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Default mode network resting-state functional connectivity and attention-deficit/disorder symptoms: perspectives from three different populations

by

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ABSTRACT

DEFAULT MODE NETWORK RESTING-STATE FUNCTIONAL CONNECTIVITY AND ATTENTION-DEFICIT/DISORDER SYMPTOMS: PERSPECTIVES FROM THREE DIFFERENT POPULATIONS.

M. John Broulidakis

Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric disorder characterised by persistent and age-inappropriate levels of inattention, hyperactivity and impulsivity. The condition is debilitating, disrupting academic and social development. In Chapters 1-4 we discuss a paradigm shift in psychopathology that has driven interest in the role of the default mode network (DMN) in ADHD and conduct disorder (CD) – a condition characterised by aggressive and rule-breaking

behaviour which frequently co-occurs with ADHD. We conclude that relatively little empirical research has investigated how alterations to the functional integrity of the DMN affect cognition.

In Chapter 5, we provide novel evidence that CD may affect the functional architecture of the DMN. Relative to age- and sex-matched healthy controls (n=29), we find adolescents with CD (n=29) show DMN core subsystem hypo-connectivity, although only after adjusting for co-occurring ADHD symptoms. In contrast, ADHD symptoms were independently associated with DMN hyper-connectivity.

In Chapter 6, we explore for the first time how DMN resting-state functional connectivity may be affected by a rare deprivation-related variant of ADHD. We studied adoptees who experienced extended, but time-limited, exposure to institutional deprivation in early childhood (n=46) compared with adoptees with <6 months exposure (n=21) and non-deprived UK adoptees (n=21) as a control group. Prolonged deprivation was associated with DMN core subsystem hyper-connectivity. There was also a deprivation-by-ADHD interaction, suggesting that deprivation moderates whether ADHD is associated with DMN hyper- or hypo-connectivity.

In Chapter 7, we explore how resting-state DMN functional connectivity may contribute to the neuropsychological profile associated with ADHD. In a clinical sample of children with ADHD (n=20) and age- and sex-matched controls (n=22) we find DMN hypo-connectivity was correlated with suboptimal inter-temporal decision making and exaggerated delay aversion, with the latter domain partially mediating the relationship between ADHD and the connectivity patterns observed.

This thesis provides robust evidence for effects of ADHD on the functional integrity of the DMN across three different samples, with the direction of connectivity changes (whether ADHD is associated with hypo- or hyper-connectivity) related to

the putative causes of ADHD. DMN hypo-connectivity may contribute to suboptimal decision-making in non-deprivation related ADHD.

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DECLARATION OF AUTHORSHIP

I, John Broulidakis, declare that this thesis and the work presented in it are my own and have been generated by me as the result of my own original research.

[**Default mode network resting-state functional connectivity and attention-deficit/disorder symptoms: perspectives from three different populations.]**

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;

2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

3. Where I have consulted the published work of others, this is always clearly attributed;

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Abbreviations

ADHD = attention deficit/hyperactivity disorder

ASD = autistic spectrum disorder

ALFF = amplitude of low frequency fluctuations

BOLD = blood oxygen level dependent

CD = conduct disorder

Conners CBRS = Conner's comprehensive behaviour rating scale

DAN = dorsal attention network

DM = default mode

DMN = default mode network

DSE = disinhibited social engagement

EEG = electroencephalography

ERA = English Romanian adoptees

ERABIS = English Romanian adoptees brain imaging study

fMRI = functional magnetic resonance imaging

FPCN = frontal parietal control network

GAD = generalised anxiety disorder

ICA = independent components analysis

IQ = intelligence quotient.

K-SADS-PL = schedule for affective disorders and schizophrenia for school-age children-present and lifetime version

LoDep = adoptees who spent less than six months or no time in deprivation

MDD = major depressive disorder

MWQ = mind wandering questionnaire

MRI = magnetic resonance imaging.

OCD = obsessive compulsive disorder

PET = positron emission tomography

PESQ = personal experience screening questionnaire

QDQ = quick delay questionnaire

Rom<6 = Romanian adoptees who spent less than six months in deprivation

Rom>6 = Romanian adoptees who spent six months or more in deprivation

SCQ = social communication questionnaire

SES = socioeconomic status

SUD = substance use disorder

YPI = youth psychopathic traits Inventory

0.1.1 Introduction

Functional magnetic resonance imaging (fMRI) is one of the few non-invasive neuroimaging techniques that can be used to measured brain activation patterns in vivo without requiring exposure to ionizing radiation. Given the ethical concerns inherent in testing children and other vulnerable populations, combined with its relatively widespread availability, fMRI has become the method of choice in studies involving children or patient groups. By virtue of its ability to provide a window into the developing brain, fMRI has been able to identify many of the neurobiological hallmarks of psychopathology (Casey, Galvan, & Hare, 2005). The overwhelming majority of fMRI studies that have investigated abnormalities in brain activity in different forms of psychopathology have been task-based; that is to say, they require patients to perform some sort of cognitive, motor or memory task thought to elicit the cognitive process of interest in the fMRI scanner. This technique involves extracting blood oxygen level dependent (BOLD) signal responses using statistical comparisons between time series, task timings and a baseline comparison condition. The averaged BOLD signal response across all patients is compared with a control group and any differences between the two groups are thought to indicate excessive or reduced activation in that particular brain region. For example, compared with controls, patients with generalized anxiety disorder show increased activity in the amygdala when viewing images that evoke feelings of fear (Shin & Liberzon, 2010). In this example, the amygdala hypersensitivity is thought to reflect increased fear responses.

However, every technique has its strengths and limitations. Analysing task-specific activation patterns can localize relatively small signal changes in task-related brain regions. These results almost always frame information processing in the brain

as proceeding on a modular basis. In other words, brain areas are postulated to act as independent processors for specific cognitive functions (e.g. face processing). Accumulating evidence has suggested that this conceptualization of information processing in the brain has serious limitations and may in fact be misleading (Fuster, 2000). Contemporary neuroscience has thus shifted away from the simplistic mapping of cognitive operations onto individual brain regions and emphasizes instead the coordinated function of brain areas working together as networks. Therefore, the first aim of this literature review will be to suggest that a focus on task-related activations may also obscure other important features of psychopathology. To this end, the review will begin by describing how task-specific activations do not fully capture the functional organisation of the brain as a complex, integrative, hierarchically organised network. This is especially true of brain areas that are *less* active during experimental conditions compared with control conditions (task-related deactivations) or non-specific neural changes linked to general engagement during task performance. This limitation was well illustrated by Raichle et al. (2001) in a meta-analysis that localized a common set of brain regions that typically show task-related deactivation. Based on the logic that in order for brain regions to show deactivation during a task, they must be active in some other non-task state, Raichle and colleagues made the insightful leap towards predicting a baseline brain state that is activated during a passive control condition, but which is attenuated when performing a task. This baseline state was termed the 'default mode' (DM) and the regions that comprise it were termed the 'default mode network' (DMN). Although initially predicted to be a passive brain network, later studies would show that increased DMN activity both during task-related and non-task related brain states contributes to several active forms of internally-directed cognition characterised by their independence from

external stimuli (so called ‘self-generated thoughts’). This review will explore the functional neuroanatomy of the DMN as a complex multi-component system thought to comprise multiple subsystems. It will then move on to discuss the role of the DMN in producing self-generated thought, investigating how abnormalities in regulating both the content of self-generated thought and the context in which such thoughts are generated may represent an important feature of many disorders.

The second aim of this literature review will be to introduce the cognitive and neurobiological profiles of two related and often overlapping neurodevelopmental disorders: conduct disorder (CD) and attention-deficit/hyperactivity disorder (ADHD). Conduct disorder is defined in terms of a persistent pattern of antisocial behaviour in which the rights of others or social norms are violated, with the diagnostic criteria encompassing aggression towards humans and animals, destruction of property, theft and the serious violation of rules (American Psychiatric Association, 2013). ADHD is a condition characterised in terms of persistently elevated, age-inappropriate levels of inattention, hyperactivity and impulsivity (American Psychiatric Association, 2013). Both conditions fall under the broad behavioural classification of disruptive behaviour disorders, an umbrella term for conditions characterised by a failure to regulate behaviour according to societal norms (American Psychiatric Association, 2013). Frameworks for understanding ADHD and CD conceptualise each disorder in terms of specific neural and cognitive impairments from which diagnostic and associated symptoms arise (Faraone et al., 2015; Noordermeer, Luman, & Oosterlaan, 2016). In ADHD these include an executive functioning network hypothesised to drive deficits in temporal processing, inhibitory control and a dysregulation of both cognition and the self-regulatory processes necessary to meet task demands (Barkley, 1997; Sagvolden, Johansen, Aase, &

Russell, 2005) and a reward network thought to lead to alterations in reward signalling and also to contribute to a developmentally acquired secondary motivation to escape or avoid delay (delay aversion) (Sonuga-Barke, 2002, 2003, 2004). In CD, dysregulation of a fronto-limbic network is thought to contribute to deficits in motivation and affect (Rubia, 2011). Within this network, closely interacting fronto-amygdala and fronto-insula circuits are hypothesised to contribute to reduced empathy and impaired decision-making in CD, particularly in those who are also high in callous-unemotional traits (Blair, 2013). This review will discuss functional imaging studies that provide robust evidence supporting abnormalities in these circuits in ADHD and CD. However, this review will also highlight an increasing number of divergent findings which suggest that impairments specifically in one or more of these circuits are unlikely to be the whole picture in both CD and ADHD.

Therefore, the third aim of this literature review will be to present evidence that the DMN may represent an important additional neurobiological system that may mediate many of the associated and diagnostic symptoms of both conditions. This review will provide a detailed account of DMN abnormalities in ADHD, suggesting a specific pattern of functioning that may be unique to the condition. It will argue that this may reflect a difficulty in regulating the content and the occurrence of self-generated thought (Sonuga-Barke & Castellanos, 2007; Sonuga-Barke, Cortese, Fairchild, & Stringaris, 2016). This impairment may manifest both as increased distractibility as attention shifts to task-irrelevant self-generated thoughts (so-called ‘mind-wandering’) and a difficulty in being able to use previous experiences to guide future decision-making. We will also argue that there is a similar impairment in accessing mental representations of previous experiences and relationships in CD, which in this case could contribute to the characteristic deficits in empathy as well as

decision-making. Finally, this literature review will conclude by considering how incorporating the DMN concept may influence how these disorders are conceptualised and will outline three studies to further this research agenda.

Chapter I. Moving towards a default mode of brain functioning

1.1.1 A paradigm shift in our understanding of psychopathology

Most, if not all, psychiatric disorders have a biological basis that can be detected in the brain. The advent of magnetic resonance imaging (MRI) provided a window that, for the first time, allowed these abnormalities to be observed and documented non-invasively with a high degree of sensitivity compared with other non-invasive methodologies (Horga, Kaur, & Peterson, 2014). Early MRI studies of psychopathology sought to localize abnormalities to specific brain areas using one of two approaches. The first approach used structural MRI methods such as voxel-based morphometry, surface-based morphometry or manual tracing to identify structural abnormalities in clinical groups, using metrics such as total brain or grey matter volume. This operated under the assumption that there is a direct relationship between brain structure and brain functioning. Dysfunction was usually inferred, either when an abnormality overlapped a brain area involved in the psychological process of interest, or, the other way around, when an associated feature of the disorder correlated with the abnormality. The second approach was to identify functional abnormalities directly. This was done by measuring task-elicited BOLD signals using an experimental manipulation thought to tap the psychological process of interest such as asking participants to view emotional or neutral images (tapping emotion processing) or recall autobiographical or semantic information (assessing memory retrieval). Using fMRI the localisation of dysfunction was inferred on the basis of increased BOLD signal in a task state relative to a baseline comparison condition (typically a condition that resembles the task in all elements except the cognitive process under investigation). This operated under the assumption that task-elicited activations capture task-related cognition in its entirety.

Over the last decade, it has however become increasingly apparent that the original goal of using structural and functional imaging methodologies in this way to directly map dysfunctional cognitive and psychological processes associated with different psychiatric disorders to one or more areas of the brain may not be possible. In hindsight, this should not be surprising, for three reasons. First, most disorders encompass multiple heterogeneous behavioural phenotypic features. These disorders cannot be simply reduced or ascribed to the operations of a single brain region without missing the complex and frequently interdependent nature of brain functioning (Fuster, 2000). For example, a difficulty in sustaining attention may reflect dysfunctional perception, dysfunctional working memory or a difficulty in inhibiting distracting thoughts or poor motivation. Impairment in any one or more of these processes will have a downstream effect on attention systems as well as on other information processing operations also reliant on these processes.

Second, it drives a focus on task specific "brain-states" whilst providing no information about how that state was reached or how it is maintained. In part, this is because a focus on task-specific activation cannot account for *deactivations* that can be task-specific (e.g. decreases within particular elements of a sensory system not directly involved in the processing of a stimulus) or largely independent of task content (Raichle & Mintun, 2006). This means that important but task-independent functions are either ignored or missed entirely, contributing to a poor or incomplete characterisation of the most basic features of dysfunctional brain systems. For example, regardless of the task being performed, inhibiting distracting thoughts is associated with non-specific deactivation (Schooler et al., 2011). A focus on task-elicited activations during a selective attention task would provide an indication of the brain state involved in attention but would not provide very much information about how inhibiting distracting thoughts may contribute to this brain state.

Third and finally, there is little actual evidence of a consistent overlap between structural and functional changes in the brains of patients with psychiatric disorders. Lesion studies have shown that functional deficits cannot necessarily be predicted on the basis of focal damage alone (Crofts et al., 2011). There is a steadily-growing literature demonstrating that divergent cognitive functions may be supported by common neural substrates (Hein & Knight, 2008). Even the functions of the primary sensory areas of the cerebral cortex, once thought to provide clear evidence of functional modularity, have been re-evaluated given evidence of cross-modal interactions (Ghazanfar & Schroeder, 2006).

In any case, it is clear that an absolute/categorical function cannot be assigned to a brain region, nor can a task-elicited activation patterns capture task-related cognition in its entirety. Given these limitations, there has been an important paradigm shift in how the neurobiological basis of psychopathology is understood. This paradigm shift is made up of two elements. The first is a shift from a modular paradigm (i.e., one that directly maps cognitive constructs onto specific brain areas) to a more distributed approach that instead emphases the conjoint function of brain regions acting together in a network. By this account, the brain is considered a single network, hierarchically organised into non-overlapping sub-networks that themselves comprise of multiple additional sub-networks (see Figure 1.1). The second element of this paradigm shift is a recognition that there are important non-task related functions of the brain, and that psychiatric disorders may be partly due to problems in such functions. This follows a more general interest in how factors related to task performance, such as participant motivation or task difficulty, may contribute to psychopathological brain states (Sonuga-Barke & Castellanos, 2007). Below we discuss each element of this paradigm shift separately, focusing first on the conceptual issues in understanding psychopathology in terms of network functioning and then considering how a focus on task-elicited brain states may miss several important features of psychopathology.

We finish by suggesting how these two elements have come together with the discovery of the DMN.

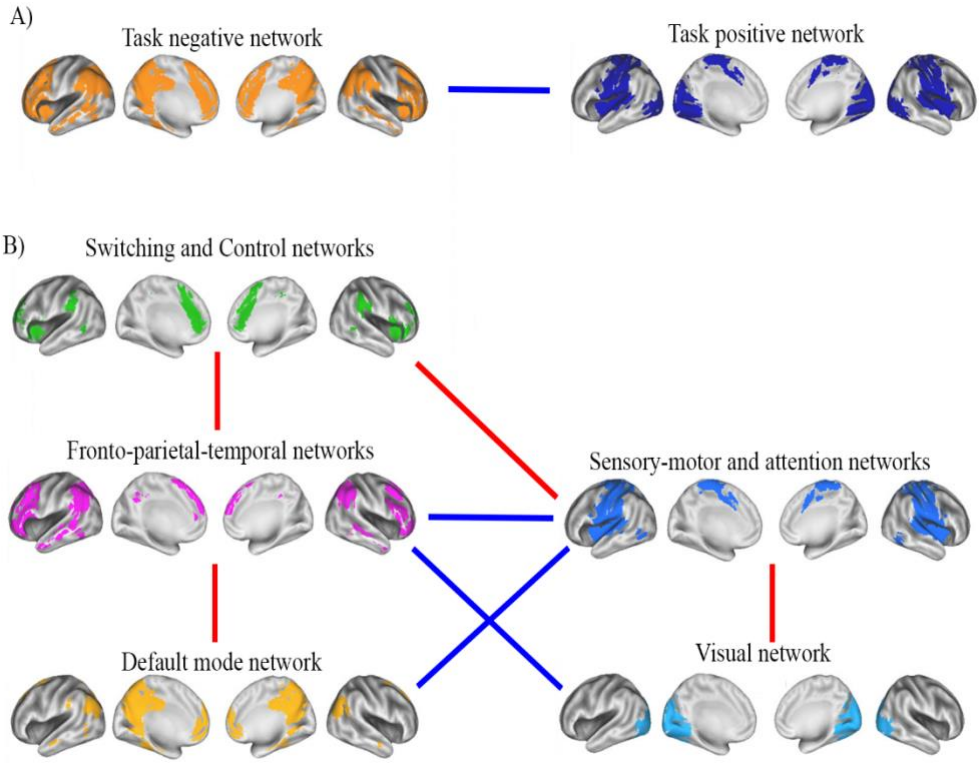

Figure 1.1. The dynamic organisation of the brain under typical resting state conditions. The spatial maps depict functional brain networks. Lines indicate statistically significant functional connectivity linking brain networks together, with red lines depicting positive correlations between brain networks and blue lines indicating anti-correlations between brain networks. A) The whole brain network split into just two components: a task negative network that is anti-correlated with a task positive network. B) The task positive network split into three components and the task negative network split into two components. The task negative circuit is made up of a default mode network, involved in the production of spontaneous thought, a fronto-parietal-temporal network involved in the manipulation/maintenance of information and a switching and control network. The default mode network and fronto-parietal-temporal networks are anti-correlated with two components of the task positive network: the sensory-motor and attention networks and the visual network. Switching and control networks are dynamically interposed between these four networks to mediate coupling (adapted from Doucet et al., 2011).

1.2.1 Element 1: A shift from a modular approach to a network approach

The first element of this paradigm shift involves moving from a modular to a network approach. A brain network is characterised as a series of brain areas (nodes) and the connections that link them together (edges) (Wig, Schlaggar, & Petersen, 2011). Generally speaking, a network can be defined either on the basis of its supposed function (a functional network) or on the basis of differences in neural architecture (a structural network). Structural networks provide a complex neuroanatomical skeleton that promotes the dynamic interactions between nodes that promote functional networks. Adopting a network paradigm conceptualises psychopathology in terms of damage or disruption to either functional or structural network nodes or edges. A node is a part of a network that performs some kind of information processing operation, and an edge is the connection that enables two nodes to communicate with each other. The implicit assumption in research into psychopathology is that abnormalities within network nodes and edges lead to dysfunctional signalling that propagates within or between networks, depending on the connectivity patterns of the impacted node (Menon, 2011).

1.2.2 Aberrant network nodes

Following a network paradigm, the function of a node is determined not only by its intrinsic properties but also by its extrinsic connections (Passingham, Stephan, & Kötter, 2002). Each node has its own unique fingerprint that distinguishes its connectivity patterns from that of other nodes. Understanding network level deficits arising from one or more nodes therefore requires analysis of how both the intrinsic and extrinsic connectivity patterns of those nodes differ from those of other networks (Bressler & Menon, 2010). This becomes complicated by the hierarchical nature of neural networks (see Figure 1.1). The node of a large-scale brain network can be split into smaller nodes, these nodes in turn encompass even

smaller nodes and so on and so forth until we reach the level of individual neurons. Each of these nodes, from the neuron to the multi-component system, exhibit its own distinct pattern of connectivity which largely determines its function. For structural MRI data, this means that at a minimum, for inferences to be made about the functional consequences of a structural abnormality, it requires knowledge of how brain areas are linked to know which interactions are possible. For example, knowing that a node has many short range connections and fewer long range connections can help inform the expected functional interactions. Unlike structural MRI data, task-elicited BOLD signal changes *can* be interpreted as occurring within task-relevant circuits, and so can permit inferences about the function of a node. Whilst this can provide information about task-specific impairment, it cannot easily identify which network is actually impaired in a given disorder without pooling data from a large number of tasks and looking for consistent patterns of activation/deactivation (Wig et al., 2011). In many cases, this limitation effectively restricts analysis to a specific set of task-related systems due to both the *a priori* prediction that the system is impaired in the disorder and the large number of (often extremely expensive and time-intensive) fMRI studies that are required to fully delineate a brain network.

1.2.3 Aberrant network edges

Dysfunctional network edges reflect either reduced integrity of axonal fibre (white matter) pathways in structural networks or abnormal correlations among measurements of neuronal activity in functional networks. Whilst task-elicited functional connectivity has aided our understanding of task-dependent systems in psychopathology, it also falls into many of the same pitfalls of a task-based approach by ignoring circuits involved in important but task-independent functions. Further, because it is limited to task related systems, it cannot show how that circuit fits within the functional hierarchy of the brain, even after identifying a

task-specific circuit. This is problematic because it makes it hard to understand how dysfunction in one circuit may propagate to others. Unlike task-elicited functional connectivity, structural connectivity has the advantage of not being restricted to task-specific systems. However, structural connectivity does not always predict functional connectivity (Wig et al., 2011). This is particularly the case with long-range interhemispheric connections (Hermundstad et al., 2013), or in children/adolescents before the brain has fully myelinated (Power, Fair, Schlaggar, & Petersen, 2010; Supekar et al., 2010). An understanding of network function/dysfunction can therefore not necessarily follow from knowledge of the short range and long range structural connections that link brain areas together.

1.2.4 Intrinsic brain activity

Many of the limitations of relying on a task-based design have been overcome with the discovery of intrinsic brain activity. Intrinsic brain activity describes a component of the BOLD signal most prevalent at low frequency oscillations (~.008-.09Hz) that appears to reflect fluctuating neuronal activity (Raichle & Mintun, 2006). Currently the only way of measuring this intrinsic activity is to measure the temporal dependency between signals, which is termed 'resting-state functional connectivity'. These signals appear to self-organise into coherent functional networks (Beckmann, DeLuca, Devlin, & Smith, 2005; Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995). These 'resting-state networks' closely mirror networks that are also active during specific cognitive operations, as well as closely overlapping with known structural networks (Greicius, Supekar, Menon, & Dougherty, 2009; Van den Heuvel & Hulshoff Pol, 2010). This means that measuring these signals provides an alternative method to measuring functional brain networks. This enables researchers to directly measure brain function/dysfunction without relying on experimental manipulations,

potentially offering a more comprehensive method of measuring the functional architecture of the brain.

Using resting-state connectivity, deficits in psychopathological populations can be inferred in two ways. The first is to use a task that does not measure the BOLD response in terms of mean signal change (e.g., Fransson (2006); H. Zhang, Gao, and Zang (2015)). Although rarely performed, this approach overcomes the requirement of an epoch-related fMRI paradigm design to shift rapidly between a task condition and a baseline comparison condition, a task-independent feature of fMRI designs that has unknown effect on psychopathological systems. The second and more common method is to measure connectivity 'independent of a task' to look for abnormalities in the brain's intrinsic functional architecture. One limitation of this approach is that resting-state connectivity is highly sensitive to even minor variations in task demands (Yan et al., 2009), and for all intents and purposes, *any* mental activity is a task in its own right. Therefore, individual differences in the mental state the participant is in during the resting-state scan may indirectly affect the intrinsic connectivity patterns that are observed (Morcom & Fletcher, 2007). Furthermore, because intrinsic connectivity is model free, studies tend to be exploratory, adopting hypothesis-free approaches. Combined with a proliferation in analytical approaches that examine the brains resting-state, this has led to difficulties in ensuring reliability and reproducibility of the findings produced, muddying the waters about how psychopathology may affect the functional architecture of the brain.

1.3.1 Element 2: A shift from task-elicited cognition to spontaneous cognition

The second element of this paradigm shift differentiates between task-related cognition (i.e., cognition related to a current (external) task) and spontaneous cognition (i.e., cognition unrelated to the current demands of the external environment) (see Table 1.1).

During task-related processing, attention is usually directed at a goal, then acted upon by increasing activity in sensory areas relevant to responding to that goal. In contrast, spontaneous cognition occurs when attention becomes disengaged from the external world, a process referred to as *perceptual decoupling* (Smallwood, Beach, Schooler, & Handy, 2007; Smallwood, Obonsawin, & Heim, 2003). It represents a sort of "default" state that is continuously, automatically and unintentionally generated and is returned too when one is not engaged in an attention-demanding activity (Vallacher & Wegner, 1987). By focusing solely on task-related interactions, one would fail to characterise how this default state contributes to cognition. In particular: 1) how task-independent spontaneous cognition may be beneficial by contributing to task-related processing and mood regulation and 2) how a failure to regulate spontaneous cognition may disrupt task-related processing.

Table 1.1. The phenomenology and nomenclature of spontaneous thought and related phenomena (adapted from Marchetti, Koster, Klinger, and Alloy (2016))

Phenomenon	Definition	When may it occur
Spontaneous thought	"*Overarching type of self-generated thought, including mind-wandering and daydreaming*". Marchetti et al. (2016), p. 4.	Occurs during either task-performance or resting states.
Daydreaming	"*Stimulus-independent thought that does not occur during a primary task*" Mrazek, Phillips, Franklin, Broadway, and Schooler (2013), p. 2.	Occurs during resting state experimental assessment. It does not occur during goal-directed task-pursuit (Smallwood & Schooler, 2006).
Mind-wandering	"*off-task thoughts during an ongoing task or activity*" Smallwood and Schooler (2006), p. 946	Occurs during task-engagement. (Smallwood & Schooler, 2006).
Self-generated thought	Process whereby the "*contents of experience arise from intrinsic changes that occur within an individual rather than extrinsic changes that are cued directly from perceptual events occurring in the external environment*" (Smallwood & Schooler, 2015, p.490).	Occurs during both resting state and internally oriented, reflective tasks (e.g., episodic memory) (Andrews-Hanna et al. (2014))

1.3.2 Spontaneous cognition as an adaptive mental process

It is estimated that as much as 50% of waking thought is spent engaged in spontaneous thought (Killingsworth & Gilbert, 2010). Perhaps it is not surprising that such an extended period of time spent engaged in internal thought will have important consequences for cognition. Closer examination into the nature of spontaneous thoughts suggest that they are both complex and heterogeneous phenomena. The phenomenology of spontaneous thought is experienced as self-generated thought that can be characterised according to three interacting dimensions (Smallwood & Schooler, 2015). These concern either: 1) the temporal focus of the thought (whether it is focused on the past/present/future), 2) how the thought relates to the affective state of the individual (negative/positive emotional valence) and, 3) the personal significance that is attached to the thought (how it relates to the self/others).

The content of spontaneous thoughts suggests that they serve an adaptive function. If so, this may explain why such a prolonged period of time is spent engaged in what appears to be a passive mental state. There are two ways in which spontaneous thought may be adaptive. The first is that spontaneous thought may provide a medium in which past experiences can be reflected upon in a meta-cognitive manner, allowing future scenarios to be planned and the subjective utility of choice alternatives appraised (McMillan, Kaufman, & Singer, 2013; Sonuga-Barke & Fairchild, 2012). The ability to build a mental representation of future events is called *prospection*. On average, adults rate their thoughts as self-focused, goal-oriented and having a prospective bias (i.e., a tendency to concern future events) (Baird, Smallwood, & Schooler, 2011). It was on this basis that Baird et al. (2011) suggested that spontaneous thought is adaptive because it serves to advance personally relevant goals. Consistent with this interpretation, high levels of spontaneous thought prior to starting a task augment performance on activities that require prospection and future goal setting to minimize suboptimal responses. For example, Baird et al. (2012) found that spontaneous thought during simple activities (i.e., mind-wandering; see Table 1.1) can promote creative incubation and problem solving. In another study, Smallwood, Ruby, and Singer (2013) found mind-wandering contributed to the successful management of long-term goals.

The second way in which spontaneous thought may be adaptive is that it contributes to affect regulation (McMillan et al., 2013). Spontaneous thought and emotionality have been shown to influence each other in a reciprocal and often complex way. Experimental manipulations that artificially increase negative mood also increase levels of spontaneous thought. Experience sampling has also shown the frequency of off-task thought correlates with future levels of unhappiness (Killingsworth & Gilbert, 2010). However, negative mood appears to be a precursor rather than a consequence of spontaneous thought (Poerio, Totterdell, & Miles, 2013; Smallwood & O'Connor, 2011). For example, Ruby,

Smallwood, Engen, and Singer (2013) found that mood tended to improve immediately after engaging in prospective thoughts, whereas retrospective thoughts (i.e., thoughts pertaining to events in the past) tended to have a detrimental effect on mood, possibly reflecting a tendency to dwell on self-critical information. Smallwood et al. (2011) argue that the relationship between spontaneous thought and psychological wellbeing depends on an ability to regulate the content of these mental experiences to maximize thoughts with positive outcomes and minimize those with negative outcomes.

1.3.3 Spontaneous cognition disrupts task-related cognition

While spontaneous thought can play a positive role in decision-making and affect regulation, there is also a potential downside. A notable feature of spontaneous thought is that engaging in it whilst also engaging a task that demands executive resources will inevitably impair performance of that task (Mooneyham & Schooler, 2013). When spontaneous cognition occurs in this way, it is referred to as mind-wandering (see Table 1.1). There are substantial individual differences in mind-wandering which are also influenced by task-dependent or task-independent factors. These include task difficulty, participant motivation, the cognitive resources available whilst performing the task and how the goal of completing the task fits within a wider hierarchy of personally relevant goals (Klinger, 2009; Unsworth & McMillan, 2013). There are two interpretations why these thoughts may be disruptive, either because they compete with the ongoing task for limited cognitive resources (Smallwood & Schooler, 2006) or because they shift the focus of attention away from the concrete goal of completing the task towards a more abstract, task-irrelevant but personally relevant goal (Klinger, 2009). To suppress mind-wandering, perceptual decoupling must prevented either proactively before it occurs (a deliberate effort to concentrate) or reactively

when it occurs (haltered when it has occurred) (Smallwood, Brown, Baird, & Schooler, 2012). Viewed in this way, mind-wandering represents a failure of executive control.

1.4.1 Summary

In summary, in the last two decades there has been a subtle but important shift in the way the neural basis of psychopathology is understood. The first element of this paradigm shift is the recognition that psychopathology is caused by impairment to one or more neural networks, and an understanding that a conventional task-based approach is not always well-suited to investigate functional impairment at a network level. The second element of this paradigm shift is the recognition that a task-based fMRI design may also fail to capture how spontaneous thought affects brain functioning. The two elements of this paradigm shift have come together with the discovery of a neural correlate of spontaneous thought that produces the self-generative aspects of spontaneous cognition (Andrews-Hanna, Smallwood, & Spreng, 2014). In the next chapter we discuss how many of the features of spontaneous thought map on to the information processing operations of the DMN. We also discuss how a DMN disturbance may represent an important correlate of psychopathological brain states.

Chapter II. The Default Mode Network (DMN) and Psychopathological Mental States

Perhaps one of the most intriguing findings in the last two decades within the field of human functional imaging has been the observation that there exists a common set of brain regions that are more active when the individual is instructed to lay still and think of nothing in particular (*rest* – the typical conditions of a 'resting state' scan), compared to when they perform a goal-directed task. This set of brain areas is termed the DMN and could be interpreted as the neural correlate of the 'default' state that was described in chapter I. Early studies of the DMN conceptualised it as both a passive brain network that has no direct contribution to information processing and as a homogeneous network (Buckner, 2012; Raichle et al., 2001). Over the last 10 years it has become apparent that both views are likely incorrect. The DMN has been shown to be a heterogeneous system that comprises multiple interacting subsystems supporting multiple component processes. These processes contribute to all aspects of cognition that require inwardly-directed attention – i.e. self-generated thought. This gives the DMN an important role in producing spontaneous thought.

2.1.1 Nodes of the DMN

Key nodes of the DMN have been identified using two approaches. At least initially, the most common approach was to pool task-elicited activation patterns during passive control states (participant lays at rest in the scanner) compared with active tasks (participant performs a task in the scanner) (Jeffrey R Binder et al., 1999;

Raichle et al., 2001; Shulman et al., 1997). This was based on the initial, erroneous assumption that the DMN is a passive brain network that does not contribute to goal directed cognition. More recent approaches involve defining DMN nodes using resting state connectivity. This approach involves testing for commonalities in the BOLD signal, with the logic that temporally correlated brain activity should cluster into coherent brain networks. This can be done using three broad ways of exploring resting-state signals. The first is to use a seed-based approach. This involves correlating low frequency resting-state signal within a pre-specified region of interest or "seed" with the averaged time series within either a) other voxels within the brain (seed-to-voxel) or b) with another seed (seed-to-seed) (e.g., Biswal et al. (1995); M. D. Fox et al. (2005)). The second is to use a data driven approach such as a) independent components analysis or b) clustering. Both approaches are broadly analogous and involve categorizing BOLD signal time series throughout the brain according to their unique spatial temporal correlations into either a) spatial maps and their associated time series in the case of independent components analysis (e.g., Beckmann et al. (2005)) or b) into temporally synchronized 'clusters' in the case of clustering. The third approach is to measure the amplitude of low frequency fluctuations (ALFF). This involves extracting the power of low frequency (<0.01Hz) oscillations in the BOLD signal time-courses. Out of all these approaches, ALFF is the most similar to the more conventional task-based fMRI measures of mean signal change (Gui et al., 2015; Zou et al., 2013; Zou, Wu, Stein, Zang, & Yang, 2009). However, as ALFF does not measure temporal correlations between BOLD time-series it cannot be said to be a true measure of functional connectivity at all. Notably, all approaches produce a strikingly consistent map of the DMN (see Figure 2.1). As such nodes that comprise the DMN have been consistently replicated. These have

shown the DMN to include the medial prefrontal cortex, posterior cingulate cortex, retrosplenial cortex, and medial temporal lobe, as well as the hippocampal formation and parahippocampal cortex, the lateral parietal cortex, spanning the angular gyrus and temporal parietal junction, and the lateral temporal cortex extending to the temporal pole.

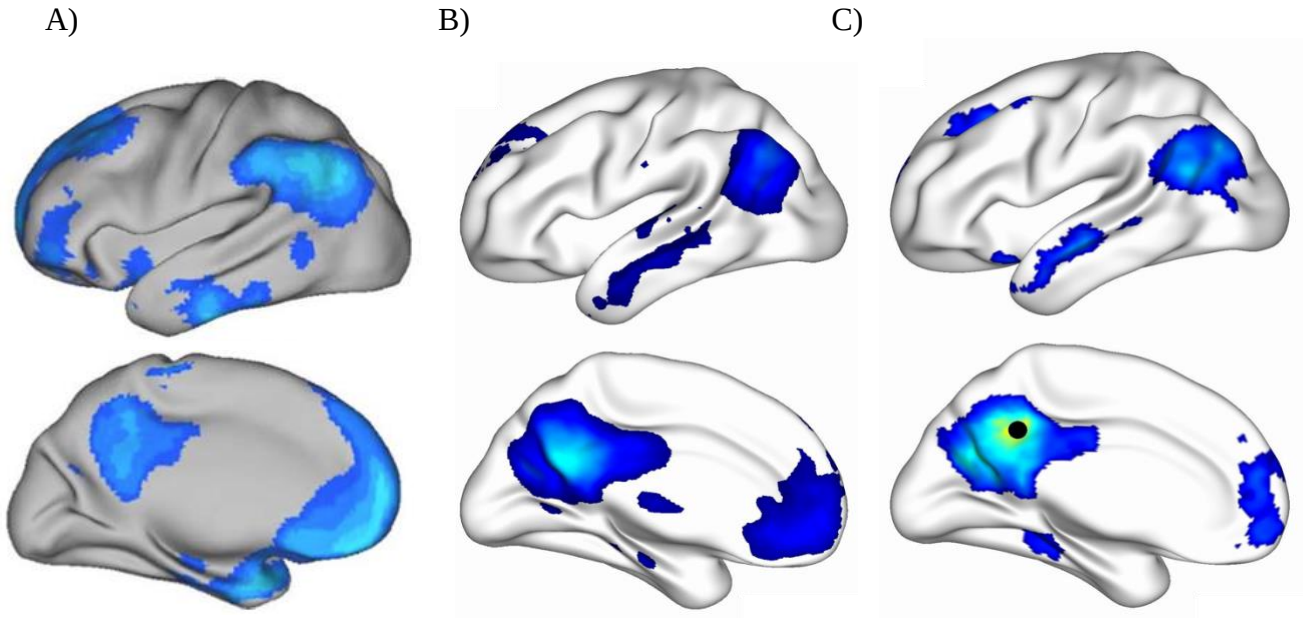

Figure 2.1. The brain's default mode network (DMN) as identified using three different neuroimaging approaches. A) Data from a meta-analysis of nine positron emission tomography studies (132 participants) reported in Shulman et al. (1998) (adapted from Buckner et al., 2008). B) The DMN component from a reanalysis of multiple functional magnetic resonance imaging studies (7,342 participants) identified using independent components analysis (Smith et al., 2009). C) The DMN identified using a seed-to-voxel approach with a posterior cingulate cortex seed (black sphere) from 29 typically developing adolescents described in Broulidakis et al. (2016). Each image shows the medial and lateral surface of the left hemisphere of a semi-inflated brain. Green/light blue colours represent regions that were most strongly activated or connected with other DMN regions.

2.2.1 Functional hierarchy of the DMN

The DMN is not a unitary system; instead, it has been argued that it can be split into three distinct subsystems. Evidence for subsystems within the DMN was first provided by Andrews-Hanna et al. (2010) who used hierarchical clustering around preselected seeds to parse the DMN according to the strength of seed-to-seed functional connectivity. One of these subsystems was termed the *dorsal medial subsystem* and comprises the dorsal medial prefrontal cortex, the temporal parietal junction, the lateral temporal cortex and the temporal pole. Another was the *medial temporal subsystem* which, they found, is made up of the hippocampal formation, the parahippocampal cortex, the retrosplenial cortex, the ventral medial prefrontal cortex and the posterior inferior parietal lobule. These two subsystems interact with each other through a tightly coupled anterior medial prefrontal cortex-to-posterior cingulate cortex *core subsystem*. Since the idea of multiple DMN subsystems was first proposed, these findings have been replicated and extended. Yeo et al. (2011) used a similar clustering approach on a dataset obtained from a much larger sample of 1000 participants. These authors were able to split the DMN into three bilateral subsystems analogous to those identified by Andrews-Hanna et al. (2010), but with several notable anatomical differences. The dorsal medial subsystem did not include the temporal parietal junction, but instead encompassed the superior temporal sulcus, additional medial prefrontal brain regions and a subdivision of the inferior parietal lobule. The medial temporal subsystem did not include the ventral medial prefrontal cortex and the core subsystem also included the parts of the precuneus and additional parts of the inferior parietal lobule. Similar results have also been reported using entirely data-driven approaches. Using independent components analysis, Doucet et al. (2011) identified strong correlations between components overlapping the three

subsystems described by Yeo and colleagues. However, differing from previous findings, the cluster that best corresponded to the dorsal medial subsystem did not appear to cluster with the DMN at all.

2.2.2 The DMN creates the self-generative aspects of spontaneous thought

Paralleling resting-state connectivity studies that have investigated how the different subsystems are linked, task-based studies have shown the contribution of these brain regions to creating the self-generative aspects of spontaneous thought. For the medial temporal subsystem, imaging studies have shown that the hippocampal formation and parahippocampal cortex are vital to recalling episodic and autobiographical experiences into memory (Rugg & Vilberg, 2012). These regions are activated in concert with the retrosplenial cortex, inferior parietal lobule and possibly the ventral medial prefrontal cortex (Nieuwenhuis & Takashima, 2011), when contextual and object information is used to generate a mental image from memory. Buckner et al. (2008) proposes that the medial temporal subsystem as a whole is specifically involved in scene construction; the ability to build a coherent mental scene. Scene construction is a critical component of both memory and imagination as both processes are usually framed within a spatial context (Hassabis & Maguire, 2007; Schacter et al., 2012). Consistent with this interpretation, the medial temporal subsystem is linked with encoding information into memory and accessing contextual and object information from long term memory (Andrews-Hanna et al., 2014).

In contrast to the medial temporal subsystem, components of the dorsal medial subsystem appear to be preferentially activated during socio-cognitive and semantic memory. Both the dorsal medial prefrontal cortex and temporal parietal junction are activated when inferring temporary goals, intentions, desires and enduring

dispositions of others, as evidenced from mentalising or moral decision-making paradigms (Gallagher & Frith, 2003; Mitchell, Macrae, & Banaji, 2006; Van Overwalle & Baetens, 2009). Other components of the dorsal medial subsystem (the superior temporal sulcus, temporal pole and lateral temporal cortex) have also been linked to broader aspects of non-reflective, inferential social cognition by drawing on stored semantic associations. In this way, the dorsal medial prefrontal cortex can use representations of previous social experiences to make predictions about others' actions and calibrate one's behaviour, an important feature of more complex and temporally extended social interaction (Spreng & Mar, 2012). Areas overlapping with the dorsal medial subsystem have also been linked to conceptual processing that does not have a social-cognitive component. In a meta-analysis of 17 task-based fMRI studies, Binder, Desai, Graves, and Conant (2009) examined the distinction between perceptually encoded knowledge (i.e., knowledge of concrete objects derived from sensory-motor experience) and verbally encoded knowledge (i.e., knowledge acquired though language). They found significant dorsal medial subsystem overlap and, consistent with the supposed functional segregation of the two subsystems, this overlap did not extend to any components of the medial temporal subsystem. It has been suggested that the dorsal medial subsystem facilitates both socio-cognitive and non-social reflective processes by retrieving and simulating stored representations of conceptual knowledge (Spreng & Andrews-Hanna, 2015). By being able to access these representations, it allows a characteristic emotion or anticipated outcome to be reflected upon in a meta-cognitive manner before an action is committed to.

Unlike the functionally specialised medial temporal or dorsal medial subsystems, brain regions in the DMN core subsystem will reliably activate across both memory-related and conceptual tasks (Jeffrey R. Binder et al., 2009; Brewer,

Garrison, & Whitfield-Gabrieli, 2013; Qin & Northoff, 2011). In the case of the core subsystem, the degree or magnitude of activation within these regions appears to be dependent on the level of personal investment in the issue under consideration. This has led to the hypothesis that the core subsystem is involved in attaching personal significance to a particular thought by flexibly coupling with either the medial temporal and/or dorsal medial prefrontal cortex subsystems (Andrews-Hanna et al., 2014; Spreng & Andrews-Hanna, 2015). The posterior cingulate cortex/precuneus in particular, exhibits connectivity with different neural networks and will adjust this connectivity according to task demands and the level of engagement with one's surroundings. As part of the DMN, these midline regions are thought to support ongoing information processing through dynamic interactions with other DMN subsystems and tight coupling with the fronto-parietal control network (FPCN), a network thought to provide top-down coordination of attention (Utevsky, Smith, & Huettel, 2014). The anterior medial prefrontal cortex is also characterised by extensive patterns of connectivity with the medial temporal and dorsal medial prefrontal cortex subsystems (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010), as well as non-DMN limbic regions including the insula, amygdala and nucleus accumbens (Ries et al., 2012). The anterior medial prefrontal cortex has been shown to contribute to the elaboration of feelings of the self, and is involved when making self-other distinctions (i.e., understanding another's mental and affective states while taking account of one's own concurrent thoughts and feelings). For example, the anterior medial prefrontal cortex activates when participants make judgments or remember trait adjectives about themselves compared to other people (D'Argembeau et al., 2011; Heatherton et al., 2006; Mitchell et al., 2006). It has been suggested that the anterior medial prefrontal cortex may be involved in the

maintenance of a self-schema; a mental framework that is used to bias information processing relevant to an individual's sense of self (Y. Wang & Hamilton, 2015). This would be consistent with the self-regulatory pattern of functioning attributed to this subsystem.

2.2.3 The dorsal attention network (DAN) is both suppressed by and suppresses patterns of spontaneous thought

The joint role of the DMN in both constructive and self-referential processing produces the self-generative aspects of spontaneous thought. These thoughts are then regulated via dynamic functional coupling with two other large-scale brain networks, the fronto-parietal control network (FPCN) and the DAN (Andrews-Hanna, Smallwood & Spreng, 2014). The DAN is reliably engaged when attention is covertly or overtly oriented to a particular spatial location (Corbetta & Shulman, 2002). The network is organised bilaterally and includes the frontal eye fields, inferior precentral sulcus, middle temporal motion complex and superior parietal lobule (Doucet et al., 2011; Yeo et al., 2011). Resting state functional connectivity studies have consistently reported strong anti-correlations between the DAN and the DMN, with activation in one network necessary for suppression of the other network (see Figure 1.1b) (Fornito, Harrison, Zalesky, & Simons, 2012; M. D. Fox et al., 2005). These patterns of anti-correlation are thought to support the competitive relationship between either the internal focus of attention that occurs during self-generated thought or the external focus of attention to an object in the environment. Where the suppression of either network is insufficient, this may impair goal-directed activity. For example, across a wide range of tasks that require attention to be directed to an external stimulus, the degree or magnitude of DMN attenuation can be used as a reliable metric for gauging

task performance (Anticevic, Repovs, Shulman, & Barch, 2010; Mason et al., 2007; Zou et al., 2013). Subjectively, this failure to suppress the DMN leads to higher levels of mind-wandering as attention shifts to task-unrelated thoughts (Andrews-Hanna et al., 2013). In the same manner, it is also hypothesized that reduced DAN suppression during an internally orientated reflective process may lead to increased distractibility, impairing the integrity of the thought under consideration Andrews-Hanna et al., 2014). However, this has yet to be empirically demonstrated.

2.2.4 The fronto-parietal control network (FPCN) and DAN regulate spontaneous thought

Both the DMN and DAN require top-down control to coordinate internal and external streams of attention. The coordination of these two modes of attention is mediated by the FPCN, a network anatomically situated between the DAN and the DMN (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Like the DMN, the FPCN is a heterogeneous system made up of two functionally segregated circuits that operate in conjunction to ensure goal directed task performance (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Seeley et al., 2007). The first is a cingulo-opercular "salience network" that consists of the dorsal anterior cingulate cortex and anterior insular cortex. The second is a frontal-parietal "executive control network" that consists of the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex and dorsomedial prefrontal cortex. The salience network serves a broad monitoring function, detecting salient information from internal and external stimuli in order to guide behaviour (Menon & Uddin, 2010). While in keeping with its name, the executive-control network through tight coupling with the DAN attends to information identified as

'salient' as behavioural choices are weighed in terms of goal relevance (Elton & Gao, 2014).

As a whole, the salience network and the executive control network are thought to function in concert as a flexible hub. The FPCN has extensive brain-wide connectivity with all major brain networks, possibly via connections with the anterior insula. As a hub, the FPCN is able to bias patterns of connectivity between it and other brain networks according to goal-relevance and will update these patterns of connectivity depending on current task demands (Cole, Repovs, & Anticevic, 2014; Cole et al., 2013). In this way, the FPCN is thought to flexibly couple with the DMN depending on whether the activity being performed requires access to internalised mental representations. For example, Ellamil et al. (2012) found that while generative tasks engaged DMN regions, evaluating how those generated images fit with task goals lead to increased connectivity between DMN *and* FPCN components. Similarly, Gerlach et al. (2014) found that relative to an odd/even control task, imagining events associated with achieving a goal also led to increased connectivity between seeds in the DMN and seeds in the FPCN. Moreover, the FPCN can actually *increase* DMN activity even during executive tasks, so long as the goals of the task require access to internalised representations of information. For example, Spreng et al. (2014) found increased activity in brain regions overlapping the DMN and FPCN during a two-back task that involved matching famous faces with anonymous faces. Collectively these findings are significant because they suggest the DMN is not a passive brain network that needs to be attenuated in order for any goal directed mental activity to be performed successfully (as was initially suggested by Fox et al. (2005))**.** Instead, and consistent with similar studies (for review see Spreng (2012)), it suggests that the

DMN can activate during externally orientated task related processing so long as the task requires self-referential processes the DMN mediates. (Spreng et al., 2014).

2.3.1 Summary

In summary, the DMN is a large-scale brain network consisting of multiple functionally dissociable subcomponents. The adaptive function of this network is to produce goal directed, self-generated thought by drawing upon fragments of autobiographical/personal narratives. According to the framework we have outlined here, each subsystem of the DMN has a specific role in performing this task that appears to overlap with the three different aspects of spontaneous thought described previously. The core subsystem allows individuals to construct personal meaning from salient information, the medial temporal subsystem facilitates constructive mental simulation and imagination and the dorsal medial subsystem is involved in social-cognitive and semantic processing. These self-generated thoughts are then regulated through dynamic functional coupling between the DMN and the FPCN and the DAN to ensure goal relevance and prevent interference. In the next section, we describe how abnormalities within the DMN may contribute to altered patterns of spontaneous thought.

2.4.1 The DMN in psychopathology

Since it was first identified, many psychiatric conditions have been linked to abnormalities within the DMN (for review see Mohan et al. (2016)). Using the framework described above to interpret these findings reveals that both the nature and locations of DMN alterations differ across disorders and frequently reflect certain symptom profiles. Andrews-Hanna et al. (2014) outlined three non-independent mechanisms to explain how psychopathological brain states can be linked to alterations in DMN functioning. Each model predicts three modes of impairment that correspond to the three features of spontaneous thought described previously. This includes: (i) a breakdown in producing spontaneous thought, (ii) a breakdown in regulating the content of spontaneous thought; and (iii), a deficit in the ability to inhibit or suppress spontaneous thought (mind-wandering).

2.4.2 The integrity hypothesis of DMN functioning

The DMN integrity hypothesis predicts that, where a condition significantly damages the integrity of one or more DMN subsystems, it should prevent that subsystem from contributing to the production of spontaneous thought (Andrews-Hanna et al., 2014). This will present as either reduced structural and functional connectivity or hypo-activity within one or more subsystems of the DMN.

Two disorders in which impairments in DMN functioning appear to play an important role are neurodegenerative disorders and schizophrenia. Alzheimer's disease and fronto-temporal dementia are two neurodegenerative disorders characterised by a progressive and ultimately fatal breakdown of large-scale brain network connectivity (Seeley, Crawford, Zhou, Miller, & Greicius, 2009). However, at least in the early stages of both conditions, they present as profound impairments

that are localized in distinct subsystems of the DMN and so can illustrate how degradation in the integrity of a subsystem can contribute to the symptomatology of the disorder. In Alzheimer's disease, the components of the DMN most likely to be affected include the posterior cingulate cortex and the middle temporal lobe subsystem, with additional subsystems becoming impaired as the disease progresses (J. Zhou & Seeley, 2014). At least initially, Alzheimer's disease is associated with deficits in episodic memory and mental scene construction (Addis, Sacchetti, Ally, Budson, & Schacter, 2009), with impairments in self-reflection, social cognition and semantic memory arising later in the course of the disease (Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000). On the other side of the coin, fronto-temporal dementia is associated with deficits in the anterior medial prefrontal cortex and components of the dorsal medial subsystem (J. Zhou & Seeley, 2014). This presents as an early deficit in semantic memory (Mathuranath et al., 2000) and a breakdown in social-cognitive processes, such as theory of mind (Snowden et al., 2003) and non-social reflective processing (Eslinger et al., 2005), with abnormalities in processes mediated by the middle temporal lobe subsystem arising later.

Schizophrenia could also be classified, at least in part, as a disorder of DMN integrity. Schizophrenia is a condition involving symptoms that encompass delusions, hallucinations and disorganised speech (American Psychiatric Association, 2013). It is characterised in terms of structural and functional hypo-connectivity both within and between subsystems of the DMN (Du et al., 2016). This is thought to present in two different ways. The first is reduced connectivity within DMN subsystems that leads to subsystem-specific deficits in information processing. For example, Dodell-Feder, DeLisi, and Hooker (2014) found that reduced connectivity only *within* the dorsal medial subsystem was correlated with a subsystem-specific impairment in

social cognition. The second way is decreased connectivity *between* DMN subsystems that is thought to contribute to a difficulty in integrating self-generated mental processes. For example, a difficulty in coordinating present mental states with episodic decisions about the future (D'Argembeau, Raffard, & Van der Linden, 2008).

2.4.3 The content regulation hypothesis of DMN functioning

The DMN content regulation hypothesis predicts that in some cases a disorder may alter the content of spontaneous thought to the point where it no longer provides an adaptive function. Where this occurs, it is experienced as polarized or excessive thoughts and a difficulty in shifting between different trains of thought, impairing the ability of spontaneous thought to regulate affect and the self-referential processes that guide decision making (Andrews-Hanna et al., 2014). It is predicted to present either in terms of DMN hyper-connectivity/hyper-activity within and/or between DMN nodes or in terms of a trade-off between hyper- and hypo-connectivity/activity among DMN subsystems and between non-DMN components thought to influence spontaneous thought (such as reward networks).

One example of a disorder in which a difficulty in regulating the content of spontaneous thought may represent an important clinical feature is major depressive disorder. Depression is a condition characterised by persistent low mood and excessive introspection in the form of negative self-focused rumination (American Psychiatric Association, 2013). Depression in general is associated with functional hyper-connectivity within the DMN core, with other DMN subsystems remaining largely unaffected (Sambataro, Wolf, Giusti, Vasic, & Wolf, 2013). While rumination in particular is associated with a circuit that overlaps both the DMN core subsystem and other non-DMN limbic regions involved in affect regulation (Hamilton, Farmer,

Fogelman, & Gotlib, 2015). The DMN core subsystem is linked to both economic goal-setting and prospection given that, by their very nature, most decisions are self-relevant (Sonuga-Barke & Fairchild, 2012). This abnormality may contribute to depressive symptomatology in two ways. First, models of depressive cognition (e.g., Beck (1979)) emphasise the role of spontaneous thought in creating a vicious circle in which otherwise adaptive thought that may stabilize the cognitive/affective system is replaced by a focus on self-critical cognition that has a dampening effect on subsequent mood. Second, rumination may influence prospection, both in terms of how previous experiences are appraised and how future situations may be expected to turn out. Sonuga-Barke et al. (2016) suggest that this may contribute to disengaged and pessimistic decision-making. Consistent with this prediction, excessive rumination predicts indecision (Di Schiena, Luminet, Chang, & Philippot, 2013) as well as a lack of confidence in decisions that have been made (van Randenborgh, de Jong-Meyer, & Hüffmeier, 2010).

2.4.4 The context regulation hypothesis of DMN functioning

The DMN context regulation hypothesis predicts that a disorder that alters the ability of the FPCN to regulate state-to-state switching will lead to excessive and harmful levels of mind-wandering (Andrews-Hanna et al., 2014). Whereas the content regulation hypothesis refers specifically to the topics of spontaneous thought (e.g. excessive focus on past instances of failure or rejection), the context regulation hypothesis refers to when such thoughts occur (i.e. appropriate to the context versus inappropriate/intrusive). In some cases, disorders will be characterised by dysregulation of both context and content and both processes frequently operate in conjunction to impair mood and disrupt task-related cognition. It is hypothesized that

the underlying mechanisms of a disorder of DMN context is hypo/hyper-connectivity between the FPCN and subsystems of the DMN.

A number of disorders are associated with elevated levels of mind-wandering that coincides with abnormal FPCN-to-DMN connectivity. Disorders that often manifest increased distractibility and negative and intrusive mental imagery. For example, obsessive-compulsive disorder (OCD) is a condition characterised by intrusive thoughts that exaggerate the likelihood and severity of personal harm (American Psychiatric Association, 2013). Consistent with the context regulation hypothesis, OCD is associated with elevated mind wandering that correlates with symptom severity and abnormal connectivity between the salience network and the dorsal medial and core subsystems (Seli, Risko, Purdon, & Smilek, 2016). In this case abnormal FPCN-to-DMN connectivity is predicted to contribute to a difficulty in disengaging from intrusive internally generated scenarios, a characteristic of spontaneous thought in OCD (Beucke et al., 2014; Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012). Individuals with depression and anxiety disorders also show elevated levels of mind wandering that correlate with their symptom severity (Smallwood, O'Connor, Sudbery, & Obonsawin, 2007). In depression in particular, rumination is associated with 'sticky thoughts' - a difficulty with disengaging with emotionally-charged material. In depressed individuals, these 'sticky thoughts' are associated with decreased FPCN connectivity, and decreased connectivity between the FPCN and the DAN, but interestingly, *increased* connectivity between the FPCN and DMN. This is thought to reflect an attention bias towards internal thoughts at the expense of engaging with the external world (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). In schizophrenia, disruptions in the integrity of both the DAN and

the FPCN are thought to contribute to both elevated levels of mind wandering and impairments in goal directed behaviour (Buckner, 2013; Gerrans, 2014).

2.4.5 Summary

In summary, Andrews-Hanna et al. (2014) produced three broad frameworks for explaining how damage or disruption to the DMN may contribute to psychopathological brain states. The first framework suggests that damage to the DMN leads to a difficulty in forming the self-generated aspects of spontaneous thought (*the integrity hypothesis of DMN functioning*). The second suggests that an alteration in signalling within the DMN turns otherwise adaptive spontaneous thought harmful, such as by shifting the focus of internally generated thought to be overly negative or overly self-relevant (*the content regulation hypothesis of DMN functioning*). The third framework proposes an impairment in the connectivity between the DMN, FPCN and DAN that disrupts when and how spontaneous thought arises, leading to excessive mind-wandering (*the context regulation hypothesis of DMN functioning*). In the next section, we discuss two neurodevelopmental conditions, namely conduct disorder (CD) and attention-deficit/hyperactivity disorder (ADHD), before going on to show how DMN disturbances might contribute to the clinical features of both.

Chapter III: Task Dependent Systems in ADHD and CD

Attention-deficit/hyperactivity disorder (ADHD) is a condition characterized by persistent and age-inappropriate levels of inattention, hyperactivity and impulsivity (American Psychiatric Association, 2013). Conduct disorder (CD) is defined in terms of a persistent pattern of antisocial behaviour in which the rights of others or social norms are violated, with diagnostic symptoms encompassing aggression towards humans and animals, destruction of property, theft and the serious violation of rules. Subtyping approaches have been put forward to better account for variation in symptomatology and expected outcomes. For ADHD, this is depending on the presence or absence of one or more of the three cardinal symptoms of the disorder: 1) distinguishing between a predominantly inattentive subtype, 2) a relatively rare hyperactive/impulsive subtype, and 3) a combined type that includes all three core symptom clusters. For CD, this is according to the age of onset, distinguishing between cases where CD symptoms emerge before (childhood-onset) or after (adolescence-onset) the age of 10. The childhood-onset variant is thought to be associated with a greater risk of adult antisocial behaviour and of emotional and behavioural dysregulation relative to the adolescence-onset variant (Moffitt, Caspi, Harrington, & Milne, 2002). CD is also subtyped according to the presence or absence of callous-unemotional traits, i.e., a lack of guilt and empathy (Frick, 2009). Those who show CD and callous-unemotional traits have poorer outcomes, including an increased risk for substance use disorders, criminality and violent offending, as

compared to youths with low callous-unemotional traits (Fanti, Frick, & Georgiou, 2008; Frick, 2009).

3.1.1 Conceptualising ADHD in terms of task dependent systems

Traditionally, both ADHD and CD have been understood in terms of task-related deficits in one or more domains of processing. For ADHD, three domains of processing are commonly implicated in the mechanisms of the disorder: 1) "cool" executive functioning, typically elicited by relatively abstract, decontextualised problem-solving, 2) "hot" executive functioning, related to motivation, affective and reward mediated processing, and 3) temporal processing, that may independently contribute to deficits in hot and/or cold executive functioning (Nigg & Casey, 2005; Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008). Hot executive functioning deficits has been evidenced from either suboptimal responses on feedback-mediated decision-making tasks or preference for immediate over-larger rewards on variants of the delay discounting task (Yang et al., 2011). Cool executive functioning deficits are seen in poor performance on tasks measuring visual-spatial and verbal working memory, inhibitory control and sustained attention (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Yang et al., 2011). Temporal processing deficits are seen in a difficulty in keeping time and in estimating how much time has elapsed during duration estimation and motor timing tasks, as well as poor temporal foresight during tasks that require participants learn and consider the future consequences of immediate reward choices (Toplak & Tannock, 2005). In addition to impairments in these three domains however, other associated features of ADHD less directly implicated in its aetiology are those related to speech and language (Tomblin & Mueller, 2012), processing speed (Kuntsi &

Klein, 2012), motor control (Fliers et al., 2009) and emotional dysregulation (P. Shaw, Stringaris, Nigg, & Leibenluft, 2014).

Neuroimaging methods in ADHD have traditionally been used to identify brain regions thought to contribute to those task-related deficits. Guided by behavioural evidence described previously, two relatively independent circuits have been linked to the mechanisms of ADHD. The first is an executive network that contributes to deficits in cold executive functioning. This network broadly overlaps components of the DAN and FPCN as well as encompassing additional limbic regions and the cerebellum. The second is a reward network or hot executive functioning network thought to underlie suboptimal reward processing. Below we review evidence for functional and structural abnormalities within these two circuits

3.1.2 Task-elicited activation within cold and hot executive functioning networks in ADHD

The majority of evidence for abnormalities within hot and cold executive functioning networks has come from pooling the results of task-based fMRI studies. By cataloguing common task-elicited activation patterns, meta-analyses and reviews have been able to reliably map poor behavioural task performance onto task-specific nodes within functionally dissociable hot and cold executive functioning networks (Bush, 2011; Cubillo, Halari, Smith, Taylor, & Rubia, 2012; Dickstein, Bannon, Castellanos, & Milham, 2006). For cold executive functioning tasks; there have been two meta-analyses testing interference and motor inhibition in ADHD. In the first, across 21 studies Hart et al. (2013) report reduced activity within the supplementary motor area, anterior cingulate cortex, caudate nucleus and thalamus, suggesting an impaired fronto-striatal circuit. The second meta-analysis, encompassing an additional

9 studies, extended these findings to also encompass the ventral medial prefrontal cortex, insula and putamen (Norman et al., 2016). A meta-analysis of 13 studies that used mental rotation and covert and overt selective and sustained attention tasks showed reduced activity within the dorsolateral prefrontal cortex, right inferior parietal cortex and caudal parts of the basal ganglia and thalamus, suggesting an impaired fronto-parietal circuit. A meta-analysis of 11 studies using delay discounting, motor timing and duration estimation tasks found reduced activity in the dorsolateral prefrontal cortex, inferior prefrontal cortex, inferior parietal lobules and the cerebellum, suggesting an impaired fronto-cerebellar circuit (Hart et al., 2013)

There also appears to be consistent evidence for abnormalities within dissimilar brain regions during hot executive functioning tasks that are functionally dissociable from the cold executive functioning network described previously. A meta-analysis of 8 region of interest studies predominantly measuring the pooled results of monetary reward anticipation tasks found hypo-activation within the substantia nigra and nucleus accumbens, components of the ventral striatum commonly associated with reward anticipation (Plichta & Scheres, 2014). Other studies also consistently reported lower activity within the ventrolateral prefrontal cortex, orbital frontal cortex, thalamus and anterior cingulate cortex in addition to the ventral striatum during temporal discounting and rewarded inhibition tasks (Plichta et al., 2009; Rubia, Halari, Cubillo, et al., 2009). However this pattern of reward network hypo-activity has not always been observed (Lemiere et al., 2012). This inconsistency is suggested to be due to a failure to control for many of the typical confounds of psychiatric research (e.g., limited statistical power, medication history) and in particular comorbid CD (Rubia, Alegria, & Brinson, 2014). Conduct disorder comorbidity is particularly important because affective processing is independently

reported to be impaired in CD (although this may present differently to deficits in affective processing in ADHD and may have conflicting effects on reward circuitry).

3.1.3 Functional connectivity within cold and hot executive functioning networks in ADHD

Functional connectivity studies show that abnormalities in brain function in ADHD children and adults are not simply the dysregulation of isolated brain regions, but are instead a disturbance in task-specific neural networks. For example, five studies have investigated functional connectivity using cold executive functioning tasks. Two of these studies reported lower functional connectivity between a seed in the inferior fontal cortex and voxels in the inferior parietal cortex, basal ganglia, thalamus and cerebellum during delay discounting (Rubia, Halari, Cubillo, et al., 2009) and duration estimation tasks (Vloet et al., 2010) in ADHD children compared with controls. This suggests timing tasks are associated with poor communication between nodes of a fronto-cerebellar circuit. In a third and fourth study, adults with ADHD showed lower connectivity between a seed in the inferior frontal cortex and voxels in the basal ganglia, anterior cingulate and inferior parietal cortex during motor response inhibition and working memory tasks (Cubillo et al., 2010; Wolf et al., 2009). This time-indicating inhibition and working memory are linked to a fronto-patietal circuit. More recently, Clerkin et al. (2013) found reduced connectivity between a seed placed in the striatum and voxels in the thalamus and cerebellum during a response preparation task. Collectively these findings illustrate how an executive functioning deficit in ADHD may be linked to task-specific deficits in subsystems of a larger cold executive functioning network. To date, no study has

measured effects of ADHD group status on task-elicited functional connectivity in hot executive functioning circuits.

Other studies have measured resting state functional connectivity within both executive and reward networks in ADHD without relying on an experimental manipulation. For the cold executive functioning network, there is evidence of reduced connectivity between the putamen and the dorsolateral prefrontal cortex (Cao et al., 2009), as well as reduced connectivity between the thalamus and the putamen that correlates with working memory performance in children with ADHD (Mills et al., 2012). Within the hot executive functioning network, there is evidence of reduced connectivity between the left putamen and the ventral striatum (Cao et al., 2009) and between the ventral striatum and anterior cingulate cortex (Posner et al., 2013). However, not every resting state study has reported intra-striatal hypo-connectivity. For example, Rhein et al. (2016) found *increased* local functional connectivity between the anterior and posterior putamen. Di Martino et al. (2013) measured functional connectivity in terms of degree centrality, a graph-analytic index of the total number of connections between a node and all other nodes in a connectome. Using a connectome that spanned every brain area, they found increased degree centrality within the putamen and caudate nucleus (each a component of the striatum), and within the posterior cingulate cortex/precuneus (a component of the DMN) in children with ADHD compared with controls. This has been interpreted in terms of decreased functional segregation between executive and reward networks (Rhein et al., 2016).

3.1.4 Structural imaging within cold and hot executive functioning networks in ADHD

Despite a potential to provide a data-driven whole-brain assessment of the effects of ADHD, typically structural imaging has sought to dovetail functional imaging by restricting analysis to pre-specified brain regions that overlap task-relevant circuits. Using a region of interest approach, the most consistent findings have usually been in children and present as lower grey matter volume/cortical thickness in major nodes of both hot and cold executive functioning networks. This includes the basal ganglia, cerebellum, supplementary motor area as well as orbitalfrontal, dorsolateral prefrontal, inferior frontal, medial prefrontal and anterior cingulate cortices (Cubillo et al., 2012; De La Fuente, Xia, Branch, & Li, 2013; Rubia et al., 2014). Curiously, despite a multitude of region of interest based structural MRI studies, only a single meta-analysis has actually been published (Valera, Faraone, Murray, & Seidman, 2007). Across 21 studies in children with ADHD, Valera et al. (2007) found the most consistent volumetric reductions were centred on regions of interest that overlapped the posterior inferior cerebellar vermis, the selenium of the corpus callosum, right caudate and various frontal regions. These results are consistent with a frontal-cerebellar deficit in ADHD. In adults, volumetric reductions have been reported overlapping a similar set of brain regions with the possible exception of the basal ganglia (A. Qiu et al., 2009; P. Shaw et al., 2013).

Comparatively fewer studies have examined structural deficits in ADHD using statistical approaches that examine every voxel within the brain simultaneously. Perhaps indicative of the interest voxelwise approaches engender however, a total of four meta-analysis on this data have been published. The first is a meta-analysis of 7 studies that found reduced grey matter centred in the right putamen/globus pallidus (Ellison-Wright, Ellison-Wright, & Bullmore, 2008). The second is a meta-analysis of 14 studies that reported reduced grey matter in the caudate (Nakao, Radua, Rubia, &

Mataix-Cols, 2011). The third is a meta-analysis of 11 studies that found reduced grey matter volume in the right globus pallidus and right putamen (Frodl & Skokauskas, 2012). The fourth and last is a comparatively larger analysis of 33 studies and found decreased grey matter volume in the right basal ganglia, insula and anterior cingulate cortex (Norman et al., 2016). Of the two meta-analyses that tested for age effects, two reported lower grey matter volume were most prevalent in children and appeared to normalise as patients reached adulthood (Frodl & Skokauskas, 2012; Nakao et al., 2011). This suggests that structural abnormalities in the basal ganglia possibly reflect delayed rather than disrupted development. This has been tied to the steadily vanishing hyperactivity symptomatology that appears to characterise the adult ADHD phenotype (De La Fuente et al., 2013).

3.1.5 Structural connectivity within cold and hot executive functioning networks in ADHD

By showing how brain regions are linked, structural connectivity can permit inferences about how a structural abnormality in ADHD may impact a functional brain network. Diffusion tensor imaging is one approach to measuring structural connectivity that has dovetailed structural MRI investigations by showing that ADHD patients have deficits not only in isolated brain regions, but also in the white matter microstructural integrity that connect brain together. For example, in the only meta-analysis published van Ewijk, Heslenfeld, Zwiers, Buitelaar, and Oosterlaan (2012) pooled the results of 9 studies that took a whole brain assessment of fractional anisotropy (an index of white matter integrity/myelination) in children with ADHD. Compared with controls lower white matter integrity was localized to the right anterior corona radiata (a white matter sheet that carries connections between the

cortex and striatal areas), the bilateral internal capsule (a white matter structure which separates the caudate nucleus from the globus palidus and putamen) and in the left cerebellum. Additional voxel based studies have also shown consistent evidence for white matter abnormalities in the corpus callosum and the right superior longitudinal fasciculus (a long bidirectional bundle that connects inferior parietal cortex with the dorsolateral prefrontal cortex) in both ADHD children and adults (see L. Chen et al. (2016) and De La Fuente et al. (2013) for reviews).

Similar results have also been demonstrated using region of interest based probabilistic tractography, a technique that restricts analysis to predefined neuronal tracts either by manual tracing or by identifying tracts that originate and/or terminate in anatomical seed regions of interest. Both approaches have demonstrated white matter abnormalities in the right anterior thalamic radiation (a major projection from the thalamus that carries reciprocal connections from limbic structures to the frontal cortex) in children with ADHD (Nagel et al., 2011; Tamm, Barnea-Goraly, & Reiss, 2012). While seed-based methodologies have shown lower fractional anisotropy within tracts interconnecting dorsolateral, ventrolateral and orbitofrontal cortices and connecting these frontal regions with basal ganglia structures including the putamen and caudate in both ADHD children (Shang, Wu, Gau, & Tseng, 2013; Silk et al., 2015) and ADHD adults (Peper et al., 2013). Interestingly, paralleling structural MRI studies - lower fractional anisotropy connecting the thalamus and the stratum (Xia et al., 2012) and inter-connectivity within the basal ganglia (Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2009) appear to normalise as children with ADHD reach adulthood. Taken as a whole, structural connectivity studies of this kind provide robust support for deficits in edges connecting major nodes of both reward and executive circuitry.

3.1.6 Summary

To summarise, research into task-dependent systems in ADHD have focused on identifying nodes of hot and cold executive functioning networks (see Figure 3.1). Consistent with the conceptualization of the brain as a hierarchically organised network, the cold executive functioning network appears to be divisible into task-specific subnetworks. An important feature of both networks is that they appear to be age dependent. While few studies have directly investigated the effects of age on functional brain networks, structural studies suggest indirectly that limbic abnormalities likely normalise with age.

3.2.1 Conceptualising CD in terms of task dependent systems

Conduct disorder is associated with task specific impairments in three relatively independent domains of processing; cold executive functioning, hot executive functioning and social cognition (Matthys, Vanderschuren, & Schutter, 2013). Cold executive functioning deficits in CD have been evidenced from poor performance on inhibition and non-affective problem solving tasks and these effects cannot be explained by ADHD comorbidity (Oosterlaan, Logan, & Sergeant, 1998; Raaijmakers et al., 2008). Similarly, independent of less specific hot executive functioning deficits in ADHD, antisocial individuals show altered sensitivity to reward and punishment and in the processing of these contingencies (for review see: Byrd, Loeber, and Pardini (2014)). Specifically, an increased affinity for immediate reward over delayed reward in delay discounting tasks (White et al., 2014). An insensitivity to punishment in reversal tasks, in which previously learned rewarded stimulus-response contingencies are no longer rewarded (Banaschewski et al., 2005). As well as increased reward seeking evidenced from gambling and risky choice tasks that require the participant avoid making suboptimal decisions that incur penalties (Crowley, Raymond, Mikulich-Gilbertson, Thompson, & Lejuez; Fairchild, van Goozen, Stollery, et al., 2009). Within the domain of social cognition, CD is associated with a difficulty in forming an isometric mental state with another (affective empathy) or in recognizing emotion in others (emotion recognition). This is evidenced from poor performance on empathy tasks that require the participant to make some sort of judgement about their own or another's mental state in a distressing scenario (e.g., viewing images of another person in pain) (Lovett & Sheffield, 2007). It can also be evidenced from a selective deficit in correctly identifying negatively valenced auditory or visual cues (e.g., differentiating a

frightened voice/face from a neural voice/face) (Dawel, O'Kearney, McKone, & Palermo, 2012).

Following a more integrated model of CD, neuropsychological studies conceptualise the neurobiology of the disorder in terms of deficits in a paralimbic/limbic system, possibly as part of a larger fronto-limbic network (see Figure 3.1D). Differing from the dissociable hot and cold executive functioning circuits implicated in ADHD, CD is thought to be mediated by a single circuit, possibly including nodes involved in both hot and cold executive functioning (see Noordermeer et al. (2016) for meta-analysis; also see Rubia (2011) for an alternative account stipulating neural impairments are restricted to hot executive brain areas only).

3.2.2 Task-elicited activation within cold and hot executive functioning networks in CD

Tasks measuring hot executive functioning and social cognition have typically followed conceptual models of CD by measuring sensitivity to reward and punishment, emotional processing of distressing scenes, and emotion recognition and empathy, all of which are thought to inhibit antisocial behaviour in some way. For example, tasks measuring reward and punishment sensitivity usually manipulate response contingencies by rewarding correct responses and/or punishing incorrect responses. When responses are punished there is *increased* activity in the ventromedial prefrontal cortex (Finger et al., 2008), amygdala (Cohn et al., 2014), hippocampus, striatum and inferior parietal cortex (Cohn et al., 2014; Finger et al., 2008; White, Pope, et al., 2013) in children with CD compared with controls. Results interpreted as a difficulty in processing the violation of reinforcement expectations.

When responses are rewarded there is *decreased* activity in the orbitofrontal cortex (Rubia, Halari, Christakou, & Taylor, 2009) and striatum (Cohn et al., 2014) in children with CD compared with controls, suggesting a diminished sensitivity to rewards. Emotional processing tasks assess the neural response to passively viewing affective (generally negatively-valenced) images. Studies of this kind have found abnormal activation in the anterior cingulate cortex and amygdala (Herpertz et al., 2008; Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005). This is in line with the notion of impaired emotion processing as a basis for aggression, given the amygdala is a key region for the processing of negative affect (Matthys et al., 2013). Emotion recognition tests require participants discriminate between facial expressions. Differences in activation in CD are in the amygdala, insula, superior temporal cortex and ventromedial prefrontal cortex, when participants view either sad or angry faces (Fairchild et al., 2014; Passamonti et al., 2010). Lastly, during empathy tasks there is decreased activity in the amygdala and insula when trying to mirror another's mental state (Decety, Michalska, Akitsuki, & Lahey, 2009; Sebastian, McCrory, Cecil, & et al., 2012). This is thought to reflect decreased responsiveness of the amygdala to the perceived distress of others. Viewed together these frequently overlapping results have been interpreted in terms of task-specific activation within nodes of a single fronto-limbic network.

A comparatively limited number of studies have investigated the neural correlates of cool executive functioning in CD (Rubia et al., 2010; Rubia, Halari, Smith, et al., 2009; Rubia, Smith, et al., 2009; J. Zhang et al., 2015). Independent of ADHD, these have found specific effects of CD status. For example, Rubia et al, (2009; 2010; 2009), conducted a collection of studies on a sample of adolescents with pure (non-comorbid) CD compared with ADHD and typically developing control

groups. Across motor response inhibition, interference inhibition and selective attention tasks, they obtained two important findings. The first was that the ADHD group showed hypo-activation of nodes of a fronto-striatal circuit with dissimilar abnormalities seen in the CD group. The second was that where CD participants did show abnormalities, they overlapped components of the fronto-limbic network that was not present in ADHD. In particular, the insula, striatum, middle/superior frontal gyrus and precuneus. Results that suggest unlike ADHD, CD is associated with a single, non-dissociable circuit involved in both hot and cold executive functioning.

3.2.3 Functional connectivity within cold and hot executive functioning networks in CD

Investigating network edges gives an indication about how localised abnormalities affects the wider functioning of the system as a whole. Studies investigating task-elicited functional connectivity in CD have shown a general pattern of reduced connectivity between nodes of a fronto-limbic network (Decety et al., 2009; Finger et al., 2012; Marsh et al., 2011; Yoder, Lahey, & Decety, 2016; J. Zhang et al., 2015). In the first of these studies, Decety et al. (2009) required youth with CD to passively perceive others being harmed accidently or intentionally. They found lower connectivity between the amygdala and the left insula in the CD group, results interpreted as a difficulty in integrating affective state information. Whilst a more recent dimensional analysis of callous and unemotional traits that adopted a similar experimental paradigm, found lower connectivity between the amygdala and anterior cingulate cortex in youth with high callous unemotional traits, interpreted as a more general difficulty in attaching emotional significance to distress cues (Yoder et al., 2016). In a third study, Marsh et al. (2011) required youth with high callous

unemotional traits to make judgments about the morality of legal compared with illegal actions. They found reduced activity within the amygdala, as well as reduced connectivity between the amygdala and ventromedial prefrontal cortex. This has been interpreted as a difficulty in associating an adverse emotional response to possible distress (explaining the amygdala hypo-activity), and the mental representation of the action that contributes to distress (which was thought to be mediated by the ventromedial prefrontal cortex) (Blair, 2013). In addition, lower connectivity has been reported between the anterior cingulate cortex and voxels overlapping the anterior insula and caudate during instrumental learning (Finger et al., 2012). Only a single study has investigated functional connectivity using tests of cool executive functioning. In contrast to evidence of a shared pathway for cold and hot executive functioning in CD, after excluding participants with ADHD, J. Zhang et al. (2015) found reduced effective connectivity within a fronto-striatal circuit analogous to that found in ADHD in participants with adolescent onset CD compared with controls during a response inhibition task.

3.2.4 Structural imaging within cold and hot executive functioning networks in CD

A number of other studies have investigated structural variation in CD compared with controls. Perhaps because unlike ADHD, CD has traditionally not been so strongly conceptualized in terms of well-established etiological pathways to facilitate specific predictions for neurobiological correlates, only 3 studies have used a region of interest approach. Using this approach regions of interest are selected because they overlap brain regions commonly associated with the socio-cognitive impairments. These have found lower grey matter volume in the left (Sterzer, Stadler,

Poustka, & Kleinschmidt, 2007) and bilateral amygdala, (Fairchild et al., 2011) and bilaterally in the insula (Fairchild et al., 2011; Sterzer et al., 2007) in males with CD. As well as lower grey matter volume in the right orbitofrontal cortex and ventral stratum in females with CD (Fairchild, Hagan, et al., 2013).

Whole brain assessments of global structural abnormalities have reported a more distributed pattern of findings. A recent, but relatively small meta-analysis of just 8 studies found lower grey matter volume in the left amygdala, bilateral insula and left medial/superior frontal gyrus (Noordermeer et al., 2016). When viewed in conjunction with functional studies, suggest CD is more commonly associated with abnormalities overlapping fronto-limbic brain regions. Notably, these effects are unlikely to be accounted for by ADHD comorbidity. In three studies that specifically excluded co-morbid cases, lower regional grey matter volume was most commonly reported in the left and bilateral insula, left and bilateral amygdala, the left dorsolateral prefrontal cortex, the cingulate cortex and either left or right inferior frontal gyrus (Fahim et al., 2011; Fairchild et al., 2011; Stevens & Haney-Caron, 2012). In contrast, across three studies that included samples with comorbid ADHD, in addition to these effects, common findings included lower grey matter volume in the temporal lobe and the cerebellum (McAlonan et al., 2007; Michalska, Decety, Zeffiro, & Lahey, 2015; Sasayama et al., 2010). Findings suggesting disorder specific effects on brain structure.

3.2.5 Structural connectivity within cold and hot executive functioning networks in CD

For the most part studies investigating structural connectivity in CD have been characterised by a high number of failed replications and occasionally by

contradictory findings. Using a region of interest based approach the most common finding has been either higher (Passamonti et al., 2012; Sarkar et al., 2013) or lower (Breeden, Cardinale, Lozier, VanMeter, & Marsh, 2015) fractional anisotropy in the in the left and occasionally right uncinate fasciculus tract, results that persist after adjusting for ADHD symptoms. The uncinate fasciculus is a major white matter tract that connects limbic brain regions in the temporal lobe to the orbitofrontal cortex. Alterations in uncinate fasciculus white-matter microstructure have been predicted to lead to impaired communication between the frontal lobe and amygdala, and to contribute to altered sensitivity to reward and punishment during decision making tasks (Olson, Heide, Alm, & Vyas, 2015). The reason why participants with CD appear to more consistently show increased fractional anisotropy (normally associated with increased structural integrity and myelination) is not currently understood, particularly given contrasting evidence of decreased orbitofrontal-limbic functional connectivity. It has been proposed this may result from an abnormal developmental trajectory in CD that somehow contributes to impaired network functioning although this has yet to be empirically demonstrated (Sarkar et al., 2013).

To the best of our knowledge, only two voxel-based studies have reported white matter abnormalities in the uncinate fasciculus in CD, with 5 studies failing to replicate this effect. In the first, decreased fractional anisotropy was reported in adolescents with CD compared with healthy controls (Haney-Caron, Caprihan, & Stevens, 2014). In the second, there were no significant differences between CD and control cases, but there was contrasting evidence of increased fractional anisotropy in the uncinate fasciculus as a function of antisocial behaviour and callous unemotional traits (Pape et al., 2015). Beyond the uncinate faciculus there is also less consistent evidence for abnormalities in four other white matter tracts that are not directly linked

to either hot or cold executive functioning. First, both increased fractional anisotropy (Haney-Caron et al., 2014; T.-Q. Li, Mathews, Wang, Dunn, & Kronenberger, 2005) and decreased radial diffusivity (diffusion metric, inversely related to white matter integrity) (Pape et al., 2015) in the superior longlitudinal faciculus. Second, either increased (Pape et al., 2015) or decreased (Haney-Caron et al., 2014) fractional anisotrophy in the cingulum bundle (a large bidirectional tract that together with the superior longitudinal fasciculus, binds the medial prefrontal cortex and the precuenus). Third, either increased (J. Zhang et al., 2014) or decreased (Haney-Caron et al., 2014) fractional anisotropy in the anterior corona radiate. Fourth, either decreased fractional anisotropy, or a contrasting dimensional relationship between psychopathic traits and lower fractional anisotropy in the corpus callosum and forceps minor (J. Zhang et al., 2014). Lastly, increased fractional anisotrophy has also been reported in the anterior thalamic radiation (a tract extending from the thalamus to visual and somatosensory cortices, thought to affect the detection and processing of facial expressions of emotion) (Haney-Caron et al., 2014; Pape et al., 2015).

3.2.6 Summary

Conduct disorder is conceptualised in terms of deficits in hot and cold executive functioning. In CD, abnormalities within a single fronto-limbic circuit is thought to underlie impaired decision making, reinforcement sensitivity and emotional processing, encompassing empathy and the recognition of emotional facial expressions (see Figure 3.1). Whilst evidence for functional hypo-activation/hypo-connectivity within task-dependent systems appears consistent, the pattern is less clear for structural networks. In particular, there appears to be no direct correspondence between the edges of functional and structural brain networks (Finger

et al., 2012). The reasons for this abnormality are unclear, possibly due to the inclusion of highly heterogeneous clinical groups combined with relatively small sample sizes. In the next section, it is argued that in addition to these task-dependent systems, spontaneous thought and the default mode network may make an important contribution to psychopathological brain states in CD.

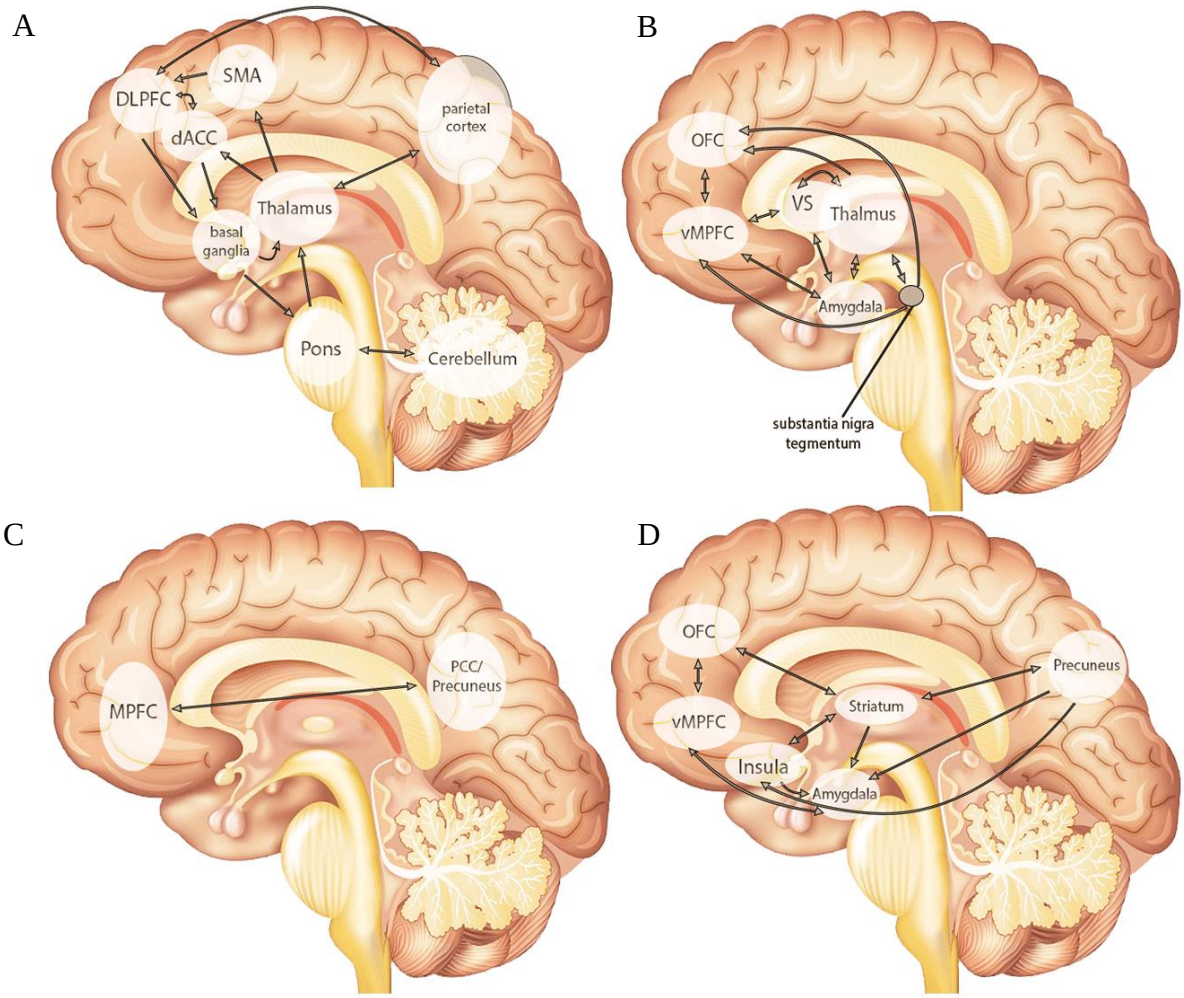

Figure 3.1. Brain mechanisms in conduct disorder (CD) and attention deficit/hyperactivity disorder (ADHD**).** Circles and lines correspond to network nodes and edges with arrow heads indicating the directionality of connectivity. A) The executive network. Hypo-activity/connectivity contribute to deficits in cold executive functioning and temporal processing in ADHD. B) The reward network. Hyper/hypo-connectivity/activity within this network contributes to deficits in hot executive functioning in ADHD. C) Two nodes of the DMN core subsystem. Abnormal connectivity between these two nodes may contribute to suboptimal decision making in CD and ADHD. D) A fronto-limbic network. Hypo-connectivity/activity within this network contributes to impaired social-cognitive processing and hot and cold executive functioning deficits in CD. Figures adapted from Noordermeer et al. (2016) and Faraone et al. (2015)). DLPFC: *dsorsolateral prefrontal cortex*, SMA: *supplementary motor area*, dACC: *dorsal anterior cingulate cortex*, OFC: *orbitofrontal cortex*, MPFC: *medial prefrontal cortex* vMPFC: *ventral medial prefrontal cortex*, VS: *ventral striatum*,PCC: *posterior cingulate cortex*

Chapter IV: A paradigm shift: spontaneous thought and the DMN in ADHD and CD

4.1.1 Conceptualising ADHD and CD in terms of task-independent systems.

For the most part, research into the mechanisms of ADHD and CD has been task-based. It has followed a philosophy that one or more "core" cognitive deficits drive the development of the other clinical and associated features of ADHD and CD as secondary manifestations of that impairment. As previously outlined, functional imaging has also been used to support this conceptual framework by mapping structural and functional abnormalities onto neural circuits associated with these "core" deficits. However, whilst this may provide a parsimonious explanation for how CD and ADHD may arise, it is unlikely to be the whole picture. For example, in ADHD there is reliable evidence suggesting that no one cognitive deficit appears to be present in all cases (Coghill, Seth, & Matthews, 2013; van der Meer et al., 2016). This is significant as it questions the direct correspondence between task-elicited cognition and the symptoms of ADHD as is normally assumed in most etiological models of ADHD. In the final chapter of this literature review, we postulate that the difficulty in reconciling the cognition of the disorder with the symptoms of the disorder may be due impart to the limitations of focusing solely on task-elicited cognition to the exclusion of task-independent processes. Below we outline ways in which spontaneous cognition may make an important impact on ADHD and CD-type symptomatology. We then link this with neurological studies, and following the

framework outlined by Andrew-Hanna et al. (2014), we explain how DMN abnormalities may contribute to the development of ADHD symptoms.

4.1.2 ADHD as a disorder of DMN context

The DMN context regulation hypothesis predicts that where there is atypical connectivity between the FPCN and the DMN it will lead to a breakdown in executive control and a failure to prevent mind-wandering. The DMN interference hypothesis predicts that a failure to inhibit mind-wandering may underlie the attention dysfunction that is a cardinal symptom of the disorder (Sonuga-Barke & Castellanos, 2007). Consistent with this prediction ADHD is associated with a greater frequency of mind-wandering thoughts that correlate with both poor ongoing-task performance and ADHD symptomatology (G. Shaw & Giambra, 1993). ADHD is also associated with breakdown in both proactive and reactive control over mind-wandering, exhibited by both a difficulty in preventing the occurrence of mind-wandering thoughts and a reduced meta-awareness that attention has wandered in the first place (Franklin et al., 2014) Consequently, this may prevent any self-regulatory attempts to halt or repair the negative outcomes of mind-wandering on task performance (Schooler et al., 2011).

A number of studies have investigated connectivity between the DMN and other brain networks in ADHD, based on the prediction that aberrant DMN connectivity may impair the ability to focus on tasks. Castellanos et al. (2008) first investigated resting state connectivity between executive control networks and the DMN in 20 adults with ADHD and equal numbers of controls. In the study, connectivity was measured from the seeds in the dorsal anterior cingulate cortex, right middle frontal gyrus and right inferior frontal gyrus. Reduced connectivity (and thus

reduced anti-correlations) was found between the dorsal anterior cingulate cortex (a node of the salience network) and posterior cingulate cortex (a node of the DMN). Supporting these findings, Cao et al. (2009) also investigated resting state connectivity in a sample of 23 children with ADHD and 21 controls. Connectivity was measured from the putamen, given its association with dysfunctional frontal-striatal circuitry in ADHD (Dickstein et al., 2006). The authors found reduced connectivity between the right putamen and the bilateral posterior cingulate cortex. Interestingly, the putamen is not a component of the DAN or FPCN and so would not be expected to modulate the DMN. Instead, it is recruited by these networks to facilitate the attentive modulation of early sensory activity (Kim, 2014). Such findings support a more generalized deficiency in modulating attenuation of the DMN in ADHD.

Building on the initial findings by Castellanos and colleagues, three additional studies have investigated the developmental trajectory of DMN connectivity with the hypothesis that abnormalities could reflect either delayed or disrupted maturation of connectivity patterns in ADHD. Sun et al. (2012) replicated evidence for reduced connectivity between the anterior cingulate cortex and posterior cingulate cortex in 19 children with ADHD compared with 23 controls. Furthermore, they found that connectivity strength was positively correlated with the age of the controls, with no corresponding linear relationship in the ADHD group. Sato, Hoexter, Castellanos, and Rohde (2012) reported similar findings in an older sample of 21 ADHD adults compared with 42 healthy controls. These findings were interpreted in terms of disrupted (rather than delayed) development in ADHD, at least in terms of dorsal anterior cingulate cortex-to-posterior cingulate cortex connectivity. Within the FPCN, the dorsal anterior cingulate cortex is a key component of a larger salience network,

which as previously discussed plays a critical role in switching between internal and external streams of attention (Goulden et al., 2014; Sidlauskaite et al., 2014). Predicting that the previously reported findings may reflect abnormalities that are specific to this circuit, Choi et al. (2013) used independent components analysis to measure the salience network as a whole (rather than restricting their analyses to a specific region of interest). They found reduced anti-correlations between the salience network and the posterior DMN in a sample of 20 children with ADHD compared with 20 age-matched controls. Consistent with previous findings, there was a linear association between age and connectivity strength in the control group that was not present in the ADHD group.

Three additional studies have sought to understand how abnormal connectivity between the DMN and FPCN may contribute to inattention, a key prediction of the DMN interference hypothesis. Sidlauskaite et al. (2015) suggested previously reported salience network-to-DMN abnormalities might reflect a difficulty in re-engaging rather than disengaging the DMN. This was tested using a novel paradigm that measured salience network modulation of the DMN moments before participants either switched from rest to performing an externally orientated task, or from performing a task to resting. Differing from prediction, comparing 19 adults with ADHD to 21 controls they found that regardless of the task performed, anticipatory rest to task modulation of the DMN was preserved in ADHD. Instead, there were abnormalities in modulating the DMN in preparation for a switch from task to rest, suggesting that attention deficits may reflect a difficulty in maintaining consistent DMN attenuation during task performance, rather than a difficulty in disengaging the DMN in the first place. This interpretation is supported by studies that have looked at connectivity between the DMN using dimensional measures of inattention. An early

investigation found that higher levels of externalising symptoms (of which inattention is a component) were associated with reduced connectivity between a seed in the posterior inferior parietal lobe and voxels centred on the dorsal anterior cingulate cortex and supplementary motor area (Chabernaud et al., 2012). More recently, Barber et al. (2015) reported a similar association in a large sample of 50 adolescents with ADHD compared with 50 controls using Go/No-go variables related to lapses of attention. The authors found that under typical resting conditions, attention control was strongly related to anti-correlations between the DMN, FPCN and visual regions. However, the nature of this relationship varied for the control group and for the ADHD group. For both groups, increased anti-correlations between the DMN and occipital regions supported better attention control. For the ADHD group alone, reduced anti-correlations between the FPCN and the DMN predicted inattention, whilst in the control group, reduced FPCN-to-DMN correlations predicted greater attention control. This was interpreted in terms of a compensatory recruitment of the FPCN in ADHD in order to maintain DMN attenuation for prolonged periods of time.

4.1.3 ADHD as a disorder of DMN content

The content regulation hypothesis predicts that the effect of psychopathology on connectivity within the DMN is in altering the content of spontaneous thought to a point at which it no longer provides an adaptive function. Sonuga-Barke and Fairchild (2012) postulate that one cognitive feature of spontaneous thought that is altered in ADHD is self-reflection. Self-reflection is critical to developing a coherent autobiographical script about personal meaning and the subjective value of past experiences based on a well-integrated concept of an individual as an economic agent. In addition, the ability to reflect on past experiences is also thought to provide a basis

for imagining and then comparing the subjective utility of future outcomes. Altering the content of spontaneous thought by making it less goal orientated is thought to prevent an ADHD individual from adequately evaluating available choice alternatives leading to suboptimal decision - an important associated feature of ADHD.

Although no study to date has directly probed the content of spontaneous thought in ADHD, there is emerging evidence individuals with ADHD have a difficulty in accessing mental representations of previous experiences. With evidence of impaired autobiographical memory (Fabio & Caprì, 2015) and a deficit in implementing an intention at a previously specified point in time whilst performing an ongoing task (time-based prospective memory) (Talbot & Kerns, 2014). Moreover Klein, Gangi, and Lax (2011) found adults with ADHD appear to have a specific difficulty in recalling self-relevant autobiographical experiences and interestingly, are unable to use a period of passive self-reflection to augment performance on an episodic-memory encoding task. This finding is particularly significant because it suggests that spontaneous thought in ADHD may be more or less 'time wasted', without conferring any of the beneficial effects of problem incubation seen in neurotypical populations (Baird et al., 2012). Consistent with this prediction ADHD individuals have a difficulty in using past experiences to guide future decision making. This includes poor long-term planning in relation to goal setting, developing planning scripts and implicating intentions (i.e., prospective memory) (for review see: Sonuga-Barke and Fairchild (2012)). Interestingly this difficulty in forming future goals may be independent of deficits in hot and cold executive functioning, suggesting poor prospection in ADHD may be an important associated feature of ADHD that has largely been overlooked (Fuermaier et al., 2013).

Consistent with the content hypothesis of DMN functioning resting-state connectivity studies have suggested that connectivity *within* the DMN is also atypical in ADHD. In the same study that was described previously, Castellanos et al. (2008) found reduced connectivity between a seed in the posterior cingulate cortex and voxels in the medial frontal cortex. Fair et al. (2010) replicated these findings in 23 children with ADHD compared with equal numbers of controls. However, adopting a neurodevelopmental approach they found the normal age-related variability in connectivity across the entire DMN (and not just the core subsystem) as a result of normal maturation was slowed in ADHD. However, these findings were significant at an uncorrected threshold only, suggesting this effect may be due to chance and therefore should be treated with caution until it can be replicated. In a considerably larger sample of 193 children with ADHD compared with 455 controls, Fair et al. (2013) found that out of all of the brain circuits studied, abnormalities in the medial prefrontal cortex and precuneus of the DMN most strongly differentiated patients with ADHD from controls. These results appear consistent with a conceptualization of ADHD as a DMN disorder . More recently, Mattfeld et al. (2014) reported DMN reduced connectivity between the medial prefrontal cortex and the posterior cingulate cortex (and not reduced FPCN-to-DMN anti-synchrony) reliably differentiated 22 adults with active ADHD compared with 13 adults with a childhood diagnosis of ADHD but who no longer met a research diagnosis for the disorder. This result is interesting as it appears to suggest a core subsystem abnormality may be central to the emergence of ADHD-type symptomatology.

The use of data driven approaches to identify network nodes under typical resting state conditions have also found within-DMN connectivity abnormalities in ADHD. M. Qiu et al. (2011) found reduced connectivity within multiple midline

DMN clusters including the posterior cingulate cortex, lateral prefrontal cortex, precuneus as well as *increased* connectivity in the medial prefrontal cortex in a relatively sample of 15 children with ADHD compared with controls. Choi, Jeong, Lee, and Go (2013) also reported reduced connectivity between midline anterior and posterior components of the DMN in 20 children with ADHD compared with equal numbers of controls. Furthermore, consistent with the pattern of delayed maturation, children with ADHD failed to show the normal pattern of age-related increases in connectivity between midline DMN regions. Uddin et al. (2008) found reduced connectivity between a region covering the DMN and a cluster in the precuneus in a sample of 20 adults with ADHD compared with 20 controls. Alonso et al. (2014) also identified reduced connectivity within the precuneus in a sample of 23 young children with ADHD compared with equal numbers of controls. While Yu et al. (2016) reported reduced connectivity between three clusters centred in the precuneus, medial prefrontal cortex and angular gyrus respectively in 30 ADHD adolescents compared with 30 controls. All three of these brain regions have been shown to comprise components of the DMN core subsystem (Yeo et al., 2011).

As discussed there appears to be a fairly consistent pattern of either hypo- or hyper- connectivity overlapping nodes of the core subsystem evidenced from both seed based and data-driven analytical approaches. Although this tendency to find abnormalities in the core subsystem may partially be due to methodological limitations that bias results to showing this outcome. Seed based studies that measure connectivity between pre-specified regions of interest have tended to restrict analysis to the core subsystem whilst ignoring the dorsal medial and medial temporal subsystems (Mattfeld et al., 2014; Sidlauskaite, Sonuga-Barke, Roeyers, & Wiersema, 2016). Likewise, seed-to-voxel studies have also tended to only measure voxelwise

connectivity from the DMN core sub subsystem (Castellanos et al., 2008; Qiu et al., 2011). Given the tightly interconnected nature of the core subsystem (Andrews-Hanna et al. 2010), this would again weight any connectivity patterns observed to other nodes of the core subsystem. Even data-driven approaches such as ICA that are at least hypothetically free of experimental bias also rely on the researcher to visually identify a spatial map of the DMN. This identification is also typically guided by first localising the distinctive inverted T shape of the core subsystem (Van den Heuvel & Hulshoff Pol, 2010) - once again biasing results towards showing a core subsystem abnormality.

Only two studies have adopted analytical approaches suited to investigating the DMN as a functionally dissociable multi-component network. First, Chabernaud et al. (2012) measured seed-to-voxel in a sample of 37 children with ADHD compared with equal numbers of controls. Differing from previous studies connectivity was measured from seed regions of interest overlapping all three subsystems of the DMN and were not restricted to the DMN core. Externalising symptoms were found to correlate with hypo-connectivity within the medial temporal subsystem and internalising symptoms with hyper-connectivity within the DMN core subsystem. Second, Anderson et al. (2014) measured functional connectivity on a large sample of 276 adults and adolescents as part of the ADHD-200 data set. Using a data-driven approach that fractionated the DMN they also observed atypical functional connectivity within the medial temporal and core subsystems, results suggestive of a much wider pattern of impairment then previously demonstrated.

4.1.4 Conduct disorder as a disorder of DMN content

It is also plausible that altering the content of spontaneous thought in CD may contribute to the development of CD-type symptomatology. There are two ways this may occur: the first is to drive poor decision making when evaluating the likely outcomes of a future action. Sonuga-Barke et al. (2016) suggest suboptimal decision making in CD arises as a complex interaction between a difficulty in estimating the subjective cost of negative future events (which reduces the impact of future risk) and a reduced sensitivity to aversive outcomes (which mitigates an ability to then learn from these negative experiences). In a similar fashion to ADHD, deficits in prospection could contribute to negative evaluation, creating a present-orientated motivational style whereby thoughts pertain to more immediate subjective concerns rather than displaying the typical prospective bias that is seen in healthy adults. Indeed, several studies have demonstrated that participants with CD have difficulties in adjusting their behaviour following negative reinforcement (Schutter, van Bokhoven, Vanderschuren, Lochman, & Matthys, 2011), show altered sensitivity to gains or losses during choice evaluation (Fairchild, van Goozen, Stollery, et al., 2009), or discount the value of a reward more sharply with the delay of its receipt (White, Clanton, et al., 2013).

The second way that altering the content of spontaneous thought in CD may contribute to the development of CD-type symptomatology is to impair the self-reflective ability to derive personal meaning from experiences and relationships. Raine and Yang (2006) predict that a difficulty in reflecting on these experiences may contribute to antisocial and rule breaking behaviours in CD. Furthermore, Immordino-Yang, Christodoulou, and Singh (2012) link the ability to reflect on a previous experience to specific social-cognitive skills including compassion, moral reasoning and empathy. Deficits in self- referential processes in CD could contribute to a

difficulty in accessing previous experiences, impairing the construction of mental representations of one's own or another's thoughts, feelings and actions. These self-other distinctions are linked to prosocial behaviour (Y. Wang & Hamilton, 2015) and possibly judgements of affective empathy (Molnar-Szakacs & Uddin, 2013).

Only two studies have investigated the DMN in CD. In first of these two studies, Dalwani et al. (2013) used independent components analysis on a sample of 20 participants with CD and comorbid substance use disorders compared with equal numbers of controls. They demonstrated abnormal connectivity within nodes of all three DMN subsystems. However, the study did not include a dedicated rest period. This is a potentially significant limitation as the connectivity patterns of the DMN can be influenced by even minor changes in task characteristics. Further, substance use disorders are independently associated with DMN abnormalities and again, this is likely to have influenced the experiment's findings. In a second study, Zhou et al. (2015) used a sample of 18 participants with CD who were free of comorbidities and a matched group consisting of equal numbers of controls. They showed reduced DMN connectivity within the posterior cingulate cortex/precuneus and inferior parietal lobule. In contrast with the results of Dalwani et al. (2013), these findings suggested reduced connectivity within the core subsystem of the DMN only. However, factors known to contribute indirectly to DMN connectivity and to vary substantially in CD populations, including ADHD symptoms (Posner, Park, & Wang, 2014), IQ (L. Wang, Song, Jiang, Zhang, & Yu, 2011) and psychopathy (Pujol et al., 2012), where not adjusted for. Therefore, the extent to which these findings are unaffected by these factors is not clear.

4.2.1 Summary

In addition to task dependent systems there is considerable evidence that ADHD and emerging evidence that CD are both associated with atypical DMN functioning. In ADHD this presents in two ways. The first is reduced anti-correlations between the DMN and the FPCN which appears to be associated with the ability to maintain attentional engagement on a task. The second is either hypo- or hyper- connectivity within the DMN, postulated to impair prospection and to contribute to suboptimal decision making. In CD there is emerging evidence for either hypo- or hyper-functional connectivity within the DMN, this is thought to contribute to a more present orientated mindset and poor empathy.

General summary and overview of the thesis

Over the course of the last decade, there has been an important change in how the human brain is understood. This paradigm shift has ultimately been a recognition that the human functional repertoire is vast and cannot simply be reduced to task-specific brain states. In this literature review, we have argued that spontaneous cognition is a task-independent process that makes a very important contribution to goal-directed cognition. The main neural system that supports spontaneous thought is the DMN and we have presented evidence that the DMN is a multicomponent network, with each component making a functionally dissociable contribution to the production of the self-generated aspects of spontaneous thought. Abnormalities in this system may lead to 1) a difficulty in producing self-generated thought, 2) a difficulty in using spontaneous thought in a useful way, and 3) problems in being able to engage and disengage spontaneous thought appropriately. We have argued that, in ADHD, abnormal connectivity within the DMN core subsystem and between the DMN and FPCN likely contribute to respective deficits in decision-making and attention, both clinical features of ADHD. Likewise, in CD, reduced connectivity within the DMN could contribute to poor socio-emotional processing and suboptimal decision-making.

In the remainder of this thesis, we will describe three studies that were designed to further this research agenda and address some unanswered questions in the literature relating to the causes and clinical correlates of atypical DMN connectivity in three distinct populations that commonly present with ADHD. Chapter V will focus on the DMN and ADHD symptomatology in individuals with CD. It will extend previous studies by examining DMN functioning using a more systematic approach by examining connectivity within and between individual

subsystems of the DMN. It will also seek to ascertain how connectivity within the DMN may be associated with other clinical features of the disorder: age of onset of CD and the presence or absence of callous and unemotional traits. By being able to show a clear indication of DMN impairment in CD, this study would provide further support for investigations into self-referential processing in CD.

In Chapter VI we move on to explore the early life determinants of altered DMN connectivity in terms of its relation to the emergence of ADHD. Although usually thought of as a highly genetic condition, rates of ADHD are substantially elevated in individuals who have suffered institutional deprivation in early life (Kennedy et al., 2017; Roy, Rutter, & Pickles, 2004). This has led to the speculation that this persistent deprivation-related variant of ADHD is caused by an early-established fundamental alteration in brain networks responsible for the condition (Rutter & O'Connor, 2004). In this chapter, we investigate the effects of deprivation though institutionalization by distinguishing between aberrant DMN edges that are the result of deprivation and those caused by ADHD. Furthermore, we investigate how any effects of this apparent "deprivation related" ADHD on DMN connectivity differ from clinically typical ADHD seen in the general population. This will be performed using a seed-based approach to measure functional connectivity within each of the three subsystems of the DMN, providing a framework that can be more clearly related to functional impairment. This will be important in establishing how early life deprivation may contribute to the emergence of ADHD.

Throughout this literature review we have taken the position that spontaneous thought has an adaptive function. However, where alterations are made to functional connectivity within the DMN it may alter the content of spontaneous thought

contributing to psychopathological mental states. In chapter VII, we test the possibility that alterations to the intrinsic functional architecture of one or more subsystems of the DMN may contribute to the clinical and neuropsychiatric characteristics of ADHD. Here we test three hypotheses for how this may occur. The first is a variant of the context regulation hypothesis described above - that atypical functional connectivity reflects a disorganisation of network dynamics that prevents adequate attenuation during a goal directed task, contributing to psychopathological levels of mind-wandering as the DMN fails to inhibit itself. The second is that altered functional connectivity in individuals with ADHD impairs prospection, leading to suboptimal decision making which may lead to the preference for an immediate small reward over a delayed large reward. The third is an extension of the delay aversion hypothesis originally proposed by Hsu, Benikos, and Sonuga-Barke (2016). In brief it states that in addition to the externalising symptoms of ADHD, self-referential thought may also be used to ameliorate the negative affections faced by waiting and thus, atypical DMN functional connectivity could be driven by an aversion to delay. These three hypothesises will be tested on a clinical sample of adolescent patients with ADHD recruited from clinics in the Hampshire area using a seed-based mediational design. To the best of our knowledge this will be the first study to directly test how intrinsic connectivity may contribute to the psychological and motivational processes the network has been predicted to support. This is important in establishing the functional consequences of atypical DMN connectivity in ADHD.

Chapter V: Reduced Default Mode Connectivity in Adolescents with Conduct Disorder

5.1.1 Abstract

Objective: Conduct disorder (CD) is characterised by impulsive, aggressive and antisocial behaviours that may be related to deficits in empathy and moral reasoning. The brain's default mode network (DMN) has been implicated in self-referential cognitive processes of this kind.

Method: We examined connectivity between key nodes of the DMN in 29 male adolescents with CD and 29 age- and sex-matched typically-developing adolescents. We ensured that group differences in DMN connectivity were not explained by comorbidity with other disorders by systematically controlling for the effects of substance use disorders (SUDs), attention-deficit/hyperactivity disorder (ADHD) symptoms, psychopathic traits and other common mental health problems.

Results: Only after adjusting for co-occurring ADHD symptoms, the CD group showed hypo-connectivity between core DMN regions relative to typically-developing controls. ADHD symptoms themselves were associated with DMN *hyper-connectivity*. There was no effect of psychopathic traits on DMN connectivity in the CD group and the key results were unchanged when controlling for SUDs and other common mental health problems.

Conclusions: Future research should directly investigate the possibility that the aberrant DMN connectivity observed in the current study contributes to CD-related deficits in empathy and moral reasoning, and examine self-referential cognitive processes in CD more generally.

5.2.1 Introduction

Conduct disorder (CD) is defined as a repetitive and persistent pattern of antisocial behaviour in which the rights of others or societal norms are violated (American Psychiatric Association, 2013). Symptoms of CD include theft, vandalism and violence towards other humans and animals. Neuroimaging studies of CD implicate dysfunction in fronto-amygdala and fronto-insula circuits as part of a disrupted ventromedial/orbitofrontal-limbic network (Arnsten & Rubia, 2012; Matthys et al., 2013; Rubia, 2011). Several recent studies have also suggested that the brain's default mode network (DMN) could also be implicated (Cohn et al., 2015; Dalwani et al., 2013; Freeman et al., 2014). The DMN is comprised of the anterior medial prefrontal cortex (anterior medial prefrontal cortex), posterior cingulate cortex, medial temporal lobe, lateral parietal cortex and temporal-parietal junction (Andrews-Hanna et al., 2014; M. D. Fox et al., 2005). The DMN consists of different subsystems (Andrews-Hanna et al., 2014), namely, the dorsal MPFC (dMPFC) subsystem, the medial temporal lobe (MTL) subsystem, and the anterior medial prefrontal cortex – posterior cingulate cortex core system. These subsystems are thought to play a critical role in self-referential cognitive processing, including the construction of mental representations of the 'self', as well as one's own and others' possible future actions, thoughts and feelings (Buckner et al., 2008; W. Li, Mai, & Liu, 2014). In particular, the dMPFC subsystem is involved in theory of mind and morality judgments (W. Li et al., 2014; Reniers et al., 2012). The MTL subsystem is involved in binding together disparate information to facilitate scene construction (Andrews-Hanna et al., 2014) and the DMN core subsytem in attaching personal significance to internally-focused thoughts (Andrews-Hanna et al., 2014) as well as

forming the self-other distinctions linked to pro-social behaviour (Y. Wang & Hamilton, 2015) and possibly judgments of affective empathy (Molnar-Szakacs & Uddin, 2013). Thus the DMN and its component subsystems represent plausible pathophysiological substrates for deficits in emotion perception (Fairchild, Van Goozen, Calder, Stollery, & Goodyer, 2009), empathy (Lovett & Sheffield, 2007) or moral reasoning (Chudzik, 2007) that have been observed in individuals with CD.

Using independent components analysis (ICA), Dalwani and colleagues (Dalwani et al., 2013) found that, relative to typically-developing controls, male adolescents with CD showed reduced connectivity between the superior, medial, and middle frontal gyrus, lingual gyrus, retrosplenial cortex and lateral temporal cortex - reflecting generalized DMN dysregulation in CD. However, all of the participants with CD also had substance use disorders (SUDs), which have been previously shown to be associated with DMN abnormalities (Ding & Lee, 2013; Schooler et al., 2011; Sutherland, McHugh, Pariyadath, & Stein, 2012). Furthermore, the study did not include a dedicated rest period - instead using a task with alternating periods of rest and stimulus processing. This is problematic because DMN connectivity is affected by such variations in task characteristics (Yan et al., 2009) and instructions (Hsu, Broyd, Helps, Benikos, & Sonuga-Barke, 2013). Another recent small-scale study (Jiansong Zhou et al., 2015) reported DMN hypo-connectivity in male adolescents with CD who were free of comorbid SUDs, also using ICA methods but, in this case, more standard procedures for collecting resting-state functional magnetic resonance imaging (fMRI) data.

In the current study, we extend this analysis of DMN dysregulation in CD in a number of ways. First, we adopted a more theoretically-driven seed-based approach, better suited to investigating which DMN subsystems are impaired by restricting the

analysis just to those regions shown to be involved in mental construction, socio- and non-social- cognitive conceptualization and self-referential thinking (Andrews-Hanna et al., 2010). This takes advantage of the functionally dissociable nature of DMN subsystems and has the potential to provide a more straightforward interpretation in terms of underlying cognitive impairments. Indeed, such an approach has already been used to identify DMN subsystem-specific abnormalities in schizophrenia and major depression (Y. Chen, Wang, Zhu, Tan, & Zhong, 2015; Dodell-Feder et al., 2014; Du et al., 2016).

Second, we systematically examined the impact of clinical heterogeneity and comorbidity on the relationship between CD and DMN connectivity. In particular, we examined the impact of SUD comorbidity on DMN connectivity in CD, given that all of the CD participants in the study by Dalwani et al. had comorbid SUDs, whereas none of the subjects in the study by Zhou et al. reported SUD comorbidity. Epidemiological studies have shown a high degree of overlap between CD and SUDs (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Disney, Elkins, McGue, & Iacono, 1999), so this is an important clinical issue, and we felt it was important to replicate these findings suggesting that CD is associated with DMN abnormalities, irrespective of SUD comorbidity. We also sought to examine whether DMN abnormalities were related to psychopathic traits in our CD sample. Psychopathy is a personality disorder characterised by a callous lack of empathy and impulsive antisocial behaviour. Although the term psychopathy is not applied to adolescents, high levels of psychopathic traits are nevertheless associated with an increased risk of violent offending in participants with CD (Fanti et al., 2008; Frick, 2009) and CD with elevated psychopathic traits has been suggested to represent a more pervasive subtype of CD (Frick, Ray, Thornton, & Kahn, 2014). A number of studies have

reported reduced connectivity between brain regions overlapping with core DMN midline regions in psychopathic adults (Motzkin, Newman, Kiehl, & Koenigs, 2011; Pujol et al., 2012). Interestingly, even within the construct of psychopathy, there are possibly differential effects of the affective/interpersonal and antisocial factors of psychopathy, with the affective/interpersonal factor associated with decreased medial-lateral DMN connectivity and the antisocial factor associated with increased connectivity between prefrontal and parietal DMN components (Philippi et al., 2015). However, to date, no study has directly investigated the effects of psychopathic traits on DMN connectivity in participants with CD. Adolescence is a developmental period in which there are widespread changes in structural connectivity (Dennis et al., 2013) that may have a bearing on the developmental course of antisocial behaviour and psychopathy. This makes it pertinent to examine whether altered DMN connectivity in those with psychopathy is observed at an earlier stage in development. We also examined the association between DMN dysregulation and attention-deficit/hyperactivity disorder (ADHD) symptoms. ADHD is a neurodevelopmental condition characterised by persistent and age inappropriate levels of inattention, hyperactivity and impulsivity (American Psychiatric Association, 2013). This condition frequently co-occurs with CD, and is present in between 25-30% of boys with CD (Waschbusch, 2002). Even in those who do not meet formal diagnostic criteria for ADHD, there is considerable overlap in symptomatology and symptom dimensions of impulsivity and hyperactivity have been associated with the development of antisocial behaviour in childhood (Barkley, Fischer, Smallish, & Fletcher, 2004). Notably, ADHD is associated with abnormal DMN connectivity, hypothesized to reflect a disorganisation of the network and an inability to appropriately regulate self-generated thought (Castellanos et al., 2008; Sonuga-Barke

& Castellanos, 2007). Finally, we examined whether there were differences in DMN connectivity according to the age-of-onset of CD – i.e., whether DMN connectivity was altered in both childhood-onset and adolescence-onset subtypes of CD, or just the former subtype. Like psychopathy, the age-of-onset of CD is thought to differentiate between subtypes of CD that differ in terms of etiology and adult outcomes (American Psychiatric Association, 2013; Moffitt, 1993). Childhood-onset CD, which emerges before age 10, has been linked to distinct cognitive (Frick & Nigg, 2012) and neurophysiological (Passamonti et al., 2010) profiles compared to adolescence-onset CD, possibly reflecting the fact that these subtypes have different etiologies (Moffitt, 2006), although see (Fairchild, van Goozen, Calder, & Goodyer, 2013) for a review challenging this idea.

In summary, we examined DMN connectivity in adolescents with CD, using a more hypothesis-driven approach than has been used previously, to investigate distinct subsystems of the DMN. To this end, we employed a seed-based approach, measuring connectivity between *a priori* regions of interest (ROIs) in limited components of the extended DMN that are potentially involved in deficits in empathy and moral decision-making observed in young people with CD (Andrews-Hanna et al., 2010). We predicted that adolescents with CD would display a generalized reduction in DMN connectivity that would be especially pronounced in the subgroup with elevated psychopathic traits. We also predicted that these effects would not be accounted for by other comorbid conditions and would therefore persist when controlling for the effects of SUDs, ADHD, and other common mental disorders.

5.3.0 Method

5.3.1 Participants

Seventy male adolescents aged between 13-18 years were recruited from schools, colleges, pupil referral units and Youth Offending Teams in the Hampshire area of the UK. Of this total sample, 6 were excluded due to gross neurological abnormalities (gray or white-matter abnormalities and cysts), 3 for excessive head movement and 3 due to major depressive disorder (MDD) and/or generalised anxiety disorder (GAD) comorbidity. This meant that data from 58 participants (29 CD and 29 controls) were available for analysis. Sixteen participants had childhood-onset CD (i.e., at least one CD symptom prior to age 10) and 13 had adolescence-onset CD (i.e., symptoms only after age 10 (American Psychiatric Association, 2013)). Seven CD participants had comorbid ADHD, but were otherwise free of all other common co-occurring disorders (with the exception of oppositional defiant disorder – ODD). Healthy control participants screened negative for current psychiatric disorders using the same diagnostic instrument (see below).

5.3.2 Diagnostic Assessment

The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman et al. (1997)) was used to assess CD, and other common mental disorders (e.g., MDD, GAD, ODD, ADHD, obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD). The K-SADS-PL is a semi-structured interview based on DSM-IV criteria (American Psychiatric Association, 2000). If a symptom is endorsed at threshold by

either the child or the parent, it is considered present (Kaufman et al., 1997). Participants were given a research diagnosis of CD if they (or their parents) endorsed at least three CD symptoms in the last 12 months. Control participants were screened using the same instrument and were free of all assessed disorders, as well as past diagnoses of CD or ODD. All participants also completed the self-report Youth Psychopathic traits Inventory (YPI; Andershed, Kerr, Stattin, and Lavander (2002)) to assess psychopathic traits. The YPI measures psychopathy as a multi-component construct encompassing a grandiose and manipulative interpersonal style (factor 1), a callous and unemotional affective style (factor 2), and impulsive and irresponsible behaviour (factor 3). The YPI is scored on a 1-4 liket scale with a possible score of between 50 – 200. Scores above 125 classified as being 'high' in psycopathic traits (Skeem & Cauffman, 2003). Substance use was assessed using the problem severity scale of the Personal Experience Screening Questionnaire (PESQ) (Winters, 1991). In line with recommended scoring guidelines, participants aged below 16 years with scores >30 or those aged 16 and above with scores >35 were assessed as being at high risk for substance use disorders. Sixteen of the 58 participants (12 from the CD group, 4 from the control group) were excluded from the supplementary analyses testing for group differences in the non-substance use disordered sub-sample – this was to ensure possible effects of CD cannot be explained by co-occurring substance use. Handedness was measured using the Edinburgh Handedness Inventory (Oldfield, 1971).

5.3.3 Procedure

Initial assessment and screening took place on a day prior to the MRI scan. During this time informed consent was obtained from the participant, or the primary

caregiver if the participant was <16 years of age. Additional exclusion criteria were: 1) a clinical diagnosis of a neuro-developmental (e.g., Down's Syndrome) or pervasive developmental disorder (i.e., autism spectrum disorder); 2) an estimated IQ <75, as assessed using the two-subtest version of the Wechsler Abbreviated Intelligence Scale (Wechsler, 1999); and 3) standard MRI exclusion criteria (cardiac pacemaker, metal in body, claustrophobia, etc.). Eligible participants were invited to take part in an MRI scan lasting 35-40 minutes on a separate day.

5.3.4 Image Acquisition

fMRI data were acquired on a 1.5-Tesla Siemens Avanto (Siemens AG, Erlangen, Germany) MRI scanner at Southampton General Hospital in the UK. A 12-channel head coil was used to detect and receive the magnetic resonance signal. T1-weighted (MP-RAGE) three-dimensional datasets (voxel size=1.2x1.2x1.2 mm, repetition time = 2400ms, flip angle = 8°, 160 slices) were acquired, with an acquisition time of 7 min 41 sec. These were obtained for the purposes of registration and to create white matter (WM) and cerebrospinal fluid (CSF) masks used to generate confound regressors. Resting state fMRI data were acquired using a T2*-weighted gradient echo planar imaging (EPI) sequence (repetition time = 3600ms, 35 slices, voxel size= 3.26 x 3.26 x 3.26 mm, in an interleaved acquisition, flip angle = 90°, 123 volumes). The resting state scan lasted 6 min 10 sec. During the scan, participants were asked to relax and fixate on a red crosshair presented against a white background (i.e., eyes-open acquisition). Participants underwent the structural scan prior to the resting state scans.

5.3.5 Image preprocessing

The FSL version 5 software package (http://fsl.fmrib.ox.ac.uk) and the Connectivity Toolbox version 13 (http://www.nitrc.org/projects/conn; Whitfield-Gabrieli and Nieto-Castanon (2012)) were used for image preprocessing. The first three volumes of each functional time-series were discarded to allow for magnetic saturation effects. Participants were excluded if: 1) relative head displacement was > 3 mm in x, y, or z coordinates and 2) the maximum rotation encompassing yaw, pitch and roll was > 2°. Preprocessing steps included: 1) identifying outlier time-points that were included as confound regressors in the first level general linear model (motion scrubbing); 2) a rigid-body correction for head motion; 3) nonlinear registration of functional data to a T1-weighted MNI template that was resampled to $4mm^3$; 4) spatial smoothing (a gaussian full width at half-maximum kernel of $6mm^3$); 5) an anatomical component-based strategy(Behzadi, Restom, Liau, & Liu, 2007) (aCompCore) that involved regression of subject specific time-series from 6 components estimated from WM and CSF masks using principle components analysis; 6) band-pass filtering (0.008 – 0.09 Hz), and 7) despiking using a hyperbolic tangent function to reduce the influence of outlier scans.

5.3.6 Regions of interest (ROIs)

Eleven *a priori* ROIs were selected from coordinates provided by Andrews-Hanna and colleagues to study connectivity in all three subsystems of the DMN associated with different internally mediated cognitive processes - see Table 5.1/Figure 5.1 for details and the relevant coordinates. Andrews-Hanna et al. (2010) identified these seeds in a young adult sample. Whilst there is evidence that long-range connectivity within the DMN continues to develop well into adolescence, by adolescence these changes are limited to increases in functional connectivity *between*

nodes, with all major DMN nodes fully formed in childhood (Sherman et al., 2014; Supekar et al., 2010). Therefore, we felt justified in using these seeds in an adolescent population. All seeds were 8mm radius spheres created using FSL. Consistent with

Table 5.1. Default mode network regions of interest and their respective coordinates using the Talairach system with the Montreal Neurological Institute (MNI) template

Subsystem	Region	Abbreviation	MNI coordinates		
			X	Y	Z
Core subsystem	Posterior cingulate cortex	PCC	-8	-56	26
	Anterior medial prefrontal cortex	aMPFC	-6	52	-2
Dorsal medial Subsystem	Dorsomedial prefrontal cortex	dMPFC	0	52	26
	Temporal parietal junction	TPJ	-54	-54	28
	Lateral temporal cortex	LTC	-60	-24	-18
	Temporal pole	TempP	-50	14	-40
Medial temporal Subsystem	Ventral medial prefrontal cortex	vMPFC	0	26	-18
	Posterior inferior parietal lobule	pIPL	-44	-74	32
	Retrosplenial cortex	Rsp	-14	-52	8
	Parahippocampal cortex	PHC	-28	-40	-12
	Hippocampal formation	HF	-22	-20	-26

previous studies (Du et al., 2016), only left lateralized and midline regions were investigated in this study to prevent biasing connectivity to mirrored ROIs.

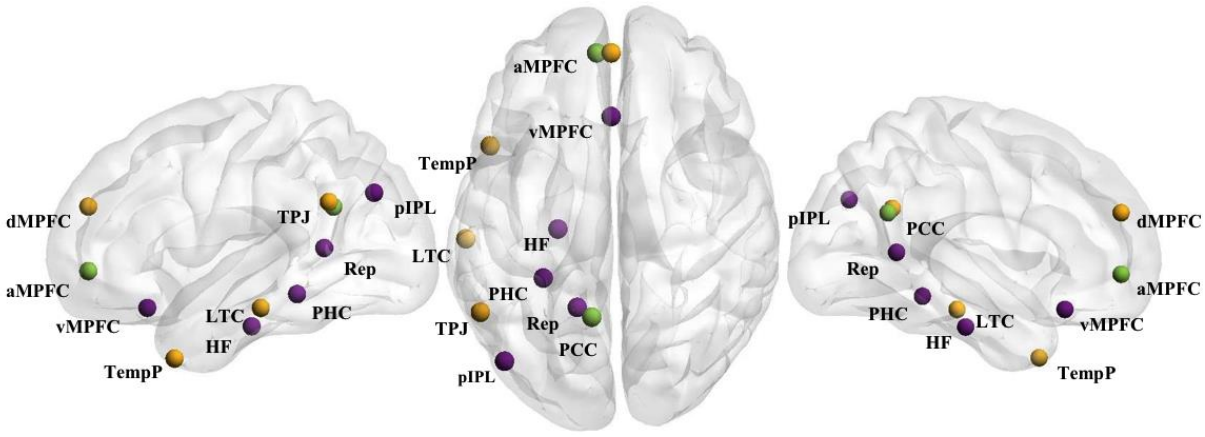

Figure 5.1. A schematic outline of the regions of interest included in this study displayed on lateral sagittal, axial and medial sagittal images of a semi-inflated brain. These overlap with the core default mode network (DMN) subsystem (green spheres), the dorsal medial subsystem (yellow spheres), the medial temporal subsystem (purple spheres). aMPFC=anterior medial prefrontal cortex, dMPFC= dorsal MPFC, HF=hippocampal formation, Rsp=retrosplenial cortex, LTC=lateral temporal cortex, PCC=posterior cingulate cortex, PHC=parahippocampal cortex, pIPL=posterior inferior parietal lobule TPJ=temporo-parietal junction, TempP=Temporal pole, vMPFC=ventral MPFC

5.3.7 Statistical analysis

The specific time-series were computed by averaging the temporally-filtered residual time series for each voxel within each seed. For each seed bivariate correlation matrices that were Fisher transformed to convert r values to an interval scale. Group comparisons used analysis of covariance (ANCOVA) to compare all subjects with CD with healthy controls in the first instance; we also compared the adolescence-onset and childhood-onset CD subgroups with healthy controls, and directly compared the adolescence-onset and childhood-onset CD subgroups. The influence of psychopathic traits on DMN connectivity was investigated using a linear regression analysis on the summed total YPI scores and each of the three separate

factors of psychopathy (i.e., interpersonal, affective and behavioural). For all second-level contrasts, age, IQ and ADHD symptoms were included as covariates of no interest. ADHD is a disruptive behaviour disorder that frequently co-occurs with CD and is independently associated with atypical DMN connectivity (Andrews-Hanna et al., 2010; Dodell-Feder et al., 2014; Posner et al., 2014). It was also important to control for age and IQ, given that development of the DMN continues well into adolescence (Sherman et al., 2014) and intelligence has been associated with connectivity strength (L. Wang et al., 2011). Results are reported at a threshold of $p<0.05$ (two-tailed), False Discovery Rate (FDR) correction at the level of the entire analysis (i.e., controlling for each seed and each target seed simultaneously). Given the reduced sample size, comparisons between the childhood-onset and adolescence-onset subtypes of CD and healthy controls were performed at an uncorrected alpha level of $p<0.01$ (two-tailed).

5.3.8. Ethics approval

This study was reviewed and approved by the University of Southampton Ethics Committee, the University Research Governance Office, the Hampshire County Council Research and Evaluation Unit, Southampton City Council Children's Services Research Governance Committee and the University Hospital Southampton NHS Trust's Research and Development Office.

5.4.0. Results

Table 5.2. Demographic and clinical characteristics of the sample.

	Conduct disorder group (n=29)	Control group (n=29)	*t-test*
Age (months)	198.38 (17.57)	196.45 (14.27)	.46
Intelligence Quotient	92.66 (10.15)	103.34 (10.22)	4.00*
Handedness	26R; 3L	25R; 3L	
ADHD symptoms[a]	7.93 (4.45)	0.69 (1.42)	8.34*
Psychopathic traits[b]	122.34 (22.00)	101.31 (15.79)	14.24*

Note. Values in parentheses show Standard Deviation, * p<.05, [a]ADHD symptoms derived from the ADHD supplement of the K-SADS-PL, [b]Psychopathic traits measured using the total score on the Youth Psychopathic traits Inventory. Handedness data missing from one control particiapant.

The groups were well matched in age and handedness. The CD group had lower IQ scores, more ADHD symptoms and higher levels of psychopathic traits than the control group (Table 5.2).

5.4.1 Conduct disorder and default mode network (DMN) connectivity

Conduct disorder was associated with reduced DMN connectivity specifically between the anterior medial prefrontal cortex and posterior cingulate cortex; $t_{(53)}$= 3.69, $p_{(\text{FDR corr})}$= 0.03 (see Figure 5.2a). Connectivity between other DMN subsystems was unrelated to group status. This reduction in connectivity in the core subsystem remained significant when excluding 16 participants with probable substance use disorders, although at an uncorrected alpha level only; $t_{(37)}$=2.75, $p_{(\text{uncorrected})}$= 0.009; (Figure 5.2b). When either the adolescence-onset or childhood-onset CD subgroups

were compared with the control group, we continued to find lower core subsystem connectivity at an uncorrected alpha level (for the adolescence-onset group only: $t_{(37)}$=2.86, $p_{(uncorrected)}$= 0.006; for the childhood-onset group only: $t_{(43)}$=3.39, $p_{(uncorrected)}$= 0.0015). There were no significant differences in connectivity between the childhood-onset and adolescence-onset CD subgroups, even at an uncorrected level. Interestingly, the CD-related effects were not significant if ADHD symptoms were not included as a covariate, suggesting that important changes in DMN connectivity in CD patients with comorbid ADHD may be obscured by the fact that CD and ADHD symptoms have opposing effects on DMN connectivity.

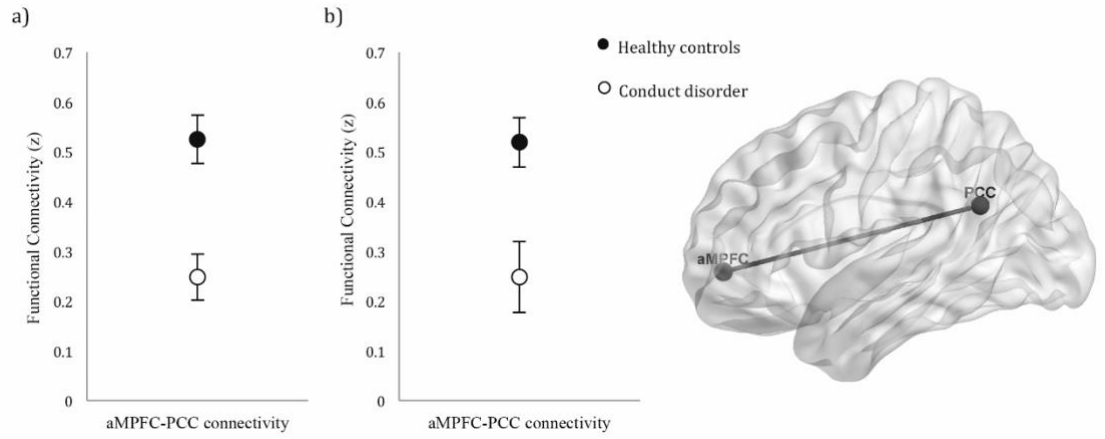

Figure 5.2. Functional connectivity (Fisher z-transformed values) as a function of group status, closed circles show the healthy control group, open circles show the conduct disorder (CD) group. Participants with CD either: a) including participants with probable substance use disorders or b) excluding participants with probable substance use disorders, showed reduced default mode network connectivity between the anterior medial prefrontal cortex (aMPFC) and posterior cingulate cortex (PCC) compared with healthy controls. Group differences in connectivity are significant at p<0.05, False Discovery Rate (FDR) correction for all seed-to-target pairs or at an uncorrected threshold of p<0.01.

To investigate this effect further and study the relative contributions of CD and ADHD to DMN connectivity, we tested the relationship between DMN connectivity and ADHD symptoms. Adopting the reverse approach to that described above by controlling for group status (i.e., CD versus control group), we found that ADHD symptoms were *positively* correlated with DMN connectivity (see Figure 5.3). Specifically, functional connectivity between the anterior medial prefrontal cortex and the posterior cingulate cortex; $t_{(53)}$=3.74, $p_{(\text{FDR corr})}$= 0.03, and the anterior medial prefrontal cortex and retrosplenial cortex; $t_{(53)}$=3.48, $p_{(\text{FDR corr})}$= 0.03, increased as a function of ADHD symptoms. These findings suggest that ADHD is linked to DMN hyper-connectivity, whereas CD is linked to hypo-connectivity in the DMN core subsystem (anterior medial prefrontal cortex- posterior cingulate cortex) only. There were no significant correlations when testing for the effects of the inattentive or hyperactive symptom dimensions of ADHD on DMN connectivity (for all seed-to-seed correlations, all $p_{(\text{FDR corr})}$ values >.10) .

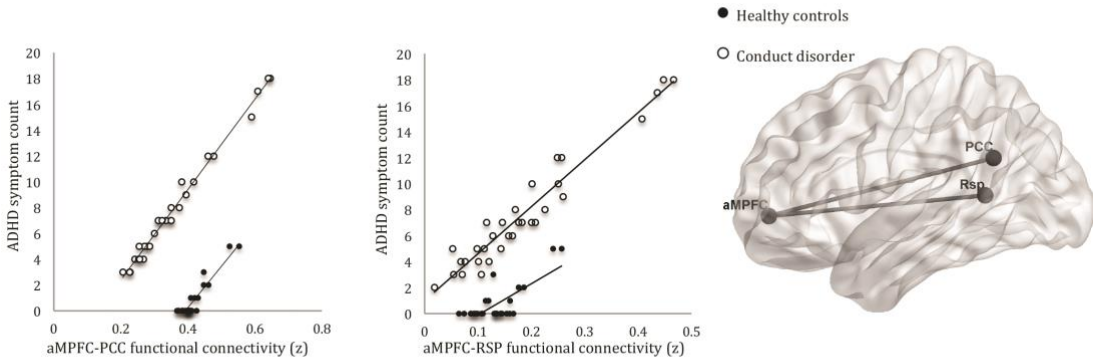

Figure 5.3. Increased functional connectivity (Fisher Z-transformed values) as a function of attention-deficit/hyperactivity disorder (ADHD) symptoms, closed circles show the healthy control group, open circles show the conduct disorder group. After controlling for group status, participants with high levels of ADHD symptoms show hyper-connectivity between the anterior medial prefrontal cortex (aMPFC) seed and two components of the DMN: the posterior cingulate cortex (PCC) and the retrosplenial cortex (Rsp). Correlations between ADHD symptoms and connectivity are significant at p<0.05, False Discovery Rate (FDR) correction for all seed-to-target pairs.

5.4.2 Psychopathy and DMN connectivity

There were no significant associations between total psychopathy scores and DMN connectivity within the CD group. This was also the case for the three psychopathy sub-factors (i.e., interpersonal, affective and behavioural) - for all seed-to-seed correlations, all $p_{(FDR\ corr)}$ values >.70.

5.4.3 Potential confounding factors

Excluding participants with probable substance use disorders or comorbid ADHD and left-handers did not substantially affect our findings (see supplementary information for Chapter V; Table S1).

Given that the CD and control groups differed in IQ, we also tested for correlations with IQ across all participants to examine whether IQ influenced functional connectivity. We found no significant correlations between IQ and DMN connectivity (for all seed-to-seed correlations, all $p_{(FDR\ corr)}$ values >.40).

5.5.1 Discussion

We tested the hypothesis that CD is associated with reduced connectivity in the default mode network (DMN) – a network previously shown to be important for self-referential and other-referential cognitions. This was done using a seed-based approach to examine connectivity between brain regions known to make up the subsystems of the extended DMN. There were a number of findings of note.

First, in support of our hypothesis, we obtained evidence that CD is linked to significantly reduced anterior medial prefrontal cortex to posterior cingulate cortex connectivity, suggesting impairment in the DMN core subsystem. This effect survived statistical correction for multiple comparisons and was present when controlling for comorbid ADHD symptoms or, at an uncorrected threshold, when excluding participants with probable substance use disorders or full ADHD diagnoses. Importantly, these effects did not extend to other DMN subsystems and therefore differed from the findings of Dalwani et al. (2013) who demonstrated a more generalized DMN deficit in adolescents with CD and comorbid substance use disorders. Our results are consistent with the recent findings of Zhou et al. (2015) who also identified DMN hypoconnectivity centred in posterior midline components of the DMN (Jiansong Zhou et al., 2015). However, unlike the study by Zhou et al. (2015), we controlled for group differences in IQ and ADHD symptoms, which have previously been shown to be associated with DMN connectivity (L. Wang et al., 2011; Waschbusch, 2002). This is important given the degree of clinical overlap between ADHD and CD, as well as the robust association between CD and lower IQ (Broyd et al., 2009; Kim-Cohen et al., 2005).

Second, we did not find effects of psychopathic traits or age-of-onset of CD, two factors suggested to delineate between meaningful subtypes of CD, on DMN connectivity. This challenges the view that age-of-onset can be used to differentiate neurophysiologically

distinct subgroups (Moffitt, 1993) and extends the literature by demonstrating that DMN abnormalities are observed in both childhood-onset and adolescence-onset CD subgroups. We also found no effect of psychopathic traits on DMN connectivity. This finding contradicts earlier evidence from adult prisoners that has demonstrated lower DMN connectivity in individuals with high levels of psychopathic traits relative to typically-developing adults. For example, Pujol et al. (2012) compared prisoners with high levels of psychopathic traits with healthy controls and Motzkin et al. (2011) compared prisoners with high versus low levels of psychopathy. Both studies found connectivity between anterior and posterior midline components of the DMN were reduced in psychopathic individuals compared with control subjects. Consistent with these findings, Sethi et al. (2015) recently compared prisoners with high levels of psychopathy and non-offender controls using diffusion tensor imaging and found reduced fractional anisotropy (a measure of structural connectivity) in the former group in the dorsal cingulum tract that connects midline posterior and anterior DMN components (Sethi et al., 2015). However, none of these studies controlled for antisocial personality disorder (an adult condition analogous to CD) and so the effects reported, which were strikingly similar to those observed in the current study, could have been due to antisocial behaviour in general rather than psychopathy *per se*. Alternatively, or perhaps in addition to this - all previous studies included adult prisoners, a population very different from the young preselected sample included in this study in terms of experience and comorbidity (Fazel, Hayes, Bartellas, Clerici, & Trestman, 2016; Nock, Kazdin, Hiripi, & Kessler, 2006). This could potentially also account for the non-replicability of our findings.

Third, the DMN effects related to CD were only present when controlling for ADHD symptoms. Indeed, ADHD symptoms were associated with *increased* connectivity within the anterior medial prefrontal cortex- posterior cingulate cortex subsystem, when controlling for CD group status. In addition, ADHD symptoms were positively correlated with anterior

medial prefrontal cortex – retrosplenial cortex connectivity. As well as highlighting the importance of controlling for ADHD symptoms in studies of CD, these findings add to the literature demonstrating ADHD-related alterations in the DMN (Castellanos et al., 2008). The results of previous studies have been inconsistent in this regard. Some have demonstrated DMN hypo-connectivity related to ADHD (Castellanos et al., 2008; Fair et al., 2010). Our study like only one previous study (Barber et al., 2015), demonstrated ADHD-related hyper-connectivity. The reason for this variation between studies is unknown, although it has been suggested these differences reflect the frequent inclusion and failure to control for comorbid disorders (most notably CD) (Barber et al., 2015). Our results suggest that ADHD is associated with intra-DMN hyper-connectivity, rather than hypo-connectivity, and that comorbid CD or disruptive behaviour disorders may have opposing effects on DMN connectivity.

It should be noted that many other psychiatric disorders have been linked to DMN dysfunction (for a review, see Broyd et al. (2009)), and therefore abnormalities in this network are not specific to CD. While we were able to demonstrate that our findings of hypo-connectivity in the core anterior medial prefrontal cortex- posterior cingulate cortex subsystem were not the result of co-occurring psychiatric disorders, establishing that this DMN impairment is specific to CD is outside the scope of the current paper, given that we did not include any psychiatric control groups. However, it is possible that the nature of the DMN dysfunction in CD is different in nature from that observed in other disorders. For example, schizophrenia appears to be associated with reduced DMN connectivity in all subsystems of the network (Du et al., 2016), and this has been correlated with subsystem-specific deficits in cognitive processes (Dodell-Feder et al., 2014). Likewise in MDD (B. Li et al., 2013), OCD (Beuke et al., 2014) and autism spectrum disorders (Assaf et al., 2010), respectively, there is emerging evidence of disorder-specific abnormalities that may be tied to

individual subcomponents of the DMN. To our knowledge, no empirical study has directly compared DMN connectivity across a range of clinical groups to test the specificity (or otherwise) of DMN disturbances. This would be an interesting avenue for future research.

In terms of the functional significance of DMN hypo-connectivity in CD, we hypothesize that this deficit may lead to impairments in self-referential processes that are required for empathy and moral decision-making in CD (i.e., judgments about the self and others). While this prediction has not been tested empirically, it may provide an alternative way of understanding the cognitive features of CD (Raine & Yang, 2006). For instance, a difficulty in accessing one's own mental states may hinder self-evaluative thinking that could lead to difficulties in learning from punishment (Raine & Yang, 2006) or impair affective empathy(Lamm, Bukowski, & Silani, 2015). Beyond social cognition, self-reflection is also an important factor in decision-making given that we frequently have to evaluate a set of possible outcomes before making our choices. Several studies have demonstrated that participants with CD have difficulties in adjusting their behaviour following negative reinforcement (Schutter et al., 2011), show altered sensitivity to gains or losses during choice evaluation (Fairchild, van Goozen, Stollery, et al., 2009), or discount the value of a reward more sharply with the delay of its receipt (White, Clanton, et al., 2013). Collectively, these findings have been interpreted as reflecting a present-orientated mindset and a difficulty in prospection (Sonuga-Barke et al., 2016) – the ability to build mental representations of future events, which is thought to be mediated by the DMN.

The current study had several strengths, including a relatively large sample, detailed assessment of psychiatric symptoms including CD and ADHD, investigation of the impact of ADHD symptoms on DMN connectivity in CD, as well as conservative treatment of fMRI artefacts. However, there were also some limitations that need to be taken into account. First,

a direct test of the impact of this pattern of altered DMN connectivity on self-referential cognitive processes was outside the scope of the current study. Nevertheless, there is a wealth of evidence suggesting that synchronization between the posterior cingulate cortex and anterior medial prefrontal cortex occurs during tasks involving self-referential thought (Jeffrey R. Binder et al., 2009; Brewer et al., 2013). Second, following Andrews-Hanna et al. (2010), we placed seeds only in the left hemisphere of the brain. This could have limited our ability to detect group differences in the right hemisphere. Third, our analyses of the effects of ADHD symptoms on DMN connectivity would have been strengthened by including individuals with non-comorbid ADHD alone, as the nature of the present sample meant that CD and ADHD symptoms were positively correlated. Fourth, as the analysis was restricted to males, the results of this study may not generalize to female populations. Fifth, group differences in IQ could have contributed to the hypo-connectivity findings that we obtained, although because we included IQ as a covariate of no interest and found no significant association between IQ and DMN connectivity, this interpretation seems unlikely. Sixth, previous studies have explained elevated functional connectivity in terms of movement (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012). It is therefore plausible that residual motion could have biased some of the connectivity patterns observed.

In summary, as predicted, CD was associated with relatively reduced connectivity between anterior and posterior components of the core hub of the DMN. This effect was only present when controlling for comorbid ADHD symptoms. Furthermore, individual differences in psychopathic traits within the CD group were unrelated to DMN connectivity, and both childhood- and adolescence-onset CD subgroups appeared to show reduced DMN connectivity compared with typically-developing controls. We hypothesize that these group differences in DMN connectivity may contribute to the difficulties seen in CD in terms of

empathy and social understanding

Chapter VI: Childhood institutional deprivation moderates the relationship between default mode network functional connectivity and adult attention-deficit/hyperactivity disorder symptoms

6.1.1 Abstract

Objective: Adults who experienced severe institutional deprivation in early childhood have substantially elevated rates of attention-deficit/hyperactivity disorder (ADHD) – but it is unclear whether deprivation-related ADHD has a distinctive neural signature. In its typical clinical presentation, ADHD is associated with reduced connectivity in the default mode network (DMN) - a set of interconnected brain regions activated during introspection and self-referential thought. Here we investigated whether this was also the case in a group of adult adoptees exposed as children to extended periods of institutional deprivation contrasting them with adoptees who experienced limited or no deprivation.

Method: Resting-state functional magnetic resonance imaging (rsfMRI) data was analysed using a seed-based approach to measure DMN connectivity in 67 Romanian adoptees (23-26 years) who had previously experienced up to 36 months of deprivation in the institutions of the Ceaușescu regime and 21 non-deprived UK adoptees. ADHD symptoms were measured using parent-report questionnaires.

Results: Overall, DMN core subsystem (medial prefrontal cortex-posterior cingulate) connectivity was elevated in Romanian adoptees exposed to >6 months deprivation compared to those exposed to <6 months deprivation and non-deprived UK adoptees. The association between DMN connectivity and elevated ADHD symptoms varied as a function of deprivation exposure – with hyperconnectivity observed in adoptees exposed to >6 months deprivation but hypo-connectivity in the other two groups.

Conclusions: Severe adversity in childhood has an enduring effect on the functional architecture of the brain. This leads to distinct neurobiological signatures for ADHD symptoms in children exposed to extended institutional deprivation.

6.2.1 Introduction

Exposure to extended periods of institutional deprivation in early childhood is associated with a higher incidence of psychological disorders later in life (Humphreys, Fox, Nelson, & Zeanah, 2017; Sonuga-Barke et al., 2017). This is supported by findings from the Young Adult Follow up of the English and Romanian Adoptees (ERA) study - a prospective longitudinal investigation of the effects of childhood exposure to severe global deprivation prior to adoption into UK families. In particular, extended deprivation (i.e., > 6 months) was associated with a strong persistence of social impairment marked by disinhibited social engagement (DSE; (Kennedy et al., 2017)), and autistic symptoms (Sonuga-Barke et al., 2017). Most strikingly, extended deprivation was associated with a seven-fold increase in the rates of adult attention-deficit/hyperactivity disorder (ADHD)– a near doubling of the deprivation-related risk compared to adolescence (Kennedy et al., 2016). The strong persistence of increased risk for ADHD, even after many years of living in enriched adoptive environments, is consistent with a deep-seated neurobiological effect resulting either directly, or indirectly, from exposure to adversity (Rutter & O'Connor, 2004). However, little is known about the underlying neurobiological mechanisms responsible for deprivation-related ADHD and whether these differ from those implicated in expressions of these disorders unrelated to early negative experiences. In general terms, deprivation could alter brain development by limiting necessary experiences during critical periods of development (a failure of 'experience-expectant programming'), by promoting an adaptation to severely depriving circumstances to prepare for continuing adverse experiences throughout life (termed 'experience-adaptive programming') or by directly causing stress-related damage (Kumsta et al., 2017; Rutter & O'Connor, 2004). In this paper we investigate such putative

effects in relation to the default mode network (DMN) - a brain system previously shown to be disrupted in clinically typical ADHD (Castellanos & Aoki, 2016) and potentially sensitive to adversity during development (Teicher, Samson, Anderson, & Ohashi, 2016).

The DMN is a large-scale brain network thought to underpin certain aspects of internally orientated and self-referential cognition (K. C. Fox, Spreng, Ellamil, Andrews-Hanna, & Christoff, 2015). It is organised into three inter-connected subsystems. The *medial temporal subsystem*, comprises ventromedial prefrontal cortex, parietal and hippocampal brain regions, and the *dorsal-medial subsystem*, comprises dorsal medial prefrontal cortex, temporal parietal junction and lateral temporal cortex extending to temporal pole (Andrews-Hanna et al., 2010; Yeo et al., 2011). The *middle temporal subsystem* is hypothesised to create mental scenes of autobiographical representations of past experiences. The *dorsal-medial subsystem* uses such stored mental representations to guide semantic and social-cognitive processes such as theory of mind (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Andrews-Hanna, Smallwood, & Spreng, 2014). A *core subsystem* – comprising anterior medial prefrontal cortex and posterior cingulate cortex - acts as a hub, biasing information processing in the other two subsystems according to self-relevance (Andrews-Hanna et al., 2010; 2014) and in combination with the mirror neuron system may simulate embodied representations of the self and others (Utevsky et al., 2014). These allow the individual to form a continuous sense of self that is stable over time and underpins the ability to envision the future - a core competence that feeds into intertemporal decision-making (Molnar-Szakacs & Uddin, 2013; Sonuga-Barke et al., 2016).

DMN dysfunction manifests in a number of different ways in clinically typical ADHD presentations (Posner et al., 2014). First, in terms of its intrinsic functional architecture, abnormalities present as hypo-connectivity in the core subsystem during rest (Posner et al., 2014) - a pattern of dysregulation hypothesized to impair prospection, leading

to more present-orientated thought and suboptimal inter-temporal decision making (Sonuga-Barke et al., 2016; Sonuga-Barke & Fairchild, 2012). Second, individuals with ADHD experience DMN hyperactivity during task performance which increases mind wandering and attentional lapses (Liddle et al., 2011)– effects hypothesized to be due to impaired rest-to-task transitioning (Sonuga-Barke & Castellanos, 2007). There is also preliminary evidence that DMN organisation is linked to early life adversity. For instance, parental conflict during childhood was associated with DMN hyperconnectivity in the core subsystem in 6 to 12-month-old infants (Graham, Pfeifer, Fisher, Carpenter, & Fair, 2015) and adults who retrospectively reported experiencing various different types of adversity in early life also show atypical DMN core subsystem connectivity (Bluhm et al., 2009; Philip et al., 2013; Teicher, Anderson, Ohashi, & Polcari, 2014; Van der Werff et al., 2013).

There is emerging evidence that the functional integrity of the DMN is sensitive to early life adversity. On the basis that the DMN is not fully formed at birth and matures rapidly during the first year of life (Doria et al., 2010; Fransson et al., 2007; Smyser et al., 2010), Graham et al. (2015) postulated that this represents a developmental period when the DMN is especially sensitive to the effects of adverse early experiences. Consistent with this, they found that inter-parental conflict predicted DMN hyper-connectivity in the core subsystem in 6 to 12-month-old infants. While there have been no similar studies in later childhood, atypical DMN functional connectivity has been found in adults who retrospectively report experiencing various different types of adversity in early life. The most consistent finding here is atypical DMN core subsystem connectivity (Bluhm et al., 2009; Philip et al., 2013; Teicher et al., 2014; Van der Werff et al., 2013).

However, many of these earlier studies linking maltreatment to altered DMN connectivity had methodological limitations (Rutter, Kumsta, Schlotz, & Sonuga-Barke, 2012). Individuals who have experienced different types of adversity (e.g., physical abuse and

neglect), of varying severity and durations are often grouped together and then compared with a non-exposed control group - although the effects of maltreatment on brain development appear to differ according to the type, developmental timing, duration and severity of exposures (Teicher et al., 2016). Exposure to early adversity may also be confounded by both genetic and later environmental risks. Parental psychopathology that predisposes parents to maltreat their children and also predisposes their children to psychopathology may both be driven by the same genes (i.e., a passive gene-environment correlation; Kim-Cohen, Moffitt, Caspi, and Taylor (2004)), and mediated by common brain networks (Teicher et al., 2014). Furthermore, children who are maltreated by their parents are more likely than their peers to be exposed to chronic adversity that persists into adolescence (Green et al., 2010). Finally, studies often use retrospective designs that over-sample individuals suffering from psychopathology (e.g., depression, anxiety, post-traumatic stress disorder, borderline personality disorder). This is problematic both because retrospective accounts of prior abuse may be distorted by current psychopathology (Fergusson, Horwood, & Woodward, 2000; Hardt & Rutter, 2004) and because neural alterations which are then attributed to maltreatment are difficult to distinguish from those related to idiopathic psychopathology at the time of testing (Teicher et al., 2014).

Using data from the ERA Young Adult Follow-up study, we aimed to address some of these limitations. The ERA study is a prospective longitudinal investigation of a relatively large sample of children who experienced up to 43 months of severe global deprivation in Romanian institutions under the Ceausescu regime of the late 1980s before being adopted into above average families in the UK (Kumsta et al., 2015). Infants were typically placed into institutions shortly after birth, making it unlikely that initial placement was due to pre-existing handicaps or differences, and remained in the institutions until they were adopted by UK families. The transition to the UK adoptive families was abrupt and precisely timed. This

made it unlikely that institutional deprivation was followed by additional maltreatment, whilst ensuring the form and duration of exposure could be objectively measured. Crucially, duration of deprivation was unlikely to be confounded by family-based or genetic factors. Of particular methodological value for the current study is the fact that children were stratified based on their age at adoption (a proxy for the duration of deprivation they experienced) with roughly equal numbers of individuals exposed to less than 6 months deprivation, between 6-24 months, and over 24 months of deprivation. There was also a comparison group of non-deprived UK individuals who were adopted before the age of 6 months, to control for the effects of adoption in general.

The ERA sample has now entered adulthood and we have conducted a brain imaging study to investigate the long-term effects of deprivation on brain structure and function and their role in deprivation-related clinical outcomes. Therefore, in the current paper we specifically addressed two related research questions: (i) Is severe institutional deprivation in early life associated with alterations in DMN connectivity in young adulthood? To answer this, we compared formerly-institutionalized Romanian adoptees with a group of non-deprived UK adoptees in terms of DMN functional connectivity; and, (ii) to what extent is DMN connectivity associated with ADHD symptomatology - and does the nature/direction of this association vary as a function of degree of deprivation (e.g., < 6 months versus > 6 months deprivation)? This cut-off was adopted on the grounds that previous ERA analyses have consistently demonstrated a step increase in disorder and impairment for those with > 6 months deprivation compared to both the non-deprived UK adoptees and the Romanian adoptees with < 6 months deprivation, who had the same low levels of problems (Kreppner et al., 2010; Sonuga-Barke et al., 2017). Based on results from clinically typical ADHD presentations, we predicted hypoconnectivity in the core subsystem of the DMN in the low deprivation group (either non-deprived or <6 months of deprivation). Although it was not

possible to formulate a strong hypothesis with regard to the effects of extended deprivation based on current limited knowledge, maltreated samples suggest DMN core subsystem hyper-connectivity following >6 months deprivation, which may be especially pronounced in more symptomatic individuals.

6.3.0 Method

6.3.1 Participants

Between February 1990 and September 1992, 165 Romanian adoptees who had spent up to 43 months in the extremely depriving Romanian orphanages of the Ceaușescu regime were adopted into intact and typically well-resourced UK families. With few exceptions, the conditions in institutions were appalling, with shortages of food and a lack of social contact. Children and their adoptive parents were identified using Department of Health and/or Home Office records based on their time of entry to the UK. The ERA study also included a comparison group of 52 UK-born children placed into adoptive families before the age of 6 months. These individuals had no documented experience of abuse, neglect or institutional rearing. In the full sample, cognitive, emotional and social development was assessed at ages 6, 11 and 15 years and in young adulthood (between 23-25 years). Of the 135 Romanian adoptees and 42 UK adoptees involved in the Young Adult Follow-up study (Sonuga-Barke et al., 2017), 81 Romanian adoptees and 23 UK adoptees also took part in the ERA brain imaging study (ERABIS). Of this sample, 11 never institutionalised Romanian adoptees were excluded from the current analysis given they had not experienced institutional deprivation but may have been deprived in other ways. A further three Romanian adoptees and two UK adoptees were excluded due to missing structural/functional MRI data. This left a final sample of 67 Romanian adoptees who had experienced some level of institutional deprivation (29 females; mean age= 25.34 years; SD= 1.10 years), and 21 non-deprived UK adoptees (8 females; mean age= 24.43 years, SD= 1.03 years) – see Table 6.1. There was no evidence of selective attrition: no clinical or demographic characteristics measured at age 15 predicted who was eventually included in the brain imaging arm of the study (see selective attrition

analysis and Table S2 in Supplementary Information for Chapter VI). All participants provided informed consent prior to taking part.

6.3.2 Clinical assessments

Clinical assessments took place as part of the ERA Young Adult Follow-up and included a wide range of different measures. For the purposes of the current analysis, we focus on common deprivation-related outcomes of ADHD (Sonuga-Barke et al., 2017). ADHD symptoms were assessed using an adapted version of the Conner's Comprehensive Behaviour Rating Scale Parent Report (CBRS-PR; Conners, Pitkanen, and Rzepa (2011)) - a validated questionnaire measure used to assess common childhood and adolescent mental health problems. It includes the 18 ADHD items from the DSM-IV (American Psychiatric Association, 2000). A symptom was considered endorsed if parents reported a score of 2 or more on a scale of 0-3 and indicating the symptom was present 'often' or 'quite a bit'. The final variable represented the total number of endorsed ADHD items. Autism symptoms were assessed using a shortened 15-item variant of the Social Communication Questionnaire (SCQ) parent report, modified to include only questions judged to be age appropriate for a young adult population ((Rutter, Bailey, & Lord, 2003); see: Sonuga-Barke et al. (2017) for excluded items). The SCQ has three subscales (social reciprocal interaction, communication, and repetitive and stereotyped behaviours) and item responses were coded on a 0 to 1 scale as either present or absent. Other measures included: IQ, assessed using the four subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), and socio-economic status, a binary measure (low versus high) based on data on parents' occupation collected at the age 15 follow-up (General Register Office, 1971).

6.3.3 MRI data acquisition.

fMRI data were acquired using a General Electric MR750 3.0 Tesla MR scanner (GE Healthcare, Milwaulkee, USA) at the Centre for Neuroimaging Sciences at King's College Hospital, London using a 12-channel head coil. T1-weighted (MP-RAGE) three-dimensional structural MRI data-sets (repetition time= 7312 ms, flip angle 11°, 256 x 256 matrix, Voxel size= 1.05x1.05x1.2 mm, 196 slices) were acquired for the purposes of registration and to produce white matter and cerebral spinal fluid masks to assist in de-noising. Resting-state fMRI data were acquired using a T2*-weighted gradient echo-planar imaging (EPI) sequence (repetition time = 2000 ms, 41 slices, voxel size = 3.75x3.75x3mm with a 0.3mm gap between slices, in a descending sequential acquisition, flip angle = 75°, 180 volumes). The resting state scan lasted for 6 min after removal of the first 4 scan volumes to limit magnetic saturation effects. During the resting-state scan, participants were instructed to lie still with their eyes open and look at a fixation cross in the centre of the projected screen, viewed through a periscopic mirror. The eyes open acquisition was selected given that resting-state test-retest correlation coefficients were found to be highest for this condition (Patriat et al., 2013). During image pre-processing volume time series were checked for relative displacement greater than 1 voxel in the x, y, z coordinates or rotations in roll, pitch and yaw greater than 3º (~0.53 radians). No scans exceeded this threshold, so all data were retained.

6.3.4 Image pre-processing.

The FSL version 5 software package (http://fsl.fmrib.ox.ac.uk) and the Connectivity Toolbox version 17e (http://www.nitrc.org/projects/conn; Whitfield-Gabrieli and Nieto-Castanon (2012)) were used for image analysis. First, rigid-body correction for head motion was applied. All scans were then registered to the Montreal Neurological Institute (MNI) space using a nonlinear registration performed with 12 degrees of freedom, after which the dataset was spatially smoothed with an isotropic full-width half-maximum kernel of 6 x 6 x 6

mm^3. To reduce the influence of spurious correlations arising from movement; outlier time-points were calculated as the intensity difference of each realigned time series to a reference volume and their first order temporal derivatives were regressed from the functional dataset (so-called motion scrubbing). We also regressed out 24 motion parameters comprising absolute rotation, displacement, their first order temporal derivatives and six quadratic expansions of these derivatives. In addition, subject-specific time series from the top five principal components estimated from binary white matter and cerebrospinal fluid masks were regressed from the functional data set. After regression, the data was bandpass filtered to restrict analysis within the slow 4 and 5 frequency bands (0.01-0.073Hz) - optimally capturing resting-state signal whilst excluding artefactual signal (Xue, Li, Weng, Northoff, & Li, 2014).

6.3.5 Regions of interest (ROIs)

Eleven *a priori* ROIs overlapping the core, dorsal medial and medial temporal subsystems of the DMN were used. Our selection of these regions and their respective coordinates was informed by Andrews-Hanna et al. (2010). These ROIs were centred on voxels identified in a young adult population as making a functional contribution to the social-cognitive and self-referential cognitive processes associated with DMN functioning – see Table 5.1 and Figure 5.1. All seeds were 8mm radial spheres created using FSL. Consistent with previous studies (Andrews-Hanna et al., 2010; Dodell-Feder et al., 2014; Du et al., 2016; Zhu, Zhu, Shen, Liao, & Yuan, 2017), only left lateralized and midline regions were investigated to prevent biasing connectivity to mirrored ROIs.

6.3.6 Statistical analysis

Mean signal time-series were extracted from each seed ROI to create subject-specific seed-to-seed bivariate connectivity matrices. This yielded correlation coefficients that were Fisher transformed into Z values to create an interval scale. Following previous studies that have used this set of ROIs, we first calculated values for all edges and then averaged these within each of the three DMN subsystems, resulting in measures of overall functional connectivity specific to each subsystem (Dodell-Feder et al., 2014; Zhu et al., 2017).

We investigated the effects of deprivation on DMN connectivity using independent sample t-tests to compare averaged connectivity within the dorsal medial, medial temporal and core subsystems separately. Participants were contrasted according to the duration of deprivation they experienced (UK, Rom<6, Rom>6) using an analysis of variance (ANOVA) and post hoc t-tests to identify direction of any observed effects. The correlation between connectivity indices and duration of deprivation exposure expressed as a continuous variable was also calculated in the Romanian adoptee group.

We next examined the relationship between ADHD and connectivity, focusing specifically on the DMN subsystems found to be significantly related to deprivation in the above analysis. In order to test whether these relationships were moderated by deprivation status a hierarchical multiple regression analysis was employed with *deprivation* (UK and Rom>6 combined (LoDep) vs Rom>6) and ADHD *symptom level* at the first level, a *deprivation* x ADHD *symptom* level interaction at the second level and DMN subsystem connectivity as the outcome variable. All analyses controlled for IQ level and autism symptoms, as these have previously been associated with deprivation and linked to altered DMN connectivity (Lynch et al., 2013). All contrasts were thresholded at $p<0.05$, False Discovery Rate (FDR) correction for the number of subsystems examined.

6.4.0 Results

6.4.1 Demographic and clinical characteristics

Romanian adoptees who experienced more than 6 months of deprivation (Rom>6) were older and showed significantly elevated ADHD symptoms compared with those with less than 6 months deprivation (Rom<6) and the non-deprived UK adopted control group (see Table 6.1). They also had a significantly lower mean IQ. The three groups did not differ significantly in terms of sex or parental socioeconomic status.

Table 6.1. Demographic and clinical characteristics of the sample.

Measure	UK (n=21)[a]	Rom<6 (n=21)[b]	Rom>6 (n=46)[c]	F	Post hoc comparisons
Age	24.43 (1.03)	24.52 (0.93)	25.72 (0.94)	18.55***	c>b,a*** b<c***
Sex	8 F/ 13 M	9 F/ 12 M	20 F/ 26 M	2.36	N/A
IQ	107.95 (18.40)	102.89 (16.52)	96.17 (12.52)	4.05*	c<a**
SES	3 low/ 18 high	1 low/ 20 high	4 low/ 37 high	1.10	N/A
Months spent in institutions	N/A	3.50 (2.52)	19.36 (8.46)		N/A
ADHD symptoms	1.20 (2.30)	2.67 (3.92)	4.85 (4.60)	5.63**	c>b*,a** b<c*
Autism symptoms	0.20 (0.70)	0.32 (0.58)	0.71 (0.90)	3.16*	c>a*

Note: *p<0.05, **p<0.01. ***p<0.001; a = UK adoptees, b = Rom<6, c = Rom>6; values in parentheses report standard deviation; Autistic symptoms were not available for 11 participants (3 Rom<6, 7 Rom>6, 1 UK adoptee); ADHD symptoms were missing for 8 participants (1 Rom>6, 6 Rom<6, 1 UK adoptee); IQ data missing from 13 participants (2 Rom<6; 10 Rom>6; 1 UK adoptee); SES (social economic status) data not available for 4 participants (4 Rom>6);

6.4.2 Effect of institutional deprivation on averaged DMN subsystem connectivity

Following Andrew-Hanna et al, (2010) we initially used a seed-to-seed resting-state fMRI approach to examine group differences within left lateralised subsystems of the larger DMN. We found elevated connectivity within the DMN core subsystem in adoptees who experienced extended deprivation (Rom>6) compared to the other two groups; $F_{(2,87)}$=5.21,

$p_{(\text{FDR correction})}$=0.021, $t_{(68)}^{\text{UK adoptees}}$=2.48, $p_{(\text{FDR correction})}$=0.046, $t_{(67)}^{\text{Rom<6}}$=2.86, $p_{(\text{FDR correction})}$=0.017 – see Figure 6.1. We then extended the analysis to the right hemisphere and found that effects were also present bilaterally; $F_{(2,87)}$=4.90, $p_{(\text{FDR correction})}$= 0.03, $t_{(68)}^{\text{UK adoptees}}$=2.40, $p_{(\text{FDR correction})}$= 0.050, $t_{(67)}^{\text{Rom<6}}$= 2.81, $p_{(\text{FDR correction})}$= 0.028). Following the same approach, we found a positive correlation between duration of deprivation (a continuous measure defined as age of entry to the UK as an estimate of time spent in institutions) and DMN connectivity both in the originally defined left (r=0.28, p=0.03) and right lateralised networks (r=0.22, p=0.04) – see Figure 6.2. There was no significant association between duration of deprivation and functional connectivity within either the dorsomedial and medial temporal subsystems – this was true for both the group-based and correlational analyses (all p-values >0.1).

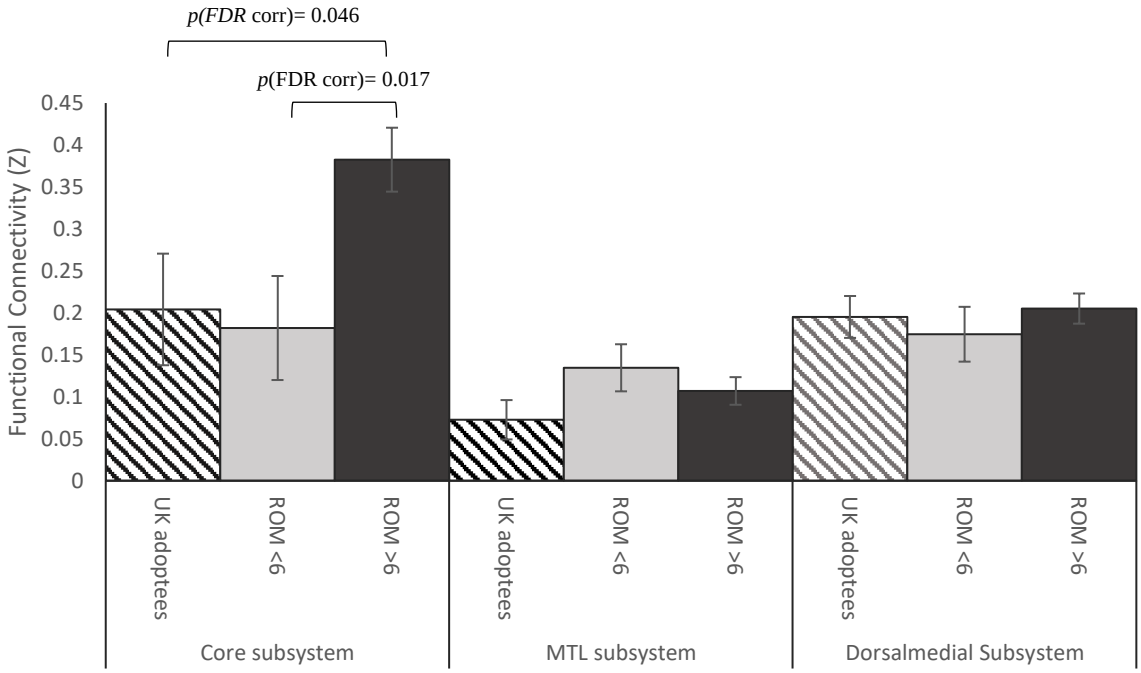

Figure 6.1. Global functional connectivity within the three subsystems that comprise the default mode network (DMN). Romanian adoptees who spent more than 6 months living in institutional deprivation (ROM>6) showed core subsystem hyper-connectivity compared with non-deprived UK adoptees and Romanians who spent less than 6 months living in deprivation (ROM<6). Error bars report standard error of the mean. MTL subsystem = medial temporal lobe subsystem

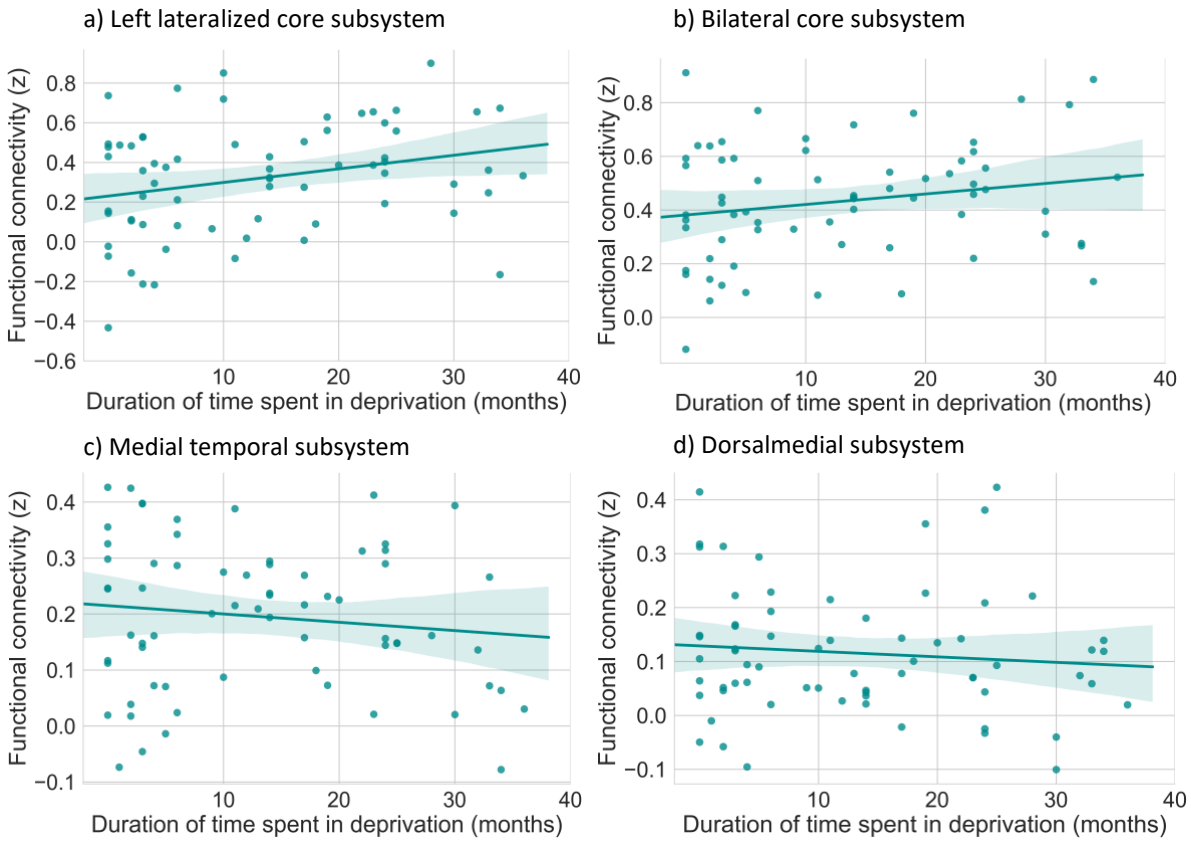

Figure 6.2. Overall functional connectivity in the three subsystems of the default mode network as a function of deprivation duration. a) Connectivity in the left lateralised and b) bilateral core subsystem correlates positively with the number of months spent in deprivation in Romanian institutions. There was no significant relationship between duration of deprivation and connectivity in either c) the medial temporal subsystem or d) the dorsal medial subsystem. Shaded areas report 95% CI

6.4.3 Associations between DMN core-subsystem connectivity and ADHD symptoms

Given that the UK and <6 groups did not significantly differ in terms of functional connectivity or ADHD symptoms, both groups were combined into a Low-Deprivation ("LoDep") group for subsequent analyses. Figure 6.3 illustrates the association between DMN core subsystem connectivity and ADHD symptoms in Rom>6 and LoDep groups. In the former, ADHD symptoms were positively correlated with core subsystem connectivity – with high levels of symptoms associated with DMN hyperconnectivity. The pattern was reversed in the LoDep group - higher ADHD symptoms were related to DMN *hypo*-connectivity.

The difference between the slopes in each case was tested using hierarchical multiple regression analyses with DMN core subsystem connectivity as the outcome variable and deprivation (LoDep vs. Rom>6), ADHD symptom severity and an ADHD x deprivation interaction term as the predictors. In the final model there was a main effect of deprivation (ß=0.17, t=2.18, p=0.03) but not ADHD (ß=0.008, t=0.99 p=0.33). Over and above this there was a significant deprivation-by-symptom level interaction (ß=0.22, t=2.99, p=0.004). Post hoc tests showed that both LoDep and Rom>6 slopes differed significantly from zero - connectivity was positively correlated with ADHD symptoms in the Rom>6 group (r=0.29, p=0.03) and negatively correlated with ADHD symptoms in the LoDep group (r=-0.47, p=0.03). Including autism symptoms and IQ in the model did not affect either the overall pattern of interaction or the main effect of deprivation (see Supplementary information for Chapter VI; table S3).

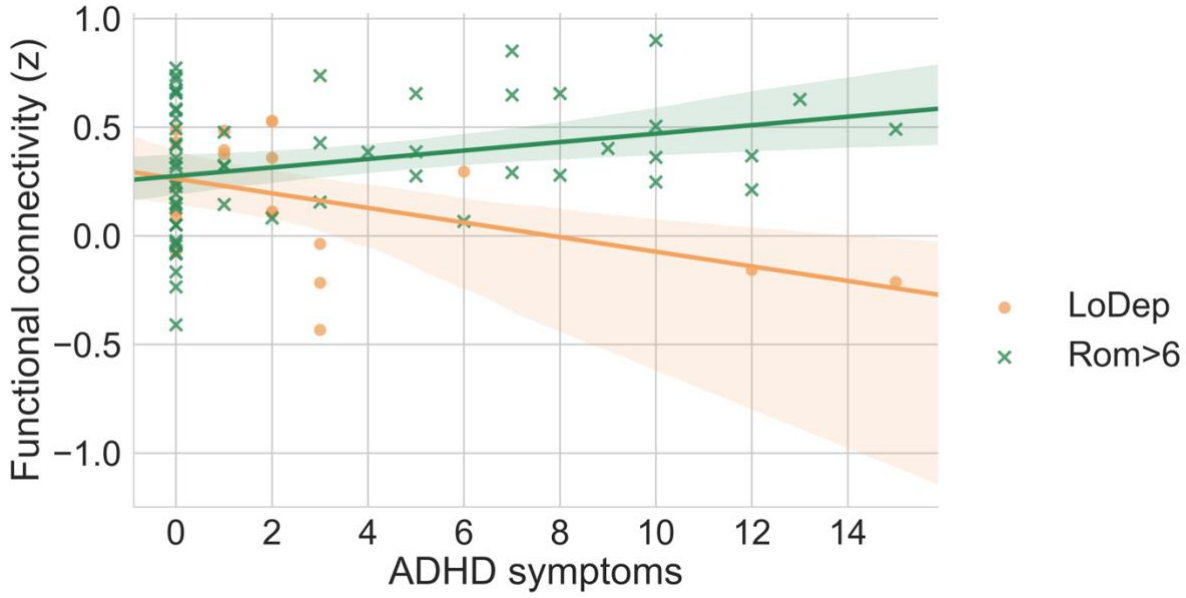

Figure 6.3. Interactions between deprivation status ((LoDep - Rom<6 and UK adoptees: orange trend line, versus extended exposure to deprivation ((Rom>6): green trend line) and symptoms of attention-deficit/hyperactivity disorder (ADHD) on default mode network core subsystem connectivity. Shaded areas report 95% CI.

6.4.1 Discussion

Using resting state fMRI data from the ERA study, we examined the long-term effects of time-limited severe deprivation in early childhood on the functional organisation of the brain in early adulthood –focusing on the DMN and its putative role in *deprivation-related* ADHD symptoms. First, extended exposure to institutional deprivation in early childhood was associated with DMN core subsystem hyperconnectivity in adulthood. Adoptees who experienced >6 months of deprivation displayed greater anterior medial prefrontal cortex - posterior cingulate cortex connectivity compared to both those who had experienced < 6 months deprivation and non-deprived UK adoptees. Within the Romanian adoptees as a whole, the number of months spent in institutional care was linearly associated with the degree of hyperconnectivity observed. The long-term nature of these effects on the functional architecture of the brain is especially striking – such effects are present in the adoptees more than 20 years after they were removed from the severely depriving institutions of the Ceaușescu regime, despite them growing up in loving, supportive and well-resourced families in the intervening years. The results, therefore, support the hypothesis that adverse experiences have long-term effects on the functional organisation of the brain, emphasising the impact of very early and time-limited deprivation on brain development. It is possible that such effects are manifestations of early programming or stress induced damage during critical periods of brain development in infancy (Rutter & O'Connor, 2004). Alternatively, the hyperconnectivity observed here may represent a compensatory reorganisation during the post-institutional period. However, if the latter alternative were true, we might expect the pattern of DMN hyperconnectivity to be linked with more positive outcomes. Unfortunately, this was not the case and the fact that ADHD symptoms were associated with DMN hyperconnectivity casts doubt that such effects are adaptive. A number of previous studies have shown a link between early adverse exposures and later brain structure or function;

however, in these studies it was challenging to draw a direct link because of design limitations (Govindan, Behen, Helder, Makki, & Chugani, 2009; Kumar et al., 2014). Because our study uses a prospective longitudinal natural experimental design, establishing a dose-response relationship between deprivation duration and DMN connectivity strengthens inferences about the causal role of exposure on subsequent brain development. This is because duration of deprivation is unlikely to be confounded with pre-existing genetic risk for ADHD in this sample, as the timing of the adoption was driven by historical events (the fall of the Communist regime in Romania) rather than characteristics of the children. This was confirmed by an analysis showing no correlation between ADHD polygenic risk scores and deprivation (Kumsta, in prep).

Second, institutional deprivation affected the DMN core subsystem only. From a functional perspective, based on these results, one would predict that the ability to construct mental simulations associated with the medial temporal subsystem (Buckner et al., 2008) or the social-cognitive and semantic abilities associated with the dorsal medial subsystem (Andrews-Hanna et al., 2014) would be intact in the extended deprivation group. Core subsystem hyperconnectivity has been linked to poor self-referential processing potentially affecting how goal-orientated decisions are evaluated (Sonuga-Barke et al., 2016) and excessive constraints to spontaneous thought by biasing thought patterns towards internally-orientated or externally-orientated stimuli (Christoff, Irving, Fox, Spreng, & Andrews-Hanna, 2016). Our findings promote the use of specific tests in to investigate these functional domains in future studies.

Third, the relationship between DMN core subsystem connectivity and ADHD symptoms varied markedly as a function of the degree of deprivation exposure. As predicted, we found the “classical” pattern of ADHD-related hypoconnectivity in the LoDep group (Castellanos & Aoki, 2016). In contrast, the pattern was reversed for individuals who

experienced extended deprivation - with high levels of ADHD symptoms associated with DMN *hyper*connectivity. This finding is of particular interest as it suggests that variants of neurodevelopmental disorders arising from extreme environmental exposures may differ in their pathophysiology from typical clinical counterparts, where genetic factors are likely to play a more central role. Therefore, our results can be understood within the broader 'ecophenotype' framework – that argues for important neurobiological and clinical differences between maltreated and non-maltreated individuals with the same diagnosis (Teicher & Samson, 2013). In this context, it is interesting to reflect on whether diagnostic systems should move towards specifying etiologic subtypes – 'deprivation-related ADHD' for instance. Given the phenomenological basis of current diagnostic approaches (i.e., focusing on symptoms rather than causes) and the substantial etiological and pathophysiological heterogeneity within neuro-developmental disorders, such a move would require solid evidence for a differential prognosis and treatment response in deprivation- and non-deprivation related subtypes. In this regard we have recently shown that ADHD occurring as a function of early deprivation seems to constitute a particularly persistent variant of the condition, which is equally common in males and females (Kennedy et al., 2016). Future studies should continue to explore the usefulness of etiological sub-typing of common disorders.

Fourth, the main effect of deprivation was independent of interaction effects related to ADHD symptoms. There are two implications of this finding. First, it addresses criticisms of prior research that have tended to confound the effects of early life adversity on brain development with the neural signature of extant psychopathology (for review see Teicher et al. (2016)). Second, there are several individuals in the Rom > 6 group that appeared to show DMN hyperconnectivity but did not display elevated ADHD symptoms. In the ERA sample more generally, we have a number of highly resilient people who were exposed to extended

periods of deprivation but seemed to suffer no enduring ill effects (Sonuga-Barke et al., 2017). Interestingly, the current analysis suggests that some of these resilient individuals might still bear the neural hallmark of the deprivation they experienced. This may confer a latent vulnerability for future disorders (De Brito et al., 2013).

This is the first study to examine the long-term effects of early institutional deprivation on DMN connectivity, and its relationship with symptoms of ADHD. It had many strengths, most crucially the natural experimental design which allowed the effects of adversity to be disentangled from other risk factors typically shared within families in which maltreatment occurs (i.e., both genetic risks and the presence of concurrent psychopathology). This permitted us to be more confident about inferring a causal role for the adverse exposures on brain development – either directly, or via compensatory processes. However, there are several limitations that need to be considered when interpreting these findings. First, there was an interval of several months – in some cases stretching to a year - between when clinical assessments were performed and MRI scanning. However, given the persistence of ADHD symptoms seen over many years in the ERA study, substantial variation in clinical presentation over this time period is unlikely (Sonuga-Barke et al., 2017). Second, the UK adoptee comparison group used in this study had a significantly higher IQ than the Rom>6 group. More generally, IQ is strongly negatively correlated with time spent in institutional deprivation, making these two constructs difficult to disentangle statistically or conceptually (Sonuga-Barke et al., 2017). However, controlling for IQ had minimal effect on our results. Third, following the approach of Andrews-Hanna et al. (Andrews-Hanna et al., 2010) the functional connectivity analyses were initially restricted to the left hemisphere and only extended bilaterally if significant effects were detected. This approach would have precluded the detection of deprivation effects that were present in the right hemisphere only. Fourth, the present analysis was restricted to the DMN and future studies investigating how

atypical DMN connectivity relates to other functional networks are now needed. Fifth, there were unequal levels of symptoms in the LoDep and Rom>6 groups and this likely reduced our statistical power to detect significant associations in the current analyses.

In summary, our findings support the hypothesis that severe and extended institutional deprivation in childhood has long-term effects on the functional architecture of the human brain - specifically the DMN core subsystem, which is involved in self-referential processing. Furthermore, altered connectivity in the core subsystem was significantly associated with symptoms of ADHD, with the nature of effects dependent on prior levels of deprivation exposure. This is consistent with the hypothesis that where these conditions emerge following exposure to environmental adversity, such deprivation-related variants may have a different pathophysiological basis from non-deprivation-related variants.

Chapter VII: Default mode network hypo-connectivity in ADHD: How is it related to individual differences in mind-wandering, delay aversion and temporal discounting?

7.1.1 Abstract

Objective: Attention-deficit/hyperactivity disorder (ADHD) has been repeatedly linked to hypo-connectivity within the brain's default mode network (DMN). However, little empirical research has examined how changes in DMN connectivity relate to neuropsychological deficits seen in ADHD. We tested hypotheses linked to mind-wandering and intertemporal choice, which are reliably altered in ADHD.

Method: Twenty male adolescents with a clinical diagnosis of ADHD and 22 sex- and age-matched controls underwent a resting-state scan so that average functional connectivity within the three subsystems of the DMN could be estimated. Individual differences in mind-wandering were measured by self-report and temporal discounting and delay aversion were assessed using validated parent-report scales.

Results: ADHD was associated with lower connectivity within the core and medial temporal subsystems and elevated levels of mind-wandering and delay aversion and temporal discounting. The pathway between group membership and DMN hypo-connectivity was partially mediated by delay aversion.

Conclusion: These results are consistent with the hypothesis that DMN hypo-connectivity in ADHD is a consequence of delay aversion. This may reflect the recruitment of self-referential processes to cope with the aversive nature of resting/waiting periods.

7.2.1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a complex and impairing neurodevelopmental condition characterised by age-inappropriate inattention and/or hyperactivity-impulsivity (Faraone et al., 2015). It is associated with structural and functional alterations in multiple brain networks responsible for diverse neuropsychological processes (Cortese et al., 2012). Indeed, functional magnetic resonance imaging (fMRI) studies have demonstrated disrupted functional connectivity in a range of resting state networks that contribute to neuropsychological processes known to be impaired in ADHD (for review see Posner et al. (2014)). For instance, studies have reported a distinctive pattern of reduced connectivity between nodes of the default mode network (DMN) in ADHD. The DMN is a multi-component brain network, made up of three interconnected subsystems (Andrews-Hanna et al., 2010; Doucet et al., 2011; Yeo et al., 2011). These include a *dorsal medial subsystem* consisting of dorsal medial prefrontal cortex, lateral temporal cortex, temporal parietal junction and temporal pole, a *medial temporal subsystem* made up of the hippocampal formation and parahippocampal cortex and ventral medial prefrontal cortex, retrosplenial cortex and inferior parietal lobule, and a *core subsystem* consisting of the anterior medial prefrontal cortex, posterior cingulate cortex and portions of the inferior parietal lobule. In general, the DMN is active during rest or self-referential and introspective states (e.g., mind wandering/day dreaming; K. C. Fox et al. (2015)) including reflecting on the past and envisioning the future (Buckner et al., 2008). It is down-regulated during conditions requiring focused attention on the external world and stimuli (Fransson, 2006). In conditions such as these, where DMN activity is not attenuated it interferes with task performance (C.-S. R. Li, Yan, Bergquist, & Sinha, 2007).

Within the general domain of self-referential and introspective cognitions, the three subsystems are functionally dissociable: the dorsal medial subsystem is linked to mentalising

and conceptual and emotional processing (Andrews-Hanna et al., 2014). The medial temporal subsystem is considered to support memory and mental scene construction by binding together disparate information (Andrews-Hanna et al., 2014). This gives it an important role in spontaneous (non-goal directed) mental time travel as events are typically recalled within a spatial context (Christoff et al., 2016; Karapanagiotidis, Bernhardt, Jefferies, & Smallwood, 2017). The core subsystem is related to self-referential cognition, biasing internally-oriented thought in the other two subsystems towards personally relevant goals (Molnar-Szakacs & Uddin, 2013; Utevsky et al., 2014). As such, the core subsystem contributes towards integrating autobiographical information related to desired future states and the ability to 'imagine' goal-orientated outcomes (Spreng et al., 2014).

Most resting state studies of ADHD have reported hypo-connectivity within the DMN core subsystem during rest (e.g., Choi et al. (2013); M. Qiu et al. (2011)). Such effects have been shown to be present in both children (M. Qiu et al., 2011) and adults (Castellanos et al., 2008). However, previous studies may have been biased toward finding core sub-system effects because of the methodological limitations and analytical approaches adopted. Indeed, many only studied the core subsystem and ignored the medial temporal and the dorsal medial systems (e.g., Dey, Rao, and Shah (2012); Sidlauskaite et al. (2016)) or adopted an approach involving calculating voxel-wise connectivity from only a core-subsystem node (e.g., Sato, Hoexter, Castellanos, and Rohde (2012)). This may have the effect of biasing observed connectivity patterns given the tightly interconnected nature of the core subsystem, thus failing to take account of the DMN's functionally dissociable nature, leading researchers to underestimate the wider effects of ADHD on DMN connectivity. Indeed, previous studies that have measured DMN connectivity from nodes outside of the core subsystem (Chabernaud et al., 2012; Fair et al., 2010) or adopted data-driven approaches that fractionate the DMN (Anderson et al., 2014), have demonstrated ADHD-related disruption in the medial

temporal subsystem. Therefore, whilst core subsystem hypo-connectivity may be expected, a comprehensive understanding of how ADHD affects DMN connectivity outside the core subsystem is lacking.

Critically, the functional consequences of DMN hypo-connectivity on (neuro)psychological function remain to be empirically determined (Christoff et al., 2016). In the current study we investigate three alternative hypotheses. The first hypothesis is that DMN hypo-connectivity underpins task-unrelated thought (mind-wandering; see Table 1.1) in ADHD, which leads to attentional impairment when there is a failure to attenuate DMN activity during the transition to task performance (Sonuga-Barke & Castellanos, 2007). Individuals with ADHD report elevated levels of mind-wandering (Franklin et al., 2014; G. Shaw & Giambra, 1993), and show a reduced ability to prevent mind-wandering during task performance and a reduced awareness that attention has wandered in the first place, preventing any self-regulatory attempts to mitigate the negative outcomes on task performance (Franklin et al., 2014; Schooler et al., 2011). DMN core sub-system activity is closely associated with patterns of mind-wandering (K. C. Fox et al., 2015) and has been shown to preferentially activate during task-unrelated than task-related thought (Stawarczyk, Majerus, Maquet, & D'Argembeau, 2011). Furthermore, temporary lesions to nodes of the core subsystem induced using transcranial magnetic stimulation have been shown to either inhibit or increase mind-wandering, suggesting this subsystem performs important self-regulatory functions that may be impaired in ADHD (Kajimura, Kochiyama, Nakai, Abe, & Nomura, 2017). DMN hypo-connectivity in ADHD has been suggested to contribute to network disorganisation, preventing adequate attenuation when transitioning to a goal directed state (Aboitiz, Ossandón, Zamorano, Palma, & Carrasco, 2014). On the basis of these findings, we predicted that reduced DMN connectivity in ADHD would be associated with increased levels of mind-wandering.

The second hypothesis is that abnormal DMN connectivity impairs prospection about the future outcomes of different choices - leading to sub-optimal intertemporal decision making, which in ADHD is characterised by a tendency to assign less value to future compared to immediate rewards (I. Marx, Hacker, Yu, Cortese, & Sonuga-Barke, 2018). First proposed by Sonuga-Barke and Fairchild (2012) (see also Sonuga-Barke et al. (2016)), the hypothesis is that DMN dysregulation undermines self-reflection by blunting the ability to envision future events, preventing the ADHD individual from fully estimating the subjective utility of different choice outcomes. Benoit, Gilbert, and Burgess (2011) found in a non-ADHD sample, that the DMN core subsystem was differentially activated when participants were imagining the value of future economic outcomes and that the degree of activation was correlated with the tendency to discount the value of delayed rewards. Based on this model and related findings, we predicted that core subsystem hypo-connectivity in ADHD would be associated with a tendency toward greater temporal discounting.

A third hypothesis is that DMN alterations in ADHD represent a compensatory response to, rather than a cause of, a patient's neuropsychological characteristics. This idea was first proposed by Hsu et al. (2016) as an extension of the delay aversion hypothesis. These authors argued that DMN activity and the introspective states it underpins (i.e., daydreaming) reduce the aversiveness of periods of idle time for people with ADHD by changing the perception of time passing. In this sense it plays a role within the delay aversion model equivalent to that of the external manifestations of ADHD - inattention and hyperactivity (Sonuga-Barke, 2002, 2003). In support of this view, Hsu et al. (2016), found that children with ADHD, relative to non-ADHD controls had elevated levels of very low frequency electroencephalography (EEG) oscillations in a network with sources overlapping the DMN during both wakeful rest and during periods when they are waiting for rewards. Crucially, DMN-related neural activity was correlated with parent-reported delay aversion.

The more activity was observed within the DMN during rest and waiting conditions, the stronger was their aversion to delay. Given these findings, we predicted that both DMN hypo-connectivity and parent-reported delay aversion would be associated with ADHD and that delay aversion would mediate the pathway between ADHD group membership and DMN hypo-connectivity.

We tested these three hypotheses by measuring functional connectivity within each of the three subsystems of the DMN and relating this to measures of mind-wandering, temporal discounting and delay aversion in children with ADHD and age-matched healthy controls.

7.3.0 Methods

7.3.1 Participants

Sixty-one male adolescents (30 ADHD/ 31controls) aged between 10- and 16-years participated. The ADHD group were recruited from local clinics using the South Hampshire ADHD Register (SHARe; http://www.southampton.ac.uk/share) and the control group from local schools and youth groups. Adolescents were excluded from the control group for reaching a DSM-IV diagnosis for any axis-1 disorder and from the ADHD group for failing to reach a research diagnosis of ADHD. Additional exclusion criteria included: a) the presence of any other commonly co-occurring conditions as assessed by clinicians (with the exception of oppositional defiant disorder (ODD) and conduct disorder (CD) given high comorbidity with ADHD (Waschbusch, 2002)); b) Medication use, excluding short acting stimulants (in which case patients were asked to withhold taking medication for 24 hours prior to testing); c) an IQ <75 assessed using a two-subtest version of the Wechsler Intelligence Scale for Children (WISC-IV) to exclude participants with probable learning difficulties; and d) standard magnetic resonance imaging (MRI) exclusion criteria (cardiac pacemaker, metal in body, claustrophobia, etc.). Diagnostic assessment was performed using parent responses to a structured psychiatric interview (DISC-IV; Shaffer, Fisher, Lucas, Dulcan, and Schwab-Stone (2000)) and parent and self-report versions of the Conner's Comprehensive Behaviour Rating Scale (Conners CBRS third edition; Conners et al. (2011)). Using these measures 9 adolescents were excluded from the control group for reaching criteria for an axis-1 disorder. A further 10 were excluded from the ADHD group (4 for failing to reach a research diagnosis of ADHD at the point of testing, 5 for withdrawing prior to completing the study and 1 for excessive head movement during the resting state scan (maximum displacement > 1 voxel). This left a final sample of 42 adolescents (20 ADHD/ 22

controls; mean age = 13.31). The University of Southampton Ethics Committee, the NHS Research Ethics Committee and the University Hospital Southampton NHS Trust's Research and Development office reviewed and approved this study (research ethics committee reference: 14/SW/1005).

7.3.2 Behavioural assessments

The behavioural assessment and screening for eligibility to take part were undertaken on a day prior to the MRI scan. Delay aversion and temporal discounting were assessed using parent responses to the Quick Delay Questionnaire (QDQ; Clare, Helps, and Sonuga-Barke (2010)). The QDQ is a validated questionnaire consisting of 10 items assessing delay aversion (e.g., "*hates waiting for things*") and temporal discounting (e.g., "*Will persevere with tasks even if they do not offer immediate rewards*"). Parents responded on a 5-point likert scale ranging from "*not at all like him"* too "*very much like him*". Mind wandering was assessed using self-report responses to the Mind Wandering Questionnaire (MWQ; Mrazek et al. (2013)). The MWQ is a 5-item questionnaire validated in adolescents to measure off-task thought (e.g., "*whilst reading, I find I haven't been thinking about the words and must therefore read it again*"). Participants responded to a 6-point likert scale ranging from "*almost never*" to "*almost always*". Both the parent-reported QDQ and the self-reported MWQ have both been shown to correlate with DMN power and connectivity respectively (Godwin et al., 2017; Hsu et al., 2016; Hsu et al., 2013). In line with recommended scoring procedures, the sum total of responses to the mind wandering questionnaire and each subscale of the QDQ formed measures of mind wandering, delay aversion and temporal discounting respectively.

7.3.3 Image acquisition

Imaging data was collected on a 3-Tesla Siemens Magneton Skyra (Siemens AG, Erlangen, Germany) at Southampton General Hospital using a 12-channel head coil. Structural scans were acquired using a T1-Weighted (MP-RAGE) three-dimensional dataset (voxel size=1 mm x 1 mm x 1 mm, repetition time = 2200ms, flip angle = 8°, 178 slices) with a scan acquisition time of 6.52 mins. These were acquired for the purposes of registration and to produce masks of white matter and cerebral spinal fluid to assist with denoising the resting state signal. Functional scans were obtained using a T2* -weighted EPI pulse sequence (repetition time = 2500ms, 44 slices, voxel size= 3.00mm x 3.00mm x 3.00mm voxels in an interleaved acquisition, flip angle = 90°, 147 volumes). After the automatic removal of the first 4 volumes to allow for magnetic stabilisation the entire resting-state scan took 5 mins and 55 seconds. During the scan participants were instructed to stare at a fixation cross that was viewed though a mirror affixed to the head coil. An eyes open acquisition was selected given evidence voxel-to-voxel correlations show the highest test-retest reliability compared with eyes closed or eyes open not staring at a cross (Patriat et al., 2013).

7.3.4 Image pre-processing

The FSL version 5 software package (http://fsl.fmrib.ox.ac.uk) and the Connectivity Toolbox version 17e (Conn; http://www.nitrc.org/projects/conn; Whitfield-Gabrieli and Nieto-Castanon (2012)) were used for image pre-processing. First rigid-body correction for head motion was applied and all scans were aligned to the Montreal Neurological Institute (MNI) space using nonlinear registration performed with 12 degrees of freedom. Functional data was spatially smoothed with an isotropic full-width half-maximum kernel of $6mm^3$. To further reduce the effects of spurious correlations arising from movement: first, outlier time-points, and their first-order temporal derivatives detected from intensity differences in unprocessed time-series compared with a reference volume, were regressed from functional

datasets (motion scrubbing). Second, 24 motion parameters consisting of the absolute displacement in the x, y and z plane, rotations in roll, pitch and yaw, the six first order temporal derivatives of these values along with 12 quadratic expansions of those derivatives were regressed from the functional data set. Third, subject-specific time-series from the top five principle components estimated from white matter and cerebral spinal fluid masks thresholded at 98% probability were regressed from the functional data set. After regression the data was bandpass filtered to restrict analysis to the slow 5 and slow 4 frequency bands (0.01-0.073Hz) thought to most optimally capture resting-state networks whilst excluding artificial signal (Xue et al., 2014). After bandpass filtering the data was despiked using a hyperbolic tangent function to further reduce the influence of outlier scans.

7.3.5 Regions of interest (ROI)

Following Andrews-Hanna et al. (2010), 11 ROIs overlapping left lateralised nodes of the core, dorsal medial, and medial temporal subsystems were included in this study (see Table 5.1 for regions and coordinates). Although the connectome employed was originally validated on young adults, by adolescence the DMN appears to have fully formed, with only limited increases in functional connectivity between DMN nodes that persist into adulthood (Sherman et al., 2014; Supekar et al., 2010). Therefore, we felt justified in using these ROIs on an adolescent population. All ROIs were 8mm radial spheres created using FSL.

7.3.6 Statistical analysis

Functional connectivity analysis was performed on the 11 ROIs mentioned above using the functional connectivity toolbox. The mean time series within each seed ROI was extracted and Pearson's correlation coefficients were calculated between any two nodes to form an 11x11 matrix. These correlation coefficients were normalised using a Fisher's r-to-z

transformation to convert correlation coefficents to an interval scale. Functional connectivity within each subsystem was calculated as the mean of all edges within the dorsal medial subsystem, the medial temporal subsystem and the core subsystem. Between subjects t-tests were used to compare group differences in averaged functional connectivity separately for each of these three subsystems. We also performed a separate analysis examining the effects of IQ and conduct disorder (CD) symptoms on DMN functional connectivity. CD is a related disruptive behaviour disorder that frequently co-occurs with ADHD and appears to be independently related to atypical connectivity within the DMN core subsystem (Broulidakis et al., 2016). Controlling for IQ is important as intelligence has been associated with connectivity strength (L. Wang et al., 2011). Statistical significance was assessed at $p<0.05$, False Discovery Rate (FDR) correction for the three subsystems examined.

We subsequently examined how the relationship between mind wandering, temporal discounting and delay aversion were associated with DMN dysregulation. First, all outcome variables were correlated with functional connectivity in each of the three subsystems. Secondly, three mediational models were used to test our three predictions (see Figure 7.1). To test the first hypothesis: group membership (i.e., ADHD vs control group) was the predictor variable, mind-wandering the outcome variable and atypical connectivity the mediator. To test the second hypothesis: group membership was the predictor variable, temporal discounting the outcome variable and atypical connectivity the mediator. To test the third hypothesis: group membership was the predictor, DMN connectivity the outcome and delay aversion the mediator. Mediation was tested though three regression models (Baron & Kenny, 1986): (i) the direct effect between the predictor variable and the outcome (path c), (ii) the relationship between the predictor variable and the mediator (path a), (iii) the indirect effects of the mediator (path c') and the predictor (path b) on the outcome variable (see Figure 7.1). Given the exploratory nature of these analyses, effects were thresholded at

p<0.05 uncorrected. Correlational and mediational analyses were performed using SPSS version 22 (IBM Corp, 2016).

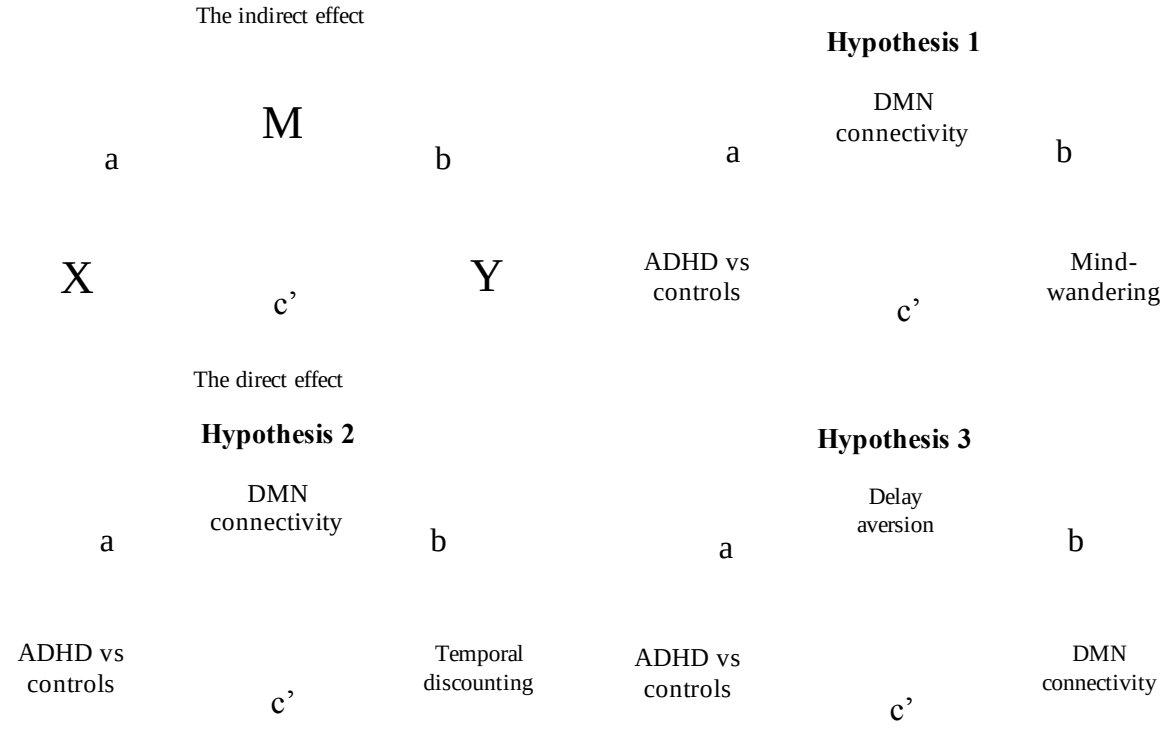

Figure 7.1. Three hypotheses for how default mode network (DMN) dysregulation may contribute to the psychological and motivational abilities this network may support in attention deficit/hyperactivity disorder (ADHD). The top left figure illustrates the mediational model. Hypothesis 1 tests if atypical DMN connectivity serves as the mediator for the relationship between group membership (i.e., ADHD vs control group) and mind-wandering. Hypothesis 2 tests if atypical DMN connectivity serves as the mediator for the relationship between group membership and temporal discounting. Hypothesis 3 tests if delay aversion is the mediator for the relationship between group membership and DMN connectivity.

7.4.0 Results

7.4.1 Demographic and behavioural data

Both groups were of a similar age, individuals with ADHD showed significantly lower IQ and elevated ODD and CD symptoms compared with controls (see Table 7.1). Relative to controls, individuals with ADHD showed increased levels of mind-wandering and had higher delay aversion and temporal discounting scores.

Table 7.1. Demographic, clinical and psychometric characteristics of the sample

	ADHD group (n=20)	Control group (n=22)	*t-test*
Age (y)	13.06 (1.61)	13.60 (1.43)	1.06
Intelligence Quotient	98.10 (9.47)	106.32 (10.28)	2.68**
Diagnostic Interview Schedule for Children (DISC)			
ADHD symptoms	16.55 (3.10)	4.41 (4.91)	9.47***
ODD symptoms	10.20 (1.77)	3.95 (3.23)	7.67***
CD symptoms	7.20 (5.04)	0.68 (1.13)	5.91***
Quick Delay Questionnaire (QDQ)			
Delay aversion	11.05 (1.73)	9.36 (1.59)	3.12**
Temporal discounting	11.70 (2.06)	8.45 (2.63)	4.47***
Mind Wandering Questionnaire (MWQ)	21.60 (4.82)	15.32 (4.52)	4.40***

Note: *p<0.05, **p<0.01, ***p<0.001. Values in parenthesis are standard deviations; ADHD=Attention-deficit/hyperactivity disorder, ODD=oppositional defiant disorder, CD= Conduct disorder

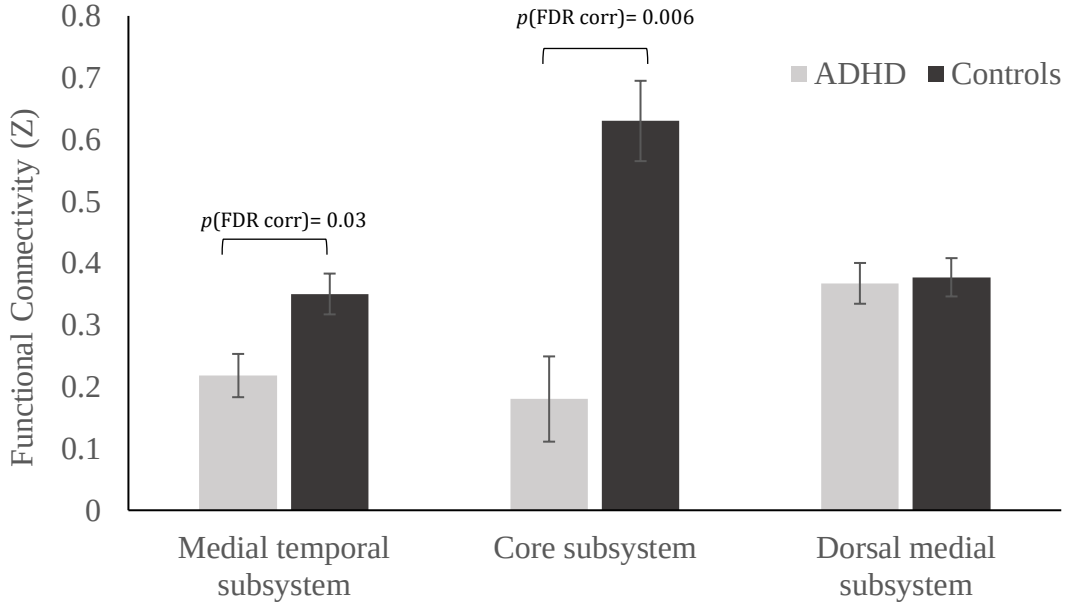

Figure 7.2. Averaged functional connectivity within the three subsystems of the default mode network (DMN), separated by group. Individuals with ADHD show hypo-connectivity within the medial temporal and core subsystems compared with controls, but no difference in the dorsal medial subsystem. Error bars report SE.

7.4.2 Effect of ADHD group status on DMN subsystem connectivity

We first investigated group differences in average within-subsystem connectivity of the DMN between the ADHD and healthy control groups. Relative to healthy controls, adolescents with ADHD exhibited significantly reduced connectivity in the core ($t_{(40)}$= 3.40, $p_{(FDRcorr)}$= 0.006) and medial temporal subsystems ($t_{(40)}$= 2.41, $p_{(FDRcorr)}$= 0.03) but not the dorsal medial subsystem ($t_{(40)}$= 0.23, $p_{(FDRcorr)}$=0.82); see Figure 7.1. To investigate if these effects were present bilaterally, we also measured averaged connectivity across and between left and right lateralised core subsystem ROIs as well as across and between left and right lateralised medial temporal subsystem ROIs. Once again, we found ADHD associated with *hypo*-connectivity in both the bilateral core subsystem ($t_{(40)}$= 2.40, $p_{(FDRcorr)}$=0.03) and the bilateral medial temporal subsystem ($t_{(40)}$= 2.81, $p_{(FDRcorr)}$=0.027).

Table 7.2. Pearson correlations between default mode network (DMN) subsystem functional connectivity and behavioural outcomes and the respective p values for the correlations

Measure	Medial temporal subsystem	Core subsystem	Dorsal medial subsystem
Delay aversion	-0.22 (0.16)	-0.47 (0.002)	-0.10 (0.51)
Temporal discounting	-0.14 (0.36)	-0.34 (0.027)	-0.03 (0.98)
Mind-wandering	-0.08 (0.62)	-0.22 (0.16)	-0.07 (0.67)

Note: values in parentheses report uncorrected p-values.

7.4.3 Correlational analysis

As illustrated in Table 7.2, there was a significant correlation between delay aversion and temporal discounting scores and core subsystem hypo-connectivity. There was no significant correlation between dorsal medial or medial temporal subsystem connectivity and any of the three neuropsychological outcome variables.

7.4.4 Mediational analysis

We first tested if core subsystem hypo-connectivity mediates elevated mind wandering in ADHD (hypothesis 1). As illustrated in Figure 7.3, there was no association between mind wandering and core subsystem hypo-connectivity, suggesting it does not contribute to elevated levels of mind-wandering common to the disorder. Next, we tested if DMN hypoconnectivity mediates the pathway between ADHD and temporal discounting (hypothesis 2). As illustrated in Figure 7.3 there was a significant direct effect of ADHD on this outcome variable. However, when ADHD was included as a covariate alongside core subsystem hypo-connectivity it reduced the relationship between connectivity and temporal discounting to non-significant levels. This suggests the pathway between ADHD and temporal discounting is a direct effect and not mediated by DMN hypo-connectivity.

Finally, we tested whether delay aversion mediated the pathway between ADHD and DMN connectivity (hypothesis 3). There was a significant direct effect of ADHD group status on DMN connectivity and after including delay aversion in the model, the direct effect between ADHD and DMN connectivity was less significant. This supports partial mediation of the relationship between ADHD and DMN connectivity by delay aversion (see Figure 7.3).

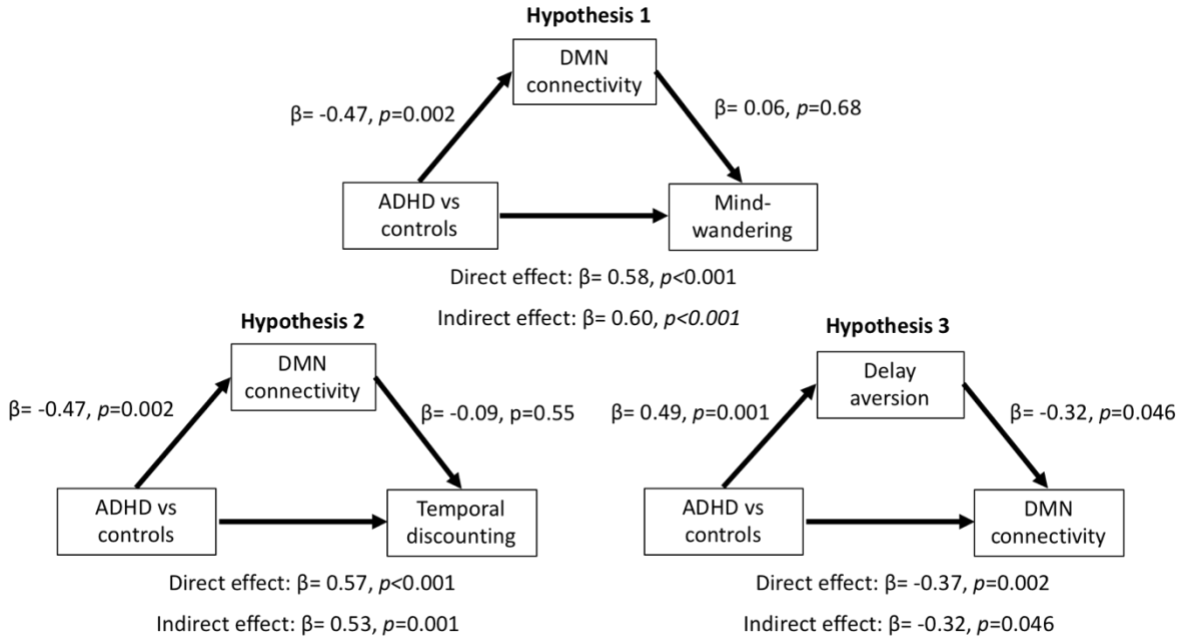

Figure 7.3. Mediational analyses testing how default mode network connectivity may contribute to the neuropsychological profile of attention deficit hyperactivity disorder (ADHD). For all three models only in hypothesis 3 does an indirect pathway operating though an increase in delay aversion partially explain the relationship between ADHD group status and DMN hypo-connectivity.

7.4.5 Alternative hypothesis

We also tested an alternative hypothesis - that delay aversion operates though core subsystem hypo-connectivity rather than vice versa. In this model the indirect pathway was mediated by DMN functional connectivity, however this was at a lower significance compared to when delay aversion was included as the mediator (ß= 0.35, *p*= 0.027). This

suggests the model described in hypothesis 3 best explains the relationship between ADHD group status and DMN hypo-connectivity.

7.4.6 Potential confounding factors

After controlling for CD symptoms, individuals with ADHD still showed hypo-connectivity within the core ($F_{(1,39)}$= 6.78, $p_{(FDRcorr)}$=0.032), and medial temporal subsystems ($F_{(1,39)}$= 5.80, $p_{(FDRcorr)}$=0.032) relative to the healthy controls.

After controlling for IQ, individuals with ADHD only showed hypo-connectivity within the DMN core subsystem ($F_{(1,39)}$= 10.70, $p_{(FDRcorr)}$=0.006), with the medial temporal subsystem not reaching formal levels of statistical significance after correction for multiple comparisons ($F_{(1,39)}$= 3.93, $p_{(FDRcorr)}$=0.08).

7.5.1 Discussion

Previous research has reported DMN core subsystem hypo-connectivity in ADHD, yet comparatively little is known about the functional consequences of such hypo-connectivity on ADHD or neuropsychological performance. In this study we tested three possibilities about the putative relationships between ADHD, DMN connectivity and neuropsychological deficits. First, that this core DMN hypo-connectivity in ADHD drives elevated levels of mind-wandering. Second, that it underpins temporal discounting of rewards in ADHD because it reduces the ability to prospect about future outcomes. Third, that rather than being a cause of neuropsychological problems, DMN alterations are a consequence or an expression of those problems - in this case delay aversion. There were a number of findings of note.

First, consistent with recent reviews of empirical findings, we found ADHD-related hypo-connectivity in both core and medial temporal subsystems of the DMN, implicating medial prefrontal cortex and posterior cingulate cortex, and the hippocampal formation and parahippocampal cortex, ventral medial prefrontal cortex, retrosplenial cortex and inferior parietal lobule, respectively (Castellanos & Aoki, 2016; Posner et al., 2014). Where previous studies have adopted methodological approaches suited to investigating connectivity outside of the core subsystem, they have also found atypical functional connectivity within the medial temporal subsystem but not the dorsal medial subsystem - although the direction of these effects (hyper- versus hypo-connectivity) have not always been consistent. For example, Anderson et al. (2016) reported hyper-connectivity within a network spatially overlapping the medial temporal subsystem in patients with ADHD, whilst Chabernaud et al. (2012) observed hypo-connectivity within the medial temporal subsystem but *hyper*-connectivity between nodes of the core subsystem. The reason for this disparity is not clear, although they have been suggested to arise from a failure to control for psychiatric

comorbidity in ADHD, most notably co-occurring CD (Barber et al., 2015; Broulidakis et al., 2016). An alternative hypothesis is that this is accounted for by as an increased sensitivity to motion induced fMRI artefacts when testing a young population with ADHD (Power et al., 2012; Van Dijk et al., 2012).

Second, ADHD was associated with elevated levels of self-reported mind-wandering, and parent-rated temporal discounting and delay aversion. This is consistent with a considerable body of evidence from studies using a range of different methods. Compared with controls, individuals with ADHD mind-wander more frequently - evidenced from questionnaire (Biederman et al., 2017; G. Shaw & Giambra, 1993) and probe caught experience sampling (Arabacı & Parris, 2018). Individuals with ADHD also show elevated delay aversion and temporal discounting evidenced from both questionnaire-based measures (Clare et al., 2010) and conventional decision-making tasks (I. Marx et al., 2018). Accordingly, mind-wandering, delay aversion and delay temporal discounting are each thought to represent important clinical features of the ADHD phenotype (Arabacı & Parris, 2018; Sonuga-Barke, 2002, 2003).

Third, despite our observation of elevated levels of mind-wandering in the ADHD group, there was no relationship between medial temporal or core subsystem hypo-connectivity and mind wandering, suggesting DMN connectivity does not mediate this relationship. The current study is the first to investigate how DMN connectivity is associated with mind-wandering in ADHD, although in healthy populations a recent meta-analysis has reported a strong association between task-unrelated thought and DMN connectivity (K. C. Fox et al., 2015). The DMN interference hypothesis postulates that low frequency temporal synchrony between these task positive systems and the DMN is required to maintain DMN attenuation during task performance, with mind-wandering and increased response time variability arising as a consequence of mind-wandering thoughts intruding on task

performance (Sonuga-Barke & Castellanos, 2007). Furthermore, Aboitiz et al. (2014) argued that reduced DMN connectivity contributes to the failure to attenuate DMN activity in the transition from resting to task states and to an increased risk of mind-wandering during task performance. One explanation for this inconsistency between results is that mind-wandering is *not* driven by within-DMN disruption *per se*, but that it arises out of reduced functional coupling between the DMN and other resting state networks such as executive control networks (Christoff et al., 2016; Sonuga-Barke & Castellanos, 2007). In fact, reduced anti-correlations between the DMN and executive control systems, and not within DMN connectivity, has been shown to correlate with poor attentional control during task performance in adolescents with ADHD (Barber et al., 2015).

Fourth, DMN core subsystem hypo-connectivity was associated with temporal discounting and appeared to mediate the links between ADHD and heightened temporal discounting - at least based on parents' ratings of their own child's willingness to choose small immediate over larger delayed rewards. This is consistent with the proposal by Sonuga-Barke and Fairchild (2012) that DMN dysfunction in the form of hypo-connectivity reduces the ability to envision the future and so, acts together with problems of executive control and reward evaluation, to impair inter-temporal decision making. Although previous studies have found a link between DMN activations and temporal discounting (Benoit et al., 2011), this is the first study to extend these investigations by exploring intertemporal decision making in ADHD. Future studies should focus on the interplay between DMN (prospection) and dorsal (executive control) and ventral (reward) fronto-striatal circuits in determining individual differences in decision making (Sonuga-Barke et al., 2016).

Fifth, there was some support for our third hypothesis relating to DMN dysregulation and delay aversion. Here we confirmed that delay aversion partially mediated the link between ADHD and core DMN hypo-connectivity - consistent with the idea that DMN hypo-

connectivity is a consequence rather than a cause of delay aversion. This novel conceptualisation of the relationship between DMN and delay aversion was first proposed by Hsu et al. (2016). They argued that individuals with ADHD may engage in self-referential processes such as daydreaming (see Table 1.1) as a form of internalised attentional distraction which may activate the DMN, although excessive recruitment of self-referential thought may be expected to be associated with hyper- not hypo-connectivity. Christoff et al. (2016) suggests that reduced connectivity in the core subsystem in ADHD reflects a difficulty in applying appropriate constraints to spontaneous thought when an individual is faced with a salient event. It is plausible that the experience of delay in individuals with ADHD is experienced as highly emotionally salient and aversive. Weakened functional integrity within the DMN therefore could be expected to contribute to elevated levels of unconstrained spontaneous thought, reflected in increased DMN power during waiting - as has been previously observed (Hsu et al., 2016; Hsu et al., 2013). Although beyond the scope of the current study, future investigations into how levels of spontaneous thought shift during goal orientated waiting in patients with ADHD would be important in confirming this prediction.

This is the first study to explore different putative neuropsychological effects of DMN dysregulation in the same study. However, there are a number of limitations that need to be taken into account when interpreting these findings. First, although comparable to much of the DMN and resting state literature on ADHD (Castellanos & Aoki, 2016; Posner et al., 2014), the sample size was small and this could have reduced our statistical power to detect associations - especially with regard to the mediational analyses. Second, given the functionally dissociable nature of the DMN, the current study focused on average connectivity within individual subsystems. Whilst this increases the sensitivity to detect network level effects, it does so at a cost of topographical specificity. There is emerging evidence highlighting the importance of individual seed level connections to different

features of spontaneous thought (Smallwood et al., 2016) and the current study may not have been able to detect these effects. Third, following previous studies that have used this set of ROIs, analyses were restricted to the left lateralised DMN (Andrews-Hanna et al., 2010; Dodell-Feder et al., 2014; Zhu et al., 2017). Although we did examine effects bilaterally this was done only after first detecting them in the left hemisphere, which would have prevented us from identifying effects of ADHD that were only present in the right hemisphere. Fourth, the assessment of mind-wandering, temporal discounting and delay aversion was based on parent and self-report measures. Although both the QDQ and MWQ have good psychometric properties (Claire et al., 2010; Mrazek et al., 2013), future studies should use a broader set of measures including laboratory tasks. Finally, the data reported was all cross-sectional – the use of longitudinal data would provide a stronger test of the mediational models. Furthermore, given the study was cross-sectional we can only speculate about any casual links between delay aversion and DMN functional connectivity.

In summary the current study represents the first to empirically link atypical DMN connectivity during wakeful rest to the network's putative psychological and motivational functions which are thought to be disrupted in ADHD. Core subsystem hypo-connectivity was correlated with delay aversion and temporal discounting in patients with ADHD. Further work needs to be undertaken to test the hypothesis that DMN dysconnectivity is a neural expression of delay aversion in ADHD.

Chapter VIII: General discussion

The primary aim of this thesis was to investigate the causes and clinical correlates of default mode network (DMN) dysregulation in ADHD and CD. We achieved this by investigating DMN connectivity in three distinct populations: in adolescents aged between 13-18 with CD and high levels of ADHD symptoms, in young adults aged between 23-25 with a rare deprivation related variant of ADHD (but comparatively few CD symptoms (Kennedy et al., 2016)) and in a clinical sample of children aged between 10-16 with a primary diagnosis of ADHD and elevated CD symptoms. In this chapter the key empirical findings from the three studies included in this thesis will be summarised and the possible interpretations of the findings discussed. Next, common patterns of findings will be integrated with a focus on illuminating how ADHD may influence the DMN. Finally, the strengths and limitations of the three studies included in this thesis will be highlighted followed by a discussion about possible future studies seeking to further this research agenda.

8.1.0 Summary of key findings

8.1.1 Reduced Default Mode Connectivity in Adolescents with Conduct Disorder (Chapter V)

In chapter V we investigated resting-state functional connectivity between seed regions of interest (ROIs) overlapping nodes of the dorsal medial, medial temporal and core subsystems of the DMN in a sample of 29 male adolescents with CD and 29 age and sex matched controls. The aim of the study was to investigate the clinical correlates of DMN connectivity in CD in a more systematic way than previous studies have done. Differing from previous findings, we found CD was associated with hypo-connectivity within the DMN core subsystem, but, unexpectedly, only after adjusting for ADHD symptoms (Dalwani et al.,

2013; Jiansong Zhou et al., 2015). This was the first study to investigate how DMN connectivity is affected by callous-unemotional traits and age of onset of CD – important clinical features of CD thought to differentiate between distinct subtypes of the disorder (Frick et al., 2014; Moffitt, 1993). Both age of onset and callous unemotional traits had no effect on DMN connectivity, although both groups differed significantly from controls in each case, suggesting CD in general is associated with DMN abnormalities. In contrast, across the sample as a whole, ADHD symptoms were found to affect the directionality of the connectivity patterns observed. In particular ADHD symptoms were strongly positively correlated with connectivity within the core subsystem of this network, suggesting that ADHD and CD have largely independent effects on DMN connectivity.

8.1.2 Childhood institutional deprivation moderates the relationship between default mode network functional connectivity and adult attention-deficit/hyperactivity disorder symptoms (Chapter VI)

In chapter VI we examined average functional connectivity within each of the three subsystems of the DMN in a sample of participants who had been exposed to severe institutional deprivation in early life. A significant proportion of the sample had significant levels of a rare deprivation related variant of ADHD. This analysis was performed on a sample drawn from the English and Romanian Adoptees' (ERA) study - 67 Romanian young adult adoptees and 21 non-deprived UK adoptee controls. The ERA study's longitudinal natural experimental design allows it to disentangle the effects of early and late adversity due to the adoption of children by loving and supportive families in the UK. This design also reduces the likelihood that adversity and risk would be correlated, as it seems to be often the case in high-risk families with gene-environment passive correlations (Moffitt, 2006). This permitted a greater degree of confidence in assigning a causal role to deprivation on the

connectivity patterns observed, despite measuring DMN connectivity more than 20 years after the exposure occurred. We found a dose-dependent increase in DMN core subsystem functional connectivity as a function of deprivation, with the other two subsystems remaining largely unaffected. There was also a significant interaction between duration of deprivation and the common deprivation related outcome of ADHD on core subsystem connectivity. This was such that ADHD was associated with hypo-connectivity in individuals who experienced less than 6 months or no deprivation (loDep) and hyper-connectivity in individuals who experienced deprivation for 6 months or more (Rom>6). The latter finding was interpreted as being in line with an ecophenotypic hypothesis where the effects of early adverse experiences may cause a clinically and neurobiologically distinct subtype of ADHD (Teicher & Samson, 2013). In this study two factors were shown to influence DMN connectivity, namely ADHD, and deprivation – with duration of exposure appearing to moderate how ADHD alters DMN functional connectivity.

8.1.3 Default mode hypo-connectivity in ADHD: How is it related to individual differences in mind-wandering, delay aversion and temporal discounting? (Chapter VII)

In chapter VII we measured DMN connectivity in a clinical sample of 20 male adolescents with ADHD who were either receiving pharmacological and/or therapeutic treatment for ADHD or on a waiting list to receive treatment for ADHD - this group was compared with 22 age and sex matched controls. This study had two aims: to localise atypical functional connectivity to one or more subsystems of the DMN and to test how the observed pattern of DMN dysregulation may contribute to three commonly associated features of ADHD that are theoretically linked to DMN disruption: mind-wandering, delay aversion and temporal discounting (Hsu et al., 2016; Sonuga-Barke & Castellanos, 2007; Sonuga-Barke &

Fairchild, 2012). We replicated previous findings of hypo-connectivity within the DMN core subsystem (Castellanos et al., 2008; Choi et al., 2013; M. Qiu et al., 2011) and the medial temporal subsystem (Chabernaud et al., 2012). Differing from chapter V, these results appeared unaffected by co-occurring CD. Default mode network connectivity negatively correlated with delay aversion and temporal discounting. We also tested formally if DMN connectivity mediated the relationship between ADHD and temporal discounting and if delay aversion mediated the relationship between ADHD and DMN connectivity, as previous studies and theoretical models have suggested may be the case (Hsu et al., 2016; Sonuga-Barke & Fairchild, 2012). Only delay aversion was found to partially mediate the pathway between ADHD and core subsystem hypo-connectivity. In other words, we found that the relationship between ADHD and core subsystem hypo-connectivity was not a direct effect but appeared to be reduced in magnitude when controlling for delay aversion, suggesting partial mediation.

8.2.1 Key issues and themes raised by our data

Table 8.1 reports common patterns of findings across the three samples. To summarise, in Chapter V functional connectivity within the DMN core subsystem increased as a function of ADHD symptom severity across the whole sample. In contrast, CD group membership was associated with hypo-connectivity within this same circuit compared with controls, but only after first adjusting for ADHD symptom severity. In chapter VI, the presence or absence of deprivation appeared to determine if ADHD symptoms were associated with DMN core subsystem hypo- or hyper-connectivity. A noticeable feature of ADHD in individuals who have experienced time-limited deprivation from exposure to institutionalisation in childhood is that CD symptomatology appears to present less frequently. For this reason, in Chapter VI parent reported CD symptoms were too low to

allow us to either group on the basis of a categorical variable or to examine as a continuous measure across the sample as a whole. This made meaningful comparisons impossible. In Chapter VII we found that ADHD in childhood was associated with hypo-connectivity within the DMN core and medial temporal subsystems. Interestingly, in contrast to Chapter V, CD symptoms appeared to have little effect on the connectivity patterns observed. Once again suggesting that the effects of ADHD on DMN connectivity cannot be explained by co-occurring CD. We also found an association between DMN hypo-connectivity and inter-temporal decision making and delay aversion, but no significant association with mind-wandering. The functional significance of these findings is discussed below.

Table 8.1. Common clinical correlates of ADHD and CD observed across the three empirical chapters of this thesis.

Clinical correlate	Effect observed
Chapter V	
CD group membership[1]	Core subsystem hypo-connectivity
ADHD symptoms[2]	Correlates with core subsystem hyper-connectivity
Psychopathy[2]	No significant effect
Age of CD onset[1]	No significant effect
Chapter VI	
Main effect of deprivation[1]	Core subsystem hyper-connectivity
Months spent in deprivation[2]	Correlates with core subsystem hyper-connectivity
Deprivation[1]-by-ADHD[1] interaction	Core subsystem hypo-connectivity in LoDep High symptom group. Core subsystem hyper-connectivity in Rom>6, High symptom group.
ADHD symptoms[2]	No significant effect
Chapter VII	
ADHD group membership[1]	Core subsystem hypo-connectivity and medial temporal subsystem hypo-connectivity
CD symptoms[2]	No significant effect
Delay aversion[2]	Correlates with core subsystem hypo-connectivity
Temporal discounting[2]	Correlates with core subsystem hypo-connectivity
Mind-wandering[2]	No significant effect

Note: [1] categorical variable, [2] continuous variable; LoDep = adoptees who spent less than six months or no time in deprivation, Rom>6 = adoptees who spent 6 or more months in deprivation, ADHD = attention deficit/ hyperactivity disorder, CD = conduct disorder

8.3.1 What are the functional consequences of DMN hypo-connectivity in idiopathic ADHD and CD?

Lower resting-state functional connectivity between two nodes is usually interpreted as evidence of damage or disruption to that circuit (Wig et al., 2011). This may reflect either poor structural integrity of the axonal fibre white matter pathways that connect two nodes together, altered computations within a node that then cascades throughout the system, or atypical network dynamics (i.e., how many edges a node possesses). Either way, the

consequences are the same – to impair the information processing operations of that system (Bressler & Menon, 2010). Based on the results of this thesis, we speculate there are two ways in which disruption to the DMN core subsystem could contribute to the psychopathology of ADHD. (i) By altering the self-referential processes the core subsystem supports, leading to suboptimal inter-temporal decision making, (ii) in the recruitment of self-referential processes to deal with the adverse experience of delay.

8.3.2. DMN hypo-connectivity is not related to inter-temporal decision making

This hypothesis was discussed in detail in chapter IV and so will only be summarised here. In brief, Sonuga-Barke and Fairchild (2012) postulated that an important aspect of goal orientated decision-making is being able to use past experiences both as a basis for constructing an autobiographical representation of the self as an economic agent and in imaging the subjective utility of choice outcomes. Hypo-connectivity within the DMN core subsystem was postulated to reflect a difficulty in engaging in the sort of self-referential goal orientated thinking required to effectively evaluate choice alternatives. This may contribute to behavioural evidence of exaggerated temporal discounting and altered sensitivity to gains or losses during choice evaluation - effects present in both ADHD and CD.

To investigate this, in chapter VII we attempted to relate DMN functional connectivity in adolescents with ADHD to neuropsychological performance in order to investigate what the functional consequences of disruption to this system may be. We found hypo-connectivity significantly correlated with heightened temporal discounting, extending previous studies (Benoit et al., 2011; Spreng & Grady, 2010) by linking inter-temporal decision making with atypical connectivity in the core subsystem in individuals with ADHD. Interestingly we did not find core subsystem functional connectivity mediated the

relationship between ADHD and temporal discounting. There are two possible interpretations of this null effect. First, it could be that the DMN simply does not directly contribute to temporal discounting. This could be because the subsystem and the self-referential processes it mediates are recruited as some sort of secondary, compensatory response to the dysfunctional reward processing typically implicated in delay discounting. Alternatively, poor evaluation of choice alternatives may represent just one aspect of suboptimal intertemporal decision making that operates in conjunction with deficits in implicit reinforcement processes and higher order executive processes (Sonuga-Barke & Fairchild, 2012). Therefore, it is plausible given the limited sample sizes employed that we did not have the statistical power to detect this effect.

8.3.3 DMN hypo-connectivity may be a manifestation of delay aversion in ADHD

A complementary hypothesis to the one described above is that heightened self-referential processing is a response to exaggerated delay aversion in individuals with ADHD. The delay aversion hypothesis suggests that the externalising symptoms of ADHD manifest as a coping strategy an ADHD child employs to make it feel as though time is flowing faster. This strategy shapes the child's social and family environment by conditioning the child to associate waiting with the punitive experience of censure. This is thought to lead to the emergence of a learnt aversion to delay, both further reinforcing the externalising symptoms of ADHD, and preventing any opportunity to develop more effective strategies to manage delay (Sonuga-Barke, 2002, 2003). Hsu et al. (2016) postulate that self-referential processing essentially has a very similar role to that of the externalising symptoms of ADHD and may be engaged when delay adverse individuals wait in order to make it seem as though time is flowing faster. In support of this view they found adolescents with ADHD compared with non-ADHD controls showed elevated low frequency electroencephalography (EEG)

oscillations when engaging in goal directed waiting compared with a period of wakeful rest. With DMN-related neural activity also found to correlate with parent reported delay aversion.

Chapter VII supports this novel extension to the delay aversion hypothesis in two ways. First, we found that DMN core subsystem hypo-connectivity correlated with delay aversion in adolescents with ADHD – at least based on parents' ratings of their own child's dislike of waiting. Second, we observed that the relationship between ADHD and core subsystem hypo-connectivity was partially mediated by delay aversion, suggesting delay aversion has an important role in determining the DMN hypo-connectivity patterns we observed. As discussed in detail in Chapter II, the DMN core subsystem has an important role in constraining spontaneous thought (Andrews-Hanna et al., 2014; Christoff et al., 2016). Where there is a breakdown in these constraints, there may be more variable, non-goal directed spontaneous thought (Christoff et al. 2016). Following the delay aversion hypothesis, this preference for engaging in unconstrained spontaneous thought may become reinforced over time because of the effect it has in reducing the negative emotions associated with waiting. Indeed, this would be consistent with one of the functional contributions of spontaneous thought in regulating negative affect (McMillan et al., 2013).

This hypothesis is notable for three reasons. First, because it suggests DMN dysregulation represents a compensatory response to, rather than a cause of, a patients neuropsychological characteristics, and in this way differs from conventional models that have sought to explain the functional significance of atypical DMN connectivity in ADHD (Aboitiz, Ossandón, Zamorano, Palma, & Carrasco, 2014; Christoff et al., 2016; Sonuga-Barke & Fairchild, 2012). Second, following the delay aversion hypothesis, it provides a clear mechanism for how atypical DMN functional connectivity in individuals with ADHD may arise in the first place – i.e., as a reinforced behaviour to cope with unavoidable delay. Third, if delay aversion does reinforce non-goal directed spontaneous thought, it raises the

interesting possibility that a difficulty in effectively engaging in goal directed self-referential processing could arise as a secondary manifestation of disruption to the core subsystem. This could possibly contribute to the pattern of suboptimal decision making described previously.

8.3.4 DMN hypo-connectivity is not related to mind-wandering in ADHD

A particularly surprising result was that we did not find atypical DMN functional connectivity was associated with the psychopathological levels of task unrelated thought, common in ADHD (Franklin et al., 2014; G. Shaw & Giambra, 1993). The DMN core subsystem has been repeatedly shown to be a neural substrate of mind-wandering - evidenced from a meta-analyses of task-based fMRI studies (K. C. Fox et al., 2015), and neuromodulation techniques (Kajimura et al., 2017). It has been hypothesised that in ADHD, hypo-connectivity within the DMN could prevent the network from attenuating correctly (Aboitiz, Ossandón, et al., 2014), contributing to neuroimaging evidence that individuals with ADHD show a difficulty in attenuating DMN activity (Liddle et al., 2011).

One explanation for this finding is that whilst the DMN core subsystem modulates spontaneous thought, it does so though tight functional coupling with other brain systems – most notably the fronto-parietal control network and the salience network (Andrews-Hanna et al. (2014); see Chapter II). The results of the current study suggest that it is not *within* DMN functional connectivity *per se* that contributes to a difficulty in suppressing mind-wandering in ADHD. Instead, we suggest that it may be due to altered functional connectivity with these executive control systems. Indeed, reduced correlations between the DMN and executive control systems and *not* within DMN connectivity has been shown to correlate with poor attentional control during task performance adolescents with ADHD (Barber et al..2016). This null effect further illustrates that the consequences of a dysfunctional DMN in ADHD extend beyond task-related inattention.

8.3.5 Alterations in dorsal medial sand medial temporal subsystems don't seem central to ADHD or CD?

The DMN is made up of three functionally and anatomically dissociable subsystems: the *dorsal medial subsystem*, the *medial temporal subsystem* and the *core subsystem*. Across all three empirical chapters we did not find any significant effects of ADHD on the functional integrity of the dorsal medial subsystem, but in Chapter VII we replicated previous evidence suggesting DMN dysregulation extends to the medial temporal subsystem (Chabernaud et al., 2012). Within the framework of a functionally dissociable DMN this implies that individuals with ADHD do not show deficits in the sort of social-cognitive conceptualising and semantic processing associated with the dorsal medial subsystem functioning (Andrews-Hanna et al., 2014). However, it does suggest that ADHD might be associated with deficits in episodic memory, episodic simulation and constructive mental processing which are normally supported by the medial temporal subsystem (Andrews-Hanna et al., 2014; Buckner et al., 2008). The latter finding is significant as it appears to support predictions that individuals with ADHD have a difficulty in accessing autobiographical representations of past experiences. Given common neural circuits involved in all three processes it can be predicted that ADHD will be associated to impairments in these mental abilities (Sonuga-Barke et al., 2016; Sonuga-Barke & Fairchild, 2012).

This prediction tallies with behavioural studies performed outside of the MRI scanner. Individuals with ADHD do not have a difficulty in accessing semantic representations of information (Hurks et al., 2004) or social-cognitive mentalising (Charman, Carroll, & Sturge, 2001), both processes associated with the dorsal medial subsystem (Andrews-Hanna et al., 2014). However, there is behavioural evidence that individuals with ADHD show poor episodic memory (Fabio & Caprì, 2015), and a difficulty in recalling self-relevant autobiographical experiences (Klein et al., 2011) - cognitive processes linked to medial

temporal lobe subsystem functioning (Andrews-Hanna et al., 2014). In retrospect, we probably should have incorporated tests of episodic memory to directly test this prediction and unfortunately it goes beyond the scope of this thesis to directly link our finding of medial temporal subsystem hypo-connectivity with behavioural evidence for suboptimal autobiographical recall in ADHD.

8.4.0 What are the effects of deprivation on DMN functioning and ADHD?

If DMN hypo-connectivity represents damage or disruption to a circuit that impairs the information processing operations of that network, hyper-connectivity represents the opposite - increased communication between network nodes indicating a system more sensitive to stimulation (Bressler & Menon, 2010). Therefore, it is unlikely that DMN core subsystem hyper-connectivity contributes to impaired prospection in the same way as hypo-connectivity may do. An alternative prediction is that rather than altering a specific set of cognitive processes, deprivation may lead to long term alterations in the experience of spontaneous thought.

Consistent with its hub-like role in biasing spontaneous thought, the DMN core subsystem is characterised by long range connections to multiple brain systems. Christoff et al. (2016) suggest that hyper-connectivity within the DMN core subsystem may represent the application of excessive automatic constraints on spontaneous thought, with the type of thought that is constrained largely dependent on which brain systems the core subsystem may be connected too. Automatic constraints exist outside of executive (i.e., conscious) control to bias thoughts towards internally or externally orientated affective or sensory salient stimuli. Christoff et al. (2016) postulate that where these constraints are “excessive” it leads to a difficulty in disengaging thoughts from the matter under consideration. For example, connectivity with cortico-thalamic-striatal circuits involved in habit formation (Yin &

Knowlton, 2006), may exert habitual automatic constraints on the core subsystem (an excess of which may be associated with obsessive compulsive disorder; Christoff et al., (2016)). Similarly, atypical connectivity with the amygdala and salience network may lead to emotionally valanced thoughts around current concerns (McVay & Kane, 2010) (an excess of which may be associated with generalised anxiety disorder; Christoff et al. (2016)).

Following this framework, it is plausible that excessive connections with a system involved in processing threat, may also bias thought patterns towards emotionally salient (i.e., threatening) stimuli. Although this interpretation is speculative in that the content of spontaneous thought in those with exposure to early adversity has not been directly sampled, there is a substantial literature suggesting a hyper-vigilance to threat is a common consequence of exposure to maltreatment in early childhood (for review see: Teicher et al. (2016)). This is most consistently seen in terms of amygdala responsiveness to threatening faces (Grant, Cannistraci, Hollon, Gore, & Shelton, 2011; McCrory et al., 2011; van Harmelen et al., 2012). There is also emerging evidence that individuals exposed to deprivation also show an elevated threat response (Tottenham et al., 2011), atypical grey matter volume in overlapping limbic and amygdala systems involved in processing threat (McLaughlin et al., 2014; Tottenham et al., 2010) and elevated connectivity between the amygdala and the medial prefrontal cortex, a brain region overlapping the DMN (Gee et al., 2013). Christoff et al. (2016) suggest that in conjunction with a difficulty in applying deliberate (i.e., goal orientated) constraints to spontaneous thought excessive levels of automatic constraints could also lead to distractibility. This could possibly contribute to the elevated levels of inattention common in deprivation related variants of ADHD, whilst explaining why not everyone we tested who showed core subsystem hyper-connectivity as a function of deprivation exposure also presented with ADHD.

8.5.0 DMN core subsystem hyper-connectivity may be a marker of deprivation related ADHD

There is consistent evidence that ADHD is associated with DMN hypo-connectivity for the most part overlapping the core subsystem (Castellanos et al., 2008; Choi et al., 2013; de Celis Alonso et al., 2014; D. A. Fair et al., 2010; Hoekzema et al., 2014; Mattfeld et al., 2014; M. Qiu et al., 2011; Sato et al., 2012; Sun et al., 2012). Of the 11 studies that have observed DMN dysregulation in ADHD, only one has reported DMN hyper-connectivity during wakeful rest (Barber et al., 2015). Therefore, it is curious that we found this pattern of findings in two of our samples - in individuals with high levels of ADHD symptoms who had experienced 6 months or more of severe, but time limited institutional deprivation, and as a function of ADHD symptom severity in individuals with CD. We speculate that these common patterns of findings could reflect a deprivation/maltreatment related subtype of ADHD that affects the DMN in a way that is different from clinically typical variants of the disorder.

There is a good reason to suspect that ADHD may be sensitive to early adversity. First a number of studies have suggested an association between childhood maltreatment and ADHD (Briscoe-Smith & Hinshaw, 2006; Ouyang, Fang, Mercy, Perou, & Grosse, 2008; Sugaya et al., 2012). Although the nature of this relationship is likely complicated by the potential effects of genetic and environmental confounding, as discussed in Chapter VI, adoption and foster-care studies have provided one important method of disentangling genetic and environmental risk (Rutter et al., 2012). Consistent with the existence of a deprivation related subtype of ADHD, these studies have reported elevated levels of ADHD relative to what would be expected in the general population following prolonged exposure to deprivation (Humphreys et al., 2017; Kennedy et al., 2016). Another approach to disentangling genetic and environmental risk has been to use twin studies. This has the

advantage of permitting analyses on a sample that is both larger and perhaps more generalisable to the possible effects of maltreatment in the population than previously institutionalised children. A recent study of over 18,000 twins reported rates of ADHD were similar in monozygotic and dizygotic twins as a function of retrospectively reported maltreatment (Capusan et al., 2016). This concords with adoption and foster care studies in suggesting pre-existing genetic vulnerability to ADHD cannot fully explain the relationship between adversity and ADHD.

Second, there is also emerging evidence for behavioural differences between adversity and non-adversity-related ADHD. A deprivation related ecophenotype of ADHD appears to be associated with a more equal sex ratio, a tendency towards inattentive over hyperactive/impulsive symptomatology and a reduced likelihood of developing co-occurring CD (Kennedy et al., 2016; Sonuga-Barke & Rubia, 2008). Interestingly, cross-sectional studies of maltreated children paint a different picture. Here childhood maltreatment is also associated with elevated inattentive symptoms (Becker-Blease & Freyd, 2008), but also with more aggressive and impulsive behaviour and a greater risk of co-occurring CD (Briscoe-Smith & Hinshaw, 2006; De Sanctis, Nomura, Newcorn, & Halperin, 2012). The reason for this difference is not known. One possibility is that ongoing maltreatment is a separate developmental pathway for CD (Blair, 2013; Richey, Brown, Fite, & Bortolato, 2016), which may be mitigated by a safe and nurturing rearing environment (Lynam et al., 2000). Another possibility is that this could arise because of the different types of adversity experienced by the child (i.e., deprivation vs maltreatment – the later usually an umbrella term for physical/emotional abuse or neglect).

Similar DMN connectivity patterns in deprivation related ADHD and in adolescents with CD was unanticipated and unfortunately, we did not measure childhood maltreatment in the latter group. However, epidemiological studies have suggested as many as 50% of

individuals with CD would have experienced childhood maltreatment at some point in their lives (Reebye, Moretti, Wiebe, & Lessard, 2000), with that number rising to around 70% of individuals placed in youth offending services - from which the majority of our CD sample were recruited (Forth & Tobin, 1995; Moore, Gaskin, & Indig, 2013). Therefore, it is plausible that a significant proportion of the sample discussed in Chapter V may have been maltreated and the hyper-connectivity patterns observed may be attributed to a maltreatment related subtype of ADHD (similar to those observed in Chapter VI). However, future studies looking at individuals with CD and co-occurring ADHD with and without histories of maltreatment would be necessary to confirm this prediction.

7.6.0 Strengths and limitations of the studies included in this thesis

The strengths and limitations of each individual study have been discussed in detail in each of the three empirical chapters. Therefore, these issues will not be revisited in detail here. Instead we will draw out common strengths and limitations that apply across the three studies.

7.6.1 Strengths

The three studies included in this thesis had a number of strengths. First, we included three different samples with ADHD or high rates of ADHD symptoms but who varied in their demographic, age, aetiology (i.e., deprivation-related versus idiopathic) and severity of ADHD and CD. This provided a comprehensive analysis into how ADHD may affect the functional architecture of the DMN.

Second, all participants were assessed using detailed, multi-informant diagnostic and neuropsychiatric assessments – ensuring the validity of the diagnoses and clinical correlates.

This is important given evidence that individuals with ADHD have a difficulty in accurately self-reporting symptom severity (Du Rietz et al., 2016).

Third, the functional architecture of the DMN was assed using resting-state functional connectivity which avoided the use of an experimental fMRI task. The samples used in Chapter V and VII were either relatively young and/or comprised a clinical group at high risk for not fully understanding or not fully engaging with a task tapping internally orientated, meta-cognitive processes. Previous studies measuring these constructs have either asked participants to make self-referential or semantic decisions concerning hypothetical events (e.g., "*Think about the major issues in your life at this moment"*; Andrews-Hanna et al. (2010)) or evaluate the self-descriptiveness of trait adjectives (D'Argembeau et al., 2011). In such tasks there is no clear way of verifying task engagement, making it challenging to assign the expected pattern of DMN hypo-connectivity/activity to either suboptimal self-referential cognition or the alternative hypothesis that this simply reflects lower levels of task engagement.

Fourth, we employed a seed-based analytical approach to measure the functional integrity of the DMN from a set of ROIs that *were* acquired from multiple tasks testing how different types of self-generated thought affect DMN functioning. Given relatively specific hypotheses about what the functional consequences of atypical DMN connectivity may be, this meant we could restrict connectivity patterns to only between those brain regions shown to activate during social-cognitive, self-referential and temporal processing. These domains were of particular interest in relation to the consequences of DMN dysregulation in CD and ADHD. The connectome used in this thesis was first identified by Andrews-Hanna et al. (2010) using task-based fMRI on a healthy population of young adults, with findings later validated using purely data-driven approaches (Doucet et al., 2011; Yeo et al., 2011). Seed ROIs overlapping the medial temporal subsystem included nodes shown to activate when

participants were asked to construct a mental scene from memory, or to simulate the future. Seeds ROIs overlapping the dorsal medial subsystem included nodes shown to activate during semantic and social processing and seed ROIs overlapping the core subsystem included nodes shown to activate when an individual places personal significance/self-relevance on an imagined scenario. Therefore, although fMRI data was not acquired using an experimental task, the observed results can be more confidently related to the hypothesised deficits than if we had investigated resting-state connectivity using an entirely data-driven approach or an alternative set of seeds (e.g., Yeo et al. (2011)).

Fifth, for Chapters VI and VII we calculated averaged functional connectivity within each of the three DMN subsystems. Although the present studies are the first to apply this analytic strategy to individuals with ADHD, this statistical approach has been used in the past to map specific symptom profiles to DMN subsystem abnormalities in individuals with major depression (Zhu et al., 2017) and schizophrenia (Dodell-Feder et al., 2014). It produces a global index of functional integrity that is potentially more sensitive to network level effects than traditional seed based, or wholly data driven approaches such as independent components analysis. Furthermore, using the framework of a functionally dissociable DMN, it also provides a more straightforward interpretation of results, in which univariate outcomes can be more clearly related to cognitive deficits.

7.6.2 Limitations

In addition, there are a number of limitations that need to be considered. First, in Chapters VI and VII we initially identified atypical DMN subsystems using a multiple comparison corrected significance level at a group level (i.e., UK adoptees vs Romanian adoptees in Chapter VI and ADHD vs healthy controls in Chapter VII). Only in subsystems in which these contrasts were significant did we move on to examine clinical correlates and

as we were looking at a restricted set of systems, significance was assessed using an uncorrected alpha level. This 'two step' approach is commonly employed to compensate for the relatively small sample sizes in fMRI studies (e.g., Zhu et al. (2017)). However, by restricting analysis to systems that have already shown a main effect of group and then correlating significant connectivity patterns with a variable (such as delay aversion in chapter VII) that strongly correlates with the grouping variable - any significant correlations are indirectly biased towards showing functional connectivity differences from the beginning. The use of uncorrected significance testing emphasises the need for future replications.

Second, all neuroimaging data included in this thesis were cross-sectional - although in the context of a prospective longitudinal design for participants recruited from the ERA study in Chapter VI. In the absence of longitudinal data, we can only speculate about any causal relations between DMN connectivity and ADHD- and CD-like behaviours we observed. Furthermore, the results of Chapter VII suggest it is quite possible that DMN hypo-connectivity may in fact not be causal at all, but rather reflects a compensatory adaptation to deal with the negative emotions that arise during waiting. Future studies seeking to test both of these predictions would benefit greatly from adopting neuromodulation techniques such as transcranial magnetic stimulation, transcranial direct current stimulation or pharmacoimaging to artificially manipulate the neural circuits of interest. This would allow researchers to directly test if perturbation of these substrates exacerbates or attenuates a behaviour, strengthening the claim that one does or does not cause the other (Bertossi, Peccenini, Solmi, Avenanti, & Ciaramelli, 2017). For example, one hypothesis discussed in this thesis is that DMN core subsystem hypo-connectivity impairs prospection. Pharmacological imaging studies showing that baseline abnormalities in the DMN core subsystem are normalised by psychostimulant treatment relative to placebo and that this normalisation is associated with improved prospection would be an important step towards drawing causal relations between

the two phenomena. In addition, previous studies have shown stimulating the DMN core subsystem can alter the content of spontaneous thought by changing its self-relevance (Bertossi et al., 2017). Hybrid transcranial stimulation/fMRI studies showing that exciting nodes of the DMN core subsystem betters the ability of an ADHD individual to more optimally estimate the subjective utility of choice alternatives can also help bridge the gap between behavioural evidence for suboptimal inter-temporal decision making and neuroimaging evidence of DMN dysregulation.

Third, despite the utility of resting state connectivity for investigating psychopathology, a strict definition of the brain's resting state is rather difficult to formulate. One of the issues here is that the brain is never really at rest at all but is continuously active. Even during wakeful rest (the typical conditions of a resting-state scan) the brain encounters a continuous barrage of internally orientated and externally orientated stimulation. This is well illustrated by the fact that asking a participant to rest with their eyes open compared with eyes closed leads to increased connectivity in the visual system and reduces connectivity in somatosensory and auditory networks (E. Marx et al., 2004; D. Zhang et al., 2015). Furthermore, both the frequency, content and emotional salience of self-generated thought that occurs during wakeful rest alters the connectivity patterns observed, particularly within a network sensitive to internally orientated stimulation like the DMN (Delamillieure et al., 2010). Indeed, EEG studies have shown very low frequency oscillations overlapping the DMN vary substantially simply by altering the instructions a participant receives prior to engaging in wakeful rest (Hsu et al., 2016; Hsu et al., 2013).

This difficulty in isolating the brain's resting-state has important implications for interpreting the findings from the three empirical chapters included in this thesis. What is termed a resting-state scan could just as easily be reframed as a goal orientated forced waiting task. With the requirement of performing the "task" being to lie still for a prolonged period of

time in an atypical (and possibly aversive) environment in exchange for financial reward in the form of reimbursement for taking part in the study. Viewed in this way it is possible that at least some of our findings could be explained, not in terms of long term alterations in the brain's intrinsic neural architecture, but that connectivity within a network highly sensitive to emotional salience (Andrews-Hanna et al., 2014), varied as function of this unintentionally created "waiting task". This could also provide an alternative explanation for why we found core subsystem hypo-functional connectivity was partially mediated by delay aversion in Chapter VII. Although emphasising the importance of using multi-modal investigations of psychopathological brain systems, unfortunately there is no ideal way of correcting for this using a resting-state design. In order to validate these findings future research is needed showing that individuals with ADHD are more likely to engage in self-referential thought during goal directed waiting.

7.7.0 Future research

In addition to the recommendations discussed throughout this chapter, this research can be extended in a number of different ways that would be of great value in understanding how the DMN and spontaneous thought contributes to psychopathological mental states in ADHD and related disorders such as CD. The current thesis highlights the importance of focusing on internally orientated cognitive processes (often referred to as 'task independent processes') to better understand the psychopathology of ADHD and CD. Future studies seeking to further this research agenda could measure task-evoked activity whilst individuals with ADHD perform a task tapping self-reflection, prospection and autobiographical recall. As well as providing an important validation of our results it would also frame findings within the much larger task-evoked fMRI literature - conceptualising the effects of ADHD on

the DMN in terms of altered information processing within a node and not simply in terms of the functional connectivity between nodes.

Perhaps because the discovery of the DMN as a substrate of spontaneous thought coincided with a reliable task-independent method of capturing it, neuroscience has jumped ahead of behavioural psychology, and little is known about how ADHD may alter the content of spontaneous thought. As discussed in Chapter I, the phenomenology of spontaneous thought can be characterised according to three interacting dimensions (Smallwood & Schooler, 2015): 1) its temporal focus, 2) how it relates to the affective state of the individual and, 3) the degree to which it concerns personally relevant goals. Informed by this hypothesis driven exploration of the DMN, we predict that spontaneous thought in ADHD: 1) lacks the future-orientated bias typically seen in individuals without ADHD and, 2) does not concern personally relevant goals. In addition, we also predict that individuals with ADHD may be more likely to engage in spontaneous thought when faced with periods of delay to reduce the negative affect associated with waiting. Future studies could investigate this using qualitative interviews and through experience sampling during prolonged periods of waiting.

Throughout this thesis we focused exclusively on the DMN to the exclusion of other brain networks. However as discussed in detail in Chapter II, the DMN does not operate in isolation - but interacts dynamically with other brain systems. There is already a substantial literature showing that altered connectivity with the salience network and wider fronto-parietal control network may prevent the ADHD individual from attenuating the DMN during goal directed task performance (Sonuga-Barke & Castellanos, 2007). However comparatively little is known about how the DMN is connected to systems not involved in executive control. Based on the results of Chapter VI we may expect atypical functional coupling between the DMN and brain regions like the amygdala when an individual with ADHD is faced with a prolonged period of delay. If in fact core subsystem hypo-connectivity

represents a compensatory recruitment of self-referential thought, this may explain why it has so far not been detected using temporal discounting tasks, as conventual epoch related or event related fMRI designs necessitate relatively short delay periods (in the order of seconds). This may be too rapid to allow individuals to draw upon spontaneous thought. Indeed, where longer delay periods have been used (in the order of minutes) increased very low frequency oscillations have been observed in regions overlapping the DMN in individuals with ADHD compared with controls (Hsu et al., 2016). Future resting-state functional connectivity studies wishing to investigate this effect further may be advised to select the amygdala and the DMN core subsystem as seed regions of interest.

7.8.0 General conclusion

In this thesis we investigated the causes and clinical correlates of DMN dysregulation in three different populations that presented with varying levels of ADHD and CD symptoms. We demonstrated effects of ADHD across all samples, although ADHD manifested differently depending on comorbidity and putative aetiology (i.e. deprivation-related versus idiopathic). In adolescents with a clinical diagnosis of ADHD or in young adults who had experienced no or only low levels of deprivation in childhood, ADHD was associated with hypo-connectivity within the core subsystem of the DMN, extending to the medial temporal subsystem in the former group. In individuals with CD, co-occurring ADHD was associated with hyper-connectivity within this same subsystem with a similar pattern of findings observed in adults who experienced 6 or more months of early life deprivation though institutionalisation. In the present chapter we discussed possible interpretations for these effects. In particular, we considered the possibility that elevated functional connectivity within the DMN core subsystem may represent a distinct ‘ecophenotype’ of ADHD related to

early adverse experiences. Furthermore, we outlined multiple different predictions for how alterations in connectivity within the DMN core subsystem could affect the content of spontaneous thought produced. Together, these studies highlight the need for increased research both into the role of the DMN in producing spontaneous thought, and how the content of spontaneous thoughts change in individuals with psychopathology.

Supplementary Information (For Chapter V)

Table S1. Default mode network connectivity differences observed when controlling for potential confounding factors.

Contrast	Connectivity	*t*	$P_{(uncorrected)}$
Main effects of conduct disorder group status, adjusting for age, IQ and ADHD symptoms. Sixteen participants with probable substance use disorders (as assessed using the problem severity scale of the PESQ) excluded.	aMPFC-PCC	2.75	.009
	aMPFC-LTC	3.01	.004
Main effects of conduct disorder group status, adjusting for age, IQ ADHD symptoms. Seven participants with comorbid ADHD excluded.	aMPFC-PCC	3.57	.0008
Main effects of conduct disorder group status, adjusting for age, IQ ADHD symptoms. Six left-handed participants excluded.	aMPFC-PCC	3.13	.003

Key: ADHD = *attention-deficit/hyperactivity disorder*; aMPFC = *anterior medial prefrontal cortex*; IQ = *intelligence quotient*; LTC = *lateral temporal cortex*; PCC = *posterior cingulate cortex*; PESQ = *Personal Experiences Screening Questionnaire* (an indicator of risk for substance use disorders)

Supplementary information (for Chapter VI)

Selective attrition analysis

Table S2. Selective attrition between the young adult follow-up study and the current imaging sub-sample.

Measure	Young adult follow-up					ERABIS				
	UK (n=42)[a]	Rom<6 (n=37)[b]	Rom>6 (n=72)[c]	F/χ^2	Post hoc comparisons	UK (n=21)[a]	Rom<6 (n=21)[b]	Rom>6 (n=46)[c]	F/χ^2	Post hoc comparisons
Gender	16 F/ 26 M	19 F/ 18 M	39 F/ 43 M	3.44	N/A	8 F/ 13 M	9 F/ 12 M	20 F/ 26 M	2.36	N/A
IQ	105.32 (15.83)	100.23 (16.14)	94.63 (12.08)	6.08**	c<a**	107.95 (18.40)	102.89 (16.52)	96.17 (12.52)	4.05*	c<a**
SES	6 low/ 36 high	5 low/ 32 high	9 low/ 59 high	0.82	N/A	3 low/ 18 high	1 low/ 20 high	4 low/ 37 high	1.10	N/A
Months spent in institution	N/A	3.89 (1.69)	20.36 (11.65)			N/A	3.50 (2.52)	19.36 (8.46)		
Autistic symptoms	0.13 (0.53)	0.29 (0.59)	0.68 (0.86)	5.92**	c>b**,a***	0.20 (0.70)	0.32 (0.58)	0.71 (0.90)	3.16*	c>a*
ADHD symptoms	1.18 (2.30)	2.17 (3.42)	5.43 (5.02)	15.81***	c>b***,a***	1.20 (2.30)	2.67 (3.92)	4.85 (4.60)	5.63**	c>b*,a** b<c*
Disinhibited social attachment symptoms	.08 (.35)	.13 (4.54)	.75 (1.02)	15.14***	c<b***,a***	0.11 (0.46)	0 (0)	.79 (0.81)	5.30***	c>b***,a* b<c***

Note. *p<0.05, **p<0.01, ***p<0.001; values in parentheses report standard deviation, a = UK adoptees; b = Rom<6; c = Rom>6, In ERABIS: IQ scores missing from 5 participants (4 Rom>6; 1 UK adoptee); Autistic symptoms missing from 11 participants (3 Rom<6; 7 Rom>6, 1 UK adoptee); ADHD symptoms missing from 8 participants (1 Rom>6, 6 Rom<6, 1 UK adoptee); disinhibited social attachment missing from 10 participants (7 Rom>6, 1 Rom<6, 2 UK adoptee); Socio-economic status missing from 4 participants (4 Rom>6); Rom<6 group excludes adoptees never placed in institutions; ADHD = *Attention-deficit/hyperactivity disorder;* SES = *socio-economic status*.

Table S2 reports demographic and clinical characteristics from the English and Romanian Adoptees' young adult follow-up compared with the English and Romanian adoptees' brain imaging study (ERABIS) from which the current study was drawn. Dropout (defined as the

absence of useable resting-state fMRI data) was assessed using all variables described in the table above: gender, socio-economic status (SES), ADHD symptoms, DSE, autism symptoms and IQ. See Sonuga-Barke et al. (2017) for an analysis of selective attrition between age 15 and young adult follow-up using the same variables

The severity of symptomatology was lower for the young adult follow-up group compared with those who continued on to take part in ERABIS. At young adult follow-up there were no significant differences between ROM<6 and the UK control group, although at ERABIS significant differences between the two groups emerged for ADHD symptoms and disinhibited social engagement. Of these variables, none were significantly associated with dropout between the young adult follow-up and ERABIS.

Table S3: Effects of- and interactions with- deprivation duration and attention deficit hyperactivity disorder (ADHD) on default mode network (DMN) core subsystem functional connectivity in Romanian and UK adoptees after adjusting for IQ

Contrast	F/t-statistics	Post Hoc tests
Effect of extended deprivation exposure (Rom>6 vs UK)	5.53*	N/A
Effect of duration of deprivation (Rom>6 vs Rom<6)	7.56**	N/A
Main effect of ADHD symptoms	0.19	N/A
ADHD symptom x deprivation interaction (high symptom low symptom vs Rom>6; LoDep)	2.83**	High symptom LoDep < Low symptom LoDep*
Symptom x deprivation interaction for ADHD symptoms after adjusting for autism symptoms (high symptom; low symptom vs Rom>6; LoDep)	2.70**	High symptom LoDep < Low symptom LoDep*

Note. *p<0.05, **p<0.01, ***p<0.001; all results reported at uncorrected p-values; Rom>6 = 6 or more months spent in deprivation; Rom<6 = less than 6 months spent in deprivation; LoDep = less than 6 months or no time spent in deprivation; UK = UK adoptee comparison group with no experience of deprivation.

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