moreover, divergent interplay between the default mode, frontoparietal, and attention networks was reported (Castellanos & Aoki, 2016). In a proposed network model that aims at harmonizing various findings, it has been suggested that aberrant engagement of the frontoparietal and

default mode network negatively affects cognition and executive control as well as self-referential processes in mental disorders, including ADHD. The imbalanced engagement could have several causes, such as poor detection and processing of salient, novel stimuli, e.g., via the ventral attentional network, or dysfunctional signaling of limbic system structures associated with reward and emotion processes (Menon, 2011). Correspondingly, aberrations of functional connectivity in emotion- and reward-related circuits, including the orbitofrontal cortex, ventromedial prefrontal cortex, ventral striatum, and amygdala, were repeatedly reported in ADHD literature (Costa Dias et al., 2013; Francx et al., 2015; Mennes et al., 2011; Posner et al., 2013; Tomasi & Volkow, 2012).

A growing body of literature gives evidence for complex atypical brain functioning in ADHD. Affected regions span across large parts of the cortex, including the medial and lateral prefrontal cortex, the parietal cortex, the orbitofrontal cortex, the cingulate cortex, and the temporal cortex. Thus, they involve multiple functional systems such as the frontoparietal network, salience network, and default mode network. In connection with subcortical structures, i.e. the basal ganglia, amygdala, and brainstem, the executive control network, reward and emotion networks, as well as noradrenergic and dopaminergic transmitter circuits appear to be affected. There has been a shift from single-cause or single-pathway models to models that describe the causes of ADHD development across multiple pathways, implying heterogeneous profiles of deficits and neurobiological abnormalities (Faraone et al., 2015). Research does not yet provide a unified neurobiological model for ADHD. Many different pieces still need to be put together to provide a conclusive picture. Deciphering the underlying neurobiology is fundamental for a better understanding of the causes of the disorder and ultimately to improve the diagnostic process and treatment of ADHD, also in the context of the frequently co-occurring comorbidities. Figure 1.1 provides a graphical summary of those brain regions and neural pathways that have been implicated in ADHD (reproduced from Faraone et al., 2015).

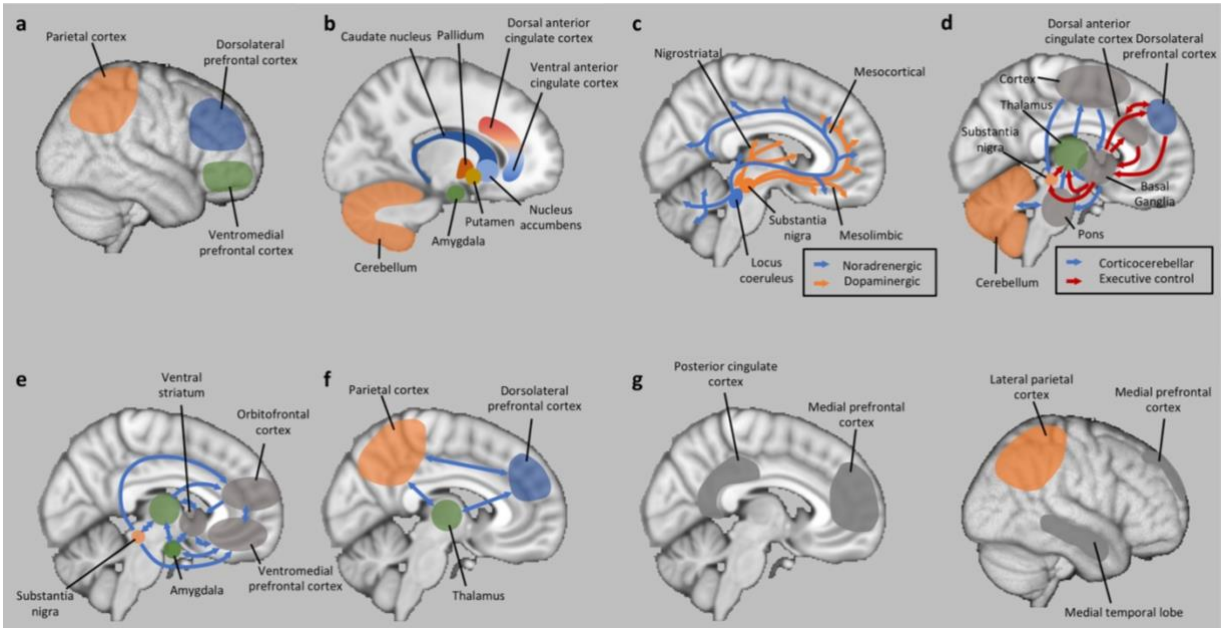

Figure 1.1: *Brain mechanisms in ADHD.* ***[a]*** *Dorsolateral prefrontal cortex (working memory), ventromedial prefrontal cortex (complex decision making & strategic planning) and parietal cortex (attentional orientation) are implicated in ADHD.* ***[b]*** *The ventral anterior cingulate cortex and the dorsal anterior cingulate cortex (affective and cognitive executive control) and basal ganglia (consisting of nucleus accumbens, caudate nucleus, palladium, and putamen), together part of the frontostriatal circuit, show structural and functional abnormalities in ADHD that extend into the amygdala and cerebellum.* ***[c]*** *The dopamine system (i.a. associated with initiation of motor responses and processing of rewards) and the noradrenergic system (i.a. associated with arousal modulation and cognitive processes) are implicated in ADHD.* ***[d]*** *Executive control and corticocerebellar networks (coordinating planning, goal-directed behaviour, inhibition, working memory) are hypoactive in ADHD.* ***[e]*** *The ventromedial prefrontal cortex, orbitofrontal cortex and ventral striatum (reward processing), thalamus, amygdala, and substantia nigra, as well as frontal and parietal cortical areas (alerting network) are implicated in ADHD.* ***[g]*** *The default-mode network (DMN; consisting of medial prefrontal cortex, posterior cingulate cortex, lateral parietal cortex and medial temporal lobe (lateral view) is desynchronized and functional connectivity to control networks is weaker. The graphic is reproduced from Faraone et al. (2015).*

Emotion regulation

Emotions are sets of cognitive, physiological, and behavior/motor states that are formed by unconscious or conscious assessments of stimuli within specific contexts and under consideration of individual goals (Gross, 2015). These states trigger fast actions aimed at beneficially altering the internal and external world. Emotions may thus be understood as a sequence of perception, valuation, and action (Etkin, Büchel, & Gross, 2015). Superordinate processes are necessary to evaluate the outcome of emotionally triggered actions, or to determine behavior in emotionally ambiguous situations. These processes may act at any stage of an emotional sequence and are referred to as emotion regulation. Emotion regulation may be defined as the adjustment of contextually inappropriate emotions in order to synchronize them with individual goals (Gross, 2015). Similar to an emotional process that can be understood as a sequence of perception, valuation, and action, emotion regulation is also assumed to be a multi-stage process. Within an identification phase, an individual determines whether regulatory intervention is necessary. This might

be the case, if a potential regulated state is considered more favorable for an individual's goals than the current emotionalized state. Based on the presumed benefit, a selection process decides at which point and how the existing emotional state should be changed. For example, the emotion-triggering situation may be reevaluated or the response behavior may be modulated. In a final stage, the regulatory plan is implemented (Gross, 2015; Sheppes, Suri, & Gross, 2015).

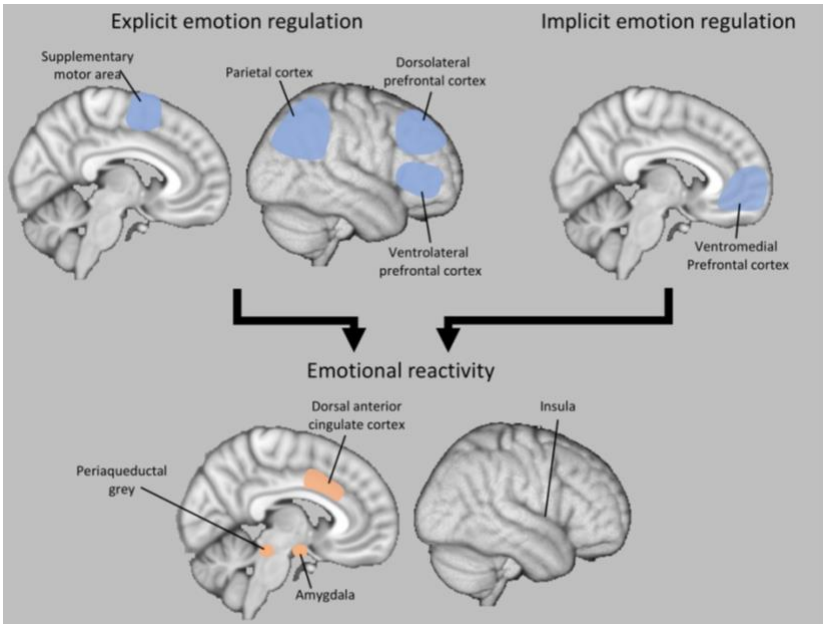

Figure 1.2: *Emotion regulation may be divided into explicit and implicit emotion regulation. Both are associated with specific brain regions and provide for the regulation of emotional processes through different processes. The graphic is reproduced from Etkin et al. (2015).*

Literature distinguishes two main types of emotion regulation (see Figure 1.2). Explicit emotion regulation requires conscious effort and is commonly achieved by applying cognitive control and reappraisal strategies. Implicit emotion regulation (also non-volitional emotion regulation), on the other hand, is an unconscious stimulus-driven process based on experience-based reward estimations (Gyurak, Gross, & Etkin, 2011). Neuroimaging techniques revealed the differing neurobiology underlying these two types of emotion regulation. Initial emotion processing involves amongst others the amygdala, ventral striatum, periaqueductal grey, insula, and the dorsal anterior cingulate cortex. In implicit emotion regulation, activity in these areas appears to be controlled by a network of ventral anterior cingulate and ventromedial prefrontal cortex (Etkin et al., 2015). Exemplary for this are fear extinction experiments, in which a formally learned association between a neutral and an aversive stimulus is eliminated by repeatedly showing the neutral stimulus without the aversive one. The process of fear extinction is marked by ventral anterior

cingulate and ventromedial prefrontal cortex activation (Etkin, Egner, & Kalisch, 2011). Explicit emotion regulation engages frontoparietal network structures, especially the ventro- and dorsolateral prefrontal cortex, while activity in primary emotion-processing structures such as the amygdala is reduced (McRae, Ciesielski, & Gross, 2012). Corresponding activation patterns can be observed when reappraisal strategies are used to reduce negative emotions. Reappraisal involves using capacities of working memory and cognitive networks to generate internal simulations of the external environment and to identify alternative meanings of stimuli (Etkin et al., 2015).

Emotion regulation is enabled by complex, partially sequential processes that act on the different stages of emotion-generating processes. Accordingly, the possibilities for imbalances that lead to dysregulation are numerous. Many psychopathological conditions are based on dysfunctional emotion regulation, or are accompanied by it (Sheppes et al., 2015). Often, it is not just a single process that is disrupted within the regulatory system. Failure often occurs at multiple stages (Sheppes et al., 2015). Due to the complexity of the constructs of emotion and emotion regulation, the difficulty of separating and measuring them independently as well as disagreements on precise definitions, there is no consensus on how best to operationalize emotion regulation (Cole, Martin, & Dennis, 2004). A wide range of measures have been utilized to obtain emotion regulation or dysregulation scores. For example, subscales of more comprehensive questionnaires have been used. These include the emotional lability subscale of the Strength and Difficulty questionnaire (van Widenfelt, Goedhart, Treffers, & Goodman, 2003). It includes items on unpredictable mood changes, temper tantrums, and tearfulness. On the other hand, there are questionnaires that investigate explicit, cognitive regulation strategies (e.g., self-blame, positive refocusing, acceptance, etc.) (Loch, Hiller, & Witthöft, 2011).

Emotion dysregulation in attention-deficit/hyperactivity disorder

Emotion dysregulation is a commonly occurring phenomenon in ADHD. In an initial description of ADHD (then called ‘minimal brain damage’), it was distinguished as one of its core symptoms (Clements, 1966; Shaw, Stringaris, Nigg, & Leibenluft, 2014). Also more recently, it has been argued that emotion dysregulation is an inherent component of ADHD (Barkley, 2015). Due to the different operationalization of emotion dysregulation in ADHD research, it is difficult to give an exact prevalence. However, the prevalence of emotion dysregulation in ADHD appears to be many times higher than in unaffected individuals. It is also thought to be age dependent, changing from 25-45% in childhood to 30-70% in adulthood (Shaw et al., 2014). No clear connection has been found between emotion dysregulation and the different ADHD presentations. While children with predominantly hyperactive-impulsive ADHD

showed significantly higher levels of emotion dysregulation than children with predominantly inattentive ADHD (Maedgen & Carlson, 2000), similar relations could not be found in adolescents (Bunford, Evans, & Langberg, 2018). This may be connected to the decrease in predominantly hyperactive-impulsive cases as age increases. Differences between ADHD presentations might become more subtle with age, which in turn might reduce presentation-specific differences in emotion dysregulation (Bunford et al., 2018). In any case, the co-occurrence of emotion dysregulation in ADHD is associated with further significant limitations in the quality of life (Bunford, Evans, & Wymbs, 2015). Affected individuals suffer from impaired peer relationships (Maedgen & Carlson, 2000; Melnick & Hinshaw, 2000), show reduced prosocial behavior (Bunford, Evans, Becker, & Langberg, 2015), demonstrate lower academic and occupational performance (Wehmeier, Schacht, & Barkley, 2010), generally report lower well-being and self-esteem (Riley et al., 2006), and tend to engage in more risky behavior (Matthies, Philipsen, & Svaldi, 2012). Furthermore, it has been shown that the persistence of ADHD throughout childhood and adolescence is related to the presence of emotion dysregulation symptoms in childhood (Caye et al., 2016; Miranda, Colomer, Fernández, Presentación, & Roselló, 2015; Sasser, Kalvin, & Bierman, 2016).

The basis for the common overlap between emotion dysregulation and ADHD may not be found in disturbances of a single, isolated process. As frequently observed in psychopathological conditions, ADHD rather seems to be accompanied by deficits at multiple stages of emotion regulation. Prior research has indicated dysregulations at different stages of emotion processing, i.e., perception, valuation, and action. Several studies addressed emotion perception in ADHD. ADHD is characterized by reduced accuracy in categorizing emotional stimuli, especially negative stimuli, which is moreover associated with other emotional deficits, i.e., higher levels of anxiety and depression (Jusyte, Gulewitsch, & Schönenberg, 2017; Schönenberg, Schneidt, Wiedemann, & Jusyte, 2019; Williams et al., 2008). At the same time, it has been shown that ADHD is associated with incoherencies in responding to emotional stimuli. While unaffected individuals show a connection between physiological (cardiac and respiratory) and behavioral (facial affect) responses, this connection is significantly reduced in children with ADHD. The incoherent responses may lead to ambiguous emotional experiences, which in turn may cause situationally inappropriate actions (Musser & Nigg, 2019).

Neuroimaging research in ADHD has found evidence of aberrations in neural circuits associated with primary emotion processing and different types of emotion regulation, i.e., implicit and explicit emotion processing. Task-based fMRI research using emotion perception and recognition tasks found aberrant amygdala activity, especially hyperactivity of the left amygdala, insula hypoactivity, and decreased activity of the ventral striatum (Brotman et al., 2010; Herpertz et al., 2008; Posner, Nagel, et al., 2011). Most task-

based studies focused on childhood ADHD, with fewer task-based studies conducted in adults with ADHD. However, also in adults aberrant amygdala and ventral striatum activity could be shown (Plichta et al., 2009; Schlochtermeier et al., 2011; Ströhle et al., 2008). Resting state functional connectivity MRI research reports on altered connectivity of the amygdala and orbitofrontal cortex within affective networks (Ho et al., 2015) and deviations of topological network properties in the area of orbitofrontal cortex and ventral striatum (Costa Dias et al., 2013; Lin et al., 2014; Tomasi & Volkow, 2012; L. Wang et al., 2009). ADHD studies correlating functional connectivity of the amygdala with emotion lability (often used as a measure for emotion dysregulation) showed that higher emotion lability was associated with reduced functional connectivity of the amygdala with the insula and frontoparietal network structures as well as increased functional connectivity between the insula and the anterior cingulate cortex (Hulvershorn et al., 2014; Yu et al., 2016). Again, the vast majority of the above studies on functional connectivity and resting-state fMRI, although not all (e.g. Lin et al., 2014), were based on childhood samples.

Task-based fMRI studies related to implicit emotion regulation, i.e., tasks using fear extinction via habituation, emotional Stroop and reappraisal paradigms, which controlled for differences in cognitive control, found ADHD-specific differences in the ventral anterior cingulate and ventromedial prefrontal cortex (Materna et al., 2019; Posner, Maia, et al., 2011; Spencer et al., 2017). Resting-state functional connectivity research indicated divergent activity of structures related to implicit regulation of emotions, specifically the ventromedial prefrontal cortex and anterior cingulate cortex (Bos et al., 2017; Marcos-Vidal et al., 2018; Posner et al., 2013; Pruim et al., 2019; Tomasi & Volkow, 2012).

In task-based fMRI research of ADHD, findings of hypoactivity in the frontoparietal and ventral attentional networks, i.e., networks associated with executive control and cognitive functioning but also explicit emotion regulation, are most commonly reported (Cortese et al., 2012). Despite sometimes very heterogeneous results, deviations in these regions are also commonly found in the resting state ADHD literature (Cortese, Aoki, Itahashi, Castellanos, & Eickhoff, 2021). Some studies suggest that dysfunctional executive control and underlying neural networks may at least partially explain emotion dysregulation in ADHD. Executive control in the form of behavioral inhibition during stop-signal tasks was found to correlate with emotion dysregulation in children with ADHD (Walcott & Landau, 2004). Also, in ADHD, control of attention toward negatively connotated emotional stimuli was shown to be deficient and associated with aberrant activity of lateral prefrontal areas. On the other hand, functional connectivity in executive attentional circuits, especially those connected to the dorsolateral prefrontal cortex, was shown to predict executive dysfunction but not emotion dysregulation in ADHD. The latter was much more associated with functional connectivity between ventral striatum and orbitofrontal cortex (Posner et al., 2013).

Although there is strong evidence that brain regions involved in emotional processes differ among individuals with ADHD, little is known about how these connections change with age and whether emotion-related (neural) covariates can predict the course of ADHD. Most fMRI-based ADHD studies continue to focus on childhood samples. However, some studies compared neural activity between groups of young adults with different categorical trajectories of previous ADHD diagnoses (e.g., remitting vs. persistent ADHD) (Shaw & Sudre, 2021). Structural abnormalities in cognitive control networks, as well as in regions associated with emotion dysregulation, have been linked to persistent ADHD (Shaw et al., 2013, 2015). By comparing individuals with different ADHD outcomes, it has also been shown that adults with persistent ADHD, but not remitted ADHD, exhibit abnormal functional connectivity in the default mode network, a network related to self-referential processing and emotion regulation (Mattfeld et al., 2014; Sudre, Szekely, Sharp, Kasparek, & Shaw, 2017).

So far, research does not provide a unified model explaining the common co-occurrence of emotion dysregulation in ADHD. Neural aberrations that possibly underlie the emotion regulation deficits in ADHD appear to be diverse and span across different neural networks. At a large scale, it seems plausible that imbalances in the engagement of anticorrelated networks for executive control and attention on the one hand (i.e., frontoparietal network) and self-referential processes and emotion evaluation (i.e., default mode network) on the other hand cause typical ADHD symptoms but also co-occurring emotion dysregulation (Menon, 2011). Nevertheless, by answering many questions that have not yet been answered satisfactorily, major contributions to improving therapy for affected individuals and thus their quality of life could be made. Central issues include the perception of emotional stimuli, ADHD presentation-specific differences in the manifestations of co-occurring emotion dysregulation, and the relationship between emotion dysregulation symptoms and the course of ADHD. The following chapters of this thesis will accordingly address these issues. In this context, methodological advances in the field of fMRI analysis provide new opportunities to explore knowledge gaps and to improve the understanding of ADHD.

Analyzing functional connectivity at rest: graph theory and structural equation modeling

Initially, fMRI research primarily focused on localizing specific functions and identifying group-specific deviations in these functions. Many hypotheses about brain functioning in the field of psychiatric disorders were thus obtained using task-based fMRI (Oldehinkel, Francx, Beckmann, Buitelaar, & Mennes, 2013). The most common method of analysis in this respect is voxel-wise general linear modeling (cf. Zhan & Yu, 2015). However, an ongoing shift toward analyzing functional connectivity between different brain regions can be observed. Research increasingly focuses on how individual regions integrate into networks and how information is transferred within and between these networks. To some extent, it is possible to study functional connectivity between brain regions in task-based designs. For example, psychophysiological interaction (PPI) models (as utilized in chapter two of this thesis) allow the analysis of functional connectivity between seed regions and other regions of the brain as a function of specific task conditions (Friston et al., 1997). In addition, especially resting-state fMRI has become an increasingly important tool to decipher the functional networks of the brain. In resting-state fMRI, subjects do not perform tasks inside the fMRI scanner, but lie still, i.e. at rest, allowing spontaneous brain activity to be recorded. Since psychopathologies are usually not assumed to involve dysfunctions of single, well-defined structures, but rather imbalances in the activity and interaction of large-scale networks, functional connectivity and, thus, resting-state fMRI are ideally suited. This is further supported by the fact that resting-state fMRI requires only limited participant compliance. There are several methods for analyzing resting-state fMRI. The most commonly used are probably seed-based functional connectivity analysis and independent component analyses. Alternative methods, however, gain more and more popularity.

Graph theory and brain networks

Graph theory is a set of mathematical methods for analyzing interacting elements of networks. Graphs are simplified models of networks in which individual elements are represented as nodes and connections between elements are represented as edges, indicating the degree of interaction. In various scientific fields graph theory has been applied to study and understand complex networks. The human brain is undoubtedly one of the most complex naturally occurring networks. Graph theory methods are applied to brain data from a variety of sources such as EEG, MEG, resting-state fMRI, or diffusion tensor imaging. The studies presented in chapters three and four also used graph theory to examine resting-state fMRI data.

Graph theory-based analysis of the brain involves dividing the brain into elements that are as homogeneous as possible. The elements, i.e. nodes, are then examined with respect to their connectivity patterns. Depending on the data source, one must distinguish between functional and structural connectivity. Structural connectivity represents anatomical connections between nodes, for example the axonal connection between two cells, or, at a larger scale, axonal tracts connecting different brain areas. Functional connectivity can be described as the degree to which two nodes exhibit synchronized activity over time. At macroscopic scale, functional connectivity is most commonly investigated using resting-state fMRI (Fornito, Zalesky, & Bullmore, 2016). Some of the relevant discussion points are mentioned below.

Application of graph theory methods in resting-state fMRI is typically based on Pearson's correlation coefficient. To this end, average time series data of all nodes are taken and a correlation matrix, i.e. adjacency matrix, is created. However, there is no consensus on the exact procedure. At many stages of the analysis, different approaches may be chosen, each with its advantages and disadvantages, which ultimately can have a decisive influence on the results.

Preprocessing. Preprocessing steps of resting-state fMRI data largely overlap with those of task-based data. They commonly include slice time correction, motion correction, temporal filtering, spatial smoothing, and nuisance regression. Since resting-state fMRI measures spontaneous, intrinsic brain activity without any task structures, contamination of the BOLD signal from other physiological sources such as respiration or heartbeat, as well as motion artifacts, can have particularly confounding effects. Thus, temporal filtering of certain frequencies related to physiological noise as well as more sophisticated methods for the identification of movements have become elementary parts of preprocessing pipelines (Oldehinkel et al., 2013). One of the more recent methods for eliminating secondary motion artifacts is ICA-AROMA. As opposed to other strategies such as scrubbing or regressing out motion volumes, ICA-AROMA mostly maintains the autocorrelation structure of fMRI time series and the temporal degrees of freedom (Pruim et al., 2015). The most controversially debated preprocessing strategy in the analyses of resting-state functional connectivity is global signal regression. Global signal regression effectively removes physiological as well as movement artifacts, but has also been reported to artificially introduce anticorrelations. Thus, using global signal regression, interpretation of results containing negative correlations may be questionable (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009).

Parcellation. The goal of parcellation is to identify homogeneous neuronal subpopulations/clusters in order to investigate the interaction between these subpopulations. Connectivity between clusters may then be used as input to create a graph network. First parcellations, e.g. the Brodmann areas, were based

on the post mortem microstructure or anatomy of the brain. Such structural parcellations, however, do not necessarily coincide with functional subdivisions. Different clustering approaches have led to a variety of functional connectivity atlases. A common basis is the Pearson's correlation between the different voxels, but simple approaches such as K-mean clustering have also been used. Some atlases were built using structural and functional MRI. The use of functional atlases also raises the question of resolution, i.e. the number of nodes. Different resolutions can lead to significant differences in network measures (Fornito et al., 2016). Thus, the choice of the atlas has an influence on the exact quantification of certain network properties, but not so much on the question whether certain properties are present or not (Yao, Hu, Xie, Moore, & Zheng, 2015). It is hence reasonable to perform connectivity-based analyses with alternative atlases to control the robustness of the results.

Adjacency matrix transformation. The adjacency matrix, often generated by correlating the time series data of different nodes, may be transformed prior to graph creation and subsequent use of graph theory methods. In many cases it is necessary to perform Fisher's z-transformation on correlation values of the matrix to arrive at a sampling distribution that is approximately normal and can be averaged across subjects (M. W. Cole, Yang, Murray, Repovš, & Anticevic, 2016). Adjacency matrices based on correlations of time series usually do not contain off-diagonal elements that are non-zero. However, some of these values are very small and since it is unrealistic to assume a fully connected brain network, a threshold may be applied and anything below this threshold may be considered to be noise (Fornito et al., 2016). While a threshold can help separate signal from noise, it also brings disadvantages. It is difficult to find the exact boundary that separates signal from noise. Any decision is arbitrary. Further, if thresholding was performed on the basis of connectivity scores, i.e. correlation coefficients, different networks might have different network densities. Comparing networks' topology measures would thus become difficult, as they greatly rely on network density. Differences between populations of weighted networks may be due to the networks' density and not targeted topological features. Density is the number of edges existing in relation to the number of edges that would exist within the network if it was fully connected. It would not be sufficient to use individual density levels for thresholding, since topological features at other levels would be neglected. By integrating topology measures of networks binarized based on a subset of different density levels, network topology can be compared between networks even if the densities of the underlying weighted networks were different (Fornito et al., 2016).

Network topology measures. By representing functional connectivity between brain regions derived from resting-state FMRI in the form of graph-based networks, it becomes possible to investigate properties of individual regions in relation to the rest of the network as well as the network as a whole. For instance,

many measures exist that aim at determining the centrality of a node within the network. A central node is a node through which pairs of other nodes are connected that would otherwise not be connected and thus could not exchange information. Different calculations have been proposed to determine centrality. Some of these are degree centrality, eigenvector centrality, betweenness and closeness. The clustering coefficient describes the extent to which neighbors of a given node are interconnected. High clustering and short average distances between network nodes, namely small-worldness, were shown to provide the topological foundation of complex brain functions (Fornito et al., 2016). A measure for determining the average distance between network nodes and thus for how effectively information passes from node to node within the network is efficiency. Efficiency is defined as the average inverse path distance from one node to all other network nodes. Depending on whether the path distances of a single node, a group of nodes directly connected to a specific node, or all nodes of the network are included in the calculation, the resulting topology measure is referred to as either nodal, local or global efficiency (Achard & Bullmore, 2007). A more detailed description of the network topology measures with visualization mentioned here can be found in the Supplementary Information for Chapter 3.

Graph-theory and network analysis are a very wide subject that in recent years has received increasing attention, especially in the field of neurosciences (see Fornito et al. (2016) for a comprehensive introduction). Only a small part of the content is presented here, which will become relevant in the following sections and should contribute to a better understanding of the matters at hand. A visualization of the processes described here, including the parcellation of fMRI resting state data and the creation of an adjacency matrix, is given in Figure 1.3.

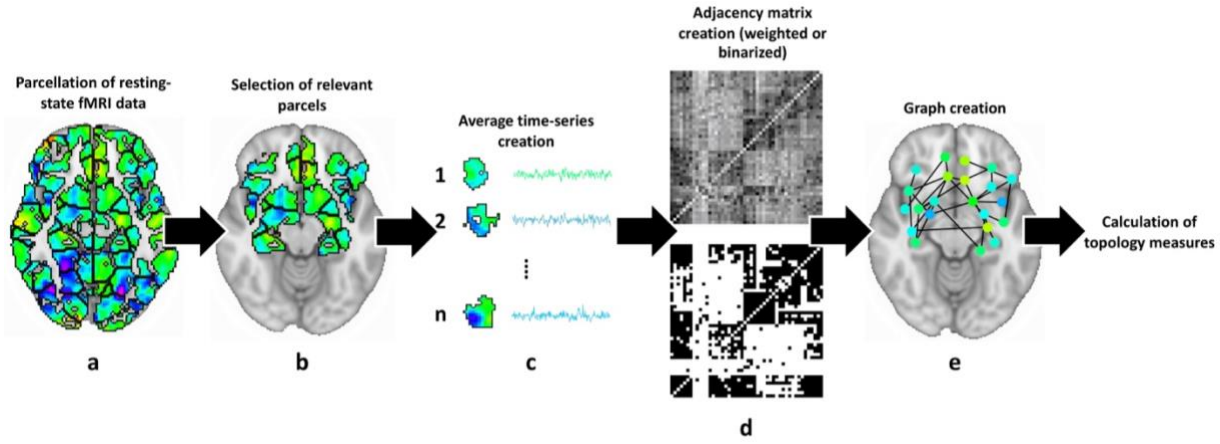

Figure 1.3: *Flow of functional graph analysis using resting-state fMRI data.* ***[a]*** *Using some parcellation scheme the volumetric data is divided into different parcels.* ***[b & c]*** *Relevant parcels are select and the average time series is calculated for each of the relevant parcels.* ***[d]*** *Individual Fisher's z-transformed correlation matrices are created and may be binarized using one or several density thresholds.* ***[d]*** *The graph is created and different topology measures may be calculated.*

Graph analysis in attention-deficit/hyperactivity disorder

Neurodevelopmental disorders are usually not rooted in single focal alterations. Childhood and adolescence are accompanied by a reshaping of brain networks to increase functionality and efficiency. Thus, with increasing age, segregating processes occur that involve greater modulation of the brain into individual subnetworks (Bassett, Xia, & Satterthwaite, 2018). Within modules, connectivity increases while between modules it decreases. As the brain matures, segregation of the frontoparietal and cingulo-opercular systems is paralleled by improvements in executive function and cognitive control. For example, segregation of the frontoparietal and cingulo-opercular systems during brain maturation is paralleled by improved executive functioning and cognitive control (Baum et al., 2017).

Consistent with the nature of neurodevelopmental disorders, ADHD research also demonstrates an increasing interest in links between network topology and the development of the disorder. An increasing number of studies uses graph theoretical methods to study ADHD. Repeatedly, ADHD has been shown to involve a pattern of reduced global and increased local efficiency (Lin et al., 2014; L. Wang et al., 2009). In accordance with this, reduced long-range connectivity and increased short-range connectivity were demonstrated (Marcos-Vidal et al., 2018; Tomasi & Volkow, 2012). For optimal brain functioning, the balance between global communication and local specialization is crucial (Bullmore & Sporns, 2009). Results suggest that information transfer between local, specialized brain regions is impaired, while exchange within such regions is increased. Brain network topology in ADHD appears to be characterized by reduced integration and increased segregation processes (Lin et al., 2014). In ADHD, maturational processes that provide for the formation and ideal functioning of brain networks may differ from those of unaffected individuals, causing topological differences and clinical symptoms (Marcos-Vidal et al., 2018).

Apart from global network topology differences in ADHD, alterations were also revealed at the node level. Differences in nodal efficiency were shown across the brain, but particularly in regions of the prefrontal cortex, i.e., the medial prefrontal and orbitofrontal cortex (Lin et al., 2014; L. Wang et al., 2009). However, corresponding results are heterogeneous and the direction of differences is partly inconsistent between studies. This may be due to differences in methodology, but also to the diversity of ADHD samples and the general heterogeneity of spontaneous brain activity in ADHD (Siqueira, Junior, Comfort, Rohde, & Sato, 2014; J.-B. Wang et al., 2017). Again, it needs to be noted that most of the existing studies refer to childhood ADHD populations.

Several studies looked at network topology alterations in individuals with different ADHD presentations. In individuals with predominately inattentive ADHD, network topology abnormalities occurred

predominantly in brain areas associated with executive functioning and cognitive control, i.e., frontoparietal network. In contrast, individuals with additional hyperactivity-impulsivity symptoms (combined ADHD) showed alterations in areas associated with self-referential processes, reward, and emotion, i.e., the anterior default mode network (Fair et al., 2013). Consistent with this, only individuals with combined ADHD were shown to exhibit functional hyper-connectivity in the anterior default mode network (Xing Qian et al., 2019). Moreover, patterns of network topology proved to be a useful tool for predicting ADHD presentations (Siqueira et al., 2014).

Structural equation modelling in neuroimaging

The studies presented in chapters three and four of this thesis are not only based on the graph theoretical analysis of functional brain connectivity but also use SEM for statistical evaluation. SEM offers a flexible framework for multivariate analyses and combines path modelling with latent variable modelling. It provides the possibility to compare a hypothetical relational model containing directed and undirected paths as well as observable and latent variables by utilizing the covariance and optionally mean structure of the observable variables. The better the observations are reproduced by the model, the better the model with its hypothesized relationships fits the data. If data is inconsistent with the model, it must either be abandoned or the relational hypotheses must be modified (Kline, 2011). In general, SEM allows for the simultaneous estimation of multiple hypotheses, the specification of directed relationships, and constructs that can be both dependent and independent variables. At the same time, it allows for inferences about latent variables underlying the observed variables (Kievit et al., 2018). A disadvantage, however, is that SEM is hardly possible when assumptions about the relationships of the investigated variables are scarce. Furthermore, SEM requires rather large sample sizes. If this is not given, statistical estimates, like standard errors, may not be accurate. A commonly cited and empirically supported rule of thumb is that the sample size-to-parameter ratio should be 10:1, ideally 20:1 or above. It is applicable when the most commonly used estimation method, maximum likelihood estimation, is used (Kline, 2011). However, it may not be advisable to categorically adhere to such heuristics. Different measures can be taken without increasing the sample size, e.g., using robust estimation methods (Kievit et al., 2018).

In the field of neuroimaging, SEM was applied quite early on. The initial focus was on the analysis of relationships between brain activity of different brain regions during task performance. For example, a stimulus may cause the activation of some brain regions that interact with each other to facilitate the processing of the stimulus. The hypothesized interactions of the brain regions may be modeled using SEM (Zhan & Yu, 2015). However, SEM models do not have to be limited to neural data only. They can also be

used to study the relational patterns between neural properties and phenotypical and/or behavioral data, i.e., cross-domain relationships. SEM is particularly suitable for the study of neural variables, where a specific value can be assigned to each individual. This of course can be the case with graph theory-based network topology measures.

Multi-group structural equation modelling: Numerous extensions have been made to SEM to incorporate different types of data. Thus, while latent variables usually have to be continuous, it is possible to include categorical observable variables. On the one hand, binary dummy variables may be incorporated into the model (similar to regression analysis), on the other multi-group SEM may be used. In multi-group SEM, a parameter of interest within the hypothesized model is estimated for each group individually. The fit of the resulting model is then compared to the fit of a similar model where the parameter is fixed across groups. It is thus possible to examine whether the path parameter between two variables (but also other kinds of parameters) differs significantly between two or more groups (Sörbom, 1974). The commonly used test, which is also generally used when comparing the fit of two hierarchical/nested SEM models, is the χ^2-difference-test. It tests the statistical significance of the change in overall fit as free parameters are removed from or added to a model. The used χ^2-values are derived from the estimated minimum values of the fit/loss functions and the sample sizes (Kline, 2011). The particular advantage of utilizing SEM to examine group-specific differences in relationships between variables is that one is not limited to using observable variables. Within one model, a latent variable underlying a set of observable variables can be estimated, and at the same time, group-specific differences in the relationship of this latent variable with some other variables can be investigated. Multi-group SEM is used in chapter three to find ADHD presentation specific differences in the relationship between neural topology and emotion dysregulation.

Latent change score modelling: Extensions of SEM were developed to incorporate longitudinal data. These include latent change score models. With latent change score models, variable change from baseline to a subsequent measurement time point is modeled as a latent change score factor (Kievit et al., 2018). The variable at the second measurement time point is defined as the sum of the baseline values and the latent change score factor. This yields an autoregressive function with the regression weight of the variable at baseline set to 1. One can add a regression parameter between the variable at baseline and the latent change score factor. Also, relationships between the change and other variables that are additionally integrated into the model can be investigated (McArdle & Hamagami, 2001). Thus, the model can be extended by adding a second domain of interest, including two measurement points and a second latent change score factor. The resulting bivariate latent change score model (BLCS) can simultaneously capture multiple relations of interest. One may gather inference about cross-domain relations at baseline,

investigate if baseline values predict changes within or across domains, and explore the cross-domain coupling of the latent change score factors (Kievit et al., 2018). BLCS provide a valuable tool for investigating relationships between change in phenotypic/behavioral variables and neural data. A strategy often used in the past is to compare neuronal data between groups with different categorical trajectory profiles (e.g., remittent vs. persistent ADHD). Such approaches often do not consider neural information from earlier phases. In contrast, BLCS allow modeling of the impact of continuous covariates at baseline on intraindividual changes during development (Kievit et al., 2018). The study presented in chapter four uses BLCS modeling to analyze the impact of baseline neural topology and emotion dysregulation on changes in ADHD severity.

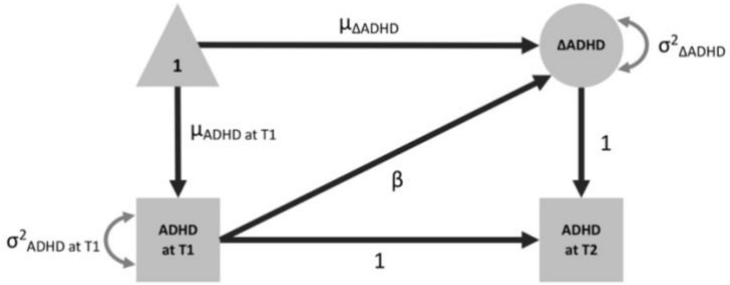

Figure 1.4: *Path model of a univariate latent change score model in which the variable ADHD is measured at two points in time (T1 & T2). The change (ΔADHD) between the two points in time is modeled as a latent variable.* $\mu_{\Delta ADHD}$ *captures the average change of ADHD between the two points in time, while* $\sigma^2_{\Delta COG1}$ *is the estimated variance of the latent variable. The graphic is reproduced from Kievit et al. (2018).*

Study design and thesis outline

This thesis is based on data from NeuroIMAGE I and II, the second and third wave of an integrated-cognition-MRI-phenotype project on ADHD (von Rhein et al., 2015). The first wave, for which no fMRI data was collected, was part of the International Multicenter ADHD Genetics study (IMAGE) (Brookes et al., 2006). NeuroIMAGE is a multi-site project aimed at examining the course of ADHD, genetic and environmental determinants, cognitive and neurobiological underpinnings, and outcomes in adolescence and adulthood. For the present thesis, only data acquired at the Donders Institute for Cognitive Neuroimaging, Radboud University Nijmegen, Netherlands, were used. Data were collected between 2009-2012 for NeuroIMAGE I and 2013-2015 for NeuroIMAGE II. Participants were either follow-up participants from previous waves or newly recruited individuals who accounted for dropouts. The samples used from NeuroIMAGE I and NeuroIMAGE II included cases with the different ADHD presentations, subthreshold ADHD cases, and unaffected individuals. The average age during NeuroIMAGE I was about

17 years and 21 years during NeuroIMAGE II. A more detailed description of the recruitment procedures may be found in the subsequent chapters and in von Rhein et al. (2015).

The thesis includes three research articles. These are presented in the following chapters two through four. Each of the three articles highlights different aspects of the relationship between emotion dysregulation and ADHD and underlying functional neuronal patterns. Articles one and two examine data from NeuroIMAGE II, and thus involve cross-sectional analyses. For these articles, I conducted group comparisons between unaffected individuals and those with a diagnosis of ADHD. Individuals with subthreshold diagnoses or those with conflicting information were not included. In the third article, a longitudinal analysis was performed with data from NeuroIMAGE I and II. Individuals with subthreshold diagnoses were also included. While coming from one project database, the samples partly contain different subjects due to the specifics of the studies and the availability of required data. For the analysis of articles two and three, I also used a novel combination of graph theoretical analysis and SEM.

The overall aim of this thesis was to improve our understanding of the relationship between ADHD and emotion dysregulation and to specifically address the relevance of certain aspects of the topic, i.e., the perception of emotional stimuli, different ADHD presentations, and the course of ADHD. The content of the empirical chapters is as follows.

Chapter 2: I argued that impaired emotion recognition in individuals with ADHD may be related to commonly observed co-occurring affective and social problems via poor emotion self-regulation. The underlying neural abnormalities and whether deficits in adolescents and young adults are similar to those in affected children remain to be investigated. I used an emotional face-matching task and functional fMRI to investigate neural responses during the processing of angry and fearful faces and visuo-spatial control stimuli. Measures for emotion dysregulation, ADHD presentation, and age were investigated in relation to the behavioral and neural fMRI data. I hypothesized that individuals with ADHD would show longer reaction times and poorer accuracy than unaffected individuals during emotional trials. Moreover, I expected this behavioral pattern to be accompanied by differences in amygdala activation and altered functional connectivity between the amygdala and prefrontal structures.

Chapter 3: While neuroimaging studies reported changes in neural activity in ADHD in brain regions associated with emotion processing and regulation, it is unclear whether deficits in emotion regulation are related to changes in the topology of the functional brain network in these regions and whether these depend on the ADHD presentation. I used a combination of graph analysis and SEM to analyze resting-state functional connectivity. The analysis was focused on nodal topology measures and aimed to identify

brain regions whose local, functional brain network integration specifically contributes to emotion dysregulation in predominately inattentive ADHD and ADHD with symptoms of hyperactivity-impulsivity. I hypothesized that an ADHD-specific association exists between the functional brain network measures for local network integration and emotion regulation.

Chapter 4: The course of ADHD from adolescence into adulthood shows large variations between individuals and determinants of the interindividual differences in change are not yet understood. Previous studies often merely investigated associations with a categorically defined ADHD trajectory rather than modeling interindividual differences in the intraindividual change of ADHD. I investigated whether emotion dysregulation and integration of emotion-related functional brain networks affect interindividual differences in the change of ADHD severity. ADHD severity and resting state neuroimaging data were measured at two points in time during late adolescence and young adulthood. Nodal efficiency values were calculated as a measure of network integration and BLCS models were applied to investigate whether emotion dysregulation and nodal efficiency during adolescence predict changes in ADHD severity. I hypothesized that both increased baseline emotion dysregulation and reduced baseline nodal efficiency of brain regions associated with emotion processing and emotion regulation negatively affect the course of ADHD.

The results of the empirical studies will be summarized and discussed in chapter 5. With this thesis I do not claim to provide an exhaustive analysis of the topic. Neither do I suggest a final comprehensive solution. The more knowledge we gather about the common co-occurrence of ADHD and emotion dysregulation, and the better we understand the causes and characteristics of this relationship, the better we will be able to provide individualized support to those affected.

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Chapter 2

Amygdala reactivity and ventromedial prefrontal cortex coupling in the processing of emotional face stimuli in attention-deficit/hyperactivity disorder

The content of chapter 2 is identical to the content of the following publication:

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Tammo Viering, Jilly Naaijen, Pieter J. Hoekstra, and Alexandra Philipsen were involved in the general conceptualization of the project. Pieter J. Hoekstra, Jilly Naaijen, and Jan K. Buitelaar contributed to the data collection process. Methodology and study design were developed by Tammo Viering, Jilly Naaijen, and Pieter J. Hoekstra. The implementation of the analysis software as well as the execution of the analysis was done by Tammo Viering. Tammo Viering wrote the initial draft of the manuscript and created all visualizations. All authors reviewed and edited the manuscript. Supervision was provided by Pieter J. Hoekstra, Jilly Naaijen, Jan Buitelaar, and Christiane M. Thiel. Pieter J. Hoekstra, Alexandra Philipsen, Jan K. Buitelaar, and Christiane M. Thiel contributed to the required resources. Financial support was acquired by Pieter J. Hoekstra and Jan K. Buitelaar. Pieter J. Hoekstra and Jan K. Buitelaar contributed to the project administration.

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Abstract

Impaired emotion recognition is common in individuals with attention-deficit/hyperactivity disorder (ADHD) and may, via deficient emotion self-regulation, relate to the frequently co-occurring affective and social problems. The present study used an emotional face-matching task and functional magnetic resonance imaging (fMRI) to investigate neural responses during the processing of angry and fearful faces and visuo-spatial control stimuli. Additionally, measures for emotion dysregulation, ADHD type, and age were investigated in relation to the behavioral and neural fMRI data. We utilized a sample of 61 adolescents/young adults with ADHD and 51 age-matched unaffected controls (age range: 12-28 years). Participants with ADHD had higher emotion dysregulation scores than controls. They also reacted slower and less accurate in response to emotional but not visuo-spatial control stimuli. Neural response differences between emotional and visuo-spatial trials were significantly smaller in cases, particularly in the left amygdala. While coupling between the right amygdala and bilateral ventromedial prefrontal cortex was stronger for emotional than visuo-spatial stimuli in control subjects, levels of positive coupling between the trial types did not significantly differ in participants with ADHD. Neither emotion dysregulation scores, nor ADHD type or age were related to the behavioral and neural processing alterations during the emotional face-matching task. Results indicate that emotion recognition deficits in ADHD are particularly associated with lower amygdala activation to emotional stimuli and alterations in the functional connections of the amygdala to medial prefrontal areas. Emotion recognition deficits and associated neural alterations were unrelated to emotion dysregulation, ADHD type, or age.

Introduction

With an estimated prevalence rate of 5.3% in children and adolescents (Polanczyk & Rohde, 2007) and 2.5% in adults (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009), attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders. Besides core symptoms of inattention and hyperactivity/impulsivity, emotion dysregulation is a frequently reported problem (Barkley, 2015; Faraone et al., 2015). Emotion dysregulation refers to the inability to appropriately modulate emotional responses (Carpenter & Trull, 2013) and is present in as many as 25-45% of children and 30-70% of adults with ADHD (Shaw et al., 2014). Its co-occurrence in ADHD is associated with worse clinical outcome, risky behavior, and social impairments (Bunford, Evans, & Wymbs, 2015; Matthies et al., 2012; Shaw et al., 2014).

An important aspect of adequate emotion regulation is the accurate recognition and interpretation of emotional stimuli. Individuals with ADHD were found to be less accurate in identifying emotions. Besides other factors, such as subconscious and experience based reward estimations or cognitive reappraisal (Etkin et al., 2015; Rubia, 2018), emotion dysregulation in ADHD may be related to emotion recognition deficits (Shaw et al., 2014), as both require the ability to direct attention toward or away from emotional stimuli. Some of the inappropriate emotional behavior may be attributed to emotion recognition deficits (Jusyte et al., 2017; Schönenberg et al., 2019; Waddington et al., 2018; Yuill & Lyon, 2007).

While most neuroimaging research in ADHD has focused on frontostriatal, frontocerebellar, and frontoparietal circuits, few studies investigated the functional connections between the amygdala and the prefrontal cortex during tasks requiring emotion recognition in ADHD. The limited number of studies regarding emotion perception and recognition/matching during functional magnetic resonance imaging (fMRI) revealed evidence for case-control differences in affective arousal structures, including the ventral striatum, cingulate cortex, anterior insula, and, most consistently, (left) amygdala. Significant results have been repeatedly shown for the amygdala, although with inconsistency regarding the laterality or direction of the effects (Marco A. Bottelier et al., 2017; Brotman et al., 2010; Herpertz et al., 2008; Malisza et al., 2011; Marsh et al., 2008; Posner, Maia, et al., 2011). Resting state fMRI and anatomical MRI research in ADHD suggest altered connectivity in related structures (anterior default mode network, ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex, & insula), which have been frequently associated with emotion recognition and regulation (Hulvershorn et al., 2014; Lin et al., 2014; Plessen et al., 2006; Posner et al., 2013; Tomasi & Volkow, 2012). Indeed, evidence for a link between amygdala – prefrontal cortex coupling and emotion recognition has been presented in healthy individuals (Motzkin, Philippi, Wolf,

Baskaya, & Koenigs, 2015; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). Together with the well-established association between frontostriatal network anomalies and ADHD, particularly with impulsivity-hyperactivity symptoms (Barkley, 2015; Dalley, Mar, Economidou, & Robbins, 2008), this suggests that the functional connections between amygdala and prefrontal cortex may be related to emotion recognition deficits in ADHD. These, in turn, may ultimately contribute to the frequent emotion dysregulation problems seen in ADHD. However, it must be emphasized that the mentioned structures and circuits take over tasks beyond the correct recognition of emotions. The frontostriatal networks, in particular, are essential for reward estimation, decision-making, emotion processing, and emotion regulation (Blair, 2008; Etkin et al., 2015).

The main objective of the present study was to investigate amygdala reactivity and functional connections of the amygdala and prefrontal cortex in adolescents and young adults with ADHD as compared to healthy controls during the processing of fearful and angry facial stimuli. We chose matching of fear and anger given the previously reported conduct problems and impairments to recognize these emotions in children with ADHD (Airdrie, Langley, Thapar, & van Goozen, 2018). A secondary objective was to investigate whether amygdala reactivity or alterations of the fronto-amygdala axis were associated with emotion dysregulation, as measured by the emotional lability subscale of the Conners' parent rating scale, with ADHD type, or age. The study utilized data of the NeuroIMAGE study (von Rhein et al., 2015) with a well-established fMRI emotional face-matching task (Marco A. Bottelier et al., 2017; Hariri et al., 2002; van Wingen et al., 2008). We hypothesized that individuals with ADHD would show longer reaction times and worse accuracy than controls during the emotional trials of the task. Further, we expected that this behavioral pattern would be accompanied by divergent amygdala activation and altered functional connectivity between the amygdala and prefrontal structures.

Methods and material

Participants and procedures

Individuals with ADHD and healthy controls participated in NeuroIMAGE II, the third wave of an integrated genetics-cognition-MRI-phenotype project focusing on ADHD (von Rhein et al., 2015). Initial inclusion criteria for first-wave participants with ADHD were a combined type ADHD diagnosis, availability of one or more siblings, age between 6-18 years, and availability of the participant, sibling, and at least one biological parent for DNA collection. Exclusion criteria applying to all participants were IQ < 70, inability to understand study procedures, diagnoses of autism or schizophrenia, and neurological disorders. For controls, it was additionally required that neither they, nor any of their first-degree relatives, had a prior ADHD diagnosis. The current wave took place 9 years after the first wave.

The diagnostic procedure was based on DSM-IV-TR criteria (American Psychiatric Association, 2000) and is described in more detail by van Rhein et al. (von Rhein et al., 2015). Clinical ADHD diagnoses conferred by experienced clinicians were confirmed by combining information from a semi-structured interview (Kiddie Schedule for Affective Disorders (K-SADS (Kaufman et al., 1997)) and parent, teacher, and self-report versions of the Conners' rating scale (CPRS-R:L (Conners, Sitarenios, Parker, & Epstein, 1998a), CTRS-R:L (Conners, Sitarenios, Parker, & Epstein, 1998b) & CAARS-R:L (Conners et al., 1999)). Emotion lability scores (as an index for emotion dysregulation) were derived from the parent-rated CPRS-R:L. The emotion lability subscale consists of three items (i.e., unpredictable mood changes, temper tantrums, and tearfulness) and has been utilized repeatedly to assess emotion lability in ADHD (Sobanski et al., 2010). All data presented in this**Error! Use the Home tab to apply Überschrift 1 to the text that you want to appear here.** study, including the diagnostic questionnaires and emotional lability scores, refer to the present wave of the project and were collected on the same day as MRI scanning.

The group examined here is a subsample of the 302 participants included in the third wave. The total group is composed of individuals who took part in the previous waves and new recruits added on account of dropouts (particularly within the control group). For the present study, however, only those individuals who could unambiguously be assigned to either the control or ADHD group were considered. These ambiguous or subthreshold participants had a symptom count that was neither indicative of an ADHD diagnosis (≤ 6 for children, ≤ 5 for adults) nor classified them as unaffected (≥ 3 for children, ≥ 2 for adults). Also, individuals who did not meet the criteria for daily living impairments or onset-age but had multiple symptoms fell into this category (for more details see von Rhein et al. (von Rhein et al., 2015)). From this

sample of 145 participants who also had available fMRI data, a number of participants were removed prior to analyses due to left-handness (n = 21, only right handed participants were studied to reduce variability due to lateralization differences), low quality of behavioral (participants whose emotional face matching accuracy was more than 3 standard deviations worse than the group average; n = 3), imaging data (n = 6, exclusion limit of 3mm on rotational and translational movement), and incomplete diagnostic data (n = 3). This resulted in a final sample of 112 individuals (n = 61 ADHD, n = 51 healthy controls, similar in age (12 – 28 years) and sex). Among the 61 participants with ADHD, 36 had predominantly inattentive ADHD, 6 predominantly hyperactive/impulsive ADHD, and 19 combined ADHD. Due to the small number of participants with hyperactive/impulsive ADHD, they were merged with participants with a combined diagnosis in all analyses.

Stimulant medication was discontinued forty-eight hours prior to testing. Data acquisition took place at the Donders Institute for Cognitive Neuroimaging, Radboud University Nijmegen, Netherlands. Participants (and their parents when <18 years old) gave written informed consent for participation. Ethical approval was granted by the regional ethics board (Centrale Commissie Mensgebonden Onderzoek: CMO Regio Arnhem Nijmegen, ABR: NL41950.091.12).

Neuropsychological task during fMRI

In two emotion matching and three visuo-spatial control blocks, each with 6 trials of 5 s in length, participants were asked to match the facial emotion (fear or anger) or spatial orientation (vertical or horizontal ellipses) of an upper stimulus with one of two lower stimuli, in line with a previous study (van Wingen et al., 2008). The three simultaneously presented facial stimuli always depicted faces of different individuals of the same sex (taken from http://www.macbrain.org). Half the trials depicted women and the other half men. Ellipses of the visuo-spatial trials consisted of scrambled face stimuli pixels. Responses were given with left or right button presses. The task is well-established and served to investigate drug effects on amygdala reactivity (Marco A. Bottelier et al., 2017; Hariri et al., 2002; van Wingen et al., 2008). Instead of neutral facial expressions, geometric shapes were used as control stimuli, since the former could be perceived ambiguously and could cause unwanted amygdala reactivity (Hariri et al., 2002; Thomas et al., 2001). Figure 2.1 summarizes the applied task.

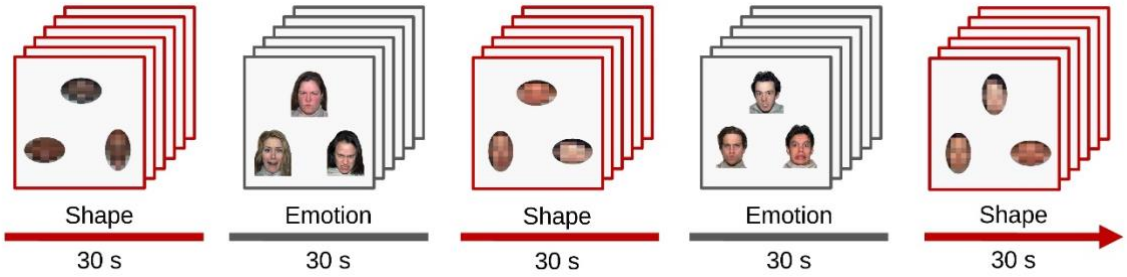

Figure 2.1: *Illustration of the emotional face-matching task applied during fMRI scanning.*

fMRI data acquisition

Functional MRI data acquisition was performed with a 1.5 T Magnetom Avanto (Siemens AG, Erlangen, Germany). To acquire T2*-weighted blood oxygen level dependent (BOLD) images, accelerated multi-echo EPI sequences, which additionally reduce image distortion and increase BOLD sensitivity, were used (TR = 2660 ms, TE1/TE2/TE3/TE4/TE5 = 7.7/17.3/27.0/37.0/46.0 ms). For each volume, 37 axial slices were generated in an interleaved and ascending order (flip angle = 90°, FoV = 224 x 224 mm^2, voxel- size = 3.5 x 3.5 x 3.0 mm^3, inter-slice gap = .5 mm, GRAPPA 2). Echo-time (TE) weighted summation was used to combine all five echoes into a single data set. T1-weighted high-resolution structural volumes were acquired with an MPRAGE sequence (TR = 2730 ms, TE = 2.95 ms, TI = 900 ms, flip angle = 9°, FoV = 256 x 256 mm^2, voxel- size = 1.0 x 1.0 x 1,0 mm^3, GRAPPA 2).

Behavioral data analysis

Reaction time and hit rate differences between the control and ADHD group during the emotion matching task trials were analyzed using mixed linear models with diagnostic status as the grouping variable and task condition as the repeated measures variable (one model for reaction time and one for hit rate). Using partial sums of squares F-tests we investigated the impact of the different model regressors. Emotion dysregulation, age, medication status, and sex were entered as additional covariates. As an intrinsic component of ADHD, IQ, with its typically strong relation with the diagnostic status, was not considered. In cases of significant interactions between diagnostic status and task condition, Bonferroni-corrected t-tests were applied to investigate the diagnosis-specific differences within the different task conditions (corrected α = .0125). The statistical analysis of the behavioral data was conducted with **R** software (Team & R Development Core Team, 2016).

fMRI data analysis

FMRIB software library (FSL 5.0.11 (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012)) was used for fMRI data processing. Functional images were skull stripped using FSL BET (Smith, 2002) and realigned to the middle volume of each time series to correct for head motion. Motion parameters for rotation and translation were calculated and the exclusion limit was set to 3 mm of absolute movement. Images were co-registered to the individual T1-weighted structural images. The volumes were spatially smoothed using a 6 mm full width at half maximum (FWHM) Gaussian kernel. To remove secondary motion artifacts, ICA-AROMA (Pruim et al., 2015) was used. High-pass filtering was applied at .008 Hz and nuisance regression was used to remove residual noise of the white matter, cerebrospinal fluid (CSF), and linear signal drifts of overall brain activity. We used CSF and white matter masks obtained during a preceding segmentation of the T1-weighted structural scan. Prior to subject-level analysis, the preprocessed images were warped to MNI152 space (Montreal Neurological Institute, Montreal, Canada). During quality assessment and all conducted preprocessing steps of the individual fMRI datasets, researchers were unaware of group memberships.

At subject level, GLM were generated with FSL FEAT (Woolrich, Ripley, Brady, & Smith, 2001) to estimate statistical parametric maps. GLM consisted of four regressors modelling the emotion and visuo-spatial control blocks (length 30 sec) and their respective temporal derivatives (Figure 2.1). All regressors were convolved with the double-gamma hemodynamic response function (HRF) provided by FSL FEAT. The contrast of interest that was used for subsequent second level analyses contrasted the responses to blocks of angry or fearful face stimuli against the responses to blocks of horizontally or vertically oriented ellipses (emotion > shape). Due to the briefness of the fMRI task and the high frequency of correct responses, an event-related model that differentiates between false and correct trials or the gender of the respective stimuli could not be used.

With the individual beta contrast maps and associated maps of variance estimates, FSL FLAME 1 was used to calculate z-value images for different contrasts and group-level models. Using the previously mentioned grouping algorithm, a two-group GLM with binary regressors for participants with ADHD and healthy controls was created (ADHD-HC GLM, n = 112). Age and sex were demeaned across participants and included as covariates of no interest. Since a somewhat lower IQ and use of medication is an intrinsic featu**Error! Use the Home tab to apply Überschrift 1 to the text that you want to appear here.**re of ADHD (Jepsen, Fagerlund, & Mortensen, 2009), IQ and medication status were originally not added as covariates for the fMRI models. To ensure that these two variables did not influence any relevant results, we ran an

additional model with these covariates and found no main or interaction effects. Consequently, they were not considered for the final model.

Statistical maps were calculated for the groups' mean effects and the between group contrasts (ADHD > HC and ADHD < HC). A similar model, but with binary regressors for the groups with predominantly inattentive ADHD and combined or hyperactive/impulsive ADHD, was created to evaluate differences between ADHD participants with and without hyperactive/impulsive symptoms. To investigate possible age- and emotion dysregulation-dependent effects, models for the two main participant groups in interaction with these continuous covariates were used.

Region of interest (ROI) analyses were conducted with ROI masks of the left and right amygdala (240 and 280 voxels per mask; calculated from the Harvard-Oxford Atlas, thresholded at 50% and binarized; Figure 2.3b). Hemisphere-specific masks were chosen because hemispheric differences in emotion processing are suspected (Baas, Aleman, & Kahn, 2004) and previous studies have rarely found bilateral but rather mostly left-sided effects (M. A. Bottelier et al., 2015; Brotman et al., 2010; Herpertz et al., 2008). Mean beta values (averaged across all voxels within the ROI) were extracted from the individual emotion > shape contrasts. Similar to the behavioral analysis, mixed linear models were constructed. Diagnostic status and laterality, as repeated measure, were used as grouping variables, while the aforementioned mean beta values of the amygdala were added as dependent variable. Again, partial sums of squares F-tests were conducted and the same variables that had been used for the behavioral analysis were considered as covariates to investigate additional main or interaction effects. Subsequent t-tests were performed to investigate the hemisphere-specific group mean differences. The statistical analysis of the mean beta values was conducted with **R** software (Team & R Development Core Team, 2016).

Further analyses used psychophysiological interaction (PPI) maps to investigate functional connectivity between BOLD responses in the left and right amygdala and other parts of the brain (amygdala seeds were taken from the Harvard-Oxford Atlas) (Friston et al., 1997). PPI analyses identify areas whose activation levels depend on the interaction between a seed region and an experimental parameter. PPI estimate contextual connectivity changes between seed regions and other brain areas (Friston et al., 1997). For the present analyses, the convolutions of the double-gamma HRF with the emotion > shape contrasts were chosen as experimental parameters. FSL FEAT with its standard procedures was used for implementation. The group level analysis was conducted using the previously described two-group GLM. Following the PPI analyses, individual time series data of the amygdala and clusters, whose coupling with the amygdala was found to significantly depend on the trial condition, were extracted to calculate estimates for condition

specific amplitudes of covariance change. In other words, we calculated by how many multiples the average covariance between activity of the amygdala and any psychophysiologically interacting area changed from the visuo-spatial to the emotional condition. The alternative use of correlations for this purpose could be problematic for the interpretation of the results since a certain ambiguity arises with regard to shared and unshared signal components (M. W. Cole et al., 2016). Results of the fMRI analyses are presented at a significance level of $p < .01$ and after cluster-level family-wise error (FWE) correction with cluster forming thresholds of 2.3 (Eklund, Nichols, & Knutsson, 2016).

Results

Sample characteristics

Demographic details are provided in Table 2.1. Age and sex did not significantly differ between the ADHD and healthy control group. Participants with ADHD showed more ADHD symptom and higher emotion dysregulation scores. Compared to controls, participants with ADHD had a significantly lower IQ (still in the normal range for both groups), were more frequently diagnosed with oppositional defiant disorder (ODD) or conduct disorder (CD), and used stimulant medication more often. ADHD type did not significantly differ with age, sex, IQ, emotion dysregulation scores, and stimulant use.

Table 2.1: *Sample characteristics of the healthy control and ADHD group as well as of presentation specific ADHD subgroups.*

GROUP	**HC**	**ADHD**			**HC vs. ADHD Group Comparisons**		
		total	**inattentive**	**combined & hyperactive/ impulsive**			
	N = 51	N = 61	N = 36	N = 25			
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Test statistic*	***ρ**-value*	*Effect-size*
Age (years)	20.2 ± 3.2	20.0 ± 3.5	20.2 ± 3.7	19.70 ± 3.2	T = .2833	.778	d = .053
IQ (WISC/WAIS)	114 ± 11.7	97 ± 18.1	98 ± 18.1	94.4 ± 18.3	T = 6.2708	< .001	d = 1.146
Emotional lability (CPRS-R:L)	43.9 ± 3.1	53.9 ± 13.2	53.83 ± 13.9	53.96 ± 12.4	U = 740.5	< .001	d = -.524
	Median (range)	*Median (range)*	*Median (range)*	*Median (range)*			
DSM-IV ADHD, inattentive (K-SADS)	0 (0-7)	7 (4-9)	7 (5-9)	7 (4-9)	U = 31.5	< .001	d = -.980
DSM-IV ADHD, hyperactive/impulsive (K-SADS)	0 (0-2)	5 (0-9)	4 (0-9)	7 (6-9)	U = 130	< .001	d = -.916
	n	*n*	*n*	*n*			
Sex (male)	29 (57%)	38 (62%)	22 (61%)	16 (64%)	χ^2 = .152	.696	φ_c = .001
Stimulant user (yes)	0 (0%)	22 (36%)	13 (36%)	9 (36%)	χ^2 = 20.662	< .001	φ_c = .430
DSM-IV ODD (K-SADS)	0 (0%)	13 (21%)	7 (19%)	6 (24%)	χ^2 = 28.310	< .001	φ_c = .503
DSM-IV CD (K-SADS)	0 (0%)	2 (3%)	1 (3%)	1 (4%)	χ^2 = 9.180	.010	φ_c = .286

Notes: Means between groups were compared with independent sample t-tests or Mann-Whitney-U-tests. Frequency distributions were compared with Pearson's Chi-square (χ^2)-test. For the CPRS-R:L t-scores are presented, while for the K-SADS symptom counts are given; **N** = number of participants; **n** = number of participants within subgroups; **SD** = Standard Deviation; **HC** = Healthy Controls; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; **ADHD** = Attention Deficit/Hyperactivity Disorder; **IQ** = Intelligence Quotient; **K-SADS** = Kiddie Schedule for Affective Disorders and Schizophrenia; **CPRS-R:L** = Conners' parent rating scale, revised, long version; **ODD** = Oppositional Defiant Disorder; **K-SADS** = Kiddie Schedule for Affective Disorders; **CD** = Conduct Disorder

Behavioral results

Two mixed linear models were constructed and partial F-tests were used to investigate the ADHD- and task condition-specific influences on the behavioral results of the emotional face-matching task. Neither for reaction times nor for hit rates did the considered covariates show significant effects. Thus, no additional covariates were entered into the final models. Diagnostic status and task condition had a significant interaction effect on the average reaction times ($F(1,110) = 20.814$, $p < .001$, partial-$\eta^2 = .159$). Post-Hoc comparisons between the two participant groups indicated significant mean difference in emotion and visuo-spatial trials (emotion trials: ADHD mean ± SD = 1.678 s ± .388 s, healthy control mean ± SD = 1.378 s ± .244 s, $t(103) = 4.946$, $p < .001$, $d = .9$; visuo-spatial trials: ADHD mean ± SD = .913 s ± .166 s, healthy control mean ± SD = .838 s ± .223 s, $t(109) = 2.053$, $p < 0.001$, d = .38). For mean hit rates, no significant interaction effect of the diagnostic status and task condition could be found. Solely a significant main effect of the diagnostic status could be detected ($F(1,110) = 7.919$, $p = .006$, partial-$\eta^2 = .159$). Although not significant, the average mean difference in hit rates between ADHD and healthy control subjects was more evident in emotion trials than in visuo-spatial trials (emotion trials: ADHD mean ± SD = .915 s ± .092 s, healthy control mean ± SD = .958 s ± .063 s; visuo-spatial trials: ADHD mean ± SD = .926 s ± .074 s, healthy control mean ± SD = .942 s ± .066 s).

fMRI results

Group comparison with whole brain analyses

To detect brain activity differences in group-specific BOLD activation during the emotion matching task (*emotion > shape* contrasts), the *ADHD > HC* and *ADHD < HC* contrasts of the *ADHD-HC* GLM were used. The *ADHD > HC* contrast did not reveal any significant clusters after FWE cluster-level correction. For the *ADHD < HC* contrast, significant clusters were present in the left amygdala, hippocampus, and subcallosal gyrus, cuneus and lingual gyrus, right superior and middle temporal, and left lateral occipital cortex and fusiform gyrus. Figure 2.2 shows neural activity in occipital and medial temporal regions derived from the *ADHD-HC* GLM analysis. Unlike the main *ADHD-HC* model, the models for ADHD with and without hyperactivity/impulsivity, the effect of emotion dysregulation scores, and the effect of age did not reveal any relevant significant results. For a complete overview of all significant clusters, see Table 2.2.

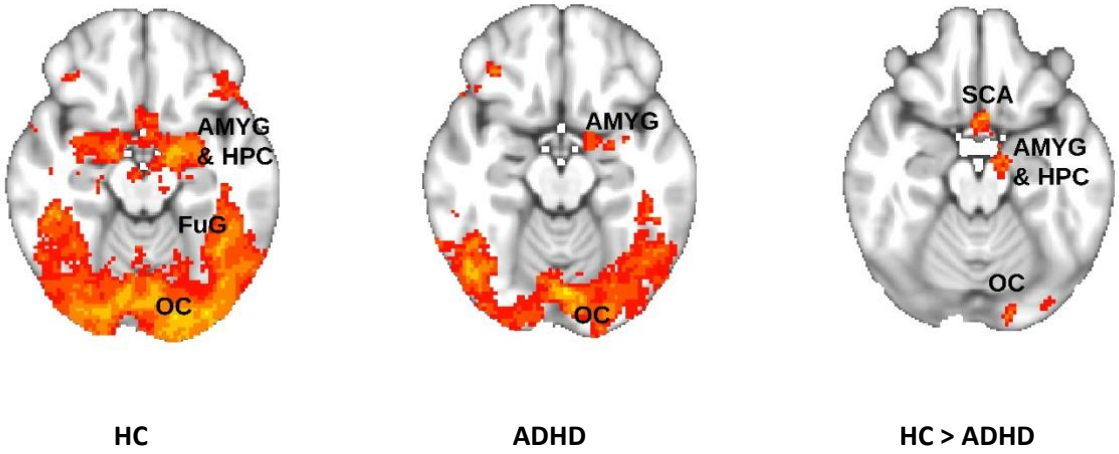

Figure 2.2: *Neural activity for emotional faces versus a visuo-spatial control condition. Single group and HC > ADHD contrasts are displayed at Z = -16/-16/-19 (p < .05; FWE corrected; left/right reversed). ADHD: Attention-deficit/hyperactivity disorder; AMYG: Amygdala; FuG: Fusiform Gyrus; HC: Healthy controls; HPC: Hippocampus; OC: Occipital cortex; SCA: Subcallosal area*

ROI analysis with left and right amygdala

To study activation differences between emotion and shape stimuli within the amygdala in more detail, an ROI analysis was performed. None of the considered covariates showed significant main or interaction effects. Accordingly, they were not entered into the final model. Using partial F-tests, a trend towards statistical significance for the interaction effect between diagnostic status and laterality was revealed ($F(1,110) = 3.120$, $p = .080$, partial-$\eta^2 = .028$). Further, a significant main effect of diagnostic status was found ($F(1,110) = 4.401$, $p = .038$, partial- $\eta^2 = .038$).

Participants with ADHD had smaller activity differences in both the right and left amygdala when compared to healthy controls (Figure 2.3a; left amygdala: ADHD mean ± SD = 1.95 ± 3.89, healthy control mean ± SD = 4.34 ± 5.32; right amygdala: ADHD mean ± SD = 2.97 ± 4.46, healthy control mean ± SD = 3.88 ± 5.21). Using post-hoc t-tests, only the mean difference of the left amygdala proved to be significant ($t(90) = 2.676$, p-value = .009, $d = .522$). Analyses of ADHD type, emotion dysregulation scores, reaction times, accuracy, and age did not reveal any significant main or interaction effects. However, we found a trend level significant interactive influence of group membership and left amygdala activity on reaction times and accuracy during the emotional trials.

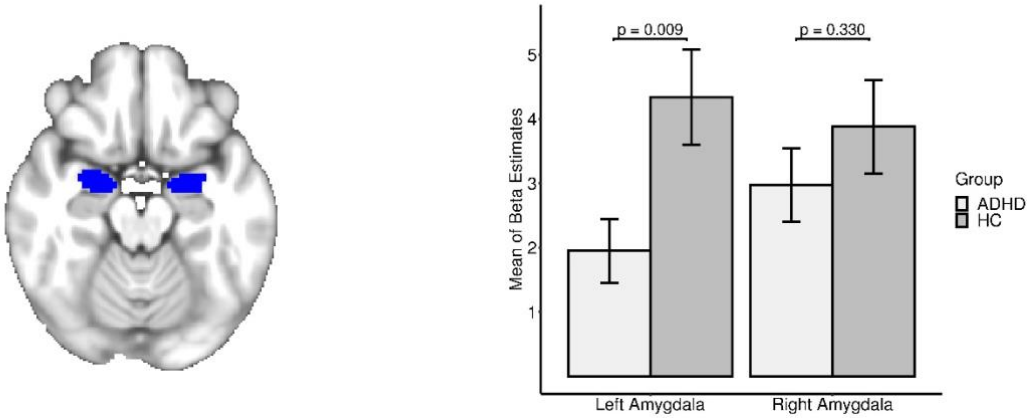

Figure 2.3: [a] *Left and right amygdala masks that were used for ROI analysis.* ***[b]*** *Barplot with means and standard errors of beta contrast values for the different participant groups for the left and right amygdala. ADHD: Attention-deficit/hyperactivity disorder; HC: Healthy controls*

Psychophysiological interaction analysis for group differences

In a third step, we investigated whether task condition dependent functional connectivity between amygdala and prefrontal structures differed between healthy controls and participants with ADHD (*HC > ADHD* contrast). In controls, the right amygdala showed significantly stronger positive coupling with the bilateral vmPFC and frontal pole in emotional as compared to visuo-spatial trials. In contrast, levels of coupling were not significantly different between the two stimuli conditions in participants with ADHD. Here, opposing tendencies were observed. Low positive coupling between the amygdala and vmPFC and frontal pole was seen during the visuo-spatial but not the emotion condition. Statistical analysis confirmed that healthy controls showed a significantly larger vmPFC and frontal pole PPI effect than participants with ADHD (Figure 2.4). The average parameter estimate for the PPI effects of the controls was .040 ± .075 and -.026 ± .067 for participants with ADHD. The amplitude of average covariance change from visuo-spatial to emotional stimuli was -6.729 for controls and –3.086 for ADHD. Changes occurred in opposite directions (i.e., from negative to positive in controls and from positive to negative in individuals with ADHD). While the distribution of PPI estimates for participants with ADHD was predominantly negative and showed slight negative skewness, the distribution of controls proved to be mainly positive and showed slight positive skewness. A complete overview of all significant PPI clusters can be found in Table 2.2.

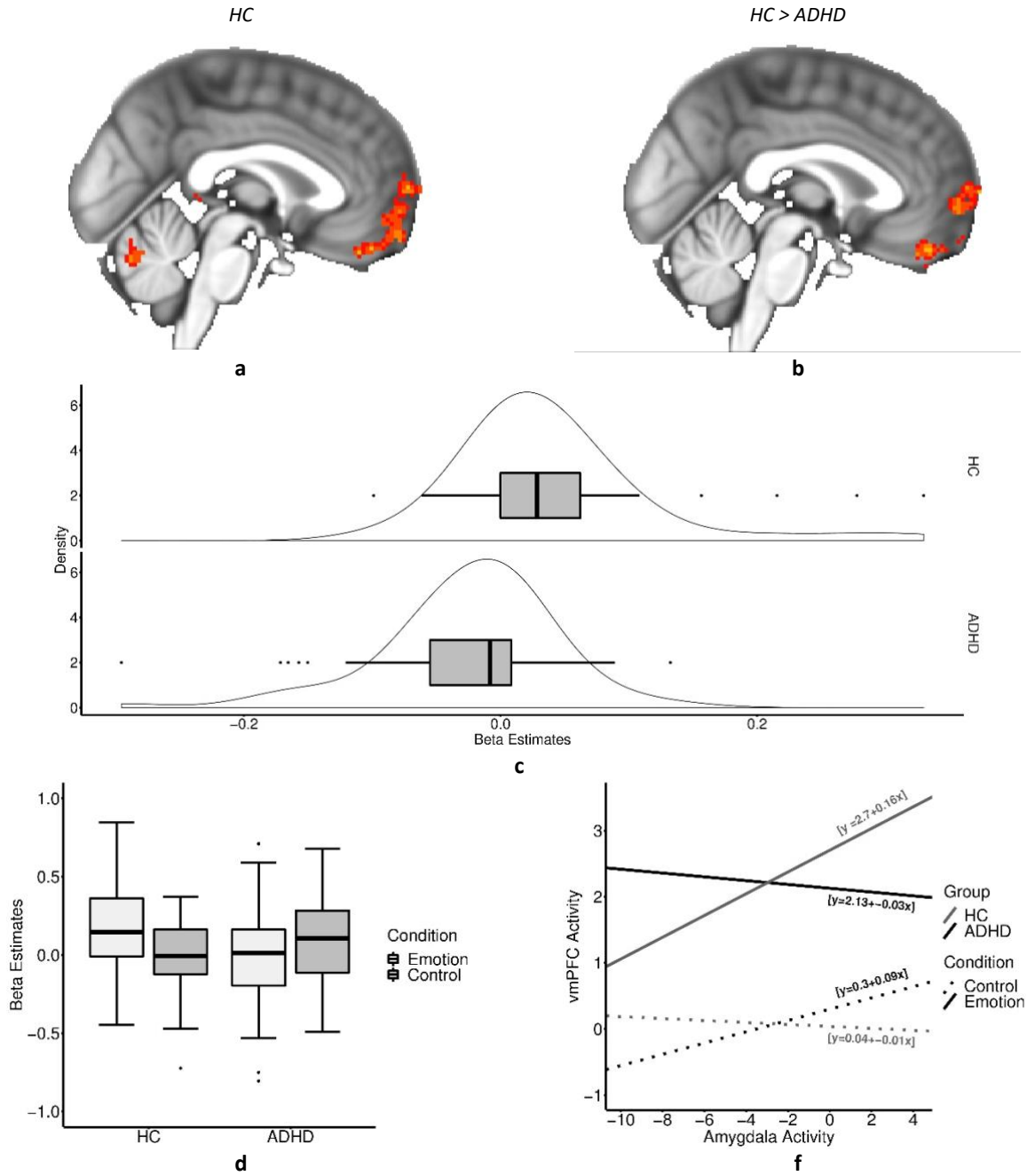

Figure 2.4: [a] *Right amygdala x emotion > shape contrast PPI effect within the healthy control (HC) group at x-coordinate = 0.* ***[b]*** *Right amygdala x Emotion > Shape contrast PPI difference between the control and ADHD groups (ADHD < HC) at x-coordinate = 0.* ***[c]*** *Boxplots and underlying approximated distributions of group specific beta estimates for the PPI effect of right amygdala activity and the trial condition on vmPFC activity.* ***[d]*** *Participant group and stimuli specific boxplots of the individual slope estimates which serve as estimates for the coupling between right amygdala and vmPFC.* ***[f]*** *Participant group and stimuli specific regression lines with median intercepts and slopes that serve as estimates for the coupling between right amygdala and vmPFC.*

Table 2.2: *Significant clusters and cluster maxima for brain regions with the individual emotion > shape and the left and right amygdala psychophysiological interaction contrasts. Results are presented for the ADHD-HC GLM with groups' mean effects and between group contrasts. Testing was conducted after FWE-cluster-correction using a z-threshold of 2.3 and a significance threshold of .01.*

			MNI Coordinates				
	Cluster Size	**Anatomical Structures**	**x**	**y**	**z**	**Z-Value**	**p-Value**
ADHD-HC MODEL							
HC							
1	40191	OP, FuG, LOC, IFG, MFG, AMYG, HPC, vmPFC, FP	-2	52	-20	4.82	< .001
ADHD							
4	11438	FuG, LG, Cerebellum	2	-78	-26	4.84	< .001
3	1785	right LOC, FuG	46	-70	-16	4.14	< .001
2	1373	left MFG, IFG	-32	12	32	4.74	< .001
1	796	left AMYG, HPC	-14	0	-12	3.70	.007
HC > ADHD							
4	311	Subcallosal Cortex, HPC, left AMYG	-2	10	-22	3.55	< .001
3	287	CUN, LG	4	-76	14	3.43	< .001
2	258	right STG, MTG	48	-32	2	3.90	< .001
1	237	left LOC, FuG	-34	-84	-26	4.05	.002
ADHD > HC							
No significant clusters							
PPI WITH LEFT AMYGDALA AND ADHD-HC MODEL							
HC							
2	616	FP, vmPFC	-8	60	10	4.21	< .001
1	143	Precuneus	-2	-64	18	3.48	.003
ADHD							
2	149	right SFG, FP	20	34	50	3.8	.003
1	134	right LOC	30	-80	14	4.13	.008
HC > ADHD							
1	163	left PHG	16	-34	-20	3.47	< .001
ADHD > HC							
No significant clusters							
PPI WITH RIGHT AMYGDALA AND ADHD-HC MODEL							
HC							
5	662	FP, vmPFC	6	66	22	4.13	< .001
4	472	OP	-10	-106	2	4.11	< .001
3	302	cerebellum	-18	-70-	-34	3.93	< .001
2	161	left LOC, MTG	48	-62	8	3.55	.004
1	148	right HPC	14	-40	4	3.79	.008
ADHD							
1	131	FP	4	58	16	3.76	.008
HC > ADHD							
4	224	right LOC, MTG	48	-62	8	3.63	< .001
3	218	FP, vmPFC	0	70	6	3.62	< .001
2	178	OP	-30	-92	-4	3.37	< .001
1	173	vmPFC	2	44	-22	4.42	.001
ADHD > HC							
1	150	left STG	-2	-4	74	3.46	.004

Notes: **AMYG**: amygdala; **CUN**: Cuneus; **FuG**: Fusiform gyrus; **FP**: Frontal pole; **HPC**: Hippocamus; **IFG**: Inferior frontal gyrus; **LG**: Lingual gyrus; **LOC**: Lateral occipital cortex; **MFG**: middle frontal gyrus; **MTG**: middle temporal gyrus; **PHG**: Parahippocampal gyrus; **STG**: Superior temporal gyrus; **vmPFC**: Ventromedial prefrontal cortex

Discussion

We investigated neural processing patterns of 112 adolescents/young adults with ADHD and healthy controls during the performance of an emotional face-matching task, and considered the influence of ADHD type, emotion dysregulation, and age. Participants with ADHD were overall slower and made more errors on emotional but not visuo-spatial control trials. During the processing of emotional faces as compared with the visuo-spatial stimuli, they showed less activity in the left amygdala and hippocampus, occipital regions, fusiform gyrus, and posterior fraction of the temporal cortex. The left amygdala finding was supported with a subsequent ROI analysis. Furthermore, healthy controls showed positive coupling between the right amygdala and vmPFC during emotional but not visuo-spatial trials. On the contrary, participants with ADHD showed negative coupling between the two structures during emotional trials but positive coupling during the visuo-spatial trials. For the ADHD participants, however, these task condition specific differences were not significant.

Behavioral findings are in line with studies in pediatric and adult ADHD samples in which evidence for a reduced accuracy and delayed responding to emotional content, such as emotional faces or social feedback, was found (Cadesky, Mota, & Schachar, 2000; Jusyte et al., 2017; Schönenberg et al., 2019; Waddington et al., 2018; Yuill & Lyon, 2007). Our results may be partly due to a generally higher degree of task difficulty in emotion recognition compared to visuo-spatial trials (matching of finely detailed features versus simple spatial orientations). Earlier theories have suggested that emotion recognition deficits in ADHD depend on general attention deficits (Barkley, 1997). Alternatively, the present as well as prior findings may also indicate specific difficulties in the processing of emotional expressions of faces. Indeed, affective and social problems in ADHD may arise from the failure to specifically attend to or process the appropriate emotional cues.

The notion of deficient emotion recognition capabilities in ADHD was, to some extent, supported by the whole-brain and ROI group comparison of the task fMRI data. While the activity differences between participants with ADHD and healthy controls in structures commonly associated with general attentional performance were primarily not significant, decreased amygdala activation was found in participants with ADHD. In addition to its central importance for general affective arousal, the amygdala is indispensable for the recognition of emotions (Calder, 1996). In connection with the worse behavioral results, the reduced left amygdala activity might indicate its relevance for deficient emotion recognition in ADHD. Previous studies, however, also found increases of left amygdala reactivity during tasks requiring emotional processing (Brotman et al., 2010; Posner, Maia, et al., 2011) and/or only significant results for sample

subgroups, e.g., only adults or children, or only in those with certain comorbidities (Shaw et al., 2014). Thus, functional alterations in relevant structures may not be homogeneous in the ADHD population, and may be task specific. Also, amygdala asymmetry in the processing of emotional stimuli was repeatedly shown (Marco A. Bottelier et al., 2017; Brotman et al., 2010; Herpertz et al., 2008); while the left amygdala may be more involved in the analysis of local, fine-grained details, the right amygdala may be more biased towards global stimuli aspects (Baas et al., 2004).

Results of the PPI analysis further suggest that not only altered amygdala activation, but also the functional connections with medial prefrontal structures may be associated with emotion recognition in ADHD. In contrast to the healthy controls, the coupling of the right amygdala and vmPFC in participants with ADHD did not significantly depend on the emotional magnitude of the stimuli. Reciprocal connections between amygdala and vmPFC and further information relay to dorsal prefrontal structures are seen as being crucial for emotion recognition and categorization (Blair, 2008; Botvinick, Cohen, & Carter, 2004; Motzkin et al., 2015; Quirk & Gehlert, 2003). The coupling pattern of the ADHD group, not significantly depending on the emotional content, may indicate a dysfunctional, unspecific relay of reinforcement expectation information. This is in line with previous research, which suggests that deficits in the vmPFC may hinder the integration of perceptual structures and structures that provide somatic markers for emotion recognition (Winston, O'Doherty, & Dolan, 2003). The reason for the asymmetry in the PPI findings may further lie in the differential roles of the vmPFC. Research indicates that the left vmPFC is more involved in reappraisal and positive emotion processing, while the right vmPFC appears to be more associated with avoidance behavior and negative emotions (as depicted by the present task's stimuli) (Bechara, 2004; Davidson, Jackson, & Kalin, 2000; Dixon, Thiruchselvam, Todd, & Christoff, 2017; Hamann, Ely, Hoffman, & Kilts, 2002).

Neither behavioral results nor neural activity during task processing were related to the emotion dysregulation scores. While this may imply that processes that cause deficient emotion regulation in ADHD are not properly covered by the applied emotion matching task, it is also possible that the validity of the emotion dysregulation symptom scores, which were derived from a parent questionnaire (CPRS-R:L), is insufficient. It was recently shown that cognitive tasks and questionnaires, which are both commonly used to measure self-regulation, frequently lack an empirical relationship, while cognitive tasks only show limited ecological validity (Eisenberg et al., 2019). Additionally, it must be considered that the CPRS-R:L is intended for individuals up to 18 years of age. We, nonetheless, decided to take the emotion lability scores of the CPRS-R:L as the alternative would have been to combine scores from different questionnaires answered by different individuals (participant, parent, or teacher). However, our approach may have

limited the validity of the scores for individuals older than 18 years. Future studies may benefit from utilizing alternative measures for emotion dysregulation since participants with ADHD did not show pronounced emotion dysregulation problems, whereas controls showed low variance in these scores.

Further, the applied task only required matching of a restricted range of emotional facial expressions without having to explicitly recognize them. Future investigations might utilize alternative experimental tasks that better capture whether a certain emotion has actually been recognized (Pistoia et al., 2019; Robbins et al., 1994). It is possible that brain activity during individual trials is not limited to the recognition of emotions, as the trial length was longer than the time typically needed for emotion recognition. Particularly with regard to the observed activity and connectivity deviations of the amygdala, it cannot be excluded that those deviations are also due to attention problems. Amygdala activity is sensitive to deviant attention allocation and in relation to individuals with autism (Dalton et al., 2005), for example, it has been shown that failure to pay attention to certain characteristics can have significant effects. Furthermore, it must be acknowledged that the task had relatively few trials, which may have affected the power and reliability of the connectivity analyses. This constraint also required us to conduct a block-model evaluation of the task. Since stimuli of both genders are present within the individual blocks, it was not possible to analyze the impact of the face-stimuli's gender on the outcome measures. Additionally, the sample sizes may have been too small to detect significant differences between the different ADHD type groups. This, however, may also be due to the fact that in individuals with ADHD, the frequency of hyperactivity/impulsivity symptoms often decreases as they grow up, whereas the opposite trend is observed in emotion dysregulation (Shaw et al., 2014). Finally, with regard to control subjects, it can be noted that for several phenotypic variables they obtained above average results, which could limit their representativeness (Schwartz & Susser, 2011).

In conclusion, the current study shows a possible link between emotion recognition deficits and ADHD in adolescents and young adults. Results showed smaller BOLD-response differences between emotion and visuo-spatial trials, particularly in the area of the left amygdala, and dysfunctional connectivity between the right amygdala and vmPFC. The results may indicate that emotion recognition deficits in ADHD are associated with abnormalities in affective arousal structures and their functional connections to medial prefrontal areas. Participants with ADHD also had more emotion regulation problems than healthy controls, however, neither this, nor ADHD type, nor age were related to emotion recognition and associated neural processing alterations.

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Chapter 3

Functional network topology of the right insula affects emotion dysregulation in hyperactive-impulsive attention-deficit/hyperactivity disorder

The content of chapter 3 is identical to the content of the following publication:

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Christiane M. Thiel

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Abstract

Emotion dysregulation is common in attention-deficit/hyperactivity disorder (ADHD). It is highly prevalent in young adult ADHD and related to reduced well-being and social impairments. Neuroimaging studies reported neural activity changes in ADHD in brain regions associated with emotion processing and regulation. It is however unknown whether deficits in emotion regulation relate to changes in functional brain network topology in these regions. We used a combination of graph analysis and structural equation modelling (SEM) to analyze resting-state functional connectivity in 147 well-characterized young adults with ADHD and age-matched healthy controls from the NeuroMAGE database. Emotion dysregulation was gauged with four scales obtained from questionnaires and operationalized through a latent variable derived from SEM. Graph analysis was applied to resting-state data and network topology measures were entered into SEM models to identify brain regions whose local network integration and connectedness differed between subjects and was associated with emotion dysregulation. The latent variable of emotion dysregulation was characterized by scales gauging emotional distress, emotional symptoms, conduct symptoms, and emotional lability. In individuals with ADHD characterized by prominent hyperactivity-impulsivity, the latent emotion dysregulation variable was related to an increased clustering and local efficiency of the right insula. Thus, in the presence of hyperactivity-impulsivity, clustered network formation of the right insula may underpin emotion dysregulation in young adult ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by core symptoms of inattention and/or hyperactivity-impulsivity that may persist well into adulthood (Faraone et al., 2015). Emotion dysregulation, although not a core symptom, is a frequently co-occurring clinical problem (Shaw et al., 2014). Emotion dysregulation refers to the inability to adequately modulate and control emotions (Carpenter & Trull, 2013). Its prevalence within the ADHD population changes with age, from 25-45% in children to 30-70% in adults, and its co-occurrence is associated with reduced well-being, risky behavior, and social impairments (Shaw et al., 2014). Especially individuals with ADHD and impulsivity-hyperactivity symptoms often suffer from emotion dysregulation (Maedgen & Carlson, 2000). However, the neural roots of ADHD associated emotion dysregulation remain unclear.

In emotion dysregulation, a distinction between explicit and implicit emotion regulation has been made. Explicit emotion regulation requires conscious effort and is commonly achieved by applying cognitive control and reappraisal strategies. While cognitive control and reappraisal are particularly associated with activity in structures of the ventral attention and frontoparietal network (Etkin et al., 2015), it is precisely these structures in which deviant - often reduced - activity is frequently found in childhood and adult ADHD studies (Faraone et al., 2015). Implicit emotion regulation, on the other hand, is an unconscious stimulus-driven process based on experience-based reward estimations. The ventromedial prefrontal cortex and the anterior cingulate cortex have been linked to implicit emotion regulation (Etkin et al., 2015). With regard to ADHD, it appears that not only structures related to explicit emotion regulation, i.e. structures for cognitive control and reappraisal, are affected, but also those associated with implicit emotion regulation and rather fundamental emotion reactivity processes (Rubia, 2018). Functional connectivity studies consistently showed deviations in structures of the limbic system including the orbitofrontal, ventromedial prefrontal and anterior cingulate cortex in patients with ADHD (Bos et al., 2017; Ho et al., 2015; Lin et al., 2014; Marcos-Vidal et al., 2018; Posner et al., 2013; Tomasi & Volkow, 2012; L. Wang et al., 2009). Also, task-based fMRI studies using emotion perception and processing tasks in individuals with ADHD found evidence for functional abnormalities in the amygdala and insula, possibly indicating increased bottom-up emotional reactivity (Brotman et al., 2010; Herpertz et al., 2008). Task-based fMRI studies related to implicit emotion regulation, i.e., using fear extinction via habituation or emotional Stroop paradigms, which controlled for differences in cognitive control, found ADHD-specific differences in the ventral anterior cingulate and ventromedial prefrontal cortex (Materna et al., 2019; Posner, Maia, et al., 2011; Spencer et al., 2017). Given the heterogeneity of ADHD, existing neuroimaging studies, and

postulated neurocognitive models, e.g., the dual-pathway model (Sonuga-Barke, 2003), one might expect ADHD-associated emotion dysregulation to be similarly complex, with both explicit and implicit regulatory processes accounting for it.

While several studies, using task-based as well as resting state fMRI, reported brain activity deviations in structures commonly associated with emotion processing and emotion regulation, few have attempted to directly correlate corresponding activation patterns with emotion dysregulation and none has investigated changes specific to ADHS presentations. Two childhood ADHD studies used seed-based connectivity approaches focusing on the amygdala. They reported associations between high emotion dysregulation scores and reduced negative connectivity with the insula and frontoparietal structures as well as increased positive connectivity with the anterior cingulate cortex (Hulvershorn et al., 2014; Yu et al., 2016). Connectivity changes beyond the amygdala have, however, not been investigated, and it remains uncertain whether the reported associations are indeed ADHD- or possibly even ADHD presentation-specific.

To investigate the relationship between emotional dysregulation and functional brain network organization, we used graph theory to analyze fMRI resting-state data from healthy individuals and individuals with ADHD with and without hyperactivity-impulsivity symptoms. We captured the centrality of each brain network node and analyzed whether nodes were highly integrated and connected, either locally towards their direct neighboring nodes or globally with the entire network. Graph theory-based methods have previously been used in ADHD research (Lin et al., 2014; Marcos-Vidal et al., 2018; L. Wang et al., 2009) to describe changes in network topology of functional connectivity. These studies show increased local connectivity and efficiency and decreased global integration. It is however unclear how such changes in information processing properties of brain networks relate to emotional deficits. We gauged emotional dysregulation through structural equation modelling (SEM), using a combination of several self and informant scales assessing emotional problems, emotional lability, and conduct problems as well as one experimental task of emotion recognition. SEM is particularly well suited for testing the significance of certain assumed (group-specific) relations while simultaneously estimating latent variables embedded within the relational model. We focused our analysis on nodal topology measures and aimed to identify those brain regions whose local, functional brain network integration specifically contributes to emotion dysregulation in predominately inattentive ADHD (ADHD-I) and ADHD with symptoms of hyperactivity-impulsivity (ADHD-C/H).

We hypothesized that an ADHD-specific association exists between the functional brain network measures for local network integration and emotion regulation. Thereby, we focused on measures of network topology within frontoparietal and limbic brain regions that have previously been associated with emotion regulation and processing. We assumed that the strongest relation would be found in individuals with predominately hyperactive-impulsive ADHD.

Methods and materials

Participants and procedures

Data were taken from NeuroIMAGE II, the third wave of an integrated genetics-cognition-MRI-phenotype project on ADHD (von Rhein et al., 2015). It includes resting-state fMRI data of 249 individuals with ADHD as well as age- and sex-matched healthy controls. Initial recruitment criteria for ADHD participants were an ADHD combined type diagnosis, availability of one or more siblings, age between 6-18 years and availability of subject, sibling, and at least one biological parent for DNA collection. Exclusion criteria (for all participants) were IQ (as measured by Wechsler Intelligence Scale for Children/Wechsler Adult Intelligence Scale) < 70, diagnoses of autism or schizophrenia, and neurological disorders. For controls, it was required that neither they nor any of their first-degree relatives had a prior ADHD diagnosis.

Reassessment of the ADHD diagnosis was established by combining information from the Kiddie Schedule for Affective Disorders (K-SADS) (Kaufman et al., 1997) and parent, teacher, and self-report versions of the Conners' rating scale (CPRS-R:L, CTRS-R:L & CAARS-R:L) (Conners et al., 1999, 1998a, 1998b). Both the K-SADS and the Conners' rating scales provide operational definitions of the 18 behavioral ADHD symptoms defined in the DSM-IV. In both, symptoms are subdivided by symptom type, i.e., inattentive symptoms and hyperactive-impulsive symptoms. All diagnostic and phenotypic data was acquired on the same day as the fMRI data. A detailed description of the diagnostic procedures is given by von Rhein et al. (von Rhein et al., 2015).

Participants with a subthreshold ADHD diagnosis (2-4 ADHD-specific symptoms), left-handedness, excessive movement during the scanning, or insufficient quality of rs-fMRI or questionnaire data were excluded. 147 participants were used for the final analysis, including 31 participants with ADHD but without hyperactivity-impulsivity symptoms, i.e., predominantly inattentive ADHD (ADHD-I), 25 participants with ADHD and hyperactivity-impulsivity symptoms (ADHD-C/H), i.e., 21 with combined type ADHD and 4 with predominantly hyperactive-impulsive ADHD, and 91 healthy controls. Demographic information are given in Table 3.1.

Forty-eight hours prior to testing, stimulant medication use was discontinued. Data acquisition took place at the Donders Institute for Cognitive Neuroimaging, Radboud University Nijmegen, Netherlands. Participants (and their parents when <18 years old) gave written informed consent for participation. In accordance with relevant guidelines and regulations, ethical approval was granted by the regional ethics

board (Centrale Commissie Mensgebonden Onderzoek: CMO Regio Arnhem Nijmegen, ABR: NL41950.091.12). Data analysis was pre-registered using the open science framework (osf.io/rdyp6) (Foster, MSLS & Deardorff, MLIS, 2017).

Resting-state fMRI data acquisition and preprocessing

Whole-brain imaging was performed on a 1.5 T Magnetom Avanto (Siemens AG, Erlangen, Germany). BOLD-sensitive resting-state functional volumes were acquired using a T2*-weighted EPI sequence (TR = 1960 ms, TE = 40 ms). Each of the 266 volumes consisted of 37 axial slices of size 64x64 (flip angle = 80°, FoV = 224 x 224 mm^2, voxel- size = 3.5 x 3.5 x 3.0 mm^3, inter-slice gap = .5 mm). T1-weighted high-resolution structural volumes were acquired with an MPRAGE sequence (TR = 2730 ms, TE = 2.95 ms, TI = 900 ms, flip angle = 9°, FoV = 256 x 256 mm^2, voxel- size = 1.0 x 1.0 x 1,0 mm^3, GRAPPA 2).

Preprocessing mostly relied on FMRIB algorithms (FSL 5.0.11, https://fsl.fmrib.ox.ac.uk/fsl/) (Jenkinson et al., 2012). The resting-state time series data were skull stripped, realigned to the middle volume of the series, co-registered to the structural T1, and spatially smoothed using a 6 mm full width at half maximum Gaussian kernel (FWHM). ICA-AROMA (Pruim et al., 2015) was used to account for secondary movement artefacts. Residual noise was further reduced by nuisance regression including a linear trend and average times series measured within the white matter and cerebrospinal fluid. High-pass filtering was conducted at .008 Hz. Prior to network analysis, time series were warped to MNI152 space (Montreal Neurological Institute, Montreal, Canada). Root mean squared framewise displacement was calculated. A threshold of .25 was applied to exclude 25 participants with extreme movement from further analysis. Root mean squared framewise displacement did not significantly differ between the groups (healthy controls: .087 ± .071; ADHD-I: .128 ± .096; ADHD-C/H: .111 ± .096).

Graph analysis

For graph analysis we used Python 3.5 (version 3.5.10, https://www.python.org) with NetworkX (version 2.2, https://networkx.org) (Hagberg, Schult, & Swart, 2008). Parcellation of preprocessed time series data was realized using a hemisphere-specific functional brain template with 268 parcels (Finn et al., 2015). It was created using graph-theory based parcellation that ensures functional homogeneity within the parcels of the atlas, even across different individuals. The atlas thus minimizes the likelihood that different functional areas lie within a single parcel (Finn et al., 2015). For 221 relevant parcels, covered by the MR measurement, subject-specific average intensity time series were calculated. Correlation matrices were

created by computing pairwise Pearson's correlations between the extracted time series. Matrices were Fisher's z-transformed and absolute values were taken. Absolute value transformation was performed as preprocessing of the present data did not involve global signal regression and as anti-correlations are thought to be functionally relevant (Murphy et al., 2009). Due to the naturally low density of negative correlations, we refrained from performing specific analysis for positive and negative correlations. To distinguish differences in network density from those of network topology (Ginestet, Nichols, Bullmore, & Simmons, 2011a), matrices were binarized based on seven equally spaced density thresholds with a minimum density of .10 and maximum density of .40 (Achard & Bullmore, 2007). In this range of low to medium network densities, previous studies found significant associations between network topology and ADHD symptoms (Lin et al., 2014; Marcos-Vidal et al., 2018; L. Wang et al., 2009). Thus, seven threshold-specific graphs for each subject were investigated in the following graph analysis. Nodal topology measures were calculated for 70 of the 221 nodes. These 70 nodes were chosen based on their association with parcels overlapping with the orbitofrontal cortex, dorsolateral prefrontal cortex, ventromedial prefrontal cortex, anterior cingulate cortex, posterior parietal cortex, insula, ventral striatum, amygdala, and hippocampus as defined by the Harvard-Oxford Brain Atlas by more than 30%. These brain regions have been previously documented to be involved in emotion processing, its regulation, and brain dysfunctions in ADHD (Rubia, 2018).

Here, we captured the centrality of each node and analyzed whether nodes were highly integrated and connected, either locally towards their direct neighboring nodes or globally with the entire network. Thus, our focus is on six nodal measures, that is betweenness, closeness, eigenvector centrality, clustering coefficient, nodal efficiency, and local efficiency, which were used in previous studies on ADHD and showed ADHD-specific deviations (Lin et al., 2014; Marcos-Vidal et al., 2018; L. Wang et al., 2009). Betweenness, closeness, and eigenvector centrality are measures that describe the centrality of a node within a network. While betweenness describes how often a node is part of the shortest path between two other nodes, closeness describes how many of the theoretically possible direct connections to other nodes actually exist. Eigenvector centrality also considers the centrality of the node's direct neighbors. The clustering coefficient of a node describes how strongly its neighboring nodes are interconnected. Efficiency values indicate how directly nodes can be reached from other nodes of the network. In the case of nodal efficiency, this refers to the shortest connection from a particular node to all other nodes, while in the case of local efficiency it refers to the efficiency amongst the nodes adjacent to a particular node of interest. See Supplementary Figure 3.2 for a more detailed description of the topology measures. All measures entered into separate SEM models described below.

Density-integrated topology measures were calculated (Ginestet et al., 2011a). Differences between populations of weighted networks may be due to the networks' wiring costs and not the targeted topological features. Density-integration of measures from binarized networks, however, can eliminate cost-related differences and also allow the assessment of topology measures under different density-thresholds. Figure 3.1 summarizes the functional connectivity and network analysis.

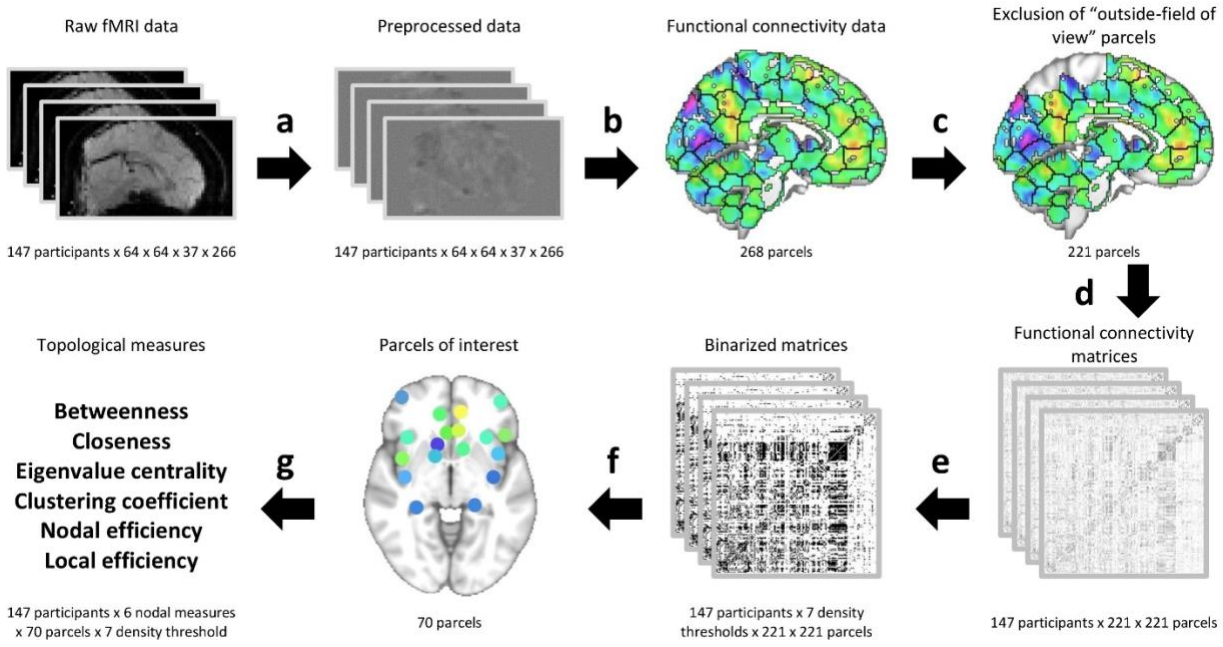

Figure 3.1: *Resting-state functional connectivity analysis pipeline. Preprocessing included skull stripping, co-registration to structural images, realignment to middle volume, spatial smoothing (6 mm FWHM), ICA-AROMA, high-pass filtering (.008 Hz), nuisance regression, and MNI152-space warping* ***[a]****. Mean activation time series for parcels of functional connectivity template (Finn et al., 2015) were extracted after exclusion of "outside-field of view" parcels (90% of the time 80% of voxels in a parcel had to have an intensity of > 1000)* ***[b & c]****. Individual Fisher's z-transformed correlation matrices were created* ***[d]****. Each correlation matrix was binarized using 7 different density thresholds (.10, .15, .20, .25, .30, .35, .40)* ***[e]****. Graphs were created based on binarized matrices and for 70 relevant nodes. Density-integrated as well as threshold-specific topological network measures were calculated* ***[f & g]****. Figure 3.1 was created using FSLeyes (version 0.22.6, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes) and R software (version 3.6.0, https://cran.r-project.org/).*

Statistical analysis and structural equation modeling

Variable Selection. Statistical analyses were conducted with **R** software (version 3.6.0, https://cran.r-project.org/) (Team & R Development Core Team, 2016). Lavaan (version 0.6-8, https://lavaan.ugent.be/) was used for SEM (Rosseel, 2012). Prior to SEM, multi-group confirmatory factor analysis was used to identify data suitable for calculation of the latent emotion dysregulation variable. NeuroIMAGE II includes 6 tasks, questionnaires, or questionnaire subscales, respectively, that gauge emotional problems, emotional lability, and associated features: the Kessler Psychological distress scale, NESDA version of K-10 (Penninx et al., 2008) with 10 items for the assessment of emotional problems including anxiety and

depression, the strength and difficulties questionnaire subscales (SDQ; five items about anxieties, worries, happiness, and physical symptoms of emotional stress for the emotional symptoms subscale & five items about temper tantrums, compliance, quarrelsomeness, stealing, and lying for the conduct symptoms subscales) (van Widenfelt et al., 2003), the emotional lability subscale of the Conners' parent rating scale (CPRS-R:L consisting of three items for unpredictable mood changes, temper tantrums, and tearfulness) (Conners et al., 1998a), the Inventory of Callous-Unemotional traits (ICU) (Kimonis et al., 2008) (24 items with a callousness and unemotional traits score), and the MINDS Testmanager's gradual emotion recognition task (GERT) (Brand, Von Borries, & Bulten, 2010) (accuracy of correct emotion classification).

Mediation structural equation model. The latent variable was used to investigate the relationship between functional brain network activity, emotion dysregulation, and ADHD. In the initial, preregistered analysis plan, we intended to use SEM mediation models in which the relationship between topological measures and the emotional latent variable was mediated by ADHD scores (CPRS-R:L) without taking into account the different ADHD presentations. However, those models did not produce good model-fit (as measured by the standard goodness-of-fit measures described below) and had no significant results. One reason may be that the ADHD scores were derived from a parents' questionnaire for children's ADHD symptoms (CPRS-R:L) which may be less valid than a clinical diagnosis.

Three-group structural equation model. Alternatively, we chose a multi-group SEM approach using the clinical diagnoses. The diagnoses reflect all available diagnostic information and may thus provide more accurate models. We investigated the group dependent differences (i.e., healthy controls, ADHD-I participants, & ADHD-C/H participants) in the association between topology measures and the latent variable gauging emotion dysregulation. Note, that by investigating group-related differences we aimed to identify associations between inter-individual differences in local brain network topology and emotional dysregulation that are specific for individuals with different ADHD presentation. This is different from a mediation model approach (see above) that aims to identify brain regions whose significant correlation with emotional dysregulation only reflects an indirect link via ADHD severity and thus might not directly involve emotion regulation. For each node of interest and each density-specific topology measure, one multi-group model was built. Models consisted of the latent variable, questionnaire scores, associated parameter estimates and variances as well as the nodal topology measure variable with its regression parameter for the latent variable (see Figure 3.2). Factor loadings of the latent variable were fixed across groups, latent variable variance was standardized, and to account for between-group mean differences, group-specific intercepts were added. Models were compared with almost identical models, in which however the regression parameters between the network topology variable and the latent emotion

dysregulation variable were fixed across groups. Model estimation was conducted using maximum likelihood procedures. To evaluate the significance of the group effects, model-specific χ^2-values were compared between the two models (χ^2-difference-test). Following the approach of Ginestet et al. (Ginestet et al., 2011a), a model was considered significant if it revealed a significant effect on the density-integrated level (averaged over densities). Subsequently, significance was tested on each density threshold to provide detailed information on whether effects were found with stronger or weaker network connections.

Post-hoc analysis, multiple comparison procedures and goodness-of-fit. We used post-hoc two-group SEMs with Bonferroni-corrected p-values to investigate pairwise between-group differences. These two-group models resembled the three-group models described above, except that each only considered participants from two of the three groups. Alpha inflation due to multiple comparisons was controlled by the Benjamini-Hochberg false discovery rate (FDR) procedure (Benjamini & Hochberg, 1995). The comparative fit index (CFI), standardized root mean square residual (SRMR), and root mean square error of approximation (RMSEA) were calculated to evaluate the models' goodness-of-fit. Acceptable goodness-of-fit measures should at least be above .95 for the CFI, below .08 for the SRMR, and below .10 for the RMSEA (Schermelleh-Engel, Moosbrugger, & Müller, 2003).

Additional analyses. To further control the robustness of the results, we evaluated whether group-specific differences in overall connectivity strength of the underlying adjacency matrices exist (van den Heuvel et al., 2017). Furthermore, an alternative parcellation scheme was used to investigate the robustness of the results with respect to the chosen parcellation approach. For this, we used the AAL atlas (Tzourio-Mazoyer et al., 2002), further subdivided with K-mean clustering to adapt the size and number of parcels to that of Finn et al. (Finn et al., 2015). Procedures for calculating topology measures and SEM analyses were conducted as described above.

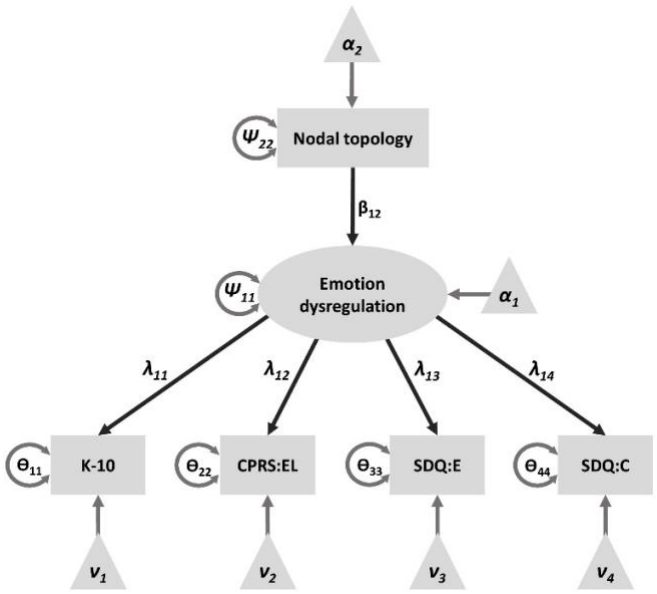

Figure 3.2: *Multi-group structural equation model. Variances (Θ & Ψ) and intercepts (α & v) are group specific. Loading parameters (λ) are fixed across groups while the regression parameter (β) is group specific. The model is compared to a model with fixed β12. All-y LISREL is used for parameter notation. K-10: Kessler Psychological distress scale, NESDA version of K-10; CPRS:EL: Conners' parent rating scale, revised, long version, emotional lability subscale; SDQ:E: Strength and Difficulties Questionnaire, emotional symptoms subscale; SDQ:C: Strength and Difficulties Questionnaire, conduct symptoms subscale. Figure 3.2 was created using Microsoft PowerPoint 2016 MSO (version 16.0.4266.1001, https://www.microsoft.com/de-de/microsoft-365/powerpoint).*

Results

Sample characteristics

Age and sex did not significantly differ between the ADHD and control group. Participants with ADHD showed higher scores on all four measures of emotional problems and dysregulation. Further, compared to controls, participants with ADHD had a significantly lower IQ, partially showed oppositional defiant disorder (ODD) or conduct disorder (CD) comorbid diagnoses and, in general, more often used stimulant medication. ADHD presentations groups did not significantly differ with regard to age, sex, IQ, the four measures of emotion dysregulation, or stimulant use. The demographic details of the sample are given in Table 3.1.

Table 3.1: *Sample characteristics of the control and ADHD groups as well as of presentation-specific ADHD subgroups.*

		ADHD					
Group	**Controls**	**Total**	**ADHD-I**	**ADHD-C/H**	**Controls vs. ADHD Group Comparisons**		
	N = 91	*N = 56*	*N = 31*	*N = 25*			
	M ± SD	*M ± SD*	*M ± SD*	*M ± SD*	*Test statistic*	*p-value*	*Effect-size*
age (years)	20.2 ± 3.5	19.6 ± 3.5	19.5 ± 3.8	19.7 ± 3.2	T = 1.004	.317	d = .170
IQ (WISC/WAIS)	111.4 ± 13.2	95.9 ± 18.0	98.0 ± 17.7	93.2 ± 18.4	U = 3846	<.001	d = .501
ADHD, inattention symptoms*	.5 ± 1.1	7.2 ± 1.4	7.2 ± 1.3	7.1 ± 1.6	U = 25.5	<.001	d = .990
ADHD, hyperactive-impulsive symptoms*	.5 ± .9	5.0 ± 2.4	3.4 ± 1.9	7.0 ± .96	U = 291.5	<.001	d = .890
K-10 psychological distress	12.9 ± 3.6	19.7 ± 5.7	19.3 ± 5.8	20.3 ± 5.6	U = 795	<.001	d = .688
CPRS-R:L emotional lability	44.2 ± 3.3	50.9 ± 9.4	49.5 ± 8.4	52.6 ± 10.5	U = 1412	<.001	d = .446
SDQ emotional symptoms	1.7 ± 1.6	2.9 ± 2.5	3 ± 2.6	2.8 ± 2.3	U = 1897	.008	d = .255
SDQ conduct symptoms	1.1 ± 1.1	2.1 ± 1.6	2.0 ± 1.6	2.2 ± 1.6	U = 1598	<.001	d = .373
	n	n	n	N			
sex (male)	48 (53%)	36 (64%)	20 (65%)	16 (64%)	χ^2 = 1.443	.230	φ_c = .010
stimulant user (yes)	3 (3%)	30 (54%)	22 (65%)	10 (40%)	χ^2 = 47.484	<.001	φ_c = .323
DSM-IV ODD (K-SADS)	0 (0%)	13 (23%)	4 (13%)	9 (36%)	χ^2 = 20.384	<.001	φ_c = .139
DSM-IV CD (K-SADS)	0 (0%)	3 (5%)	1 (3%)	2 (8%)	χ^2 = 2.658	.103	φ_c = .018

Notes: Means between groups were compared with independent sample t-tests or Mann-Whitney-U-tests. Frequency distributions were compared with Pearson's Chi-square (χ^2)-test. For the CPRS-R:L t-scores are presented, while for the SDQ and K-10 the questionnaire scores are given. **ADHD** = Attention Deficit/Hyperactivity Disorder; **ADHD-C/H**: attention-deficit/hyperactivity disorder, combined or predominantly impulsive/hyperactive attention-deficit/hyperactivity disorder; **ADHD-I**: predominately inattentive attention-deficit/hyperactivity disorder; **CD** = Conduct Disorder; **CPRS-R:L** = Conners' parent rating scale, revised, long version; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; **HC** = Healthy Controls; **IQ** = Intelligence Quotient; **K-SADS** = Kiddie Schedule for Affective Disorders and Schizophrenia; **K-10** = Kessler Psychological distress scale, NESDA version; **N** = number of participants; **n** = number of participants within subgroups; **ODD** = Oppositional Defiant Disorder; **SD** = Standard Deviation; **SDQ** = Strength and Difficulties Questionnaire; **WAIS:** Wechsler Adult Intelligence Scale; **WISC:** Wechsler Intelligence Scale for Children.
* combined symptom counts were derived from DSM-IV subscales of K-SADS and the Conners' rating scales

Structural equation models

To identify brain regions in which emotion dysregulation is specifically linked with functional brain network topology as a function of ADHD presentation we combined graph analysis with SEM.

Variable selection. In a first step, several tasks, questionnaires, or questionnaire subscales that capture different aspects of emotion dysregulation were examined to identify variables for estimating a latent emotion dysregulation variable. To construct the latent emotion dysregulation variable, we used multi-group confirmatory factor analysis. Significant loadings for the constructed latent variable were found for the emotional distress scores of K-10 (z = 6.008, p < .001, β = .909), SDQ's emotional symptoms subscale (z = 4.745, p < .001, β = .603), SDQ's conduct symptoms subscale (z = 3.734, p < .001, β = .546), and CPRS-R:L's emotional lability subscale (z = 3.044, p = .002, β = .428). These variables were considered for the subsequent SEM, while MINDS-GERT for emotion recognition (z = .019, p = .983, β = .002) and ICU for callousness-unemotional traits (z = 1.953, p = .051, β = . 163) were discarded. Compared to healthy controls (s^2_{HC}=.300) and participants with ADHD-C/H ($s^2_{ADHD-C/H}$ = .340), latent variable variance of participants with ADHD-I (standardized variance, s^2_{ADHD-I} = 1) was greatest.

Three-group structural equation model. Second, to identify group dependent differences between network topology and the latent variable gauging emotion dysregulation, we used three-group SEM and estimated regression parameters for the group-specific relationship between the latent emotion dysregulation variable and measures of nodal network topology. Pooling over different density levels of connectivity, the SEM revealed group differences in the relation between clustering coefficient as well as local efficiency measures, respectively, and the latent variable for emotion dysregulation in the right insula (see Figure 3.3a). For participants with ADHD-C/H the regression parameter estimates of the SEM were greatest, while they were smallest for participants with ADHD-I (see Figure 3.3b). Table 3.2 displays the group-specific z-values for the relation between the latent variable and the right insula's clustering and local efficiency measures. It also shows p-values (uncorrected), and parameter estimates of the completely standardized solution. Further, Table 3.2 gives model-specific χ^2, degrees of freedom, p-values of the models, goodness-of-fit measures (CFI, SRMR, & RMSEA), p-values that are the result of the χ^2-difference tests between the main models and the corresponding models with fixed regression parameters, and significant pairs of the post-hoc two-group SEM.

Only in the ADHD-C/H group were the topology measures of the insula significantly related to emotion dysregulation. The respective models showed satisfactory goodness-of-fit measures. Results were highly significant for the density-integrated models and significant group-specific differences were found across

multiple density thresholds below 25% connectivity (see Figure 3.3c & d). Results for SEM with clustering coefficients and local efficiency were very similar, as the measures themselves are very similar. Correspondingly, both measures, at the integrated level, showed a correlation of .913 for the right insula. Post-hoc two-group comparisons revealed significant group differences between the participants with ADHD-I and ADHD-C/H as well as between participants with ADHD-C/H and controls. For the other nodal topology measures no significant results were found in the right insula.

While not surviving FDR-controlling procedures on the integrated level, SEM with density thresholds between 35 and 40% connectivity revealed group differences in the relationship between eigenvector centrality and the latent variable for emotion dysregulation in the right DLPFC. For participants with ADHD-C/H the regression parameter estimates of the SEM were greatest, while they were smallest for healthy controls. Significant group-specific differences in the relation between topology measures and emotion dysregulation on the uncorrected level occurred for measures of nodes in the right ventromedial prefrontal cortex, frontal pole, right insula, right anterior mid-cingulate cortex, and left insula (all uncorrected p-values <.01). For none of the other regions examined did we find significant group-specific differences in the relationship between the latent emotion dysregulation variable and measures of nodal network topology.

Additional analyses. Robustness of the results was controlled by evaluating the group-specific differences in overall connectivity strength of the individual networks. The analysis of overall connectivity did not reveal significant group differences. Finally, the multi-group SEM analysis was repeated using an alternative parcellation scheme to investigate the robustness of the results with respect to the chosen parcellation. The repetition of the main analysis with an alternative parcellation scheme revealed a group-specific difference in the relation between the clustering or local efficiency, respectively, and emotion dysregulation in the right insula. Further significant differences were found for the left insula and the right ventromedial prefrontal corex and frontal pole. The significant frontal pole difference also showed for the density-integrated values and after applying FDR-controlling procedures (clustering coefficient: p = .047, FDR-corrected; see Supplementary table 3.1). The significant right insula result, however, was not revealed using threshold-integrated values but only with a density threshold of 25% connectivity and not after FDR-controlling procedures (clustering coefficient: p = .033, uncorrected; local efficiency: p = .030, uncorrected).

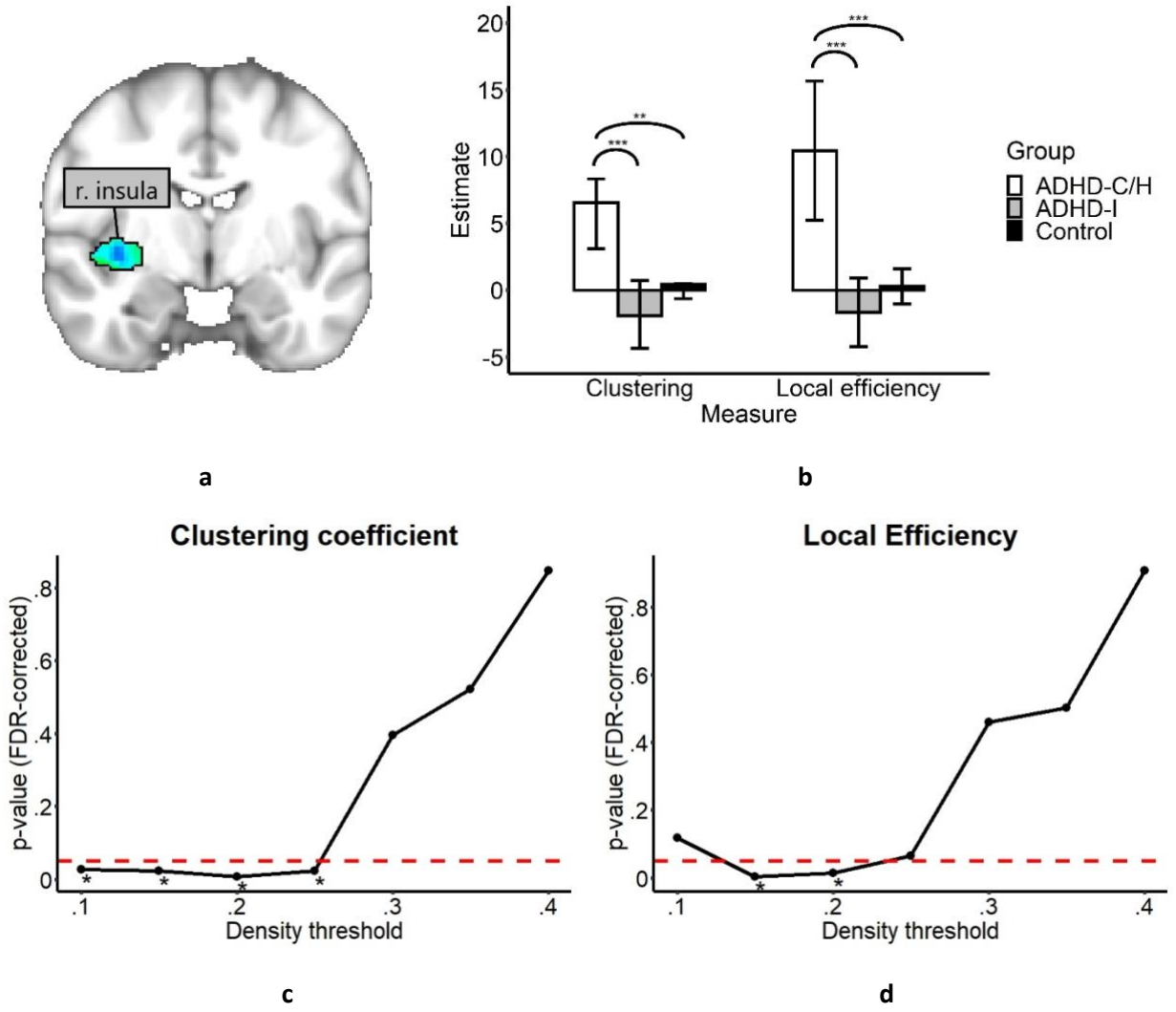

Figure 3.3: *Brain nodes whose nodal network properties are associated with emotional dysregulation in young adult participants with ADHD. Results are shown for the latent variable in relation to local efficiency and clustering measures of the right insula.* ***[a]*** *The right insula showed a significant association with emotional dysregulation. Here the underlying parcel is shown.* ***[b]*** *Group-specific parameter estimates for the relation between the emotional latent variable and the topology measures (density-integrated) significantly differed between the participants with ADHD-I and ADHD-C/H as well as between participants with ADHD-C/H and controls. 95% confidence interval are displayed. Asterisks give significant group-specific differences (as calculated with χ2 difference tests) of the corresponding post-hoc two-group SEM (*** p < .001, ** p < .01, * p < .05; ADHD-C/H: attention-deficit/hyperactivity disorder, combined or predominantly impulsive/hyperactive attention-deficit/hyperactivity disorder; ADHD-I: predominately inattentive attention-deficit/hyperactivity disorder).* ***[c & d]*** *Group-specific differences in the relation between the latent variable and topology measures exist across graphs with different density thresholds (below .25). p-values of the χ2 difference tests are shown. Asterisks signify significance after FDR-correction. The dashed red line represents p = .05. Figure 3.3a was created using FSLeyes (version 0.22.6, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes). Figures 3.3b, 3.3c, and 3.3d were created with R software (version 3.6.0, https://cran.r-project.org/).*

Table 3.2: *Results of multi-group structural equation model analysis. Significant results after FDR-correction are given for the SEM with local efficiency, clustering coefficient of the right insula. All but the last column refer to the three-group SEM with group-specific regression parameter estimates. Group-specific z-statistics for the relation between the latent emotion dysregulation variable and the topology measures, parameter-specific p-values (uncorrected), which were obtained by using the quotient of the estimates and their standard error as a test statistic, and β estimates of the completely standardized solution are displayed for significant density-integrated models and the corresponding density-specific models (as calculated with χ2-difference tests). The table also displays model-specific χ2, degrees of freedom, p-values of the models, goodness-of-fit measures (CFI, SRMR, & RMSEA), p-values that are the result of χ2 difference tests between the main models and the corresponding models with fixed regression parameters, and significant pairs of the post-hoc two-group SEM. Significant two-group differences mainly exist between the ADHD-C/H group and the other two groups.*

Measure	Density	HC			ADHD-I			ADHD-C/H			χ^2	df	p-value	Fit-measures CFI | SRMR | RMSEA	χ^2-difference test p-value (FDR-corr.)	Sig. pairs in Post-hoc χ^2-difference tests (Bonferroni-corr.)
		z	*p*-value	β	*z*	*p*-value	β	*z*	*p*-value	β						
Right insula																
Clustering	.10	-.609	.543	-.060	-.167	.868	.543	3.512	<.001	.754	25.652	21	.220	.944|.880|.067	.042	- HC vs. ADHD-C/H - ADHD-I vs. ADHD-C/H
	.15	-.483	.629	-.246	-1.453	.146	-.246	3.308	.001	.735	26.140	21	.201	.939|.087|.071	.035	- HC vs. ADHD-C/H - ADHD-I vs. ADHD-C/H
	.20	1.539	.124	.172	-2.110	.035	-.366	3.293	.001	.734	23.578	21	.314	.970|.075|.050	.012	- HC vs. ADHD-I - HC vs. ADHD-C/H - ADHD-I vs. ADHD-C/H
	.25	1.256	.209	.140	-2.206	.027	-.392	3.339	.001	.733	21.857	21	.408	.990|.063|.029	.034	- HC vs. ADHD-I - HC vs. ADHD-C/H - ADHD-I vs. ADHD-C/H
	integrated	.820	.412	.091	-1.559	.119	-.279	3.746	<.001	.844	23.472	21	.319	.971|.075|.049	.008	- HC vs. ADHD-C/H - ADHD-I vs. ADHD-C/H
Local efficiency	.15	-1.086	.277	-.108	-1.322	.186	-.215	3.730	<.001	.830	25.535	21	.225	.948|.084|.066	.005	- HC vs. ADHD-C/H - ADHD-I vs. ADHD-C/H
	.20	1.435	.151	.158	-1.761	.078	-.301	3.297	.001	.740	22.604	21	.365	.980|.073|.039	.023	- HC vs. ADHD-C/H - ADHD-I vs. ADHD-C/H
	integrated	.424	.672	.046	-1.259	.208	-.222	3.919	<.001	.882	23.693	21	.308	.969|.078|.051	.005	- HC vs. ADHD-C/H - ADHD-I vs. ADHD-C/H

Notes: **ADHD-C/H**: combined or predominantly impulsive/hyperactive attention-deficit/hyperactivity disorder; **ADHD-I**: predominately inattentive attention-deficit/hyperactivity disorder; **HC**: healthy controls

Discussion

Emotion dysregulation is a key component of many psychiatric conditions, including young adult ADHD. We identified properties of functional brain network topology related to a latent measure of emotion dysregulation by using a combination of graph theoretical methods with structural equation modelling. Our results provide evidence that only in individuals with ADHD-C/H emotion dysregulation is accompanied by increases in local efficiency and clustering of the right insula.

Local efficiency and clustering measure how interconnected a node's neighbors are to each other. Increases imply stronger functional connections between structures directly connected to the respective brain region. Here the insula was identified as showing increased connections to its nearest neighbors contributing to emotion dysregulation in ADHD-C/H. The insula integrates interoceptive states with emotional information via connections to other limbic regions such as the amygdala (Gogolla, 2017). It plays an essential role in implicit emotion regulation via reciprocal connections with the ventromedial prefrontal cortex and other regions particularly associated with experience-based reward estimations (Clark et al., 2008). Throughout brain maturation, functional network formation is characterized by specific patterns of integrative and segregating processes (Fair et al., 2009). These processes are also reflected in measures such as the clustering coefficient and local efficiency. Local efficiency in particular has previously been used as a measure of local brain segregation and it was suggested that increased local efficiency goes along with a loss of global brain network integration. For example, it was shown that higher local efficiency is associated with lower global efficiency and reduced performance during cognitive tasks (Giessing, Thiel, Alexander-Bloch, Patel, & Bullmore, 2013). Prior research consistently provides evidence of delays in the neural maturation of individuals with ADHD (Bos et al., 2017; Castellanos & Aoki, 2016; Sripada, Kessler, & Angstadt, 2014). Increases in the insula's clustering and local efficiency, i.e. functional connectivity increases between neighboring nodes, may indeed, originate from reduced or delayed network-forming processes. This may negatively affect the efficiency with which the insula performs its integrative tasks and helps to appropriately evaluate emotional stimuli or to facilitate emotion regulation. Our results may reflect ADHD presentation-specific deficiencies in functional network forming processes. At the behavioral level, this could lead to inappropriate behavior and some of the commonly observed emotional problems in ADHD.

The positive association between the functional connectivity of structures directly connected to the insula, i.e. local efficiency and clustering, and emotional functioning in ADHD-C/H was neither found in healthy controls nor participants with ADHD-I. Our results are consistent with expectations, given that this

subgroup was shown to be most severely affected by co-occurring emotion dysregulation (Maedgen & Carlson, 2000). Indeed, in the comparison of the different ADHD presentations, the combined type had shown local functional hyperconnectivity in regions associated with emotion processing and implicit emotion regulation, namely the vmPFC (X. Qian et al., 2019). Previously, it was observed that deviations of functional connectivity in ADHD-I occur most clearly in areas of the frontoparietal network, especially the dorsolateral prefrontal cortex, whereas for ADHD-C deviations are most pronounced in areas of the default mode network, i.e. in areas associated with motivation and emotion processing. Since ADHD-I is predominantly characterized by inattention symptoms, it has been suggested that problems in top-down control systems are more likely to underlie this presentation, whereas predominately combined ADHD appears to be more clearly associated with motivation and emotion processing networks (Fair et al., 2013). This could not be confirmed with the analysis carried out here. We found no evidence that nodal topology in top-down control regions would be associated with emotion dysregulation in ADHD-I. On the contrary, the right dorsolateral prefrontal cortex showed an ADHD-C/H dependent association between eigenvector centrality and emotion dysregulation. However, these results should be regarded with caution, as they were only seen at two density thresholds. Taken together, the clinical distinction between ADHD presentations with and without hyperactivity-impulsivity symptoms and the associated prevalence differences commonly observed in co-occurring problems such as emotion dysregulation may be reflected in differential deviations of the underlying functional organization of the brain.

Significant results were found for the *right* insula only. While ADHD is not understood as a generally right-lateralized disorder, some functions are more strongly associated with right hemisphere processing (Blaskey, Harris, & Nigg, 2008). Indeed, the right hemisphere is assumed to take a dominant role in emotion processing. Regarding the regulation of emotions, findings are not as conclusive. However, evidence concerning the insula suggests that processes for integrating interoceptive and emotional/motivational information are rather right lateralized (Lindell, 2013). Note that the left insula yielded – like the dorsolateral prefrontal cortex, right ventromedial prefrontal cortex, frontal pole and cingulate cortex - similar but weaker results, which did, however, not survive correction for multiple comparisons on the integrated level.

The latent variable for emotion dysregulation encompassed self-reported emotional distress, emotional and conduct symptoms and informant-reported emotional lability. Callous-unemotional traits and emotion recognition did not contribute significantly. Their relation to the other emotional measures (i.e., emotional distress & lability) appeared to be rather negligible. This is not surprising as callous-unemotional traits are characterized by deficient affect and lack of empathy, which is a conceptually different aspect of

emotion (Koglin & Petermann, 2012). While emotion recognition is an important prerequisite for the regulation of emotions, adolescents with and without emotion dysregulation have shown similar abilities in recognizing emotions, suggesting again a conceptual difference (Legenbauer et al., 2018). Nevertheless, deficits in both are frequent in ADHD, a common occurrence is, however, not imperative (Sjöwall, Roth, Lindqvist, & Thorell, 2013).

The novel combination of SEM and graph theory presented here enabled us to reliably assess the functional network topology underlying emotion dysregulation. By using a SEM approach, it was possible to simultaneously determine emotional dysregulation as a latent variable of several emotion questionnaires and assess the group-specific relationships of emotion dysregulation with different measures of nodal brain topology. Previous approaches were limited in focusing on seed based functional connectivity of the amygdala only (Hulvershorn et al., 2014; Yu et al., 2016) and using only unidimensional emotional measures. Compared to prior neuroimaging studies, we used a relatively large and well characterized sample of young adult ADHD participants and healthy controls. Also, cases with missing values were excluded from the data set before performing the analyses. Nevertheless, even larger sample sizes may be required in future studies to obtain appropriate power and avoid parameter biases in SEM (see Supplementary Figure 3.1). Note however that simple models, as used here, require smaller samples (e.g., about 30 cases for a simple CFA with four indicator variables) and larger samples are often only necessary if missing values exist (Wolf, Harrington, Clark, & Miller, 2013). The robustness of the findings was further tested by conducting an additional analysis with an alternative parcellation scheme. Even though we were able to replicate the increased local efficiency and clustering in core regions of the implicit emotion regulation network, effects in the insula were weaker and those in ventromedial prefrontal cortex and frontal pole more pronounced. The present study focused on static functional connectivity, not considering the dynamic changes that functional connectivity may show across time, e.g., across the duration of MRI data acquisition. Increasingly, it is suggested that dynamics of functional connectivity are related to behavior and psychopathology (Rabany et al., 2019), making it a worthwhile target for potential future studies investigating emotion dysregulation in ADHD.

In conclusion, the present study shows a positive relation of the right insula's clustering and local efficiency with emotion dysregulation in young adult individuals with ADHD-C/H. A similarly strong connection was not found for individuals with ADHD-I or healthy controls. The results suggest ADHD-type specific deficiencies in network forming processes that are associated with emotion processing and its implicit regulation. The commonly observed emotional problems in ADHD may partially be linked to the present findings. Given that emotion dysregulation is present in many other psychiatric disorders it is interesting

to note that several of those, i.e. major depressive disorder, bipolar disorder, anxiety disorders and schizophrenia are also associated with changes in the structural and functional connectivity of the insula (Namkung, Kim, & Sawa, 2017), which may represent a worthwhile target area for future treatment efforts.

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Chapter 4

Emotion dysregulation and integration of emotion-related brain networks affect intraindividual change in ADHD severity throughout late adolescence

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Abstract

The course of attention deficit hyperactivity disorder (ADHD) from adolescence into adulthood shows large variations between individuals; nonetheless determinants of interindividual differences in the course are not well understood. A frequent problem in ADHD, associated with worse outcomes, is emotion dysregulation. We investigated whether emotion dysregulation and integration of emotion-related functional brain networks affect interindividual differences in ADHD severity change. ADHD severity and resting state neuroimaging data were measured in ADHD and unaffected individuals at two points during adolescence and young adulthood. Bivariate latent change score models were applied to investigate whether emotion dysregulation and network integration affect ADHD severity changes. Emotion dysregulation was gauged from questionnaire subscales for conduct problems, emotional problems and emotional lability. Better emotion regulation was associated with a better course of ADHD (104 participants, 44 females, age range: 12-27). Using graph analysis, we determined network integration of emotion-related functional brain networks. Network integration was measured by nodal efficiency, i.e., the average inverse path distance from one node to all other nodes. A pattern of low nodal efficiency of cortical regions associated with emotion processing and high nodal efficiency in subcortical areas and cortical areas involved in implicit emotion regulation predicted a better ADHD course. Larger nodal efficiency of the right orbitofrontal cortex was related to a better course of ADHD (99 participants, 42 females, age range: 10-29). We demonstrated that neural and behavioral covariates associated with emotion regulation affect the course of ADHD severity throughout adolescence and early adulthood beyond baseline effects of ADHD severity.

Introduction

The course of attention deficit/hyperactivity disorder (ADHD) in young adulthood differs strongly between individuals. While many ADHD patients showed no or only mild symptoms in young adulthood, others show a high level of persistence (Biederman, Petty, Clarke, Lomedico, & Faraone, 2011). Variables that account for interindividual differences in the development of ADHD are not well understood, but there is strong evidence that the ability to regulate emotions is one key factor of individual changes (Sudre et al., 2020). Whereas emotion processing refers to the process of assigning an emotional value towards a perceived stimulus, either positive or negative, emotion regulation describes starting, stopping, or modulating the trajectory of emotions to reach individual goals (Etkin et al., 2015). Dysregulation of emotion belongs to the most frequently observed co-occurring problems in ADHD (Shaw et al., 2014) and its presence in ADHD is associated with significant reductions in quality of life (Bunford, Evans, & Wymbs, 2015; Riley et al., 2006; Wehmeier et al., 2010). The prevalence of ADHD decreases with age from approximately 11.4% in elementary school-aged children to 5.0% in young adults (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014; Willcutt, 2012). In contrast, the proportion of individuals with ADHD affected by emotion dysregulation increases from around 25-45% in childhood to 30-70% in young adulthood (Shaw et al., 2014). Clinical studies comparing categorical ADHD trajectories confirmed that emotion dysregulation, besides other variables like conduct problems, anxiety and depression, significantly relates to persistent ADHD (Caye et al., 2016; Sasser et al., 2016).

At the neural level, several brain imaging studies support that ADHD is a heterogeneous disorder in which alterations are not limited to neural circuits of cognitive control. They also comprise structures associated with emotion processing and implicit (i.e., automatized and non-volitional) emotion regulation (Posner et al., 2014; Rubia, 2011) that is performed without conscious monitoring or awareness (e.g., inhibition of fear) (Etkin et al., 2015). Accordingly, altered functional connectivity in persons with ADHD is commonly found in the ventromedial prefrontal cortex, orbitofrontal cortex, frontal pole, amygdala, and ventral striatum (Bos et al., 2017; Costa Dias et al., 2013; Ho et al., 2015; Posner et al., 2013). Studies on ADHD using graph theory-based methods found alterations of brain network topology in medial and orbital prefrontal regions (Lin et al., 2014; L. Wang et al., 2009). In childhood ADHD, emotion dysregulation was shown to be correlated with functional connectivity of the amygdala, anterior cingulate, and insula (Hulvershorn et al., 2014; Yu et al., 2016). Moreover, task-based fMRI research using emotion perception and processing tasks in ADHD found evidence for abnormalities in the amygdala and insula (Brotman et al., 2010; Herpertz et al., 2008), while implicit emotion regulation in ADHD, investigated with fear

extinction via habituation or emotional Stroop paradigms, was shown to be characterized by differences in the ventral anterior cingulate and ventromedial prefrontal cortex (Materna et al., 2019; Posner, Maia, et al., 2011; Spencer et al., 2017). In summary, there is strong evidence that brain regions involved in emotion processing and implicit emotion regulation strongly deviate in participants with ADHD. Following this line of evidence, we focused on functional brain network topology of brain regions involved in emotion processing and implicit emotion regulation rather than areas commonly associated with top-down processes of cognitive control.

Despite the strong evidence that brain regions involved in emotion processing differ in participants with ADHD, little is known on the covariates that predict the course of ADHD. Previous studies compared neural activation between young adult groups with different categorical trajectories of prior ADHD diagnoses (e.g., remittent vs. persistent ADHD) (Shaw & Sudre, 2021). Those studies revealed that persistent ADHD is associated with atypical frontoparietal activity, i.e., activity of neural circuits associated with cognitive control (Francx et al., 2015; Schulz et al., 2017; Szekely, Sudre, Sharp, Leibenluft, & Shaw, 2017). Structural abnormalities in cognitive control networks, but also in regions associated with emotion regulation were found to be associated with persistent ADHD (Shaw et al., 2013, 2015). By comparing individuals with different ADHD outcomes, it has been further shown that adults with persistent ADHD, but not remittent ADHD, exhibit abnormal functional connectivity in the default mode network, a network related to self-referential processing and emotion regulation (Mattfeld et al., 2014; Sudre, Szekely, Sharp, Kasparek, & Shaw, 2017). However, since most studies only examined brain activity at an adult age, they do not inform on whether respective differences existed previously (Mattfeld et al., 2014; Sudre et al., 2017). Hence, to our knowledge previous studies did not collect neural data at baseline to predict the course of ADHD. We here consider functional imaging data measured at baseline to examine how it affects interindividual differences in the change of ADHD severity. In contrast to previous studies, which categorically defined ADHD trajectory, we here investigated ADHD severity as continuous variable and modelled interindividual differences in the intraindividual change of ADHD to better gauge individual changes.

Here, we examined the relationship of baseline emotion dysregulation and functional brain network topology of regions associated with emotion processing and implicit dysregulation with interindividual differences in the change of ADHD severity measured at two time-points, in late adolescence and after about four years in early adulthood. Resting-state fMRI data was obtained at the same two time points as the ADHD severity information and analyzed using graph theory. Functional graphs were constructed considering functional connectivity of brain regions associated with both emotion dysregulation and ADHD. We focused on nodal efficiency, a parameter that describes how well a node is integrated within a

network. Reduced efficiency (nodal as well as global) of functional brain networks has been associated with deficits in a wide variety of processes and is found in neurological, as well as psychiatric disorders (Achard & Bullmore, 2007; Cai et al., 2020; Ma et al., 2018; Rocca et al., 2016; Shim, Im, Kim, & Lee, 2018; Y. Wang, Zhao, Nie, Liu, & Chen, 2018). Deficits in efficiency were also related to emotion dysregulation and ADHD (Y. Chen et al., 2019; Lin et al., 2014; Pan et al., 2018; L. Wang et al., 2009).

In order to analyze early indicators of later change in ADHD severity, we used latent change score models. As recently proposed, they allow modeling of the impact of continuous covariates on intraindividual changes during development (Kievit et al., 2018). In a first latent change score model, we investigated emotion-related and ADHD severity data aiming to explore whether emotion dysregulation predicts changes in ADHD severity approximately three to four years later. In a second model, using neural data, we assessed the efficiency of brain networks involved in emotion regulation and investigated possible underlying neural mechanisms of between–person differences in intraindividual ADHD courses. We hypothesized that both increased baseline emotion dysregulation and reduced baseline nodal efficiency of brain regions associated with emotion processing and emotion regulation negatively affect the course of ADHD.

Materials and methods

Participants and procedures

The present data were taken from NeuroIMAGE I and II, the second and third wave of an integrated-cognition-MRI-phenotype project on ADHD (von Rhein et al., 2015). No fMRI data were collected during the first wave, which was part of the International Multicenter ADHD Genetics study (IMAGE). Thus, data were taken from a well-established ADHD cohort. Previous studies investigating this data set already documented neural correlates of ADHD and associated problems like cognitive dysfunctions (Duan et al., 2018; Hoogman et al., 2019; Pruim et al., 2019). For instance, prior results suggest that cognitive dysfunctions (i.e., decreased working memory performance) in ADHD are mediated by inferior fronto-striato-cerebellar networks (Duan et al., 2018). In the following, the second and third wave are referred to as T1 and T2. Initially, individuals with combined presentation ADHD and unaffected individuals were recruited. For 244 individuals, phenotypical data was collected at both time points. A purely phenotypical analysis was performed on 104 (females: 44, average age at T1: 16.53, average age at T2: 20.09) of the 244 participants, for whom all required questionnaire data was available. From 119 of the 244 participants, resting-state fMRI (rs-fMRI) data was acquired at T1 and T2. Of those 119 participants, 10 were excluded from rs-fMRI analysis due to left-handedness, as differences between left- and right-handed individuals exist in ADHD prevalence (Simões, Carvalho, & Schmidt, 2017). Another 10 participants were excluded due to excessive movement in the scanner (root mean squared framewise displacement > .25). Thus, the current rs-fMRI analysis was conducted on a sample of 99 individuals (females: 42, average age at T1: 17.22, average age at T2: 20.97). 58 individuals were part of both the phenotypic and neuroimaging sample. Further sample characteristics are summarized in the results section and supplementary table 4.1.

All diagnostic and phenotypic data were acquired at the dates of the fMRI data collection. ADHD diagnoses were reassessed by combining information from the Kiddie Schedule for Affective Disorders (K-SADS) (Kaufman et al., 1997) and parent, teacher, and self-report versions of Conners' rating scale (CPRS-R:L, CTRS-R:L, & CAARS-R:L) (Conners et al., 1999, 1998a, 1998b). A combined symptom count derived from the K-SADS and the different versions of Conners' rating scale (von Rhein et al., 2015) was used as an indicator for ADHD severity. Here, the CTRS-R:L was used for individuals under 18 years of age, while the CAARS-S:L was used for individuals over 18. K-SADS and Conners' rating scales provide DSM-IV-based definitions of ADHD symptoms. If a symptom was present in at least one of them, it counted towards the final symptom sum score with one point. Emotion dysregulation was gauged as a linear combination of

three questionnaire subscales. These subscales are the emotional lability subscale of CPRS-R:L (three items for unpredictable mood changes, temper tantrums, and tearfulness) and the emotional problem (five items for anxieties, worries, happiness, and physical symptoms of emotional stress) and conduct problem (five items for temper tantrums, compliance, quarrelsomeness, stealing, and lying) subscales of the Strengths and Difficulties Questionnaire (SDQ) (van Widenfelt et al., 2003). For a detailed description of the diagnostic procedures, the creation of the combined symptom counts and the initial recruitment we refer to Rhein et al. (2015).

Forty-eight hours prior to testing, stimulant medication use was discontinued. Data acquisition took place at the Donders Institute for Cognitive Neuroimaging, Radboud University Nijmegen, Netherlands. Participants (and their parents when <18 years old) gave written informed consent for participation. Ethical approval was granted by the regional ethics board (Centrale Commissie Mensgebonden Onderzoek: CMO Regio Arnhem Nijmegen, ABR: NL41950.091.12). The data is stored in the Donders Institute for Cognitive Neuroimaging and may be requested via the corresponding author.

Resting-state fMRI data acquisition and preprocessing

Identical scanning protocols were used for NeuroIMAGE I and II. Imaging was performed on a 1.5 T Magnetom Avanto (Siemens AG, Erlangen, Germany). BOLD-sensitive resting-state functional volumes were acquired using a T2*-weighted EPI sequence (TR=1960 ms, TE=40 ms). Each of the 266 volumes consisted of 37 axial slices of size 64 x 64 (flip angle = 80°, FoV = 224 x 224 mm2, voxel- size = 3.5 x 3.5 x 3.0 mm3, inter-slice gap = .5 mm). T1-weighted high-resolution structural volumes were acquired with an MPRAGE sequence (TR = 2730 ms, TE = 2.95 ms, TI = 900 ms, flip angle = 9°, FoV = 256 x 256 mm2, voxel-size = 1.0 x 1.0 x 1,0 mm3, GRAPPA 2). Root mean squared framewise displacement was calculated (mean=.071, SD=.040). A threshold of .25 was applied to exclude 10 participants with extreme movement at either T1 or T2 from further analysis. Using a linear mixed effects model with subjects as random effects, it was tested whether root mean squared framewise displacement significantly depends on age, nodal efficiency measures (principal component scores) or the diagnostic status. Type II/III Wald F-tests were conducted. None of the investigated variables showed a significant impact (age: $F(1, 156.69) = 0.074$, $p = .787$; diagnosis(categorical): $F(2, 146.03) = 1.085$, $p = .341$; nodal efficiency: $F(1, 191.85) = 1.632$, $p = .203$). We therefore assume that to a large extent motion effects did not influence the results of our analysis to a large extent.

Preprocessing was mainly conducted using FSL FMRIB algorithms (FSL 5.0.11) (Jenkinson et al., 2012). After dropping the first five scans of the resting-state time series, the images were skull stripped, realigned to the middle volume of the series, and co-registered to the structural T1. ICA-AROMA was applied to account for motion artefacts (Pruim et al., 2015). In addition, nuisance signal was reduced by regressing out the average BOLD time courses of the white matter and cerebrospinal fluid, and the linear trend. High-pass filtering was conducted at 0.01 Hz. Finally, the data was warped into MNI152 space (Montreal Neurological Institute, Montreal, Canada).

Graph analysis

Python 3.5 with NetworkX (Hagberg et al., 2008) was used for graph analysis. Parcellation of preprocessed time series data was realized using a hemisphere-specific functional brain template with 268 parcels (Finn et al., 2015; Shen, Tokoglu, Papademetris, & Constable, 2013). This atlas was chosen as it was created using a graph-theoretically based parcellation approach that ensures functional homogeneity within the parcels of the atlas. To ensure that the analysis yields similar results regardless of the parcellation scheme selected, the analysis described below was additionally performed using an alternative brain template with 246 functionally homogenous nodes (Fan et al., 2016).

Emotion network extraction. The current study aimed to relate changes in ADHD severity with network integration of brain nodes involved in emotion dysregulation. Hence, 48 parcels of the selected template were chosen that overlapped with the orbitofrontal cortex, ventromedial prefrontal cortex, anterior cingulate cortex, insula, ventral striatum, amygdala, and hippocampus as defined by the Harvard-Oxford Brain Atlas by more than 30%. These brain regions have been previously shown to be involved in emotion processing, its implicit regulation, and brain dysfunctions in ADHD (Materna et al., 2019; Rubia, 2018; Shaw et al., 2014). The focus here is not on structures that achieve emotion regulation via cognitive control and reappraisal (e.g., frontostriatal network), but rather on those that are related to emotion processing and implicit emotion regulation (Etkin et al., 2015). All subsequent rs-fMRI analyses including the calculation of nodal efficiency measures described below were performed on the functional connectivity of these 48 nodes.

Graph construction. Subject-specific average BOLD time series were calculated for each of the 48 parcels. Correlation matrices were created by computing pairwise Pearson's correlations between the extracted time series. The matrices were Fisher's *Z*-transformed and transformed into absolute values as negative correlations are also thought to be functionally relevant (Hallquist & Hillary, 2019). Due to the relatively

low number of negative correlations (22.1% of all edges), we refrained from performing specific analysis for positive and negative correlations. To distinguish differences in network density from those of network topology (Ginestet, Nichols, Bullmore, & Simmons, 2011b), the matrices were binarized based on eight equally spaced density thresholds with a minimum density of 0.10 and a maximum density of 0.45 (Achard & Bullmore, 2007). In this range of low to medium network densities, previous studies found significant associations between network topology and ADHD symptoms (Lin et al., 2014; L. Wang et al., 2009). Thus, for each of the binarized matrices a density-specific network graph was created. A detailed discussion of the advantages and disadvantages of density-based thresholds can be found in van Heuvel et al. (2017).

Analysis of nodal integration. Nodal efficiency is a measure related to the average number of edges that must be traversed to connect a given node to all other nodes of the network. Nodes with high nodal efficiency need few edges to connect with other nodes and easily propagate information to other nodes in the network. Brain network efficiency is associated with a wide range of neural processes, such as cognition and emotion regulation, as well as neurological and psychiatric disorders, especially ADHD (L. Wang et al., 2009). The current analysis focused on a set of selected brain nodes to investigate whether differences in the integration and the formation of the emotional subnetwork affects the individual ADHD severity. A summary of the functional connectivity and network analysis is provided by Supplementary Figure 3.2.

Statistical analysis and bivariate latent change score models

Overview. By means of a bivariate latent change score (BLCS) model with phenotypical data, we investigated whether emotion dysregulation at T1 is related to change in ADHD severity from T1 to T2. Within this model, the relationships of change in emotion dysregulation from T1 to T2 with ADHD severity at T1 and change in ADHD severity were also estimated. By applying a BLCS model on neuroimaging data, we further investigated whether the integration of nodes linked to emotion processing and implicit regulation, i.e. nodal efficiency, at T1 predicts change in ADHD severity from T1 to T2. Within these models, the relationships of change in nodal efficiency from T1 to T2 with ADHD severity at T1 and change in ADHD severity were also estimated. Due to the small number of participants with complete phenotypical and neuroimaging data, we refrained from using one model that includes rs-fMRI as well as emotion-related data.

Advantages of bivariate latent change score. BLCS analyses were performed by using the **R** Software for Statistical Computing (Team & R Development Core Team, 2016) and the lavaan library (Rosseel, 2012).

These models are a powerful and flexible class of structural equation models (SEM) which allow testing a wide range of developmental hypotheses (Kievit et al., 2018). For two variables that are measured at two different points in time, the change of the variable across time is estimated as a latent change score. The variables for which change scores are modeled may themselves be latent, thus, reflected by a set of measured variables. In contrast to cross-sectional comparisons or other longitudinal modeling approaches, BLCS models allow estimating parameters that capture the extent to which the change between time points depends on baseline values and other not directly observable, latent variables (Kievit et al., 2018). For example, we can capture the extent to which changes in ADHD severity are a function of ADHD severity at baseline, and also of latent emotion dysregulation scores or nodal efficiency at T1. While not directly revealing causal relations, BLCS models may be used to test model-based predictions of causal hypotheses (Kievit et al., 2018).

Robustness of the approach. Prior to model generation and parameter estimation, the measured variables were checked for multivariate normality using Mardia's multivariate skewness and kurtosis coefficients (Mardia, 1970) and outliers using Mahalanobis' distance. Mahalanobis' distance measures typically follow a χ^2-distribution. Consistent for both BLCS approaches, an outlier exclusion threshold of $p > 0.001$ was applied to exclude individuals with extreme behavioral or neural data (see below for further explanations). In order to further minimize the influence of potential outliers and violations of multivariate normality, a robust maximum likelihood estimator was used for SEM (Yuan & Zhong, 2013). Thus, several attempts were made to secure the robustness of the results.

Significance testing and further indices of model quality. The significance of SEM parameter estimates was assessed by the Wald-test statistic. Regression coefficient estimates relevant for the research question were additionally tested by means of a χ^2-difference test. To this end, nested BLCS models were compared in which the respective regression parameter was freely estimated vs. fixed to zero. The regression and intercept parameters estimated within the BLCS model are partial coefficients, implying that influences of other modeled variables are accounted for. Individuals with missing values were not included in any analysis. Standardized parameter estimates are reported.

Whenever appropriate, goodness of fit measures, namely the comparative fit index (CFI), standardized root mean square residual (SRMR), and root mean square error of approximation (RMSEA) are reported. Acceptable goodness-of-fit measures should at least be above .95 for the CFI, below .08 for the SRMR, and below .10 for the RMSEA (Schermelleh-Engel et al., 2003).

BLCS model with emotion dysregulation data

See Figure 4.1a for a path diagram of the applied BLCS model. The aim of the first analysis was to investigate the relationships of ADHD severity and emotion dysregulation at T1 with changes in emotion dysregulation and ADHD severity from T1 to T2. The model additionally provides parameter estimates indicating the relationship between the change scores.

The BLCS model included latent variables describing emotion dysregulation at T1 and T2. These latent variables were derived from three aforementioned questionnaire subscales of emotional lability, emotional problems, and conduct symptoms. Thus, emotional dysregulation at T1 and T2 was estimated as latent variable summarizing the three phenotypical scales. For the latent emotion dysregulation scores as well as for ADHD severity latent change scores were estimated. They capture the average change of the respective variables from T1 to T2 and the variance of change across individuals.

Severity of ADHD at T2 was modelled by the sum of ADHD severity at T1 and the change in ADHD severity from T1 to T2. Emotion dysregulation at T2 was modelled according to the same principle. The model provides covariance estimates between ADHD severity and emotion dysregulation at T1. Likewise, the covariance between the two change score variables was estimated as well. Factor loadings onto the latent emotion dysregulation variable were assumed to be invariant across time and thus fixed to equality. To account for the shared method variance due to measurement repetitions, residual covariances were allowed over time.

BLCS model with functional brain network data

See Figure 4.2b for the path diagram illustrating the BLCS model including the neural data. The aim of the second analysis step was to investigate the relationship of ADHD severity and nodal efficiency at T1 with the change in nodal efficiency and ADHD severity from T1 to T2. The models also estimated the relationship between the changes scores.

Cost-integrated nodal efficiency (see 2.3) was investigated in two separate BLCS analyses. Both analyses addressed the relationship of nodal efficiency in emotional brain networks with ADHD severity across two points in time. The first analysis was performed on node-integrated values summarizing nodal efficiency information from all 48 nodes. Principal component analyses (PCA) were separately computed for time point T1 and T2 to integrate nodal efficiency of each individual subject across the 48 brain nodes The first PC score, which is a linear combination of nodal efficiency from all 48 nodes was modeled in BLCS. We focused on the first PC considering it to be a low dimensional and robust summary of individual nodal

efficiency that reflect the maximum variability between individuals. Thus, the PC scores were entered into a BLCS model to assess possible relationships between ADHD severity and an integrated estimate summarizing nodal efficiency of the network associated with emotion processing and implicit emotion regulation. The second analysis only used node-specific information. 48 different models were estimated, each for one node only. Alpha inflation due to multiple comparison was controlled by the Benjamini-Hochberg false-discovery (FDR) procedure (Benjamini & Hochberg, 1995).

For both analyses, latent change scores were created for ADHD severity and the nodal efficiency variables. Severity of ADHD at T2 was modelled by the sum of ADHD severity at T1 and the change in ADHD severity from T1 to T2. Nodal efficiency at T2 was modelled following the same principle. The covariance between ADHD severity and the latent emotional problems variable was estimated as well. Likewise, the covariance between the two change score variables was specified.

Additional analyses

Correlation analyses were conducted to investigate whether nodal efficiency and the associated first PCs are related with the latent emotion dysregulation variable derived from questionnaire data. Individual factor scores for the latent variables were obtained using factor score regression with the lavPredict-function of lavaan (Devlieger, Mayer, & Rosseel, 2016). Using analysis of variance (ANOVA), we additionally investigated the impact of medication status on the change in ADHD severity. Participants were divided into four groups. The first group consisted of those who took stimulant medication during T1 and T2, group two and three of those who took stimulant medication at T1 or T2, and the final group of those who did not take stimulant medication at any time.

Results

Sample characteristics

Participants were on average 17.22 years old at T1 and 20.97 years at T2. On average, the time period between T1 and T2 was 3.75 years (*SD* = .503, Range = 2.64-5.18). Using the Wilcoxon signed rank test, a significant decrease was observed for ADHD hyperactivity-impulsivity symptoms scores (W = 1401.5, p = .006, r = .344). Average IQ increased significantly (t(97)=-2.370, p = .020) and significant changes in the use of stimulants were observed (χ^2 = 12.042, p < .001). All other relevant variables remained constant. Demographic details of the sample are summarized in Table 4.1. Sample characteristics as a function of subgroup can be found in Supplementary Figure 4.2 and Supplementary Table 4.1 of the Supplement.

Table 4.1: *Characteristics of the resting-state fMRI sample at both data collection phases (T1 and T2).*

	NeuroIMAGE I (T1)		*NeuroIMAGE II (T2)*		*Difference test between T1 and T2*		
N = 99							
	Mean	*SD*	*Mean*	*SD*	Test statistic	p-value	Effect-size
ADHD,hyperactivity-impulsivity symptoms	2.88	2.83	2.55	2.54	W = 1401.5	.006	r = .34
ADHD, inattention symptoms	3.68	3.24	3.05	3.01	W = 1476	.167	r = .014
age (years)	17.22	3.15	20.97	3.09	t = -74.04	< .001	δ = 7.44
IQ (WISC/WAIS)	102.93	14.74	105.43	17.80	t = -2.37	.020	δ = .24
CPRS-R:L emotional lability*	47.91	9.37	45.88	5.09	W = 487.5	.091	r = .28
SDQ emotional symptoms**	2.14	1.87	2.41	2.00	W = 425	.288	r = .16
SDQ conduct symptoms**	1.37	1.29	1.44	1.33	W = 376.5	.286	r = .18
	count		*count*				
females	42		42				
individuals with ADHD-related impairments	51		45		χ^2 = 2.50	.114	g = .30
Stimulant users	35		18		χ^2 = 12.04	<.001	g = .38
DSM-IV MDD (K-SADS)***	2		1		χ^2 = 0.50	.480	g = .50
DSM-IV anxiety (K-SADS)***	6		3		χ^2 = 1.33	.248	g = .50
DSM-IV ODD (K-SADS)***	12		6		χ^2 = 2.08	.149	g = .25
DSM-IV CD (K-SADS)***	2		1		χ^2 = 0	1	g = .17

Notes: Means between time points were either compared with paired-sample t-tests or Wilcoxon signed rank tests. Frequency distributions were compared using McNemar's test. For the CPRS-R: L t-scores are presented, while for the SDQ questionnaire scores are given. Cohen's δ or Cohen's g were used for effect sizes. ; **ADHD** = Attention Deficit/Hyperactivity Disorder; **CD** = Conduct Disorder; **CPRS-R:L** = Conners' parent rating scale, revised, long version; **IQ** = Intelligence Quotient; **K-SADS** = Kiddie Schedule for Affective Disorders and Schizophrenia; ***MDD*** = major depressive disorder; ***N*** = number of participants; **ODD** = Oppositional Defiant Disorder; **CD** = Conduct Disorder; **SD** = standard deviation; **SDQ** = Strengths and Difficulties Questionnaire; ***t*** = test statistic for t-tests; **W** = test statistic for Wilcoxon signed rank test.

* data was available for 78 participants at T1 and 80 participants at T2

** data was available for 59 participants at T1 and 80 participants at T2

*** individuals diagnosed with respective disorder

BLCS model with emotion dysregulation data

We first investigated whether emotion dysregulation at T1 is associated with change in ADHD severity. Prior to model estimation, one participant was identified as outlier and discarded due to large Mahalanobis' distance.

Confirmatory factor analysis was conducted for initial variable selection. Significant loadings (fixed to be invariant across time points) were found for the emotional lability subscale of CPRS-R:L, (z = 4.356, p < .001, λ = 0.521), SDQ's emotional symptoms subscale (z = 3.342, p = .001, λ = .515), and SDQ's conduct symptoms subscale (z = 3.436, p = 0.001, λ = 0.485). Thus, all variables were considered for the BLCS model.

The BLCS model revealed a significant relationship of the latent emotion dysregulation at T1 with change in ADHD severity (z = 2.117, p = .034, β = .456; χ^2-difference-test: χ^2 = 5.545, p = .019). Higher emotion dysregulation at T1 was associated with less favorable change (smaller decrease of symptoms) in ADHD severity from T1 to T2. The relationship of ADHD severity at T1 with change in emotion dysregulation and the relationship of the changes were not significant. Respective parameters were set to zero for the final parameter estimation. The final BLCS model ($\chi^2(17)$ = 22.257, p = .175) provided satisfactory goodness-of-fit (CFI = .987, SRMR = .047, RMSEA = .055). Figure 4.1 summarizes the results of the BLCS model with phenotypical data.

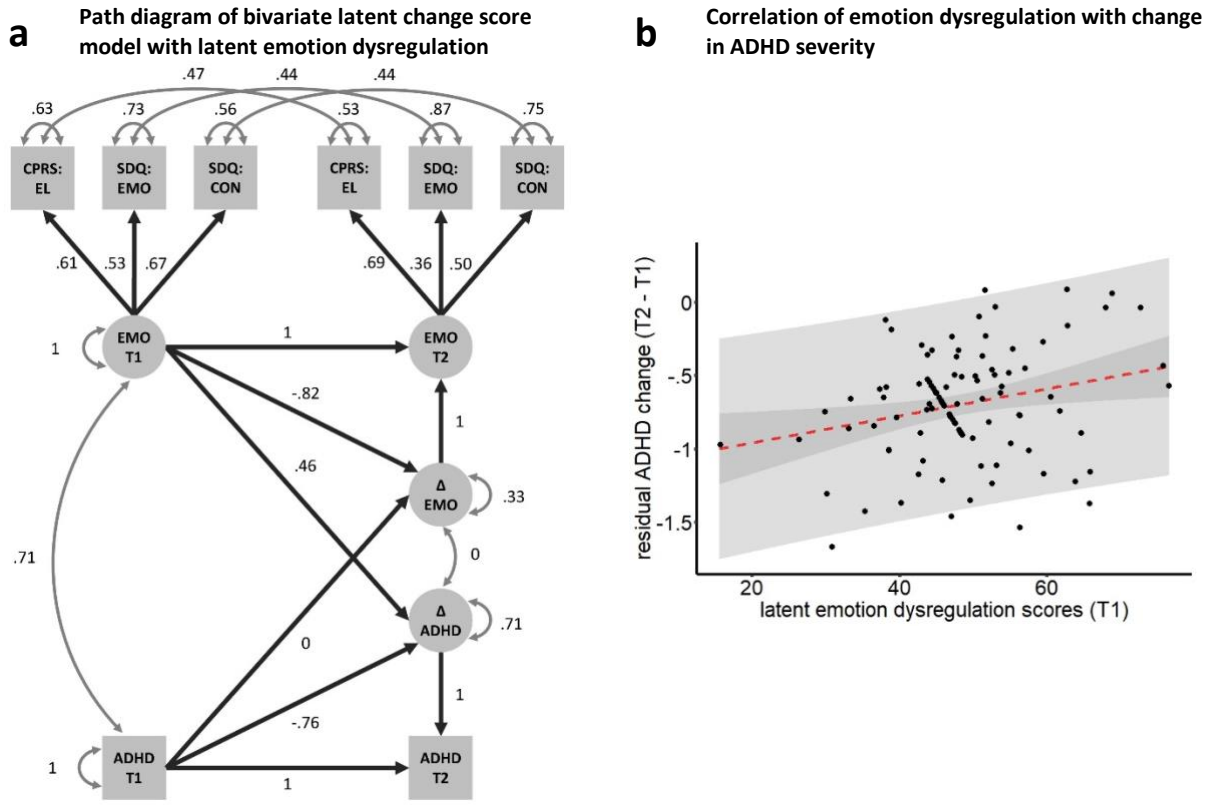

Figure 4.1: *Results of bivariate latent change score analysis with latent emotion dysregulation scores.* ***[a]*** *Path diagram of bivariate latent change score model with latent emotion dysregulation: Standardized parameter estimates are included as path coefficients (regression weights). Non-significant parameters were set to zero. Results of the phenotypical analysis using latent emotion dysregulation scores are displayed.* ***[b]*** *Correlation of emotion dysregulation with change in ADHD severity: A scatter plot with the linear fit was created for emotion dysregulation at T1 and individual change in ADHD severity from T1 to T2. The dark gray area indicates 95%-confidence intervals. The light gray area indicates 95%-prediction intervals. The points forming a line represent those individuals that received an ADHD severity score of zero at T1 and T2 and whose estimated change was derived solely from their emotion dysregulation scores at T1 (n = 23).*

BLCS model with functional brain network data

Whole-network BLCS analysis with nodal efficiencies after PCA

To investigate whether nodal efficiency of the emotion-related network was related to change in ADHD severity, a whole-network BLCS model was used such that nodal efficiency was combined across the emotion-related network using PCA. Nodes of the dorsal anterior cingulate cortex and insula were found to contribute negatively to the first PC and nodes of the basal ganglia, medial prefrontal cortex, orbitofrontal cortex, and hippocampus contributed positively (see Figure 4.2c). The first PC captured 20.6 % of the variance. Using Mahalanobis' distances and an alpha-threshold of .001, three participants were identified as outliers and discarded from the analysis.

The whole-network BLCS model revealed a significant relationship between the first PC at T1 and change in ADHD severity (z = -2.207, p = .027, β = -.192; χ^2-difference-test: χ^2 = 5.1383, p = .023). The higher the PC scores at T1 were, the better was the change in ADHD severity from T1 to T2 (larger decreases of symptoms). The relationship of ADHD severity at T1 with change in the PC and the relationship of the changes were not significant. Respective parameters were set to zero for the final parameter estimation. The final BLCS model ($\chi^2(2) = 0.857$, p = .651) provided satisfactory goodness-of-fit measures (CFI = 1, SRMR = .023, RMSEA = 0). The analysis was repeated using density-specific nodal efficiency. The significant relationship of the first PC at T1 with change in ADHD severity, shown for density-integrated nodal efficiency, was confirmed with density thresholds .2 and .25 (see Figure 4.2d). Figure 4.2 summarizes the results of the BLCS model with network data after PCA.

Node-specific BLCS analysis

We used 48 BLCS models with node-specific efficiency to investigate the relationship of nodal efficiency of brain regions associated with emotion processing and implicit emotion regulation with change in ADHD severity. Mahalanobis' distances for the measured variables were calculated for all 48 BLCS models to identify outliers. Multivariate normality was evaluated separately for each model.

A significant relationship between nodal efficiency at T1 and change in ADHD severity was detected for the right orbitofrontal cortex (z = -3.972, p = .003 (BH-corrected), β = -.272; χ^2-difference-test: χ^2 = 12.547, p = .019 (BH-corrected for multiple comparisons)). The higher the nodal efficiency values at T1 were, the better were the changes in ADHD severity from T1 to T2 (larger decreases of symptoms). Parameter estimation of the associated BLCS model was conducted after exclusion of one outlier. The relationship of ADHD severity at T1 with change in nodal efficiency and the relationship of the changes were not significant. Respective parameters were set to zero for the final parameter estimation. The final BLCS model ($\chi^2(2) = 1.827$, p = .401) provided satisfactory goodness-of-fit measures (CFI = 1, SRMR = .035, RMSEA = 0). The analysis was repeated using density-specific nodal efficiency. The significant relationship of nodal efficiency at T1 with change in ADHD severity, shown for density-integrated nodal efficiency, was confirmed with four density thresholds between .3 and .45 (see Figure 4.3d). None of the other nodal BLCS models revealed a significant relationship between nodal efficiency and change in ADHD severity.

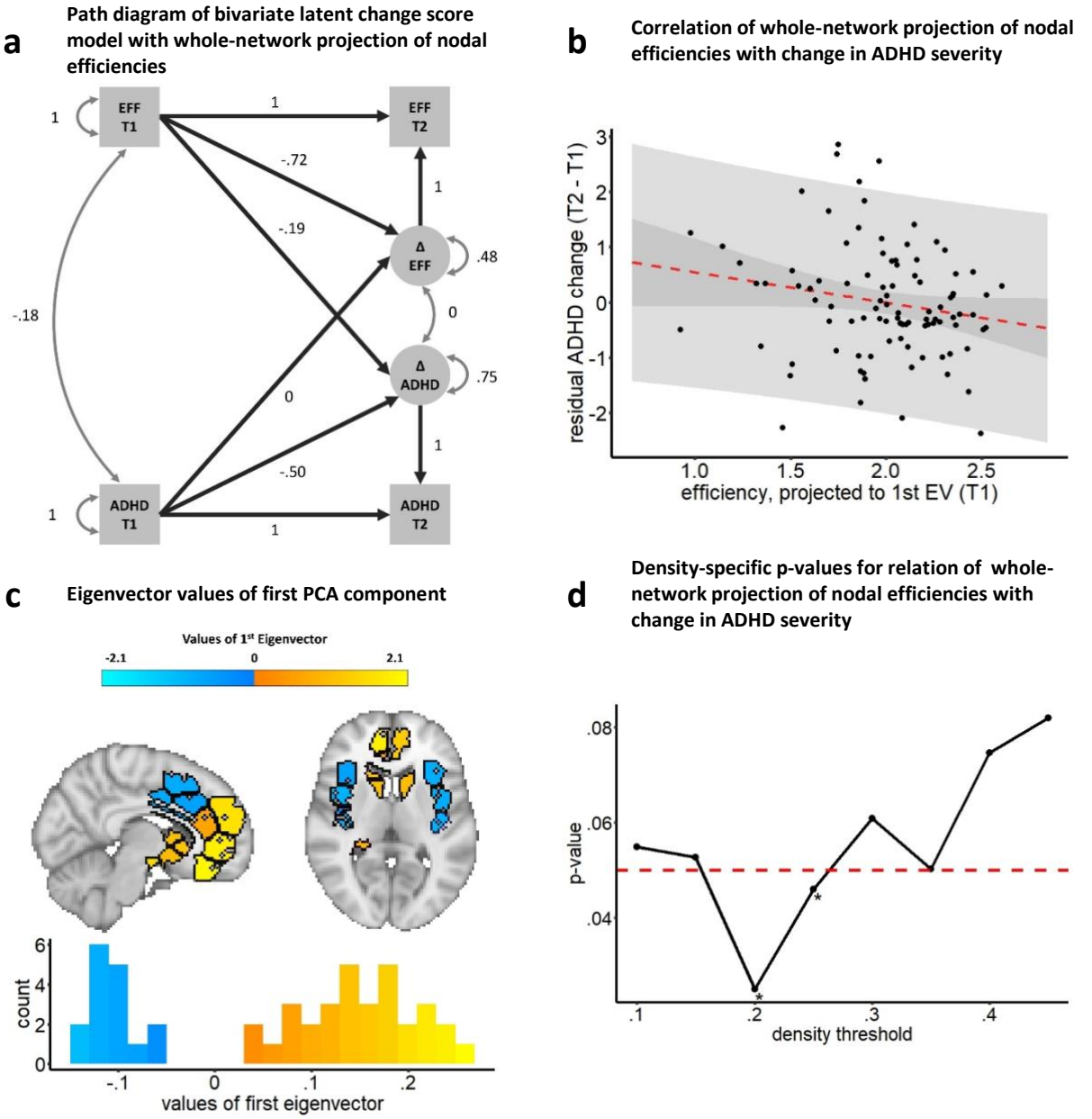

Figure 4.2: *Results of bivariate latent change score analysis with nodal efficiency of the whole emotional network summarized by their first principal component.* ***[a]*** *Path diagram of significant bivariate latent change score model with whole-network projection of nodal efficiencies: Standardized parameter estimates are included as path coefficients (regression weights). Non-significant parameters were set to zero. Results of the whole-network analysis with nodal efficiencies after principal component analysis are presented.* ***[b]*** *Correlation of whole-network projection of nodal efficiencies with change in ADHD severity: A scatter plot with the linear fit was created for the first PC at T1 and individual change in ADHD severity from T1 to T2. The dark gray area indicates 95%-confidence intervals. The light gray area indicates 95%-prediction intervals.* ***[c]*** *Eigenvector values of first PCA component: The values of the first eigenvector are associated with specific brain parcels. They reflect how strongly each node contributes to the first PCA component. The higher the absolute eigenvector value of a node, the more it contributes to the first PCA component. Dorsal anterior cingulate cortex and insula nodes were found to contribute negatively to the first PC while nodes of the basal ganglia, medial prefrontal cortex, orbitofrontal cortex, and hippocampus contributed positively.* ***[d]*** *Density-specific p-values for relation of whole-network projection of nodal efficiencies with change in ADHD severity: Density-specific p-values were calculated. The relation of the first PCA component at T1 with change in ADHD severity was investigated. χ2-difference tests were used to obtain p-values. At each density-level an individual BLCS model was estimated.*

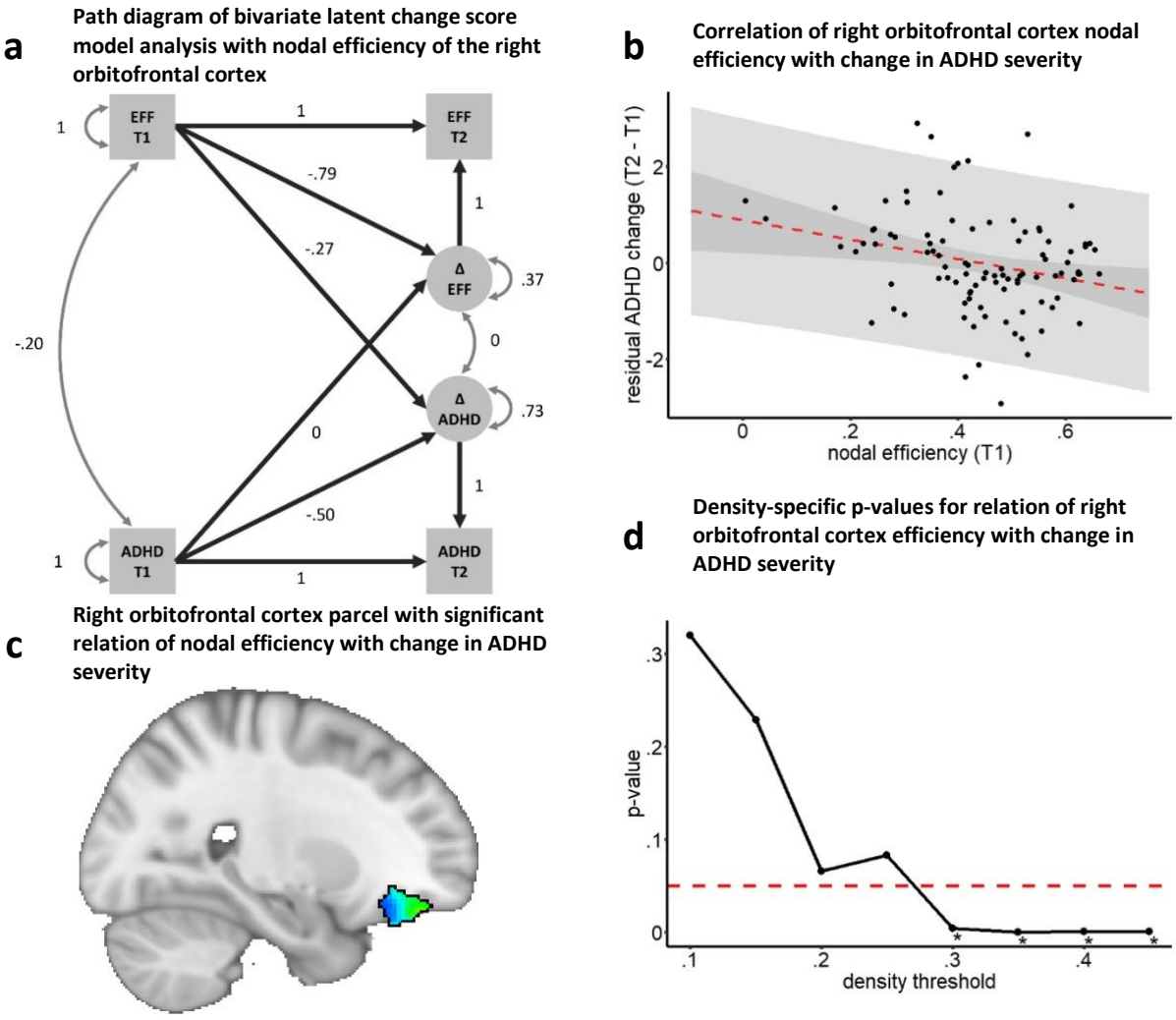

Figure 4.3: *Results of bivariate latent change score analysis with nodal efficiency of right orbitofrontal cortex.* ***[a]*** *Path diagram of bivariate latent change score model analysis with nodal efficiency of the right orbitofrontal cortex: Standardized parameter estimates are included as path coefficients (regression weights). Non-significant parameters were set to zero.* ***[b]*** *Correlation of right orbitofrontal cortex nodal efficiency with change in ADHD severity: A scatter plot with the linear fit was created for nodal efficiency of the right orbitofrontal cortex at T1 and individual change in ADHD severity from T1 to T2. The dark gray area indicates 95%-confidence intervals. The light gray area indicates 95%-prediction intervals.* ***[c]*** *Right orbitofrontal cortex parcel with significant relation of nodal efficiency with change in ADHD severity: Right orbitofrontal cortex nodal efficiency at T1 affected change in ADHD severity from T1 to T2.* ***[d]*** *Density-specific p-values for relation of right orbitofrontal cortex efficiency with change in ADHD severity: Density-specific p-values were calculated after applying FDR-procedures. The relation of nodal efficiency at T1 with change in ADHD severity from T1 to T2 was investigated. χ2-difference tests were used to obtain p-values. At each density-level an individual BLCS models were estimated.*

Additional analyses

Correlation analysis of nodal efficiency and emotion dysregulation at T1. To investigate whether baseline nodal efficiencies and emotion dysregulation were related, a correlation analysis was conducted. Emotion-related questionnaire subscales and rs-fMRI data were available for N = 58 participants. Using their latent emotion dysregulation scores at T1, it was shown that no significant correlations were present with node-integrated nodal efficiency (r = .165, t(56) = 1.252, p = .215) and nodal efficiency of the right orbitofrontal cortex (r = .136, t(56) = 1.027, p = .309) at T1.

BLCS analyses with alternative parcellation scheme. To show the robustness of our results, the BLCS analyses described above were repeated using an alternative parcellation scheme. The general pattern of results corresponded to that of the analyses using the primary parcellation scheme. In agreement with the previous analysis, a significant relationship of nodal efficiency of the right orbitofrontal cortex at T1 and change in ADHD severity was shown at a density threshold of .35 (z = 3.316, p = .049 (BH-corr.), β = -.277). At the integrated level, however, the results did not remain significant after FDR correction (z = 3.149, p = .265 (BH-corr.), β = -.263).

ANOVA for impact of medication status on ADHD severity scores. We used ANOVA to investigate if the medication status influences the change in ADHD severity scores. The change in ADHD severity did not significantly depend on the medication status at T1 and T2 (F(3,94) = 1.893, p = .136).

Discussion

We examined whether emotion dysregulation and nodal efficiency of brain regions associated with emotion processing and implicit emotion regulation, both measured during late adolescence, predicted change in ADHD severity across a period of three to four years. To this end, BLCS models were used to analyze the influence of nodal efficiency, derived using graph theory methods, and questionnaire data on emotional problems, conduct problems and emotional lability. At the symptom level, lower baseline emotion dysregulation was associated with more favorable change in ADHD severity. At the neural level, nodal efficiency integrated across emotion-related brain regions predicted changes in ADHD severity. Especially higher nodal efficiency in the area of the right orbitofrontal cortex was associated with more favorable course of ADHD. Baseline nodal efficiency and emotion dysregulation were however not significantly correlated.

It was previously shown that conduct problems, emotional problems and emotion dysregulation during childhood may be related to the course of ADHD (Biederman et al., 2011; Caye et al., 2016; Miranda et al., 2015). We add to this knowledge by showing that a latent variable derived from these variables, here referred to as emotion dysregulation, affects the course of ADHD severity from late adolescence to early adulthood. The results join a body of research that identified a clear link between emotion dysregulation and ADHD, specifically relating emotional and associated problems to the outcome of ADHD. Previous studies showed that individuals with emotional comorbidities and problems are often those with worse ADHD outcomes later in life (Biederman et al., 2011; Caye et al., 2016; Miranda et al., 2015; Sasser et al., 2016). Our findings, however, differ from most others in that we did not consider childhood ADHD, but ADHD in later stages of life, i.e., late adolescence and early adulthood. Also, rather than merely examining cross-sectional data or categorical outcome variables (e.g., persistent or remittent ADHD), we examined change and its dependence on emotion dysregulation through the use of latent change score models. In contrast to models that analyze aggregated data, these models can capture change at the individual level and detect differences in intraindividual changes (Baltes, Reese, & Nesselroade, 1988). Our results suggest that emotion dysregulation predicts the development of ADHD severity independent from ADHD severity at baseline and therefore may have clinical relevance.

The principal component analysis with nodal efficiencies of the whole network revealed that brain regions contributed differently to the first principal component. Cortical brain regions associated with emotion processing, e.g., the dorsolateral anterior cingulate cortex and the insula, contributed negatively, whereas regions associated with implicit emotion regulation, e.g., the medial prefrontal and orbitofrontal cortex,

contributed positively (cf. Etkin et al., 2015). In agreement with our original hypothesis, this pattern of opposed loadings indeed suggested that the investigated brain regions compose two anti-correlated, functionally separated subnetworks (emotion processing versus regulation). This clear separation on the cortical level was, however, not found on the subcortical level. Amygdala, striatum and parts of the brainstem, i.e., regions highly associated with fundamental emotional processes, showed positive loading. While subcortical structures extract rather simple emotional and motivational features, the insula provides additional interoceptive information (Uddin, Nomi, Hébert-Seropian, Ghaziri, & Boucher, 2017). The anterior cingulate cortex relates the emotional content to other emotional information (Etkin et al., 2015).

In summary, high individual scores in the first principal component were thus characterized by low nodal efficiencies in cortical regions of emotion processing and high nodal efficiencies in cortical regions of implicit emotion regulation, i.e., large differences in nodal efficiencies between these two subnetworks. The first principal component was found to predict the course of ADHD severity from late adolescence into early adulthood over and above baseline effects of ADHD severity. Thus, a pattern of low nodal efficiency within cortical structures associated with emotion processing and of high nodal efficiency within subcortical structures and cortical structures involved in implicit regulation may have a positive impact on the future course of ADHD. The results of the principal component-based analysis of the whole network support the view that, in ADHD, circuits related to emotion processing and implicit emotion regulation are relevant in addition to circuits associated with cognitive control and attention. They thus fit into a large body of literature that points to the importance of the regions studied in the present network analyses. For instance, ADHD-specific altered functional connectivity was repeatedly found in the ventromedial prefrontal cortex, orbitofrontal cortex, frontal pole, amygdala, and ventral striatum (Bos et al., 2017; Costa Dias et al., 2013; Ho et al., 2015; Lin et al., 2014; Posner et al., 2013; L. Wang et al., 2009). Also, it was shown that differences in default mode network connectivity are associated with persistent ADHD outcomes (Mattfeld et al., 2014; Sudre et al., 2017). However, respective findings were derived from cross-sectional analyses and provide little insight into associations between changes in ADHD and preceding brain activity. Neither can they directly capture change at the individual level, nor can they directly related those changes to additional baseline factors (Kievit et al., 2018).

The node-specific analysis revealed a significant positive relationship between nodal efficiency at baseline and the course of ADHD severity for the right orbitofrontal cortex. Higher nodal efficiency values were associated with more favorable changes in ADHD severity over time. The present results extend literature that linked altered orbitofrontal cortex activation during cognitive control to persistent ADHD (Schulz et al., 2017). While also being thought to be influenced by cognitive processes (Rolls, 2019), the orbitofrontal

cortex is particularly linked to the extinction or reevaluation of emotion processing. Similar to the ventromedial prefrontal cortex, the orbitofrontal cortex is considered essential for integrating information to allow emotional processes to be affected by goals, motivational states, or experiences. In primarily implicit processes, it provides contextual information, and thus helps to confine emotions to an appropriate range (Braunstein, Gross, & Ochsner, 2017). For instance, it has been suggested that altered functional connections between the amygdala and the orbitofrontal cortex, which are particularly relevant for emotional outcome evaluation, may lie at the core of emotion network dysregulation in ADHD (Christiansen, Hirsch, Albrecht, & Chavanon, 2019). The present results suggest that the course of ADHD severity depends on the efficiency with which the orbitofrontal cortex is functionally integrated with regions associated with emotion processing and implicit emotion regulation. Beyond this, they suggest that functional connectivity alterations relevant for the course of ADHD severity extend beyond regions commonly associated with cognitive control. In sum, nodal efficiency and thus the strength of integration of the orbitofrontal cortex with other regions involved in emotion processing and implicit regulation appear to have a positive impact on future changes in ADHD severity.

Contrary to our expectations, emotion dysregulation at baseline was not significantly correlated with nodal efficiency at baseline. However, both the latent emotion dysregulation variable and nodal efficiency are merely approximations for the true underlying concept of "emotion dysregulation". Presumably they show a non-significant correlation since they cover only partly overlapping aspects. For example, regions of the brain associated with cognitive control of emotions, e.g. via cognitive reappraisal, were not taken into account in the definition of the present emotion network. With respect to the orbitofrontal cortex, other variables associated with emotions, such as reward and motivation, may be more strongly correlated with nodal efficiency (Braunstein et al., 2017).

It is noticeable that both latent change score models that analyzed nodal efficiency showed significant effects in different ranges of network density. While the principal component-based model, which analyzed nodal efficiency of the whole network, revealed significant effects in the low to medium range of densities, the model investigating orbitofrontal nodal efficiency yielded significant results at the high end of density ranges (see Figures 4.2d and 4.3d). Thus, for the former model, particularly strong functional connectivity between nodes seems to drive the significant relationship between the observed pattern of nodal efficiencies and change in ADHD severity, whereas for the latter model, medium-strong functional connectivity between the orbitofrontal cortex and the other nodes of the network appears to be most relevant. Following the approach of Ginestet et al. (2011) we applied density thresholding to separate effects of network topology from differences in functional connectivity strength. However, in some cases,

density thresholding can bias the correlation between efficiency and external variables. Possibly, interindividual differences in efficiency are associated with individual differences in functional connectivity and subjects with low values in mean functional connectivity might be more affected by noisy, spurious connections (van den Heuvel et al., 2017). However, for both change score models the correlation between individual efficiency scores and mean functional connectivity values were not significant (BLCS model after PCA: r=.077, p=.443; BLCS model with orbitofrontal cortex: r=.086, p=.399). Thus, we found no evidence that interindividual differences in spurious connections influenced our results.

BLCS models provided an elegant method for studying change and the effect of behavioral and neural covariates on this change (Kievit et al., 2018). Although our sample was relatively large compared to other neuroimaging studies, nevertheless, for BLCS models the number of individuals used was rather low (Wolf et al., 2013). Yet, we were able to validate the robustness of the findings by conducting the analyses with an alternative parcellation scheme.

In the present analysis, emotion dysregulation was gauged from questionnaire subscales for conduct problems, emotional problems and emotional lability. Thus, it also entailed information strongly associated with other psychiatric disorders like depression, anxiety or conduct disorder (Vugteveen, de Bildt, Theunissen, Reijneveld, & Timmerman, 2021). While a relatively high proportion of patients with corresponding comorbidities can be expected in the general ADHD population (Biederman, Newcorn, & Sprich, 1991), only few subjects showed these comorbidities in the present sample. Accordingly, it is rather unlikely that the results presented here are driven by comorbidities such as depression or anxiety.

We examined if emotion dysregulation and nodal efficiency of regions associated with emotion processing and implicit emotion regulation predicted change in ADHD severity from late adolescence into early adulthood. A pattern of low nodal efficiency in cortical brain regions associated with emotion processing and high nodal efficiency in subcortical regions and cortical regions of implicit emotion regulation predicted a less severe course of ADHD. Further, we showed that higher nodal efficiency of the right orbitofrontal cortex was related to a more favorable course of ADHD. Moreover, emotion dysregulation, gauged as a latent variable from emotion problems, conduct problems and emotional lability captured from questionnaires was associated with more severe ADHD courses. Our study thus supports the involvement of emotion dysregulation and brain regions associated with emotion processing and implicit emotion regulation in the course of ADHD. Knowing that individuals with emotion regulation problems are at higher risk for a negative progression of ADHD, such individuals should receive special attention and additional interventions.

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Chapter 5

General summary and discussion

The aim of the present thesis was to investigate neural determinants for the occurrence of emotion dysregulation in ADHD. An improved understanding of the relationship between emotion dysregulation and ADHD, as well as underlying mechanisms, is essential for providing affected individuals with the best possible support. This thesis comprises three studies dealing with the relation between emotion dysregulation in young adults with ADHD and its underlying neurobiology. Specifically, the studies targeted [1] the perception of emotional stimuli in ADHD and underlying neural activity, [2] the association between brain network topology and emotion dysregulation in different ADHD presentations, and [3] the course of ADHD and emotion-related neurobiological and phenotypical predictors. This final chapter of this thesis integrates the contents of the three research articles described in the previous chapters. Common themes of the articles are then discussed in the context of existing literature. Finally, strengths and limitations are assessed and an outlook on possible future research is given.

In *chapter 2*, an emotional face-matching task during fMRI was used to investigate neural responses during the processing of angry and fearful faces and visuo-spatial control stimuli. Additionally, measures for emotion dysregulation, ADHD presentation, and age were investigated in relation to the behavioral and fMRI data. Individuals with ADHD were compared with healthy controls. Individuals with ADHD had higher scores on emotion dysregulation than the control group. They also responded more slowly and less accurately to emotional, but not to visuo-spatial control stimuli. Neural response differences between emotional and visuo-spatial trials were significantly lower in the affected individuals, particularly in the left amygdala. While coupling between the right amygdala and the bilateral ventromedial prefrontal cortex was stronger in control subjects for emotional than for visuo-spatial stimuli, coupling strength did not differ significantly between trial types in the participants with ADHD. Neither emotion dysregulation scores, nor ADHD presentation, nor age were related to behavioral and neural processing changes during the emotional face-matching task.

In *chapter 3*, I used a combination of graph analysis and SEM to investigate resting-state functional connectivity in young adults with ADHD and age-matched healthy controls. Emotion dysregulation was measured with four scales from questionnaires and operationalized by a latent variable from SEM. Graph analysis was applied to resting-state data, and measures of network topology were entered into SEM models to identify brain regions where the association between local network integration and emotion dysregulation differed between ADHD presentations. The latent variable of emotion dysregulation was characterized by scales that capture emotional distress, emotional symptoms, behavioral symptoms, and emotional lability. In individuals with ADHD characterized by marked hyperactivity-impulsivity, the latent variable of emotion dysregulation was associated with increased clustering and local efficiency of the right

insula. Neither healthy control subjects nor subjects with ADHD exhibiting only symptoms of inattention showed this pattern.

In *chapter 4*, I investigated whether emotion dysregulation and integration of emotion-related functional brain networks affect interindividual differences in the change of ADHD severity. ADHD severity and resting state neuroimaging data were measured in individuals with ADHD and healthy controls at two points in time during late adolescence and young adulthood. Bivariate latent change score models were applied to investigate whether emotion dysregulation and network integration during adolescence affect changes in ADHD severity. Emotion dysregulation was gauged from questionnaire subscales for conduct problems, emotional problems and emotional lability. Better emotion regulation was associated with a more favorable course of ADHD. Using graph analysis, I identified network integration of emotion-related functional brain networks. Network integration was measured by nodal efficiency, i.e., the average inverse path distance from one node to all other nodes. A pattern of low nodal efficiency in brain regions associated with fundamental emotional processes and high nodal efficiency in regions of implicit emotion regulation predicted a less severe course of ADHD. Further, larger nodal efficiency of the right orbitofrontal cortex was related to a better course of ADHD.

ADHD is a heterogeneous disorder. The disorder presentation, i.e. predominantly inattentive ADHD, predominantly hyperactive-impulsive ADHD, or combined ADHD, its longitudinal course and profile of co-occurring problems and disorders differ strongly between individuals. It is not possible to pinpoint a single causal factor for ADHD. Rather, ADHD is thought to be caused by a combination of various genetic and environmental risk factors that in combination lead to changes in functional and structural brain networks. It is thought that imbalances in large scale functional brain networks, which include a variety of cortical and subcortical structures, may be involved. Previous research described associations with networks linked with executive control and attentional processes, e.g., frontoparietal and ventral attentional networks, but also with networks linked with emotions and their regulation, e.g., limbic and medial prefrontal structures (Faraone et al., 2015). Emotion regulation is facilitated by complex, sometimes sequential processes that act on various stages of emotion-generating processes. Often, it is not just a single process that is dysfunctional within the regulatory system and failure often occurs at multiple stages (Etkin et al., 2015). Consequently, the common overlap between emotion dysregulation and ADHD may not be found in disturbances of a single, isolated process. The underlying neuronal changes appear to be diverse and extend across different neuronal networks. Thus, providing a unified model explaining the frequent co-occurrence of emotion dysregulation in ADHD is difficult and beyond the scope of the present thesis. Instead, different aspects of the topic were addressed in order to contribute to a better

understanding of emotion dysregulation in ADHD, but also of ADHD in general. While the findings of each article are discussed in their respective discussion sections in chapters two through four, the following section discusses the findings in more general terms with respect to their common overarching goal of providing us with a better understanding of the neurobiology of emotion dysregulation in ADHD and ADHD in general. In all three studies, my investigation focused on functional brain activity, particularly functional connectivity, of neuronal structures within emotion-related networks and its relation to the common co-occurrence of emotion dysregulation in ADHD.

The neural basis of ADHD and associated emotion dysregulation

Among the most prevalent psychiatric disorders, comorbidities are very common. This also applies to ADHD, where comorbidities are the rule rather than the exception (Faraone et al., 2015). The most common comorbidities in ADHD include conduct anxiety, and mood disorders,, as well as other neurodevelopmental disorders such as autism spectrum disorder (Bernardi et al., 2012; Q. Chen et al., 2018). Naturally, the frequent occurrence of psychiatric comorbidities is a topic of intense research interest. Two principle mechanisms for the development of comorbidities may be distinguished. It may be that the existence of one psychiatric disorder favors the development of another. For example, inadequate behavior, common in conduct disorders, can negatively affect an individual's social performance and well-being, which in turn could cause depression. Alternatively, the manifestation of any two psychiatric disorders may depend on the same underlying dispositional and most likely latent feature or two such features that correlate. Consistent with the latter mechanism, it was suggested that depression and anxiety disorders share the same underlying temperamental liability toward strong negative affect (Krueger & Markon, 2006; Wilkie, Orimoto, Miyamoto, Stalk, & Mueller, 2018). Identifying and describing such features is key to the understanding of psychiatric disorders and the relationships between those disorders. Underlying causal features may be defined on a behavioral level but also on a neural level. Taking this perspective, one can consider the research articles presented in the previous chapters as an attempt to identify neural features that may determine the co-occurrence of emotion dysregulation and ADHD.

Looking at early neural models of ADHD that focused mainly on executive functioning and attention (cf. Barkley, 1997), one might get the impression that the assumption of common features underlying both emotion-related problems and ADHD is not plausible. On the contrary, one could assume that the high prevalence of emotional problems in ADHD is solely due to the reduced social functioning and quality of life associated with ADHD. However, even models that attribute deficits in ADHD primarily to executive functioning point to the potential negative impact on affect and motivation. For example, Barkley (1997) attributed ADHD to deficient behavioral inhibition through deficient executive functioning systems, and described how this may in turn negatively affect emotion regulation. Moreover, research findings increasingly suggested that characterizing ADHD as a pure executive dysfunction disorder is inadequate. Within the dual pathway model of ADHD, the additional importance of the mesolimbic system and associated structures, including the medial prefrontal cortex, was emphasized. The model postulated that deficits in these structures could cause delay aversion, which in turn could lead to emotion dysregulation (Sonuga-Barke, 2003). Even though the dual pathway model arguably does not provide a completely satisfactory explanation for ADHD, subsequent ADHD research has indeed shown that differences in neural activity are not limited to executive function and attentional structures, but are much more extensive. As mentioned in previous chapters, task-based fMRI research using emotion perception and recognition tasks found aberrant amygdala activity, especially hyperactivity of the left amygdala, insula hypoactivity, and decreased activity of the ventral striatum (Brotman et al., 2010; Herpertz et al., 2008; Posner, Nagel, et al., 2011; Schlochtermeier et al., 2011). Resting state functional connectivity MRI research reported on altered connectivity of the amygdala and orbitofrontal cortex within affective networks (Ho et al., 2015) and deviations of topological network properties in the area of orbitofrontal cortex and ventral striatum (Costa Dias et al., 2013; Lin et al., 2014; Tomasi & Volkow, 2012; L. Wang et al., 2009). The research articles reported in the preceding chapters not only converge but extend the existing literature by specifically examining the link between emotion dysregulation and ADHD as well as related neural activity in regions associated with emotion processing and implicit emotion regulation. As such, abnormalities were found in the amygdala and its coupling with the ventromedial prefrontal cortex. While the amygdala is essential in fundamental emotion processing, particularly its reciprocal connections with the ventromedial prefrontal cortex and further information relay to dorsal prefrontal structures are seen as being crucial for emotion recognition and categorization (Blair, 2008; Motzkin et al., 2015). Furthermore, I could also show that functional connectivity or, more specifically, network topology of certain structures that are elementally involved in fundamental emotional processes, namely the insula, are not only associated with emotion dysregulation, but that this association is ADHD presentation-specific. This may indicate that the underlying neurobiological aberrations in ADHD at least partially depend on the presentation. Finally,

functional connectivity patterns (i.e., nodal efficiency) of structures related to emotion processing and implicit emotion regulation, most notably the orbitofrontal prefrontal cortex, have been shown to predict the course of ADHD in adolescence.

Comparing the results of the different chapters, there is a clear heterogeneity in the neuronal regions found to be significant. For instance, I found that the regions with ADHD presentation-specific differences in the relationship to emotion dysregulation are different from those predicting symptom progression in late adolescence. The diversity of the findings presented here, i.e., significant results in different parts of emotion-related networks, further illustrates the complexity and multi-layered nature of the neural processes underlying ADHD.

With increasing research on psychiatric disorders and continuous advances in neuroimaging methods, it has become evident that causes of psychiatric disorders cannot be found in isolated brain systems. Corresponding models do not usually account for the complexity of the disorders, which are often characterized by heterogeneous phenotypes and comorbidities. The current literature associates ADHD with abnormalities of several cortical and subcortical regions involved in multiple neural systems, including executive function networks, attention and salience networks, reward and emotion networks, and noradrenergic and dopaminergic transmitter circuits (Faraone et al., 2015). Thus, the research focus increasingly shifts to the interaction of different brain systems and the consequences of disturbed interaction. An example of a model that has emerged from this line of research and that attempts to explain psychopathology is the triple network model. The model suggests that unbalanced engagement of the frontoparietal and default mode networks could negatively affect cognition and executive control as well as self-referential processes in psychopathological disorders, including ADHD. This, in turn, could have several causes, such as poor recognition and processing of salient, novel stimuli, e.g., via the ventral attentional network, or dysfunctional signaling of limbic system structures associated with reward and emotion processes (Menon, 2011). Global and network-oriented models for psychiatric disorders may provide support to long-existing literature that is critical of categorical definitions of psychiatric disorders, such as those used in the DSM-5, and favors dimensional assessment (Widiger, 1992). For example, in an effort to account for the heterogeneity of cases within single diagnostic categories, the Research Domain Criteria initiative was launched to attempt to understand mental disorders and neural development as a function of several basic domains of functioning (e.g., negative and positive valence, cognitive systems, and arousal/regulatory systems) that span the spectrum of human behavior from normal to abnormal (Cuthbert & Insel, 2013). In this context, the question arises to what extent it is possible and useful to distinguish related disorders, such as different forms of anxiety disorders, at the neuronal level. In any

case, more global approaches, which do not try to pinpoint the causes of psychiatric disorders to single, well-defined subsystems, but also investigate imbalances in the interaction of neural networks, seem to be more plausible. Such global models could also explain why alterations of neuronal activity and connectivity in ADHD are not limited to specific systems associated with executive functions or emotions, but are found distributed across the entire brain. For instance, significant ADHD-specific local network topology differences were found to be widely distributed across the brain, including the cerebellum, frontal, temporal parietal, and subcortical regions (Lin et al., 2014).

Within this thesis evidence was provided that neural activity of and functional connectivity between emotion-related brain structures may be related to the common co-occurrence of emotion dysregulation and ADHD. Thus, it also provides further evidence that both ADHD and the frequently co-occurring emotional problems should not be attributed exclusively to deficient executive functions and cognitive control and associated brain structures. Neural aberrations appear to be much more extensive and involve brain structures associated with emotion processing as well as implicit emotion regulation, namely, the amygdala, orbitofrontal cortex, medial prefrontal cortex and insula. Future models seeking to explain ADHD must account for both the heterogeneity of the disorder and the complexity of the underlying neural systems. Also, in order to provide an overarching picture, they must also include the factor of age and consider prevalence as well as underlying neurobiology in this context. In any case, the present results are in line with literature that shifts from single-cause or single-pathway models to models that describe the causes of ADHD development across multiple pathways, implying heterogeneous profiles of deficits and neurobiological abnormalities (cf. Faraone et al., 2015). Evidence suggests that ADHD is rooted in imbalances between wide-ranging functional brain networks. It is important to assess each ADHD case individually and consider deficits, including ADHD symptoms, co-occurring (emotional) problems and comorbidities, as well as possible strengths. Only in this way can optimal support be provided.

As mentioned above, another aspect that should not go unmentioned in the consideration of ADHD and its neuronal basis in general, but especially in relation to accompanying emotion regulation problems, is the factor of age. As previously mentioned, emotion dysregulation in ADHD is thought to be age dependent, changing from 25-45% in childhood to 30-70% in adulthood (Shaw et al., 2014). Nevertheless, most fMRI-based research focuses on emotion dysregulation in childhood ADHD. Understanding the biology of the disorder and its connections to emotion dysregulation, however, does not only imply investigating it for a certain subgroup of affected individuals but for all, including different age groups and different subtypes. Accordingly, the studies presented here provide further evidence underscoring the complexity of the disorder and the involvement of emotion-related brain systems not only in childhood

ADHD but also late adolescence and early adulthood. Furthermore, in chapter 4, by using data from two measurement time points, I was able to show a direct relation between emotion dysregulation and neuronal activity on the one hand and the progression of ADHD symptoms into young adulthood on the other.

Strengths and limitations

Some of the strengths and limitations are specific to the studies described in the previous chapters. Accordingly, these will not be discussed in detail here. The following section covers strengths and limitations that apply to some extent to all parts of this thesis.

All three research articles are based on data from the NeuroIMAGE project. More specifically, for articles one and two, data from the third wave and for article three, data from the second and third waves of the NeuroIMAGE project were used. Compared with conventional single-site MRI studies, it was therefore possible to use a relatively large number of participants. This allowed for analyses that could not be performed with a smaller number of participants. Moreover, a variety of different phenotypic, behavioral, and neural variables with multiple measurement time points could be used. This has also given me great flexibility with regard to the conducted analyses. For example, to gauge emotion dysregulation we could use several emotion-related scales and several potentially influential variables, e.g. comorbitities, could be considered and presented in the individual studies. However, the use of the NeuroIMAGE datasets also resulted in limitations. This thesis was planned on the basis of already existing data. As is the case with all data from larger databases, the data were not collected to achieve an ideal fit for the questions addressed here, but to allow for a wide range of different research questions. Thus, only a limited number of phenotypic scales or subscales existed that could be used for the estimation of latent emotion dysregulation variables. MRI scanning was planned to allow for a wide range of different structural and functional measurements. However, considering the fact that many subjects were diagnosed with ADHD, the total scan time had to be kept relatively short. Consequently, not all scanning protocols included all MRI measurements. For example, in NeuroIMAGE I, only 67% of participants had a resting-state scan (von Rhein et al., 2015). At the same time, the scanning time for certain task-based scans was kept relatively short. This in turn limited analysis options and the significance of results. For instance, in the emotional face-matching task of chapter 2, it was not possible to conduct an event-related analysis and sensitivity of the analysis would have been larger with longer scanning times.

The shift to neural networks and the interaction between the networks in psychiatric disorders is largely driven by the availability of appropriate methods. Graph theory methods have become an invaluable tool for understanding global and local aspects of brain architecture. Indeed, the research articles presented in chapters three and four include analyses based on graph theory methods and different sets of local and global network features were investigated. Thus, methods were used that are essential to gain a better understanding of disorders that are rooted in imbalances in the commutation of wide-ranging brain networks. To deal with the complexity of psychiatric disorders such as ADHD, it is not sufficient to look at the isolated activity of individual brain areas. Functional connectivity and network topology must be considered (Menon, 2011). The use of graph theory, however, is also connected with some pitfalls (see chapter 1). The selection of the parcellation scheme and the associated number of nodes can have a particularly strong impact. Thus, for both the second and third research article, the main analyses were additionally conducted with alternative parcellation schemes to ensure the robustness of the results with respect to atlas selection. To further ensure the robustness of the results, it may also be useful to repeat the analysis with a replication study. In reality, however, this is rarely possible due to restricted resources and a limited number of participants.

Above, I have discussed the diversity of the present findings and the diversity of neuroimaging results in the context of ADHD in general. While it can be assumed that this is at least partly due to the nature of the disorder (ADHD is considered a heterogeneous disorder with observable abnormalities in a number of neural systems), the impact of the differences in the applied methods, particularly with respect to the network analyses, should not be neglected. As mentioned in chapter one, graph-theoretical brain analyses are based on several decisions that can have a considerable impact on the results. In comparing the analyses of chapters 3 and 4, it becomes apparent that efforts were made to keep the analysis pipelines as similar as possible. This applies in particular to the preprocessing, but also to the density-based thresholding processes. However, other aspects of the analyses differ. Nodal topology measures in chapter 3 are based on the whole brain network, while in chapter 4 a subnetwork was used that consisted of nodes associated with emotion processing and implicit emotion regulation.

The concept of emotion regulation describes a variety of heterogeneous conscious and unconscious processes aimed at harmonizing emotional states with individual needs and situational circumstances. There is little consensus on how to operationalize emotion (dys-)regulation and how to best separate it from related processes, e.g., basic emotion processing prior to any regulatory activity. Frequently, research merely uses single subscales of more extensive questionnaires, e.g., the emotion stability scale of Conners' rating scales, without considering further information. For the research articles presented in chapters

three and four, SEM was used and latent variables were created to account for information from various emotion dysregulation-related scales. This approach was chosen to obtain robust measures of emotion dysregulation at the behavioral level. In addition, SEM offered further advantages. In the second article, we were able to simultaneously estimate the latent emotion dysregulation variable and assess the ADHD presentation-specific relationships of emotion dysregulation with different measures of nodal brain topology. In the third article, we used BLCS modeling, a special type of SEM that deals with longitudinal data from two different domains. Thus, I was able to examine individual changes in ADHD severity and the impact of behavioral, i.e., a latent emotion dysregulation variable, and neural covariates, i.e., measures of nodal network topology, on this change. The use of SEM, however, can also be tied to some disadvantages. Although the sample sizes of the present analyses were comparatively large, even larger sample sizes may be needed to obtain adequate power and avoid parameter bias in SEM.

Relevance for practice and future research

To achieve optimal outcome, i.e. best possible reduction of symptom severity and increase of quality of life, a combination of pharmacological treatment and psychosocial treatment is usually recommended in the treatment of ADHD. Stimulants, especially methylphenidate and amphetamines, are the first-line medications (Faraone et al., 2015). In terms of psychosocial treatment, there are many different options, such as behavioral therapy, parent training, or social skills training (Daley et al., 2018; Wolraich et al., 2019). These can be flexibly adapted to an affected individual's needs and are particularly well suited for treating co-occurring problems (Jensen et al., 2001). These are usually emotion-related, i.e. depression or anxiety. Naturally, the knowledge of how ADHD relates to its common comorbidities is essential for adequate treatment. It makes a difference whether emotional problems are a mere consequence of the reduced functioning and well-being that accompany the presence of ADHD or whether it is an intrinsic feature of the individual's ADHD presentation. Understanding the underlying neurobiology may help in this endeavor. Although the research findings presented here cannot be used as the sole basis for practical recommendations, they demonstrate that the activity of structures associated with fundamental emotion processing and implicit emotion regulation are relevant to understanding deficits in emotion recognition and regulation in ADHD. Future research should focus even more on the functional connectivity patterns of the brain, not only on emotion-related structures, but also on the connectivity between major brain systems, to further our understanding of ADHD and its link to emotion dysregulation. This knowledge may

eventually stimulate the establishment of novel treatment approaches. In this context, this thesis highlighted some aspects that could be of interest, namely, the perception of emotional stimuli, different ADHD presentations, and the course of ADHD. At the same time, it is important not to lose sight of the underlying goal of the research efforts, which is to improve the lives of the people affected or inform clinical practice in a way that knowledge can be used to improve the lives of people who feel affected. Often research, including the present work, is quite far from directly meeting this aspiration. Compared to other disorders, such as neurological disorders, the neurobiological causes of mental disorders are usually very diffuse. In psychiatry, fMRI is mainly a research tool without much relevance for individual diagnosis or treatment (Schleim & Roiser, 2009). Of course, as described above, it can be used to refine pathophysiological models and to study the effects of pharmacological treatments in specific populations. However, to have an even greater impact on clinical applications, it may be necessary to further develop the methodology to improve the robustness and reproducibility of MRI results (Specht, 2020). The field is driven by constant methodological progress, most recently, for example, through the use of graph theoretical network analysis or machine learning algorithms. In the future, this progress could further increase the importance of MRI in clinical applications and provide an even better understanding of ADHD and associated conditions.

Final conclusion

The goal of this work was to improve our understanding of the relationship between ADHD and emotion dysregulation and of the role of the underlying neural circuits and functional connectivity. I targeted specific aspects of this relationship, namely the perception of emotional stimuli, the impact of different ADHD presentations, and the course of ADHD. Results showed reduced differences in brain activity of individuals with ADHD compared to controls between emotion processing and neutral stimuli, particularly in the left amygdala, and dysfunctional connectivity between the right amygdala and the ventromedial prefrontal cortex. This may indicate that deficits in emotion recognition in ADHD are associated with abnormalities in affective arousal structures and their functional connections to medial prefrontal areas. Furthermore, I found a positive association of network topology, i.e. nodal efficiency and clustering, of the right insula with emotion dysregulation in individuals with ADHD and with hyperactivity-impulsivity symptoms. A similarly strong association was not found in individuals with predominantly inattentive ADHD or healthy controls. The results suggest ADHD-specific deficits in network-forming processes

associated with emotion processing and its implicit regulation. Finally, I found better emotion regulation to be associated with a more favorable course of ADHD, with a pattern of low nodal efficiency in brain regions associated with fundamental emotional processes and high nodal efficiency in regions of implicit emotion regulation predicting a less severe course of ADHD. Thus, it was shown that neural activity of and functional connectivity between emotion-related brain structures may be related to the common co-occurrence of emotion dysregulation and ADHD. ADHD and the often co-occurring emotional problems should not be attributed to single isolated systems, e.g. for executive functions and cognitive control. The neurobiological roots seem to be complex and heterogeneous, involving the interplay of different partly emotion-related brain networks.

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Appendix

Supplementary Information for Chapter 3

Results of multi-group structural equation model analysis with alternative parcellation scheme

Supplementary Table 3.1: *Results of multi-group structural equation model analysis with alternative parcellation scheme. Results are given for the SEM with clustering coefficient measures of the right frontal pole. All but the last column refer to the three-group SEM with group-specific regression parameter estimates. Group-specific z-statistics for the relation between the latent emotion dysregulation variable and the topology measures, parameter-specific p-values (uncorrected), which were obtained by using the quotient of the estimates and their standard error as a test statistic, and β estimates of the completely standardized solution are displayed for significant density-integrated models and the corresponding density-specific models (as calculated with χ2-difference tests). The group of participants with ADHD-C/H shows the largest β estimates. As compared to the other two groups, all of their estimates indicate significant group-specific relations between the latent variable and the respective topology measure. The table also displays model-specific χ2, degrees of freedom, p-values of the models, goodness-of-fit measures (CFI, SRMR, & RMSEA), p-values that are the result of χ2-difference tests between the main models and the corresponding models with fixed regression parameters, and significant pairs of the post-hoc two-group SEM. Significant two-group differences mainly exist between the ADHD-C/H group and the other two groups.*

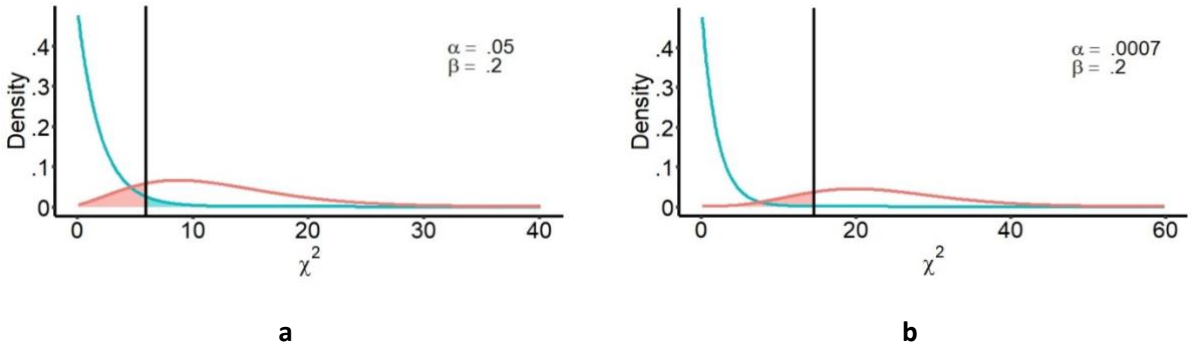
Measure	Density	HC			ADHD-I			ADHD-C/H			χ^2	df	p-value	Fit-measures CFI|SRMR|RMSEA	χ^2 difference test p-value (FDR-corr.)	Sig. pairs in Post-hoc χ^2 difference tests (Bonferroni-corr.)
		z	*p*-value	β	z	*p*-value	β	*z*	*p*-value	β						
Frontal pole and ventromedial prefrontal cortex																
Clustering	.15	-1.889	.059	-.217	.304	.761	.057	3.025	.002	.756	38.684	21	.011	.813|.092|.131	.048	- HC vs. ADHD-C/H - ADHD-I vs. ADHD-C/H
	.20	-1.848	.065	-.213	-.037	.971	-.007	3.040	.002	.734	38.995	21	.010	.811|.090|.132	.044	- HC vs. ADHD-C/H - ADHD-I vs. ADHD-C/H
	integrated	-1.863	.062	-.215	.838	.846	-.279	3.029	.002	.748	38.734	21	.011	.812|.091|.131	.047	- HC vs. ADHD-C/H - ADHD-I vs. ADHD-C/H

Notes: **ADHD-C/H**: combined or predominantly impulsive/hyperactive attention-deficit/hyperactivity disorder; **ADHD-I**: predominately inattentive attention-deficit/hyperactivity disorder; **HC**: healthy controls

Results of a priori power analysis for required sample size estimation

Since data collection was already completed when the present analysis was planned, we did not perform any a priori power analysis but used all available data (n=249). We are hesitant to perform a post-hoc power analysis since observed power and p-values are directly related and non-significant p-values naturally correspond to low observed power and vice versa(Hoenig & Heisey, 2001). Reporting power for outcomes already observed is conceptually flawed and analytically misleading(Zhang et al., 2019). However, we performed an analysis to examine if the existing sample size was close to the sample size estimates of an a priori power analysis for SEM. In SEM, power analyses can be based on χ^2-distributions. If the null hypothesis holds (e.g., model-implied covariance matrix is equal to population covariance matrix), the χ^2-distribution is derived from the degrees of freedom, which in turn can be inferred from the number of manifest variables and free parameters within the model. However, if the alternative hypothesis is true, the distribution additionally depends on a non-centrality parameter. Different non-centrality measures of the effect can be chosen (e.g., RMSEA), all of which depend on the population covariance matrix and the model-implied covariance matrix of the observed variables. One can perform power analyses for SEM with respect to the overall fit of a SEM model or individual parameters. Also, the analyses can be conducted with multi-group SEM(Jak, Jorgensen, Verdam, Oort, & Elffers, 2020).

We used the **R** toolbox semPower to perform a power analysis for SEM(Moshagen & Erdfelder, 2016). To obtain the population covariance matrix (required for calculating the non-centrality parameter), population values were chosen for all parameters present within the three-group model (medium-sized standardized loadings: .5; group-specific regression parameters: -.5, 0, .5). Note, that we did not estimate these effects from our estimated model since, due to our significant p-values and moderate sample size, our findings might overestimate these effects. Assuming standard values for α and β (α = .05, β = .2) and given a non-centrality parameter of 9.614, a sample size of 37 participants per group was shown to be required in the investigation of the three-group model's regression parameter. This is relatively close to the actual group sizes. However, if we take into account the need for alpha correction due to multiple testing (α=.0007, β=.2), the required sample size changes considerably. Per group, 79 observations are required at a non-centrality parameter of 20.831.



a **b**

Supplementary Figure 3.1: *Depiction of central and non-central χ2-distribution with associated α- and β-areas and the critical χ2-value. [a] Distributions with required sample sizes of 34 persons per group to obtain α = .05 and β = .2. [b] Distributions with required sample sizes of 134 persons per group to obtain α = .0007 and β = .2. Supplementary Figures S1a and S1b were created with R software (version 3.6.0, https://cran.r-project.org/).*

Description of implemented nodal topology measures with example visualization

Betweenness: The proportion of shortest paths between all pairs of nodes that pass through a given node is described by the centrality measure betweenness. In Supplementary Figure S2a, a high betweenness value is given for node 10 with 36% of all paths leading through it ($C_B(10) = .362$), whereas not a single shortest path leads through node 14 ($C_B(14) = 0$). Betweenness centrality of node i in a graph is given as follows (Fornito et al., 2016):

$$C_B(i) = \frac{1}{(N-1)(N-1)} \sum_{h \neq i \neq j} \frac{\rho_{hj}(i)}{\rho_{hj}},$$

where ρ_{jh} is the total number of shortest paths between node *j* and *h*, $\rho_{jh}(i)$ is the number of those paths that go through *i* and *N* is the number of nodes in the graph.

Closeness: Closeness is based on the average shortest path length, where the shortest path length is the minimum number of edges that have to be traversed to travel from one node to another. To obtain closeness, the inverse of the average shortest path length is taken, resulting in a high closeness value for nodes with low average shortest path lengths and vice versa. In Supplementary Figure S2b, high values can be observed for the most central nodes ten ($C_C(10) = .556$) and 11 ($C_C(11) = .613$), while particularly noncentral nodes have very low values. Closeness centrality of node *i* in a graph is given as follows (Fornito et al., 2016):

$$C_C(i) = \frac{N-1}{\sum_{j \neq i} l_{ij}},$$

where l_{ij} is the shortest path length between nodes *i* and *j* and *N* is the number of nodes in the graph.

Eigenvector centrality: Node degrees are the basis of eigenvector centrality. The degree of a node describes the number of edges connecting the node to all other nodes of the network. Based on this, the eigenvector centrality considers not only the degree of the node in question but also those of its neighbors. The required information is contained in the graph's adjacency matrix and the eigenvector centrality of node *i* within a network is given by entry *i* of the eigenvector belonging to the largest eigenvalue of the adjacency matrix. Unlike betweenness and closeness, eigenvector centrality specifically emphasizes the centrality of the 11 ($C_E(11) = .357$). node (see Supplementary Figure S2c), since not only this node but also its neighboring nodes have high node degrees. Eigenvector centrality of node *i* in a graph can be derived from the eigenvector equation (Fornito et al., 2016):

$$C_E(i) = \frac{1}{\lambda_1} \sum_{j=1}^{N} A_{ij} x_j,$$

where *A* is the adjaceny matrix of the graph, λ_1 is the largest eigenvalue, *x* is the associated eigenvector and *N* is the number of nodes in the graph.

Clustering coefficient: The clustering coefficient of a node is the fraction of its neighbors that are also connected to each other. It thus describes how close its neighbors are to being a clique, i.e. a complete graph. For several nodes of Supplementary Figure S2d (namely nodes 9, 12, 17), maximum clustering coefficient values are given, indicating that they are located in a highly interconnected cluster. At the same time, however, it is also evident that a high clustering coefficient can arise from a node only having very few connections (node 14). In contrast, the centrally located node 10 has seven connections and correspondingly 28 connections between its neighbors are possible. Only eight of these actually exist and its clustering coefficient accordingly is *Cl(i) = .285*. The clustering coefficient of node *i* is defined as(Fornito et al., 2016):

$$Cl(i) = \frac{2t_i}{k_i(k_i-1)},$$

where t_i denotes the number of edges connecting the k_i neighbors of node *i*.

Local efficiency: The local efficiency is another measure based on shortest path lengths. To calculate it, only those nodes are considered that are directly connected with a certain node of interest. For all node pairs within the resulting subgraph, the reciprocal of the shortest path length is calculated. Subsequently, the mean of the reciprocals is taken to determine the local efficiency. The conceptual similarity to the clustering coefficient is also reflected in the results of the example graph. Values that are high in one topology measure are also high in the other and vice versa (see Supplementary Figures S2d & S2e). Local efficiency of node *i* is obtained as follows(Fornito et al., 2016):

$$E_{loc}(i) = \frac{1}{k_i(k_i-1)} \sum_{j,h=1}^{k_i} \frac{1}{l_{jh}},$$

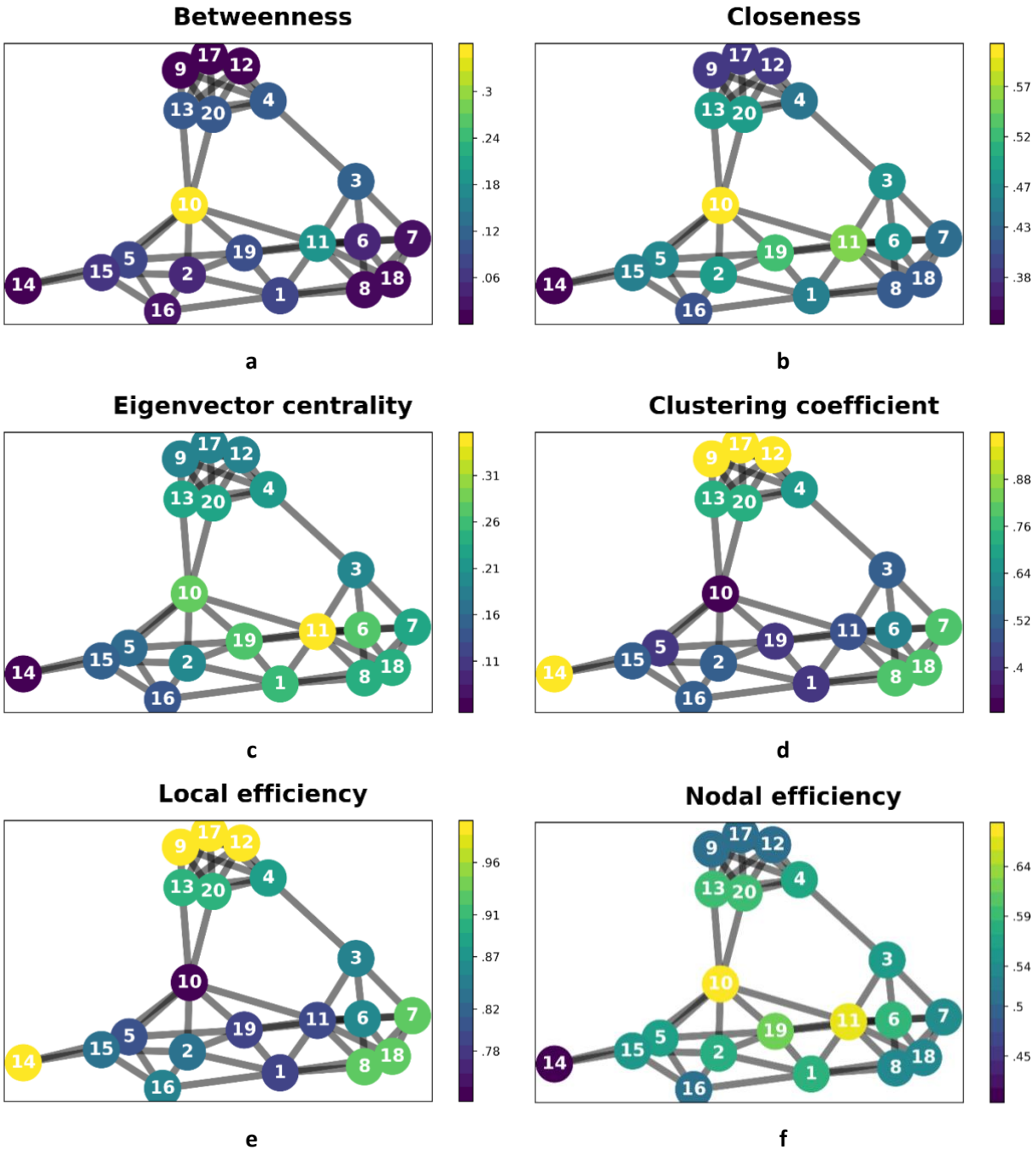
where l_{jh} is the shortest path length between two nodes *j* and *h* directly connected to node *i* and k_i is the number of direct neighbors of node *i*.

Nodal efficiency: To calculate the nodal efficiency, the reciprocals of the short path lengths between a target node and all other nodes of the graph are required. To determine the nodal efficiency of the target node, the average of the reciprocals is taken. The nodal efficiency indicates how well a given region is integrated into a network via its shortest paths. This is especially the case for node 10 ($E_{nod}(10) = .684$), but also node 11 ($E_{nod}(11) = .675$; see Supplementary Figures 2f). Nodal efficiency of node *i* is obtained as follows(Fornito et al., 2016):

$$E_{nod}(i) = \frac{1}{N-1}\sum_{i\neq j}\frac{1}{l_{ij}},$$

where l_{ij} is the shortest path length between nodes *i* and *j* and *N* is the number of nodes in the graph.

To obtain more details about the calculation of graph topology measures, we refer to the fundamental literature by Fornito, Zalezky, and Bullmore(Fornito et al., 2016).



Supplementary Figure 3.2: *Example graph with subplots visualizing different nodal topology measures. The example graph was created with the random geometric graph function from NetworkX (version 2.2, https://networkx.org)(Hagberg et al., 2008). The values of the node-specific topology measures are indicated by the nodes' colors. Supplementary Figure S2 was created using Python (version 3.5.10, https://www.python.org) and the associated library Matplotlib (version 2.2.3, https://matplotlib.org/).*

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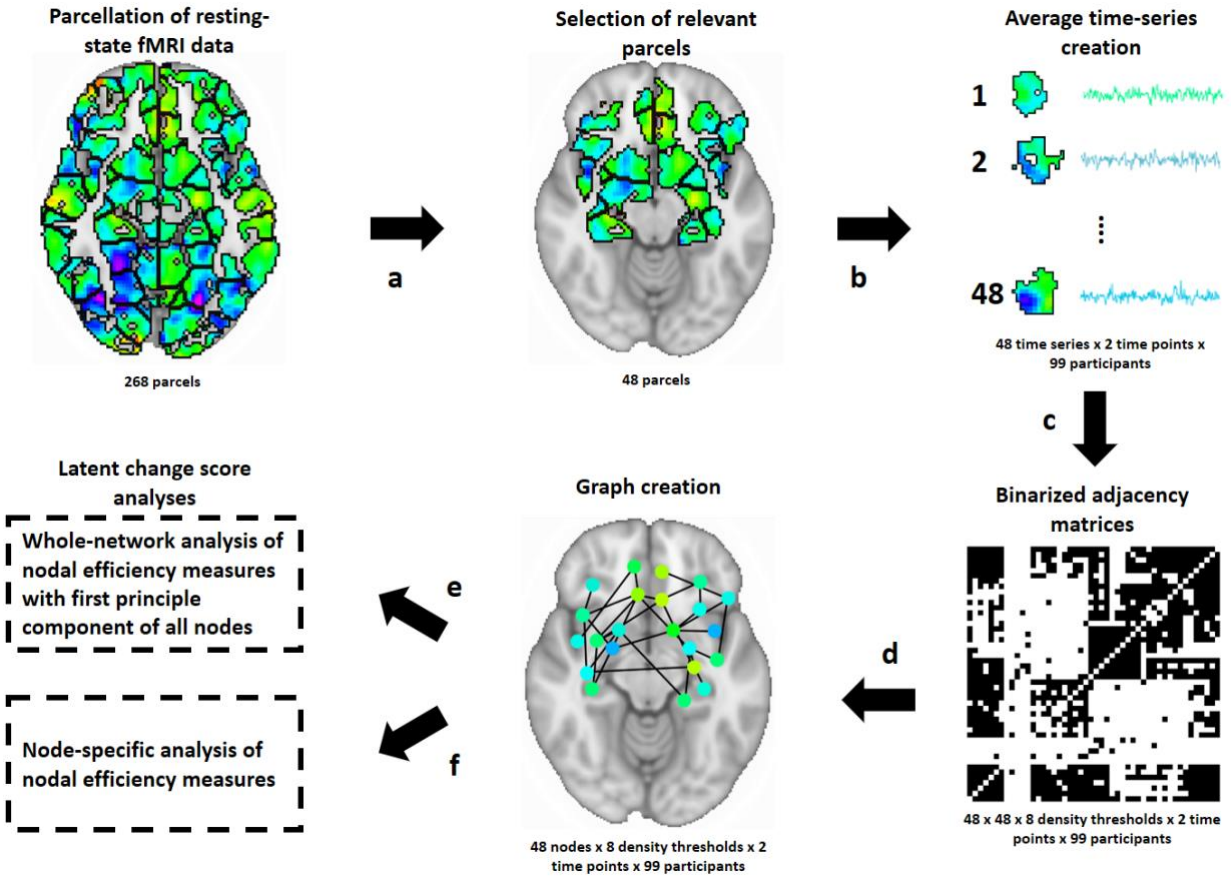
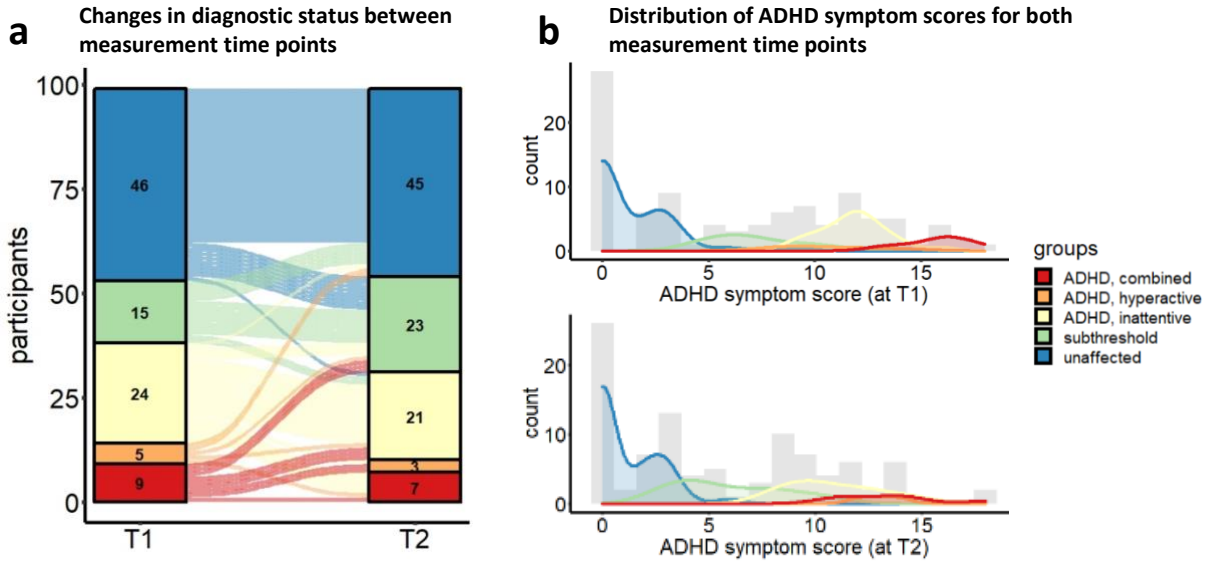
Supplementary Information for Chapter 4

Flow of functional graph analysis of resting-state fMRI data



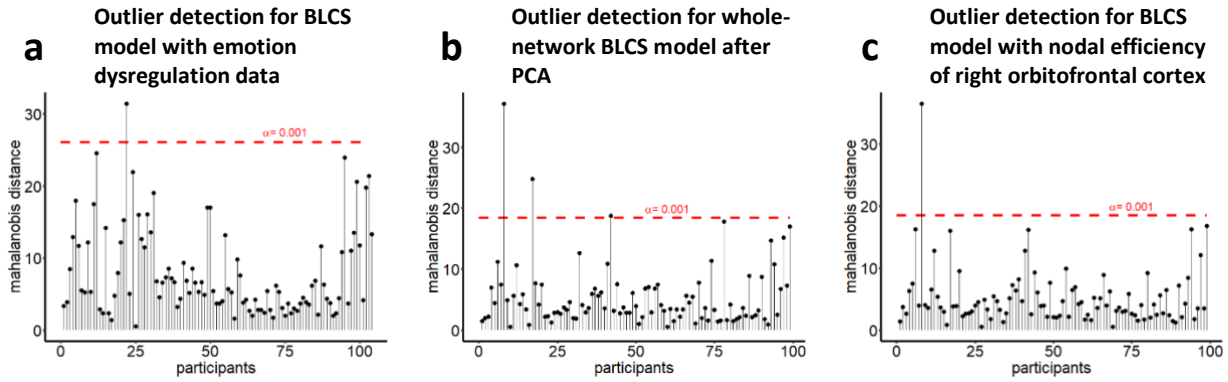
Supplementary Figure 4.1: *Flow of functional graph analysis of resting-state fMRI data. The processing scheme was applied to scans from both time points.* ***[a & b]*** *The analyses aimed to relate changes in ADHD severity with functional connectivity of brain nodes involved in emotion processing and associated dysregulations. The mean BOLD time series of 48 parcels were selected.* ***[c]*** *Individual Fisher's z-transformed correlation matrices were created and binarized using 8 density thresholds (.10, .15, .20, .25, .30, .35, .40, .45).* ***[d]*** *Graphs were created based on binarized matrices.* ***[e & f]*** *Subsequent statistical analysis was conducted based on nodal efficiency measures.* ***[e]*** *Within the whole-network analysis, we computed the first principal component analysis component of individual nodal efficiencies and entered them into latent change score models. As linear combination of the original individual nodal efficiencies it reflects a large part of the individual differences in nodal integration.* ***[f]*** *In the node-specific analysis we investigated each node of the 48 nodes separately.*

Information on changes in diagnostic status and associated ADHD symptom scores



Supplementary Figure 4.2: [a] *Changes in diagnostic status between measurement time points: Between the two measurement time points, case numbers decreased for all three ADHD presentations and the unaffected. The number of subthreshold or ambiguous cases increased.* ***[b]*** *Distribution of ADHD symptom scores for both measurement time points (T1 and T2): Histograms for the entire sample and density plots for diagnosis-specific subsamples are displayed. Graphs are split by data collection phase. For both collection phases continuous, not normal distributions are shown. While individuals classified as unaffected scored between zero and five, those with any type of ADHD diagnosis had an ADHD severity score of six or higher. Subthreshold or ambiguous cases that could not be classified as either unaffected or as having an ADHD diagnosis fell between the other groups.*

Mahalanobis' distance measures for outlier detection



Supplementary Figure S3: *Mahalanobis' distance measures for outlier detection. Calculations were based on the measured variables that were included in the BLCS model. The measures typically follow a χ2-distribution. The α-threshold for outlier detection was set to α = .001.*

Appendix

Sample characteristics split by diagnostic group

Table 4.1: *Sample characteristics for samples (N = 99 & N= 104) and both collection phases (T1 & T2) split by diagnostic group.*

Sample for bivariate latent change score model with emotion dysregulation data (N = 104)

	NeuroIMAGE I (T1)			**NeuroIMAGE II (T2)**		
Group	**unaffected**	**subthreshold/ambiguous**	**ADHD**	**unaffected**	**subthreshold/ambiguous**	**ADHD**
continuous variables						
	n = 53	*n = 8*	*n = 43*	*n = 53*	*n = 16*	*n = 35*
	M ± SD	*M ± SD*	*M ± SD*	*M ± SD*	*M ± SD*	*M ± SD*
ADHD symptom count	.7 ± 1.15	8.38 ± 2.77	12.56 ± 2.81	.85 ± 1.34	6.5 ± 2.71	12.17 ± 2.78
age (years)	17.23 ± 3.19	16.99 ± 2.19	15.58 ± 3.41	20.64 ± 3.2	20.67 ± 2.72	18.99 ± 3.63
IQ (WISC/WAIS)	109.23 ± 14.02	102.88 ± 17.13	100.02 ± 18.12	113.04 ± 14.42	101.31 ± 17.6	98.11 ± 19.41
CPRS-R:L emotional lability	44.25 ± 4.47	52.62 ± 15.6	53.86 ± 11.99	44.15 ± 2.86	44.69 ± 3.68	50.31 ± 9.12
SDQ emotional symptoms	1.68 ± 1.61	3 ± 2.33	3.26 ± 2.31	2 ± 1.72	1.81 ± 1.22	3.43 ± 2.51
SDQ conduct symptoms	.79 ± .86	1.75 ± 1.58	2.33 ± 1.54	.94 ± .95	1.38 ± 1.2	2.11 ± 1.47
categorical variables						
	size of subgroup	*size of subgroup*	*size of subgroup*	*size of subgroup*	*size of subgroup*	*size of subgroup*
sex (female)	27	4	23	28	7	19
ADHD-related impairments (yes)	2	6	43	6	6	33
stimulant user (yes)	1	3	29	1	3	22
DSM-IV ODD (K-SADS)	0	1	5	0	0	5
DSM-IV CD (K-SADS)	0	0	1	0	0	2

Sample for bivariate latent change score model with functional brain network data (N = 99)

	NeuroIMAGE I (T1)			**NeuroIMAGE II (T2)**		
Group	**unaffected**	**subthreshold/ambiguous**	**ADHD**	**unaffected**	**Subthreshold/ambiguous**	**ADHD**
continuous variables						
	n = 46	*n = 15*	*n = 38*	*n = 45*	*n = 23*	*n = 31*
	M ± SD	*M ± SD*	*M ± SD*	*M ± SD*	*M ± SD*	*M ± SD*
ADHD symptom count	1.26 ± 1.91	7.47± 2.56	12.61 ± 2.49	1.11 ± 1.5	5.96 ± 2.55	11.84 ± 2.61
age (years)	17.39 ± 3.24	17.7 ± 3.27	16.83 ± 3.4	21.42 ± 3.24	20.48 ± 2.9	20.67 ± 3.02
IQ (WISC/WAIS)	107.8 ± 14	98.4 ± 11.17	98.82 ± 15.32	111.13 ± 14.83	101.7 ± 17.75	99.94 ± 19.79
CPRS-R:L emotional lability *	45.21 ± 6.69	47.69 ± 9.95	55.29 ± 29	44.1 ± 2.84	44.88 ± 3.66	49.7 ± 6.87
SDQ emotional symptoms **	1.79 ± 1.61	2.44 ± 2.24	3.07 ± 2.37	1.9 ± 1.34	2.29 ± 1.53	3.39 ± 2.92
SDQ conduct symptoms **	.97 ± .85	1.67 ± 1.5	2 ± 1.47	1.2 ± 1.16	1.24 ± 1.2	2 ± 1.57
categorical variables						
	size of subgroup	*size of subgroup*	*size of subgroup*	*size of subgroup*	*size of subgroup*	*size of subgroup*
sex (female)	22	7	13	21	12	9
ADHD-related impairments (yes)	3	8	38	2	9	27
stimulant user (yes)	1	4	30	0	5	13
DSM-IV ODD (K-SADS)	1	1	10	0	1	3
DSM-IV CD (K-SADS)	0	0	2	0	0	1

CD = Conduct Disorder; **CPRS-R:L** = Conners' parent rating scale, revised, long version; **IQ** = Intelligence Quotient; **K-SADS** = Kiddie Schedule for Affective Disorders and Schizophrenia; ***M*** = mean; ***N*** = number of participants; **ODD** = Oppositional Defiant Disorder; **CD** = Conduct Disorder; **SD** = standard deviation; **SDQ** = Strengths and Difficulties Questionnaire.

* for the respective sample (N=99), data was available for 78 participants at T1 and 80 participants at T2

** for the respective sample (N=99), data was available for 59 participants at T1 and 80 participants at T2

Acknowledgment

The writing of a thesis such as this a lengthy process that involves a lot of work, organization, and patience. It is far from being the project of a single person and is thus not possible without the help others. As a doctoral student, one is dependent on the existence of certain organizational structures as well as the willingness of others to show commitment and enthusiasm. First of all, I would like to thank the Universities of Groningen and Oldenburg for establishing the Oldenburg-Groningen Joint Graduate Research Training Group, an environment in which not only young scientists can pursue their interests, but also intercultural and scientific exchange between Germany and the Netherlands is promoted. In this context Pieter J. Hoekstra and Alexandra Philipsen initiated the project of which I was allowed to be a part. Pieter was a great help to me during the whole time and especially helped me not to lose focus when working on clinical topics. Furthermore, special thanks go to Christiane Thiel. Christiane took over Alexandra's role after Alexandra left Oldenburg and was a tremendous help to me at all times. No matter with which matter I came to her, I always had the feeling that I could count on a helpful answer within no time. I also have to thank her especially for strengthening me in phases when I was struggling with the progress of the project and for helping me not to lose my motivation. In connection with my work in Oldenburg, my special thanks go to Carsten Gießling, with whom I worked extremely closely, especially in writing the articles reproduced here in Chapters 3 and 4. As I am particularly interested in applying different methods and expanding my methodological knowledge, it was a pleasure to work with Carsten, who was always looking for creative approaches to analyzing data and making the most of the available data. The project of my doctoral thesis would not have been possible without the cooperation with the Donders Institute in Nijmegen. As mentioned above, I have worked exclusively with data collected within the Donders Institute in the context of the NeuroIMAGE project. So naturally my thanks go to all those who are directly or indirectly connected with this project, but especially to Jan Buitelaar and Jilly Naaijen. Jan has not only been a major part of the organization of this project, but has also been a constant help to me and has been able to support me in the writing of my manuscripts with his profound clinical knowledge. In the contact with Nijmegen Jill was always my main contact person. No matter what issue I came to her with, she took excellent care of everything. Our work was especially close during the writing of the first article (Chapter 2) and at that stage, when I was still relatively new to the academic work environment, she was a great help. Finally, I would like to thank all those who are not mentioned here by name, be they co-authors, members of the different research groups or people in my private environment, who have supported me over the past three and a half years.

Author’s independence declaration

I declare that I have written this thesis entitled "Deviations in neural activity and network integration underpinning the co-occurrence of emotion dysregulation and attention- deficit/hyperactivity disorder: Analyses of fMRI task activations and functional brain network topology" myself and independently and that it has not been submitted for any other degree or professional qualification. I certify that the work submitted is my own work, unless the work was part of a jointly authored publication. My contribution and the contribution of the other authors are specifically identified in the respective chapters of this thesis (see Chapters 2 through 4). I acknowledge that reference has been made to the work of other authors in this thesis. All resources used haven been fully specified. Moreover, I declare that the regulations on good scientific practice of the Carl von Ossietzky University Oldenburg have been followed. No commercial consulting services have been used in connection with my doctoral thesis.

Tammo Viering

Oldenburg, 25th November 2021