Attention-deficit/hyperactivity disorder and preterm birth as a risk factor: a cognitive-neurophysiological sibling-pair investigation

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Attention-deficit/hyperactivity disorder and preterm birth as a risk factor: a cognitive-neurophysiological sibling-pair investigation

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This is dedicated to my Welsh Stars.

Abstract

This thesis uses a multi-disciplinary approach to study cognitive-neurophysiological processes underlying attention-deficit/hyperactivity disorder (ADHD), and the underlying risk pathways from preterm birth to ADHD. In the first part of the thesis we use a measure of peripheral arousal (skin conductance) to better understand arousal dysregulation in ADHD and how it relates to cognitive performance. We show, using a large ADHD and control sibling sample, that ADHD is associated with peripheral hypo-arousal, and that a familial aetiology underlies the relationship between hypo-arousal and fluctuating reaction times, and between hypo-arousal and ADHD. Our findings further suggest that peripheral hypo-arousal is an enduring deficit in ADHD, as it is observed in both ADHD remitters and ADHD persisters in our follow-up investigation. The second part of the thesis focuses on preterm birth as a risk factor for ADHD: we compare data we obtain from a new sample of preterm-born adolescents and their siblings to data from ADHD and control sibling pairs. First, we find that preterm-born individuals show several of the same cognitive-neurophysiological impairments as individuals with ADHD, but they also show further, additional impairments. Second, our results indicate that cognitive-neurophysiological impairments in the preterm group differentiate into those that are in line with a causal effect of preterm birth, and those that are not. Third, our findings further suggest that the association between ADHD symptoms and specific cognitive impairments is largely due to familial influences among term-born individuals, but largely due to non-shared effects (including preterm birth as an environmental insult) among preterm-born individuals. Overall, by using a combination of cognitive, neurophysiological, developmental and sibling-comparison designs, our findings provide new insight into arousal dysregulation in individuals with ADHD, and inform on cognitive-neurophysiological and aetiological processes that may underlie the association between preterm birth and ADHD.

Statement of authorship

The results reported in this thesis are based on data from two projects. First, results in chapters 2, 3, 4, and 6 include data from a follow-up project of an ADHD and control sibling-pair sample (Sibling EEG Follow-up Study; SEFOS), which was led by Professor Jonna Kuntsi, and supported by generous grants from Action Medical Research and the Peter Sowerby Charitable Foundation (grant reference GN1777). Second, results in chapters 4, 5 and 6 include data from the Study of Preterm birth and Inattention (SPIN), which assessed preterm-born adolescents and their siblings. This study was also led by Professor Jonna Kuntsi, and was supported generously by Action Medical Research (grant reference GN2080). I am grateful for all the participating families and individuals who took part in these studies, and to the co-investigators for allowing me to work with these datasets.

The present thesis represents my own work. For the SEFOS-only chapters (chapters 2 and 3), I formulated the research questions, processed data, conducted analyses and interpreted the findings under the guidance of supervisors Professor Jonna Kuntsi and Dr Fruhling Rijsdijk, with further the advice from Dr Grainne McLoughlin, Professor Philip Asherson and Dr Celeste Cheung. For chapters 4, 5 and 6, using data from the SPIN and SEFOS samples, I formulated research questions, contributed to data collection, processed and analysed data, conducted the model-fitting analyses and interpreted the findings under the supervision of Professor Jonna Kuntsi, Dr Fruhling Rijsdijk and Dr Gráinne McLoughlin. For the SPIN project, collection of clinical and EEG data, as well as processing of the data, was shared between myself, research workers Hannah Sims, Rachel Sparrow and Stacey Eyers, as well as colleagues Dr Anna Rommel and Giorgia Michelini.

Publications relevant to this thesis

Chapter 2 is adapted from the following publication in press (available under the Creative Commons licence): **James S-N**, Cheung CHM, Rijsdijk F, Asherson P & Kuntsi J. (in press). Modifiable arousal in attention-deficit/hyperactivity disorder and its aetiological association with fluctuating reaction times. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.*

Chapter 3 is adapted from the following publication in submission:

James S-N, Cheung CHM, Rijsdijk F, McLoughlin G, Brandeis D, Banaschewski T, Asherson P & Kuntsi J (under review). Peripheral hypo-arousal but not preparation-vigilance impairment endures in ADHD remission. *Journal of Attention Disorders.*

Chapter 4 is adapted from the following publication in submission:

James S-N, Rommel AS, McLoughlin G, Brandeis D, Banaschewski T, Asherson P & Kuntsi J (under review). Associations of preterm birth with ADHD-like cognitive and response preparation impairments and additional subtle impairments in attention and arousal malleability. *Psychological Medicine.*

Chapter 5 is adapted from the following publication in preparation:

James S-N, Rommel AS, Rijsdijk F, McLoughlin G, Brandeis D, Banaschewski T, Asherson P & Kuntsi J. (in prep). Cognitive and neurophysiological impairments between adolescents born preterm and full-term born siblings.

Chapter 6 is adapted from the following publication in preparation:

James S-N, Rommel AS, Rijsdijk F, McLoughlin G, Brandeis D, Banaschewski T, Asherson P & Kuntsi J. (in prep). Investigating the moderation effects of preterm birth on the familial and non-shared effect paths between cognitive-neurophysiological impairments associated with ADHD.

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1 Table of Contents

Table of Figures

Table of Tables

Abbreviations

Abbreviation	Meaning
5HTT	Serotonin transporter gene
A	Additive genetic effects
ADHD	Attention-deficit/ hyperactivity disorder
ADHD-C	ADHD combined type
ADHD-HI	Predominantly hyperactive/ impulsive type
ADHD-IA	Predominantly inattentive type
ASD	Autism spectrum disorder
BFIS	Barkley's functional impairment scale
BOLD	Blood Oxygen Level Dependent
C	Shared environment
CE	Commission error
CNS	Central nervous system
CNV	Contingent negative variation
CPRS-S	Revised Conners' Parent Rating Scale
CPT-OX	Continuous performance test
CSCT	Cross-sibling-cross-trait
D	Non-additive or dominant genetic effects
DAT1	Dopamine transporter gene
DIVA	Diagnostic Interview for ADHD in adults
DNA	Deoxyribonucleic acid
DRD4	Dopamine D4 receptor gene
DRD5	Dopamine D5 receptor gene
DSB	Digit span backward
DSF	Digit span forward
DSM	Diagnostic and Statistical Manual of Mental Disorders
DZ	Dizygotic
E	Non-shared environment
EEG	Electroencephalography

EF	Executive functioning
EOG	Electro-oculograms
ERN	Error-related negativity
ERP	Event-related potentials
F	Familial
fMRI	Functional magnetic resonance imaging
GA	Gestational age
GWAS	Genome-wide association studies
h^2	Heritability
HR	Hazard ratio
ICA	Independent component analysis
ICD	International Classification of Diseases
IQ	Intelligence quotient
kΩ	Kiloohm
MEG	Magnetoencephalography
MRT	Mean reaction time
MTA	Multimodal treatment study of ADHD
MZ	Monozygotic
NE	Non-shared effects
NHS	National Health service
NICE	National Institute for Health and Care Excellence
OE	Omission error
OR	Odds ratio
PCHR	Personal Child Health Record
QEEG	Quantitative electroencephalography
Rph	Phenotypic correlation
Rph-F	Extent of phenotypic correlation due to familial effects
Rph-NE	Extent of phenotypic correlation due to non-shared effects
RR	Relative risk
RT	Reaction time

RTV	Reaction time variability
SC	Skin conductance
SCL	Skin conductance level
SCR	Skin conductance response
SD	Standard deviation
SD	Standard deviation
SNS	Sympathetic nervous system
WASI	Wechsler Abbreviated Scale of Intelligence
µV	Microvolt

Chapter 1 - INTRODUCTION

1.1 Abstract

In this introductory chapter I will give an overview of attention-deficit/ hyperactivity disorder (ADHD), and highlight the context and issues relevant to the research of this thesis. The chapter first describes clinical features, diagnostic criteria, epidemiology, treatment, and associated outcomes of ADHD. This is followed by an overview of ADHD aetiology, and a brief introduction to quantitative genetic approaches used to study aetiology in this thesis. Cognitive theories of ADHD are discussed, with a focus on arousal-related theories, which are of particular relevance in this thesis. The chapter then provides an overview of methods and results of investigations into cognitive and neurophysiological impairments in ADHD. The chapter then shifts to review a major theme in this thesis: epidemiological and cognitive and neurophysiological findings of preterm birth as a risk factor for ADHD. I conclude with a summary of the overarching aims and research questions of this thesis.

1.2 Introduction to ADHD as a clinical disorder

ADHD is characterised by developmentally inappropriate and impairing levels of inattention and/or hyperactivity and impulsivity (American Psychiatric Association, 2013). Despite the common misconception that ADHD is a disorder of modern prevalence, the earliest record, to describe the core symptoms as a medical disorder, was made in 1775 (Barkley & Peters, 2012). Although the exact definition, underlying concepts and nomenclature have evolved over time, the impairing nature of the disorder has consistently been acknowledged (Lange, Reichl, Lange, Tucha, & Tucha, 2010).

Whilst early accounts of symptoms and associated impairments were recorded as case studies throughout the 18th and 19th century, due to a shift in the 20th century to classify psychiatric disorders based on empirical evidence, the first mention of ADHD – classified as “hyperactive child syndrome” - was included in the 2nd edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II) (American Psychiatric Association, 1968). The concept of ADHD has

since evolved based on the recognition of heterogeneity of the manifestation of inattentive, hyperactive and impulsive symptoms, and subsequently the DSM-IV and DSM-IV-TR definition of ADHD incorporated subtypes - inattentive subtype, hyperactive/impulsive subtype and combined type (American Psychiatric Association, 1994). The research in this thesis classifies ADHD based on DSM-IV criteria (see Table 1.1). Recent revisions to the ADHD classification, in DSM-V, have included a description of commonly associated disorders, raised the age of onset of symptoms from aged seven to aged twelve, and lowered the minimum amount of symptoms that individuals aged over 17 need to meet (American Psychiatric Association 2013). These changes have been made to more accurately characterize the experience of adults, as it allows children with sub-threshold levels of ADHD symptoms and limited impairment to meet diagnosis criteria for ADHD later in life (Asherson, Buitelaar, Faraone, & Rohde, 2016).

1.2.1 Diagnostic criteria of ADHD

As the research in this thesis classifies ADHD based on DSM-IV criteria, the following section provides an introduction to the DSM-IV diagnostic criteria only. The DSM-IV criteria set out eighteen items - nine inattention symptoms, six hyperactivity symptoms and three impulsivity symptoms - which are grouped into inattentive and hyperactive-impulsive subscales of ADHD. The DSM-IV criteria require an individual to meet the criteria for six or more symptoms for at least one of the two subscales (See Table 1.1). The criteria further stipulate that the onset of symptoms has to be before the age of seven, the symptoms have to be present for at least 6 months, and the symptoms have to be present across more than ones setting (e.g home and school) to a degree that is not developmentally appropriate and results in impairment (for example affecting academic or social functioning). If all criteria are met, and the symptoms do not occur exclusively during the course of a pervasive developmental or psychiatric disorder, and are not better explained by any other psychiatric disorders, a diagnosis of ADHD is made. There are three subtypes of ADHD diagnosis recognized by the DSM-IV: predominately inattentive type (ADHD-IA) is diagnosed when six or more inattentive symptoms are present; predominately hyperactive/impulsive type (ADHD-HI) which is diagnosed when six or more hyperactive/impulsive symptoms are present; and ADHD

combined type (ADHD-C) which is diagnosed when at least six symptoms are present on both subscales. Based on the criteria in the DSM-IV, adults can only be diagnosed if they had symptom onset before the age of seven, met diagnostic criteria in childhood, and continue to meet the full criteria during adulthood.

An alternative diagnostic criterion is the International classification of Diseases (ICD-10), which refers to ADHD as “Hyperkinetic disorder” (World Health Organization, 1992). The ICD-10 classification is more stringent than the DSM-IV definition, as it does not distinguish between subtypes; symptoms from all inattention, hyperactivity and impulsivity domains need to be present for a diagnosis. Therefore, the ICD-10 is thought to capture a more severely affected group.

Table 1.1. Diagnostic items for ADHD based on DSM-IV

Inattention symptoms	
1	Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities
2	Often has difficulty sustaining attention in tasks or play activities
3	Often does not seem to listen when spoken to directly
4	Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure of comprehension)
5	Often has difficulty organizing tasks and activities
6	Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
7	Often loses things necessary for tasks or activities at school or at home
8	Is often easily distracted by extraneous stimuli (may include unrelated thoughts)
9	Is often forgetful in daily activities
Hyperactivity symptoms	
10	Often fidgets with hands or feet or squirms in seat
11	Often leaves seat in classroom or in other situations in which remaining seated is expected
12	Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to feeling restless)
13	Often has difficulty playing or engaging in leisure activities quietly
14	Often talks excessively
15	Is often 'on the go' or often acts as if 'driven by a motor'
Impulsivity symptoms	
16	Often has difficulty awaiting turn in games or group situations
17	Often blurts out answers to questions before they have been completed
18	Often interrupts or intrudes on others, e.g. butts into other children's games

Items replicated from the revised version of DSM-IV (DSM-IV-TR; American Psychiatric Association 2000).

1.2.1.1 Methodological considerations: Parent, teacher or self-reports?

The clinical guidelines for assessing ADHD symptoms in childhood recommend obtaining reports of symptoms from the individual concerned, as well as obtaining reports by multiple informers such as parents and teachers. Multi-informants are valuable in assessing the presence, severity and pervasiveness of symptoms across different settings (Taylor et al., 2004). Despite the recommendations, methods used to evaluate symptoms of ADHD tend to vary with the life span. Often, childhood diagnoses of ADHD are made based on parent, teacher and child ratings, whilst adult diagnoses of ADHD are usually based on self-ratings alone, partly due to the difficulty in obtaining multi-informant reports in adulthood (Asherson, 2005).

Studies assessing multi-informant reports demonstrate low to modest agreement (correlations ranging from 0.3 to 0.5) between inter-rater correlations between parent-, teacher- and self-reports (Achenbach & Rescorla, 2001; Goodman, 2001; Sollie, Larsson, & Mørch, 2013; Wolraich et al., 2004), and also demonstrate varying heritability estimates of ADHD symptoms between informers (Achenbach & Rescorla 2001; Goodman 2001; Wolraich et al. 2004; Sollie et al. 2013). Parent ratings of ADHD symptoms scores show the highest heritability estimates (h^2=70-80%) (Nikolas & Burt, 2010). The predictive validity of parent-reports on long-term outcomes of ADHD have also been demonstrated to be better compared to self-reports (Barkley, Fischer, Smallish, & Fletcher, 2002). In addition, a large longitudinal, population-based twin study (n=4000) demonstrated that parental ratings of ADHD show stability across development in childhood (Kuntsi, Rijsdijk, Ronald, Asherson, & Plomin, 2005). They further showed that additional genetic influences - not shared with genetic influences at an earlier age - were responsible for the stability of genetic influences underlying parental rated ADHD symptoms (Kuntsi, Rijsdijk, Ronald, Asherson, & Plomin, 2005).

Heritability estimates of self-ratings in adolescent (Ehringer, Rhee, Young, Corley, & Hewitt, 2006; Martin, Scourfield, & McGuffin, 2002; Merwood et al., 2013; Young, Stallings, Corley, Krauter, & Hewitt, 2000) and adults (Boomsma et al., 2010; Haberstick et al., 2008; H Larsson et al., 2013; Schultz, Rabi, Faraone, Kremen, & Lyons, 2006; van den Berg, Willemsen, de Geus,

& Boomsma, 2006) samples have been demonstrated to have the lowest heritability (h^2<50%). Proposed explanations for the lower heritability estimates in self-ratings are that people with ADHD may lack insight into their behavioural levels (Hoza et al., 2005; Knouse, Bagwell, Barkley, & Murphy, 2005; Murphy & Schachar, 2000; Owens, Goldfine, Evangelista, Hoza, & Kaiser, 2007), or alternatively, given that measurement error is contained in non-shared environment component of twin models, if there is a greater measurement error, this will deflate the true heritability estimates, making the self-ratings the least reliable (Franke et al., 2012; Martin et al., 2002; Merwood et al., 2013).

It has been recently demonstrated, using the ADHD-control sample that is used in this thesis, that parent-report of childhood ADHD symptoms is the strongest predictor for ADHD outcome at follow up, and the stability of ADHD symptoms was also evident from objectives measures, which are not subject to rater bias (Cheung et al. 2015). In contrast, teacher ratings of childhood ADHD symptoms did not predict ADHD symptoms at follow up, suggesting that the validity of teacher reports in older children may be compromised (Cheung et al. 2015). Based on this notion, and to allow consistency between samples in our research group (Cheung et al. 2016; Kitsune et al. 2014; Michelini et al. in press; Cheung et al. 2015), the ADHD diagnosis status in this thesis was based on parent-reported DSM-IV ADHD symptoms during a structured clinical interview.

1.2.2 Epidemiology

According to the most recent meta-analysis of 41 studies across the world, the estimated prevalence of ADHD in children and adolescent is 3.4% (CI 95% 2.6-4.5) (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Epidemiological comparisons worldwide demonstrate that whilst the prevalence is largely consistent across countries, there is heterogeneity from assessment methods, for example, variation in the diagnostic criteria and informants used. It is notable, however, that there are fewer prevalence studies from low-income and middle income countries, and the prevalence rates obtained seem lower than the population average, indicative of under-diagnoses (McCarthy et al., 2012). Epidemiological longitudinal studies have further explored trends of ADHD symptoms and diagnosis over three decades,

and conclude that whilst the rate of ADHD symptoms and diagnosis has not increased over time (Collishaw, 2015; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014), there has been an increase in the number of medication prescribed across developed countries (Dalsgaard, Østergaard, Leckman, Mortensen, & Pedersen, 2015; McCarthy et al., 2012). The rise in medication rates could be attributed to an increased awareness of ADHD, changes in ADHD management, or changes in the way that symptoms impact and impair individuals with ADHD.

1.2.2.1 Developmental trajectories in ADHD

Whilst ADHD was traditionally thought to be a childhood disorder, it has been increasingly recognized that the symptoms and associated impairments can persist and be present in adulthood. Population-based meta-analyses have estimated worldwide adult ADHD prevalence rates ranges from 2.5% to 3.4% (Fayyad et al., 2007; Simon et al., 2009). Longitudinal studies have further demonstrated that ADHD symptoms can persist into adulthood (Cheung et al. 2015; Faraone et al. 2006; Langley et al. 2010). However, as there is a lack of large, longitudinal studies assessing the trajectories of ADHD, it is difficult to deduce the clear developmental trajectories of ADHD. One major issue in longitudinal studies that could explain discrepancies about persistence rates is the variation in the definition used to classify persistence or remittance of ADHD. For example, a meta-analysis of children with ADHD follow-up showed that whilst only 15% retained the full diagnostic criteria at age 25, 50% of the sample who met the original childhood criteria of ADHD, still had persistence of ADHD symptoms causing impairments, but they were sub-threshold of the ADHD criteria (Faraone et al. 2006).

Whether lower adult ADHD prevalence rates, compared to child ADHD prevalence rates, reflect true prevalence estimates attributed to ADHD diagnostic remission is being debated (Asherson et al. 2016). For example, it has been speculated that the lower adult ADHD population-based prevalence rates could be partly attributed to under-diagnosis of ADHD in adults, which is in line with studies demonstrating under-diagnosis of ADHD in prison, adult addition units and general mental health services (Deberdt et al., 2015; Huntley et al., 2012; van de Glind et al., 2014; Young, Moss, Sedgwick, Fridman, & Hodgkins, 2015). Under-

diagnosis could be attributed to differences in informants between child and adult samples, as ADHD diagnoses in adults rely heavily, and often exclusively, on self-report, which tend to report lower estimates, whereas ADHD diagnoses in children rely mostly on parent and teacher reports. In addition, discrepancies in prevalence rates could be due to the more stringent ADHD criteria for adults, as until the DSM-V, an ADHD diagnosis for adults could only be made based on symptoms descriptions developed for children, and adults may not have met the threshold for a diagnosis in childhood (Asherson et al. 2016).

A recent area of debate has focused on findings that not all adults meet diagnosis criteria for ADHD in childhood (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015). This indicates that children with sub-threshold levels of ADHD symptoms and/or no impairment to meet the diagnostic criteria in childhood may have increased symptoms and/or impairments throughout different developmental stages which can lead to a full diagnosis of ADHD. One explanation of this suggests that children with good external scaffolding (such as supportive homes, schools, high IQ, strong executive function (EF) skills), are able to not be impaired, but once the scaffolding is removed, or the individual is unable to cope, the full manifestation of the syndrome and associated impairments could emerge (Asherson et al., 2016; Faraone & Biederman, 2016). An alternative hypothesis is that, in the presence of risk factors, whether or not a neurodevelopmental disorder is diagnosed - such as ADHD – may depend on the efficiency of executive function processes at the time (Johnson, 2012). Another alternative interpretation is that there could be a late-onset ADHD syndrome, which doesn't have any substantial childhood symptoms, and reflects a differentiate syndrome (Moffitt et al. 2015; Agnew-Blais et al. 2016; Caye et al. 2016). Evidence for this notion has come from three recent large-scale longitudinal population-based studies, which have demonstrated 87%-67.5% of the adults who met ADHD criteria as adults did not meet the ADHD criteria in childhood. This raises the possibility of two phenotypically similar syndromes, with differentiating onset, distinct developmental trajectories, and potentially different aetiology. However, these findings are recent and may reflect challenges with methodological considerations of ADHD, such as the measurement scales and informers. Until we gain further clarification about the clinical presentation of adults who met ADHD criteria in adulthood but not in childhood, the findings should be interpreted with caution (Asherson et al. 2016).

Nevertheless, there is adequate evidence for impairments occurring into adulthood in some individuals, but more research needs to establish the developmental trajectories and the manifestation of ADHD in adulthood.

1.2.2.2 Gender differences

In childhood studies, it is well reported that there is a higher proportion of males diagnosed with ADHD, compared to females (Willcutt, 2012). Worldwide estimates of the gender ratio in children are 3-4:1 in epidemiological studies and 8:1 in clinical populations (Erskine et al., 2013; Gaub & Carlson, 1997; Nussbaum, 2012; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). On the contrary, whilst there are fewer studies in adults, epidemiological and clinical population studies report a more equal ratio of males and females (Biederman et al., 1994; Biederman, Faraone, Monuteaux, Bober, & Cadogen, 2004; Rucklidge, 2010). The inconsistency between gender ratios in childhood and adulthood seeks further clarification of whether it reflects an under-diagnosis of girls, or whether there are true distinctions of gender ratios across the lifespan.

One interpretation of the gender ratio inconsistency between childhood and adulthood is that the higher male incidence observed in childhood represents an underrepresentation of girls with ADHD due to referral bias (Biederman et al. 2005). It has been proposed that as disruptive behaviours tend to drive clinical referral in childhood, girls remain undetected because they exhibit fewer disruptive behaviours regardless of their ADHD (Biederman et al., 2002; Brassett-Harknett & Butler, 2007). A study supporting this notion showed that females with ADHD are more likely to meet diagnostic criteria for ADHD-IA, compared to ADHD-HI, which is associated with more disruptive behaviours (Willcutt 2012). Another interpretation of the gender ratio inconsistency across the lifespan attributes it to differences in referrals in childhood and adulthood. It has been shown that as adults, many women self-refer and this may result in a better-balanced gender distribution (Arcia & Conners, 1998; Biederman et al., 1994; Joseph Biederman et al., 2004). A proposed explanation for the sex discrepancies in childhood is a “female protective effect” model, which proposes that, compared to males, females need greater exposure to risk factors in order to display ADHD symptoms which

requires a diagnosis (Jacquemont et al., 2014). A recent study which used two population-based twin samples supported this notion by demonstrating that cotwins of female ADHD probands had increased ADHD traits than cotwins of male ADHD probands, indicating that females undergo greater exposure to aetiological factors in order to develop ADHD, compared to males (Taylor et al., 2016). However, research investigating whether there are sex differences in ADHD symptom severity in people diagnosed with ADHD is inconsistent: studies have demonstrated that, compared to males, ADHD symptom severity is increased in females (Elkins, Malone, Keyes, Iacono, & McGue, 2011; Fedele, Lefler, Hartung, & Canu, 2010; Robison et al., 2008), decreased in females (Arnett, Pennington, Willcutt, DeFries, & Olson, 2015; Gaub & Carlson, 1997; Gershon, 2002), or have no differences between male and female symptom severity (Das, Cherbuin, Butterworth, Anstey, & Easteal, 2012; de Zwaan et al., 2012; Rasmussen & Levander, 2009; Retz-Junginger, Rösler, Müller, & Retz, 2012; Wilens et al., 2009).

1.2.2.3 Psychiatric comorbidities

Studies on both general population (Kadesjö & Gillberg, 2001; Kraut et al., 2013; Larson, Russ, Kahn, & Halfon, 2011) and clinic-referred (Ghanizadeh, 2009; Skirrow & Asherson, 2013) samples consistently show a high incidence of psychiatric comorbidity in ADHD, although rates of comorbidities are greater in clinically referred samples (Woodward, Dowdney, & Taylor, 1997). A recent review (Asherson 2016) suggested that the comorbidities of ADHD could be grouped into three areas based on their clinical features and treatment implications: first are the psychiatric conditions that symptoms and impairments of ADHD can mimic, due to an overlap of core ADHD symptoms. These include anxiety, depression and bipolar disorder. General population and clinical samples have also demonstrated co-occurring anxiety disorders in 20-35%, and co-occurring depressive disorders in 10-30% (Bauermeister et al., 2007; Biederman et al., 2012; Bloemsma et al., 2013; Hesson & Fowler, 2015). In addition, a systematic review demonstrated that 5-20% of adults with ADHD meet the criteria of bipolar disorder (Asherson et al., 2014).

The second proposed group of ADHD comorbidities are of overlapping neurodevelopmental traits and neurodevelopmental disorders, including autism spectrum disorders (ASD), dyslexia and dyspraxia. A high comorbidity of around 20-50% has been demonstrated between people with ADHD and ASD (Banaschewski, Poustka, & Holtmann, 2011; Lai, Lombardo, & Baron-Cohen, 2014; Polderman, Hoekstra, Posthuma, & Larsson, 2014; Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). Twin studies have further demonstrated that there are overlapping aetiological factors between ADHD and autistic traits (Pinto, Rijsdijk, Ronald, Asherson, & Kuntsi, 2016; Ronald, Edelson, Asherson, & Saudino, 2010; Ronald, Larsson, Anckarsäter, & Lichtenstein, 2014; Taylor et al., 2013).

The third comorbidity grouping is considered to be co-occurring disorders which may manifest in response to complications of ADHD, for example, children with ADHD are more likely to develop substance misuse disorders, anxiety, personality disorders and criminal behaviors (Asherson 2016). The most frequently co-occurring disorders with ADHD, which are also associated with worse long- term outcomes in ADHD, are conduct disorder (CD) and oppositional defiant disorder (ODD), which are found to co-occur in around 10-70% of children and adolescents with ADHD (Bauermeister et al., 2007; Biederman et al., 2008; Freitag et al., 2012; Ghanizadeh, 2009, 2015; Harpold et al., 2007; Jensen & Steinhausen, 2015; Kadesjö & Gillberg, 2001; Henrik Larsson, Dilshad, Lichtenstein, & Barker, 2011; Vitola et al., 2012).

1.2.3 Treatment and interventions of ADHD

Given the prominent prevalence and wide-ranging impairments associated with ADHD, there is a continued need for efficient management of ADHD. As recommended by the National Institute for Health and Care Excellence (NICE) guidelines, the first line of treatment for children and adolescents with milder ADHD is behavioural interventions - such as optimized classroom strategies, parental education and behavioural managed techniques (National Collaborating Centre for Mental Health, 2013). The second line of treatment, as an alternative for children with moderate levels of impairments, children who refuse non-drug interventions and children who did not respond to psychological treatments, is pharmacological treatment.

However, it is recommended that pharmacological treatment should be in conjunction with behavioural interventions. For adults, first line treatment is pharmacological treatment.

In pharmacological treatments, stimulants such as methylphenidate and dexamfetamine are the first-line drugs (National Collaborating Centre for Mental Health 2013), and a noradrenaline reuptake inhibitor, atomoxetine, is a second-line treatment. A robust body of evidence from randomised control trials and meta-analyses demonstrate the efficacy and moderate to large clinical effects of psychostimulant as well as non-psychostimulant medication, such as atomoxetine, in reducing the symptoms and cognitive impairments associated with ADHD in children and adolescents (Abikoff et al., 2004; Brown et al., 2005; Garnock-Jones & Keating, 2009) and in adults (Faraone & Glatt, 2010; Moriyama, Polanczyk, Terzi, Faria, & Rohde, 2013; Surman, Hammerness, Pion, & Faraone, 2013). However, complete normalization of symptoms is rare and not everyone responds to medication (Banaschewski et al., 2006); consequently a personalized management plan would be beneficial.

A variety of other non-pharmacological interventions for ADHD, such as using psychological (cognitive training, neurofeedback, and behavioural training) and dietary (restricted elimination diets, artificial food colour exclusions, and free fatty acid supplementation) approaches, have been investigated over the years. The only non-pharmacological interventions that are currently recommended are behavioural interventions. Results from the largest trial of ADHD interventions to date, the multimodal treatment study of children with ADHD (MTA), suggest that pharmacological treatment and behavioural treatment, compared to pharmacological treatment alone, may be beneficial to decrease associated negative impairments and to decrease the lower drug dose (the MTA 1999). However the beneficial effects seem to attenuate after treatment has terminated (Hinshaw & Arnold, 2015). Despite efforts into non-pharmacological interventions, conclusions from interventions studies have been limited due to problems in blinding. Blinded evidence for significant reductions in ADHD symptoms has so far only been found for free fatty acid supplementation and artificial food colour exclusion (Sonuga-Barke et al., 2013). Further

blinded non-pharmacological treatment studies need to be conducted to better assess the effectiveness of these treatments.

Another alternative non-pharmacological intervention, which has gained increasing interest, is neurofeedback. In neurofeedback training, individuals with ADHD learn to match their neurophysiological profile to that of typically developing children, and can learn to control certain aspects of neural activity, such as attentional states, or arousal, and to modulate them on demand (Arns, Conners, & Kraemer, 2013; Arns, Heinrich, & Strehl, 2013; Gevensleben et al., 2014). Results from a meta-analysis showed a moderate to large effect size for treatment effects of neurofeedback, but after taking into account a lack of sufficiently blinded studies, effect sizes were reduced to moderate and at a trend level of significance (Sonuga-Barke et al. 2013). The efficacy of neurofeedback remains to be established.

1.2.4 Summary of ADHD as a clinical disorder

ADHD is a worldwide, common, psychiatric disorder associated with impairing symptoms and negative adverse outcomes. Whilst the trajectories of ADHD development are not well understood, it is thought that symptoms and impairments frequently span from childhood into adolescence and adulthood. Prevalence estimates in children indicate a higher incidence of affected males, but a more equal gender distribution is reported in adulthood, although the reasons for the gender differences across the lifespan are not well understood. ADHD shows high comorbidities and associations with many negative outcomes, which emphasizes the importance of early identification and interventions to help minimize the impairments associated with ADHD.

1.3 Aetiology of ADHD

ADHD is a multifactorial disorder arising from a complex interplay of genetic and environmental factors. A key focus of research has been to try to understand how the combined effect of genetic and environmental factors contribute to increased ADHD risk, and

to try to disentangle and identify underlying mechanisms and pathways that mediate genetic and environmental influences to behavioural changes seen in ADHD. Quantitative genetic and molecular genetics studies have emphasised the important role of genetic factors in ADHD, and provide insight into the underlying genetic contributions related to the development of ADHD, and how these may affect brain function and relevant behaviours. Equally, research has also demonstrated the key role of many environmental factors which increase the risk of developing ADHD. This chapter aims to give an overview and outline of methods and findings of quantitative genetic studies, as well as outlining key findings from molecular genetic studies and environmental risk factors.

1.3.1 Quantitative genetic studies

Based on the genetic relatedness of family members, quantitative genetic studies investigate the extent to which genetic and environmental influences account for the variation of an observed trait within a population. The method quantifies the contribution of genetic influences (additive, A or dominant, D), and divides the environmental factors into what makes family members similar (shared environmental, C) or dissimilar (non-shared/individuals-specific environment, E), without specifying what the exact genetic and environmental factors are. Twin studies provide a unique perspective to disentangle the contribution of environmental and genetic factors by comparing monozygotic (MZ) and dizygotic (DZ) twin pairs who are raised together (Plomin et al., 2013). Classic twin modelling is based on the notion that 1) MZ twins are 100% genetically identical whereas DZ twins only share 50% of their alleles, 2) shared environment (C) influences between MZ and DZ are perfectly correlated and are environmental influences that make both twins similar, 3) E is calculated as the residual variance which has not been accounted for by genetic or shared environment variables, representing environmental influences that make MZ and DZ dissimilar and measurement error (Rijsdijk & Sham, 2002). Using these assumptions, structural equation modelling programmes can use maximum likelihood estimation to decompose the variance and covariance of traits into A, C and E influences.

1.3.1.1 Sibling model fitting (James et al. in press, Cheung et al. under review)

Using the information that siblings reared together share, on average, 50% of their alleles, sibling model fitting can use within-trait correlations (e.g. ADHD symptoms of sibling 1 and ADHD symptoms of sibling 2) to decompose the variation into influences that make siblings similar (familial, F) and dissimilar (non-shared effects, NE). As sibling models cannot disentangle the shared genetic from shared environmental sources, it is assumed that F compromises of 50% of A (as sibling share around 50% of their alleles), and 100% of C. A particularly informative approach is bivariate or multivariate modelling, which estimates the contribution of F and NE influences underlying the covariation (or overlap) between two or more traits, based on cross-sibling cross-trait (CSCT) correlations (e.g. ADHD symptoms of sibling 1 and IQ of sibling 2). Significant CSCT correlations imply familial influences in the phenotypic overlap between the traits, whereas non-significant CSCT correlations indicate non-shared effects. In addition, by using the correlations between the F and NE factors, and the standardized estimates of the F and the NE influences, we can estimate the extent to which the phenotypic correlation (Rph) between any traits is due to F (Rph-F) and NE (Rph-NE). Using these contributions, we can then express them as proportions of Rph. Further details of the models can be found in Chapters 2 and 6, which use this approach.

1.3.1.2 Findings from quantitative genetics in ADHD

Family studies show that there is a two-to-eight fold increased risk for first-degree relatives of children with ADHD, compared to unaffected controls (Biederman, 2005). Twin studies consistently report high heritability estimates of ADHD, ranging from 60-90%, which makes it one of the most highly heritable psychiatric disorders (Faraone et al., 2005; Geschwind & Flint, 2015; Hawi et al., 2015; Nikolas & Burt, 2010; Wood & Neale, 2010). Heritability estimates in adult populations are lower (h^2<50%), which is thought to be partly due to self-rater measurement error (Larsson et al., 2013; Merwood et al., 2013). Heritability estimates for the inattentive and hyperactive-impulsivity symptom domains have shown similar estimates (Nikolas & Burt 2010), and multivariate modelling has indicated the domains are partially overlapping and share half of the genetic influences (rA=0.55) (Greven, Asherson, Rijsdijk, & Plomin, 2011; Larsson et al., 2013; McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007).

Overall, twin studies reveal the large contributing role of genetic influences underlying ADHD; yet, heritabilities are significantly below 100%, indicating a role additionally for the environment.

1.3.2 Molecular genetic studies

Several genetic variants have been associated with ADHD in molecular genetic investigations (Gizer et al. 2009). Before the recent advancement of large whole-genome investigations, linkage or association studies had explored the relationship between ADHD and candidate genes associated with dopamingergic, serotonergic and noradrenergic systems which are implicated in clinical response to medication, and to neural networks of attention and memory (Faraone et al., 2005; Gizer, Ficks, & Waldman, 2009). A meta-analysis revealed significant associations between ADHD and several candidate genes (e.g. DAT1, DRD4, DRD5 and 5HTT), but the effect sizes of these associations were small, with odds ratios ranging from 1.12 to 1.33, with considerable variability (Gizer et al., 2009). In addition, findings from candidate gene studies should be interpreted with caution due to the likelihood of false positives (Kendler, 2013). More recent approaches to study the genetic architecture include genome-wide association studies (GWAS) and polygenic risk score analysis. These techniques use markers across the complete genome and have revolutionized the methods of genetic research. Despite the exciting promise of GWAS studies, to date, ADHD GWAS studies in childhood (Hinney et al., 2011; Lasky-Su et al., 2008; Mick et al., 2010; Neale et al., 2008; Neale, Medland, Ripke, Anney, et al., 2010; Stergiakouli et al., 2012; Yang et al., 2013), meta-analyses of the childhood studies (Ebejer et al., 2013; Neale, Medland, Ripke, Asherson, et al., 2010) and studies in adulthood (Lesch et al., 2008; Zayats et al., 2015), have not yet identified significant common risk variants of genome-wide significance. However, the failure may be ascribed, at least partly, to not reaching a large enough sample samples as the statistical power to detect associations in GWAS is generally very low (≥80% power) and, therefore, extremely large samples are required (Hawi et al., 2015). However, preliminary results suggest that genome-wide significant hits have now emerged for ADHD (unpublished data, Faraone 2016). Combining findings from a multitude of methods, including meta-analyses, GWAS, large-scale linkage and animal research, a recent study highlighted ten genes which

are associated with ADHD (Hawi et al., 2015). Genes largely separated out into those involved in monoaminergic neurotransmission (dopamine and serotonin receptors) and others involved in synaptic transmission (Hawi et al., 2015). Whilst single genetic associations have small effect sizes, understanding which genes are implicated in ADHD may guide future research into affected pathways.

1.3.3 Environmental risk factors

Whilst the strong role of genetic influences in ADHD has been acknowledged, quantitative genetic studies, as well as a wealth of research, indicate the contributing role of environmental factors. For example, multiple environmental risk factors, such as preterm birth, low birth weight, maternal smoking, maternal stress, dietary factors, psychosocial factors, environmental toxins, have all been associated with ADHD (Thapar, Cooper, Eyre, & Langley, 2013). However, whether the associations between environmental risk factors and ADHD are due to the environmental risk factor per se or due to other environmental or genetic risk factors that characterise families with ADHD is hard to infer, as in most studies, people with ADHD are compared to unrelated controls, and, as such, the groups may have differed on unmeasured confounding familial risk factors (Thapar & Rutter, 2009). In addition, other psychosocial risks associated with ADHD, including low income and family adversity, may not be involved in the causal pathway to ADHD, but may shape the developmental trajectory, severity and outcomes (Thapar & Cooper, 2015).

1.3.3.1 Sibling-comparison method

The issue of whether associations observed between environmental risk factors and ADHD are due to the environmental risk factor per se, or due to other 'background' (shared environmental or genetic) risk factors that characterise families with ADHD, is addressed by using powerful quasi-experimental designs. Whilst twin studies are usually an excellent method for disentangling genetic and shared environmental influences from non-shared environmental influences underlying an association for most traits, they often cannot be used to study risk factors associated with pregnancy or birth, given that twins in a pair have typically both been exposed to the same pregnancy and birth event. Quasi-experimental

designs (D'onofrio, Class, Lahey, & Larsson, 2014; Lindström, Lindblad, & Hjern, 2011), including sibling-comparison designs, can overcome this issue by examining the association between environmental factors and outcomes whilst controlling for confounding familial influences (D'Onofrio et al., 2013; Donovan & Susser, 2011; Skoglund, Chen, D'Onofrio, Lichtenstein, & Larsson, 2014). The sibling comparison analysis uses a within-sibling fixed-effect model to estimate associations as a function of within-pair associations only (D'Onofrio et al., 2013; Donovan & Susser, 2011; Lahey & D'Onofrio, 2010; Neuhaus & McCulloch, 2006). This allows the effect of the environmental risk factor to be estimated between siblings whilst controlling for unmeasured confounding factors (i.e., all genetic and environmental factors that make siblings alike, including risk factors associated with the environmental factor itself). If there is a significant association between the environmental risk factor and outcome, whilst controlling for unmeasured familial confounding factors, this is consistent with a causal inference. For example, a sibling-comparison study which investigates the association between preterm birth and ADHD would compare the association between preterm birth and ADHD in preterm-born individuals compared to their term-born siblings growing up in the same family (D'Onofrio et al. 2013). If there is a significant association between preterm birth and ADHD, independent of familial factors (including familial risk factors associated with preterm birth itself), this would be in line with a causal inference of preterm birth. This approach is used in Chapter 5 and more detail can be found there.

1.3.3.2 Findings from sibling-comparison methods in ADHD

Studies have started to utilise powerful family designs, which can control for familial confounding factors to establish the causality of between environmental factors associated with ADHD. For example, the relationship between maternal smoking during pregnancy and ADHD in the child was investigated in 813,030 individuals born in Sweden between 1992 and 2000. The study found that whilst maternal smoking predicted ADHD in the child, with hazard ratios (HRs) ranging from 1.89 to 2.50 depending on how much the mother smoked, the association was not significant when controlling for unmeasured confounders (i.e., comparison between siblings) (Skoglund et al., 2014), not in line with a causal inference. This demonstrates that until more sensitive family designs can investigate, or rule out, the role of confounding familial factors, environmental associations should be interpreted with caution.

Making use of the genetically sensitive design to investigate the association between preterm birth and ADHD, a population-based cohort study, combining Swedish registries to identify all individuals born in Sweden from 1973 to 2008 (3,300,708 offspring of 1,736,735 mothers), reported a robust association between early gestation (23-27 weeks' gestation) and ADHD diagnosis (HR=2.3), which was largely independent of shared familial confounds, consistent with a causal inference of preterm birth (D'Onofrio et al., 2013). Preterm birth is a key topic of this thesis and is discussed in more detail below (section 1.6 and chapters 4, 5 and 6).

1.3.4 Environment and gene-environment interplay

Whilst studies tend to focus on genetic and environmental influences of ADHD separately, it is likely that they interact (Nigg, Nikolas, & Burt, 2010; Purcell, 2002). For example, the effect of environmental factors may have arisen due to gene-environmental interactions (i.e. variation of genetic variants may make an individual more susceptible and exposed to the way that environmental risk or protective factors work) or the genetic architecture may increase the likelihood of exposure to certain environmental influences (gene-environment correlation) (Purcell, 2002). Studies investigating gene-environmental interplay in ADHD have been limited, and have little success in replicating the findings (Nigg et al., 2010; Thapar et al., 2013). However, clearer evidence for gene-environment interplay has been found for other psychiatric disorders, such as depression (Caspi et al., 2003; Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Thapar, Collishaw, Pine, & Thapar, 2012), which highlights the possibility of genes and environmental interplay, and highlights that more research needs to be done to elucidate this in ADHD.

Epigenetic processes are thought to mediate environmental and genetic effects and could explain how environmental factors may influence gene expression in ADHD (Cortessis et al., 2012; Mill & Petronis, 2008). Whilst there is evidence that environmental exposures result in biological changes, brain structure, function and epigenetic processes, this field is still at an

early stage. For example, changes in DNA methylation and histone acetylation have also been shown in initial epigenetic studies of children with ADHD (van Mil et al., 2014; Xu et al., 2015).

1.4 Cognitive models of ADHD

Findings from interdisciplinary teams have demonstrated the complex role of genetic and environmental influences underlying the aetiology of ADHD. Over the last few decades, a range of theories have been suggested to help explain the underlying processes that may mediate genetic and environmental influences to the behaviour observed in ADHD. Many cognitive models of ADHD try to identify the underlying mechanisms behind observed slower and poorer task performance in ADHD, and some models further try to understand how factors such as presentation rate and incentives can improve cognitive performance. In this section, I will give a brief overview of the major developing cognitive theories of ADHD.

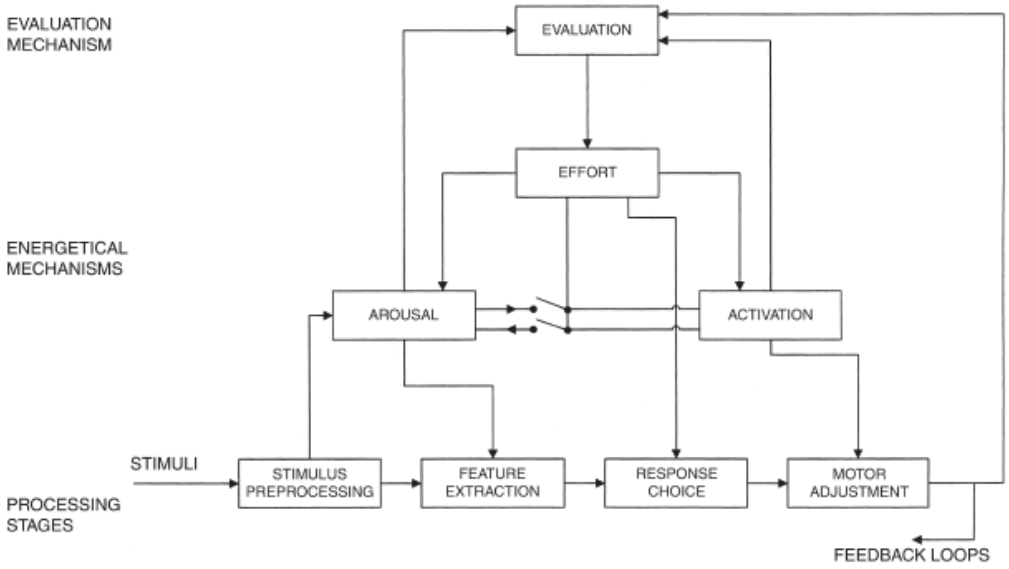
1.4.1 Arousal dysfunction theories of ADHD

Since the Cognitive-Energetic Model proposed by Sanders (1983) emerged, many theories of ADHD have incorporated the notion that problems with arousal regulation may underlie cognitive performance deficits observed in ADHD. Arousal dysfunction theories are a key topic of this thesis and are discussed further in chapters 2 and 3.

The State Regulation hypothesis (Sergeant, Geurts, Huijbregts, Scheres, & Oosterlaan, 2003; Sergeant, 2005; van der Meere, 2005) posits that there is a state regulation deficit in ADHD, which contributes to difficulties in maintaining an optimal energetic state (particularly in unstimulated environments), which underpins cognitive impairments. The theory postulates that the efficiency of how a task is performed is regulated by three levels: *computational processes* (structural attention processes of stimulus encoding, memory search, decision and motor preparation), *state factors* (arousal, activation and effort), and overall control by an *evaluation mechanism* (planning, monitoring, detection of errors and their correction) (See Figure 1.1. for an illustration). The theory posits that the availability of computational

processes is related to arousal and activation levels; arousal and activation levels are modulated by effort systems; and the effort system is influenced by an evaluation mechanism. The theory proposes that whilst computational processes are intact in ADHD, there are deficits in the state regulation and it is this problem which then leads to sub-optimal states, which then leads to deficits of allocation of cognitive resources, reflected by cognitive performance impairments observed in ADHD (van der Meere, 2005). The theory also proposes that state regulation is impaired and, subsequently, cognitive deficit manifest mostly in boring, non-optimised conditions, but are minimal in an optimal state. This further raises the notion that manipulations could be made to optimise arousal and effort states to minimise impairments. This offers a potential explanation of the heterogeneity observed in the cognitive performance of people with ADHD, across a wide range of measures.

Figure 1.1. Cognitive-energetic Model of ADHD (from Van der Meere 2005).



More recent models integrate the idea of state regulation deficits occurring with other key deficits in ADHD, in a complex multi-process model. For example, the Arousal-attention model (Johnson et al. 2007; O'Connell et al. 2008) posits arousal processes in sub-cortical arousal regulation structures (bottom-up), in combination with influences from cortical control (top-down), influence attention levels. The model further hypothesises that cognitive impairments

in ADHD arise due to deficits from both components, whereby problems in arousal regulation only partially for observed impairments, and are responsible for decreasing vigilance due to decreasing arousal levels, whereas the top-down cortical control contributes to problems in functions of attention (Johnson et al. 2007). Halperin et al (2008) further proposed a developmental framework which is also based on the notion of two core neurocognitive processes underlying impairments in ADHD: problems with state regulation and prefrontal executive control (see further detail below in section 1.4.4: neurodevelopmental model of ADHD) (Halperin, Trampush, Miller, Marks, & Newcorn, 2008).

Despite the conceptual appeal of these arousal-related models, direct objective evidence of arousal dysregulation and how it may account for fluctuating cognitive performance in ADHD is limited to date. However, theories that incorporate a sub-optimal activation state in ADHD are supported by findings of cognitive performance during within-task manipulations in ADHD groups (Kuntsi et al. 2009). As slower stimulus-presentation rate may evoke arousal under-activation, the tasks don't optimise energetic states and this is reflected by slower, inaccurate responses. On the contrary, the theory posits that tasks, which engage and optimise energetic states, should lead to improved performance (van der Meere, 2005).

One of the most consistently reported cognitive impairments in ADHD, especially in slow event rates, is variable and inconsistent performance on reaction times, leading to high reaction time variability (RTV), which is thought to reflect lapses of attention (Kopfler 2013). It is proposed that high RTV in ADHD may reflect problems stemming from sub-optimal arousal and activation. As task manipulations, such as using faster-stimulus rates and incentives, are thought to optimise arousal and effort states, studies have sought out to investigate if there is improved RTV performance when tasks are manipulated. A meta-analysis of eight studies of varying designs suggested an overall significant, though small, effect of incentives in improving RTV in ADHD (Kofler et al. 2013). As RTV performance is improved and modulated by event rate and incentives, it suggests the involvement of energetic (arousal) and/or motivational factors.

Methods trying to measure arousal have also supported these theories. A method considered to be an index and biomarker for peripheral arousal levels is to measure skin conductance (SC) (See section 1.5 for further details of this method). One key study applied SC measurement in individuals with ADHD and investigated performance on a sustained attention to response task (O'Connell et al., 2008). Although the authors did not report correlations between SC and the cognitive performance measures, they note that SC and RTV followed a similar pattern: block-by-block increases in RTV were accompanied by gradual decreases in SCR, indicating a drop in arousal response over time (O'Connell et al., 2008), in line with the notion that arousal is related to cognitive performance in ADHD. In addition, a meta-analysis from MRI studies showed dysfunction in the sub-cortical structures associated with arousal in children with ADHD (Frodl & Skokauskas, 2012). Overall, there is limited, but encouraging, evidence for theories that emphasise altered arousal-regulation processes in ADHD. However, it is yet to be established how arousal relates to cognitive performance in ADHD.

1.4.2 Executive dysfunction of ADHD

Whilst there is no unifying definition of executive functioning (EF), it is thought to be an umbrella term used to explain a variety of higher order neurocognitive processes (Alvarez & Emory, 2006; Pennington & Ozonoff, 1996). Functions include working memory, planning, inhibition, sequencing, reasoning, shifting and control of attention (Alvarez & Emory, 2006; Pennington & Ozonoff, 1996).

One of the first theories, prominent in the ADHD literature, was the executive dysfunction theory of ADHD. This theory proposes that symptoms develop in ADHD as a consequence of a core deficit in reduced executive control, which then contributes to impairments in other EF processes (Barkley, 1997). The model proposes that behaviours arise from deficient inhibitory control, which is caused by abnormalities in fronto-parietal and fronto-striatal neural networks, and as a consequence, other executive-control processes which try to help regulate and improve behaviour, are affected (Barkley, 1997).

Converging evidence, as demonstrated by a large meta-analysis of 83 studies (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), showed evidence for significant deficits across many EF domains, independent of IQ. The most replicated deficits in ADHD were for spatial working memory, response inhibitory and sustained attention (Willcutt et al. 2005). However, whilst there is supporting evidence for EF deficits in individuals with ADHD, especially on tasks with response inhibition, sustained attention and EF problems, the effect sizes tend to be of medium size (Cohen d=0.43 to 0.60), and do not explain the whole amount of symptoms in ADHD (Willcutt et al. 2005). In addition, not all individuals with ADHD display deficits in EF, for example, in one meta-analysis, less than 50% of people with ADHD had a deficit on any EF test (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). There has also been a commonality of EF deficits reported in other psychiatric disorders such as ASD (Hill et al 2004), obsessive-compulsive disorders (Olley et al., 2007), and Tourette's syndrome (Plessen et al., 2009), which displays the lack of specificity of EF problems in ADHD. Therefore, there has been an increasing acceptance that EF and prefrontal symptoms are not a core feature of ADHD, but are part of a more general affected process. Alternatively, it has been suggested that, instead of poor EF skills being a core symptom of ADHD, the association between low EF and ADHD is due to those with better EF skills compensating for a-typicalities earlier in life, and are therefore less likely to receive a diagnosis (Johnson, 2012).

1.4.3 Neurodevelopmental models of ADHD

The neurodevelopmental model of ADHD (Halperin & Schulz, 2006) proposes a developmental framework, which is based on the notion that there are two core processes affected in ADHD - top-down and bottom-up processes - which separate with developmental trajectories of remittance or persistence of ADHD. The model hypotheses that the *aetiology* of ADHD is due to sub-cortical dysfunction which endures throughout the lifetime, whereas the developmental *outcome* of ADHD (remittance or persistence of ADHD) is related to the maturation of the prefrontal cortex. The model further proposes that neural and functional development of the prefrontal cortex may lead to improvement of prefrontal control and is associated with reduced ADHD symptoms, and, subsequently, is associated with ADHD remission (Halperin & Schulz 2006). The proposed mechanism for this effect is that

improvements in the development of prefrontal cortex could contribute to improved frontal-mediated EF, which could lead to improvements in cognitive and neural mechanisms compensatory mechanisms, which consequentially would adequately compensate for deficits in sub-cortical areas and lead to improvements in cognitive functioning and reduced ADHD symptoms and impairments. Based on this model, impairments in indexes of arousal (skin conductance, heart rate variability, EEG frequency bands) and cognitive and neurophysiological performance related to sub-cortical automatic processes (such as reaction time variables), would endure throughout development regardless of symptom improvement (Halperin & Schulz 2006), whilst impairments related to prefrontal cortex such as frontal-mediated executive control (such as inhibition and errors) would vary with developmental trajectory, and improve with ADHD remission and remain impaired in persistent ADHD. The cognitive and neurophysiological impairments of ADHD remitters and ADHD persisters are reviewed in section 1.5.2.7.

1.5 Cognitive and neurophysiological methods and impairments associated with ADHD

A key focus of recent research has been to try and identify the underlying processes that underlie behavioural changes seen in ADHD. One way to provide insight into pathways of the biological basis of ADHD is to identify cognitive, neurophysiological (nervous system processes), and anatomical differences which are unique to people with ADHD. Identifying processes underlying ADHD can help provide targets for interventions, prevention and diagnosis tools. This section offers a brief outline of cognitive and neurophysiological methods used in the thesis, and provides an overview of cognitive and neurophysiological impairments which are associated with ADHD.

1.5.1 Cognitive and neurophysiological techniques

1.5.1.1 Cognitive methods

Assessments of cognitive performance in ADHD are usually performed using standardised assessment instruments, ranging from IQ tests to cognitive-performance computer tasks. Cognitive performance measures of processes associated with ADHD tend to be assessed using neuropsychological tests. Cognitive tests used in ADHD often measure the time between a stimulus-onset and the participants' response, obtaining measures of mean reaction time (MRT), and the standard deviation of reaction time, reaction time variability (RTV). RTV has been shown to be highly sensitive to ADHD-control differences, and is thought to reflect fluctuations and lapses of attention in ADHD (Kofler et al., 2013). A widely used cognitive-performance paradigm, which assesses the maintenance of focused attention over a period of time - sustained attention -, is a Continuous performance test (CPT). Whilst there are adapted versions of the CPT, a typical CPT task requires participants to only respond to a certain type of stimuli whilst ignoring distracting stimuli. The typical measures gained are MRT, RTV, errors of omission (OE, not responding to a target) which is thought to reflect behavioural inattention and problems in sustained attention, and commission errors (CE, responding to non-targets) which is thought to reflect response inhibition and impulsivity (Asherson et al. 2016). Another paradigm used frequently in ADHD groups is Go/No-Go and flanker paradigms which assess inhibitory processes. From Go/NoGo and flanker tasks, you can obtain measures of task accuracy (errors) and error monitoring (Using ERPs). The cognitive performance paradigms used in this thesis use an adapted continuous performance task (CPT-OX), a flanker task (flanker arrow task) and a simple reaction time task (The Fast Task). More detail about ADHD impairments on these tasks are given in section 1.5.2.1. More information about the specific cognitive tasks used in this thesis is given in the methods section of Chapters 2-6 and in Supplementary Material 7.1.

1.5.1.2 EEG method

Electroencephalography (EEG) directly measures the electrical activity on the scalp, which allows electrical indexes of the brain to be obtained. Measuring EEG with specific task paradigms can allow high temporal resolution indexes of brain activity patterns and

neurophysiological processes to be obtained, which can provide novel insight into the covert processes underlying cognitive impairment. The two parameters used the most frequently in EEG research are quantitative EEG (QEEG), which categorises the range of frequencies and oscillation patterns related to different processes, and event-related potentials (ERPs), which categorise the brain patterns in response to a specific event. Whilst both QEEG and ERP measures provide a reliable, sensitive method for measuring brain functions across a wide age range (Tye, McLoughlin, Kuntsi, & Asherson, 2011), QEEG studies in ADHD have yielded less consistent results than ERP studies, and the EEG parameters used in this thesis focus on ERPs.

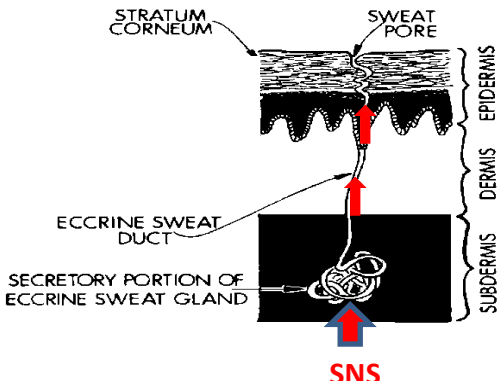
ERPs are small voltage fluctuations in response to a cognitive, sensory or affective stimulus (or 'event'), which are locked to an event and averaged across trials. The averaging helps remove random background noise and allow a clearer measure of neural activity linked to event processing. The high temporal resolution and event-related specificity of ERPs allows insight into covert attention and inhibitory processes underlying cognitive impairments, and allows a sensitive delineation of neurophysiological processes and impairments between groups (see section 1.5.2 for an overview of ERP-indexed impairments associated with ADHD). The nomenclature for ERP components is often dictated by their polarity - where 'P' stands for positive and 'N' stands for negative - as well as their order of occurrence within the waveform (P1, P2, P3 etc.). ERPs can be obtained for Go tasks where indexes thought to reflect response execution at targets (P3 in parietal locations) and response preparation (contingent negative variation; CNV, in frontocentral locations) can be obtained. The P3 component is widely investigated at shows a parietal distribution, and is thought to reflect a variety of executive functions including attention allocation and control (Pollich 2007). ERPs can also be extracted during CPT performance (see section 1.5.1.1 for CPT task description), whereby indexes thought to reflect attentional orienting (Cue-P3 in parietal regions), response preparation (CNV in frontocentral locations), response execution at targets (Go-P3), conflict monitoring (NoGo-N2), and response inhibition (NoGo-P3 in central regions) are commonly obtained (Tye et al. 2011). ERPs can also be obtained during flanker task performance (see section 1.5.1.1 for flanker task description), where indexes of conflict monitoring (N2-congruent, N2-incongreunt in frontocentral locations), automatic error

processing (error related negativity; ERN or Ne in frontocentral locations) and conscious error processing (error related positivity; Pe in frontocentral locations) are frequently obtained (Tye et al. 2011).

1.5.1.3 Skin conductance (SC) methods

Measuring SC is thought to capture a robust neurophysiological index of peripheral arousal, as it sensitively captures changes in electrodermal activity, which is controlled by the sympathetic nervous system (SNS), a key system in influencing arousal and alertness (Boucsein et al., 2012; Dupuy, Clarke, Barry, Selikowitz, & McCarthy, 2014; Satterfield, 1974; VaezMousavi, Barry, Rushby, & Clarke, 2007; van Lang et al., 2007) (See Figure 1.2). This method is based on the principle that the skin has electrical properties which can alter in a short time frame and is controlled by the SNS and associated to cognitive states (Boucsein et al., 2012). Whilst SNS activity is commonly known to be involved in the fight or flight response and preparing the body for alertness and exertion, SNS activity also occurs at lower levels, helping maintain homeostasis of the body. The SNS, being part of the autonomic system, mainly has automatic effects on arousal and energy states. More SNS activation stimulates more sweat production, which fills up more sweat glands and increases skin conductivity.

Figure 1.2. Diagram of a typical eccrine sweat gland. The sympathetic nervous system (SNS) stimulates sweat production in the secretory portion of eccrine sweat glands found in the subdermis layer of the skin. Sweat then rises up into eccrine sweat ducts and sweat pores. More SNS activation leads to more sweat being produced and secreted which leads to increased sweat electrolyte solution in more sweat ducts, and increased skin conductivity. Adapted from (Hassett 1978).



SC is typically measured by placing electrodes on the palms or fingers of the non-dominant hand of a person and a small voltage is passed through the electrodes (0.5 V), which is unobservable to the individual. By keeping the external voltage constant you can measure current flow and determine how well the skin conducts electricity and understand the changes in peripheral arousal over time (Figner & Murphy, 2011). Two commonly used measurements of SC are skin conductance level (SCL), which represents a tonic level of arousal (averaged over a given time-window), and skin conductance response (SCR) amplitude, which represents a phasic (transient) event-related change in SC (Figner & Murphy 2011). Increased SCL indexes an increase in peripheral arousal, whereas increased SCR amplitude indicates a stronger, higher intensity arousal response (Boucsein et al. 2012).

While the neuroanatomical basis of SC is not fully understood, the central structures are thought to be located in the medulla of the brainstem (Boucsein et al. 2012). Neuroimaging studies have additionally demonstrated the excitatory and inhibitory modulatory role of the prefrontal cortex on sub-cortical arousal structures (Williams et al., 2000; Zhang et al., 2012, 2014), which is thought to reflect modulation of arousal based on task demands (Foucher, Otzenberger, & Gounot, 2004; Fredrikson et al., 1998; Roy, Boucsein, Fowles, & Gruzelier, 1993).

1.5.2 Phenotypic and quantitative genetic studies of cognitive and neurophysiological impairments associated with ADHD

1.5.2.1 Phenotypic studies of cognitive impairments in individuals with ADHD

One of the most robust findings of cognitive impairments in ADHD is that of increased RTV. A meta-analysis of 319 studies demonstrated a large effect size for RTV in children and adolescents with ADHD (Hedges' g=0.76), and a moderate effect size in adults (g=0.56). It has also been demonstrated that RTV impairments can be improved, and a meta-analysis of 8 studies demonstrated the, albeit small, but significant effect size of rewards in individuals with ADHD (Kofler et al. 2013). A stronger effect has emerged when using a combination of

faster stimulus rate and incentives on a simple four-choice reaction time task – "The Fast Task"- when rewarding specifically a reduction in RTV (instead of the inhibition tasks used in most other studies that reward improved inhibition performance) (Andreou et al., 2007; Kuntsi et al., 2013; Tye et al. 2016). The changes and sensitivity to task manipulations suggest that increased RTV is a malleable dynamic impairment in individuals with ADHD.

As previously stated in section 1.4.2, EF is an umbrella term used to explain a variety of higher order neurocognitive processes, including working memory, planning, inhibition, sequencing, reasoning, and control of attention (Alvarez & Emory 2006; Pennington & Ozonoff 1996). Many studies have demonstrated impairments in various EF components in ADHD groups and a meta-analysis of 83 studies showed that the most replicated deficits in ADHD, with medium effect sizes (ranging from Cohen's d=0.46-0.69), were for spatial working memory, response inhibition, and sustained attention (Willcutt et al. 2005).

Lower IQ has consistently been associated with ADHD, and a meta-analysis estimated a 7-11-point difference in IQ score (Cohen's d effect size=0.61) between children with ADHD and controls (Frazier et al., 2004). Population-based studies have also demonstrated associations between lower IQ scores and higher ADHD symptoms, with correlations ranging from –0.2 to –0.4 (Kuntsi et al., 2004; Wood, Asherson, Van Der Meere, & Kuntsi, 2010). Converging evidence from follow-up studies (Cheung et al. 2015) and longitudinal treatment studies (Handen, Janosky, & McAuliffe, 1997; E. B. Owens et al., 2003), has provided evidence for a moderating role of IQ, whereby higher IQ is associated with a better treatment response and improved ADHD outcome. However, the exact mechanisms underlying the moderation effect of IQ are unclear.

As stated in section 1.5.1.1, CPT tasks are widely used to assess sustained attention. A meta-analysis of 47 CPT studies confirmed the association between ADHD and sustained attention deficits by demonstrating large to moderate effect sizes for sustained attention deficits (OE), response inhibition deficits (CE), and increased fluctuations and lapses of attention (RTV) in children with ADHD (Huang-Pollock, Karalunas, Tam, & Moore, 2012). Sustained attention

deficits on the CPT have also been reported in adults (Antshel et al., 2010; Gallagher & Blader, 2001; Lijffijt, Kenemans, Verbaten, & Van Engeland, 2005; Malloy-Diniz, Fuentes, Leite, Correa, & Bechara, 2007). A meta-analysis of Go/NoGo tasks in 30 studies confirmed the association between children with ADHD and response inhibition (CE) (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012), and these impairments have also been found in adults with ADHD (Bekker et al., 2005; Bekker et al., 2005; Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2010; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Lampe et al., 2007; Lijffijt et al., 2005). Altogether, these findings support that the association of ADHD with sustained attention and response inhibition deficits occurs throughout the lifespan.

1.5.2.2 Phenotypic studies of ERP impairments in individuals with ADHD

From the CPT, ERP measures of Cue-P3 with a parietal distribution, is thought to reflect attention orientation, and CNV in frontocentral locations, thought to index response preparation, have been shown to be attenuated in studies of children (Albrecht et al., 2013; Banaschewski et al., 2003, 2008; Hennighausen, Schulte-Körne, Warnke, & Remschmidt, 2000; Perchet, Revol, Fourneret, Mauguière, & Garcia-Larrea, 2001; Tye, Asherson, et al., 2014; van Leeuwen et al., 1998) and adults (McLoughlin et al., 2010, 2011; Valko et al., 2009; Woltering, Liu, Rokeach, & Tannock, 2013) with ADHD. A meta-analysis of 6 studies in adults showed an attenuated Cue-P3 amplitude in adults with ADHD (n=154), with a medium effect size (Cohen d=-0.55), compared to controls (n=140) (Szuromi, Czobor, Komlósi, & Bitter, 2011). However, the first follow-up study of ERP measures in the CPT demonstrated that the CNV, but not the Cue-P3, was attenuated in young adults with ADHD (n=11), when compared to controls (n=12) ((Doehnert, Brandeis, Schneider, Drechsler, & Steinhausen, 2013), although the discrepancy may be attributed to the small sample size and the improvement of ADHD symptoms.

Another ERP-index which is obtained when a target stimulus is presented infrequently or randomly is Go-P3, at a parietal region, which is obtained when participants are required to make a response on Go-trials and is thought to index attentional resource allocation (Key,

Dove, & Maguire, 2005). Whilst studies investigating Go-P3 in ADHD are sparse, converging evidence from four studies suggest that Go-P3 is attenuated in children with ADHD (Banaschewski et al., 2004; Lawrence et al., 2005; Overtoom et al., 1998; Strandburg et al., 1996). The P3 component can also be obtained from traditional Go/NoGo tasks, or visual/auditory oddball paradigms. A review of ERP deficits across paradigms concluded that reduced P3 amplitude was the most robust ERP association in children with ADHD. As P3 is thought to reflect attention resources and allocation, this finding suggests that there is inadequate attentional resources in ADHD (Barry, Johnstone, & Clarke, 2003).

Another ERP, NoGo-P3 in frontocentral regions, is obtained when participants need to suppress a response on NoGo-trials, and it is thought to represent response inhibition. NoGo-P3 has been more extensively studied and is consistently reported to be reduced in studies of children (Albrecht et al., 2013; Banaschewski et al., 2003; Brandeis, van Leeuwen, Steger, Imhof, & Steinhausen, 2002; Fallgatter et al., 2004, 2005; Tye, Asherson, et al., 2014; van Leeuwen et al., 1998) and adults (Dhar, Been, Minderaa, & Althaus, 2010; McLoughlin et al., 2010, 2011; Valko et al., 2009) with ADHD. Together, these findings from the CPT provide strong evidence of attentional, preparatory brain processes and response inhibition impairments in individuals with ADHD.

From Go/NoGo and flanker tasks, measures of task accuracy and error monitoring can be obtained. A typical ERP index of performance monitoring is N2 in frontocentral regions, which occurs after a correct response to a target. Results of N2 in ADHD have been inconsistent, with some studies reporting a reduced N2 in children (e.g. Albrecht et al., 2008; Broyd et al., 2005; Johnstone, Barry, Markovska, Dimoska, & Clarke, 2009; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006; Wild-Wall, Oades, Schmidt-Wessels, Christiansen, & Falkenstein, 2009), adolescents (Gow et al., 2012) and adults (McLoughlin et al., 2009) with ADHD, but some studies report no differences between individuals with ADHD compared to controls (Fisher, Aharon-Peretz, & Pratt, 2011; Johnstone & Galletta, 2013; Jonkman, van Melis, Kemner, & Markus, 2007; Wiersema, van der Meere, Antrop, & Roeyers, 2006). Other ERP indexes of performance monitoring, obtained after an error are error-related components (error related negativity (ERN) or Ne), which are thought to reflect automatic

error processing, and error-related positivity (Pe), which is thought to reflect conscious error monitoring. A meta-analysis of 7 studies showed that Ne/ERN was reduced in adolescents and adults with ADHD compared to controls, with a moderate effect size (Cohen's d=50) (Geburek, Rist, Gediga, Stroux, & Pedersen, 2013). The meta-analysis also reported a moderate effect size (Cohen d=0.42), although a non-significant effect, of reduced Pe in children and adults with ADHD (Geburek et al. 2013). Results that are more consistent are needed before drawing any clear inferences, but the results so far indicate that ERP-indexed performance monitoring impairments are associated with ADHD.

1.5.2.3 Phenotypic studies of SC impairments in individuals with ADHD

Early interest in investigating SC impairments in ADHD yielded conflicting results, with some studies demonstrating decreased SCL, indicating hypo-arousal, in unmedicated children with ADHD (Satterfield & Dawson 1971; Lazzaro et al. 1999; Mangina et al. 2000) whilst other studies reported no difference to controls (Spring, Greenberg, Scott, & Hopwood, 1974; Zahn, Abate, Little, & Wender, 1975). However, SC technique has vastly improved, and more recent studies in ADHD demonstrate more consistently hypo-arousal in children with ADHD (Barry et al., 2012; Dupuy et al., 2014; Hermens et al., 2004; Lazzaro et al., 1999). However, discrepancies remain, as some studies report no differences in SCL between adults with and without ADHD (Hermens et al., 2004; Mayer, Wyckoff, & Strehl, 2015). However, very few studies have investigated how SC measures relate to ADHD, and to cognitive performance in ADHD. A study applying SC biofeedback in which participants learnt to modulate their own SC levels reported that SC and RTV followed a similar pattern: participants with the alertness training had increased SC, indicating increased transient arousal, and a more consistent RTV over testing sessions and made fewer commission errors, but they did not report direct correlations between SC and RTV (O'Connell et al. 2008). Chapter 2 therefore focuses on the phenotypic and aetiological relationship between SC, RTV, and ADHD.

1.5.2.4 Quantitative genetic studies of cognitive impairments in individuals with ADHD

Family studies investigating impairments in unaffected siblings of individuals with ADHD have reported impairments in EF (such as response inhibition) and increased RTV (Bidwell et al.

2007; Crosbie & Schachar 2001; Chen et al. 2008; Gau & Shang 2010; Goos et al. 2009; Loo et al. 2008; Slaats-Willemse et al. 2007; Lin et al. 2015; Nikolas & Nigg 2015; Pironti et al. 2014; Andreou et al. 2007; Uebel et al. 2010). Univariate twin analyses have shown genetic influences largely underlie RTV, working memory and inhibition (Kuntsi et al., 2006).

Twin studies have demonstrated that the relationship between IQ and ADHD is largely accounted for by genetic factors. A large study of five-year-old twins demonstrated that genetic influences accounted for 86% of the phenotypic correlation (r=-0.30) between ADHD symptoms and IQ, and 100% of the association between ADHD research diagnosis and IQ (Kuntsi et al., 2004). This demonstrates a substantial amount of shared genetic influences underlies this association, in line with results from other population-based samples of childhood with ADHD (Greven, Kovas, Willcutt, Petrill, & Plomin, 2014; Paloyelis, Rijsdijk, Wood, Asherson, & Kuntsi, 2010; Polderman et al., 2006; Wood, Asherson, et al., 2010). Recently, a genetically sensitive cross-lagged model, in a population-based sample of twins, demonstrated that ADHD symptoms at age 12 were a stronger predictor of IQ at age 14 than vice versa, suggesting that ADHD symptoms may drive the risk for decreased IQ scores (Rommel, Rijsdijk, Greven, Asherson, & Kuntsi, 2015). This study also demonstrated that although time-specific aetiological influences emerged for each trait at ages 14 and 16 years, the aetiological factors involved in the association between ADHD symptoms and IQ were stable over time (Rommel et al. 2015). Evidence from twin (Wood, Asherson, et al., 2010) and multivariate modelling (Rommelse et al., 2008; Wood et al., 2011) further demonstrated that aetiological influences between ADHD and IQ are largely separate from aetiological influences underlying other cognitive impairments in ADHD (Rommelse et al., 2008; Wood et al., 2011; Wood, Asherson, van der Meere, & Kuntsi, 2010).

Multivariate quantitative genetic model fitting analyses can also address questions such as whether there are one or more familial factors that underlie the multiple cognitive impairments in ADHD. A large study of ADHD and control sibling pairs (n=1265) used a multivariate familial factor analysis approach to demonstrate that two such familial cognitive impairment factors emerged (Kuntsi et al. 2010). The first, larger factor reflected 85% of the familial variance of ADHD, and a smaller, second, factor captured 13% of the familial variance

of ADHD. The larger factor captured 98% to 100% of familial influences on MRT and RTV, whereas the second smaller factor captured 62% to 82% of familial influences of CE and OE (Kuntsi et al. 2010). A subsequent investigation of 238 ADHD families and 147 control families also demonstrated two familial cognitive impairment factors (Frazier-Wood et al., 2012). The first familial factor captured familial influences on intra-individual variability measures and the second those on working memory; a portion (33%) of the familial influences on IQ were shared with the second factor, but the majority of the familial influences on IQ remained unaccounted for by the model (Kuntsi et al. 2010). Further, multivariate genetic model fitting analyses on a population twin study demonstrated that RTV and commission errors showed no significant shared genetic influences (rA=-0.10), in line with the separate aetiology underlying these cognitive impairments, though RTV shared genetic influences with inattention symptoms (rA=0.64) (Kuntsi et al., 2014). Overall, these findings suggest that the underlying aetiology of cognitive processes in ADHD separate out into two familial factors: one familial cognitive factor capturing the slow and highly variable RT responses, and another familial factor capturing executive control (inhibition, working memory) (Frazier-Wood et al. 2012; Kuntsi et al. 2010). In addition, the familial influences shared by ADHD and IQ are largely separate (Frazier-Wood et al., 2012; Rommelse et al., 2008; Wood, Asherson, et al., 2010; Wood et al., 2011).

1.5.2.5 Quantitative genetic studies of ERP impairments in individuals with ADHD

Twin studies have estimated that genetic influences account for 41%-60% of ERP components (Anokhin, Heath, & Myers, 2004; van Beijsterveldt & van Baal, 2002). Family studies have also demonstrated that attentional (Cue-P3), preparatory (CNV), inhibitory processes (NoGo-P3), conflict monitoring (N2) and error processing (ERN) impairments associated with ADHD, are also observed in unaffected siblings in childhood (Albrecht et al., 2013; Bjoern Albrecht et al., 2008; Björn Albrecht et al., 2010) and adulthood (McLoughlin et al., 2009, 2011). There are few model fitting studies that investigate the shared aetiology underlying ADHD and ERP impairments. However, substantial genetic overlap between ADHD symptoms and elevated theta power (Tye, Rijsdijk, & McLoughlin, 2014), and between frontal midline theta activity and RTV (McLoughlin, Palmer, Rijsdijk, & Makeig, 2014), has been reported.

1.5.2.6 Quantitative genetics studies of SC impairments in individuals with ADHD

There have been limited quantitative genetic studies exploring the aetiological associations of SC measures with ADHD. However, a few studies have investigated the degree to which genetic, shared environmental vs non-shared environmental influences account for SC. A longitudinal twin study across adolescence (n=1157) demonstrated that genetic influences largely accounted for the variability in SC, and the remaining variance was explained by non-shared environmental factors (Tuvblad et al., 2012). This study also reported high genetic correlations across time points, indicating that genetic contributions underlying SC were moderately stable across childhood and adolescence, although there were additional age-specific genetic effects with development (Tuvblad et al., 2012). In line with these findings, a smaller twin study in adults (n=790) demonstrated that the majority of the variance underlying SC was attributed to genetic factors, whereas non-shared environmental influences attributed to the remaining variance, indicating a negligible role for shared environmental effects (Crider et al., 2004). In line with evidence of the genetic contribution underlying SC measures, the molecular genetic basis of SC in a population twin and parent sample (n=4424) was analysed using a genome wide association study (GWAS) approach (Vaidyanathan et al., 2014). The study found that at least 50% of the SC variance was heritable and provided evidence that SC is influenced by multiple genes of small effect sizes (Vaidyanathan et al., 2014). Whilst studies are overall limited, the existing studies suggest that genetic influences are likely to account for at least half of the variability of SC, and non-shared environmental influences account for the remaining variability, with a negligible role of shared environmental influences. Chapter 2 further focuses on understanding the aetiological association between ADHD and SC.

1.5.2.7 Phenotypic studies of cognitive, ERP and SC impairments in individuals with ADHD remission

Only a small number of studies have investigated the cognitive and neurophysiological impairments in ADHD remission. The first study to examine differences in quantitative EEG and ERP measures is based on the sample that is used in this thesis: a 6-year follow-up study

of 110 children and adolescence with ADHD (Cheung et al. 2016; Michelini et al. in press). Findings from the sample so far, from a cued continuous performance task (CPT-OX) and an arrow flanker task, have identified measures of preparation-vigilance and error detection as markers of ADHD remission (Cheung et al. 2016; Michelini et al. in press). These measures – reaction time variability (RTV), omission errors, congruent errors, ERPs of response preparation and error detection, delta and theta activity – showed impairments in ADHD persisters only, with ADHD remitters indistinguishable from controls. In contrast, measures of inhibition, working memory, speed of processing and conflict monitoring were not sensitive to ADHD remission/persistence (Cheung et al. 2016; Michelini et al. in press). These results are in line with other recent studies that demonstrate executive control measures are not associated with ADHD remission (Biederman et al., 2009; McAuley, Crosbie, Charach, & Schachar, 2014; Pazvantoğlu et al., 2012; van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013). However, they are not in line with previous studies which demonstrated that measures of executive processes (commission and omission errors) were markers of remission and were only observed ADHD persisters (Halperin et al., 2008) that inhibition was a marker of ADHD remission (Bédard, Trampush, Newcorn, & Halperin, 2010). To date, no studies have investigated the SC profile of ADHD remitters. Chapter 3 further explores whether impairments in ERP indexes of attention and SC are markers of remission, or reflect enduring deficits.

1.5.3 Summary of cognitive and neurophysiological impairments associated with ADHD

Studies investigating cognitive and neurophysiological impairments in ADHD have been valuable in highlighting processes that are impaired in ADHD, providing insight into underlying pathophysiology in ADHD. Studies report associations of decreased general cognitive ability in ADHD, as well as impairments in EF and attention. Genetically-sensitive studies of cognitive impairments in ADHD have demonstrated these associations to be largely attributable to genetic influences. Whilst inconsistencies remain, neurophysiological methods have helped to elucidate covert processes affected in ADHD. There is evidence from ERP studies for impairments in children and adults with ADHD in preparatory brain processes (as indexed by CNV), attentional process (as indexed by P3 components), deficits in performance monitoring

processes (as indexed by N2, ERN/Ne and Pe), and response inhibition (NoGo-P3). Whilst there are limited studies investigating the aetiological structures underlying ERPs impairments associated with ADHD, studies demonstrate that familial/genetic influences largely underlie these associations, with non-shared environment account for the remaining variance. In addition, there is converging evidence from different approaches (including studies incorporating skin conductance or within-task manipulations) of likely arousal deficits in ADHD. However, very few studies have used genetically-sensitive approaches to investigate the aetiology underlying these associations. More research is needed to elucidate the aetiological associations between SC and ADHD in particular.

Utilising interdisciplinary approaches of cognitive and neurophysiological measurement in genetically sensitive studies is a valuable approach in understanding the aetiology and underlying processes in ADHD. By identifying underlying processes and gaining insight into the neurobiology, researchers aim to define targets for interventions to minimise associated impairments.

1.6 Preterm birth

Individuals born preterm have an increased risk of developing ADHD and are reported to have similar impairments in cognitive and neurophysiological processes to individuals with ADHD, yet it is not clear whether they reflect truly identical impairments. In addition, whilst the aetiological nature of cognitive and neurophysiological impairments in ADHD is well documented, very few studies have investigated the aetiological nature of impairments in preterm birth. A better understanding of the overlap and aetiology of cognitive and neurophysiological impairments in preterm born individuals could help to identify processes to target interventions.

1.6.1 Epidemiology of preterm birth

Preterm birth is defined as a birth that occurs before 37 weeks' gestation (World Health Organization, 1977). 8.6% of live births in developed countries are considered to be preterm

(Blencowe et al., 2012). However, incidence rates of preterm birth are thought to be increasing in developed countries, partly due to rising numbers of multiple gestations associated with assisted reproductive technology (Hamilton et al. 2006). Preterm birth can be further categorized according to gestational age: 60% of preterm births occur at 34 to <37 weeks' gestation (late preterm), 20% occur at 32 to <34 weeks' (moderately preterm), 15% occur at 28 to <32 weeks' (very preterm) and 5% occur at <28 weeks' (extremely preterm) (Goldenberg, Culhane, Iams, & Romero, 2008b).

1.6.1.1 Gender differences

Epidemiological studies demonstrate that 55% of preterm births are male, indicting a higher male incidence of preterm birth (Blencowe et al., 2013; Ingemarsson, 2003; Kent, Wright, & Abdel-Latif, 2012; Vatten & Skjaerven, 2004; Zeitlin, 2002; Zeitlin, Ancel, Larroque, & Kaminski, 2004). Studies further demonstrate that, even at the same gestational age, males have poorer long-term outcomes compared to females, including an increased likelihood of perinatal mortality and postnatal complications (Brothwood, Wolke, Gamsu, Benson, & Cooper, 1986; Costeloe, Hennessy, Gibson, Marlow, & Wilkinson, 2000; Hack & Fanaroff, 2000; Hintz, Kendrick, Vohr, Kenneth Poole, & Higgins, 2006; Kent et al., 2012; Månsson, Fellman, & Stjernqvist, 2015; Peacock, Marston, Marlow, Calvert, & Greenough, 2012; P. Roy, Kumar, Kaur, & Faridi, 2014; Stevenson et al., 2000). Yet, the mechanisms underlying gender differences of the incidence and outcomes of preterm birth are unclear. It has been proposed that males have a greater susceptibility to particular medical complications associated with preterm birth, such as pregnancy-induced hypertension or infection (Campbell, MacGillivray, Carr-Hill, & Samphier, 1983; MacGillivray & Davey, 1985), have problems in sex-linked biochemical processes (Cooperstock & Campbell, 1996). It has also been proposed that, even at the same gestational age, males are relatively immature compared to females (Peacock et al., 2012), which may contribute to preterm males having more negative outcomes.

1.6.1.2 Associated outcomes of preterm birth

Preterm birth is associated with many adverse long-term outcomes, and the risk is increased with earlier gestational age. Among such outcomes are an increased risk of childhood and

young adult mortality (D'Onofrio et al., 2013; Fellman et al., 2009; Moster, Lie, & Markestad, 2008; Patel et al., 2015) (Crump, Sundquist, Sundquist, & Winkleby, 2011), unemployment and criminal activity (D'Onofrio et al., 2013; Lindström, Winbladh, Haglund, & Hjern, 2007; Männistö et al., 2015; Moster et al., 2008; Saigal et al., 2009), academic difficulties (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; D'Onofrio et al., 2013; Lindström et al., 2011; McGowan, Alderdice, Holmes, & Johnston, 2011; Moster et al., 2008), cognitive and neurophysiological difficulties (reviewed below in section 1.6.2) (Johnson et al. 2011; Lee et al. 2011; Johnson & Marlow 2011; Potgieter et al. 2003), and developing a wide range of psychiatric disorders (D'Onofrio et al., 2013; L. W. Doyle & Anderson, 2010; McCormick, Litt, Smith, & Zupancic, 2011). The association between ADHD and preterm birth is a core theme to this thesis, and the literature is reviewed in greater detail in section 1.6.4.

A recent sibling-comparison study, which provided key insight into the relationship between mortality and morbidity associated with preterm birth, is a large Swedish epidemiological cohort study, which firstly investigated all individuals born in Sweden between 1973 and 2008 (n=3,300,708 offspring of 1,736,735 mothers), and secondly investigated within-siblings effects only. In the whole population, earlier GA (<28 weeks) was linked to ADHD (hazard ratio (HR)=2.3), autism spectrum disorders (HR=3.2), psychotic or bipolar disorders (HR=3.2), and a lower educational attainment (HR=1.7) (D'Onofrio et al. 2013). When the sibling analyses were conducted, the magnitude of the association between gestational age and mortality, and gestational age and psychiatric disorders, was significant within sibling pairs and largely independent of familial factors, consistent with a causal inference. On the contrary, the magnitude of the association between educational attainment and GA was greatly attenuated, falsifying the hypothesized causal effect of preterm birth, and instead suggests that confounding familial factors shared by siblings, which include factors correlated with preterm birth (i.e maternal genetic risk for giving birth preterm, socio-economic status, family upbringing, and other shared genetic and environmental factors), may account for this association (D'Onofrio et al. 2013). This study emphasized that associations between preterm birth and negative outcomes can be disentangled into causal and non-causal inferences. This notion is further explored in Chapter 5.

1.6.2 Aetiology of preterm birth

About 30-35% of preterm birth cases births are induced, or planned for caesarean births, due to medical complications usually associated with pre-eclampsia, eclampsia or intrauterine growth restriction. About 65-70% of preterm births follow spontaneous labour, which is often associated with more complications (Goldenberg et al., 2008). The cause of preterm labour is regarded as a complex syndrome resulting from multiple causes, with implicated mechanisms including intrauterine infections, inflammations, vascular complications, uterine over-distension and other immunological processes (Romero et al., 2006). However, in most cases it is difficult to identify the key causal mechanism; subsequently, studies have tried to identify risk factors of preterm birth which may help to elucidate the underlying aetiology of preterm birth.

Multiple risk factors have been associated with preterm birth, including maternal genetic risk, family history of preterm birth, low socioeconomic status, low maternal educational status, low or high maternal age, black ethnicity, single marital status, smoking and alcohol during pregnancy, and pre-existing health problems of the mother (Blencowe et al., 2012; Goldenberg et al., 1996, 2008; Plunkett & Muglia, 2008). The familial risk of preterm birth has been demonstrated by family studies demonstrating that women have an increased risk of delivering preterm if their mother, sisters (Winkvist, Mogren, & Högberg, 1998), or even great-grandmother (Porter et al., 1997) gave birth preterm. Whilst epigenetic processes have been proposed to mediate the effects of risk factors on preterm birth (Novakovic et al., 2011; Parets, Bedient, Menon, & Smith, 2014; Schroeder et al., 2011; Tobi et al., 2011), the exact mechanisms underlying risk pathways are still unknown.

1.6.3 Cognitive and neurophysiological impairments associated with preterm birth

1.6.3.1 Studies of cognitive impairments in individuals born preterm

A wide-range of cognitive impairments has been associated with preterm birth, with most research focusing on problems with academic achievement, IQ, and working memory. A meta-analysis of 14 studies demonstrated that very preterm (≤33 weeks gestation) or very

low birth weight (≤1500g) children scored 0.60 SD lower on mathematics tests, 0.48 SD lower on reading tests, and 0.76 SD lower on spelling tests than term-born peers (Cornelieke Sandrine Hanan Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009). The risk of poorer academic achievement is even greater with earlier gestational age (Aarnoudse-Moens et al., 2009; Ahlsson, Kaijser, Adami, Lundgren, & Palme, 2015; S Johnson et al., 2009; Quigley et al., 2012; Taylor, Espy, & Anderson, 2009). For example, a recent large longitudinal Swedish study (n=1,643,958) demonstrated that, compared to term-born peers, school grades were 3.85 centiles lower for preterm children born at 31-33 weeks gestation, and 23.15 centiles lower for preterm children born at 22-24 weeks gestation (Ahlsson et al., 2015). However, findings from a large multigenerational study (n=10,835) demonstrated that the association between earlier gestation age and worse grades in language was only present in individuals who had parents with a low education, suggesting that familial factors may underlie this association (Gisselmann, Koupil, & De Stavola, 2011). In addition, studies consistently demonstrate that preterm birth is associated with lower IQ scores (Anderson & Doyle, 2003; Hutchinson et al., 2013; Johnson et al., 2009; Litt et al., 2012). A meta-analysis of 27 studies found that compared to term-born individuals (n=3,540), preterm individuals (n=3,504) scored an average of 11.94 IQ points lower, and demonstrated a strong linear association between decreased IQ and earlier gestational age ($r=-0.88$, $p<0.01$) (Kerr-Wilson, Mackay, Smith, & Pell, 2012), indicating that gestational age is a major predictor of IQ in preterm-born individuals. Whilst impairments in working memory have been demonstrated in preterm-born children (Aarnoudse-Moens et al., 2009; Anderson & Doyle, 2004; Baron, Erickson, Ahronovich, Litman, & Brandt, 2010; Hutchinson et al., 2013; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Rose, Feldman, Jankowski, & Van Rossem, 2011), evidence from cross-sectional and follow-up studies suggests that working memory impairments decrease with age (Curtis, Lindeke, Georgieff, & Nelson, 2002; Rushe et al., 2001; Saavalainen et al., 2007). Whilst clear associations of cognitive impairments in preterm-born adolescents have been demonstrated, it is not yet clear how these cognitive impairments relate to other cognitive and neurophysiological deficits (Lee, Yeatman, Luna, & Feldman, 2011; Loe, Lee, Luna, & Feldman, 2012).

Results from a meta-analysis demonstrated moderate to large effects of EF and attention impairments in preterm-born children compared to term-born children, indicating differences in verbal fluency (Cohen's d=0.69), planning ability (Cohen's d=0.40), inhibition (Cohen's d=0.50), selective attention (Cohen's d=0.58) and sustained attention (Cohen's d=0.67), and showing that the effect sizes were all stronger with earlier gestational age (Mulder, Pitchford, Hagger, & Marlow, 2009). A second meta-analysis of 14 studies showed that very preterm (≤33 weeks gestation) or very low birth weight (≤1500g) children scored 0.57 SD lower for verbal fluency, 0.36 SD lower on working memory and 0.49 SD lower for cognitive flexibility, compared to term-born controls (Aarnoudse-Moens et al., 2009). Similar EF impairments, to those demonstrated by meta-analyses in children, have also been found in preterm-born adolescents (Burnett et al., 2015; Taylor, Minich, Bangert, Filipek, & Hack, 2004) and adults (Nosarti et al., 2007; Stålnacke, Lundequist, Böhm, Forssberg, & Smedler, 2014), suggesting that impairments in EF may persist across the lifespan. Whilst fewer studies of attention impairments have been conducted in preterm-born adolescents and adults, results from a cohort study of extremely preterm-born adolescents (38 weeks' gestation) were partly in line with the child results of attention impairments: preterm-born adolescents (n=228) were 2.5 times more likely to have impairments in selective, shifting and divided attention than term-born controls, but were not more likely to develop sustained attention impairments (Wilson-Ching et al., 2013). Further research should investigate EF and attention performance in preterm-born adolescents and adults to establish whether impairments in preterm birth occur across the lifespan.

1.6.3.2 Studies of ERP impairments in individuals born preterm

Despite the extensive research effort of using EEG approaches to investigate neurophysiological impairments in preterm-born infants in neonatal intensive care units (Meijer et al., 2014; Victor, Appleton, Beirne, Marson, & Weindling, 2005) or in the postnatal period (Beckwith & Parmelee, 1986; Duffy, Als, & McAnulty, 1990; González et al., 2011; Hayakawa et al., 2001; Vecchierini, André, & d'Allest, 2007), very few EEG neurophysiological studies have been conducted in preterm-born children, adolescents or adults. Whilst ERP studies investigating neurophysiological impairments in preterm-born populations are lacking, studies have also used other imaging approaches to investigate impairments in

preterm-born individuals, such as functional magnetic resonance imaging (fMRI) and magneto-encephalography (MEG). For example, MEG studies during cognitive tasks have demonstrated altered cortical activation and inter-regional connectivity in preterm-born children compared to term-born controls (Boersma et al., 2013; Doesburg et al., 2011; Frye et al., 2009, 2010; Moiseev, Doesburg, Herdman, Ribary, & Grunau, 2014). In addition, fMRI studies have demonstrated that, compared to term-born control groups, preterm-born children demonstrate different activation levels (indexed by Blood Oxygen Level Dependent (BOLD) contrast) during cognitive performance tasks (Damaraju et al., 2010; Griffiths et al., 2013; Silja Torvik Griffiths et al., 2013, 2014; Lawrence et al., 2009; Ment et al., 2006; Nosarti et al., 2006; Peterson et al., 2002; Schafer et al., 2009).

The few ERP studies conducted in preterm-born children have used oddball paradigms. A study using an auditory oddball paradigm in very preterm-born children (<29 gestation) aged 5 (n=70), demonstrated that the preterm group showed impairments in P1 amplitude (reflecting auditory processing) and auditory N2 (reflecting attention orientation), compared to term-born controls (n=15) (Hövel et al., 2014). This is in line with the results of a smaller ERP study of preterm-born children aged 5 (n=28) (Mikkola et al., 2007). Results from a visual oddball paradigm showed impairments in NoGo-N2 amplitude (thought to reflect inhibition) and P3 amplitude (thought to reflect attention allocation) were only demonstrated in preterm-born children with ADHD, compared to term-born controls and preterm-born children without ADHD (Potgieter et al., 2003). Similar impairments in attention orientation and inhibition have also been reported in children with neurodevelopmental disorders such as ADHD, autism spectrum disorders and dyslexia (Albrecht et al., 2008; Gow et al., 2012; Hämäläinen, Leppänen, Guttorm, & Lyytinen, 2007; Johnstone et al., 2009; McLoughlin et al., 2009; Oades, Dittmann-Balcar, Schepker, Eggers, & Zerbin, 1996). Recently, the first ERP study in preterm-born adults (n=30) was conducted (Aasen et al., 2016). This study demonstrated, using a go/no-go task, that preterm-born adults showed impairments in attention allocation (P3 amplitudes) to non-targets compared to term-born controls, suggesting that preterm-born individuals allocate more attention to behaviourally irrelevant information (Aasen et al. 2016). Recently, our research group has conducted, to our knowledge, the first ERP study of preterm-born adolescents (Rommel et al. under review, Rommel et al. in prep), and compared

them to unrelated term-born controls. To further explore the increased risk for ADHD among individuals born preterm, we also compared them to term-born adolescents with ADHD; more detail is reported in section 1.6.4. We demonstrated, on a cued continuous performance test (CPT-OX), compared to unrelated term-born control group (n=135), that the preterm group (n=186) showed ERP-indexed impairments in indexes of response preparation (contingent negative variation, CNV), response inhibition (NoGo-P3) and executive response control (Go-P3) (Rommel et al. under review). We also demonstrated that, in a flanker task, compared to the term-born control group, the preterm group showed ERP-indexed impairments in indexes of conflict monitoring (N2) and error processing (error positivity, Pe, and error-related negativity, ERN). However, despite this initial evidence for impairments in ERP measures of attention in preterm-born individuals, research investigating ERP measures in preterm-born children, adolescents and adults is overall scarce.

1.6.3.3 Studies of SC impairments in individuals born preterm

Whilst SC approaches are widely used in preterm infants, as a way to assess the sympathetic nervous system response to painful stimuli (Storm, 2000), to our knowledge, no study to date has used SC approaches to investigate peripheral arousal regulation in preterm-born children, adolescents or adults.

1.6.4 Preterm birth and ADHD

1.6.4.1 Co-occurrence of symptoms and diagnosis

Many studies have provided evidence that preterm-birth (born before 37 gestational age) is a risk factor for ADHD, whether ADHD is considered as a continuum (Cornelieke Sandrine Hanan Aarnoudse-Moens et al., 2009) a categorical diagnosis (Bhutta et al., 2002). A meta-analysis of 16 studies found that preterm-born children (<37 weeks' gestation) (n=1556) had a 2.64-fold risk for developing ADHD compared to term-born controls (n=1720) (Bhutta et al., 2002). Furthermore, a UK cohort study found that at age 11, extremely preterm-born children (<26 weeks' gestation) (n=219) had a 4.3-fold increased risk for developing ADHD, and a 10.5 increased risk for developing ADHD inattentive subtype, representing a higher risk for ADHD

than for any other psychiatric disorder (Johnson et al., 2010). The association between preterm birth and ADHD has been confirmed by genetically-sensitive population studies of over one million children, and have further revealed insight into the causes of the relationship (D'Onofrio et al., 2013; Lindström et al., 2011). For example, a Swedish study demonstrated a stepwise increase in odds ratios for ADHD medication with decreasing gestational age and established, using a within-mother-between-pregnancy analysis, that the association between preterm birth and ADHD is not explained by genetic, perinatal or socio-economic confounding factors (Lindström et al. 2011). This study further demonstrated that the relationship between preterm birth and ADHD is not modified by growth retardation (being small for gestational age), but is modified by low maternal education (Lindström et al., 2011). In addition, in the largest epidemiological study to date of gestational age, a Swedish population-based study utilising the powerful sibling comparison method which accounts for confounding familial factors, reported a dose-response relationship between gestational age and ADHD, which was principally independent of familial factors shared by siblings, consistent with a causal inference (D'Onofrio et al. 2013). A large-scale Norwegian population study of over a million adults further demonstrated that preterm birth remains a risk factor for ADHD in adulthood, and showed a 1.3-fold increased risk for ADHD in preterm-born (<37 weeks gestation) adults, and a 5-fold increased risk for ADHD in extremely preterm-born (<28 weeks) adults (Halmøy et al., 2012), indicating that the risk persists up to 40 years after birth.

Evidence consistently supports the idea that diagnosed ADHD reflects the extreme end of a continuous dimension of ADHD symptoms (Chen et al., 2008) and studies on preterm samples focusing on ADHD symptoms as a continuum report a similar pattern of findings as found by studies focusing on ADHD diagnoses. Population-based studies consistently demonstrate that preterm-born children (≤37 weeks gestation), especially extremely preterm-born children (≤28 weeks gestation), perform worse on attention scales than term-born children (Delobel-Ayoub et al., 2009; Elgen, Sommerfelt, & Markestad, 2002; Hille et al., 2001; Samara, Marlow, Wolke, & EPICure Study Group, 2008). In addition, a meta-analysis of 9 studies (n=930), demonstrated that very preterm (≤33 weeks gestation) or very low birth weight (≤1500g) children scored 0.59 SD higher on parent-ratings of attention problems and 0.43 SD higher on teacher-ratings of attention problems (Aarnoudse-Moens et al., 2009). Despite the

robust association between preterm birth and ADHD, the underlying risk pathways from preterm birth to ADHD remain poorly understood.

Some studies have indicated a higher risk for inattentive problems, relative to hyperactivity/impulsivity symptoms, and for the inattentive subtype (Hack et al., 2009; Johnson et al., 2010; Johnson & Marlow, 2011), whilst others have reported associations with all subtypes (Anderson et al., 2011; D'Onofrio et al., 2013; Scott et al., 2012). Studies also have reported that notable comorbidities that are frequently associated with ADHD, such as conduct disorders, are not observed in preterm-born individuals with ADHD (Elgen et al., 2002; Hack et al., 2009; Johnson et al., 2010; Scott et al., 2012), which has led to the suggestion that preterm-born individuals with ADHD may be better descripted as an *"inattentive subtype disorder with a neurodevelopmental origin"* (Hille et al., 2001; Samantha Johnson & Marlow, 2011, 2013).

1.6.4.2 Comparison of cognitive and neurophysiological impairments in individuals born preterm and ADHD samples

Whilst individuals born preterm are also reported to have cognitive and neurophysiological impairments that resemble impairments associated with ADHD, including attention, inhibitory difficulties (Aarnoudse-Moens et al. 2012; Aarnoudse-Moens et al. 2009; Anderson et al. 2011; Geva and Feldman 2008; Johnson et al. 2011; de Kieviet et al. 2012; Lawrence et al. 2009; Mulder et al. 2009; Nosarti et al. 2006), very few direct comparisons have been made between preterm-born individuals and full-term born individuals with ADHD. It has therefore remained unclear whether the impairments reported in individuals born preterm are truly identical to those observed in full-term born individuals diagnosed with ADHD. One study directly compared ERPs between ADHD and preterm-born samples (n=41 across four groups), using a visual oddball paradigm reporting impairments (increased inhibition NoGo-N2 and increased MRT, RTV and errors) only among term and preterm-born children with ADHD, compared to term-born controls and preterm-born participants without ADHD (Potgieter et al. 2003). However, the sample was small and these findings require replication.

Our group has recently performed detailed investigations of the cognitive-neurophysiological impairments in adolescents born preterm, when compared to unrelated term-born control adolescents and term-born adolescents with ADHD (Rommel et al. under review, Rommel et al. in prep). Overall, the findings showed both ADHD-like and additional, unique impairments in cognitive-neurophysiological processes in preterm-born adolescents, when compared to unrelated term-born controls and adolescents with ADHD. The findings further demonstrated that the preterm group showed increased ADHD symptoms and impairments that were similar to those observed in the ADHD group in working memory, short-term memory, IQ and event-related potentials of response preparation (contingent negative variation, CNV), response inhibition (NoGo-P3), conflict monitoring (N2) and error processing (error positivity, Pe, and error-related negativity, ERN) (Rommel et al. under review, Rommel et al. in prep). The preterm-born group was further uniquely impaired on executive response control (Go-P3), compared to both ADHD and control groups suggesting more wide-ranging neurophysiological deficits in the preterm group (Rommel et al. under review). To date, there has been no direct comparison assessing SC between preterm-born individuals and individuals with ADHD.

Despite this initial evidence for impairments in ERP measures of attention in preterm-born individuals, whether preterm-born individuals have an increased risk of developing ADHD-like impairments in other attentional indexes and arousal is yet to be established.

1.6.5 Summary: preterm birth

Preterm birth has a high incidence worldwide but the underlying causes are not well understood. Whilst survival rates are increasing, there is growing evidence that preterm birth is associated with many long-term negative outcomes, yet the underlying pathways are unclear. Understanding the underlying processes affected in preterm-born individuals may help define targets for early identification of problems and to direct targeted interventions. One of the most consistently reported psychiatric outcomes of preterm birth is ADHD, whether ADHD is considered as a continuum or a categorical diagnosis. Cognitive and neurophysiological impairments reported in preterm-born individuals, such as lower IQ,

attentional problems and EF difficulties are also associated with ADHD. Yet, few studies have directly compared preterm-born individuals to individuals with ADHD, which would help to understand the ADHD-preterm phenotypic and aetiological association, to further guide interventions.

1.7 Aims and objectives

This thesis uses a multi-disciplinary approach to study cognitive-neurophysiological processes underlying ADHD, and the underlying risk pathways from preterm birth to ADHD.

1.7.1 Chapters 2 and 3

ADHD has long been proposed to link to problems with the arousal system that could contribute to cognitive performance impairments in ADHD, yet, direct, objective evidence of the proposed arousal dysregulation is limited. Based on this notion, the first two research-based chapters of this thesis focus on the impairments and associations underlying a measure of peripheral arousal (skin conductance) in ADHD. The aim of the first study (Chapter 2) is to explore peripheral arousal impairments and malleability in individuals with ADHD using SC and within-task manipulations during cognitive performance. The study further aims to investigate the phenotypic and familial association underlying peripheral arousal, fluctuating reaction times, and ADHD, using a large sample of ADHD and control sibling pairs. This is the first study to investigate the aetiological association between ADHD and peripheral arousal and therefore holds the potential for providing novel insight into these processes.

Chapter 3 further examines the relationship between ADHD and arousal regulation by taking a more developmental approach, investigating whether arousal, as well as associated ERP-indexes of attentional and response preparation, vary with the developmental trajectory of ADHD remittance. Whilst previous studies have investigated whether other specific cognitive and neurophysiological impairments improve with ADHD remission, this is the first study, to

our knowledge, that investigates whether markers of peripheral arousal are markers of ADHD remission or reflect enduring deficits unrelated to ADHD outcome.

1.7.2 Chapters 4, 5 and 6

The second part of the thesis (Chapters 4, 5 and 6) focuses on the association between preterm birth and ADHD using a combination of cognitive, neurophysiological and sibling-comparison methods. The overall purpose of these studies is to identify pathways underlying the increased risk for ADHD among preterm-born individuals, which will highlight processes that could be targeted for early identification and intervention.

Chapter 4 aims to further our understanding of the overlap of cognitive and neurophysiological processes in preterm-born adolescents compared to term-born adolescents with ADHD. We aim to directly compare preterm-born adolescents to term-born adolescents with ADHD and term-born controls on specific cognitive, ERP and peripheral arousal measures, to identify whether preterm-born adolescents show identical or additional cognitive-neurophysiological impairments compared to term-born adolescents with ADHD.

Chapter 5 addresses the potential causal pathways contributing to the cognitive and neurophysiological processes observed in preterm-born individuals. As many environmental and potential genetic risk factors characterise families with preterm-born children, in most studies it is difficult to disentangle whether associations with preterm birth are due to the preterm birth per se or due to other familial risk factors (such as low socioeconomic status, maternal education and maternal genetic risk). Within-sibling analyses can be applied to account for unmeasured familial confounding factors. In Chapter 5, we employ a within-sibling design - comparing preterm-born adolescents to their term-born siblings - to investigate whether the associations of preterm-birth with the specific cognitive-neurophysiological impairments are consistent with a causal inference of preterm birth.

The final study (Chapter 6) combines all three sibling-pair samples that have been assessed on identical test batteries – ADHD, control and preterm sibling samples – to examine if the association between ADHD symptoms and specific cognitive-neurophysiological impairments is largely due to non-shared effects (consistent with preterm birth as an environmental insult) among preterm-born individuals, but largely attributed to familial factors (shared genetics and shared environment) among term–born individuals.

Chapter 2 - MODIFIABLE AROUSAL IN ADHD AND ITS AETIOLOGICAL ASSOCIATION WITH FLUCTUATING REACTION TIMES.

2.1 Abstract

Background: Cognitive theories of attention-deficit/hyperactivity disorder (ADHD) propose that high within-subject fluctuations of cognitive performance in ADHD, particularly reaction time (RT) variability (RTV), may reflect arousal dysregulation. Yet, direct evidence of arousal dysregulation and how it may account for fluctuating reaction times in ADHD is limited. We used skin conductance (SC) as a measure of peripheral arousal and aimed to investigate its phenotypic and familial association with RTV in a large sample of ADHD and control sibling pairs. **Methods:** 292 adolescents and young adults, consisting of 73 participants with ADHD and their 75 siblings, as well as 72 controls and their 72 siblings, completed the baseline (slow, unrewarded) and fast-incentive conditions of a RT task, whilst SC was simultaneously recorded. **Results:** A significant group by condition interaction emerged for SC level (SCL). Participants with ADHD had decreased SCL, compared to controls, in the baseline but not fast-incentive condition. Baseline SCL was negatively associated with RTV and multivariate model fitting demonstrated that the covariance of SCL with RTV, and of SCL with ADHD, was mostly explained by shared familial effects. **Conclusions:** ADHD is associated with decreased, but modifiable, tonic peripheral arousal. A shared familial aetiology underlies the relationship between arousal and RTV, and between arousal and ADHD. Given the malleability of SCL, if our findings are replicated, it warrants further exploration as a potential treatment target for ADHD.

2.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD) has long been proposed to link to problems with the arousal system. Cognitive theories of ADHD, such as the state regulation model (Sergeant, 2005; van der Meere, 2005) or more recent dual-process models (Halperin & Schulz, 2006; Johnson et al., 2007; O'Connell, Dockree, Robertson, et al., 2009), propose that the high within-subject fluctuations of cognitive performance in ADHD may reflect problems in regulating arousal. Yet, direct objective evidence of arousal dysregulation and how it may account for fluctuating cognitive performance in ADHD is limited to date.

Measuring skin conductance (SC) provides an objective, reliable measurement of arousal in the peripheral nervous system (Boucsein, 1992). SC sensitively measures electrical changes in electrodermal activity, which is stimulated by the autonomic sympathetic nervous system, a key system in influencing arousal and alertness (Boucsein, 1992; Critchley, 2002; van Lang et al., 2007). Two commonly used measurements of SC are skin conductance level (SCL), which represents a tonic level of arousal (averaged over a given time-window), and skin conductance response (SCR) amplitude, which represents a phasic (transient) event-related change in SC (Figner & Murphy, 2011). Increased SCL indexes an increase in peripheral arousal, whereas increased SCR amplitude indicates a stronger, higher intensity arousal response (Boucsein, 1992). While early studies of SC in ADHD yielded conflicting findings (Satterfield & Dawson, 1971; Satterfield, 1974; Spring et al., 1974; Zahn et al., 1975), a number of more recent studies, benefiting from advancements in SC technique, report attenuated SCL in children with ADHD at rest and in task conditions, indicating hypo-arousal (Barry et al., 2012; Conzelmann et al., 2014; Dupuy et al., 2014; Iaboni, Douglas, & Ditto, 1997; Lazzaro et al., 1999; Mangeot et al., 2001; Mangina et al., 2000; O'Connell, Bellgrove, Dockree, & Robertson, 2004). However, discrepancies still remain, as some studies report no differences in SCL between adults with and without ADHD (Hermens et al., 2004; Mayer et al., 2015).

The aspect of cognitive performance that most strongly fluctuates in people with ADHD is their speed of responding on standard reaction time tasks, leading to high reaction time variability (RTV) (Antonini, Narad, Langberg, & Epstein, 2013; Kofler et al., 2013; Kuntsi &

Klein, 2012). Our previous analyses on a large sample of ADHD and control sibling pairs showed how RTV captured a large proportion of the familial influences underlying ADHD and separated from a second familial cognitive impairment factor that captured executive function impairments, such as response inhibition (Kuntsi et al., 2010). In twin analyses the genetic association of RTV was observed particularly strongly with inattention symptoms (Kuntsi et al., 2014). RTV can, however, improve in individuals with ADHD under certain circumstances: a meta-analysis of eight studies of varying designs suggested an overall significant, though small, effect of incentives (Kofler et al., 2013). While most of these studies have rewarded successful inhibition, we have examined the effects of rewarding specifically on a reduction in RTV, and have further combined the effects of rewards with a faster event rate, to maximise potential RTV improvement. Under such conditions, using the "Fast Task", we have consistently observed ADHD-sensitive improvement in RTV from baseline to a fast-incentive condition (Andreou et al., 2007; Kuntsi & Klein, 2012; Kuntsi et al., 2009).

Applying SC measurement in a study on ADHD, O'Connell et al. (2008) investigated performance on a sustained attention to response task (O'Connell et al., 2008). SC was measured before and after taking part in either Self-Alert Training, whereby participants learnt to modulate their own arousal levels – transiently increasing their arousal at regular intervals with the aim of reducing momentary lapses of attention – or a placebo training condition. Compared to pre-training performance, ADHD and control adult participants with the alertness training had increased SCR indicating increased transient arousal, a more consistent RTV over testing sessions and made fewer commission errors. Contrarily, ADHD participants and controls in the placebo training condition, who were not taught to modulate their arousal levels, had decreased SCR with time, indicating a decrease in stimulus-related arousal, as well as increased RTV, compared to their pre-training performance. Although the authors did not report correlations between SC and the cognitive performance measures, they note that SC and RTV followed a similar pattern: block-by-block increases in RTV were accompanied by gradual decreases in SCR, indicating a drop in arousal response over time (O'Connell et al., 2008).

We aimed to perform a detailed investigation of SC, as an objective measure of peripheral arousal, and its potential association with fluctuating RTs in a large sample of ADHD and control sibling pairs. First, we aimed to investigate if people with ADHD differ from controls in SCL and SCR amplitude during baseline (slow, unrewarded) RT performance. Second, we aimed to test if a fast-incentive condition increases SC-indexed arousal, and if it did, whether it increases more in the ADHD than control group. Third, for the SC variables that show group differences, we aimed to investigate their familial association with RTV and ADHD diagnosis, using sibling model fitting analyses, and to consider specific causal models that may explain the relationships that emerge.

2.3 Methods

2.3.1 Sample

Participants are members of the Sibling EEG Follow-Up Study (SEFOS) (Cheung et al. 2016; Cheung et al. 2015; Kitsune et al. 2014), which investigates neurophysiological and cognitive measures in a follow-up sample of ADHD and control sibling pairs. ADHD and control participants who had taken part in our previous research (Chen et al., 2008; Kuntsi et al., 2010), were invited to take part in this study. ADHD participants were included if they had ADHD in childhood and met DSM-IV criteria for any ADHD subtype at follow up. Exclusion criteria included IQ<70, autism, epilepsy, brain disorders and any genetic or medical disorder associated with externalising behaviours that might mimic ADHD. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

From the original follow up sample of 404 participants, 311 had SC measured, (as SC data collection only started after initial participants had already been assessed). We excluded from the analyses 10 ADHD participants (SC equipment failure (9), extreme drowsiness (1)) and 9 control participants (SC equipment failure (8) and met ADHD criteria based on parent report (1)). The final sample consisted of 73 ADHD probands (mean age: 18.3, SD=2.9, 87% male), 75 siblings of ADHD probands (mean age: 18.3, SD=2.9, 48% male), 72 controls (mean age: 17.48, SD=1.8, 94% male) and 72 control siblings (mean age: 17.11, SD=2.4, 68% male).

For the ADHD-control group differences analyses (aims 1 and 2), both members of control sibling pairs formed the control group (n=144); siblings of ADHD probands were excluded unless they had an ADHD diagnosis themselves. For these analyses, the ADHD and control groups did not differ in gender ($\chi 2=1.64$, $p<0.2$), but did differ in age ($t=0.54$, $p=0.04$) and IQ ($t=6.01$, $p<0.001$). In all these analyses we included age as a covariate and in additional analyses we added IQ as a second covariate. For the model fitting analyses (aim 3), all participants were included and differed in age ($t=1.97$, $p=0.05$), gender ($\chi 2=35.2$, $p<0.01$) and IQ ($t=22.46$, $p<0.01$). In these analyses we therefore used age and gender as covariates, with additional analyses also including IQ as a further covariate. All participants were of European Caucasian descent.

2.3.2 Procedure

The Fast Task was administered as part of a longer assessment session at the research centre. For those prescribed stimulants, a 48-hour ADHD medication-free period was required. Participants abstained from caffeine, smoking and alcohol on the day of testing. Face-to-face or telephone clinical interviews were administered to the parent of each ADHD proband shortly before or after the participant's assessment.

2.3.3 Measures

2.3.3.1 IQ

The vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1991) were administered to all participants to derive an estimate of IQ.

2.3.3.2 ADHD diagnosis

The Diagnostic Interview for ADHD in Adults (DIVA (Kooij & Francken, 2007)), a semi-structured interview based on the DSM-IV criteria, was conducted with the parent for current

symptoms only, because in all cases a clinical and research diagnosis of combined type ADHD had already been established (Chen et al., 2008). The Barkley's functional impairment scale (BFIS; (Barkley & Murphy, 2006)) was used to assess functional impairments commonly associated with ADHD in five areas of their everyday life. Each item ranges from 0 (never or rarely) to 3 (very often). Participants were classified as "affected", if they scored a "yes" on ≥ 6 items on the DIVA for either inattention or hyperactivity-impulsivity based on parent report, and scored ≥ 2 on ≥ 2 areas of impairments on the BFIS, rated by their parent.

2.3.3.3 The Fast Task

For a detailed description of the task, please see Supplementary Material 7.1. In brief, the slow-unrewarded (baseline) condition consists of 72 trials, which followed a standard warned four-choice RT task. Four empty circles (warning signals, arranged horizontally) first appeared for 8 s, after which one of them (the target) was coloured in. Participants were asked to press the response key that directly corresponded to the position of the target stimulus. Following a response, the stimuli disappeared from the screen and a fixed inter-trial interval of 2.5 s followed. Speed and accuracy were emphasized equally in the task instructions. If the child did not respond within 10 s, the trial terminated. A comparison condition of 80 trials with a fast event rate (fore-period of 1 s) and incentives followed the baseline condition (Andreou et al., 2007). The fast-incentive condition is always administered after the baseline condition. SC measures and cognitive performance measure (RTV) from each condition was included in this analysis. Due to the longer fore-period in the slow condition, the two conditions were not matched on task length, but were matched on the number of trials. We analysed RTV and SC performance on both the full slow condition and between 3 4-minute length-matched segments (Supplementary Table 1 and 2) (Andreou et al., 2007).

2.3.3.4 Skin conductance

SC data were measured by attaching a pair of reusable 8mm diameter silver-silver chloride electrodes on the on the palm of the hand (thenar eminence and hypothenar eminence) of participant's non-dominant hand at the start of the testing session. A non-saline gel was used

to increase impedance and help establish an electrical signal. A constant imperceptible voltage (0.5 V) was applied.

SC was recorded using PSYCHLAB SC5 24 bit equipment system, which has an absolute accuracy of +/- 0.1 microsiemens (μS) (PSYCHLAB, UK). The SC5 was connected to a computer to run the PSYCHLAB software, where data were monitored, recorded in real time and automatically digitized data. Stimulus onset and participant response events were recorded on a common timeline, which enabled SC activity to be stimulus-locked.

For a more detailed description of the SC data processing steps please see Supplementary Material 7.2. In brief, SC data values were calculated using a skin conductance system which is based on a SC sigmoid-exponential model that allows the tonic measure of SC level (SCL) to be disentangled from phasic, stimulus-associated, SC responses (SCR), and further allows the decomposition of overlapping SCRs (Lim et al., 1997; Williams et al., 2001) (Boucsein, 1992; Figner & Murphy, 2011). This system, therefore, is appropriate to use in conditions with long and short inter-stimulus-intervals (Williams et al., 2000). The statistical model was applied to each condition, as a whole. SCR amplitude (change in SC from the baseline to the highest point of the SCR) was derived from this method, and was calculated on a trial-by-trial basis. The criteria for the smallest SCR were set at 0.02 μS. Means of SC variables (SCL and SCR amplitude) were calculated per participant, across each condition.

2.3.4 Analyses

2.3.4.1 Covariates

Age was used as a covariate in all analyses. Analyses were initially performed without controlling for IQ, but we subsequently re-ran all analyses with IQ as a covariate to examine IQ effects. Gender was not included as a covariate in the group analyses to avoid controlling for ADHD status (Cheung et al., 2016). Instead, we explored the effect of gender by re-running all analyses with the females (n=15) removed; the pattern of results remained the same (results are available upon request). Analyses were rerun using anxiety and depression scores

from the Clinical Interview Schedule-Revised (Lewis, Pelosi, Araya, & Dunn, 1992) to investigate their confounding effects, but the significance of the results did not change (Supplementary Table 6). All variables were skewed and transformed using the optimized minimal skew (lnskew0) command in Stata version 11.1 (Stata Corporation, College Station, TX). Tests assessing sphericity and equality of variances were performed to ensure assumptions were met.

2.3.4.2 ADHD-control group comparisons

To test for main effects of group (ADHD vs controls), condition (baseline vs fast-incentive) and interactions for SC variables and RTV, the data were analysed using random intercept models and logistic regression in Stata. The random intercept model is a multilevel regression model that can be used as an alternative to ANCOVA to control for genetic relatedness (where both siblings from a pair are included in analyses) in a repeated-measures design, using a "robust cluster" command to estimate standard errors (Cheung et al., 2016; Tye et al., 2012; Wood, Asherson, Rijsdijk, & Kuntsi, 2009).

2.3.4.3 Structural Equation Modelling on sibling data

Structural equation modelling in OpenMx (Boker et al., 2011) was used on sibling-pair data to decompose the variance of traits into aetiological factors. Whereas in twin studies, comparison between monozygotic (MZ) and dizygotic (DZ) twin pairs enables estimation of additive genetic (A), shared environmental (C) and non-shared environmental (E) influences, sibling pairs (all sharing 50% of their alleles and 100% of the environment they grow up in) only enable estimation of the combined effects of A and C (familial, F effects). In addition to familial effects, non-shared effects (NE) are estimated, representing effects due to non-shared environment/genes as well as possible measurement error.

Multivariate modelling on sibling data uses the additional cross-sib cross-trait information to decompose the observed phenotypic correlation between traits into aetiological factors. Similar sibling design analyses have been previously performed by our group (see (Cheung et

al., 2012) for a more detailed description and rationale of the analysis). In addition, by using the correlations between the F and NE factors, and the standardized estimates, we calculated the extent to which the phenotypic correlation (Rph) between any two variables is due to F (Rph-F) and NE (Rph-NE).

2.3.4.4 Phenotypic correlations

Before FE modelling (described above), sibling correlations were estimated from a constrained correlation model to give maximum likelihood estimates of correlations between the traits within and across pairs while applying some constraints. Applied constraints reflect the assumptions of the familial model, i.e. that phenotypic correlations across traits within individuals is the same across siblings and that cross-trait cross-sibling correlations are independent of sibling order. Variables used in the sibling model fitting were selected by running phenotypic correlations on variables which showed group differences, and only variable(s) which had a significant relationship with RTV were further analysed.

2.3.4.5 Phenotypic mediation model

To further investigate a more aetiological model that may account for the relationship between SC variable(s) which are associated with both RTV and ADHD, and given the theoretical scope that RTV (an observed behavioural response) may reflect hypo-arousal (an internal physiological process), we hypothesised that RTV may mediate the relationship between SC-indexed arousal and ADHD. A phenotypic mediation model was fitted with SC variable(s) that may be causally associated with both RTV and ADHD. Significant (partial) mediation occurs when a third variable explains some of the association between two other variables (Baron & Kenny, 1986). The phenotypic mediation model was specified to account for the sibling-structure and selected nature of the data using similar constraints as the correlation model described above. The phenotypic relationship across traits within individuals is specified by means of causal paths, which were constrained to be equal across siblings. The sibling-structure was accounted for by specifying correlational paths across sibling variables.

2.3.4.6 Ascertainment correction

To account for the selected nature of the sample (selection on ADHD probands), the selection variable (ADHD status) was included in all models with its parameters fixed to population-known values. In the correlation and mediation model this involves fixing the sibling correlation for ADHD status to 0.40 and in the FE models fixing F to .40, representing 80% genetic variance (in case C=0). In addition, the threshold on ADHD liability was fixed to a z-value of 1.64 to correspond to a population prevalence of 5% (see Rijsdijk et al. 2005 for further explanation and validation of this approach) (Rijsdijk et al., 2005).

2.4 Results

2.4.1 ADHD-control group comparisons

For SCL data, a random intercept model indicated a significant main effect of condition ($z=8.95$, $p=0.01$) and group-by-condition interaction ($z=1.89$, $p=0.04$), but no main effect of group ($z=0.19$, $p=0.85$) (Figure 1A). Post-hoc regression analyses revealed that, compared to controls, individuals with ADHD showed significantly lower SCL in in the baseline condition ($t=-5.64$, $p<0.001$), but not in the fast-incentive condition ($t=1.1$, $p=0.27$) (Table 1). Both ADHD and control groups had a significant within-group increase from the baseline to fast-incentive condition ($t=7.52$, $p<0.01$, $t=6.44$, $p<0.01$ respectively), but the ADHD group had a greater increase than controls ($t = 1.94$, $p<0.05$).

For SCR amplitude data, a random intercept model showed no significant main effects of group ($z=0.46$, $p=0.61$), condition ($z=0.42$, $p=0.28$) or group-by-condition interaction ($z=0.69$, $p=0.51$) (Figure 1b).

All group analyses were re-run with IQ as a covariate, but the significance of results remained unchanged. Analyses were rerun using three length-matched segments from the baseline

condition and testing them separately against the fast-incentive condition, but the significance of results did not change (Supplementary Table 1 and 2). Although our sample had a 48-hour medication-free period, to explore the longer-term use of medication, we ran the following additional analyses: (1) SC comparison tests between unmedicated vs medicated participants with ADHD; (2) using current stimulant medication as an additional covariate; (3) analyses in un-medicated children only. The significance of results did not change in any additional analyses (Supplementary Table 3, 4 and 5).

We ran additional phenotypic correlations to examine the SCL-RTV and SCR-RTV relationship in ADHD and control groups separately (Supplementary Table 7). In the baseline condition, lower SCL significantly predicted higher RTV in the ADHD group ($r=-0.31$, $p<0.01$), but this correlation did not reach significance in the control group ($r=-0.12$ $p=0.15$) and Fisher's z test indicated that the correlations between the groups differed from one another at a trend level ($z=-1.37$, $p=0.08$). In the fast-incentive condition, the RTV-SCL correlations were not significantly different between the groups ($z=-0.97$, $p=0.16$; $r=-0.29$, $p<0.01$ in the ADHD group and $r=-0.16$, $p=0.06$ in the control group). There were no significant SCR-RTV correlations.

2.4.2 Familial association between SCL, RTV and ADHD

Given that SCL showed a significant group-by-condition interaction, a significant correlation with RTV with large effect sizes and the biggest significant group difference in the baseline condition, we next investigated the phenotypic and aetiological overlap between SCL, RTV and ADHD in the baseline condition. The maximum likelihood phenotypic, cross-sibling and cross-sibling-cross-trait correlations across SCL, RTV and ADHD are presented in Table 2.

Sibling-pair multivariate model fitting was performed to decompose variance/covariance of traits into aetiological factors F and NE (Figure 2). We calculated the extent to which the phenotypic correlation (Rph) between any two variables is due to F (Rph-F) and NE (Rph-NE) and express these contributions as a percentage (Table 3). Shared familial influences accounted for 55% of the total phenotypic correlation between SCL and ADHD, 94% of the

phenotypic correlation between SCL and RTV, and 59% of the phenotypic correlation between ADHD and RTV.

2.4.3 Phenotypic mediation model

Given the significant phenotypic and familial relationship of baseline SCL with RTV, and with ADHD, we tested whether baseline RTV mediated the relationship between baseline SCL and ADHD status. In the mediation model, the causal paths specified were all significant and partial mediation by RTV was indicated (Figure 3). However, model fit statistics demonstrate that the causal mediation model was not a good fit (BIC=2511, RMSEA=0), which is demonstrated by a significant chi-squared statistic ($-\Delta\chi 2$=-70.09, Δdf=1, $p<0.01$).

2.5 Discussion

In a large sibling study of 292 participants, we show that tonic peripheral arousal, indexed with SCL, is decreased in young people with ADHD during performance on a baseline RT task but normalises in a faster condition with incentives, indicating modifiable arousal dysregulation in ADHD. We further show that a substantial degree of familial sharing accounts for the significant phenotypic associations between SCL and RTV, and between SCL and ADHD.

The SC measure associated with ADHD was SCL. Lower SCL during baseline RT performance indicated a lower tonic level of peripheral arousal in individuals with ADHD, consistent with accounts of hypo-arousal (Barry et al., 2012; Barry, Clarke, Johnstone, McCarthy, & Selikowitz, 2009; Conzelmann et al., 2014; Dupuy et al., 2014; Lazzaro et al., 1999)**.** No group differences emerged for SCR amplitude. Whilst SCL and SCR are commonly used measurements of SC, they are thought to index different processes (Zhang et al., 2014). For example, neuroimaging studies show that the activity of the ventromedial prefrontal cortex and orbitofrontal cortex is associated with SCL (Nagai, Critchley, Featherstone, Trimble, & Dolan, 2004), whereas anterior prefrontal cortex and limbic regions are associated with SCR (Nagai et al., 2004;

Zhang et al., 2014). Our results, therefore, suggest that while the processes involved in tonic level of peripheral arousal (SCL) are impaired in individuals with ADHD during baseline performance, the processes involved in the phasic, discrete, arousal response elicited by stimulus onset (SCR amplitude), are not affected. The separation that we observed between SCL and SCR amplitude in their association with ADHD is also supported by studies suggesting that treatment with methylphenidate, an effective medication used to reduce ADHD symptoms, is associated more directly with increased SCL arousal (Conzelmann et al., 2014; Lawrence et al., 2005; Zahn et al., 1975).

Tonic peripheral arousal (SCL) normalised in the ADHD group in the fast-incentive condition, as indicated by a significant group by condition interaction and lack of a group difference in the fast-incentive condition. The malleability of SCL is in line with results of modifiable SC-indexed arousal (Barry et al., 2012; Conzelmann et al., 2014; O'Connell et al., 2008) and resembles the pattern observed for RTV (Kuntsi et al., 2009). The overall pattern of findings is therefore suggestive of an arousal dysregulation, rather than stable hypo-arousal, in individuals with ADHD.

To investigate the familial association between SCL and RTV directly, we focused on the baseline condition that is most sensitive to ADHD. The SCL-RTV correlation was largely (94%) accounted for by shared familial influences, demonstrating that the association of under-arousal with attentional fluctuations is mostly due to overlapping familial effects. Of the familial influences on RTV, half were correlated with those on SCL, indicating that peripheral arousal captures half of the familial influences that contribute to the attentional fluctuations. These findings are in line with theories linking RTV to arousal dysregulation (Andreou et al., 2007; Johnson et al., 2007; Kuntsi, Oosterlaan, & Stevenson, 2001; Scheres, Oosterlaan, & Sergeant, 2001; Sergeant et al., 2003; Tamm et al., 2012). However, as half of the familial influences on RTV were not correlated with those on SCL, this implies there are also non-overlapping, distinct, familial influences that contribute to RTV, in line with a multifactorial aetiology of increased RTV (Tamm et al., 2012).

We further investigated the familial association between SCL and ADHD, and found that shared familial effects accounted for 59% of the phenotypic correlation between them, providing further support for an aetiological link between under-arousal and ADHD. Of the familial influences on ADHD, a third correlated with those on SCL, demonstrating that peripheral arousal captures a third of the familial influence contributing to ADHD. Yet, two-thirds of the familial influences on ADHD did not correlate with those on SCL, implying that there are also non-overlapping familial influences that contribute separately to ADHD. These findings are in agreement with the view that arousal dysregulation is not the only contributing factor to ADHD, in line with the multifactorial nature of ADHD (Halperin & Schulz, 2006; Johnson et al., 2007; O'Connell, Dockree, Bellgrove, et al., 2009; O'Connell, Dockree, Robertson, et al., 2009; Scheres et al., 2001; Sergeant et al., 2003).

In a novel attempt to investigate the causal pathways that underlie the phenotypic relationship between SCL-indexed arousal, RTV and ADHD, we fitted a model which tests whether there are causal pathways from a) SCL to RTV and b) RTV to ADHD; and c) whether RTV mediates the association between SCL-indexed arousal and ADHD, or whether there is a direct causal pathway from SCL to ADHD. The mediation and causal paths between all variables were significant, suggesting that there are two pathways from SCL-indexed arousal to ADHD: an indirect causal pathway from arousal to RT fluctuations to ADHD, and a direct causal pathway from arousal to ADHD. Overall, our statistical model is consistent with ADHD theories that suggest a role for arousal dysregulation in the aetiology of ADHD and the observed lapses of attention (Halperin & Schulz, 2006; K. A. Johnson et al., 2007; O'Connell, Dockree, Robertson, et al., 2009). It is further suggestive of complex relationships between the variables: while the association between under-arousal and ADHD was partially mediated by attentional fluctuations (RTV), under-arousal had additional direct influences on ADHD. However, the causal mediation model did not fit the data very well, and therefore these causal pathway results should be interpreted with caution and further explored in future research.

Since this is the first family study on skin conductance and ADHD, our findings await replication. SC should also be studied in relation to other cognitive tasks, to investigate the generalisability of the findings. In addition, twin studies are required to establish whether the familial influences we identified reflect largely shared genetic rather than shared environmental influences; as previous research suggests limited role for shared environmental effects for ADHD (Burt, 2009), SC (Tuvblad et al., 2012; Vaidyanathan et al., 2014) and RTV (Kuntsi et al., 2013), a strong genetic component seems likely.

In conclusion, we identify SCL as an informative index of underlying, malleable hypo-arousal in ADHD. The demonstration of a link between SCL, RTV and ADHD provides physiological support for the arousal dysregulation accounts (Halperin & Schulz, 2006; Johnson et al., 2007; O'Connell, Dockree, Robertson, et al., 2009; Sergeant, 2005; van der Meere, 2005). If our findings are replicated in future research, SCL warrants further exploration as a potential treatment target.

Table 2.1. Descriptive statistics of gender, IQ, age, RTV and SC measures and group comparisons between the control and ADHD group. Age has been controlled for in the analyses on SC and RT variables. Cohen's effect sizes (*d*) are presented without and with IQ as a covariate.

		Control	*ADHD probands*	*Group comparisons*		*Effect size of group comparison*	
		Mean (SD)	Mean (SD)	t/f	p	Cohen's *d*	Cohen's *d*: IQ controlled
Demographics							
	Male %	81%	87%	1.64	0.20		
	IQ	109.60 (12.52)	98.60 (14.50)	601	<.01		
	Age	17.30 (2.15)	18.30 (2.90)	0.54	0.60		
RTV							
	Baseline	3.80 (0.40)	4.70 (0.80)	6.59	0.001	-1.20	-0.95
	Fast-incentive	3.33 (0.60)	3.70 (0.70)	1.49	0.14	-0.9	-0.9
SCL							
	Baseline	1.84 (0.30)	1.56 (0.30)	-5.64	0.001	0.72	0.67
	Fast-incentive	3.20 (2.00)	3.70 (2.10)	1.10	0.27	-0.17	-0.15
SCR amplitude							
	Baseline	0.41 (0.30)	0.45 (0.60)	1.32	0.20	-0.06	-0.06
	Fast-incentive	0.34 (0.20)	0.32 (0.23)	0.07	0.91	0.05	0.03

Reaction time variability (RTV); skin conductance level (SCL); skin conductance response (SCR) amplitude. Group means of transformed data and subsequent group comparison tests are listed.

Table 2.2. Maximum-likelihood phenotypic, cross-sibling and cross-sibling cross-trait correlations across baseline skin conductance level (SCL), reaction time variability (RTV) and ADHD.

Correlations	*R*	*CI*
Phenotypic correlations within individual		
SCL-RTV	-0.15*	(-0.23,-0.01)
SCL-ADHD	-0.31*	(-0.42,-0.19)
RTV-ADHD	0.35*	(0.23,0.46)
Cross-sibling correlations		
SCL	0.26*	(0.07,0.40)
RTV	0.26*	(0.10,0.40)
ADHD	FIXED 0.4	
Cross-sibling-cross-trait correlations		
SCL-RTV	-0.15*	(-0.24,-0.01)
SCL-ADHD	-0.14*	(-0.27,-0.02)
RTV-ADHD	0.20*	(0.07,0.30)

*p<0.05. 95% Confidence intervals (CI) are indicated in brackets.

Table 2.3. Phenotypic correlations (rph) and the phenotypic correlations due to familial effects (rph-F) and non-shared effects (rph-NE) across skin conductance level (SCL), reaction time variability (RTV) and ADHD.

	Phenotypic correlations (rph)	Phenotypic correlation due to F (rph-F)	Phenotypic correlation due to NE (rph-NE)
SCL-RTV	-0.15*	-0.14	-0.01
	(-0.25,-0.02)	(94%)	(6%)
SCL-ADHD	-0.31*	-0.17	-0.14
	(-0.39,-0.16)	(59%)	(41%)
RTV-ADHD	0.35*	0.20	0.16
	(0.23,0.45)	(57%)	(43%)

Figure 2.1. Skin conductance variables measured in control (black) and ADHD (grey) groups during performance on the baseline and fast-incentive conditions of the Fast Task. * Indicates p<0.05 significance. A) skin conductance level (SCL) B) skin conductance response (SCR) amplitude.

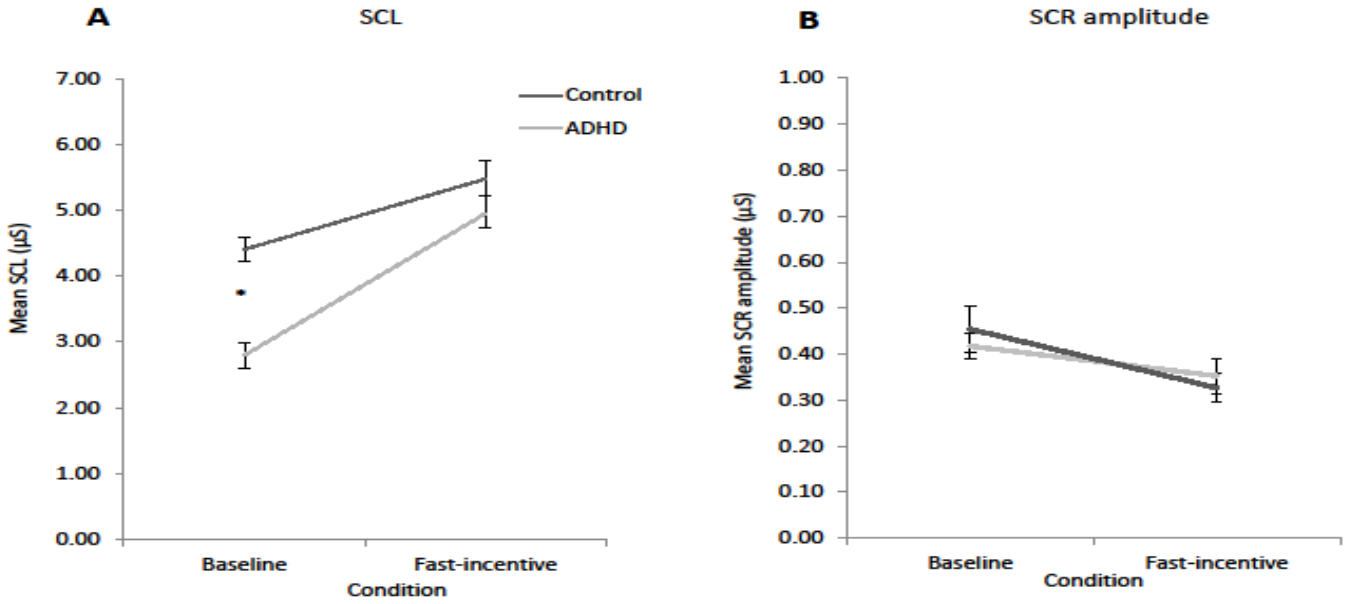


Figure 2.2. Standardised solution of the full correlated factor model across skin conductance level (SCL), reaction time variability (RTV) and ADHD in the baseline condition.

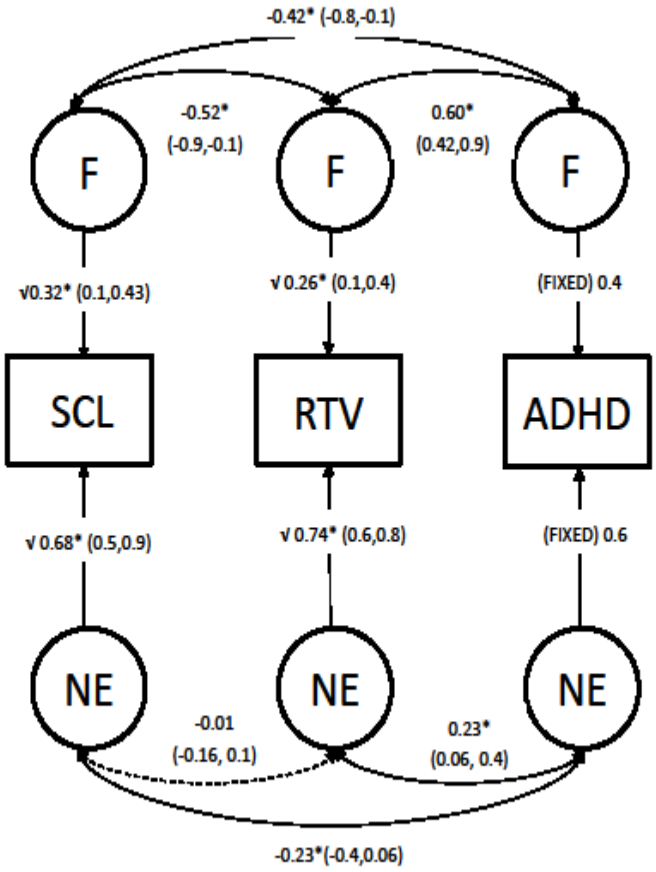
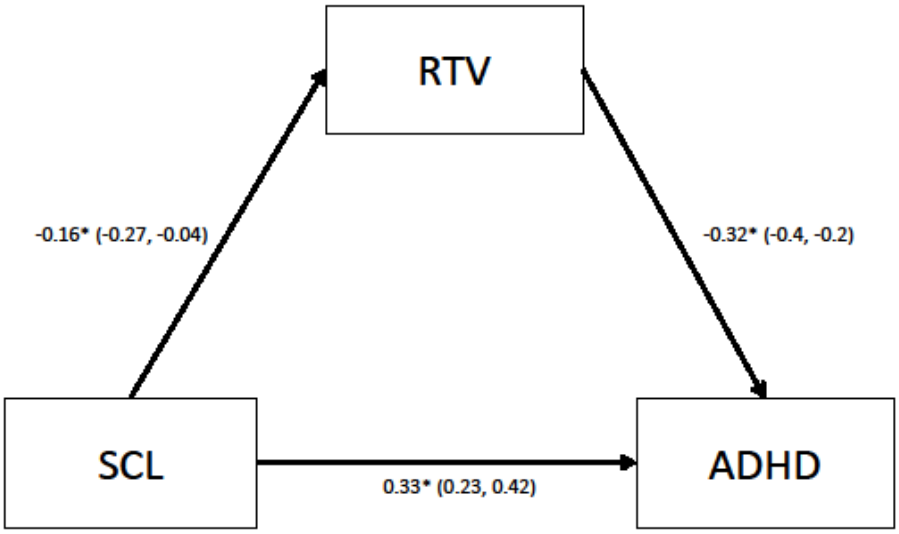


Figure 2.3. Reaction time variability (RTV) as a mediator of skin conductance level (SCL) and ADHD in the baseline condition.



Chapter 3 - PERIPHERAL HYPO-AROUSAL BUT NOT PREPARATION-VIGILANCE IMPAIRMENT ENDURES IN ADHD REMISSION.

3.1 Abstract

Background: Persistent attention-deficit/hyperactivity disorder (ADHD) is linked to impaired attention allocation (P3 amplitude) and peripheral hypo-arousal (attenuated skin conductance level, SCL) during reaction time performance, as well as to an inability to adjust the preparatory state (contingent negative variation, CNV) in a changed context. We examine whether these neurophysiological measures reflect enduring deficits unrelated to ADHD outcome or are markers of ADHD remission, improving concurrently with ADHD symptoms, similar to previously reported findings for preparation-vigilance processes and error detection. **Methods:** On average six years after initial diagnostic assessments, 91 young people with childhood ADHD (73 persisters and 18 remitters) and 144 controls were compared on event-related potential and SCL measures during two conditions (baseline and fast-incentive) of a four-choice reaction time task. ADHD outcome was examined with parent-reported symptoms and functional impairment measures using a categorical (DSM-IV) and a dimensional approach. **Results:** ADHD remitters differed from persisters, and were indistinguishable from controls, on baseline P3 amplitude and fast-incentive CNV amplitude (both $p \leq 0.05$). ADHD remitters differed from controls ($p \leq 0.01$), and were indistinguishable from persisters ($p > 0.05$), on baseline SCL. In dimensional analyses on all participants with childhood ADHD, ADHD impairment scores correlated significantly with baseline P3 and fast-incentive CNV ($r = -0.36$, $r = 0.30$; $p \leq 0.05$), but were not correlated with baseline SCL ($p > 0.05$). **Conclusions:** We obtain further evidence for event-related potential measures of preparation-vigilance as markers of ADHD remission. In contrast, hypo-arousal, as measured with skin conductance during baseline reaction time performance, emerges as an enduring deficit that is unrelated to ADHD symptom improvement. Future studies should aim to explore potential compensatory mechanisms that enable efficient preparation-vigilance processes, even in task conditions that induce persisting hypo-arousal, in ADHD remitters.

3.2 Introduction

In many individuals with childhood attention-deficit/hyperactivity disorder (ADHD) the symptoms and impairments persist into adolescence and adulthood (Faraone et al., 2006; Polanczyk et al., 2007; Simon et al., 2009). Yet others show significant improvement, such that they no longer obtain the diagnosis and appear free of clinically significant impairment (Faraone et al., 2006). By studying those whose ADHD improves over time, we can gain insight into the pathways to remission.

In our recent follow-up study from childhood to adolescence and early adulthood, ADHD persistence rate was 79% (Cheung et al. 2015; Cheung et al. 2016). We used cognitive and electroencephalography (EEG) and event-related potential (ERP) measures to investigate whether the cognitive-neurophysiological impairments associated with ADHD improve together with symptom improvement, or reflect enduring deficits. Data from a cued continuous performance task (CPT-OX) and an arrow flanker task identified measures of preparation-vigilance and error detection as markers of ADHD remission (Cheung et al. 2016; Michelini et al. in press). These measures – reaction time variability (RTV), omission errors, congruent errors, ERPs of response preparation and error detection, delta and theta activity – showed impairments in ADHD persisters only, with ADHD remitters indistinguishable from controls. In contrast, measures of inhibition, working memory, speed of processing and conflict monitoring were not sensitive to ADHD remission/persistence. Our results are in line with other recent studies that found executive control measures not being associated with ADHD remission (Biederman et al., 2009; McAuley et al., 2014; Pazvantoğlu et al., 2012; van Lieshout et al., 2013); yet this pattern was not observed in three other studies (Bédard et al., 2010; Francx et al., 2015; Halperin et al., 2008).

Further candidates as markers of remission are other measures that show malleability in individuals with ADHD. Using the Fast Task, a four-choice reaction time task under two conditions (a slow, unrewarded baseline condition and a fast condition with rewards), we have studied the extent to which individuals with ADHD can improve their performance and associated neurophysiological functions between the two conditions. The baseline condition

of the Fast Task induced impairments in RTV, attention allocation (P3 amplitude) and hypo-arousal (skin conductance (SC) level, SCL) in adolescents and young adults with persistent ADHD, but each of these improved significantly more between conditions in the ADHD compared to control group, indicating malleability of these measures in individuals with ADHD (Cheung et al. under review; James et al. in press). In the fast-incentive condition individuals with ADHD were indeed now indistinguishable from controls on attention allocation (P3) and peripheral arousal (SCL), yet another impairment was still observed, as the participants with ADHD, unlike controls, were not able to adjust their preparatory state (CNV amplitude) in a changed context (Cheung et al. under review; James et al. in press).

While our recent analyses indicated that RTV consistently emerges as a marker of remission across various tasks, the most robust effect was in the Fast Task (Cheung et al. 2016; Michelini et al in press). However, it is unclear whether other impairments that emerged on the Fast Task in ADHD persisters are similarly markers of ADHD remission, or reflects enduring deficits. Here, we compare the group differences between ADHD persisters, remitters and controls on attenuated attention allocation (P3 amplitude) and peripheral hypo-arousal (SCL) in the baseline condition, and attenuated preparatory state (CNV amplitude) in the fast-incentive condition of the Fast Task to investigate how these impairments relate to ADHD outcome.

3.3 Methods

3.3.1 Sample

The sample consists of 279 participants, who were followed up on average 5.8 years (SD=1.1) after initial assessments: 110 had a diagnosis of DSM-IV combined-type ADHD in childhood (10 sibling pairs and 90 singletons) and 169 were control participants (76 sibling pairs and 17 singletons). Full details on this sample can be found elsewhere (Cheung et al. 2016; Cheung et al. 2015). Briefly, participants with ADHD were initially recruited from specialized ADHD clinics (Kuntsi et al., 2010), and control participants from schools in the UK. Exclusion criteria at both assessments included: IQ < 70, autism, epilepsy, brain disorders and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD. At follow

up, we excluded six control participants who met DSM-IV ADHD criteria based on the parent-reported Barkley Informant Rating Scale (Barkley & Murphy, 2006) and six participants with ADHD who had missing parent ratings of clinical impairments. Two participants with childhood ADHD, who did not meet ADHD symptom criteria but met clinical levels of impairment at follow up, were also excluded to minimise heterogeneity in the sample.

Among those with childhood ADHD, 87 (79%) continued to meet clinical (DSM-IV) levels of ADHD symptoms and impairment (ADHD 'persisters'), while 23 (21%) were below the clinical cut-off (ADHD 'remitters') (Cheung et al. 2016; Cheung et al. 2015). Among ADHD remitters, 14 displayed ≥ 5 items on either the inattention or hyperactivity/impulsivity symptom domains, but did not show functional impairment. Almost half (47%) of the participants with childhood ADHD were being treated with stimulant medication at follow up. Parents of all participants gave informed consent following procedures approved by the London-Surrey Borders Research Ethics Committee (09/H0806/58).

From the original follow-up sample, 252 participants (82 ADHD persisters, 18 ADHD remitters, 78 controls and 74 control siblings) had SC measured (as SC data collection only started after initial participants had already been assessed). Due to SC equipment failure, ten ADHD persistent participants and eight control participants were excluded. For analyses, both members of control sibling pairs formed the control group (n=144); siblings of ADHD probands were excluded unless they had an ADHD diagnosis themselves. The final sample consisted of 73 ADHD persisters (71 singletons and 1 sibling pair; mean age=18.1, SD=2.9), 18 ADHD remitters (18 singletons; mean age=19.05, SD=2.68) and 144 controls (72 sibling pairs; mean age=17.3, SD=2.15) (Table 3.1). At follow up, ADHD persisters, remitters and controls differed in age and IQ, and there were significantly more males in the remitted group than in the other two groups (Table 3.1).

3.3.2 Procedure

The Fast Task was administered as part of a longer assessment session at the research centre. For those prescribed stimulants, a 48-hour ADHD medication-free period was required. All participants were asked to abstain from caffeine, smoking and drug and alcohol use on the day of testing. Face-to-face or telephone clinical interviews were administered to the parent of each ADHD proband shortly before or after the participant's assessment.

3.3.3 Measures

3.3.3.1 IQ

The vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1991) were administered to all participants to derive an estimate of IQ.

3.3.3.2 ADHD diagnosis

The diagnostic interview for ADHD in adults (DIVA) (Kooij & Francken, 2007) was conducted by trained researchers with parents of the ADHD probands, to assess DSM-IV-defined ADHD presence and persistence for the sample. Evidence of impairment commonly associated with ADHD was assessed with the Barkley's functional impairment scale (BFIS) (R A Barkley & Murphy, 2006) during interviews with parents. Each item ranges from 0 (never or rarely) to 3 (very often). Participants were classified as 'affected' at follow-up if they scored a 'yes' on ≥ 6 items in either the inattention or hyperactivity/impulsivity domains on the DIVA and if they scored ≥ 2 on two or more areas of impairments on the BFIS. We defined ADHD outcome using a categorical definition of persistence based on diagnoses.

3.3.3.3 The Fast Task (Andreou et al., 2007)

The slow-unrewarded (baseline) condition followed a standard warned four-choice RT task. A warning signal (four empty circles, arranged side by side) first appeared on the screen. At the end of the fore-period (presentation interval for the warning signal), the circle designated as the target signal for that trial was filled (coloured) in. The child was asked to make a

compatible choice by pressing the response key that directly corresponded in position to the location of the target stimulus. Following a response, the stimuli disappeared from the screen and a fixed inter-trial interval of 2.5 s followed. Speed and accuracy were emphasized equally. Speed and accuracy were emphasized equally. If the child did not respond within 10 s, the trial terminated. The fast-incentive condition is always administered after the baseline condition. The slow condition, with a fore-period of 8s and consisting of 72 trials, then followed.

3.3.3.4 EEG recording and pre-processing

The EEG was recorded from 62 channels DC-coupled recording system (extended 10–20 montage), with a 500 Hz sampling rate, impedances kept under 10 kΩ, and FCz as the reference electrode. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi. The EEG data were analysed using Brain Vision Analyser (2.0) (Brain Products, Germany). For a more detailed description of the ERP data processing steps please see Supplementary Material 7.2. In brief, after down-sampling the data to 256 Hz, the EEG data were re-referenced to the average and filtered offline with digitally band-pass (0.1–30 Hz, 24 dB/oct) Butterworth filters. Ocular artefacts were identified from the data using Independent Component Analysis (ICA). The extracted independent components were manually inspected and ocular artefacts were removed by back-projection of all but those components. Data with other artefacts exceeding +100mV in any channel were rejected. All averages contained at least 20 sweeps. P3 amplitude was analysed as the area amplitude measure (μV*ms) at Pz between 250 and 450ms, to reduce bias due to the varying noise levels induced by the different task conditions (Luck, 2005). For the P3 analyses, all the accepted trials were baseline-corrected using a pre-stimulus baseline of 200ms. The mean amplitudes of this pre-target period (-200ms to 0ms, using a technical zero baseline as in previous CNV work (Albrecht et al., 2013; Banaschewski et al., 2003)) at Cz were also analyzed separately as a CNV measure. As the CNV is maximal at Cz, we computed CNV at Cz only, to reduce the number of statistical comparisons (Cheung et al. under review). This short interval not only corresponded to the P3 baseline, but also captured the short CNV in the fast-incentive condition with its one-second cue target interval (Cheung et al. under review).

3.3.3.5 Skin conductance (SC)

SC data were measured by attaching a pair of reusable 8mm diameter silver-silver chloride electrodes on the palm of the hand (thenar eminence and hypothenar eminence) of participant's non-dominant hand at the start of the testing session. A non-saline gel was used to increase impedance and help establish an electrical signal. A constant imperceptible voltage (0.5 V) was applied. SC was recorded using PSYCHLAB SC5 24 bit equipment system, which has an absolute accuracy of +/- 0.1 microsiemens (μS) (PSYCHLAB, UK). The SC5 was connected to a computer to run the PSYCHLAB software, where data were monitored, recorded in real time and automatically digitized data. Stimulus onset and participant response events were recorded on a common timeline, which enabled SC activity to be stimulus-locked (James et al. in press).

SC data values were calculated using a SC system which is based on a SC sigmoid-exponential model that allows the tonic measure of SC level (SCL) to be disentangled from phasic, stimulus-associated, SC responses (SCR), and further allows the decomposition of overlapping SCRs (Boucsein, 1992; Figner & Murphy, 2011; Lim et al., 1997; Williams et al., 2001). This system, therefore, is appropriate to use in conditions with long and short inter-stimulus-intervals (Williams et al., 2000). The statistical model was applied to each condition, as a whole. SCR amplitude (change in SC from the baseline to the highest point of the SCR) was derived from this method, and was calculated on a trial-by-trial basis. The criteria for the smallest SCR was set at 0.02 μS. Means of SCL were calculated per participant, across each condition (James et al. in press).

3.3.4 Statistical analyses

Age was used as a covariate in all analyses. Analyses were initially performed without controlling for IQ, but we subsequently re-ran all analyses with IQ as a covariate to examine IQ effects. Gender was not included as a covariate in the group analyses to avoid controlling for ADHD status (Cheung et al. 2016; Michelini et al. in press; James et al. in press). Instead,

we explored the effect of gender by re-running all analyses with the females (n=15) removed; the pattern of results remained the same (results are available from first author upon request). RTV and SCL data were skewed and transformed using the optimized minimal skew (lnskew0) command in Stata version 11.1 (Stata Corporation, College Station, TX). As these were sibling data, the data were analysed using random intercept models and regression in Stata. The random intercept model is a multilevel regression model that can be used as an alternative to ANCOVA to control for genetic relatedness (where both siblings from a pair are included in analyses) in a repeated-measures design, using a "robust cluster" command to estimate standard errors (Cheung et al.2016; Tye et al. 2012; Wood, Asherson, Rijsdijk, & Kuntsi, 2009). We first computed the main effects of group (ADHD persistent vs ADHD remittent vs controls), condition (baseline vs fast-incentive) and group-condition interactions for all measures. Post-hoc analyses were then conducted to investigate the differences between ADHD remitters and persisters, and controls. Means and standard deviations of measures in the baseline and fast-incentive condition are reported in Table 3.1. Cohen's d effect sizes were calculated, where 0.2 is considered a small effect, 0.5 a medium effect and 0.8 a large effect. By controlling for differences in the baseline condition, we were additionally able to investigate if groups differed in the slope from the baseline to fast-incentive condition, indexing the degree of change. Pearson correlations were also conducted on these measures to examine their associations with DIVA ADHD symptom scores, and clinical impairment within those who had a childhood ADHD diagnosis, with age and gender included as covariates.

3.4 Results

The results for comparisons involving the ADHD-remittent group are new (apart from baseline RTV; Cheung et al. 2016) and are the focus of the present study. For ease of comparison and completeness, here we also report on the statistics from the ADHD-persistent and control comparisons, which have previously been reported (Cheung et al. under review; James et al. in press). However, the sample included in the current study is not exactly the same as reported in our previous studies, as we included only participants with complete SC measures.

3.4.1 RTV

For RTV data, a random intercept model indicated a significant main effect of condition (z=-10.26, p<0.01), main effect of group (z=4.37, p<0.01), but no main group-by-condition interaction (z=-0.73, p=0.46) (Figure 3.1A). Post-hoc analyses revealed that, in the baseline condition, ADHD remitters had significantly decreased RTV compared to ADHD persisters (t=-2.49, p<0.05, d=0.79), but did not differ from controls (t=1.21, p=0.12, d=0.17); ADHD persisters had significantly increased RTV compared to controls (t=7.06, p<0.05, d=1.20). In the fast-incentive condition, ADHD remitters had significantly decreased RTV compared to ADHD persisters (t=-1.62, p<0.05, d=0.47) but did not differ from controls (t=1.40, p=0.10, d=0.31) (Figure 3.1A); ADHD persisters had significantly increased RTV compared to controls (t=6.16, p<0.05, d=0.90). The within-group decrease from the baseline to fast-incentive condition was significant in ADHD remitters (t=-2.34, p<0.05), ADHD-persisters (t=-8.09, p<0.05), and controls (t=-8.09, p<0.05). The slope in RTV (indexing the degree of change from the baseline to the fast-incentive condition) in ADHD remitters was significantly less steep compared to ADHD persisters (t=-1.87, p=0.05, d=0.47), but was not significantly different compared to controls (t=0.58, p=0.56, d=0.12). The slope in RTV was significantly greater in ADHD persisters compared to controls (t=-2.26, p<0.05, d=0.31).

3.4.2 CNV amplitude

For CNV amplitude, a random intercept model indicated a significant main effect of condition (z=-15.37, p<0.01), main effect of group (z=2.59, p<0.05) and a trend level significance of group-by-condition interaction (z=-1.66, p=0.09) (Figure 3.1B). Post-hoc analyses revealed that, in the baseline condition ADHD remitters did not differ in CNV amplitude compared to ADHD persisters (t=0.57, p<0.51) or controls (t=1.17, p<0.24) (Figure 3.1B, Figure 3.2A); ADHD persisters also did not differ in CNV amplitude compared to controls (t=0.80, p=0.21, d=0.13). In the fast-incentive condition, ADHD remitters showed significantly increased CNV amplitude, compared to ADHD persisters (t=2.44, p<0.01, d=0.74), but were not significantly different compared to controls (t=-0.12, p=0.91, d=0.02) (Figure 3.1B, Figure 3.2C); ADHD persisters had significantly decreased CNV amplitude compared to controls (t=4.72, p<0.05,

d=0.76). There was a significant within-group increase in CNV amplitude from the baseline to fast-incentive condition in ADHD remitters (t=5.01, p<0.01), ADHD-persisters (t=5.35, p<0.05) and controls (t=12.81, p<0.05). In ADHD remitters, the slope in CNV amplitude (indexing the degree of change from the baseline to the fast-incentive condition) was significantly steeper compared to ADHD persisters (t=3.25, p<0.01, d=0.88), but did not differ compared to controls (t=-0.79, p=0.43, d=0.19); the slope in CNV amplitude was significantly steeper in controls compared to ADHD persisters (t=4.34, p<0.01, d=0.68).

3.4.3 P3 amplitude

For P3 amplitude, a random intercept model indicated a significant main effect of condition (z=47.76, p<0.01), but no main effect of group (z=-0.09, p=0.92), or group-by-condition interaction (z=-0.24, p=0.81) (Figure 3.1C). Post-hoc analyses revealed that, in the baseline condition, ADHD remitters showed significantly increased P3 amplitude compared to ADHD persisters (t=3.51, p<0.05, d=0.56), but were not different compared to controls (t=-1.64, p=0.12, d=0.18) (Figure 3.1C, Figure 3.2B); ADHD persisters had significantly decreased P3 compared to controls (t=1.88, p<0.05, d=0.30). In the fast-incentive condition, ADHD remitters were not significantly different in P3 amplitude compared to ADHD persisters (t=1.22, p<0.01, d=0.20) or controls (t=-0.22, p=0.81, d=0.13) (Figure 3.1C, Figure 3.1D); ADHD persisters did not differ in P3 amplitude compared to controls (t=1.20, p<0.12, d=0.31). There was a significant within-group increase in P3 amplitude from the baseline to fast-incentive condition in ADHD remitters (t=23.44, p<0.01), ADHD-persisters (t=26.84, p<0.05) and controls (t=32.90, p<0.05). The slope in P3 amplitude between the baseline to fast-incentive condition in ADHD remitters was significantly less than in ADHD persisters (t=2.22, p<0.05, d=0.57), but did not differ from controls (t=1.51, p=0.13, d=0.31); the slope in P3 amplitude was significantly greater in ADHD persisters, compared to controls (t=1.45, p<0.05, d=0.31).

3.4.4 SCL

For SCL data, a random intercept model indicated a significant main effect of condition (z=25.43, p<0.01), a significant group-by-condition interaction (z=2.33, p<0.05) but no

significant main effect of group (z=-0.34, p=0.73) (Figure 3.1D); Post-hoc analyses revealed that, in the baseline condition, ADHD remitters did not differ from ADHD persisters (t=-0.52, p=0.61, d=0.15), but had decreased SCL compared to controls (t=-3.70, p<0.01, d=0.89) (Figure 3.1D); In the fast-incentive condition, no group differences emerged between ADHD remitters and ADHD persisters (t=0.23, p=0.81, d=0.08), or between ADHD remitters and controls (t=0.30, p=0.77, d=0.09). Analyses between ADHD persisters and controls in the identical sample have previously been reported: ADHD persisters had significantly decreased SCL in the baseline condition, but the groups did not differ in the fast-incentive condition (James et al.in press). The within-group increase in SCL from the baseline to fast-incentive condition was significant in ADHD remitters (t=8.86, p<0.01). Significant within-group increases in SCL, from the baseline to fast-incentive condition, in ADHD persisters and controls have previously been reported (James et al. in press). The slope in SCL between the baseline to fast-incentive condition in ADHD remitters did not differ from ADHD persisters (t=0.20, p=0.84, d=0.06) or controls (t=1.03, p=0.31, d=0.24); the slope in SCL was steeper in ADHD persisters, compared to controls (t=1.94, p<0.05, d=0.31).

The analyses were re-run with IQ as a covariate, and re-run on a male-only sample, but the significance of results remained unchanged.

Associations with the continuums of ADHD symptoms and impairments

In those with childhood ADHD (n=91), ADHD impairment at follow up correlated significantly with baseline RTV and P3 amplitude, and with CNV amplitude in the fast-incentive condition (Table 3.2). The only significant correlation with ADHD symptoms was observed for RTV in the baseline condition, as reported previously for the full follow-up sample of those with childhood ADHD (n=110) (Cheung et al. 2016). No other significant associations were observed.

3.5 Discussion

We have previously linked persistent ADHD to impaired attention allocation (P3 amplitude) and peripheral hypo-arousal (SCL) during baseline reaction time performance, as well as to an inability to adjust the preparatory state in a changed context (CNV amplitude in a fast condition with incentives) (Cheung et al. under review; James et al. in press). In a comparison between ADHD persisters, ADHD remitters and controls on these neurophysiological indices, we now find that P3 amplitude and CNV amplitude are markers of remission, consistent with previously reported findings for RTV and other markers of preparation-vigilance (Cheung et al. 2016; Michelini et al. in press). In contrast, hypo-arousal, as measured with SC during baseline RT performance, emerges as a enduring deficit, that is unrelated to ADHD symptom improvement.

The finding of SCL-indexed hypo-arousal reflecting an enduring impairment in the baseline condition is therefore not mirroring the remission pattern observed for RTV as expected, because we have previously found a link between SCL-indexed hypo-arousal and RTV in individuals with persistent ADHD, under identical testing conditions (James et al. in press). Overall, these data suggest that, as ADHD remitters show peripheral under-arousal during baseline RT performance, improved arousal regulation does not account for the strong, control-group level cognitive-EEG performance now observed among the ADHD remitters. The current findings therefore indicate that SCL is not associated with ADHD symptoms, and is unlikely to be a suitable treatment target. Future research should investigate further potential compensatory processes and pathways to improved attentional performance in ADHD remitters.

Analyses on continuous measures of ADHD outcome further confirmed the lack of an association between skin conductance measures of arousal and either ADHD symptoms or impairment at follow up. The ERP markers of remission in the group analyses – P3 in the baseline condition and CNV in the fast-incentive condition – were significantly associated with the continuous impairment scores, though only RTV was significantly associated with both ADHD symptoms and impairment (Cheung et al. 2016).

The main limitation of our study is the modest number of remitters, which also means we cannot run more complex multivariate analyses across variables. Further, we had a male-only remittent group, making it unfeasible to investigate whether there are differences in cognitive-neurophysiological measures between male and female individuals with remittent ADHD. As our sample involved adolescents and young adults who are still undergoing cortical development, future follow-up studies when all participants have reached adulthood will be beneficial to further elucidate developmental trajectories towards remittance or persistence.

Overall, our results indicate an enduring deficit in peripheral hypo-arousal during baseline RT performance in ADHD remitters, whereas preparation-vigilance processes (P3 amplitude in the baseline condition and CNV amplitude in the fast-incentive condition, as well as RTV (Cheung et al. 2016)) are markers of remission, being impaired among ADHD persisters only. This indicates there may be alternative compensatory mechanisms to counteract the peripheral hypo-arousal in ADHD remitters. Yet peripheral hypo-arousal is context-dependent, rather than a stable deficit, in ADHD remitters as they, similar to ADHD persisters (James et al. in press), were indistinguishable from controls on SCL in the faster condition with rewards. Future studies should aim to explore potential compensatory mechanisms that enable efficient preparation-vigilance processes, even in task conditions that induce persisting hypo-arousal, in ADHD remitters.

Table 3.1. Descriptive statistics: means and standard deviations (SD) for measures in the baseline and fast-incentive conditions.

	ADHD persisters (n=73)	ADHD remitters (n=18)	Controls (n=144)
Mean age	18.10 (2.90)	19.50 (2.70)	17.30 (2.10)
Male (%)	84	100	81
IQ	98.61 (14.54)	104.05 (12.23)	109.61 (12.52)
Cognitive performance measures			
RTV (baseline)	182.32 (129.20)	122.98 (77.00)	102.10 (82.82)
RTV (fast-incentive)	100.12 (92.02)	95.41 (156.51)	57.12 (20.40)
Event related potential measures			
CNV (baseline)	0.07 (1.40)	0.23 (1.10)	0.09 (1.17)
CNV (fast-incentive)	-1.32 (2.16)	-2.96 (2.13)	-3.01 (2.61)
P3 (baseline)	7.35 (0.27)	7.50 (0.17)	7.44 (0.30)
P3 (fast-incentive)	8.17 (0.14)	8.21 (0.13)	8.22 (0.15)
Skin conductance level (SCL)			
SCL (baseline)	1.56 (0.31)	1.54 (0.31)	1.84 (0.31)
SCL (fast-incentive)	3.72 (2.10)	3.08 (1.72)	3.21 (2.00)

ADHD-attention-deficit/hyperactivity disorder. ERP-Event related potential; RTV-reaction time variability; CNV-contingent negative variation; SCL-skin conductance level. Standard deviation indicted in brackets. CNV amplitude at Cz, P3 amplitude at Pz.

Table 3.2. Pearson correlations of cognitive performance (RTV), ERP (CNV amplitude and P3 amplitude) and skin conductance (SCL) measures with interview-based DIVA ADHD symptoms and clinical impairment within the ADHD group only (n=91) without controlling for IQ. Data from RTV in the baseline condition in the full sample has already been reported (Cheung et al. 2016), but for ease of comparison, results have been replicated here in the sub-sample with + denoting previously reported results.

		ADHD symptoms r	Impairment r
Baseline condition	RTV	**0.20*+**	**0.27*+**
	CNV	0.20	0.05
	P3	-0.16	**-0.36***
	SCL	0.01	-0.18
Fast-incentive condition	RTV	0.13	0.15
	CNV	0.18	**0.30***
	P3	-0.11	-0.02
	SCL	-0.06	-0.10

+ denotes this correlation has previously been reported in the full-sample (Cheung et al. 2016). * and bold text denote $p<0.05$. ADHD-attention-deficit/hyperactivity disorder; ERP-Event related potential; RTV-reaction time variability; CNV-contingent negative variation; SCL-skin conductance level. CNV amplitude at Cz, P3 amplitude at Pz.

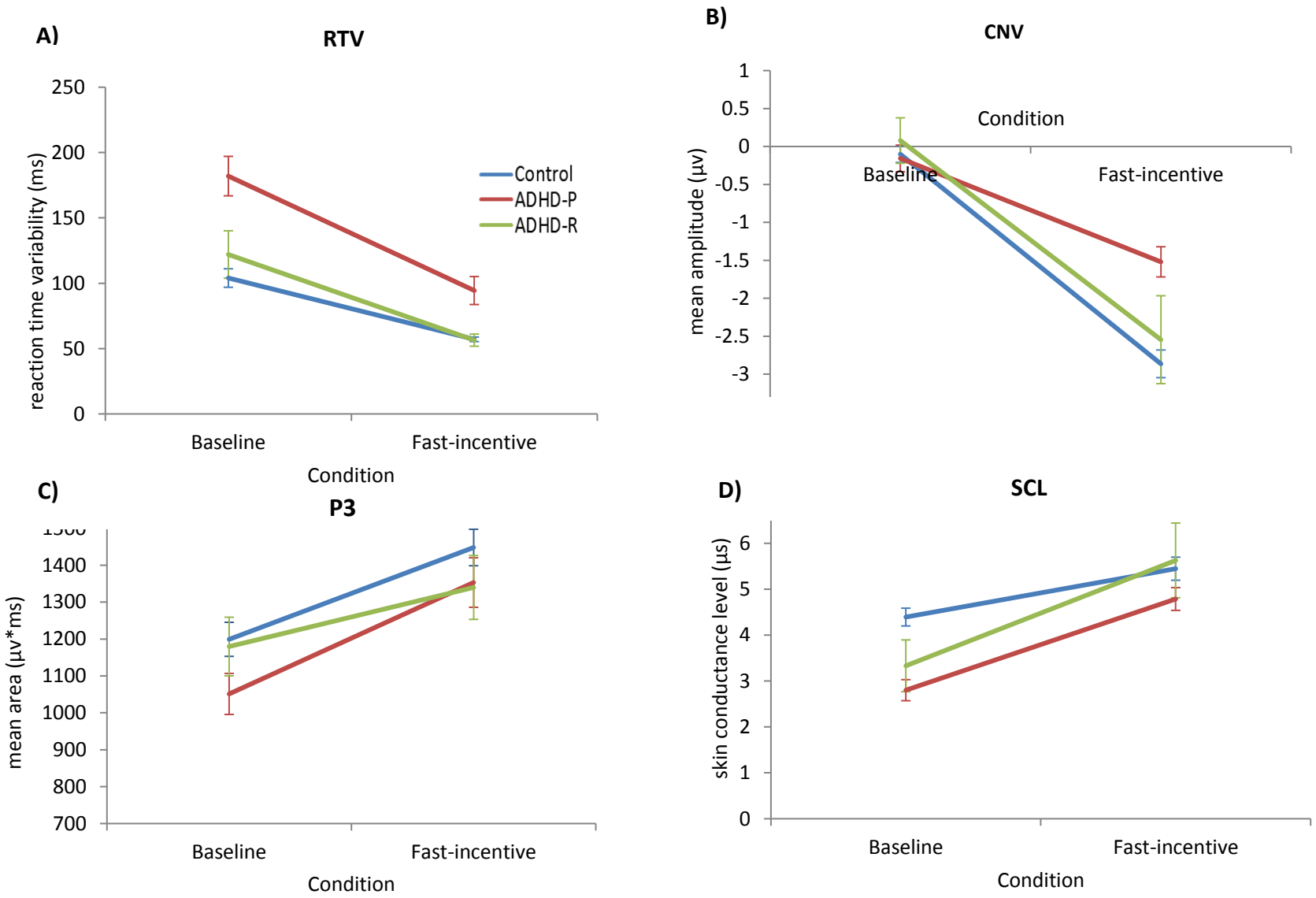


Figure 3.1. Group comparisons between ADHD remitters, ADHD persisters and controls on A) reaction time variability (RTV) B) Contingent Negative Variation (CNV) at Cz C) P3 amplitude at Pz D) skin conductance level (SCL) across baseline and fast-incentive conditions of the Fast Task. ADHD remitters (ADHD-R, in green), ADHD persisters (ADHD-P, in red) and control participants (controls, in blue). Data from ADHD persisters and control participants in the full sample have already been presented for RTV, CNV and P3 (Cheung et al. under review), and SCL (James et al. in press), but for ease of comparison, results specific to this analysis have been replicated here with the additional ADHD remitter group.

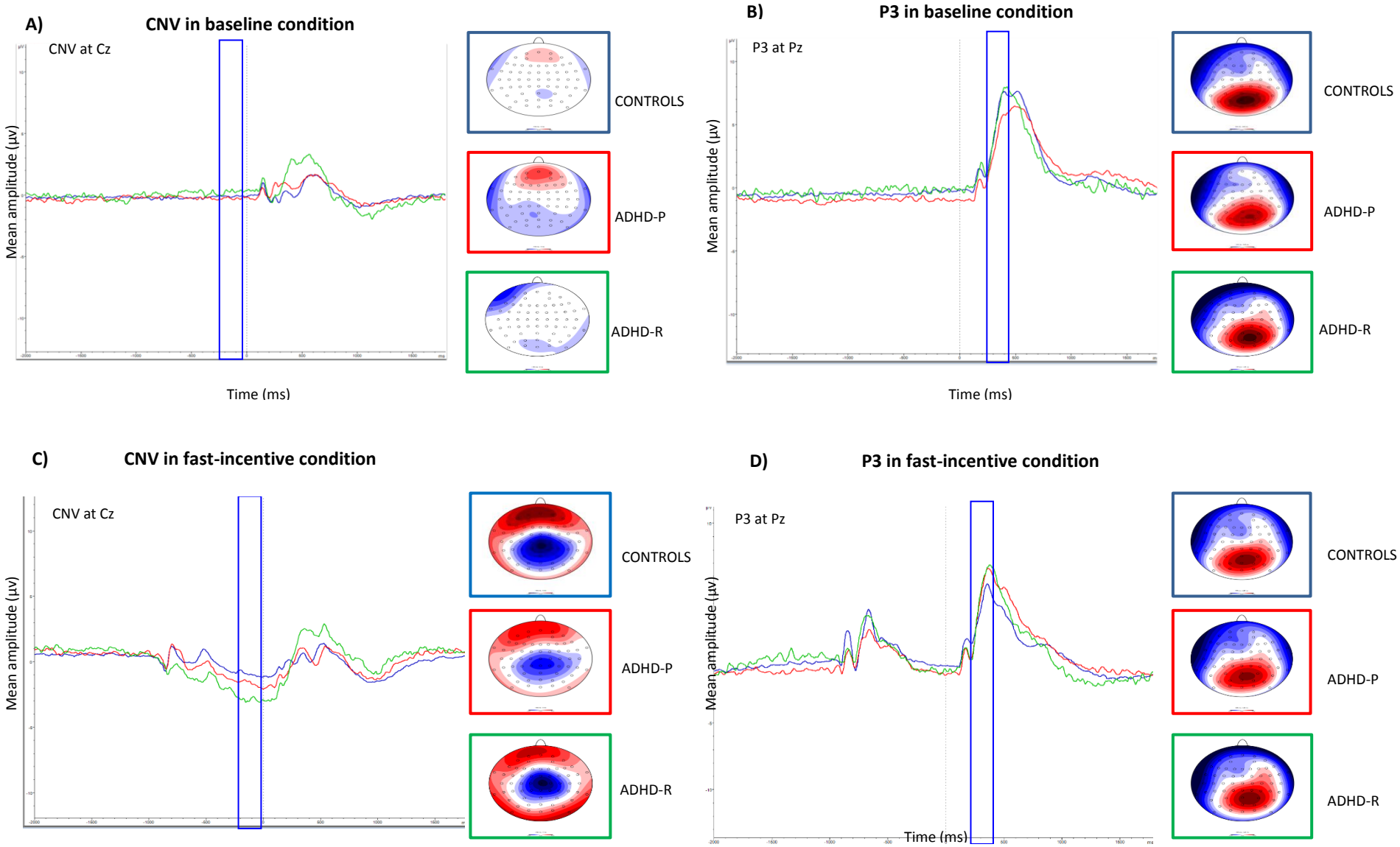


Figure 3.2. Grand averages for ADHD remitters, ADHD persisters and controls on stimulus-locked ERPs of the CNV at Cz electrode between -200-0 ms (shown on the left), and of the P3 at Pz electrode between 250-450 ms (shown on the right), in both the baseline (A & B) and fast-incentive conditions (C & D) of the Fast Task. ADHD remitters (ADHD-R, in green), ADHD persisters (ADHD-P, in red) and control participants (Controls, in blue), with topographic maps. Data from ADHD persisters and control participants in the full sample have already been presented for CNV and P3 (Cheung et al. under review), but for ease of comparison, results specific to this analysis have been replicated here with the additional ADHD remitter group.

Chapter 4 - ASSOCIATIONS OF PRETERM BIRTH WITH ADHD-LIKE COGNITIVE AND RESPONSE PREPARATION IMPAIRMENTS AND ADDITIONAL SUBTLE IMPAIRMENTS IN ATTENTION AND AROUSAL MALLEABILITY

4.1 Abstract

Background: Preterm-born individuals have an increased risk of developing ADHD-like symptoms, and are reported to have cognitive and neurophysiological impairments that resemble impairments associated with ADHD, including attention and arousal regulation problems. Yet, direct comparisons across preterm and ADHD groups are scarce. **Methods:** We directly compared preterm-born individuals (n=186) to term-born individuals with ADHD (n=69) and term-born controls (n=135), aged 11-23, on cognitive-performance, event-related potentials and skin conductance level (SCL) measures associated with attention and arousal from a baseline (slow, unrewarded) condition and fast-incentive condition, previously shown to discriminate between the adolescents with ADHD and controls (Cheung et al. under review, James et al. in press). We aimed to establish whether preterm-born adolescents show a) identical cognitive-neurophysiological impairments to term-born adolescents with ADHD, and b), additional impairments. **Results:** The preterm group, like the term-born ADHD group, showed increased mean reaction time (MRT) and reaction time variability (RTV) in the baseline condition, and attenuated contingent negative variation (CNV) amplitude (reflecting response preparation) in the fast-incentive condition. The preterm group, unlike the term-born ADHD or control groups, showed attenuated P3 amplitude (reflecting attention allocation) in the fast-incentive condition, and did not show significant within-group adjustments in P3 amplitude (reflecting adjustment of attention allocation) and SCL (reflecting adjustment of peripheral arousal). In dimensional analyses on preterm-born participants, ADHD symptoms and impairment scores correlated significantly with MRT, RTV (baseline) and CNV amplitude (fast-incentive), but were not correlated with P3 amplitude (fast-incentive/slope of adjustment) or SCL (slope of adjustment). **Conclusions:** Our investigation of preterm-born adolescents indicates both impairments in cognition and brain function (response preparation) that are linked to increased ADHD symptoms. Our findings

also indicate further, subtle impairments in lack of malleability in specific neurophysiological processes (attention allocation and peripheral arousal) that are unrelated to ADHD symptoms. Our results show how such impairments in preterm-born individuals extend to atleast adolescence, even in a well-functioning sample recruited from mainstream schools. Future studies should extend these investigations into adulthood.

4.2 Introduction

The incidence of preterm birth (<37 weeks' gestation) in most developed countries is 5-8% of live births (Office for National Statistics, 2013; Tucker & McGuire, 2004). Whilst survival rates are improving (Goldenberg, Culhane, Iams, & Romero, 2008a), preterm birth places an individual at an increased risk for a range of negative long-term outcomes (Bhutta et al., 2002; D'Onofrio et al., 2013). One such outcome, where an elevated association is reported with preterm birth, is attention-deficit/hyperactivity disorder (ADHD) (Bhutta et al., 2002; D'Onofrio et al., 2013; Halmøy et al., 2012; Sucksdorff et al., 2015). Yet, the underlying risk pathways from preterm birth to ADHD remain poorly understood.

Beyond the observable behavioural symptoms that are used to diagnose ADHD, individuals born preterm are also reported to have cognitive and neurophysiological impairments that resemble impairments associated with ADHD, including attention, inhibitory control and arousal regulation difficulties (Aarnoudse-Moens et al. 2012; Aarnoudse-Moens et al. 2009; Anderson et al. 2011; Geva and Feldman 2008; Johnson et al. 2011; de Kieviet et al. 2012; Lawrence et al. 2009; Mulder et al. 2009; Nosarti et al. 2006). For example, an fMRI study reported brain activation differences between 26 preterm-born and 11 control adults in task-relevant regions of attention allocation and inhibitory processing (Lawrence et al., 2009). Direct comparisons between preterm-born individuals and full-term born individuals with ADHD are sparse, but would be needed to address whether the impairments reported in preterm groups are truly identical to those observed in ADHD groups. A method that enables a particularly sensitive analysis of the processes underlying observable cognitive impairments is electroencephalography (EEG). From EEG data we can extract event-related potentials (ERPs), which are electrical potentials generated by the brain in response to internal or external events, such as stimuli and responses, and allow the direct measurement of covert brain processes (Banaschewski & Brandeis, 2007; Luck, 2005; McLoughlin, Makeig, & Tsuang, 2014). Another informative neurophysiological method is skin conductance (SC): it is a simple, robust biomarker of sympathetic nervous system innervation and thus indexes peripheral arousal (Boucsein, 1992; van Lang et al., 2007).

We recently reported findings from a comparison between preterm-born adolescents and young adults and term-born ADHD adolescents on the cued continuous performance test: while we observed response preparation (the ERP index of contingent negative variation, CNV) and response inhibition (NoGo-P3) impairments in both groups, compared to a term-born control group, the preterm group showed an additional impairment in executive response control (GoP3), which was not associated with ADHD symptoms, suggestive of more wide-ranging neurophysiological deficits in the preterm group (Rommel et al. under review). Only one other study to date, to our knowledge, has directly compared ERPs between preterm-born and ADHD groups (Potgieter et al., 2003)**.** Using a visual oddball paradigm, on a small sample (n=41 across four groups), this study reported impairments (increased inhibition NoGo-N2 and increased MRT, RTV and errors) only among term and preterm-born children with ADHD, compared to term-born controls and preterm-born participants without ADHD. Overall, research investigating preterm-born individuals on neurophysiological measures that sensitively capture ADHD-control differences is scarce.

In addition to the insight about the underlying processes that can be obtained from ERP and SC data, another informative method that has been successfully applied in ADHD research is within-task manipulations, whereby we investigate whether a specific cognitive impairment is a stable characteristic or improves under certain conditions. While increased RTV – the fluctuating speed of responding on reaction time tasks – is phenotypically and genetically strongly associated with ADHD (Kofler et al. 2013; Kuntsi et al. 2012; Kuntsi et al. 2010) it can improve in individuals with ADHD under certain conditions. A meta-analysis, whilst including a range of designs, demonstrated a small, though overall significant, effect of incentives on RTV (Kofler et al. 2013). In a four-choice reaction time task, the Fast Task, we have previously combined the effects of rewards with a faster event rate to maximise reduction of RTV, demonstrating that RTV improves significantly more in participants with ADHD than in controls (Andreou et al., 2007; Kuntsi et al., 2013). Recently, we have further measured EEG and SC simultaneously, while participants have performed the Fast Task. We found that, in the baseline (slow, unrewarded) condition, the ADHD group had impaired attentional allocation (P3 amplitude) (Cheung et al. under review) and hypo-arousal (decreased skin conductance level, SCL) (James et al. in press). In the fast-incentive condition participants with

ADHD improved both their P3 amplitude and SCL, more than the controls, but they now differed from controls on response preparation (CNV amplitude) (Cheung et al. under review; James et al. in press). These results show that although attentional allocation and hypo-arousal improved, the individuals with ADHD were not able to adjust their response preparation adequately in a changed context.

Given the informative, ADHD-sensitive findings that have emerged across the two conditions of the Fast Task when combining cognitive performance (MRT, RTV), ERP (CNV amplitude, P3 amplitude) and skin conductance (SCL) measures, we now compare the data from the term-born ADHD and control samples to new data on identical Fast Task measures obtained from preterm-born individuals. We aim to establish, first, whether preterm-born individuals show identical cognitive-neurophysiological impairments to those observed in term-born individuals with ADHD. Second, we investigate whether any additional impairments are observed in the preterm group, compared to the term-born control group. Third, for any impairments observed in the preterm group, we will examine their association with ADHD symptoms and clinical impairment.

4.3 Methods

4.3.1 Sample

The sample consisted of 186 preterm-born participants (41 sibling pairs, 104 singletons), 69 ADHD participants (4 sibling pairs, 61 singletons) and 135 controls (61 sibling pairs, 13 singletons). As previously reported (Rommel et al., under review), the groups differed significantly in terms of age, IQ, gender distribution, gestational age (GA) and ADHD symptom scores (replicated from Rommel et al. under review in Table 4.1). The ADHD group showed significantly higher ADHD symptoms and functional impairment than both the preterm ($t=-16.55$, $df=178$, $p<0.01$, $d=2.53$; $t=-17.23$, $df=178$, $p<0.01$, $d=2.94$ respectively) and control groups ($t=20.06$, $df=134$, $p<0.01$, $d=3.74$; $t=19.70$, $df=134$, $p<0.01$, $d=3.72$ respectively). The preterm group further demonstrated significantly higher ADHD symptoms and functional impairment than the control group ($t=4.71$, $df=213$, $p<0.01$, $d=0.53$; $t=3.83$, $df=213$, $p<0.01$,

d=0.45 respectively). While only 4% of the preterm participants were treated with stimulant medication, 47% of the ADHD participants were treated with stimulant medication at the time of the assessment. A 48-hour ADHD medication-free period was required prior to assessments. Written informed consent was obtained following procedures approved by the London-Surrey Borders Research Ethics Committee (09/H0806/58) and the National Research Ethics Service Committee London - Bromley (13/LO/0068).

The preterm group was recruited from secondary schools in Southeast England. All preterm participants had one full sibling available for ascertainment, and were born before 37 weeks' gestation. Siblings of preterm-born individuals were included in the preterm group if they were also born preterm (before 37 weeks' gestation) to maximise the number of participants in the preterm group. Term-born siblings of preterm-born individuals were not included in this analysis. Most preterm-born participants were of European Caucasian decent (84.6%). The other ethnicities represented were British Asian (3.7%), Mixed-White and Black Caribbean (2.1%), Mixed-White and British Asian (1.6%), Indian (1.1%), Mixed-White and Indian (1.1%), Black Caribbean (0.5%), Mixed-Black and British Asian (0.5%) and Other (2.7%). Seven individuals from the preterm sample were excluded because medical birth records could not corroborate GA or preterm status ≥37 weeks). One individual was excluded because of IQ<70. Eight preterm-born individuals met diagnostic criteria for a research diagnosis of ADHD. Since here preterm birth is investigated as a potential risk factor for ADHD, preterm-born individuals who demonstrated high levels of ADHD symptoms were not excluded from the analysis (for an analysis without preterm-born individuals who met a research diagnosis for ADHD, see Supplementary Material 4.1).

ADHD and control sibling pairs, who had taken part in our previous research (Chen et al., 2008; Kuntsi et al., 2010), were invited to take part in a follow-up study (Cheung et al., 2016). All participants were of European Caucasian decent and had one full sibling available for ascertainment. Participants with ADHD and their siblings were included in the ADHD group if they had a clinical diagnosis of DSM-IV combined-type ADHD during childhood and met DSM-IV criteria for any ADHD subtype at follow-up. Siblings of individuals with ADHD who did not meet DSM-IV criteria for any ADHD subtype at follow-up were not included in this analysis.

The control group was initially recruited from primary (ages 6–11 years) and secondary (ages 12–18 years) schools in the UK, aiming for an age and sex-match with the ADHD sample. Control individuals and their siblings were included in the control group if they did not meet DSM-IV criteria for any ADHD subtype either in childhood or at follow-up.

Exclusion criteria for all groups were IQ<70, cerebral palsy or any other medical conditions that affects motor co-ordination including epilepsy, as well as brain disorders and any genetic or medical disorder that might mimic ADHD. In addition, preterm birth was an exclusion criterion in the ADHD and control groups, because this study aimed to establish whether the cognitive impairments associated with preterm birth reflect identical neurophysiological impairments in term-born individuals with ADHD.

We followed up the sample on average 5.8 years (SD=1.1) after initial assessments. The ADHD and control groups were previously included in a study investigating ADHD case-control differences on cognitive and neurophysiological markers of ADHD in the Fast Task (Cheung et al., under review). While ADHD-control differences for this sample have been reported previously, here a subsample of term-born ADHD and control groups are compared to an additional group of preterm-born individuals.

At follow-up, six participants from the ADHD-sibling pair sample were excluded from the group analyses because of missing parent ratings of clinical impairment. Therefore, their current ADHD status could not be determined. Two additional participants from the ADHD-sibling pair sample were excluded because of drowsiness during the cognitive task session. Two participants with childhood ADHD, who did not meet ADHD symptom criteria but met clinical levels of impairment at follow-up, were excluded to minimize heterogeneity in the ADHD sample. In addition to these exclusions, which are identical to our previous analysis (Cheung et al., 2016), we also excluded six participants from the ADHD-sibling pair sample, who were born preterm, as well as 12 individuals from the ADHD-sibling pair sample, who provided no information on GA.

Six control participants were removed from the analyses for meeting DSM-IV ADHD criteria based on the parent-rated Barkley Informant Rating Scale (Barkley & Murphy, 2006). In addition to these exclusions, which are identical to our previous analysis (Cheung et al., 2016), we also excluded 37 participants from the control-sibling pair sample because no GA information was available.

4.3.2 Procedure

The Fast Task was administered as part of a longer assessment session at the research centre. For those prescribed stimulants, a 48-hour ADHD medication-free period was required. Participants abstained from caffeine, smoking and alcohol on the day of testing. Face-to-face or telephone clinical interviews were administered to the parent of each ADHD proband shortly before or after the participant's assessment.

4.3.3 Measures

4.3.3.1 The Diagnostic Interview for ADHD in adults (DIVA)

The Diagnostic Interview for ADHD in Adults (DIVA) (Kooij & Francken, 2007) is a semi-structured interview designed to evaluate the DSM-IV criteria for both adult and childhood ADHD symptoms and impairment. It consists of 18 items used to define the DSM-IV symptom criteria for ADHD. Each item is scored affirmatively if the behavioural symptom was present *often* within the past six months.

4.3.3.2 The Barkley Functional Impairment Scale (BFIS)

The Barkley's functional impairment scale (BFIS) (Barkley & Murphy, 2006) is a 10-item scale used to assess the levels of functional impairments commonly associated with ADHD symptoms in five areas of everyday life: family/relationship; work/education; social interaction; leisure activities; and management of daily responsibilities. Each item ranged from 0 (never or rarely) to 3 (very often).

In the preterm and ADHD groups, ADHD was assessed using parental ADHD symptom ratings on the DIVA and the BFIS for all participants, for consistency. If participants were usually on stimulant medication, parents were instructed to consider their children's ADHD symptoms off medication. A research diagnosis of ADHD was made if participants scored six or more on either the inattention or hyperactivity-impulsivity subscales of the DIVA and if they received two or more positive scores on two or more areas of impairment on the BFIS. In the control group, ADHD was assessed using parental ADHD symptom ratings on the BFIS for all participants, for consistency. Control participants were excluded from the analysis if they received two or more positive scores on two or more areas of impairment on the BFIS.

4.3.3.3 IQ

The vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence Fourth Edition (WASI-IV) (Wechsler 1999) were administered to all participants to derive estimates of IQ.

4.3.3.4 The Fast Task (Andreou et al. 2007, Kuntsi et al 2006)

The slow-unrewarded (baseline) condition consists of 72 trials, which followed a standard warned four-choice RT task. Four empty circles (warning signals, arranged horizontally) first appeared for 8 s, after which one of them (the target) was coloured in. Participants were asked to press the response key that directly corresponded to the position of the target stimulus. Following a response, the stimuli disappeared from the screen and a fixed inter-trial interval of 2.5 s followed. Speed and accuracy were emphasized equally in the task instructions. If the child did not respond within 10 s, the trial terminated. A comparison condition of 80 trials with a fast event rate (fore-period of 1 s) and incentives followed the baseline condition (Andreou et al., 2007). The fast-incentive condition is always administered after the baseline condition. Cognitive-performance measures obtained from the Fast Task include MRT (mean latency of response after target onset in milliseconds), RTV (standard deviation of target reaction time) from correct trials. Due to the longer fore-period in the slow condition, the two conditions were not matched on task length, but were matched on the number of trials. We analysed cognitive-neurophysiological performance on both the full slow

condition and between 3 4-minute length-matched segments (results are available upon request) (Andreou et al., 2007).

4.3.3.5 EEG recording and preprocessing

The EEG was recorded from 62 channels DC-coupled recording system (extended 10–20 montage), with a 500 Hz sampling rate, impedances kept under 10 kO, and FCz as the recording reference electrode. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi.

The EEG data were analysed using Brain Vision Analyzer (2.0) (Brain Products, Germany). After down-sampling the data to 256 Hz, the EEG data were re-referenced to the average and filtered offline with digital band-pass (0.1 to 30 Hz, 24 dB/oct) Butterworth filters. Ocular artifacts were identified from the data using Independent Component Analysis (ICA, (Jung et al., 2000)). The extracted independent components were manually inspected and ocular artefacts were removed by back-projection of all but those components. All ERP averages contained at least 20 artefact-free segments. Data with other artifacts exceeding ± 100µV in any channel were rejected. P3 amplitude was analysed as the area amplitude measure (µV*ms) at Pz between 250 and 450ms, to reduce bias due to the varying noise levels induced by the different task conditions (Luck, 2005). For the P3 analyses, all the accepted trials were baseline-corrected using a pre-stimulus baseline of 200ms. The mean amplitudes of this pre-target period (-200ms - 0ms, using a technical zero baseline as in previous CNV work (Albrecht et al., 2013, Banaschewski et al., 2003)) at Cz were also analysed separately as a CNV measure. This short interval not only corresponded to the P3 baseline, but also captured the short CNV in the fast-incentive condition with its one-second cue – target interval (Cheung et al., under review) (Figures 1c & 1d).

4.3.3.6 Skin conductance

SC data were measured by attaching a pair of reusable 8mm diameter silver-silver chloride electrodes on the thenar eminence and hypothenar eminence of participant's non-dominant

hand at the start of the testing session. A non-saline gel was used to increase impedance and help establish an electrical signal. A constant imperceptible voltage (0.5 V) was applied. SC was recorded using PSYCHLAB SC5 24 bit equipment system, which has an absolute accuracy of +/- 0.1 microsiemens (μS) (PSYCHLAB, UK). The SC5 was connected to a computer to run the PSYCHLAB software, where data were monitored and recorded in real time. Stimulus onset and participant response events were recorded on a common timeline, which enabled SC activity to be stimulus-locked.

SC data values were calculated using a skin conductance system which is based on a SC sigmoid-exponential model that allows the tonic measure of SC level (SCL) to be disentangled from phasic, stimulus-associated, SC responses (SCR), and further allows the decomposition of overlapping SCRs (Boucsein, 1992; Figner & Murphy, 2011; Lim et al., 1997; Williams et al., 2001). This system, therefore, is appropriate to use in conditions with long and short inter-stimulus-intervals (Williams et al., 2000). The statistical model was applied to each condition, as a whole. Means of SC variables (SCL) were calculated per participant, across each condition.

4.3.4 Statistical analyses

Sixteen preterm-born participants (8%) and five term-born participants with ADHD (7%) were excluded from the ERP analysis for CNV amplitude and P3 amplitude due to having fewer than 20 acceptable segments available as required for averaging of EEG data, but they were included in analyses for other variables. Nine participants from the preterm group (4%), four participants from the term-born ADHD group (5%) and sixteen participants from the term-born control group (11.1%) were excluded from the SC analysis due to missing data, but they were included in analyses for other variables. MRT, RTV and SCL data were skewed and transformed using the optimized minimal skew (lnskew0) command in Stata version 11.1 (Stata Corporation, College Station, TX).

Regression-based corrections for age were applied to raw scores and residual scores were analysed. All analyses controlled for gender. In addition, we reran all analyses on a carefully

age-matched subsample (aged between 14 and 19 years) due to significant group mean differences in age and the possibility of age effects on ERP measures (Supplementary Material 4.2). All analyses were re-run with IQ as an additional covariate (Supplementary Material 4.3). Data were analysed using random intercept models in Stata, to control for non-independence of the data (i.e. data coming from siblings of one family), using a 'robust cluster' command to estimate standard errors (Tye et al., 2012; Wood et al., 2009). We first computed the main effects of group (preterm group vs term-born ADHD group vs term-born control group), condition (baseline vs fast-incentive) and group-by-condition interactions for all measures. Post-hoc analyses were then conducted to investigate the differences between groups. Means and standard deviations of measures in the baseline and fast-incentive condition are reported in Table 4.2. By controlling for differences in the baseline condition, we were additionally able to investigate if groups differed in the slope from the baseline to fast-incentive condition, indexing the degree of change. Means and confidence intervals of the slope are reported in Table 3. Effect sizes (Cohen's d), which were calculated using the difference in the means divided by the pooled standard deviation (Cohen, 1988), are reported. According to Cohen (1988), d=0.20 constitutes a small effect, d=0.50 a medium effect and d=0.80 a large effect. To investigate if the impairments observed in the preterm group are related to ADHD symptoms and clinical impairment, Pearson correlations were calculated between the age-regressed cognitive-neurophysiological measures showing impairment in the preterm group and ADHD symptom scores and ADHD-related impairment. Sex was used as a covariate. Correlations were run for impairments observed in the baseline condition, fast-incentive condition, and the slope from the baseline to fast-incentive condition. If impairments were observed in both the baseline and fast-incentive condition for the same variable, correlations were run using the baseline condition only - which is more sensitive to ADHD (J Kuntsi et al., 2013), in order to reduce the number of statistical comparisons.

4.4 Results

While all the results for comparisons involving the preterm group are new and the focus here, we also report the statistics from the term-born ADHD-control comparisons (previously

reported for the full sample in Cheung et al. under review, James et al. in press, for RTV, P3 amplitude, CNV amplitude and SCL), for completeness. As described above, we had to exclude 18 participants from the ADHD group and 37 participants from the control group for the present analyses due to prematurity or unknown GA.

4.4.1 Cognitive performance measures

For MRT data (Figure 4.1A), a random intercept model indicated a significant main effect of condition ($z=-31.04$, $p<0.01$) and a main effect of group ($z=1.98$, $p<0.05$), but no significant group-by-condition interaction ($z=-1.06$, $p=0.29$). Post-hoc analyses revealed that, in the baseline condition, the preterm group showed significantly decreased MRT compared to the term-born ADHD group ($t=-3.78$, $p<0.01$, $d=0.34$), but significantly increased MRT compared to the term-born control group ($t=1.98$, $p<0.05$, $d=0.30$) (Table 4.2). In the fast-incentive condition, the preterm group showed significantly decreased MRT compared to the term-born ADHD group ($t=-2.71$, $p<0.05$, $d=0.46$), but significantly increased MRT compared to the term-born control group ($t=2.80$, $p<0.05$, $d=0.35$). The term-born ADHD group showed significantly greater MRT compared to the term-born control group in both the baseline ($t=3.52$, $p<0.01$, $d=0.94$) and fast-incentive ($t=3.05$, $p<0.01$, $d=0.89$) conditions. The within-group difference in MRT from the baseline to fast-incentive condition was significant in the preterm group ($t=-13.53$, $p<0.01$), the term-born ADHD group ($t=-11.75$, $p<0.01$) and the term-born control group ($t=-16.18$, $p<0.01$). Post-hoc tests showed that the slope in MRT, indexing the extent of change from the baseline to fast-incentive condition, in the preterm group was not significantly different compared to the term-born ADHD group ($p=-1.37$, $p=0.17$), but was significantly greater compared to the term-born control group ($t=-1.78$, $p<0.05$) (Table 4.3). The slope in MRT was significantly greater in the term-born ADHD group ($t=-2.90$, $p<0.01$) than the term-born control group.

For RTV data (Figure 4.1B), a random intercept model indicated a significant main effect of condition ($z=-13.40$, $p<0.01$), a main effect of group ($z=3.40$, $p<0.01$) and a significant group-by-condition interaction ($z=-2.05$, $p<0.05$). Post-hoc analyses revealed that, in the baseline condition, the preterm group showed significantly decreased RTV compared to the term-born

ADHD group (t=-2.05, p<0.05, d=0.22), but significantly increased RTV compared to the term-born control group (t=3.68, p<0.01, d=0.46) (Table 4.2). In the fast-incentive condition, the preterm group did not differ in RTV compared to the term-born ADHD group (t=-1.36, p=0.18, d=0.14), but showed significantly increased RTV compared to the term-born control group (t=5.38, p<0.01, d=0.64). The term-born ADHD group showed significantly greater RTV compared to the term-born control group in the baseline (t=3.42, p<0.01, d=1.03) and fast-incentive (t=2.58, p<0.01, d=0.74) conditions. The within-group difference in RTV from the baseline to fast-incentive condition was significant in the preterm group (t=-6.01, p<0.01), the term-born ADHD group (t=-6.23, p<0.01) and the term-born control group (t=-11.06, p<0.01). The slope in RTV in the preterm group was, at a trend level of significance, less steep compared to the term-born ADHD group (t=-1.82, p=0.07), but was significantly greater than in the term-born control group (t=2.52, p<0.05) (Table 4.3). The slope in RTV was significantly greater in the term-born ADHD group compared to the term-born control group (t=-2.89, p<0.01).

4.4.2 ERP measures

For CNV amplitude (Figure 4.1C), a random intercept model indicated a significant main effect of condition (z=-16.61, p<0.01), a significant main effect of group (z=3.47, p<0.01) and a significant group-by-condition interaction (z=9.19, p<0.01). Post-hoc analyses revealed no group differences in the baseline condition between the preterm group and the term-born ADHD group (t=-1.48, p=0.14, d=0.02) between the preterm group and the term-born control group (t=-0.83, p=0.41, d=0.11) and between the term-born ADHD group and the term-born control group (t=1.24, p=0.22, d=0.10) (Table 4.2, Figure 4.2A). In the fast-incentive condition, the preterm group was not significantly different compared to the term-born ADHD group (t=0.98, p=0.33, d=-0.16), but the preterm group had a significantly reduced CNV amplitude compared to the term-born control group (t=5.89, p<0.01, d=-0.85) (Table 4.2, Figure 4.2C). The term-born ADHD group showed significantly reduced CNV amplitude compared to the term-born control group in the fast-incentive condition (t=4.10, p<0.01, d=0.67). The within-group difference in CNV amplitude from the baseline to fast-incentive condition was significant in the preterm group (t=-5.59, p<0.01), term-born ADHD (t=-6.98, p<0.01) and

term-born control (t=-10.55, p<0.01) groups. The slope in CNV amplitude in the preterm group, from the baseline to fast-incentive condition, was significantly less steep compared both to the term-born ADHD (t=-2.54, p<0.01) and control (t=-7.52, p<0.01) groups (Table 4.3). Compared to the term-born control group, the CNV slope was significantly less steep in the term-born ADHD group (t=-3.12, p<0.01).

For P3 amplitude (Figure 4.1D), a random intercept model indicated a significant main effect of condition (z=2.01, p<0.05), a main effect of group (z=-3.43, p<0.01) and a significant group-by-condition interaction emerged (z=-5.46, p<0.01). Post-hoc analyses revealed that, in the baseline condition, the preterm group was not significantly different compared to either the term-born ADHD (t=-0.34, p=0.73, d=0.02) or control (t=-0.74, p=0.46, d=0.14) group. The term-born ADHD group showed significantly decreased P3 amplitude compared to the term-born control group in the baseline condition (t=2.62, p<0.01, d=0.64) (Table 4.2, Figure 4.2B). In the fast-incentive condition, the preterm group showed significantly decreased P3 amplitude compared both to the term-born ADHD (t=-3.04, p<0.01, d=0.44) and term-born control (t=-5.26, p<0.01, d=0.69) groups (Table 4.2, Figure 4.2D). P3 amplitude in the fast-incentive condition did not differ between the term-born ADHD and term-born control groups (t=1.61, p=0.14, d=0.17). The within-group difference in P3 amplitude from the baseline to fast-incentive condition was not significant in the preterm group (t=-1.57, p=0.16), but was significant in the term-born ADHD (t=-3.96, p<0.01) and term-born control (t=-6.44, p<0.01) groups. The slope in P3 amplitude in the preterm group was less steep compared to both the term-born ADHD (p=2.72, p<0.01) and term-born control (t=4.05, p<0.01) groups (Table 4.3). The slope in P3 amplitude did not differ between the term-born ADHD group compared to the term-born control group (t=-0.41, p=0.68).

4.4.3 SC measures

For SCL (Figure 4.1E), a random intercept model indicated a significant main effect of condition (z=-5.74, p<0.01), but no main effect of group (z=0.02, p=0.99), and a trend towards a group-by-condition interaction (z=-1.68, p=0.09). Post-hoc analyses revealed that, in the baseline condition, the preterm group showed significantly increased SCL compared to the

term-born ADHD group (t=4.01, p<0.01, d=0.49), but did not differ from the term-born control group (t=0.30, p=0.76, d=0.04) (Table 4.2). In the fast-incentive condition, the preterm group was not significantly different compared to the term-born ADHD group (t=-0.10, p=0.91, d=0.04) or compared to the term-born control group (t=-1.02, p=0.31, d=0.15). The term-born ADHD group showed significantly decreased SCL compared to the term-born control group in the baseline condition (t=-4.55, p<0.01, d=0.73), but not in the fast-incentive condition (t=0.91, p=0.36, d=0.15). The within-group difference in SCL from the baseline to fast-incentive condition was not significant in the preterm group (t=0.83, p=0.41), but was significant in the term-born ADHD (t=9.29, p<0.01) and term-born control (t=4.85, p<0.01) groups. The slope in SCL in the preterm group was less steep compared to both the term-born ADHD (p=2.62, p<0.01) and term-born control (t=-1.89, p<0.05) groups (Table 4.3). The slope in SCL was significantly steeper in the term-born ADHD group compared to the term-born control group (t=2.60, p<0.05).

Excluding the eight preterm-born individuals meeting diagnostic criteria for a research diagnosis of ADHD (Supplementary Material 4.1), using an age-match subsample (Supplementary Material 4.2) or re-running the analysis with IQ as a covariate (Supplementary Material 4.3), did not change the significance of the results.

4.4.4 Associations with the continuums of ADHD symptoms and impairments

Correlations were run in the preterm group (n=186) to investigate if the cognitive-neurophysiological differences observed in the preterm group, compared to term-born controls, are related to ADHD symptoms and ADHD-related clinical impairments. In order to reduce the number of statistical comparisons, correlations were run using the baseline condition only - which is more sensitive to ADHD (J Kuntsi et al., 2013) – if impairments were observed in both the baseline and fast-incentive condition for the same variable. In the preterm group, baseline performance of MRT and RTV, and the slope of MRT and RTV, were significantly correlated with ADHD symptoms and ADHD impairment (Table 4.4). CNV amplitude in the fast-incentive condition was correlated with ADHD symptoms and ADHD impairment, but the correlation with the slope in CNV amplitude did not reach significance

(Table 4.4). P3 amplitude in the fast-incentive condition, the slope in P3 amplitude, and the slope in SCL, were not significantly correlated with ADHD symptoms or ADHD impairment (Table 4.4).

Table 4.1. Descriptive statistics. This information has already been reported (Rommel et al. under review), but for ease of comparison, results have been replicated here.

	Preterm	ADHD	Control	Statistic	df	p-value
	n=186	n=69	n=135	-	-	-
GA in weeks (SD)	33.0 (3.0)	39.9 (1.4)	39.9 (1.3)	t=-23.0	253	<0.01
IQ (SD)	104.7 (12.3)	97.7 (13.8)	110.4 (12.2)	t=-3.2	253	0.02
Age (SD)	14.9 (1.9)	18.5 (3.0)	17.8 (2.1)	t=-12.0	253	<0.01
Age range	11.0-20.0	12.7-25.9	11.9-21.6	-	-	-
Males %	54.3	88.4	75.6	t=4.61	253	<0.01
Conners parent-rated ADHD symptom score (SD)	11.2 (9.4)	35.8 (10.6)	7.0 (5.6)	t=1.97	253	0.05
BFIS score (SD)	3.7 (4.1)	16.4 (5.4)	2.1 (2.5)	t=-2.23	253	0.03

Note: ADHD=attention-deficit/ hyperactivity disorder; GA=gestational age; SD=standard deviation, BFIS= Barkley Functional Impairment Scale.

Table 4.2. Cognitive and neurophysiological measures from the baseline and fast-incentive conditions of the Fast Task: means, standard deviation (SDs) and effect sizes (Cohen's d) for the preterm, ADHD and control groups.

Variables	Condition	Preterm (n=186)				ADHD (n=69)				Control (n=135)				Cohen's d effect size		
		Mean		SD		Mean		SD		Mean		SD		a	b	c
MRT	Baseline	594.5	(68.3)	166.3	(163.5)	616.8	(120.3)	119.1	(116.2)	530.1	(27.1)	94.0	(91.1)	0.34**	-0.94**	-0.30*
	Fast-incentive	466.8	(-59.4)	95.7	(93.1)	475.2	(-21.2)	95.3	(100.3)	415.7	(-87.3)	55.5	(56.8)	0.46*	-0.89**	-0.35**
RTV	Baseline	161.7	(43.3)	143.2	(142.3)	175.9	(72.9)	110.4	(111.0)	98.3	(-8.0)	55.9	(55.0)	0.22	-1.03**	-0.46**
	Fast-incentive	97.6	(-20.7)	57.7	(57.3)	92.2	(-10.8)	80.4	(84.2)	57.1	(-49.3)	22.4	(22.9)	0.14	-0.74**	-0.64**
CNV (CZ)	Baseline	0.0	(0.7)	1.1	(1.16)	0.0	(1.0)	1.6	(1.6)	-0.1	(0.9)	1.3	(1.3)	0.02	0.10	0.11
	Fast-incentive	-1.0	(-0.2)	1.8	(1.8)	-1.6	(-0.5)	1.9	(1.8)	-2.9	(-1.9)	2.2	(2.2)	-0.16	0.67*	-0.85*
P3 (PZ)	Baseline	1038.9	(-86.8)	954.1	(105.1)	1017.5	(-68.0)	567.3	(67.0)	1190.1	(63.6)	627.8	(53.2)	0.02	0.64*	0.14
	Fast-incentive	912.5	(-213.3)	1001.2	(73.4)	1379.8	(242.0)	601.7	(71.4)	1455.4	(359.7)	630.0	(53.7)	0.44*	0.17	0.69*
SCL	Baseline	4.9	(-0.1)	3.9	(3.8)	2.8	(-1.7)	1.6	(1.6)	4.4	(-0.2)	2.2	(2.2)	-0.49*	0.73*	-0.04
	Fast-incentive	5.3	(0.2)	4.2	(4.2)	4.9	(0.3)	2.1	(2.1)	5.5	(0.8)	3.1	(3.0)	0.04	0.15	0.15

Note: Values represent raw scores. Regression-based corrections in parentheses. Whilst comparisons between ADHD and control participants in the full sample have already been presented for RTV, CNV, P3 and SCL (Cheung et al. under review, James et al. in press), for ease of comparison, results specific to this analysis (ADHD and control term-born subsample) have been replicated here with the additional preterm group. *p<0.05, **p<0.01; a=ADHD vs Preterm: b=ADHD vs Control: c=Preterm vs Control; ERP=event related potential; ADHD=attention-deficit/ hyperactivity disorder; MRT=mean reaction time in milliseconds; RTV=reaction time variability in milliseconds; CNV=contingent negative variation; SCL=skin conductance level.

Table 4.3. Means and post-hoc group tests in the slope generated from plotting the baseline and fast-incentive condition of cognitive performance, ERP and skin conductance measures. 95% confidence intervals are indicated in brackets.

	Means and 95% confidence intervals (CI)			**Post-hoc group comparisons**					
	Preterm (n=186)	**ADHD (n=69)**	**Controls (n=135)**	**a**		**b**		**c**	
	Mean (CI)	Mean (CI)	Mean (CI)	t	p	t	p	t	p
MRT slope	-125.95	-143.24	-114.21	-1.37	0.17	-2.90	<0.01	-1.78	0.04
	(-137.75,-114.14)	(-161.49,-124.99)	(-122.62,-105.78)						
RTV slope	-62.47	-85.54	-41.15	-1.82	0.07	-2.89	<0.01	-2.52	<0.01
	(-75.89,-49.05)	(-104.67,-66.41)	(-46.26,-36.05)						
CNV slope (Cz)	-0.95	-1.58	-2.92	-2.54	<0.01	-3.12	<0.01	-7.52	<0.01
	(-1.19,-0.70)	(-1.96,-1.21)	(-3.25,-2.59)						
P3 slope (Pz)	-135.34	253.58	327.77	2.72	<0.01	0.41	0.68	4.05	<0.01
	(-266.17,-4.52)	(150.97,356.20)	(249.76,405.78)						
SCL slope	0.41	2.18	1.07	2.62	<0.01	2.60	<0.01	1.89	0.04
	(-0.23,1.05)	(1.87,2.48)	(0.76,1.38)						

Note: Mean values represent slope values from regression-based corrections. Whilst comparisons between ADHD and control participants in the full sample have already been presented for RTV, CNV, P3 and SCL (Cheung et al. under review, James et al. in press), for ease of comparison, results specific to this analysis (ADHD and control term-born subsample) have been replicated here with the additional preterm group. a=ADHD vs Preterm: b=ADHD vs Control: c=Preterm vs Control; ERP=event related potential; ADHD=attention-deficit/ hyperactivity disorder; MRT=mean reaction time in milliseconds; RTV=reaction time variability in milliseconds; CNV=contingent negative variation; SCL=skin conductance level.

Table 4.4. Pearson correlations (two-tailed) between cognitive-neurophysiological impairments observed in the preterm group with interview-based ADHD symptoms and clinical impairment, within the preterm group only (n=186).

	ADHD symptoms		Impairment	
	r	p	r	p
MRT Baseline	0.23	<0.01	0.19	<0.01
RTV Baseline	0.24	<0.01	0.20	<0.01
CNV Fast-incentive	0.15	0.04	0.13	0.05
CNV slope	0.08	0.28	0.06	0.41
P3 Fast-incentive	-0.10	0.17	-0.09	0.17
P3 slope	-0.06	0.41	-0.12	0.10
SCL slope	-0.08	0.22	-0.11	0.14

Note: In order to reduce the number of statistical comparisons, correlations were run using the baseline condition only - which is more sensitive to ADHD – if impairments were observed in both the baseline and fast-incentive condition for the same variable. Baseline=Baseline condition; Fast-incentive=Fast incentive condition; slope=the slope generated from plotting performance from the baseline to fast-incentive condition. ADHD=attention-deficit/ hyperactivity disorder; DIVA=Diagnostic Interview for ADHD in Adults; MRT=mean reaction time in milliseconds; RTV=reaction time variability in milliseconds; CNV=contingent negative variation amplitude at Cz; P3=P3 amplitude at Pz; SCL=skin conductance level.

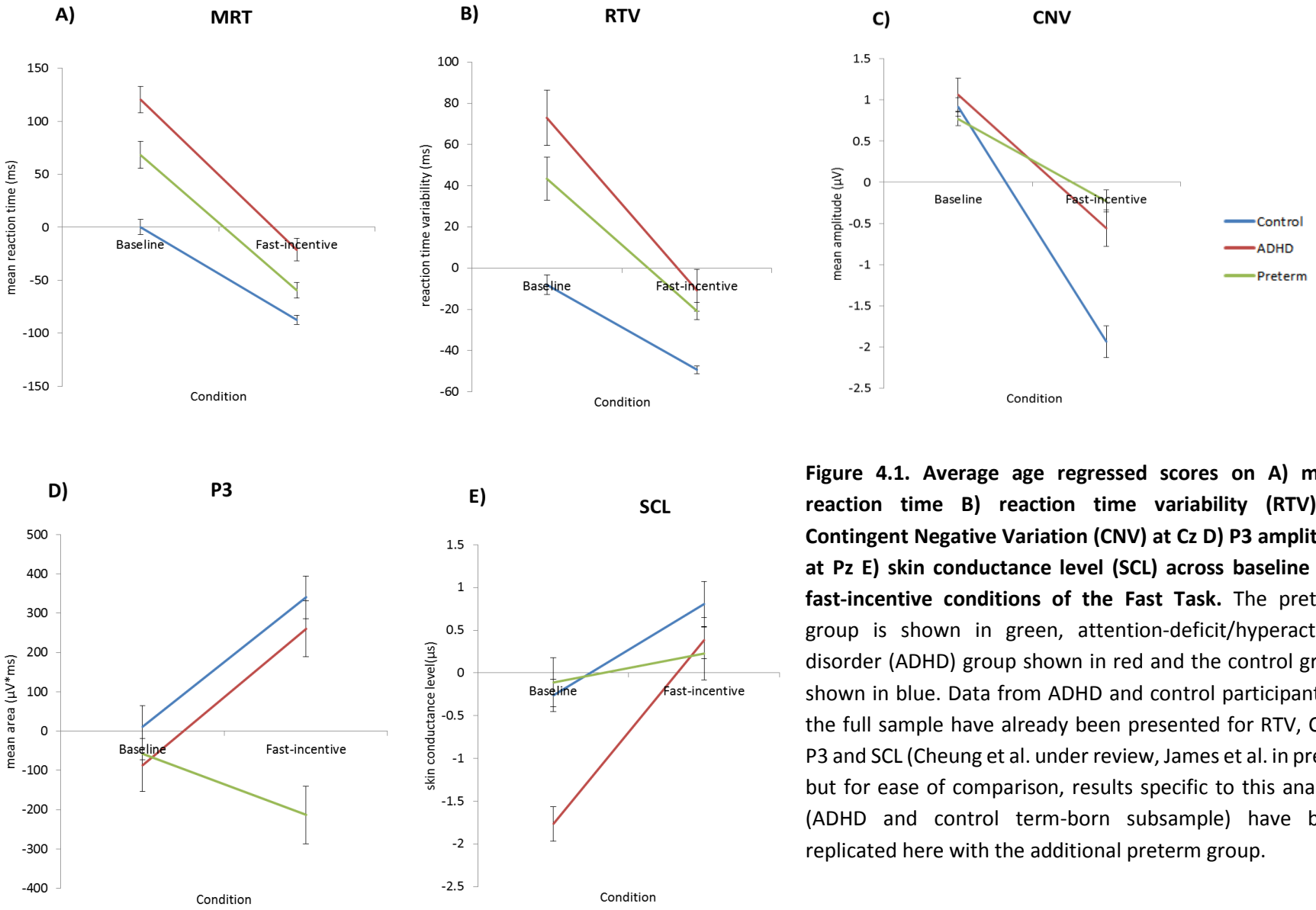
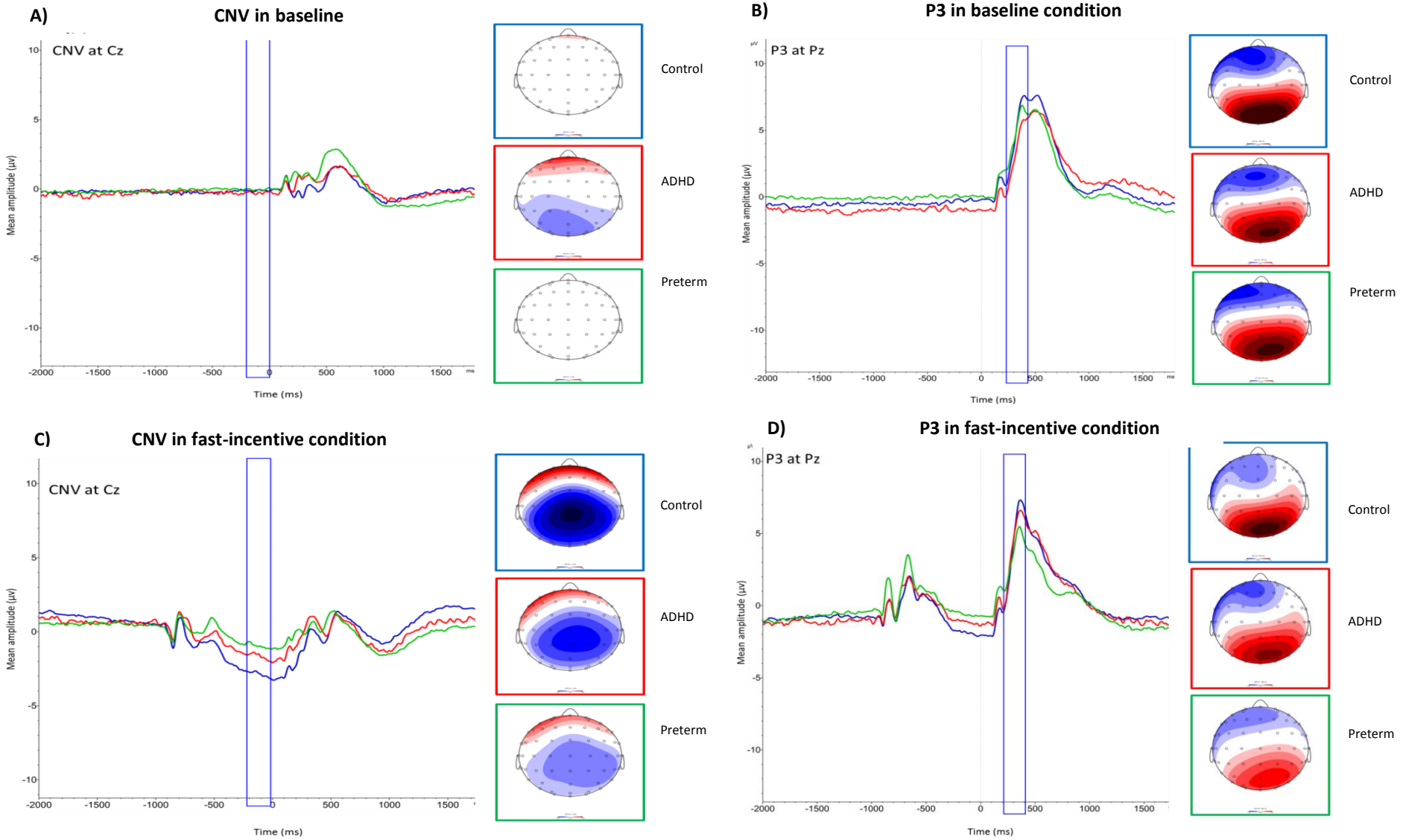


Figure 4.1. Average age regressed scores on A) mean reaction time B) reaction time variability (RTV) C) Contingent Negative Variation (CNV) at Cz D) P3 amplitude at Pz E) skin conductance level (SCL) across baseline and fast-incentive conditions of the Fast Task. The preterm group is shown in green, attention-deficit/hyperactivity disorder (ADHD) group shown in red and the control group shown in blue. Data from ADHD and control participants in the full sample have already been presented for RTV, CNV, P3 and SCL (Cheung et al. under review, James et al. in press), but for ease of comparison, results specific to this analysis (ADHD and control term-born subsample) have been replicated here with the additional preterm group.

Figure 4.2. Grand averages in the preterm, ADHD and control groups for stimulus-locked ERPs of the CNV at Cz electrode between -200-0 ms (shown on the left), and of the P3 at Pz electrode between 250-450 ms (shown on the right), in both the baseline (A & B) and fast-incentive conditions (C & D) of the Fast Task. The preterm group is shown in green, term born attention-deficit/hyperactivity disorder (ADHD) group shown in red and the term born control group shown in blue. Data from ADHD and control participants in the full sample have already been presented for RTV, CNV, P3 and SCL (Cheung et al. under review, James et al. in press), but for ease of comparison, results specific to this analysis (ADHD and control term-born subsample) have been replicated here with the additional preterm group.



4.5 Discussion

In a detailed analysis of cognitive-neurophysiological processes during reaction time performance under baseline and fast-incentive conditions, we provide evidence, first, for ADHD-like impairments in individuals born preterm in speed and variability of reaction times (MRT and RTV in baseline condition) and in response preparation (CNV in fast-incentive condition). These findings from group comparisons were further confirmed by within-group analyses that showed how each of these impairments correlated with the continuum of ADHD symptoms (and impairments) in individuals born preterm. Second, the adolescents born preterm did not show ADHD-like impairments in the ERP index of attention allocation (P3) or skin conductance-measured arousal (SCL) in the baseline condition, but were unlike either the ADHD or control group in showing an unusual lack of malleability in P3 amplitude and SCL from baseline to fast-incentive condition. Within-group analyses confirmed how the P3 amplitude and SCL slopes, measuring malleability in attention allocation and arousal from the baseline to fast-incentive condition, did not correlate with ADHD symptoms (and impairments) in the individuals born preterm. Overall, we show how specific impairments in cognitive and brain function observed among preterm-born individuals relate to their increased ADHD symptoms, and show how their additional impairments are unrelated to ADHD symptoms.

Our finding that the ERP-index of response preparation (CNV) shows an ADHD-like impairment in adolescents born preterm replicates our previous CNV finding on the continuous performance task in the same sample (Rommel et al. under review). These observations are line with previous evidence of abnormalities in response preparation and attentional orienting in children born preterm (Hövel et al., 2014; Mikkola et al., 2007, 2010), and we now show how these impairments are linked to the increased ADHD symptoms in individuals born preterm. The further ADHD-like impairments we observed in the preterm-born group in the speed and variability of reaction times (MRT and RTV) were significantly milder among the preterm-born than in individuals with ADHD, although both groups significantly differed from controls. In our previous analysis on continuous performance task data on the same sample we did not observe

differences in MRT and RTV between the preterm and controls groups (Rommel et al. under review), suggesting that the milder MRT and RTV impairments in individuals born preterm may only be observed in tasks that show particularly strong impairments in individuals with ADHD. Increased MRT and RTV in preterm-born children have also been reported for a visual oddball task (Potgeiter et al. 2003), and an attention network test study reported increased lapses of attention (tau) in preterm-born individuals (de Kieviet et al. 2012). We now show how the increased MRT and RTV in individuals born preterm, like (attenuated) CNV, are related to their increased ADHD symptoms.

While the above findings point to specific ADHD-like impairments in cognition and brain function, our further findings on attention allocation (indexed P3) and peripheral arousal (SCL) indicate that preterm birth is associated with only some, and not all, impairments seen in ADHD, as well as with further unique impairments not associated with ADHD. The adolescents born preterm did not show the ADHD-like impairment in attention allocation (indexed by P3) and peripheral hypo-arousal (SCL) in the baseline condition. Yet subtle impairments in P3 amplitude and SCL were observed in the preterm group in the lack of adjustment and malleability from baseline to fast-incentive condition that are seen in the other groups. For response preparation (indexed by CNV), both preterm and ADHD groups showed reduced change between task conditions, compared to controls, but the lack of adjustment was significantly stronger for the preterm than term-born ADHD group. Overall, the reduced neurophysiological sensitivity to the effects of incentives and a faster event rate in the individuals born preterm is intriguing, calling for further investigation in future research.

A limitation of our study is the small sample of females in the ADHD group (n=8): whilst we controlled for gender, we could not directly examine sex differences between the groups. We were also unable to investigate whether risk factors for being born preterm (e.g. poverty, malnutrition) might account for the findings in our sample. We show, however, that the impairments are not due to IQ; controlling for IQ did not change the results.

In conclusion, our investigation of preterm-born adolescents indicates both impairments in cognition and brain function that are linked to increased ADHD symptoms as well as further, subtle impairments in lack of malleability in specific neurophysiological processes that are unrelated to ADHD symptoms. We show how such impairments in individuals born preterm extend to at least adolescence, even in a well-functioning sample recruited from mainstream schools. Future studies should extend these investigations into adulthood.

Chapter 5 - ARE COGNITIVE-NEUROPHYSIOLOGICAL IMPAIRMENTS AND INCREASED ADHD SYMPTOMS IN PRETERM-BORN ADOLESCENTS CONSISTENT WITH A CAUSAL INFERENCE?

5.1 Abstract

Background: Preterm birth is associated with an increased risk for specific cognitive-neurophysiological impairments and neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD). Whether the associations are causally related to the preterm birth or due to other risk factors that characterise families with preterm-born children, is largely unknown. We apply a sibling-comparison design to test if the associations of preterm-birth with the cognitive-neurophysiological impairments and increased ADHD symptoms hold in an adolescent sample when controlling for unmeasured familial confounding factors. **Method:** A within-sibling fixed effect model was applied between 104 preterm-born adolescents and their 104 term-born siblings. Siblings were compared on detailed cognitive, EEG and skin conductance measures previously associated with impairments in the preterm group in comparisons with unrelated controls. If within-sibling associations with preterm birth still hold, the results would be consistent with a causal inference. The effects of preterm birth were explored as a dichotomous (preterm or term) and continuous (gestational age) variable. **Results:** Preterm birth and earlier gestational age were significantly associated with increased ADHD symptoms and specific cognitive-neurophysiological impairments, such as IQ, preparation-vigilance measures (increased speed and variability of reaction times, response preparation (CNV)), performance monitoring measures (conflict monitoring (N2), conscious error processing (Pe)), and neurophysiological impairments in adjustment in a changed context (for CNV, attention allocation (P3) and peripheral hypo-arousal). There was no association between preterm birth or earlier gestational age with executive control measures of inhibition (NoGo-P3), working and short term memory (digit span forward and backward), congruent errors or automatic error processing (ERN). **Discussion:** The robust within-siblings associations between preterm birth and specific cognitive-neurophysiological impairments, including IQ, as well as with increased ADHD

symptoms, are consistent with a causal inference. The lack of an association between preterm birth and other cognitive-neurophysiological impairments indicates that familial risk factors associated with preterm birth, but not a causal effect of preterm birth as an environmental insult, underlie these previously observed associations. By distinguishing impairments that are consistent with a causal inference of preterm birth from those that are not, our results provide stepping stones towards better targeted interventions into those that are preterm-birth specific and those that address family-level risk factors.

5.2 Introduction

Preterm birth – born before 37 completed weeks of gestation – occurs in 8.6% of live births in developed countries (Blencowe et al., 2012). Whilst survival rates are improving, preterm birth is associated with many negative long-term outcomes (Bhutta et al., 2002; D'Onofrio et al., 2013; Goldenberg et al., 2008). Among such outcomes are an increased risk of academic difficulties (Moster et al., 2008), cognitive and neurophysiological impairments (Johnson et al. 2011; Lee et al. 2011; Johnson & Marlow 2011; Potgieter et al. 2003; Rommel et al. under review), and neurodevelopmental disorders (D'Onofrio et al., 2013), including a 2.64-fold increased risk for developing attention-deficit/hyperactivity disorder (ADHD) (Bhutta et al., 2002).

Whether the association of preterm birth with the negative outcomes is due to the preterm birth *per se* or to other environmental or genetic risk factors that characterise families with preterm-born children, is difficult to entangle in most previous studies, as preterm-born children have been compared to unrelated controls and, as such, the groups may have differed on unmeasured risk factors (Thapar & Rutter, 2009). Risks associated with preterm birth include low socio-economic status, low maternal educational status, low or high maternal age, black ethnicity, single marital status, family history of preterm birth, smoking and alcohol during pregnancy, pre-existing health problems in mother and maternal genetic risk (Goldenberg et al. 2008; Blencowe et al. 2012; Plunkett & Muglia 2008; Goldenberg et al. 1996). Whilst twin studies are an excellent method for disentangling genetic and shared environmental influences from non-shared environmental influences underlying an association for most traits, they cannot be used to study adverse birth outcomes or preterm birth as environmental insults, given that twins in a pair have typically both been exposed to the same birth event. Studies have started to address this dilemma by applying quasi-experimental designs (D'onofrio et al., 2014; Lindström et al., 2011), including sibling-comparison designs that can account for confounding familial factors (D'Onofrio et al., 2013; Donovan & Susser, 2011; Skoglund et al., 2014). In a sibling-comparison study on preterm birth, preterm-born individuals are compared to their term-born siblings growing up in the same family (D'Onofrio et al., 2013). The design controls for familial factors shared by siblings,

such as maternal genetic risk factors for giving birth preterm and socio-economic status, as well as all other shared environmental and shared genetic risks. A recent example of a sibling-comparison approach is a large Swedish epidemiological study that found a significant dose-response relationship between earlier gestational age and increased likelihood of an ADHD diagnosis, even when controlling for familial factors shared by siblings, consistent with a causal inference (D'Onofrio et al., 2013). However, no study, to our knowledge, has applied the sibling-comparison approach to investigate cognitive and neurophysiological impairments associated with preterm birth. If the association between preterm birth and specific cognitive-neurophysiological impairments remains when familial factors are controlled for, this would be consistent with a causal inference.

We have recently performed detailed investigations of the cognitive-neurophysiological impairments in preterm-born adolescents, when compared to unrelated term-born control adolescents (Rommel et al. under review, Rommel et al. in prep., James et al. in prep - Chapter 4). To further explore the increased risk for ADHD among preterm-born individuals, we also compared them to term-born adolescents with ADHD. The preterm group showed increased ADHD symptoms and impairments that were similar to those observed in the ADHD group in increased mean reaction time (MRT) and reaction time variability (RTV), working memory, short-term memory, IQ and event-related potentials (ERPs) of response preparation (contingent negative variation, CNV), response inhibition (NoGo-P3), conflict monitoring (N2) and error processing (error positivity, Pe, and error-related negativity, ERN) (Rommel et al. under review, Rommel et al. in prep., James et al. in prep – Chapter 4). The preterm group was further uniquely impaired on executive response control (Go-P3), compared to both ADHD and control groups (Rommel et al. under review). We further explored if the preterm group showed ADHD-like malleability in some of the impairments when rewards and a faster event rate is introduced in a simple reaction time task. While this was the case for MRT and RTV, the preterm group was unlike the ADHD group on attention allocation (P3) and peripheral arousal (skin conductance level, SCL) as they showed no impairment in the baseline condition, and unlike either ADHD or control groups, showed no improvement from baseline to the fast-rewarded condition in either P3 or

SCL (James et al. in prep – Chapter 4). Yet the fast-rewarded condition elicited a reduced adjustment of response preparation (CNV) in both the preterm and ADHD groups. Overall, we observed both ADHD-like and additional, unique impairments in cognitive-neurophysiological processes in preterm-born adolescents, when compared to unrelated term-born controls and adolescents with ADHD.

We now have available new data from term-born siblings of these same preterm-born adolescents whom we previously compared to unrelated controls (as well as to an unrelated ADHD group; Rommel et al. under review, Rommel et al. in prep, James et al. in prep – Chapter 4). By comparing the preterm-born adolescents to their term-born siblings, we now aim to test if the associations of preterm-birth with increased ADHD symptoms and the specific cognitive-neurophysiological impairments hold in our adolescent sample when controlling for unmeasured familial confounding factors, which would be consistent with a causal inference. We investigate the effects of preterm birth, firstly, as a dichotomous variable and, secondly, by using a continuous index of gestational age.

5.3 Methods

5.3.1 Sample

The preterm group was recruited from secondary schools in Southeast England. All preterm participants had one full sibling available for ascertainment, and were born before 37 weeks' gestation. Siblings of preterm-born individuals were included in the preterm group if they were also born preterm (before 37 weeks' gestation) to maximise the number of participants in the preterm group. Term-born siblings (after 37 weeks' gestation) of preterm-born individuals were included in this analysis. Most preterm-born participants were of European Caucasian decent (84.6%). The other ethnicities represented were British Asian (3.7%), Mixed-White and Black Caribbean (2.1%), Mixed-White and British Asian (1.6%), Indian (1.1%), Mixed-White and Indian (1.1%), Black Caribbean (0.5%), Mixed-Black and British Asian (0.5%) and Other (2.7%). Exclusion

criteria for all groups were IQ<70, cerebral palsy or any other medical conditions that affects motor co-ordination including epilepsy, as well as brain disorders and any genetic or medical disorder that might mimic ADHD. Seven individuals from the preterm sample were excluded because medical birth records could not corroborate preterm status (gestational age (GA) ≥37 weeks). One individual was excluded because of IQ<70 (Rommel et al. under review).

The eligible sample consisted of 145 sibling pairs (n=290): 104 preterm-born participants (gestational age ranged from 23 weeks to 36) with 104 term-born siblings (gestational age ranged from 37 to 42 weeks), and 41 preterm-born participants (gestational age ranged from 26 weeks to 36) with 41 preterm-born siblings (gestational age ranged from 30 weeks to 36). The fixed model analysis only uses discordant sibling pairs where one sibling is preterm born and the other is term. Therefore, the final sample in this analysis consisted of 208 participants: 104 preterm-born participants (gestational age ranged from 23 weeks to 36, mean age at testing=15.10, SD=2.03, 57% male) and their 104 term-born siblings (gestational age ranged from 37 to 42 weeks, mean age at testing=15.02, SD=2.44, 58% male). Siblings did not differ in age (z=1.69, p=0.09) or gender (χ^2=-0.10, p=0.89). A 48-hour ADHD medication-free period was required prior to assessments. Written informed consent was obtained following procedures approved by the National Research Ethics Service Committee London - Bromley (13/LO/0068).

5.3.2 Procedure

Participants attended a single 4.5h research session, which included an EEG assessment, an IQ test and clinical interviews. As part of the EEG assessment, participants completed a cued continuous performance test (CPT) with flankers (CPT-OX) (Doehnert, Brandeis, Imhof, Drechsler, & Steinhausen, 2010), a flanker task with low- and high-conflict conditions (Bjoern Albrecht et al., 2008; McLoughlin, Palmer, et al., 2014; McLoughlin et al., 2009) and the Fast Task, a four choice reaction time task with two conditions (Andreou et al. 2007; Kuntsi et al. 2005). Face-to-face clinical interviews were administered to the parent of each participant shortly before or after the participant's assessment.

5.3.3 Measures

5.3.3.1 Gestational Age

Gestational age information was obtained from Personal Child Health Records (PCHR) (also known as the "red book") which is the national standard health and development record given to parents by the National Health Service (NHS). The analyses used two different representations for gestational age. For dichotomous assessment, preterm birth was considered as <37 gestational weeks and term was considered ≥37 weeks. For continuous assessment, we converted gestational age to a linear scale that was referenced at 40 gestational weeks and ranged from –17.0 weeks (raw gestational age, 23 weeks) to 0 weeks (40+ weeks) (D'Onofrio et al., 2013).

5.3.3.2 IQ

The vocabulary and block design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999) were administered to all participants to derive estimates of IQ.

5.3.3.3 Digit span

The digit span subtest from the WISC-III (Wechsler, 1991) or the WAIS-III (Wechsler, 1997) was administered to participants aged below 16 and aged 16 or above, respectively, to obtain digit span forward (DSF) and backward (DSB). The forward test measures short-term verbal memory, while the backward test is a measure of working memory.

5.3.3.4 The Diagnostic Interview for ADHD in adults (DIVA)

The DIVA is a semi-structured interview designed to evaluate the DSM-IV criteria for both adult and childhood ADHD symptoms and impairment. It consists of 18 items used to define the DSM-

IV symptom criteria for ADHD, including scales for inattention and hyperactivity/impulsivity. Each item is scored affirmatively if the behavioural symptom was present often within the past six months.

5.3.3.5 Cued continuous performance test (CPT-OX)

The CPT-OX is a cued Go/NoGo task that probes attention, preparation and response inhibition. The task consisted of 400 black letter arrays, made up of a centre letter and incompatible flankers on each side to increase difficulty. The presented arrays included the cue letter 'O', the target letter 'X' as well as the distractors 'H', 'B', 'C', 'D', 'E', 'F', 'G', 'J' and 'L'. Cue and target letters ('O' and 'X' respectively) were flanked by incompatible letters ('XOX' and 'OXO' respectively). Participants were instructed to ignore the flanking letters and respond as quickly as possible to cue-target sequences ('O'-'X'). Eighty cues ('XOX') were followed by the target ('OXO') in 40 trials (Go condition), and by neutral distractors in the remainder of trials (NoGo condition). On 40 trials, the target letter 'X' was not preceded by a cue 'O' and had to be ignored. Letters were presented every 1650 ms s for 150ms in a pseudo-randomised order. Ten practice trials preceded the main task and were repeated, if required, to ensure participant comprehension. Participants were further asked to withhold the response in the presence of a NoGo stimulus, in the presence of a Go stimulus not preceded by a cue, or in the presence of any other irrelevant letters. Task duration was 11 min. Cognitive-performance measures of MRT, RTV, commission errors (CE, i.e. response to NoGo), omission errors (OE, i.e. non-response to Go) were obtained from this task.

5.3.3.6 The flanker task

The task was an adaptation of the Eriksen flanker paradigm designed to increase cognitive load as used in previous studies (Bjoern Albrecht et al., 2008; McLoughlin, Palmer, et al., 2014; McLoughlin et al., 2009). In each trial a central black fixation mark was replaced by a target arrow (a black 18 mm equilateral triangle). Participants had to indicate whether this arrow pointed towards the left or right by pressing corresponding response buttons with their left or right index

fingers. Two flanker arrows identical in shape and size to the target appeared 22 mm above and below the centre of the target arrow 100 ms prior to each target arrow. Both flankers either pointed in the same (congruent) or opposite (incongruent) direction to the target. As such, conflict monitoring is maximal during the incongruent condition. When the target appeared, both target and flankers remained on the screen for a further 150 ms, with a new trial being presented every 1650 ms. Trials were arranged in ten blocks of 40 trials. The task took approximately 13 minutes. Cognitive-performance measures of number of errors (left-right errors occurring when participants chose the wrong left or right response) were calculated separately for congruent conditions.

5.3.3.7 The Fast Task (Andreou et al. 2007, Kuntsi et al 2005)

Participants performed a four-choice RT task with a baseline condition (72 trials) with four empty circles (warning signals, arranged horizontally) first appearing for 8000ms, after which one of them (the target) was coloured in (Andreou et al., 2007). Participants were asked to press the response key that directly corresponded to the position of the target. Following a response, the stimuli disappeared from the screen and a fixed inter-trial interval of 2.5s followed. Speed and accuracy were emphasized equally. If the participant did not respond within 10s, the trial terminated. A comparison condition with a fast event rate (1s) and incentives followed the baseline condition (Andreou et al., 2007). Cognitive-performance measures of MRT, and RTV (SD of RTs) were calculated for each condition. In addition to measures obtained from the baseline and fast-incentive conditions, we calculate also the slope from the baseline to fast-incentive condition, indexing the degree of change between the conditions.

5.3.3.8 EEG recording and pre-processing

The EEG was recorded from 62 channels DC-coupled recording system (extended 10–20 montage), with a 500 Hz sampling rate, impedances kept under 10 kΩ, and FCz as the recording

reference electrode. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi.

The EEG data were analysed using Brain Vision Analyzer (2.0) (Brain Products, Germany). After down-sampling the data to 256 Hz, the EEG data were re-referenced to the average and filtered offline with digital band-pass (0.1 to 30 Hz, 24 dB/oct) Butterworth filters. Ocular artifacts were identified from the data using Independent Component Analysis (ICA) (Jung et al., 2000)). The extracted independent components were manually inspected and ocular artefacts were removed by back-projection of all but those components. All ERP averages contained at least 20 accepted sweeps. Data with other artifacts exceeding ± 100µV in any channel were rejected. ERPs were extracted from the CPT-OX (CNV, Go-P3, NoGo-P3), flanker task (N2, Pe, ERN, incongruent condition only) and Fast Task (CNV amplitude and P3 amplitude) following procedures used on previous analyses of this sample (Rommel et al. under review, Rommel et al. in prep, James et al. in prep – Chapter 4). For the CPT-OX task, stimulus-locked epochs (stimulus window from −200 to 1650ms) were averaged based on three different response conditions: Cue, Go and NoGo. Averages were calculated for trials with correct responses (Go) or correctly rejected trials (NoGo and Cue), which included at least 20 artefact-free segments. Based on previous research (McLoughlin et al. 2010; Doehnert et al. 2013; Albrecht et al. 2013), ERP measures were identified within selected electrodes and latency windows for which effects were expected to be largest. These measures were then confirmed separately for the three groups using topographic maps (Rommel et al. under review). In Cue trials, the P3 was measured at Pz between 300-650ms, and the CNV was measured at Cz and CPz between 1300-1650ms. In Go trials, the P3 was measured at CPz and Pz between 250-500ms. No clear N2 was observed in Go trials, consistent with other studies employing tasks with low conflict-monitoring demands (Gajewski and Falkenstein 2013; Michelini et al. in press) and was, therefore, not included in the analysis. In NoGo trials, the P3 was measured at FCz and Cz between 250-550ms and the N2 was measured at Fz between 175-325ms. The CNVs were analysed as mean amplitudes between 1300 and 1650ms following cues over the central electrode (CPz). The Cue-P3 had a parietal maximum and was defined as the most positive peak between 250 and 600 ms following cue trials at electrode Pz. The NoGo-P3

was defined as the most positive peak between 250 and 600 ms following No-Go trials at electrode Cz (Rommel et al. under review).

Analyses of ERPs of performance monitoring in the flanker task were restricted to the incongruent condition, as the task used in this study is known to elicit strong N2, error related negativity (ERN) and positivity (Pe) components in high-conflict, but not in low-conflict, conditions (Albrecht et al., 2008; McLoughlin, Palmer, et al., 2014; McLoughlin et al., 2009). Baseline correction was applied using the -300 to -100 ms pre-target (-200 to 0 ms pre-flanker) interval, following the protocol of previous ERP analyses on the flanker task (Michelini et al. in press). Data were segmented based on (1) stimulus-locked incongruent trials where a correct response was made and (2) response-locked (error-related) incongruent trials where an incorrect response was made. Individual averages were created based on each condition, requiring ≥ 20 clean segments for each participant. After averaging, the electrodes and latency windows for ERP analyses were selected based on previous studies (Albrecht et al. 2008; McLoughlin et al. 2009; Groom et al. 2010; Nieuwenhuis et al. 2001, Michelini et al. in press) topographic maps and the grand averages. The N2 was measured as maximum negative peak at Fz and FCz between 250-450 ms after target onset. The ERN was defined with respect to the preceding positivity (PNe, -100-50 ms) in order to obtain a more robust measure of this component, and was measured at FCz between 0-150 ms. The Pe was measured as maximum positive peak at CPz between 150-450 ms after an erroneous response on incongruent trials.

In the Fast Task, P3 amplitude was analysed as the area amplitude measure (μV*ms) at Pz between 250 and 450ms, to reduce bias due to the varying noise levels induced by the different task conditions (Luck, 2005). For the P3 analyses, all the accepted trials were baseline-corrected using a pre-stimulus baseline of 200ms. The mean amplitudes of this pre-target period (-200ms - 0ms, using a technical zero baseline as in previous CNV work (Albrecht et al., 2013, Banaschewski et al., 2003)) at Cz were also analysed separately as a CNV measure. This short interval not only corresponded to the P3 baseline, but also captured the short CNV in the fast-incentive condition

with its one-second cue – target interval (Cheung et al., under review, James et al. in prep – Chapter 4).

5.3.3.9 Skin conductance

SC data were measured by attaching a pair of reusable 8mm diameter silver-silver chloride electrodes on the thenar eminence and hypothenar eminence of participant's non-dominant hand at the start of the testing session. A non-saline gel was used to increase impedance and help establish an electrical signal. A constant imperceptible voltage (0.5 V) was applied. SC was recorded using PSYCHLAB SC5 24 bit equipment system, which has an absolute accuracy of +/- 0.1 microsiemens (μS) (PSYCHLAB, UK). The SC5 was connected to a computer to run the PSYCHLAB software, where data were monitored and recorded in real time. Stimulus onset and participant response events were recorded on a common timeline, which enabled SC activity to be stimulus-locked. SC measures were extracted from the Fast Task (SCL) following procedures used on previous analyses of this sample (James et al. in press - Chapter 2, James et al. in prep - Chapter 3). SC data values were calculated using a skin conductance system which is based on a SC sigmoid-exponential model that allows the tonic measure of SC level (SCL) to be disentangled from phasic, stimulus-associated, SC responses (SCR), and further allows the decomposition of overlapping SCRs (Boucsein, 1992; Figner & Murphy, 2011; Lim et al., 1997; Williams et al., 2001). This system, therefore, is appropriate to use in conditions with long and short inter-stimulus-intervals (Williams et al., 2000). The statistical model was applied to each condition, as a whole. SCR amplitude (change in SC from the baseline to the highest point of the SCR) was derived from this method, and was calculated on a trial-by-trial basis. The criteria for the smallest SCR were set at 0.02 μS. Means of SC variables (SCL) were calculated per participant, across each condition (James et al. in press).

5.3.4 Statistical analyses

ADHD symptoms and cognitive-neurophysiological measures which we have previously shown to be impaired in the preterm group, compared to unrelated term-born controls, are included in this analysis (Rommel et al. under review, Rommel et al. in prep, James et al. in prep – Chapter 4; reviewed above). In order to reduce the number of statistical comparisons, for previous analyses that included ERPs from multiple electrode sites, in this analysis we only chose one electrode where the previous preterm-control differences were maximal, and consequently analysed Go-P3 from Pz only, CNV at CPz only in the CPT-OX, and N2 at Fz only. In addition, in the Fast Task, cognitive performance measures of MRT and RTV from the baseline condition only are included in this analysis, as the baseline condition is more sensitive to preterm-control differences in cognitive performance (James et al. in prep – Chapter 4). According to these criteria the following measures were retained for inclusion: IQ, working memory (DSF and DSB); executive response control (Go-P3 at Pz), response preparation (CNV at CPz), response inhibition (NoGo-P3 at Cz) from the CPT-OX; congruent errors, conflict monitoring (N2 at Fz), automatic error processing (ERN at FCz), conscious error processing (Pe at CPz) from the flanker task; MRT and RTV (baseline condition), response preparation (CNV at Cz in the fast-incentive condition), response preparation adjustment (CNV slope at Cz), attention allocation (P3 at Pz in the fast-incentive condition), attention allocation adjustment (P3 slope at Pz) and peripheral arousal adjustment (SCL slope) from the Fast Task.

The relationship of preterm birth with cognitive and neurophysiological measures was investigated using a within-sibling fixed-effect model (D'Onofrio et al., 2013; Donovan & Susser, 2011; Lahey & D'Onofrio, 2010; Neuhaus & McCulloch, 2006), which models within-sibling pair differences in cognitive and neurophysiological measures as a function of within-pair differences of preterm birth. Thus, the analysis allows the effect of preterm birth on cognitive and neurophysiological measures to be estimated while accounting for unmeasured confounding factors (i.e., all genetic and environmental factors that make siblings alike). That is, siblings are similar due to sharing 50% of their inherited DNA sequence and aspects of the family

environment that impacts on them equally (including the maternal risk of having a preterm birth). Preterm birth was first studied as a dichotomous variable (preterm birth: born before <37 weeks' gestation) and secondly as a continuous variable, where gestational age was explored as a linear variable. Cognitive and neurophysiological measures were studied as continuous variables. Models were fitted to standardised (z) cognitive and neurophysiological measures. All analyses were conducted in Stata 13 software. Age and sex effects were regressed out from all analyses as is standard practice for quantitative family studies (McGue & Bouchard, 1984). IQ was used as an additional covariate (Supplementary Material I and II). Because the analyses were carried out using standardized (z) scores for cognitive-neurophysiological variables, the β coefficients presented in this section represent a 1–unit change in preterm birth (born preterm or term) or gestational age (a week), which leads to the β coefficient change in standard deviation (SD) in the dependent variables.

5.4 Results

5.4.1 Preterm birth

The within-siblings, fixed-effect model revealed that preterm birth was significantly associated with increased parent-rated total ADHD symptoms (Table 5.2). Of cognitive measures, significant associations emerged between preterm birth and lower IQ, as well as with increased MRT and RTV in the baseline condition of Fast Task, but not with DSF, DSB; or congruent errors on the flanker task (Table 5.2). Of neurophysiological variables, significant associations with preterm birth emerged for decreased CNV amplitude at CPz on the CPT-OX task, decreased Go-P3 amplitude at Pz on the CPT-OX task, decreased N2 amplitude at Fz on the flanker task, decreased Pe on the flanker task, decreased CNV amplitude at Cz and decreased P3 amplitude at Pz on the fast-incentive condition of Fast Task, and reduced slopes in CNV amplitude at Cz, P3 amplitude at Pz and SCL in the Fast Task. Preterm birth was not significantly associated with NoGo-P3 amplitude on the CPT-OX or ERN on the flanker task (Table 5.2). Including IQ as an additional covariate did not alter the significance of the results (Supplementary Material 5.1).

5.4.2 Gestational age

The within-siblings, fixed-effect model revealed that earlier gestational age was significantly associated with increased parent-rated total ADHD symptoms (Table 5.3). Of cognitive measures, significant associations emerged between earlier gestational age and lower IQ, as well as with increased MRT and RTV in the baseline condition of Fast Task, but not with DSF, DSB or congruent errors on the flanker task (Table 5.3). Of neurophysiological variables, significant associations with earlier gestational age emerged for decreased CNV amplitude at CPz on the CPT-OX task, decreased Go-P3 amplitude at Pz on the CPT-OX task, decreased N2 amplitude at Fz on the flanker task, decreased Pe on the flanker task, decreased CNV amplitude at Cz and decreased P3 amplitude at Pz on the fast-incentive condition of Fast Task, and reduced slopes in CNV amplitude at Cz, P3 amplitude at Pz, and SCL in the Fast Task. Earlier gestational age was not significantly associated with NoGo-P3 amplitude on the CPT-OX or ERN on the flanker task (Table 5.3). When IQ was used as an additional covariate the association between earlier gestational age and CNV at Cz in the fast incentive condition of the Fast Task was at a trend level of significance. The significance of all other results remained unchanged (Supplementary Material 5.2).

Table 5.1. Descriptive statistics: means and standard deviations (SD) for the term and preterm group.

	Variables	Term n=104		Preterm n=104	
	Male (%)	58%		57%	
	Age	15.02	(2.44)	15.10	(2.03)
	Gestational age	39.19	(1.22)	32.88	(3.14)
	ADHD symptoms	2.88	(3.73)	4.12	(4.10)
Cognitive performance measures	IQ	105.86	(11.33)	103.86	(13.06)
	DSF	16.74	(3.29)	16.56	(3.88)
	DSB	6.59	(1.91)	6.31	(2.12)
	Congruent Errors	50.56	(21.31)	50.20	(18.27)
	MRT	551.05	(132.40)	590.45	(169.12)
	RTV	99.65	(68.97)	97.72	(58.38)
ERP measures	CNV (CPz)	8.06	(3.79)	7.38	(3.48)
	Go-P3 (Pz)	9.22	(4.24)	8.21	(4.88)
	Nogo-P3 (Cz)	8.17	(4.95)	8.04	(4.86)
	N2 (Fz)	-5.01	(4.02)	-4.34	(4.22)
	N2 (Fcz)	-10.99	(5.32)	-9.28	(5.65)
	Pe (CPz)	8.47	(4.56)	8.71	(4.67)
	ERN (Fcz)	551.05	(132.40)	590.45	(169.12)
	CNV (Cz) (fast-incentive)	-1.17	(1.70)	-1.04	(1.77)
	CNV slope (Cz)	1.18	(2.07)	1.03	(2.12)
	P3 (Pz) (fast-incentive)	291.36	(920.07)	78.06	(872.97)
	P3 slope (Pz)	4.81	(4.51)	4.77	(3.80)
Skin conductance measures	SCL slope	3.43	(2.86)	2.06	(2.30)

ADHD=attention-deficit/hyperactivity disorder; DSF=digit span forwards; DSB=digit span backwards; Congruent Errors=errors in the congruent condition of the flanker task; MRT=mean reaction time in the baseline (slow, unrewarded) condition of the Fast Task; RTV=reaction time variability in the baseline (slow, unrewarded) condition of the Fast Task; CNV=contingent negative variation in the cued continuous performance test; Go-P3=P3 amplitude in the go condition from the cued continuous performance test; NoGo-P3=P3 amplitude in the NoGo condition from the cued continuous performance test; N2=N2 amplitude in the incongruent condition of the flanker task; Pe=positive related negativity in the incongruent condition of the flanker task; ERN=error related negativity in the incongruent condition of the flanker task; CNV fast-incentive= contingent negative variation amplitude in the fast-incentive condition of the Fast Task; CNV slope=slope in contingent negative variation amplitude between the baseline and

fast-incentive condition of the Fast Task; P3 fast-incentive= P3 amplitude in the fast-incentive condition of the Fast Task; P3 slope=slope in P3 amplitude between the baseline and fast-incentive condition of the Fast Task; SCL slope=slope in skin conductance level between the baseline and fast-incentive condition of the Fast Task.

Table 5.2. Within-siblings, fixed effect model of preterm birth on standardised scores (controlling for age and sex) (n=208).

	Variable	β Coef	p	95% CI
	ADHD symptoms	**0.19**	**<0.01**	**0.05,0.33**
Cognitive performance measures	IQ	**-0.18**	**0.05**	**-0.36,-0.01**
	DSF	-0.01	1.00	-0.15,0.15
	DSB	-0.07	0.38	-0.22,0.08
	Congruent Errors	0.15	0.21	-0.08,0.37
	MRT	**0.18**	**0.04**	**0.01,0.35**
	RTV	**0.14**	**0.05**	**0.00,0.27**
Event-related potentials measures	CNV (CPz)	**0.47**	**0.02**	**0.10,0.84**
	Go-P3 (Pz)	**-0.20**	**0.02**	**-0.36,-0.04**
	Nogo-P3 (Cz)	0.00	0.99	-0.16,0.16
	N2 (Fz)	**0.14**	**0.05**	**0.01,0.29**
	Pe (CPz)	**-0.14**	**0.05**	**-0.33,-0.06**
	ERN (Fcz)	0.01	0.91	-0.15,0.17
	CNV (Cz) (fast-incentive)	**0.14**	**0.05**	**0.07,0.26**
	CNV slope (Cz)	**-0.13**	**0.04**	**-0.20,-0.04**
	P3 (Pz) (fast-incentive)	**-0.22**	**0.02**	**-0.40,-0.03**
	P3 slope (Pz)	**-0.14**	**0.02**	**-0.33,-0.04**
Skin conductance measures	SCL slope	**-0.09**	**0.03**	**-0.30,-0.02**

Note: p<0.05 indicated in bold. ADHD=attention-deficit/hyperactivity disorder; DSF=digit span forwards; DSB=digit span backwards; Congruent Errors=errors in the congruent condition of the flanker task; MRT=mean reaction time in the baseline (slow, unrewarded) condition of the Fast Task; RTV=reaction time variability in the baseline (slow, unrewarded) condition of the Fast Task; CNV=contingent negative variation in the cued continuous performance test; Go-P3=P3 amplitude in the go condition from the cued continuous performance test; NoGo-P3=P3 amplitude in the NoGo condition from the cued continuous performance test; N2=N2 amplitude in the incongruent condition of the flanker task; Pe=positive related negativity in the incongruent condition of the flanker task; ERN=error related negativity in the incongruent condition of the flanker task; CNV fast-incentive= contingent negative variation amplitude in the fast-incentive condition of the Fast Task; CNV slope=slope in contingent negative variation amplitude between the baseline and fast-incentive condition of the Fast Task; P3 fast-incentive= P3 amplitude in the fast-incentive condition of the Fast Task; P3 slope=slope in P3 amplitude between the baseline and fast-incentive condition of the Fast Task; SCL slope=slope in skin conductance level between the baseline and fast-incentive condition of the Fast Task.

Table 5.3. Within-siblings, fixed effect model on linear gestational age on standardised scores (controlling for age and sex) (n=208).

	Variable	β Coef	P	95% CI
	ADHD symptoms	**-0.06**	**<0.01**	**-0.09,-0.02**
Cognitive performance measures	IQ	**0.03**	**0.02**	**0.00,0.06**
	DSF	0.01	0.48	-0.02,0.05
	DSB	0.03	0.14	-0.01,0.07
	Congruent Errors	0.03	0.08	-0.00,0.07
	MRT	**-0.06**	**0.01**	**-0.10,-0.01**
	RTV	**-0.05**	**0.02**	**-0.09,-0.01**
Event-related potential measures	CNV (CPz)	**-0.08**	**0.02**	**-0.15,-0.01**
	Go-P3 (Pz)	**0.05**	**0.02**	**0.01,0.09**
	Nogo-P3 (Cz)	0.03	0.10	-0.01,0.06
	N2 (Fz)	**-0.06**	**0.01**	**-0.09,-0.02**
	Pe (CPz)	**0.05**	**0.01**	**0.01,0.08**
	ERN (Fcz)	**-0.04**	**0.02**	**-0.08,-0.01**
	CNV (Cz) (fast-incentive)	**-0.06**	**0.05**	**-0.05,-0.02**
	CNV slope (Cz)	**0.05**	**0.04**	**0.01,0.06**
	P3 (Pz) (fast-incentive)	**0.04**	**0.05**	**0.01, 0.07**
	P3 slope (Pz)	**0.05**	**0.05**	**0.00,0.07**
Skin conductance measures	SCL slope	**0.02**	**0.04**	**0.01,0.08**

Note: p<0.05 indicated in bold. ADHD=attention-deficit/hyperactivity disorder; DSF=digit span forwards; DSB=digit span backwards; Congruent Errors=errors in the congruent condition of the flanker task; MRT=mean reaction time in the baseline (slow, unrewarded) condition of the Fast Task; RTV=reaction time variability in the baseline (slow, unrewarded) condition of the Fast Task; CNV=contingent negative variation in the cued continuous performance test; Go-P3=P3 amplitude in the go condition from the cued continuous performance test; NoGo-P3=P3 amplitude in the NoGo condition from the cued continuous performance test; N2=N2 amplitude in the incongruent condition of the flanker task; Pe=positive related negativity in the incongruent condition of the flanker task; ERN=error related negativity in the incongruent condition of the flanker task; CNV fast-incentive= contingent negative variation amplitude in the fast-incentive condition of the Fast Task; CNV slope=slope in contingent negative variation amplitude between the baseline and fast-incentive condition of the Fast Task; P3 fast-incentive= P3 amplitude in the fast-incentive condition of the Fast Task; P3 slope=slope in P3 amplitude between the baseline and fast-incentive condition of the Fast Task; SCL slope=slope in skin conductance level between the baseline and fast-incentive condition of the Fast Task.

5.5 Discussion

In this novel sibling-comparison study we compared preterm-born adolescents to their full-term siblings to identify which previously established associations between preterm birth and cognitive-neurophysiological impairments were still associated with preterm birth when controlling for unmeasured familial confounding factors. We find evidence for significant associations between preterm birth and increased ADHD symptoms, as well as with specific cognitive-neurophysiological impairments, such as IQ, preparation-vigilance processes (RTV, CNV), conscious error processing (Pe) and conflict monitoring (N2), when controlling for unmeasured familial confounding factors. These robust within-siblings associations indicate that preterm birth (or genetic factors associated with preterm birth), is likely in the causal pathway leading to these identified impairments. In contrast, we find evidence for a lack of an association between preterm birth and specific other cognitive-neurophysiological impairments, such as short-term memory (DSF), working memory (DSB), inhibition (NoGo-P3) and automatic error processing (ERN), when controlling for unmeasured familial confounding factors. The previously obtained statistical associations between preterm birth and these latter processes (Rommel et al. under review, Rommel et al. in prep) are therefore unlikely to be due to preterm birth itself, but may have arisen due to other characteristics that differentiate families with a preterm-born child from other families.

The impairments that we establish as consistent with a causal inference of preterm birth (or genetic factors associated with preterm birth), are studied in the quasi-experimental sibling-comparison design for the first time in the present study, with one exception. Our finding on the association between preterm birth and increased ADHD symptoms replicates and extends previous findings from a large-scale population study that also applied a sibling-comparison approach (D'Onofrio et al. 2013). Of the many cognitive-neurophysiological processes that we establish as independent of shared familial confounds, consistent with a causal inference, a noteworthy one, first of all, is that of lower IQ. Whilst multiple studies have indicated that preterm birth is consistently associated with decreased IQ (Kerr-Wilson et al., 2012), we also

know that families with a preterm-born child differ from other families on background variables such as socio-economic status (Goldenberg et al., 2008), highlighting the importance of confirming that the association between preterm birth and IQ is independent of such shared familial confounds. In addition to lower IQ scores, other ADHD-like cognitive-neurophysiological impairments where we obtain evidence consistent with a causal inference of preterm birth are increased MRT and RTV, response preparation (CNV), conflict monitoring (N2), conscious error processing (Pe), and attenuated response preparation (CNV) and attention allocation (P3) in a fast-incentive condition of an RT task. Additional preterm-specific impairments that we established as independent of familial confounds were attenuated executive response control (Go-P3), and decreased adjustment in a changed context (from baseline to fast-incentive condition) for response preparation (CNV), attention allocation (P3) and peripheral hypo-arousal (SCL). When we further explored associations of the impairments with the continuous measure of gestational age within the sibling-comparison design, the same pattern of significant associations emerged for every variable, indicating that these impairments are more severe with decreasing gestational age, consistent with a causal inference. Future research should explore the specific mechanisms whereby the insult of preterm birth (or genetic factors associated with preterm birth), leads to these cognitive-neurophysiological impairments and increased ADHD symptoms. For example, it has been shown that proliferation and strengthening of brain connections, vital for complex brain networks, is the dominant neurodevelopmental process throughout the third trimester (29 to 40 weeks' gestation). As such, it is feasible that giving birth prematurely could result in disruption of developing brain networks associated with ADHD, as well as disruption of other networks associated with additional impairments (Ball et al., 2014; van den Heuvel et al., 2014).

In contrast, although we had previously reported significant associations with preterm birth in comparison to unrelated controls (Rommel et al. under review), in the present analysis, when controlling for familial factors, we failed to replicate the associations between preterm birth and decreased working and short term memory (DSF and DSB), attenuated response inhibition

(NoGo-P3), and performance monitoring task measures of increased congruent errors and attenuated automatic error processing (ERN). The lack of associations falsifies the hypothesised causal inference of preterm birth and instead suggests that familial factors shared by siblings, which include factors correlated with preterm birth (i.e. maternal genetic risk for giving birth preterm, socio-economic status, family upbringing, and other shared genetic and environmental factors), may account for these associations previously observed in preterm individuals when compared to unrelated controls. The findings that short term and working memory are not on the causal pathway from preterm birth are in line with results from a recent study which demonstrated that short term and working memory (DSF and DSB) are not on the causal pathways between birth weight and ADHD symptoms in adolescents (Morgan et al., 2016). In our further analyses on the continuous measure of gestational age, we obtained the same pattern of non-significant associations for each of these variables, confirming the results that emerged from the group-based analyses. Future research should aim to identify the background risk factors that characterise families with a preterm-born child and account for the impairments that distinguish them from families without preterm-born children. Another direction for future research is to aim to better understand the specific split we observe between cognitive-neurophysiological impairments that are consistent with a causal inference of preterm birth and those that are not. We note that some of the key processes we identify here as not on the causal pathway from preterm birth to cognitive and brain impairments - such as working memory and inhibition – are the same as those we have previously identified as not mediating ADHD outcome (ADHD persistence vs remittance in adolescence and young adulthood; Cheung et al. 2016; Michelini et al. in press).

The present study is, to our knowledge, the first study investigating the effects of preterm birth on cognitive-neurophysiological measures in adolescents in a quasi-experimental sibling design, which is essential for drawing stronger causal inferences. However, as is the case for all such non-randomized quasi-experimental studies, we cannot rule out all confounding factors underlying the associations between cognitive-neurophysiological impairments and preterm birth

(D'Onofrio et al., 2013). In addition, the sibling-comparison design does not control for sibling-specific genetic influences that could influence preterm birth, and, as such, the causal role of genetic influences cannot be ruled out. However, twin studies have suggested a negligible role for sibling-specific genetic factors in determining gestational age (Svensson et al., 2009). Further, whilst our adolescent sample offers a unique perspective, adolescence is a period of changes in brain development and it would be informative to examine the hypotheses again in future follow-up assessments when all participants have reached adulthood, as well as in independent samples.

In conclusion, our findings provide novel insight into the potential causal pathways to cognitive-neurophysiological impairments and increased ADHD symptoms in adolescents born preterm. By distinguishing impairments that are consistent with a causal inference of preterm birth from those that are instead linked to background characteristics of families with a preterm-born child, our results provide stepping stones towards better targeted interventions into those that are preterm-birth specific and those that address family-level risk factors.

Chapter 6 - DOES PRETERM BIRTH MODERATE THE AETIOLOGICAL INFLUENCES UNDERLYING THE RELATIONSHIP BETWEEN COGNITIVE-NEUROPHYSIOLOGICAL IMPAIRMENTS AND ADHD SYMPTOMS?

6.1 Abstract

Introduction: Preterm birth is associated with an increased risk for ADHD symptoms and ADHD-like cognitive and neurophysiological impairments, but the underlying risk pathways are unknown. We now aim to investigate whether the aetiology between ADHD symptoms and specific cognitive-neurophysiological impairments is significantly different between preterm-born and term-born individuals. **Methods:** Data were obtained from samples of preterm-born, ADHD and control sibling pairs (total n=647 participants), aged 11-25. Multivariate model fitting was conducted on ADHD symptoms and cognitive measures, previously shown to be impaired in preterm and term-born ADHD groups. The effects of preterm birth were explored as a dichotomous (preterm or term) and continuous (gestational age) moderator. **Results:** Preterm birth, and gestational age, significantly moderated the aetiological pathways underlying the relationship between ADHD symptoms and IQ, mean reaction time (MRT) and reaction time variability (RTV). The majority of the aetiological relationship between IQ, MRT, and RTV, and ADHD symptoms was accounted for by non-shared effects in the preterm group, and by familial influences in the term group. **Discussion:** We demonstrate that preterm birth and gestational age moderates the aetiological pathways contributing to the relationship between ADHD symptoms and IQ, and between ADHD symptoms and speed and variability of reaction times. The pattern of findings indicates that the association between ADHD symptoms and the specific cognitive impairments is largely due to familial influences among term-born individuals, but largely due to non-shared effects (including preterm birth as an environmental insult) among preterm-born individuals.

6.2 Introduction

Preterm birth (born before 37 weeks' gestation) has been established as a risk factor for attention-deficit/hyperactivity disorder (ADHD), whether ADHD is considered as a continuum (Aarnoudse-Moens et al. 2009) or a categorical diagnosis (Bhutta et al., 2002). Preterm-born individuals are also reported to have an increased risk of developing cognitive and neurophysiological impairments (Aarnoudse-Moens et al., 2012; Aarnoudse-Moens et al., 2009; Anderson et al., 2011; de Kieviet et al., 2012; Geva & Feldman, 2008; Samantha Johnson & Marlow, 2011; Lawrence et al., 2009; Mulder et al., 2009; Nosarti et al., 2006). Yet, the underlying risk pathways between this association remain poorly understood.

In order to directly assess the overlap of cognitive-neurophysiological impairments between preterm and ADHD groups, we recently conducted one of the first direct comparisons and evaluated whether the preterm group had identical cognitive-neurophysiological impairments to the term-born ADHD group and term-born control group (Rommel et al. under review, Rommel et al. in prep. James et al. in prep - Chapter 4). Compared to an unrelated term-born control group, we found that the preterm group showed increased ADHD symptoms and ADHD-like impairments across many cognitive-neurophysiological variables, including increased mean reaction time (MRT), reaction time variability (RTV), IQ and event-related potentials (ERPs) of response inhibition (NoGo-P3) (Rommel et al. under review, Rommel et al. in prep., James et al. in prep – Chapter 4). These variables were additionally associated with ADHD symptoms in the preterm group. We also found further evidence of additional impairments in the preterm group on measures such as executive control (Go-P3) and attention allocation (P3), indicating subtler and wide-ranging neurophysiological impairments in the preterm group. Whilst this was one of the first studies to investigate how cognitive and neurophysiological impairments in preterm-born individuals are associated to ADHD symptoms, the phenotypic and aetiological association underlying this relationship is yet to be established.

Whilst studies investigating the aetiological pathways of preterm birth and cognitive-neurophysiological impairments are very limited, the aetiology and interrelationships of cognitive-neurophysiological impairments and ADHD have been widely studied (Andreou et al. 2007; Kuntsi et al. 2010; Wood et al. 2011; Tye et al. 2012; McLoughlin et al. 2011; McLoughlin et al. 2010; Cheung et al. 2012; Cheung et al. 2016; James et al. in press). Twin studies have demonstrated that ADHD is highly heritable, and show that genetic influences largely contribute to the aetiology of ADHD, whilst the rest of the variance is accounted for by non-shared (environmental) influences; implying a negligible role for shared environmental influences (Burt, 2009). The large contributing role of genetic influences has also been demonstrated for cognitive impairments in ADHD. For example, evidence from family and twin studies has demonstrated that shared genetic or familial influences largely account for the association observed between ADHD and cognitive impairments, including high reaction time variability (RTV), inhibition, aspects of attention (Doyle et al., 2005; Rommelse et al., 2008) and IQ (Kuntsi et al., 2004; Wood et al., 2010). Multivariate model fitting analyses on large sibling-pair samples have further identified two partially separable familial factors underlying the multiple cognitive impairments in children with combined-type ADHD (Frazier-Wood et al., 2012; Kuntsi et al., 2010).

To investigate the causal effect between preterm birth and cognitive-neurophysiological impairments, we recently used a sibling-comparison study to evaluate whether the associations were independent of familial factors, consistent with a causal inference (Chapter 5). We found that preterm birth and earlier gestational age were significantly associated with increased ADHD symptoms, consistent with a causal inference and in line with large genetically-sensitive population studies demonstrated that the association between preterm birth and ADHD is not explained by genetic factors (Lindström et al., 2011), and is largely independent of shared familial confounds (D'Onofrio et al., 2013). We also found that preterm birth and specific cognitive-neurophysiological impairments, such as IQ and preparation-vigilance measures (increased speed and variability of reaction times, response preparation (CNV)) had robust within-sibling associations, in line a causal inference. We also found evidence of a lack of associations between preterm birth with executive control measures of inhibition and short and working memory,

indicating that familial risk factors associated with preterm birth, but not a causal effect of preterm birth as an environmental insult per se, underlie these impairments in preterm-born individuals (Chapter 5). Whilst the causal effect of cognitive-neurophysiological impairments in preterm birth have been assessed, the aetiological influences underlying the association between cognitive-neurophysiological impairments and ADHD symptoms in preterm birth, and how this may differ between preterm-born and term-born individuals, is yet to be established.

To further explore the aetiological relationship between the ADHD symptoms and the previously identified overlapping cognitive-neurophysiological impairments between preterm and ADHD groups, we now combine data from ADHD and control sibling pairs (Cheung et al. 2016, James et al. in press), with preterm sibling pairs (Chapter 5). In this large sibling-pair design, we now aim to investigate whether the aetiology between ADHD symptoms and specific cognitive-neurophysiological impairments is significantly different between preterm-born and term-born individuals. Specifically, we aim to examine if the association between ADHD symptoms and specific cognitive-neurophysiological impairments is largely due to non-shared effects (consistent with preterm birth as an environmental insult) among preterm-born individuals, but largely attributed to familial factors (shared genetics and shared environment) among term–born individuals. The moderating effects of preterm birth were explored as a dichotomous (preterm or term) and continuous (gestational age) variable.

6.3 Methods

6.3.1 Sample

The preterm group was recruited from secondary schools in Southeast England (Rommel et al. under review). All preterm participants had one full sibling available for ascertainment, and were born before 37 weeks' gestation. Exclusion criteria for the preterm group included IQ<70, cerebral palsy and any other medical conditions that affects motor co-ordination including

epilepsy. One individual was excluded because of IQ<70 and one individual was excluded due to suspected epileptic charge.

ADHD and control sibling pairs, who had taken part in previous research (Chen et al., 2008; Kuntsi et al., 2010b), were invited to take part in a follow-up study (Cheung et al., 2015; Cheung et al., 2016). All participants were of European Caucasian decent and had one full sibling available for ascertainment. The control group was recruited from primary (ages 6–11 years) and secondary (ages 12–18 years) schools in the UK, aiming for an age and sex-match with the ADHD sample. Exclusion criteria for both groups included IQ<70, autism, epilepsy, brain disorders and any genetic or medical disorder associated with externalising behaviours that might mimic ADHD. We followed up the sample on average 5.8 years (SD=1.1) after initial assessments.

Thirty-two individuals from the ADHD-sibling pair sample, and thirty-seven participants from the control-sibling pair sample were excluded because no GA information was available. The final sample consisted of 145 preterm-born probands (8 with an ADHD diagnosis), 146 siblings of preterm-born probands (31 preterm born, 12 with an ADHD diagnosis), 70 ADHD probands from the original ADHD sample (8 preterm born, 62 with a current ADHD diagnosis), 46 siblings of the ADHD probands (2 preterm born, none with an ADHD diagnosis), and 70 controls (9 preterm born, none with an ADHD diagnosis) and 70 siblings of controls (2 preterm born, none with an ADHD diagnosis). Therefore, the final sample consisted of 197 preterm-born individuals and 342 term-born individuals. The preterm and term groups differed significantly in terms of age at testing, sex, gestational age, and were significantly different, at a trend level of significance, in IQ (Table 6.1), which are taken into account in the analyses (see more detail below). A 48-hour ADHD medication-free period was required prior to assessments. Written informed consent was obtained following procedures approved by the London-Surrey Borders Research Ethics Committee (09/H0806/58) and the National Research Ethics Service Committee London - Bromley (13/LO/0068).

Table 6.1. Descriptive statistics of the term (n=347) and preterm (n=192) groups.

	Term (n=347)	**Preterm (n=192)**	**Statistic**	**p-value**
Age at testing (SD)	17.07 (2.90)	15.12 (2.10)	-8.49	<0.01
Age range	11-25	11-22		
IQ (SD)	106.11 (12.97)	103.73 (12.82)	-1.86	0.07
Males %	70%	54%	12.55	<0.01
GA in weeks (SD)	39.60 (1.39)	33.06 (3.04)	-25.43	<0.01
Range of GA	37-40	23-36		

GA=gestational age. SD=standard deviation.

6.3.2 Procedure

Participants attended a single 4.5h research session, which included an EEG assessment, an IQ test and clinical interviews. As part of the EEG assessment, participants completed a CPT with flankers (CPT-OX) (Doehnert et al. 2010), an arrow flanker task with low- and high-conflict conditions (Albrecht et al. 2008; McLoughlin et al. 2009; McLoughlin et al. 2014) and the Fast Task, which is a four choice reaction time task with two conditions (Andreou et al. 2007; Kuntsi et al. 2005). Face-to-face clinical interviews were administered to the parent of each participant shortly before or after the participant's assessment.

6.3.3 Measures

6.3.3.1 Gestational Age

For the preterm-sibling pairs, gestational age information was obtained from Personal Child Health Records (PCHR) (also known as the "red book") which is the national standard health and development record given to parents by the National Health Service (NHS). For the ADHD and control sibling pairs, gestational age information was obtained by parental recall. The analyses use two different representations for gestational age. For dichotomous assessment, preterm birth was considered as <37 gestational weeks and term birth was considered ≥ 37 weeks. For continuous assessment, we converted gestational age to a linear scale that was referenced at 40 gestational weeks and ranged from –17.0 weeks (raw gestational age, 23 weeks) to 0 weeks (40+ weeks) (D'Onofrio et al. 2013).

6.3.3.2 ADHD symptoms (Conners)

Parents were asked to rate the behaviour of each sibling using the Revised Conners' Parent Rating Scale (CPRS-R) (Conners et al. 1998). The CPRS-R has two DSM-IV symptom sub-scales (inattentiveness and hyperactivity-impulsivity), each consisting of nine items that map onto DSM-

IV criteria. The sum of all 18 items calculates a total DSM-IV ADHD symptom score (values between 0 and 54), with a greater score indicating a greater rating of ADHD symptoms.

6.3.3.3 IQ

The verbal and performance design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999) were administered to all participants to derive estimates of IQ.

6.3.3.4 Digit span

The digit span subtest from the WISC-III (Wechsler, 1991) or the WAIS-III (Wechsler, 1997) was administered to participants aged below 16 years and aged 16 years or above, respectively, to obtain digit span forward (DSF) and backward (DSB). The forward test measures short-term verbal memory, while the backward test requires is a measure of working memory.

6.3.3.5 Cued flanker continuous performance task (CPT-OX)

This CPT task consists of 400 letter arrays formed of a centre letter with incompatible flankers on each side, and probes attention, preparation and response inhibition (Doehnert, Brandeis, Straub, Steinhausen, & Drechsler, 2008; Valko et al., 2009). The test consists of 400 letters presented for 150ms with a stimulus onset asynchrony of 1.65s in a pseudorandomised order at the centre of a computer monitor. The task involves the presentation of 80 Cues (XOX) followed either by 40 Go (OXO) and 40 NoGo (XDX) stimuli, alternated with random letter arrays as distractors. Participants were instructed to respond only to Cue-Go sequences, and to withhold the response in presence of a NoGo stimulus, of a Go not preceded by a Cue (40 trials), or of any other irrelevant letters. Cognitive-performance measures of MRT, RTV, commission errors (CE, i.e. response to NoGo), omission errors (OE, i.e. non-response to Go) were obtained from this task.

6.3.3.6 Arrow flanker task

The task was an adaptation of the Eriksen Flanker paradigm designed to increase cognitive load as used in previous studies (Albrecht et al., 2008; McLoughlin et al., 2009; McLoughlin et al., 2014). In each trial a central black fixation mark was replaced by a target arrow (a black 18mm equilateral triangle). Participants had to indicate whether this arrow pointed towards the left or right by pressing corresponding response buttons with their left or right index fingers. Two flanker arrows identical in shape and size to the target appeared 22mm above and below the centre of the target arrow 100ms prior to each target arrow. Both flankers either pointed in the same (congruent) or opposite (incongruent) direction to the target. As such, conflict monitoring is maximal during the incongruent condition. When the target appeared, both target and flankers remained on the screen for a further 150ms, with a new trial being presented every 1.65s. Trials were arranged in ten blocks of 40 trials. The task took approximately 13 minutes. Cognitive-performance measures of MRT, RTV and number of errors (left-right errors occurring when participants chose the wrong left or right response) were calculated separately for congruent and incongruent conditions.

6.3.3.7 Fast Task

Participants performed a four-choice RT task with a baseline condition (72 trials) with four empty circles (warning signals, arranged horizontally) first appearing for 8s, after which one of them (the target) was coloured in (Andreou et al., 2007). Participants were asked to press the response key that directly corresponded to the position of the target. Following a response, the stimuli disappeared from the screen and a fixed inter-trial interval of 2.5s followed. Speed and accuracy were emphasized equally. If the participant did not respond within 10s, the trial terminated. A comparison condition with a fast event rate (1s) and incentives followed the baseline condition (Andreou et al., 2007). Cognitive-performance measures of MRT, and RTV (SD of RTs) were calculated for each condition.

6.3.3.8 Electrophysiological recording and ERP analysis

The EEG was recorded from a 62 channel DC-coupled recording system (extended 10–20 montage), using a 500 Hz sampling-rate, impedances under 10 kΩ, and FCz as the recording reference. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi. EEG data were analyzed using Brain Vision Analyzer 2.0 (Brain Products, Germany). Raw EEG recordings were down-sampled to 256 Hz, re-referenced to the average of all electrodes, and filtered using Butterworth band-pass filters (0.1-30 Hz, 24 dB/oct). All trials were visually inspected and sections of data containing electrical or movement artifacts were removed manually. Ocular artifacts were identified using the infomax Independent Component Analysis algorithm (ICA) (Jung et al., 2000). Sections of data containing artifacts exceeding ± 100 μV or with a voltage step greater than 50 μV were automatically rejected. ERPs were extracted from the CPT-OX (Cue-P3, CNV, NoGo-P3) and arrow flanker (N2, ERN, Pe) tasks following procedures used on previous analyses on this sample (Cheung, Rijsdijk, McLoughlin, Brandeis, et al., 2015; Michelini et al., in press; Rommel et al. under review, Rommel et al. in prep. James et al. in prep – Chapter 5); see also Supplementary Material 6.2.

6.3.4 Statistical analyses

Regression-based corrections for age and sex were applied to cognitive and neurophysiological measures as is standard practice (McGue & Bouchard, 1984), before being transformed to ensure normality assumptions were met. MRT, RTV, NoGo-P3 residuals were skewed and log-transformed. IQ, DSF, DSB, CNV residuals were normally distributed. These measures were included as continuous variables. ADHD symptoms were explored as a continuous variable (Conners' Parent Rating Scale). Preterm birth was first studied as a dichotomous variable (preterm birth: born before <37 weeks' gestation) and secondly explored as a continuous variable (gestational age).

6.3.4.1 Variable selection and phenotypic correlations

The starting point for variable selection were ADHD symptoms and cognitive-neurophysiological measures which were previously shown to be impaired in a preterm group and term-born ADHD group, compared to unrelated term-born controls, in a sub-sample of the current study (i.e. excluding the unaffected siblings) (Rommel et al. under review, Rommel et al. in prep, James et al. in prep – Chapter 4). In order to reduce the number of statistical comparisons, for ERPs at multiple sites, we only used electrodes where previous preterm-control differences were maximal, and consequently analysed Go-P3 from Pz only, CNV at CPz only in the CPT-OX, and N2 at Fz only. In addition, in the Fast Task, cognitive performance measures of MRT and RTV from the baseline condition only are included in this analysis, as the baseline condition is more sensitive than the fast-incentive condition to preterm-control and ADHD-control differences in cognitive performance (James et al. in prep – Chapter 4; Cheung et al. under review). Finally, as CNV was obtained from two tasks (the CPT-OX and fast-incentive condition of the Fast Task), only the CNV from the CPT-OX was included in this analysis, as the CNV in the CPT-OX is more sensitive to preterm-control and ADHD-control differences (Rommel et al. under review, Cheung et al. under review, Cheung et al. 2016). According to these criteria the following 11 measures were retained for inclusion for further selection processes: IQ, short term memory (DSF), working memory (DSB); MRT and RTV (baseline condition) from the Fast Task, response preparation (CNV), response inhibition (NoGo-P3) from the CPT-OX; and congruent errors, conflict monitoring (N2), automatic (ERN), conscious (Pe) error processing from the arrow flanker task.

Using the whole sample in this analysis, individuals were separated into term (n=342) and preterm (n=197) groups. Using the 11 cognitive-neurophysiological variables previously selected, correlation models were carried out in the term and preterm group separately to further select variables which had a modest (Cohen, 1988) phenotypic correlation with ADHD symptoms (rPh>.20) in both groups (Supplementary Material 6.1). Maximum likelihood estimates of phenotypic correlations between ADHD symptoms and each cognitive-neurophysiological measure were estimated from a constrained correlation model in OpenMx, calculated separately

for term and preterm groups. Constraints to control for sibling relatedness and corrections for ascertainment on ADHD were applied. According to these criteria, IQ, and MRT and RTV in the baseline condition of the Fast Task, could be retained for inclusion for further analysis in the bivariate FNE moderation models (Supplementary Material 6.1).

6.3.4.2 Structural Equation Modelling on sibling data

Structural equation modelling in OpenMx was applied to sibling-pair data to decompose the variance of traits into aetiological factors. Whereas in twin studies, comparison between monozygotic (MZ) and dizygotic (DZ) twin pairs enables estimation of additive genetic (A), shared environmental (C) and non-shared environmental (E) influences, sibling pairs (all sharing 50% of their alleles and 100% of the environment they grow up in) only enable estimation of the combined effects of shared A and C (familial, F effects). In addition to familial effects, non-shared effects (NE) are estimated, representing effects due to non-shared environment/genes as well as possible measurement error (James et al. in press). Bivariate modelling on sibling data uses the cross-sib cross-trait information to decompose the observed phenotypic correlation between traits into aetiological factors (F and NE).

6.3.4.3 Cholesky decomposition to assess moderation effects on F/NE paths

The moderation effects of preterm birth as a dichotomous variable (term or preterm) were assessed by using a bivariate Cholesky decomposition (Rijsdijk & Sham, 2002) (Figure 6.1a) to decompose the covariation between the cognitive-neurophysiological variables and ADHD symptoms into contributions of F and NE influences. Decompositions were estimated for term and preterm groups separately to model the moderation effects of preterm birth (term or preterm) on the variance/covariance of F and NE paths (Figure 6.1a). Chi-square tests were conducted to indicate the goodness of fit between the aetiological pathways estimated for the

term and preterm groups. The significant Chi-square result showed that the model fit was significantly worse, and, as such, the moderator effect (term/preterm) was not removed from the model (Table 6.2).

The moderation effects of preterm birth as a continuous variable (gestational age) were assessed using a bivariate Cholesky decomposition to decompose the F and NE pathways for the following gestational age bins: 23-26 weeks (n=9), 27-28 weeks (n=12), 29-30 weeks (n=16), 31-32 weeks (n=29), 33-34 weeks (n=42), 35-36 weeks (n=84), 37-38 weeks (n=83), 39 (n=57), 40+ weeks (n=207). Similar constraints to the dichotomous preterm model were applied. A moderation coefficient was obtained for F and NE shared paths (f2,1, Ne2,1) and confidence intervals indicated their significance. Using the moderation coefficient, the covariance of cognitive-neurophysiological variables and ADHD symptoms attributed to F and NE influences can be estimated across gestational age (Figure 6.3).

6.3.4.4 Correlated factor solution to estimate the extent of F and NE influences

The correlated factors solution of the Cholesky decomposition (Figure 6.1b) are presented to provide an indication of the degree of overlap between F and NE aetiological influences between two variables at a time (e.g. F correlation between IQ and ADHD symptoms). Similar sibling design analyses have previously been performed by our group (see Cheung et al. 2012 for a more detailed description and rationale of the analysis). By using the correlations between the F and NE factors, and the standardized estimates, we calculated the extent to which the phenotypic correlation (Rph) between any two variables is due to F (Rph-F) and NE (Rph-NE), for the preterm and term groups separately, and express these contributions as a percentage where possible (Rph-F% and Rph-NE% respectively) (Figure 6.2).

6.3.4.5 Ascertainment correction

To account for the selected nature of the sample (selection on ADHD probands), the selection variable (ADHD) was included in all models with its parameters fixed to population-known values. This involves fixing the mean of ADHD symptoms to the mean population value. In addition, for the correlation and F-NE models the sibling correlation for ADHD symptoms and the F were fixed to 0.40, corresponding to a population reported heritability of 80% (in this case C=0) (see Rijsdijk et al. 2005 for further explanation and validation of this approach) (Rijsdijk et al. 2005).

6.4 Results

6.4.1 Moderating effects of preterm on F/NE paths

Chi-square tests showed that preterm birth, as a dichotomous variable (term or preterm), significantly moderated the aetiological pathways underlying the covariance between increased ADHD symptoms and lower IQ, increased MRT in the baseline condition of the Fast Task, and increased RTV in the baseline condition of the Fast Task (Table 6.2).

6.4.1.1 Extent of familial effects (F) and non-shared effects (NE)

We conducted further sibling-pair bivariate modelling on the cognitive-neurophysiological measures which had a significant moderating effect (Figure 6.1b). We calculated the extent to which the phenotypic correlation (Rph) between cognitive-neurophysiological measures and ADHD symptoms is due to F (Rph-F) and NE (Rph-NE), in the preterm and term groups, and express these contributions as a percentage (Rph-F% and Rph-NE% respectively) (Figure 6.2). In the preterm group, NE influences accounted for the majority (>55%) of the covariance between ADHD symptoms and IQ (Rph-NE%=59%, Rph=-0.24), MRT in the baseline condition of the Fast Task (Rph-NE%=95%, Rph=0.20) and RTV in the baseline condition of the Fast Task (Rph-

NE%=91%, Rph=0.22 (Figure 6.2). In the term group, F influences accounted for the majority of the covariance between ADHD symptoms and IQ (Rph-F%=66%, Rph=-0.42), MRT in the baseline condition of the Fast Task (Rph-F%=73%, Rph=0.33) and RTV in the baseline condition of the Fast Task (Rph-F%=73%, Rph=0.44) (Figure 6.2).

6.4.2 Moderating effects of gestational age on F/NE paths

The continuous variable of gestational age showed a significant moderating effect on the aetiological pathways underlying the covariance between increased ADHD symptoms and lower IQ, increased MRT in the baseline condition of the Fast Task, and RTV in the baseline condition of the Fast Task. Specifically, there was a significant moderating effect of gestational age on both NE and F pathways underlying the relationship between ADHD symptoms and IQ, and RTV, in the baseline condition of the Fast Task (Table 6.3). The significant moderating effect of gestational age on only the F pathways was observed for the relationship between ADHD symptoms and MRT in the baseline condition of the Fast Task (Table 6.3).

6.4.2.1 Extent of Familial effects (F) and non-shared effects (NE)

For the associations showing a significant moderating effect, we further plotted the extent to which the covariance between cognitive-neurophysiological measures and ADHD symptoms is due to F and NE influences, across gestational age (Figure 6.3). For the covariance between ADHD symptoms and IQ, and between ADHD symptoms and RTV, the extent of covariance that is attributed to NE influences significantly decreases with increasing gestational age, whereas the extent that is attributed to F influences significantly increases with increasing gestational age. For the covariance between ADHD symptoms and MRT, the extent attributed to NE influences does not significantly change with increasing gestational age, whereas the extent that is attributed to F influences does significantly change with increasing gestational age (Figure 6.3).

Table 6.2. Fit statistics to assess the moderation effect of preterm birth on the aetiological pathways underlying the association between cognitive variables and ADHD symptoms.

Variable	$\Delta\chi^2$	Δdf	p
IQ	**24.53**	**2**	**<0.01**
MRT	**16.33**	**2**	**<0.01**
RTV	**9.25**	**2**	**<0.01**

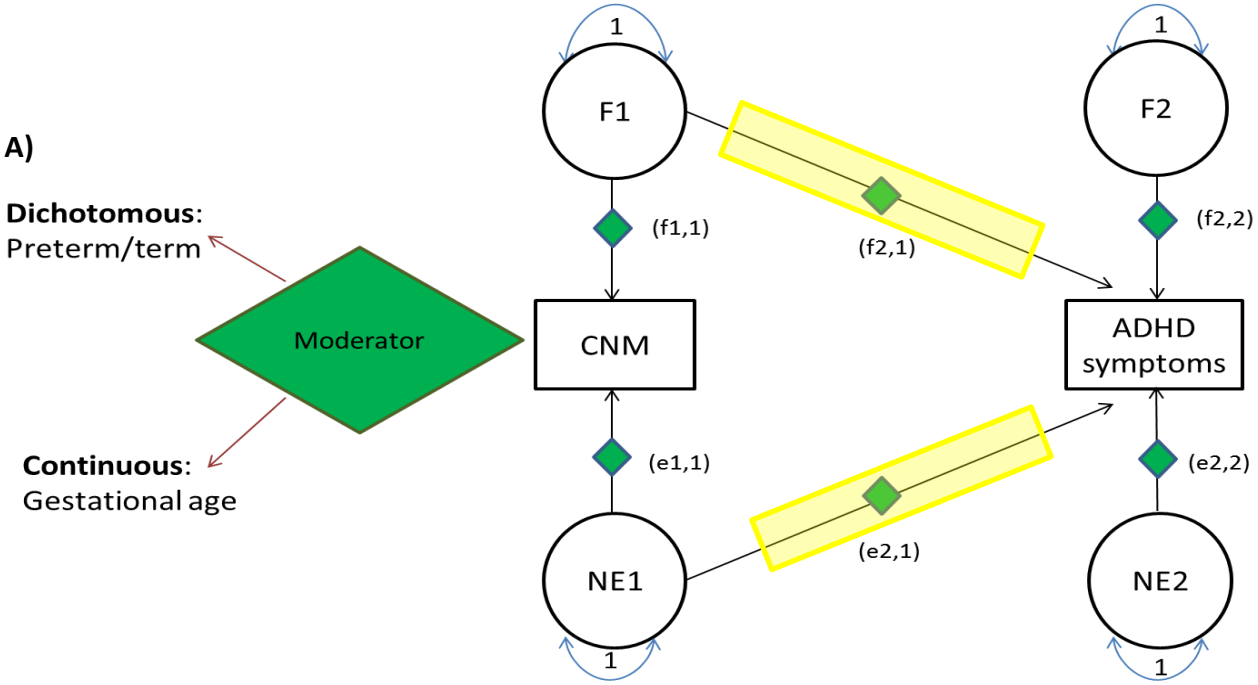
A significant moderation effect of preterm birth is indicated by a significant ($p<0.05$) chi-squared test, which assesses the goodness of fit between the aetiological pathways estimated for term and preterm groups. $p<0.05$ indicated in bold. MRT=mean reaction time in ms; RTV=reaction time variability in ms. $\Delta\chi^{2=}$change in chi-squared; Δdf=change in degrees of freedom.

Table 6.3. The moderating effect of gestational age on the extent that familial (F) and non-shared effects (NE) pathways underlying the association between cognitive variables and ADHD symptoms.

	Moderation coefficient of gestational age	
Variables	F pathways	NE pathways
IQ	**1.56 (1.11, 1.99)**	**1.36 (0.96, 1.78)**
MRT	**0.85 (0.40, 1.24)**	0.01 (-0.26, 0.28)
RTV	**1.00 (0.67, 1.33)**	**-1.06 (-1.62, -0.53)**

Pathways that are significant ($p<0.05$) are indicated in bold. MRT=mean reaction time in ms; RTV=reaction time variability in ms.

Figure 6.1. Bivariate graphical models between cognitive-neurophysiological measures (CNM) and ADHD symptoms to show A) the Cholesky decomposition model which is used to test the effects of a dichotomous (preterm or term) or continuous (gestational age) moderator: the highlighted yellow paths denote the pathways used to assess the underlying covariance between CNM and ADHD symptoms. B) Standardised solution of the full correlated factor model used to assess the effects of the dichotomous moderator. * Indicates p<0.05.



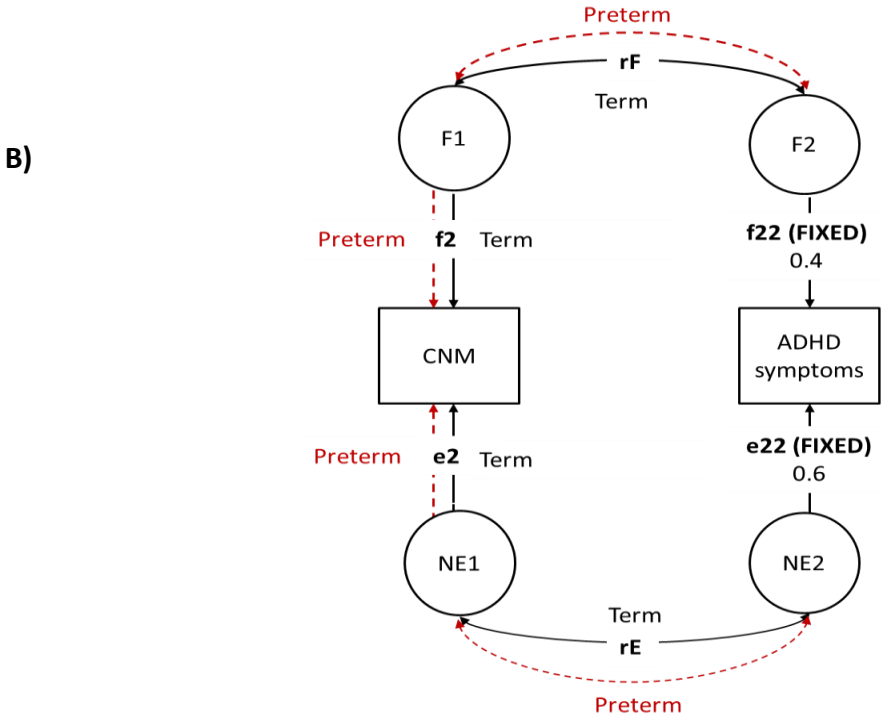


Figure 6.2. Graphical representation of percentage of familial (Rph-F%) and non-shared effects (Rph-NE%) underlying the phenotypic association between selected cognitive variables and ADHD symptoms, in preterm and term groups.

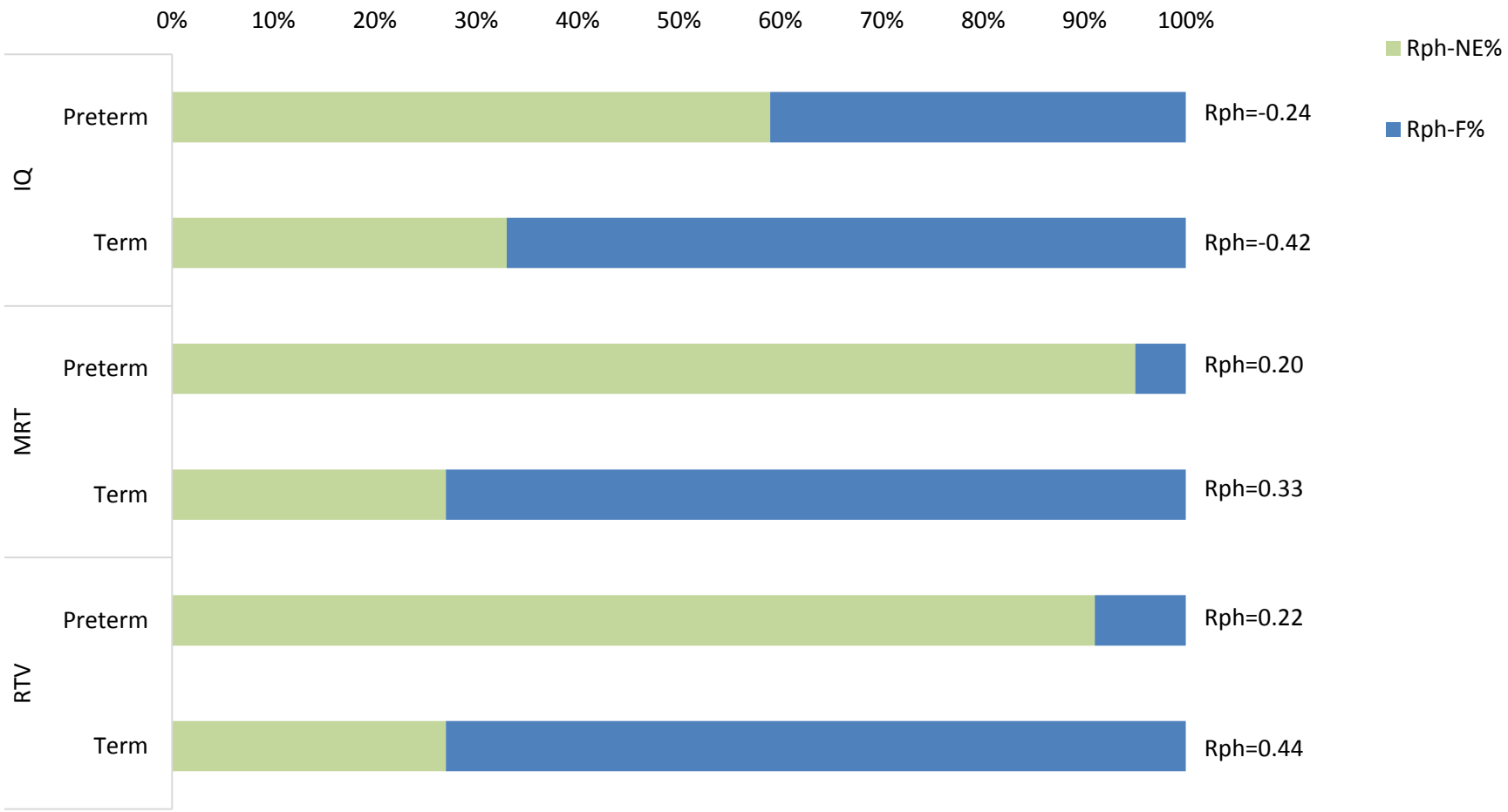
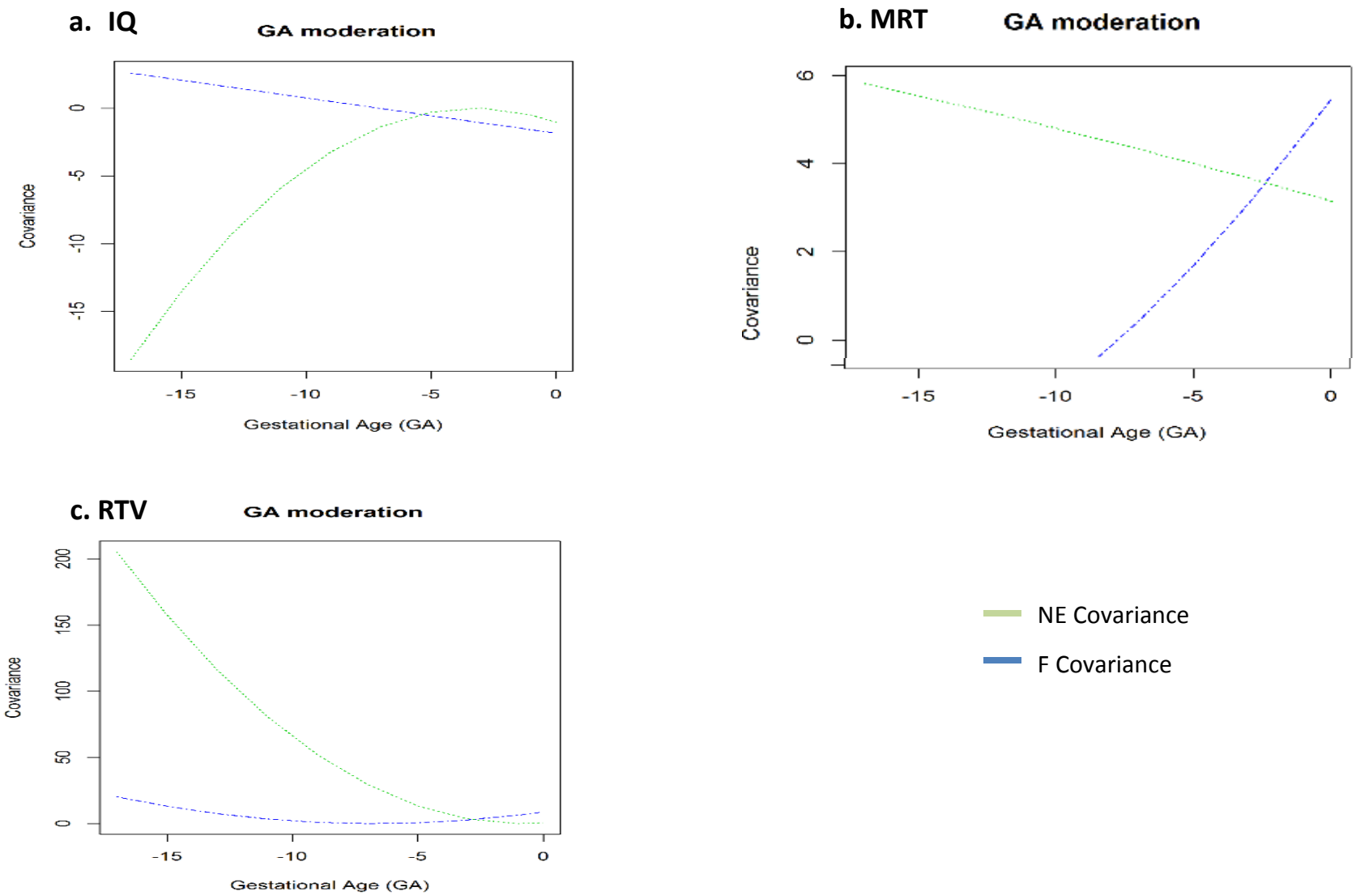


Figure 6.3. Graphical representation of the covariance of cognitive variables and ADHD symptoms explained by familial (F) and non-shared effects (NE) influences estimated at each gestational age.



6.5 Discussion

In this novel large scale sibling-study, we found that the aetiology between ADHD symptoms and specific cognitive-neurophysiological impairments is significantly different between preterm-born and term-born individuals. We find, first, that preterm birth significantly moderates the aetiological pathways underlying the relationship between increased ADHD symptoms and IQ, and speed (MRT) and variability (RTV) of reaction times. Second, we find that, the majority of the aetiological relationship between ADHD symptoms and IQ, and speed and variability of reaction times, was accounted for by non-shared effects in the preterm group, and by familial influences in the term group. The pattern of findings indicate that the association between ADHD symptoms and the specific cognitive impairments is largely due to familial influences among term-born individuals, but largely due to non-shared effects (including preterm birth as an environmental insult) among preterm-born individuals. Overall our findings provide novel insight into the relationship between preterm birth and aetiological pathways to ADHD symptoms and associated impairments and suggest differentiating aetiological pathways of the association between cognitive impairments and ADHD symptoms between individuals born preterm and term.

We establish a significant moderating effect of preterm birth on the aetiological relationships between cognitive impairments and ADHD symptoms. A noteworthy one, first of all, is our finding that preterm birth significantly alters the aetiological relationships underlying the covariance of ADHD symptoms and lower IQ. Whilst meta-analyses between IQ and preterm (Kerr-Wilson et al., 2012) and ADHD (Frazier et al., 2004) groups, have demonstrated a strong and consistent association between lower IQ in both preterm and ADHD groups, little is known about the aetiological relationship between IQ and ADHD in preterm groups. We can demonstrate, for the first time, that the association between lower IQ and increased ADHD symptoms, has varying aetiological influences depending on preterm birth status. In addition to the association between ADHD symptoms and lower IQ scores, we found that preterm birth was a significant moderator of the underlying covariance between increased ADHD symptoms and increased speed and

variability of reaction times. These findings indicate that for preterm and term-born individuals, the same observed association between ADHD symptoms and IQ and reaction time performance impairments may have differentiating underlying aetiological influences.

For the associations between cognitive-neurophysiological impairments and ADHD symptoms which showed significant moderating effects of preterm birth, we investigated to what extent the familial and non-shared influences accounted for the phenotypic relationship, which revealed the following pattern: for preterm-born individuals, non-shared effects accounted for the majority (over >55%) of the aetiological overlap between ADHD symptoms and all of the investigated cognitive impairments; on the contrary, for term-born individuals, familial influences attributed to the majority of the aetiological overlap. This pattern indicates that the association between ADHD symptoms and IQ, and the speed and variability of reaction times, is largely due to familial influences among term-born individuals, but largely due to non-shared effects (including preterm birth as an environmental insult) among preterm-born individuals. These findings indicate that whilst the associations between increased ADHD symptoms and lower IQ, and between ADHD symptoms and increased speed and variability of reaction times, may look similar from an observational perspective, the association may have different underlying causes and consequential pathophysiological processes between term-born and preterm-born individuals.

When we further explored associations of the moderating effect of the continuous measure of gestational age, the same pattern of significant associations emerged, indicating that gestational age significantly moderates the aetiological pathways underlying the covariance between increased ADHD symptoms and increased IQ, and increased speed and variability of reaction times. This emphasises the need of future research to explore the specific mechanisms whereby earlier gestational age leads to these cognitive impairments and increased ADHD symptoms, and to create early identification and intervention strategies to minimise impairments, especially in early born individuals at the greatest risk.

The present study is, to our knowledge, the first family study to investigate the moderating effects of preterm birth on the association between cognitive-neurophysiological measures and ADHD symptoms. Whilst our adolescent and young adult sample offers a unique perspective, it would be informative to examine the hypotheses again in future follow-up assessments at a later stage in adulthood to assess the stability of the aetiological association between ADHD symptoms and cognitive impairments, as well as in independent samples.

In conclusion, our findings provide novel insights into the differentiating aetiological pathways to cognitive impairments and increased ADHD symptoms in preterm-born and term-born individuals. Focusing on cognitive impairments among preterm-born adolescents, our findings reflect a potential preterm-birth related pathway (as a non-shared effects insult pathway) to ADHD symptoms and impairments in IQ and speed and variability of reaction times. Future research should explore the specific mechanisms whereby the environmental insult of preterm birth may lead to these cognitive impairments and increased ADHD symptoms.

Chapter 7 - GENERAL DISCUSSION AND CONCLUSIONS

7.1 Abstract

This concluding chapter summarises the key findings from this thesis. I will consider the wider implications of the research for individuals with attention-deficit/hyperactivity disorder (ADHD), and for preterm-born individuals. I will then provide an overview of general strengths and limitations to this body of work and suggest future directions. The chapter finishes with final conclusions.

7.2 Thesis aims

The first part of this thesis used a combination of cognitive, neurophysiological, developmental and sibling-comparison approaches to better understand arousal dysregulation in ADHD. Specifically, we used a measure of peripheral arousal (skin conductance), and explored the phenotypic association of peripheral arousal in ADHD during a slow, unrewarded condition and a faster condition with rewards, and investigated the aetiological association with fluctuating reaction times and ADHD (Chapter 2). We further investigated whether arousal, as well as impairments in attention processes, improve in ADHD remitters or reflect enduring deficits in all individuals with childhood ADHD (Chapter 3).

The second part of this thesis aimed to investigate the association between preterm birth and ADHD using a combination of cognitive, neurophysiological and sibling-comparison methods. The objective of Chapter 4 was to identify – on the same task used in Chapters 2 and 3 - whether preterm-born adolescents show identical or additional cognitive-neurophysiological impairments compared to term-born adolescents with and without ADHD. Previous research by our research group had established that the preterm group showed ADHD-like impairments in short-term and working memory, IQ, and ERP indexes of response preparation, response

inhibition, conflict monitoring and error processing (Rommel et al. under review, Rommel et al. in prep), and additional impairments on indexes of executive response control, suggestive of more wide-ranging neurophysiological deficits in the preterm group (Rommel et al. under review). We now aimed to investigate whether preterm-born adolescents showed ADHD-like or additional impairments on measures associated with attention and arousal from a baseline (slow, unrewarded) condition and fast-incentive condition. What had further remained unclear was whether the associations between preterm birth and specific cognitive-neurophysiological impairments are causally related to the preterm birth or due to other risk factors that characterise families with preterm-born children. In this light, the aim of Chapter 5 was to apply a within-sibling comparison design – comparing the preterm-born adolescents to their term-born sibling which controls for unmeasured familial confounding factors - to investigate if the previously established associations between preterm birth with increased ADHD symptoms and the specific cognitive-neurophysiological impairments still held when controlling for unmeasured familial confounding factors, consistent with a causal inference. The effects of preterm birth were explored as a dichotomous (preterm or term) and continuous (gestational age) variable. The final study (Chapter 6) combined all three sibling-pair samples that had been assessed on identical test batteries – ADHD, control and preterm sibling samples – to examine if the association between ADHD symptoms and specific cognitive-neurophysiological impairments is largely due to non-shared effects (consistent with preterm birth as an environmental insult) among preterm-born individuals, but largely attributed to familial factors (shared genetics and shared environment) among term–born individuals.

7.3 Key findings

7.3.1 Modifiable arousal in ADHD and its aetiological association with fluctuating reaction times.

Although a dysregulation of the arousal system has long been implicated in ADHD and is proposed to contribute to the fluctuations of cognitive performance consistently seen in ADHD, there has been limited direct evidence of this. Using a measure of peripheral arousal (skin conductance

level, SCL) in a large sample of ADHD and control sibling pairs we first investigated whether there was evidence of peripheral arousal problems in a slow, unrewarded (baseline) condition of a four-choice reaction time task – The Fast Task - and whether peripheral arousal was malleable in a fast-incentive condition. We found that participants with persistent ADHD had lower peripheral arousal compared to controls in the baseline condition, suggestive of under-arousal in ADHD. However, no group differences emerged in the fast-incentive condition, indicating that the under-arousal impairments observed in persistent ADHD is modifiable.

In addition, using multivariate sibling model fitting analyses we further investigated the phenotypic, aetiological relationship between peripheral arousal (in the baseline condition), fluctuating reaction times (indexed by reaction time variability, RTV), and ADHD. We found that decreased peripheral arousal was associated with increased fluctuating reaction times and that the covariance between peripheral arousal and fluctuating reaction times, and between peripheral arousal and ADHD, was mostly explained by shared familial effects. We further found evidence of two pathways from peripheral arousal to ADHD: an indirect causal pathway from arousal to fluctuating reaction times to ADHD, and a direct causal pathway from arousal to ADHD. Together these findings identify SCL as an informative index of underlying, malleable peripheral hypo-arousal in ADHD, and the demonstration of a link between peripheral arousal, fluctuating reaction times and ADHD provides physiological support for the arousal dysregulation account.

7.3.2 Peripheral hypo-arousal but not preparation-vigilance impairment endures in ADHD remission.

By studying those whose ADHD improves over time, we can gain valuable insight into the pathways to remission (Faraone, Biederman, & Mick, 2006; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Simon et al., 2009). During performance of the Fast Task we have previously demonstrated - including the findings from Chapter 2 (Chapter 2 - James et al. in press) - that persistent ADHD is linked to increased fluctuating reaction times (indexed by RTV),

impaired attention allocation (indexed by P3 amplitude) and peripheral hypo-arousal (indexed by SCL) during a slow, unrewarded baseline condition, as well as to an inability to adjust the preparatory state (indexed by contingent negative variation amplitude, CNV) in a changed context (Cheung et al. under review; James et al. in press). While fluctuating reaction times in the slow, unrewarded condition had already emerged as a marker of remission that improves with ADHD symptoms (Cheung et al. 2016), similar to fluctuating reaction times in a continuous performance test (CPT-OX) and flanker task (Michelini et al. in press; Cheung et al. 2016), we now extended our analyses to examine whether the neurophysiological measures in the Fast Task reflect enduring deficits unrelated to ADHD outcome or are markers of ADHD remission, improving concurrently with ADHD symptoms. We found that ADHD remitters differed from ADHD persisters, and were indistinguishable from controls, on markers of attentional allocation and response preparation, in line with previous studies indicating that ERP measures of preparation-vigilance are markers of remission. However, there were no group differences between ADHD remitters and persisters for peripheral hypo-arousal and dimensional analyses of ADHD symptoms and impairment outcome further confirmed the lack of an association between ADHD improvement and peripheral arousal. These results are unexpected, as we previously found a link between SCL-indexed hypo-arousal and fluctuating reaction times in individuals with persistent ADHD (Chapter 2 - James et al. in press), but our results suggest that peripheral hypo-arousal is an enduring deficit that is unrelated to ADHD symptom improvement, and does not mirror the remission pattern observed for fluctuating reaction times. As this was the first study to investigate peripheral arousal in ADHD remitters, our findings require replication. If replicated, our findings indicate that there may be alternative compensatory mechanisms that enable efficient preparation-vigilance processes, even in task conditions that induce persisting hypo-arousal in ADHD remitters. Yet it is notable that peripheral hypo-arousal is context-dependent, rather than a stable deficit, in ADHD remitters as they, similar to ADHD persisters, were indistinguishable from controls on peripheral arousal in the faster condition with rewards, demonstrating the malleability of the impairment.

7.3.3 Associations of preterm birth with ADHD-like impairments of attention and distinct impairments of attention and arousal malleability

Whilst preterm-born individuals have an increased risk of developing ADHD-like symptoms, and are reported to have cognitive and neurophysiological impairments that resemble impairments associated with ADHD, including attention and arousal regulation problems, direct comparisons across preterm and ADHD groups are scarce. Using the same task that was used in Chapters 2 and 3 – the Fast Task with a baseline (slow, unrewarded) condition and a faster condition with rewards - this study aimed to investigate directly whether preterm-born adolescents show identical or additional impairments in attention and arousal measures, compared to term-born groups with and without ADHD. This investigation of preterm-born adolescents indicated both impairments in cognition (speed and variability of reaction times) and brain function (indexes of response preparation; CNV amplitude) that are linked to increased ADHD symptoms. Our findings also indicated further, subtle impairments in a lack of malleability in specific neurophysiological processes of attention allocation (indexed by P3 amplitude) and peripheral arousal (SCL) that were unrelated to ADHD symptoms. Our results show how impairments in cognition and brain function in preterm-born individuals extend to at least adolescence, even in a well-functioning sample recruited from mainstream schools.

7.3.4 Are cognitive-neurophysiological impairments and increased ADHD symptoms in preterm-born adolescents consistent with a causal inference?

Including the results from Chapter 4, we have recently performed detailed investigations of the cognitive-neurophysiological impairments observed in preterm-born adolescents, when compared to unrelated term-born control adolescents (Rommel et al. under review, Rommel et al. in prep, James et al. in prep - Chapter 4). However, whether the associations are causally related to the preterm birth or due to other risk factors that characterise families with preterm-born children, has been largely unknown. To address this, we applied a within-sibling comparison design – comparing the preterm-born adolescents to their term-born sibling which controls for

unmeasured familial confounding factors - to investigate if the previously established associations between preterm birth with increased ADHD symptoms and the specific cognitive-neurophysiological impairments still held, consistent with a causal inference. The effects of preterm birth were explored as a dichotomous (preterm or term) and continuous (gestational age) variable. We found evidence for significant associations between preterm birth and increased ADHD symptoms, as well as with specific cognitive-neurophysiological impairments, such as IQ, preparation-vigilance processes (reflected by fluctuating reaction times and contingent negative variation), conscious error processing (reflected by Pe) and conflict monitoring (reflected by N2), when controlling for unmeasured familial confounding factors. These robust within-siblings associations indicate that preterm birth, or genetic factors associated with preterm birth, is likely in the causal pathway leading to these identified impairments. In contrast, we found evidence for a lack of an association between preterm birth and specific other cognitive-neurophysiological impairments, such as short-term and working memory (indexed by digit span forward and backwards), response inhibition (indexed by NoGo-P3) and automatic error processing (indexed by ERN), when controlling for unmeasured familial confounding factors. The previously obtained statistical associations between preterm birth and these latter processes (Rommel et al. under review, Rommel et al. in prep, James et al in prep – Chapter 4) are therefore unlikely to be due to preterm birth itself, but may have arisen due to other characteristics that differentiate families with a preterm-born child from other families. By distinguishing impairments that are consistent with a causal inference of preterm birth from those that are not, our results provide stepping stones towards better targeted interventions into those that are preterm-birth specific and those that address family-level risk factors.

7.3.5 Does preterm birth moderate the aetiological influences underlying the relationship between cognitive-neurophysiological impairments and ADHD symptoms?

Whilst in Chapters 4 and 5 we found that preterm birth is associated with an increased risk for ADHD symptoms, and ADHD-like cognitive and neurophysiological impairments, the pathways underlying the association between ADHD symptoms and ADHD-like impairments are still

unknown. Combining the preterm, ADHD and control sibling pairs used in this thesis, we aimed to investigate whether the aetiology between ADHD symptoms and specific cognitive-neurophysiological impairments is significantly different between preterm-born and term-born individuals. Specifically, we aimed to examine if the association between ADHD symptoms and specific cognitive-neurophysiological impairments was largely due to non-shared effects (consistent with preterm birth as an environmental insult) among preterm-born individuals, but largely attributable to familial factors (shared genetics and shared environment) among term–born individuals. We found that preterm birth, and gestational age, significantly moderated the aetiological pathways underlying the relationship between ADHD symptoms and IQ, and speed (mean reaction time (MRT) and variability (RTV) of reaction times. The majority of the aetiological association of ADHD symptoms with IQ and speed and variability of reaction times was accounted for by non-shared effects in the preterm group, and by familial influences in the term group. This pattern indicates that the association between ADHD symptoms and the specific cognitive impairments is largely due to familial influences among term-born individuals, but largely due to non-shared effects (including preterm birth as an environmental insult) among preterm-born individuals. Whilst the association between these cognitive impairments and increased ADHD symptoms may look similar from an observational perspective, our findings suggest that the association may have different underlying causes and consequential pathophysiological processes between term-born and preterm-born individuals.

7.4 Wider implications

7.4.1 Arousal dysregulation in ADHD

Our aims of Chapter 2 and 3 were based on exploring a measure of peripheral arousal in ADHD. Combining our findings, we find evidence of hypo-arousal in a slow, unrewarded condition in ADHD persisters (Chapter 2), and further show that hypo-arousal is an enduring deficit in ADHD, as it is not related to ADHD symptom improvement (Chapter 3). Whilst this is the first study to

investigate arousal in ADHD remitters, the finding of hypo-arousal in ADHD supports theories which have long proposed that arousal dysregulation is involved in ADHD aetiology.

In addition, in ADHD persisters we found that impairments in fluctuating reaction time were associated with hypo-arousal, and that shared familial influences accounted for the covariance (Chapter 2); whilst in ADHD remitters, we found no impairments in fluctuating reaction times, or other preparation-vigilance processes, despite the hypo-arousal (Chapter 3). This pattern raises the possibility that ADHD remitters may have compensatory mechanisms that enable efficient preparation-vigilance processes, even in task conditions that induce persisting hypo-arousal (Chapter 3). In this context it is worth noting that in our sibling modelling we obtained (preliminary) evidence of two pathways from peripheral arousal to persistent ADHD diagnosis: an indirect causal pathway from arousal to fluctuating reaction times to ADHD, and a direct causal pathway from arousal to ADHD (Chapter 2). It is plausible that ADHD remitters have differentiating processes (such as compensatory mechanisms) that moderate the causal pathways from hypo-arousal to ADHD.

In addition, it is notable that our findings from both studies demonstrate how peripheral hypo-arousal is context-dependent, rather than a stable deficit, in both ADHD persisters (Chapter 2) and ADHD remitters (Chapter 3); in the faster condition with rewards, both groups were indistinguishable from controls, demonstrating the malleability of this impairment.

7.4.2 Preterm birth as a risk factor for ADHD and associated cognitive-neurophysiological impairments

The results in Chapter 4 extends our prior analyses by investigating the attentional and arousal profile of preterm-born adolescents compared to term-born adolescents with and without ADHD. Our results firstly, pointed to specific ADHD-like impairments in cognition and brain function, that are further linked to increased ADHD symptoms in the preterm-born individuals.

This is in line with studies suggesting that preterm birth may represent a risk factor for developing ADHD-like cognitive and neurophysiological impairments. However, our findings also indicate further, subtle impairments in lack of malleability in specific neurophysiological processes (attention allocation and peripheral arousal) that are unrelated to ADHD symptoms, indicating there are differentiating neurophysiological processes in the preterm group. The reduced neurophysiological sensitivity to the effects of incentives and a faster event rate in the preterm-born individuals is intriguing, calling for further investigation in future research; for example, by investigating whether preterm-born individuals with ADHD also display this reduced sensitivity. Overall, our findings between ADHD and preterm groups suggest that preterm birth is associated with only some, and not all, impairments seen in ADHD, as well as with further unique impairments not associated with ADHD.

7.4.3 Preterm birth as a causal risk factor for ADHD and associated cognitive-neurophysiological impairments

In Chapter 5 we found robust within-siblings associations between preterm birth and increased ADHD symptoms, as well as with specific cognitive-neurophysiological impairments, such as IQ, preparation-vigilance processes (RTV, CNV), conscious error processing and conflict monitoring, indicating that preterm birth,

or genetic factors associated with preterm birth, is likely in the causal pathway leading to these identified impairments. In chapter 6, we further provide evidence that that non-shared effects pathways (including preterm-birth as an environmental insult) largely account for the association between preterm birth and increased ADHD symptoms and lower IQ, as well as increased MRT and RTV in preterm-born individuals, whereas in term-born individuals, these associations are largely due to familial influences. These findings are in line with preterm birth being on a causal pathway to ADHD symptoms, lower IQ, and impairments in speed and variability of reaction times, reflecting lapses of attention in preterm-born individuals.

From our converging evidence from Chapters 4, 5 and 6, it is increasingly clear that being born preterm places an individual at an increased risk of developing ADHD symptoms, some ADHD-like cognitive-neurophysiological impairments, and additional cognitive-neurophysiological impairments. Future research should explore the specific mechanisms whereby the environmental insult of preterm birth can lead to these cognitive-neurophysiological impairments and increased ADHD symptoms. For example, it has been shown that proliferation and strengthening of brain connections, vital for complex brain networks, is the dominant neurodevelopmental process throughout the third trimester (29 to 40 weeks gestation). As such, it is feasible that giving birth prematurely could result in disruption of developing brain networks associated with ADHD, as well as disruption of other networks associated with additional impairments (Ball et al., 2014; van den Heuvel et al., 2014). Identification, prevention and intervention strategies could be developed based on targeted interventions into those impairments that have a causal inference of preterm birth, or genetic factors associated with preterm birth, including the association between preterm birth and ADHD symptoms.

7.4.4 Preterm birth as a family-level risk factor for ADHD

In contrast to preterm birth being a causal risk factor, in chapter 5, we find evidence for a lack of an association between preterm birth and specific other cognitive-neurophysiological impairments, such as short-term memory, working memory and inhibition, when controlling for unmeasured familial confounding factors, inconsistent with a causal inference of preterm birth. Instead these results imply that the previously obtained statistical associations between preterm birth and these processes (Rommel et al. under review, Rommel et al. in prep, James et al. in prep – Chapter 4) are therefore unlikely to be due to preterm birth as itself, but may have arisen due to other characteristics that differentiate families with a preterm-born child from other families. By distinguishing impairments that are consistent with a causal inference of preterm birth from those that are not, our results provide stepping stones towards better targeted interventions into those that are preterm-birth specific and those that address family-level risk factors. Identification, prevention and intervention strategies could be developed based on targeted

interventions into these impairments that are associated with family-level risk factors in preterm-born individuals.

7.4.5 Preterm birth impairments and implications on education

Research suggests that teachers may lack awareness of the increased risk of ADHD symptoms and affected cognitive ability outcomes of children born preterm (Henderson, Beer, Wolke, & Johnson, 2012). Due to the lack of awareness among teachers, it is plausible that many preterm-born individuals with cognitive and neurophysiological impairments, and ADHD-like symptoms, are not identified and receiving the appropriate support (Brogan et al., 2014; Samantha Johnson et al., 2014). The under-detection of problems in preterm-born individuals has led to the notion for routinely screening preterm-born individuals for ADHD in an educational setting to help identify subtle, subclinical difficulties (Brogan et al., 2014; Johnson et al., 2014); based on our findings of impairments in preterm-born individuals, this notion warrants further investigation. It is striking that even within our preterm sample, who were a well-functioning sample recruited from mainstream schools, we still observe clear differences between preterm-born individuals compared to term-born peers (Chapter 4), or term-born siblings (Chapter 5), which emphasises how impairments are still present in preterm-born individuals at least a decade after the preterm birth event.

7.4.6 Categorical and dimensional approaches to ADHD and preterm birth

Throughout this thesis, we have used both categorical and dimensional approaches to ADHD and preterm birth. Using continuous measures of preterm birth and ADHD is likely to parallel pathophysiology, and has been valuable in understanding the relationship between ADHD symptoms and decreasing gestational age. For example, studying ADHD symptoms instead of ADHD diagnosis in Chapter 6 was valuable to investigate the increased risk of ADHD symptoms in preterm-born adolescents, given that studies have showed that, even in the absence of an ADHD diagnoses, there is a generally higher level of attention difficulties among preterm-born

adolescents which still impacts negatively on their educational performances (Samantha Johnson & Wolke, 2013). As another example of how using both approaches was helpful, in Chapter 5, whilst using the categorical definition of preterm birth was useful in ascertaining the causal pathways of preterm birth to associated cognitive-neurophysiological outcomes, by also using gestational age, we could conclude that these impairments are more severe with decreasing gestational age, which highlights that the most preterm born individuals are at the highest risk for developing impairments caused by preterm birth insults.

7.5 Strengths and limitations

7.5.1 Age range

The age range of the samples used this thesis - the ADHD and control sibling pair sample (Chapters 2, 3, 4 and 6), and the preterm sibling pair sample (Chapters 4, 5 and 6) - was 11-25, therefore restricting all of the analyses in this thesis to adolescents and young adults. As very few studies have investigated the cognitive-neurophysiological profiles of adolescents and young adults with ADHD, or in preterm-born adolescents and young adults, the age range of the samples in this thesis offers a novel, exciting aspect to the research. However, the wide age range of the samples may result in heterogeneity in the cognitive-neurophysiological profiles. In addition, as our adolescent and young adult participants may still be undergoing cortical development, it is unclear to what extent the results from this thesis can be generalized to later stages of development. Future follow-up studies will be beneficial to further elucidate the stability of cognitive-neurophysiological profiles and impairments in ADHD and preterm-born groups.

7.5.2 Sample sizes

One of the greatest strengths of this thesis is the size of the samples used. The ADHD and control sibling-pair samples (used in chapters 2, 3, 4 and 6) consisted of over 400 participants in total, making it one of the largest cognitive, EEG and SC studies of ADHD to date. Even with some

missing data (311 participants from the original 404 participants had SC measured due to SC data collection starting after initial participants had been assessed), it is still the largest SC study of ADHD. However, due to the large persistence rates in the ADHD follow-up sample, the sample size for the ADHD remittance group was small (n=23). The preterm sibling-pair sample (Chapter 4, 5 and 6) consisted of over 300 participants, making it the largest cognitive, EEG, and SC study of preterm-born individuals to date. Combining these samples in this thesis has also allowed us to perform one of the largest cognitive-neurophysiological comparisons between ADHD and preterm groups.

7.5.3 Categorical and dimensional definitions of ADHD and preterm birth

Another strength of this thesis is the use of both categorical and dimensional approaches to ADHD and preterm birth. Whilst most studies dichotomize preterm birth and ADHD, continuous measures of preterm birth and ADHD improve statistical power and are thought to parallel pathophysiology (Morgan, Loo, & Lee, 2016). Categorical and dimensional approaches of ADHD and preterm birth were applied throughout the thesis.

7.5.4 Gestational age confirmation

For the preterm sibling pair sample, gestational age information was obtained from Personal Child Health Records (PCHR) (also known as the "red book"), which is the national standard health and development record given to parents by the National Health Service (NHS). Yet, for the ADHD and control sibling-pair samples, gestational age was assessed retrospectively. Whilst there are discrepancies in the methods used between the samples used in this thesis, it has been reported that parental recall of preterm birth is highly correlated with medical record data of gestational age (Yawn et al., 1998).

7.5.5 Sibling studies

A main strength to this thesis is that the samples in this thesis are sibling-pair samples – ADHD, control and preterm sibling-pair samples. The sibling design allowed us to gain valuable insight in whether there are similarities or differences in certain traits between affected and unaffected siblings growing up in the same family. The advantage of having this information (similarities/differences between siblings) is that it allows one to control for familial risk factors which are shared between families, such as maternal genetic risk factors for giving birth preterm, socio-economic status, ethnicity, as well as all other shared environmental and shared genetic risks. When certain cognitive-neurophysiological impairments or traits are similar in both affected and unaffected siblings, this infers that the impairments are probably related to an overall familial increased risk of developing the impairments, and that familial factors (such as shared genetics and shared family environment) are in the aetiological causal pathways to these disorders (Oerlemans et al., 2016). On the contrary, if certain cognitive-neurophysiological impairments or traits are different between affected and unaffected siblings, this infers that the impairments observed are probably caused by influences that make the siblings different (including non-shared environment and sibling-specific genetics). This information is crucial in inferring causality of pre- and perinatal factors, including preterm birth and birth weight. In most studies investigating the associations between pre- and perinatal influences on later outcomes, because groups may have differed on unmeasured risk factors, it is difficult to deduce whether the association with the negative outcomes is due to the pre- and perinatal factor per se or due to other environmental or genetic risk factors that characterise families (Thapar & Rutter, 2009). For example, risks associated with preterm birth include low socio-economic status, low maternal educational status, low or high maternal age, black ethnicity, single marital status, family history of preterm birth, smoking and alcohol during pregnancy, pre-existing health problems in mother and maternal genetic risk (Blencowe et al., 2012; Goldenberg et al., 1996, 2008a; Plunkett & Muglia, 2008); these are factors that can be controlled for in a sibling-comparison study. Whilst twin studies are an excellent method for disentangling genetic and

shared environmental influences from non-shared environmental influences underlying an association for most traits, they cannot be used to study adverse birth outcomes or preterm birth as environmental insult, given that twins in a pair have typically both been exposed to the same birth event. In contrast, sibling studies can be used to investigate the association between birth events and later outcomes, and can disentangle the extent that familial influences (influences that make siblings alike including shared genetic and environmental influences) and non-shared influences (influences that make siblings different including non-shared environment and sibling-specific genetics) underlie traits. However, sibling studies are unable to control for sibling-specific genetic influences. Consequently, in a sibling control design, when non-shared influences are found to largely account for associations, for example between gestational age and ADHD, whilst the causal role of shared-environment influences underlying this association can largely be ruled out, the causal role of genetic influences cannot. Therefore, we can only deduce that non-shared environmental influences and/or non-shared genetic influences are implicated in the causal pathway underlying the relationship between gestational age and ADHD. However, we can also draw from the strength of another study which investigated the association between gestational age and psychiatric outcomes - in a large population-based cohort study – who were able to conduct multiple sensitivity quasi-experimental designs (including sibling-comparison studies and cousin-comparison studies). They similarly reported, independent of shared familial confounds, earlier gestational age was, robustly, associated with an increased risk of ADHD (D'Onofrio et al., 2013). The same population-based cohort was also used in an analysis which suggested that sibling-specific genetic factors do not account for much of the variability in gestational age, implying the negligible role of sibling-specific genetics in our inferences (Svensson et al., 2009). The consistency between the results reported in this thesis on a UK sample, and between the large Swedish population sample, further strengthens the inferences we were able to draw, and gives the causal inference of preterm birth more credibility.

In order to make causal inferences it is important to reduce confounding factors. Sibling-comparison design are especially helpful, as, whilst they are unable to account for all

confounding factors, they can account for all genetic and environmental confounding factors that make sibling similar, therefore greatly reducing confounds which enables causal inferences to be strengthened. The design also helps to separate out the role of risk factors shared by siblings, and those that are specific to certain sibling-specific events. Therefore, sibling-comparison designs that can account for confounding familial factors are at the forefront of this field (D'Onofrio et al., 2013; Donovan & Susser, 2011; Lahey & D'Onofrio, 2010; Skoglund et al., 2014), and the application of sibling-comparison designs will remain invaluable in understanding the causality of pre- and perinatal factors on later negative outcomes.

7.5.6 Rater effects

Throughout the thesis, ADHD symptom ratings have been based on parent report. Whilst clinical guidelines for establishing an ADHD diagnosis recommended evaluating multi-informant accounts (including self-, parent-, teacher- ratings) in order to assess the presence, severity and pervasiveness of ADHD symptoms (Taylor et al., 2004), parent-rated reports of ADHD-symptoms have the highest and most consistent estimates compared to self- and teacher- ratings (Nikolas & Burt, 2010). In addition, a recent analysis, using one of the samples included in this thesis, has demonstrated that parent-reported ADHD symptoms had a greater agreement with objective markers of ADHD outcomes compared to self-reported ADHD symptoms (Du Rietz et al., 2016), in line with previous studies which showed a better predictive validity of parent-report to long-term outcomes of ADHD (Barkley et al., 2002).

7.5.7 Medication effects

For all samples used in this thesis, participants had to abstain from taking stimulant medication 48 hours before testing. This ensured that the results of the studies in this thesis could not be accounted for by short-term effects of medication. Although our additional analyses in Chapter 2 indicated no significant long-term effects of medication use on SC in our data, the long-term

effects of medication use cannot be precluded for our other findings. Potential effects of medication pose a difficult challenge to psychiatric research.

7.5.8 ERP methodology

Throughout the thesis, we chose to exclusively examine ERP amplitude measures and to analyse ERPs with and without prestimulus baseline correction. We chose to focus on ERPs for two reasons: 1) we were interested in event-specific electrical activity; 2) to make easier comparisons of our results to previous research in our group (Cheung et al., 2016; McLoughlin et al., 2009; Michelini et al., in press). In addition, for ERP measures, we chose only to explore amplitude measures and did not explore differences on peak latencies because: 1) results investigating amplitude measures in ADHD have more consistency and stronger evidence for ADHD-sensitive differences (Johnstone, Barry, & Clarke, 2013); 2) P3 in the Fast Task (Chapters 3, 4, 5) was examined using an area under the curve measure so latency could not be obtained. There is discrepancy in the ADHD literature about whether to routinely remove prestimulus ERP activity in preprocessing. It is reasoned that removing prestimulus ERP activity enables ERPs to be obtained which reflects the absolute change of neural activity. On the contrary, it has also been argued that not removing prestimulus ERP activity can enable ERP measures to be obtained that are thought to reflect absolute state of neural activity measured at the time. Our approach in this thesis, to obtain a complete understanding of our ERP results, was to analyse our ERP data (Chapter 3, 4, 5) both with (results reported in the main body of text of that Chapter) and without (results reported in the supplementary material or available from author) prestimulus baseline correction. However, the significance of the results did not change whether ERPs were or were not baseline corrected.

7.5.9 Sample Ascertainment

The ADHD and control sibling pairs in this thesis had taken part in previous research (Chen et al., 2008; Kuntsi et al., 2010), and were invited to take part in the Sibling EEG Follow-up Study (SEFOS)

(Cheung et al., 2015; Cheung et al., 2016). The ADHD probands were initially recruited through clinics and the control group was recruited from mainstream schools in the UK. Due to the requirements of the original recruitment, exclusion for both groups included IQ<70, a diagnosis of autism, epilepsy, brain disorders and any genetic or medical disorder associated with externalising behaviours that might mimic ADHD. However, given that ADHD and autism are highly comorbid (Mulligan et al., 2009), the exclusion of autism in this sample may not be fully representative of ADHD groups, and the generalisability of these findings may be limited to other ADHD populations. Future studies could explore whether our ADHD sensitive findings also apply to individuals who have ADHD and comorbid autism.

The preterm group were recruited from mainstream secondary schools in Southeast England. The ascertainment of the preterm group is largely consistent with the recruitment of the control group, aiming for an age and sex match. Therefore, the exclusion criteria of the preterm group were similar to the exclusion criteria in the control and ADHD groups (IQ<70, epilepsy, brain disorders and any genetic or medical disorder associated with externalising behaviours that might mimic ADHD), apart from one exception, that we did not exclude having a diagnosis of autism. We did not exclude preterm-born individuals who showed increased levels of any psychiatric disorder, including autism spectrum disorder, because preterm birth is also known to be associated with these disorders, and so excluding them would lead to a less representative preterm sample (D'Onofrio et al., 2013). Whilst it has been demonstrated that preterm birth increases the risk of being in a special education school (Chaikind & Corman, 1991; Pinto-Martin et al., 2004), individuals with significant difficulties would not have been able to perform the cognitive-EEG test battery in our study, for example, having motor problems could confound their ability to performing the reaction time tasks, and having an IQ<70 may limit their understanding of the required tasks. However, the ascertainment of the preterm group from mainstream schools only, may limit the representativeness of the preterm group. In addition, recruitment of the preterm sample may be subject to ascertainment bias, as the families who were willing to take part in the research may not be representative of the general population (Dollinger & Leong, 1993). However, we may expect cognitive-neurophysiological impairments to be even greater in

preterm-born individuals who are not in mainstream schools and from families who are not as willing to voluntarily take part in research. Therefore, it is striking that in this thesis, we find impairments in preterm-born adolescents compared to term-born adolescents, even in a relatively well-functioning sample recruited from mainstream schools, and in willing, volunteering families.

7.5.10 Multiple Testing

In line with the multidisciplinary approach of this thesis, I have gained insight into processes by testing and comparing multiple measures between groups. Throughout the analyses in this thesis, I used $p<0.05$ as the level of significance, in line with standard procedures, which enabled me to gain insight into where significant differences may occur. However, using a p-value of $p<0.05$ raises two issues. First, multiple comparisons can potentially provide multiple testing challenges and increase the likelihood of type-I errors (a "false-positive" result) (Sullivan & Feinn, 2012). Second, using a p value to deem the significance cannot inform about the size of the effect (Sullivan & Feinn, 2012). To address the issue of multiple testing in this thesis, I have used bonferroni corrections. Taking extra caution over this issue in Chapters 2, 5 and 6, I also tried to reduce the number of statistical comparisons by only selecting variables that previously demonstrated sensitivity between groups. To gain additional information about the size of the effect, I reported the effect size in addition to the significance level. Whilst significant p values help to understand if findings are due to chance, the effect size helps to understand the magnitude of differences found. Therefore, reporting both approaches is helpful to understand the full impact of the results.

7.6 Future directions

7.6.1 Replication

All of the studies in this thesis are novel and the findings require replication in larger, independent samples, in order to make strong inferences about the conclusions. Our study investigating the phenotypic and familial relationship between arousal, cognitive measures and ADHD was the first of it its kind, and future studies should confirm these associations. Twin studies may also further establish whether the familial influences we identified reflect largely shared genetic influences. Investigating skin conductance in ADHD remitters has not previously been studied therefore our finding of enduring hypo-arousal in ADHD remitters requires further replication in an independent, larger sample (Chapter 3). There have been few ERP and SC studies in preterm-born individuals to date; subsequently our findings in Chapter 4, 5 and 6 require replication in independent samples and in samples at different developmental stages to understand the stability of cognitive-neurophysiological profiles in preterm-born individuals across the lifespan.

7.6.2 Advanced EEG approaches

In line with commonly used approaches to ERP analyses, the ERPs obtained in this thesis relied on averaging ERP data to enhance the signal-to-noise ratio in order to obtain meaningful waveforms. However, this approach assumes that the signal in each trial has stable characteristics such as amplitude, latency and waveform across all the trials. Therefore, the ERP obtained when averaged across trials consists of multiple components may present a gross crude estimate of neural processes, potentially diminishing the inter-trial variability of ERP components. For example, when we observe a diminished amplitude in ADHD persisters (Chapter 3, 4, 5) or in preterm-born individuals (Chapter 4, 5), this could instead represent a greater inter-trial variability in these groups, whereby the ERP components vary more from trial to trial and thus result in a diminished averaged component and distorted ERP. Whilst the differences observed between groups are still informative, given that ADHD has been associated with high variability in performance measures and cognitive-neurophysiological response (Castellanos et al., 2005; Frazier-Wood et al., 2012; Kuntsi & Klein, 2012; Uebel et al., 2010), it would be useful in future research to investigate the underlying intra-individual variability in cognitive-neurophysiological responses within our data. Indeed, a recent study used single-trial event-

related approaches and demonstrated that individuals with ADHD showed greater variability in response-locked ERP latencies (Saville et al., 2014).

Recently advanced approaches, such as time-frequency analysis or individual-level independent component analysis (ICA), can avoid group-level averaging, offer finer resolution and have the potential to explore the intra-individual variability of ERP data on a trial-by-trial basis. Therefore, in future, ICA approaches could be applied, within our data, to examine the effects of intra-individual variability and inter-trial variability.

7.6.3 Preterm birth or low birth weight

Whilst a large focus of this thesis has been investigating preterm birth as a risk factor for ADHD, low birth weight has also been implicated as a causal risk factor for ADHD symptoms (Groen-Blokhuis, Middeldorp, van Beijsterveldt, & Boomsma, 2011). Whilst some studies provide evidence that gestational age is a stronger predictor ADHD than low birth weight (Linnet et al., 2006; Oerlemans et al., 2016), the relative importance of birth weight versus gestational age in the link with ADHD diagnosis and symptoms remains unclear. In future analyses we plan to further investigate, using the preterm and control sibling pairs, whether ADHD symptoms and cognitive-neurophysiological impairments are associated with birth weight in our sample.

7.6.4 Specificity of impairments in preterm-born individuals

A further future direction for our research, using the preterm and term sibling pairs, is to elucidate whether preterm birth predicts ADHD symptoms specifically, or if preterm birth is sensitive to other psychiatric symptoms, such as anxiety and ASD. For example, whilst twin studies have been valuable in establishing that the high co-morbidity between ADHD and ASD is attributed largely by shared genetic factors (Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008), genetic factors do not account for all the covariation and non-shared environmental effects,

including the effects of preterm birth, could partly contribute to the comorbidity. However, a recent study, combining ASD and ADHD cohorts in a stratification approach (n=1,234), demonstrated that whilst pre- and perinatal factors (including preterm birth) are associated with ADHD, and with ASD, the co-morbidity of ASD and ADHD is not likely explained by shared pre- and perinatal factors (Oerlemans et al., 2016).

7.6.5 Pathways mediating association between preterm birth and ADHD symptoms

Although the causal effects of preterm birth on ADHD symptoms have been implicated, the pathways mediating this association are not well known. That is, if preterm birth is a causal risk factor, there are, plausibly, risk processes that mediate this association, and identifying these risk processes is key to developing targeted, effective prevention and intervention schemes (Morgan et al., 2016). Future studies could further investigate what cognitive-neurophysiological impairments mediate, and are in the causal pathways, from preterm birth to subsequent ADHD symptoms. For example, a recent study investigating the plausible neurocognitive mediators of birth weight and ADHD symptoms in adolescents reported that fluid reasoning, as reflected by arithmetic, is part of a causal pathway between birth weight and ADHD symptoms (Morgan et al., 2016), although a substantial variance remained unexplained. This study also reported that short term or working memory (digit span forward and backward) did not mediate the association between birth weight and ADHD symptoms, implying they are not on the causal pathway (Morgan et al., 2016). The findings that short term and working memory are not on the causal pathways between birth weight and ADHD symptoms are in line with our findings in Chapter 5 of this thesis, which suggest that short term and working memory are not on the causal pathways from preterm birth.

7.7 Overall conclusions

In summary, this thesis conducted an in-depth cognitive-neurophysiological and sibling-pair investigation to study the aetiological influences underlying arousal dysregulation in ADHD and

how it changes with the developmental course of ADHD, and to study preterm birth as a risk factor of ADHD. We used both categorical and dimensional approaches to investigate preterm birth and ADHD. Our results and conclusions in this thesis demonstrate the rich insight that can be gained by combining multidisciplinary approaches to understanding ADHD and the association with preterm birth, gaining information of familial or non-shared influences underlying observed distinctions from a brain, cognitive and behavioural level.

The findings in this thesis suggest there is an enduring deficit in arousal in ADHD, which is unrelated to symptom improvement, but is shown to be malleable with a faster stimulus rate and incentives. The findings also inform on the relationship of preterm birth as a risk factor of ADHD. We find evidence of overlapping cognitive-neurophysiological impairments between individuals with ADHD and preterm-born individuals, and find additional impairments in the malleability of neurophysiological measures in the preterm group, indicative of more wide-ranging impairments and differentiating neurophysiological profiles. The findings from this thesis further suggest that cognitive-neurophysiological impairments in the preterm group differentiate into those which are in line with a causal effect of preterm birth (or genetic influences associated with preterm birth), and those in line with the effects of familial factors. The results additionally indicate that the association between ADHD symptoms and the specific cognitive impairments is largely due to familial influences among term-born individuals, but largely due to non-shared effects (including preterm birth as an environmental insult) among preterm-born individuals. Overall, by using a combination of cognitive, neurophysiological, developmental and sibling-comparison approaches, our findings provide new insights into the cognitive-neurophysiological processes underlying ADHD and into the underlying risk pathways between preterm birth and ADHD symptoms.

Chapter 8 - REFERENCES

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Chapter 9 – SUPPLEMENTARY MATERIAL

Supplementary Table 1. Means and group differences in SCL and SCR amplitude between 3 four-minute segments of baseline condition and the fast-incentive condition (controls=144, ADHD=73). Baseline 1: 0-3.59mins, Baseline 2: 4-7.59mins, Baseline 3: 8-11.59mins. Fast–incentive condition: 0-4 minutes.

	Control	*ADHD probands*	*Group comparisons*	
	Mean	Mean	t	p
SCL				
Baseline 1	1.86	1.56	2.41	0.01*
Baseline 2	1.83	1.52	1.99	0.03*
Baseline 3	1.79	1.51	2.10	0.03*
Fast-incentive	3.20	3.70	1.10	0.27
SCR amplitude				
Baseline 1	0.41	0.40	0.25	0.40
Baseline 2	0.37	0.37	1.21	0.20
Baseline 3	0.39	0.41	0.52	0.60
Fast-incentive	0.34	0.32	0.07	0.91

Group means of transformed data and subsequent group comparison tests are listed. Skin conductance level (SCL); skin conductance response (SCR) amplitude. *p<0.05.

Supplementary Table 2. Main effect of group (ADHD vs control), condition (segment of baseline condition vs the fast-incentive condition), and group x condition interaction, controlling for age (controls=144, ADHD=73). Baseline 1: 0-3.59mins, Baseline 2: 4-7.59mins, Baseline 3: 8-11.59mins. Fast–incentive condition: 0-4 minutes.

Condition	Main effects	T	p
SCL			
Baseline 1 vs fast-incentive	group	1.37	0.17
	condition	4.58	0.01
	group x condition	2.48	0.01
Baseline 2 vs fast-incentive	group	1.22	0.22
	condition	4.59	0.01
	group x condition	2.21	0.04
Baseline 3 vs fast-incentive	group	1.55	0.12
	condition	2.10	0.03
	group x condition	2.03	0.04
SCR amplitude			
Baseline 1 vs fast-incentive	group	1.39	0.16
	condition	0.81	0.42
	group x condition	0.75	0.45
Baseline 2 vs fast-incentive	group	0.95	0.34
	condition	0.52	0.61
	group x condition	0.45	0.34
Baseline 3 vs fast-incentive	group	0.78	0.30

	condition	0.55	0.56
	group x condition	0.69	0.49

Skin conductance level (SCL); skin conductance response (SCR) amplitude.

Supplementary Table 3. Means and group differences in SCL and SCR amplitude between unmedicated and medicated ADHD participants in the baseline condition and the fast-incentive condition (unmedicated=35, medicated=38), controlling for age.

	Unmedicated ADHD	*Medicated ADHD*	*Group comparisons*	
	Mean (SD)	Mean (SD)	t	p
SCL				
Baseline	1.66 (0.40)	1.56 (0.38)	0.67	0.50
Fast-incentive	5.27 (1.54)	5.49 (2.01)	0.76	0.45
SCR				
Baseline	-0.94 (0.49)	-0.83 (0.59)	-0.68	0.49
Fast-incentive	-1.32 (0.65)	-1.26 (0.76)	0.06	0.95

Note: raw scores are reported. Skin conductance level (SCL); skin conductance response (SCR) amplitude.

Supplementary Table 4. Main effect of group (ADHD vs control), condition (whole baseline condition vs fast-incentive condition), and group x condition interactions, controlling for age and stimulant medication use (controls=144, ADHD=73).

Main effect	t	P
SCL		
Group	0.10	0.91
Condition	29.94	<0.01
Group x condition	2.55	0.01
SCR amplitude		
Group	0.21	0.84
Condition	0.37	0.71
Group x condition	0.71	0.48

Skin conductance level (SCL); skin conductance response (SCR) amplitude.

Supplementary Table 5. Main effect of group (ADHD vs control), condition (whole baseline condition vs fast-incentive condition), and group x condition interactions in an un-medicated sample (controls=144, ADHD=35), controlling for age.

Main effect	t	P
SCL		
Group	1.47	0.14
Condition	20.88	<0.01
Group x condition	2.24	0.01
SCR amplitude		
Group	0.07	0.94
Condition	0.25	0.80
Group x condition	0.98	0.33

Skin conductance level (SCL); skin conductance response (SCR) amplitude.

Supplementary Table 6. Main effect of group (ADHD vs control), condition (whole baseline condition vs fast-incentive condition), and group x condition interactions controlling for age, and anxiety, and depression scores (controls=144, ADHD=73). Anxiety and depression scores are taken from the Clinical Interview Schedule-Revised (CIS-R).

Covariates	ADHD mean (SD)	Control Mean (SD)	t	p
Anxiety	*0.45 (0.93)*	*0.19 (0.54)*	2.00	0.05
Depression	*0.31 (0.80)*	*0.22 (0.56)*	0.73	0.47

Covariates	Main effect	t	P
Age and anxiety score			
	SCL		
	Group	0.58	0.56
	Condition	23.63	<0.01
	Group x condition	2.47	0.01
	SCR amplitude		
	Group	1.35	0.14
	Condition	0.87	0.49
	Group x condition	0.78	0.48

Age and depression score			
	SCL		
	Group	0.58	0.56
	Condition	23.63	<0.01
	Group x condition	2.47	0.01
	SCR amplitude		
	Group	1.31	0.19
	Condition	0.88	0.41
	Group x condition	0.72	0.47

Skin conductance level (SCL); skin conductance response (SCR) amplitude.

Supplementary Table 7. **Pearson correlations in ADHD and control groups separately, between skin conductance level (SCL), skin conductance response (SCR) amplitude and reaction time variability (RTV), in the baseline and fast-incentive condition.**

	SCL	SCR amplitude
Control		
RTV-baseline	-0.12	-0.10
RTV-fast-incentive	-0.16	-0.02
ADHD		
RTV-baseline	-0.31**	-0.09
RTV-fast-incentive	-0.29**	-0.32

** p<0.01. Skin conductance level (SCL); skin conductance response (SCR) amplitude.

Supplementary Material 4.1. Results without preterm-born individuals with a research diagnosis of ADHD.

Cognitive performance measures

For MRT data, a random intercept model indicated a significant main effect of condition (z=-30.88, p<0.01) and a main effect of group (z=1.99, p<0.05), but no significant group-by-condition interaction (z=-0.90, p=0.37). Post-hoc analyses revealed that, in the baseline condition, the preterm group showed significantly decreased MRT compared to the term-born ADHD group (t=-2.58, p<0.01), but significantly increased MRT compared to the term-born control group (t=2.62, p=0.03). In the fast-incentive condition, the preterm group showed significantly decreased MRT compared to the term-born ADHD group (t=-1.96, p<0.05), but significantly increased MRT compared to the term-born control group (t=2.96, p<0.05). The term-born ADHD group showed significantly greater MRT compared to the term-born control group in both the baseline (t=3.52, p<0.01) and fast-incentive (t=3.05, p<0.01) conditions. The within-group difference in MRT from the baseline to fast-incentive condition was significant in the preterm group (t=-16.45, p<0.01), the term-born ADHD group (t=-11.40, p<0.01) and the term-born control group (t=-16.45, p<0.01). Post-hoc tests showed that the slope in MRT, indexing the extent of change from the baseline to fast-incentive condition, in the preterm group was not significantly different compared to the term-born ADHD group (p=-1.28, p=0.20), but was significantly greater compared to the term-born control group (t=1.78, p=0.04). The slope in MRT was significantly greater in the term-born ADHD group (t=-2.90, p<0.01) than the control group.

For RTV data, a random intercept model indicated a significant main effect of condition (z=-14.60, p<0.01), a main effect of group (z=2.79, p<0.01) and a significant group-by-condition interaction (z=-2.04, p<0.05). Post-hoc analyses revealed that, in the baseline condition, the preterm group showed significantly decreased RTV compared to the term-born ADHD group (t=-1.48, p<0.05), but significantly increased RTV compared to the term-born control group (t=2.81, p<0.01). In the fast-incentive condition, the preterm group did not differ in RTV compared to the term-born ADHD group (t=-0.60, p=0.55), but showed significantly increased RTV compared to the term-

born control group (t=4.48, p<0.01). The term-born ADHD group showed significantly greater RTV compared to the term-born control group both in the baseline (t=3.42, p<0.01) and fast-incentive (t=2.58, p<0.01) conditions. The within-group difference in RTV from the baseline to fast-incentive condition was significant in the preterm group (t=-5.79, p<0.01), the term-born ADHD group (t=-6.23, p<0.01) and the term-born control group (t=-11.06, p<0.01). The slope in RTV in the preterm group was less steep compared to the ADHD group (t=-2.25, p=0.03), but was significantly greater than in the control group (t=-3.08, p<0.01). The slope in RTV was significantly greater in the term-born ADHD group compared to the term-born control group (t=-2.80, p<0.01).

ERP measures

For CNV amplitude, a random intercept model indicated a significant main effect of condition (z=-16.99, p<0.01), a significant main effect of group (z=3.21, p<0.01) and a significant group-by-condition interaction (z=8.87, p<0.01). Post-hoc analyses revealed no group differences in the baseline condition between the preterm group and the term-born ADHD group (t=-1.23, p=0.22), between the preterm group and the term-born control group (t=-0.91, p=0.37) and between the term-born ADHD group and the term-born control group (t=0.09, p=0.93). In the fast-incentive condition, the preterm group was not significantly different compared to the term-born ADHD group (t=1.20, p=0.23), but the preterm group had a significantly reduced CNV amplitude compared to the term-born control group (t=5.65, p<0.01). The term-born ADHD group showed significantly reduced CNV amplitude compared to the term-born control group in the fast-incentive condition (t=2.92, p<0.01). The within-group difference in CNV amplitude from the baseline to fast-incentive condition was significant in the preterm group (t=-5.60, p<0.05), term-born ADHD (t=-6.94, p<0.01) and control (t=-10.50, p<0.01) groups. The slope in CNV amplitude in the preterm group, from the baseline to fast-incentive condition, was significantly less steep compared both to the term-born ADHD (p=-2.37, p<0.05) and control (t=-7.34, p<0.01) groups. Compared to the term-born control group, the CNV slope was significantly less steep in the term-born ADHD group (t=-3.17, p<0.01).

For P3 amplitude, a random intercept model indicated a significant main effect of condition ($z=2.70$, $p<0.01$), a main effect of group ($z=-3.63$, $p<0.01$) and a significant group-by-condition interaction emerged ($z=-5.14$, $p<0.01$). Post-hoc analyses revealed that, in the baseline condition, the preterm group was not significantly different compared to either the term-born ADHD ($t=-0.48$, $p=0.63$) or control ($t=-1.43$, $p=0.16$) group. The term-born ADHD group showed significantly decreased P3 amplitude compared to the term-born control group in the baseline condition ($t=2.61$, $p<0.01$). In the fast-incentive condition, the preterm group showed significantly decreased P3 amplitude compared both to the term-born ADHD ($t=-2.74$, $p<0.01$) and control ($t=-5.18$, $p<0.01$) groups. P3 amplitude in the fast-incentive condition did not differ between the term-born ADHD and control group ($t=1.43$, $p=0.17$). The within-group difference in P3 amplitude from the baseline to fast-incentive condition was not significant in the preterm group ($t=-1.21$, $p=0.23$), but significant in the term-born ADHD ($t=-3.76$, $p<0.01$) and the control ($t=-6.61$, $p<0.01$) groups. The slope in P3 amplitude in the preterm group was less steep compared to both the term-born ADHD ($p=2.54$, $p<0.01$) and term-born control ($t=3.78$, $p<0.01$) groups. The slope in P3 amplitude did not differ between the term-born ADHD group compared to the term-born control group ($t=-0.39$, $p=0.70$).

SC measures

For SCL, a random intercept model indicated a significant main effect of condition ($z=-6.04$, $p<0.01$), but no main effect of group ($z=0.40$, $p=0.69$), or group-by-condition interaction ($z=-1.31$, $p=0.19$). Post-hoc analyses revealed that, in the baseline condition, the preterm group showed significantly increased SCL compared to the ADHD group ($t=-2.75$, $p<0.01$), but did not differ from the control group ($t=0.67$, $p=0.50$). In the fast-incentive condition, the preterm group was not significantly different compared to the ADHD group ($t=-0.08$, $p=0.94$) or compared to the control group ($t=-0.64$, $p=0.52$). The term-born ADHD group showed significantly decreased SCL compared to the term-born control group in the baseline condition ($t=-2.09$, $p<0.05$), but not fast-incentive condition ($t=0.89$, $p=0.37$). The within-group difference in SCL from the baseline to

fast-incentive condition was not significant in the preterm group ($t=1.06$, $p=0.29$), but was significant in the term-born ADHD ($t=9.29$, $p<0.01$) and control ($t=4.85$, $p<0.01$) groups. The slope in SCL in the preterm group was less steep compared to both the ADHD ($p=2.37$, $p<0.01$) and control ($t=-1.89$, $p<0.05$) groups. The slope in SCL was significantly steeper in the term-born ADHD group compared to the term-born control group ($t=2.24$, $p<0.05$).

Supplementary Material 4.2. Analysis of an age-matched subsample

Cognitive performance measures

For MRT data, a random intercept model indicated a significant main effect of condition ($z=-30.88$, $p<0.01$) and a main effect of group ($z=1.99$, $p<0.05$), but no significant group-by-condition interaction ($z=-0.90$, $p=0.37$). Post-hoc analyses revealed that, in the baseline condition, the preterm group showed significantly decreased MRT compared to the term-born ADHD group ($t=-2.58$, $p<0.01$), but significantly increased MRT compared to the term-born control group ($t=2.62$, $p=0.03$). In the fast-incentive condition, the preterm group showed significantly decreased MRT compared to the term-born ADHD group ($t=-1.96$, $p<0.05$), but significantly increased MRT compared to the term-born control group ($t=2.96$, $p<0.05$). The term-born ADHD group showed significantly greater MRT compared to the term-born control group in both the baseline ($t=3.52$, $p<0.01$) and fast-incentive ($t=3.05$, $p<0.01$) conditions. The within-group difference in MRT from the baseline to fast-incentive condition was significant in the preterm group ($t=-16.45$, $p<0.01$), the term-born ADHD group ($t=-11.40$, $p<0.01$) and the term-born control group ($t=-16.45$, $p<0.01$). Post-hoc tests showed that the slope in MRT, indexing the extent of change from the baseline to fast-incentive condition, in the preterm group was not significantly different compared to the term-born ADHD group ($p=-1.28$, $p=0.20$), but was significantly greater compared to the term-born control group ($t=1.78$, $p=0.04$). The slope in MRT was significantly greater in the term-born ADHD group ($t=-2.90$, $p<0.01$) than the control group.

For RTV data, a random intercept model indicated a significant main effect of condition ($z=-13.40$, $p<0.01$), a main effect of group ($z=2.91$, $p<0.01$) and a significant group-by-condition interaction ($z=-2.04$, $p<0.05$). Post-hoc analyses revealed that, in the baseline condition, the preterm group showed significantly decreased RTV compared to the term-born ADHD group ($t=-1.65$, $p<0.05$), but significantly increased RTV compared to the term-born control group ($t=3.04$, $p<0.01$). In the fast-incentive condition, the preterm group did not differ in RTV compared to the term-born ADHD group ($t=-0.71$, $p=0.48$), but showed significantly increased RTV compared to the term-born control group ($t=4.57$, $p<0.01$). The term-born ADHD group showed significantly greater RTV

compared to the term-born control group both in the baseline (t=3.42, p<0.01) and fast-incentive (t=2.58, p<0.01) conditions. The within-group difference in RTV from the baseline to fast-incentive condition was significant in the preterm group (t=-5.99, p<0.01), the term-born ADHD group (t=-6.23, p<0.01) and the term-born control group (t=-11.06, p<0.01). The slope in RTV in the preterm group was, at a trend level of significance, less steep compared to the ADHD group (t=-1.75, p=0.08), but was significantly greater than in the control group (t=-2.63, p<0.01). The slope in RTV was significantly greater in the term-born ADHD group compared to the term-born control group (t=-2.80, p<0.01).

ERP measures

For CNV amplitude, a random intercept model indicated a significant main effect of condition (z=-16.88, p<0.01), a significant main effect of group (z=2.92, p<0.01) and a significant group-by-condition interaction (z=9.13, p<0.01). Post-hoc analyses revealed no group differences in the baseline condition between the preterm group and the term-born ADHD group (t=-1.48, p=0.14, between the preterm group and the term-born control group (t=-1.29, p=0.20) and between the term-born ADHD group and the term-born control group (t=0.09, p=0.93). In the fast-incentive condition, the preterm group was not significantly different compared to the term-born ADHD group (t=1.18, p=0.24), but the preterm group had a significantly reduced CNV amplitude compared to the term-born control group (t=5.69, p<0.01). The term-born ADHD group showed significantly reduced CNV amplitude compared to the term-born control group in the fast-incentive condition (t=2.92, p<0.01). The within-group difference in CNV amplitude from the baseline to fast-incentive condition was significant in the preterm group (t=-5.58, p<0.05), term-born ADHD (t=-6.94, p<0.01) and control (t=-10.50, p<0.01) groups. The slope in CNV amplitude in the preterm group, from the baseline to fast-incentive condition, was significantly less steep compared both to the term-born ADHD (p=-2.49, p<0.01) and control (t=-7.53, p<0.01) groups. Compared to the term-born control group, the CNV slope was significantly less steep in the term-born ADHD group (t=-3.17, p<0.01).

For P3 amplitude, a random intercept model indicated a significant main effect of condition ($z=2.03$, $p<0.04$), a main effect of group ($z=-3.71$, $p<0.01$) and a significant group-by-condition interaction emerged ($z=-5.48$, $p<0.01$). Post-hoc analyses revealed that, in the baseline condition, the preterm group was not significantly different compared to either the term-born ADHD ($t=-0.18$, $p<0.81$) or control ($t=-1.24$, $p<0.21$) group. The term-born ADHD group showed significantly decreased P3 amplitude compared to the term-born control group in the baseline condition ($t=2.61$, $p<0.01$). In the fast-incentive condition, the preterm group showed significantly decreased P3 amplitude compared both to the term-born ADHD ($t=-2.73$, $p<0.01$) and control ($t=-5.35$, $p<0.01$) groups. P3 amplitude in the fast-incentive condition did not differ between the term-born ADHD and control group ($t=1.43$, $p=0.17$). The within-group difference in P3 amplitude from the baseline to fast-incentive condition was not significant in the preterm group ($t=-1.55$, $p=0.17$), but significant in the term-born ADHD ($t=-3.76$, $p<0.01$) and the control ($t=-6.61$, $p<0.01$) groups. The slope in P3 amplitude in the preterm group was less steep compared to both the term-born ADHD ($p=2.77$, $p<0.01$) and term-born control ($t=4.09$, $p<0.01$) groups. The slope in P3 amplitude did not differ between the term-born ADHD group compared to the term-born control group ($t=-0.39$, $p=0.70$).

SC measures

For SCL, a random intercept model indicated a significant main effect of condition ($z=-5.72$, $p<0.01$), but no main effect of group ($z=0.59$, $p=0.55$), and a trend towards a group-by-condition interaction ($z=-1.70$, $p=0.08$). Post-hoc analyses revealed that, in the baseline condition, the preterm group showed significantly increased SCL compared to the ADHD group ($t=-3.13$, $p<0.01$), but did not differ from the control group ($t=0.89$, $p=0.37$). In the fast-incentive condition, the preterm group was not significantly different compared to the ADHD group ($t=-0.20$, $p=0.84$) or compared to the control group ($t=-0.76$, $p=0.45$). The term-born ADHD group showed significantly decreased SCL compared to the term-born control group in the baseline condition ($t=-2.09$, $p<0.05$), but not fast-incentive condition ($t=0.89$, $p=0.37$). The within-group difference in SCL from the baseline to fast-incentive condition was not significant in the preterm group

(t=0.81, p=0.42), but was significant in the term-born ADHD (t=9.29, p<0.01) and control (t=4.85, p<0.01) groups. The slope in SCL in the preterm group was less steep compared to both the ADHD (p=2.60, p<0.01) and control (t=-1.89, p<0.05) groups. The slope in SCL was significantly steeper in the term-born ADHD group compared to the term-born control group (t=2.24, p<0.05).

Supplementary Material 4.3. Analysis controlling for IQ

Cognitive performance measures

For MRT data, a random intercept model indicated a significant main effect of condition (z=33.04, p<0.01) and a main effect of group (z=1.98, p<0.01), but no significant group-by-condition interaction (z=-1.03, p=0.30). Post-hoc analyses revealed that, in the baseline condition, the preterm group showed significantly decreased MRT compared to the term-born ADHD group (t=-2.61, p<0.01), but significantly increased MRT compared to the term-born control group (t=2.62, p<0.05). In the fast-incentive condition, the preterm group showed significantly decreased MRT compared to the term-born ADHD group (t=-1.94, p<0.05), but significantly increased MRT compared to the term-born control group (t=2.96, p<0.05). The term-born ADHD group showed significantly greater MRT compared to the term-born control group in both the baseline (t=3.52, p<0.01) and fast-incentive (t=3.05, p<0.01) conditions. The within-group difference in MRT from the baseline to fast-incentive condition was significant in the preterm group (t=-13.72, p<0.01), the term-born ADHD group (t=-11.40, p<0.01) and the term-born control group (t=-16.45, p<0.01). Post-hoc tests showed that the slope in MRT, indexing the extent of change from the baseline to fast-incentive condition, in the preterm group was not significantly different compared to the term-born ADHD group (p=-1.25, p=0.21), but was, at a trend level of significance, greater compared to the term-born control group (t=1.66, p=0.09). The slope in MRT was significantly greater in the term-born ADHD group (t=-2.88, p<0.01) than the control group.

For RTV data, a random intercept model indicated a significant main effect of condition (z=-13.40, p<0.01), a main effect of group (z=2.91, p<0.01) and a significant group-by-condition interaction (z=-2.04, p<0.05). Post-hoc analyses revealed that, in the baseline condition, the preterm group showed significantly decreased RTV compared to the term-born ADHD group (t=-1.65, p<0.05), but significantly increased RTV compared to the term-born control group (t=3.04, p<0.01). In the fast-incentive condition, the preterm group did not differ in RTV compared to the term-born ADHD group (t=-0.71, p=0.48), but showed significantly increased RTV compared to the term-born control group (t=4.57, p<0.01). The term-born ADHD group showed significantly greater RTV

compared to the term-born control group both in the baseline (t=3.42, p<0.01) and fast-incentive (t=2.58, p<0.01) conditions. The within-group difference in RTV from the baseline to fast-incentive condition was significant in the preterm group (t=-5.99, p<0.01), the term-born ADHD group (t=-6.23, p<0.01) and the term-born control group (t=-11.06, p<0.01). The slope in RTV in the preterm group was, at a trend level of significance, less steep compared to the ADHD group (t=-1.75, p=0.08), but was significantly greater than in the control group (t=-2.63, p<0.01). The slope in RTV was significantly greater in the term-born ADHD group compared to the term-born control group (t=-2.80, p<0.01).

ERP measures

For CNV amplitude, a random intercept model indicated a significant main effect of condition (z=-16.88, p<0.01), a significant main effect of group (z=2.92, p<0.01) and a significant group-by-condition interaction (z=9.13, p<0.01). Post-hoc analyses revealed no group differences in the baseline condition between the preterm group and the term-born ADHD group (t=-1.49, p=0.14), between the preterm group and the term-born control group (t=-1.29, p=0.20) and between the term-born ADHD group and the term-born control group (t=0.09, p=0.93). In the fast-incentive condition, the preterm group was not significantly different compared to the term-born ADHD group (t=1.18, p=0.24), but the preterm group had a significantly reduced CNV amplitude compared to the term-born control group (t=5.69, p<0.01). The term-born ADHD group showed significantly reduced CNV amplitude compared to the term-born control group in the fast-incentive condition (t=2.92, p<0.01). The within-group difference in CNV amplitude from the baseline to fast-incentive condition was significant in the preterm group (t=-5.58, p<0.01), term-born ADHD (t=-6.94, p<0.01) and control (t=-10.50, p<0.01) groups. The slope in CNV amplitude in the preterm group, from the baseline to fast-incentive condition, was significantly less steep compared both to the term-born ADHD (p=-2.67, p<0.01) and control (t=-7.51, p<0.01) groups. Compared to the term-born control group, the CNV slope was significantly less steep in the term-born ADHD group (t=-3.17, p<0.01).

For P3 amplitude, a random intercept model indicated a significant main effect of condition ($z=2.03$, $p<0.05$), a main effect of group ($z=-3.71$, $p<0.01$) and a significant group-by-condition interaction emerged ($z=-5.48$, $p<0.01$). Post-hoc analyses revealed that, in the baseline condition, the preterm group was not significantly different compared to either the term-born ADHD ($t=-0.18$, $p=0.81$) or control ($t=-1.24$, $p=0.21$) group. The term-born ADHD group showed significantly decreased P3 amplitude compared to the term-born control group in the baseline condition ($t=2.61$, $p<0.01$). In the fast-incentive condition, the preterm group showed significantly decreased P3 amplitude compared both to the term-born ADHD ($t=-2.73$, $p<0.01$) and control ($t=-5.35$, $p<0.01$) groups. P3 amplitude in the fast-incentive condition did not differ between the term-born ADHD and control group ($t=1.43$, $p=0.17$). The within-group difference in P3 amplitude from the baseline to fast-incentive condition was not significant in the preterm group ($t=-1.55$, $p=0.17$), but significant in the term-born ADHD ($t=-3.76$, $p<0.01$) and the control ($t=-6.61$, $p<0.01$) groups. The slope in P3 amplitude in the preterm group was less steep compared to both the term-born ADHD ($p=2.77$, $p<0.01$) and term-born control ($t=4.09$, $p<0.01$) groups. The slope in P3 amplitude did not differ between the term-born ADHD group compared to the term-born control group ($t=-0.39$, $p=0.70$).

SC measures

For SCL, a random intercept model indicated a significant main effect of condition ($z=-5.72$, $p<0.01$), but no main effect of group ($z=0.59$, $p=0.55$), and a trend towards a group-by-condition interaction ($z=-1.70$, $p=0.08$). Post-hoc analyses revealed that, in the baseline condition, the preterm group showed significantly increased SCL compared to the ADHD group ($t=-3.13$, $p<0.01$), but did not differ from the control group ($t=0.89$, $p=0.37$). In the fast-incentive condition, the preterm group was not significantly different compared to the ADHD group ($t=-0.20$, $p=0.84$) or compared to the control group ($t=-0.76$, $p=0.45$). The term-born ADHD group showed significantly decreased SCL compared to the term-born control group in the baseline condition ($t=-2.09$, $p<0.05$), but not fast-incentive condition ($t=0.89$, $p=0.37$). The within-group difference in SCL from the baseline to fast-incentive condition was not significant in the preterm

group (t=0.81, p=0.42), but was significant in the term-born ADHD (t=9.29, p<0.01) and control (t=4.85, p<0.01) groups. The slope in SCL in the preterm group was less steep compared to both the ADHD (p=2.60, p<0.01) and control (t=-2.09, p<0.05) groups. The slope in SCL was significantly steeper in the term-born ADHD group compared to the term-born control group (t=2.24, p<0.05).

Supplementary Material 5.1. Within-siblings, fixed effect model of preterm birth on standardised scores (controlling for age, sex and IQ) (n = 208).

	Variable	β Coef	P	95% CI
	ADHD symptoms	**0.16**	**0.04**	**0.01,0.31**
Cognitive performance measures	Congruent Errors	0.14	0.21	-0.08,0.36
	MRT	**0.16**	**0.05**	**0.01,0.33**
	RTV	**0.13**	**0.04**	**0.01,0.26**
Event-related potentials measures	CNV (CPz)	**0.46**	**0.03**	**0.05,0.87**
	Go-P3 (Pz)	**-0.18**	**0.03**	**-0.33,-0.02**
	Nogo-P3 (Cz)	0.04	0.60	-0.12,0.21
	N2 (Fz)	**0.15**	**0.05**	**0.00,0.30**
	Pe (CPz)	**-0.18**	**0.05**	**0.35,0.00**
	ERN (Fcz)	0.04	0.63	-0.12,0.20
	CNV (Cz) (fast-incentive)	0.11	0.07	0.08, 0.25
	CNV slope (Cz)	**-0.14**	**0.05**	**-0.19,-0.10**
	P3 (Pz) (fast-incentive)	**-0.20**	**0.02**	**-0.39,-0.02**
	P3 slope (Pz)	**-0.16**	**0.05**	**-0.31,-0.05**
Skin conductance measures	SCL slope	**-0.17**	**0.02**	**-0.32,-0.09**

Note: p<0.05 indicated in bold. ADHD=attention-deficit/hyperactivity disorder; Congruent Errors=errors in the congruent condition of the flanker task; MRT=mean reaction time in the baseline (slow, unrewarded) condition of the Fast Task; RTV=reaction time variability in the baseline (slow, unrewarded) condition of the Fast Task; CNV=contingent negative variation in the cued continuous performance test; Go-P3=P3 amplitude in the go condition from the cued continuous performance test; NoGo-P3=P3 amplitude in the NoGo condition from the cued continuous performance test; N2=N2 amplitude in the incongruent condition of the flanker task; Pe=positive related negativity in the incongruent condition of the flanker task; ERN=error related negativity in the incongruent condition of the flanker task; CNV fast-incentive= contingent negative variation amplitude in the fast-incentive condition of the Fast Task; CNV slope=slope in contingent negative variation amplitude between the baseline and fast-incentive condition of the Fast Task; P3 fast-incentive= P3 amplitude in the fast-incentive condition of the Fast Task; P3

slope=slope in P3 amplitude between the baseline and fast-incentive condition of the Fast Task; SCL slope=slope in skin conductance level between the baseline and fast-incentive condition of the Fast Task.

Supplementary Material 5.2. Within-siblings, fixed effect model of gestational age on age-regressed standardised scores (controlling for age, sex and IQ) (n = 208).

	Variable	β Coef	p	95% CI
	ADHD symptoms	**-0.05**	**0.01**	**-0.08,-0.01**
Cognitive performance measures	Congruent Errors	0.03	0.12	-0.02,0.09
	MRT	**-0.05**	**0.02**	**-0.09,-0.01**
	RTV	**-0.05**	**0.03**	**-0.09,-0.01**
Event-related potentials measures	CNV (CPz)	**-0.08**	**0.03**	**-0.14,-0.01**
	Go-P3 (Pz)	**0.04**	**0.03**	**0.00,0.08**
	Nogo-P3 (Cz)	0.02	0.21	-0.01,0.06
	N2 (Fz)	**-0.06**	**0.01**	**-0.09,-0.02**
	Pe (CPz)	**0.04**	**0.03**	**0.00,0.08**
	ERN (Fcz)	**-0.04**	**0.03**	**-0.08,-0.00**
	N2 (Fcz)	**-0.05**	**0.02**	**-0.09,-0.01**
	CNV (Cz) (fast-incentive)	**0.04**	**0.03**	**0.06,0.01**
	CNV slope (Cz)	**0.04**	**0.05**	**0.03,0.07**
	P3 (Pz) (fast-incentive)	**0.04**	**0.04**	**0.01,0.07**
	P3 slope (Pz)	**0.04**	**0.02**	**0.01,0.08**
Skin conductance measures	SCL change	0.03	0.12	-0.02,0.09

Note: p<0.05 indicated in bold. ADHD=attention-deficit/hyperactivity disorder; Congruent Errors=errors in the congruent condition of the flanker task; MRT=mean reaction time in the baseline (slow, unrewarded) condition of the Fast Task; RTV=reaction time variability in the baseline (slow, unrewarded) condition of the Fast Task; CNV=contingent negative variation in the cued continuous performance test; Go-P3=P3 amplitude in the go condition from the cued continuous performance test; NoGo-P3=P3 amplitude in the NoGo condition from the cued continuous performance test; N2=N2 amplitude in the incongruent condition of the flanker task; Pe=positive related negativity in the incongruent condition of the flanker task; ERN=error related negativity in the incongruent condition of the flanker task; CNV fast-incentive= contingent negative variation amplitude in the fast-incentive condition of the Fast Task; CNV slope=slope in contingent negative variation amplitude between the baseline and fast-incentive condition of the

Fast Task; P3 fast-incentive= P3 amplitude in the fast-incentive condition of the Fast Task; P3 slope=slope in P3 amplitude between the baseline and fast-incentive condition of the Fast Task; SCL slope=slope in skin conductance level between the baseline and fast-incentive condition of the Fast Task.

Supplementary Material 6.1. Phenotypic constrained correlation models of cognitive and neurophysiological measures with ADHD symptoms (parent rated conners), within term (n=342) and preterm (n=197) groups (using age and sex regressed data, controlling for sibling relatedness, and ascertainment bias).

		ADHD symptoms in Term		ADHD symptoms in Preterm	
		r	(95 % CI)	r	(95 % CI)
Cognitive measures	IQ	-0.35	(-0.45, -0.25)	-0.23	(-0.45, -0.09)
	DSF	-0.26	(-0.36, -0.16)	-0.18	(-0.30, -0.04)
	DSB	-0.16	(-0.26, -0.04)	-0.15	(-0.24, -0.02)
	Congruent errors	0.16	(0.05, 0.27)	0.09	(-0.05, 0.34)
	MRT	0.24	(0.12, 0.34)	0.22	(0.07, 0.36)
	RTV	0.33	(0.23, 0.43)	0.21	(0.06, 0.34)
ERP measures	CNV (CPz)	0.26	(0.15, 0.37)	0.15	(0.07, 0.36)
	Nogo-P3 (Cz)	-0.17	(-0.28, -0.05)	-0.15	(-0.27, -0.02)
	N2 (Fcz)	0.12	(0.01, 0.23)	-0.08	(-0.14, 0.12)
	Pe (CPz)	-0.18	(-0.29, -0.08)	-0.07	(-0.18, 0.09)
	ERN (Fcz)	-0.14	(-0.24, -0.03)	-0.09	(-0.23, 0.04)

Note: Variables for modelling highlighted in grey (criteria= r>0.20 in both the term and preterm groups). DSF=digit span forward, DSB=digit span backwards; MRT=mean reaction time in ms; RTV=reaction time variability in ms; ERP=event related potential; CNV=contingent negative variation; Pe=positive related negativity; ERN=error related negativity.

Supplementary Material 6.2. Event related potential (ERP) extraction.

Cued continuous performance test (CPT-OX)

For the CPT-OX task, stimulus-locked epochs (stimulus window from −200 to 1650ms) were averaged based on three different response conditions: Cue, Go and NoGo. Averages were calculated for trials with correct responses (Go) or correctly rejected trials (NoGo and Cue), which included at least 20 artefact-free segments. Based on previous research (McLoughlin et al. 2010; Doehnert et al. 2013; Albrecht et al. 2013), ERP measures were identified within selected electrodes and latency windows for which effects were expected to be largest. These measures were then confirmed separately for the three groups using topographic maps (Rommel et al. under review). In Cue trials, the P3 was measured at Pz between 300-650ms, and the CNV was measured at Cz and CPz between 1300-1650ms. In Go trials, the P3 was measured at CPz and Pz between 250-500ms. No clear N2 was observed in Go trials, consistent with other studies employing tasks with low conflict-monitoring demands (Gajewski and Falkenstein 2013; Michelini et al. in press) and was, therefore, not included in the analysis. In NoGo trials, the P3 was measured at FCz and Cz between 250-550ms and the N2 was measured at Fz between 175-325ms. The CNVs were analysed as mean amplitudes between 1300 and 1650ms following cues over the central electrode (CPz). The cue-P3 had a parietal maximum and was defined as the most positive peak between 250 and 600 ms following cue trials at electrode Pz. The nogo-P3 was defined as the most positive peak between 250 and 600 ms following No-Go trials at electrode Cz (Rommel et al. under review).

The flanker task

Analyses of ERPs of performance monitoring were restricted to the incongruent condition, as the task used in this study is known to elicit strong N2, error related negativity (ERN) and positivity (Pe) components in high-conflict, but not in low-conflict, conditions (Albrecht et al. 2008; McLoughlin et al. 2009; McLoughlin et al. 2014). Baseline correction was applied using the -300 to -100 ms pre-target (-200 to 0 ms pre-flanker) interval, following the protocol of previous ERP analyses on the flanker task (Michelini et al. in press). Data were segmented based on (1) stimulus-locked incongruent trials where a correct response was made and (2) response-locked (error-related) incongruent trials where an incorrect response was made.

Individual averages were created based on each condition, requiring ≥ 20 clean segments for each participant. After averaging, the electrodes and latency windows for ERP analyses were selected based on previous studies (Albrecht et al. 2008; McLoughlin et al. 2009; Groom et al. 2010; Nieuwenhuis et al. 2001, Michelini et al. in press) topographic maps and the grand averages. The N2 was measured as maximum negative peak at Fz and FCz between 250-450 ms after target onset. The ERN was defined with respect to the preceding positivity (PNe, -100-50 ms) in order to obtain a more robust measure of this component, and was measured at FCz between 0-150 ms. The Pe was measured as maximum positive peak at CPz between 150-450 ms after an erroneous response on incongruent trials.

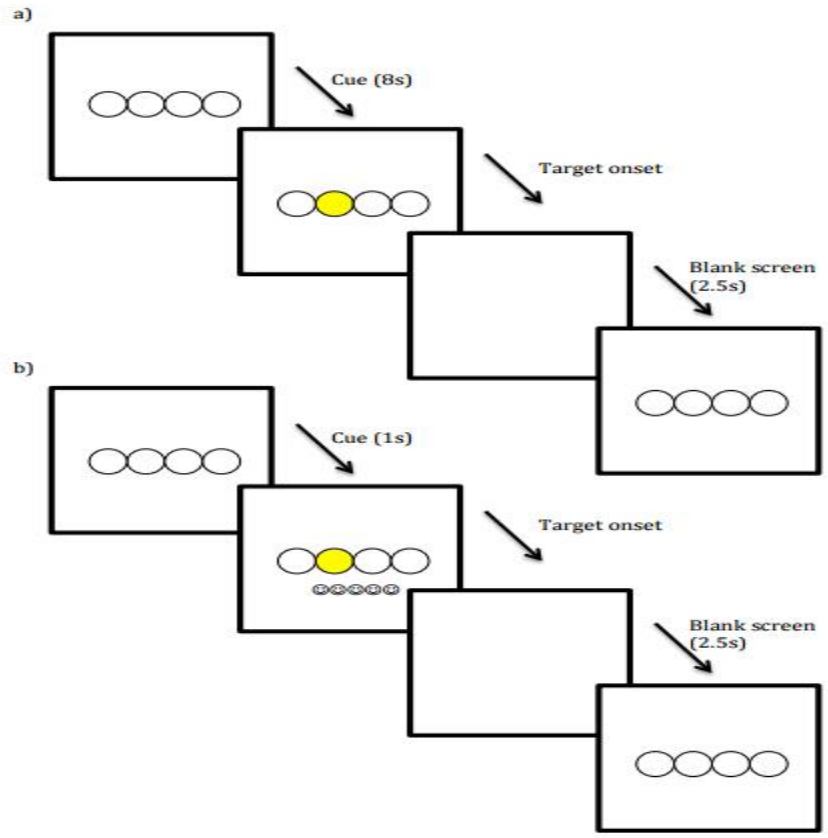
Supplementary Material 7.1. Detailed task description.

All tasks took place in a clinical research suite in a South London research centre. During data collection, participants were seated on an adjustable chair in an acoustically shielded, slightly dimmed, video-monitored room, whilst EEG was being simultaneously measured. Participants sat upright in front of a computer monitor at the viewing distance of 120 cm. The visual angle of the stimuli used was at 0.5 degrees.

9.1.1.1 The Fast Task (Andreou et al. 2007, Kuntsi et al 2006).

The Fast Task is a standard warned four-choice reaction time task made up of two conditions, the baseline (slow, unrewarded) condition, and a fast-incentive condition (Supplementary Figure 7.1). Before beginning the task, all of the participants received standardised instructions and had to respond correctly to five consecutive trials in the baseline condition.

Supplementary Figure 7.1: A schematic illustration of the temporal sequence of events in the a) baseline and b) fast-incentive conditions of the Fast Task (Cheung 2014).



The stimuli (warning signal) were four circles, 3 cm in diameter, arranged side by side (horizontally) in the centre of a computer screen. The circles were positioned on the far left, inner left, inner right, and far right of the computer monitor against a light grey background (Supplementary Figure 7.1). Each trial began with a warning signal that consisted of the appearance of four empty circles (which remained on the screen for the length of the foreperiod). At the end of the foreperiod, the circle designated as the target signal for that trial was filled (coloured) in yellow. The participants were instructed to make a compatible choice response by pressing the response key that directly corresponded in position to the location of the target stimulus. These were four, clearly marked, keys on the centre row of the computer keyboard (in the positions of the letters S, F, J and L). Both the target circle and the three other (non-target) circles remained in view until the response was made. Following a response, the next trial was initiated after a fixed intertrial interval of 2500 ms. Speed and accuracy were emphasized equally. The baseline condition consisted of 72 trials and had a fore-period of 8 s (Leth-Steensen et al. 2000).

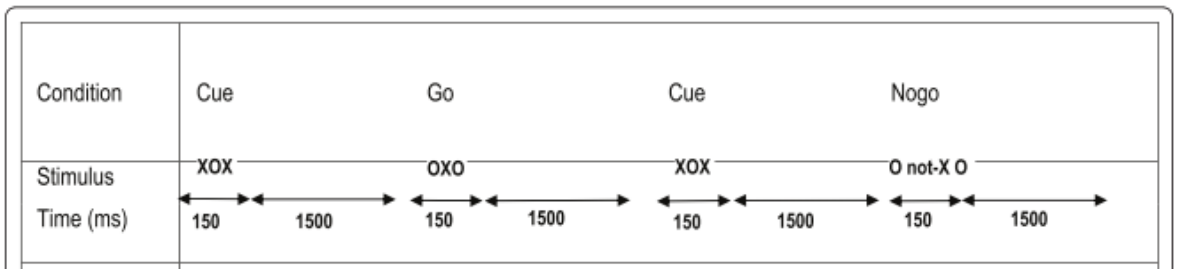
To investigate the extent to which a response style characterized by slow and variable speed of responding can be maximally reduced, the task includes a comparison condition that uses a fast event rate (fore-period of 1 s) and incentives (Andreou et al. 2007, Kuntsi et al 2006). The fast-incentive condition started immediately after the baseline condition and consisted of 80 trials and a fixed inter-trial interval of 2.5 s (Supplementary Figure 7.1). Speed and accuracy were emphasized equally. The participants were told to respond really quickly one after another, to win smiley faces and earn real prizes in the end. The participants won a smiley face for responding faster than their own MRT during the baseline (first) condition consecutively for three trials. The baseline MRT was calculated here based on the middle 94% of responses (the exclusion of the top and bottom 3% of responses is only used when calculating a baseline mean RT for the set-up of the fast-incentive condition, and is not used for analyses), therefore excluding extremely fast and extremely slow responses. The smiley faces appeared below the circles in the middle of the screen and were updated continuously. The response variables are MRT and standard deviation of the RTs (SD of RTs; RT variability), calculated for each condition based on correct responses only. The fast-incentive condition is

always administered after the baseline condition and, as such, does not involve a similar learning phase. The participants earned small prizes (£5) after the task battery.

9.1.1.2 Cued continuous performance test (CPT-OX) (McLoughlin et al. 2010; Doehnert et al. 2013; Albrecht et al. 2013, Banaschewski et al. 2004, McLoughlin et al. 2011).

The CPT-OX is a cued Go/NoGo task that probes attention, preparation and response inhibition. Before beginning the task, all of the participants received standardised instructions, performed ten practice trials before the main task, and were repeated, if required, to ensure participant comprehension (Supplementary Figure 7.2).

Supplementary Figure 7.2: CPT-OX paradigm. The relationship between condition and task stimulus (McLoughlin et al. 2011).



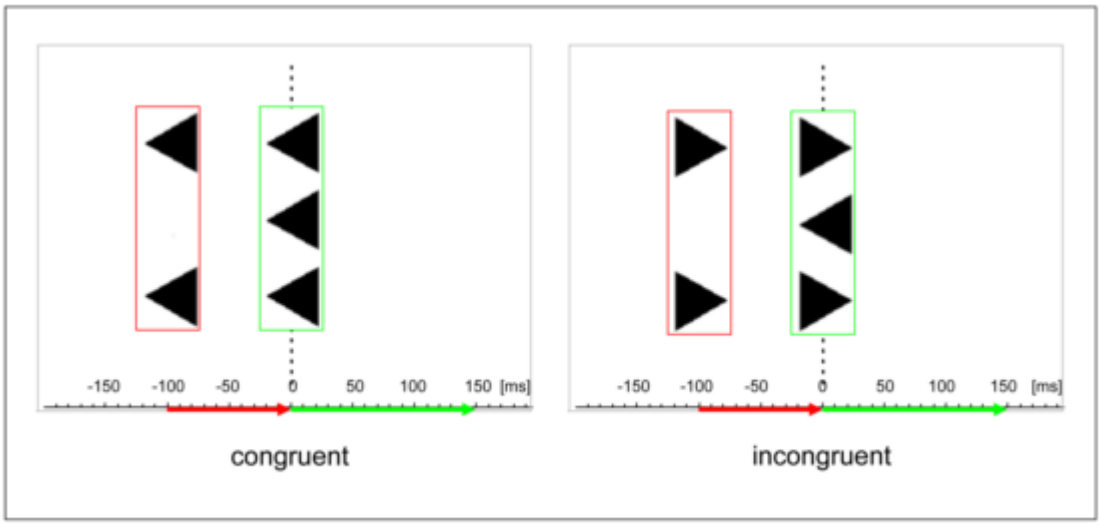
The task consisted of 400 black letter arrays, made up of a centre letter and incompatible flankers on each side to increase difficulty. The presented arrays included the cue letter 'O', the target letter 'X' as well as the distractors 'H', 'B', 'C', 'D', 'E', 'F', 'G', 'J' and 'L'. Letters were presented centrally on the computer monitor against a light grey background. Cue and target letters ('O' and 'X' respectively) were flanked by incompatible letters ('XOX' and 'OXO' respectively). Participants were instructed to ignore the flanking letters and respond as quickly as possible to cue-target sequences ('O'-'X'). 80 cues ('XOX') were followed by the target ('OXO') in 40 trials (Go condition), and by neutral distractors in the remainder of trials (NoGo condition) (Supplementary Figure 7.2). On 40 trials, the target letter 'X' was not preceded by a cue 'O' and had to be ignored. Letters were presented every 1.65 s for 150 ms in a pseudo-randomised order. Participants were instructed to respond only to Cue-Go

sequences by pressing a button as quickly as possible with the index finger of their preferred hand. Participants were further asked to withhold the response in the presence of a NoGo stimulus, in the presence of a Go stimulus not preceded by a cue, or in the presence of any other irrelevant letters. Task duration was 11 minutes. Cognitive-performance measures obtained from the CPT-OX included target MRT (i.e. mean latency of responding in milliseconds after target onset), RTV (measured as standard deviation of target reaction time) and number of errors. MRT and RTV were obtained from correct Go trials. Errors included total omission errors (non-responses to Go trials) and total commission errors (responses to Cue, NoGo or distractor stimuli).

9.1.1.3 Arrow flanker task (Albrecht et al., 2008)

The task took place in a clinical research suite in a South London research centre. During data collection, participants were seated on an adjustable chair in an acoustically shielded, slightly dimmed, video-monitored room, whilst EEG was being simultaneously measured. Participants sat upright in front of a computer monitor at the viewing distance of 120 cm. The visual angle of the stimuli used was at 0.5 degrees. Before beginning the arrow-flanker task, all of the participants received standardised instructions and performed two practice blocks with 24 trials before the main task. The practice was repeated, if required, to ensure participant comprehension (Supplementary Figure 7.3).

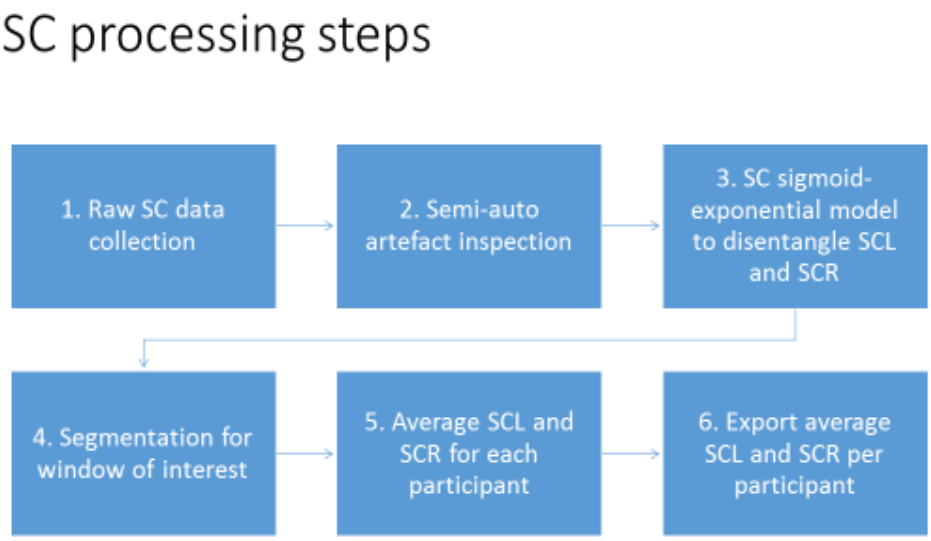
Supplementary Figure 7.3: Task description of the arrow flanker task (Albrecht et al., 2008). Flanker arrowheads (red) preceed the presentation of the central target and flanker arrow heads (green) by 100ms). Conditions were congruent or incongruent and responses were required either to the left or right.



The arrow flanker task was an adaptation of the Eriksen flanker paradigm designed to increase cognitive load as used in previous studies (Albrecht et al., 2008; McLoughlin, Palmer, et al., 2014; McLoughlin et al., 2009). The flanker-task consisted of ten blocks of 40 trials each. Columns of black arrowheads (equilateral triangles with 18 mm edge length at 3 positions with 23mm distance centre to centre) were presented in the centre of a 17" monitor against a light grey background at 120cm viewing-distance. On every trial, a fixation mark in the centre of the screen was replaced by the stimuli. Initially, only flankers (two arrowheads pointing to the same direction above and below the position of the fixation mark) were presented for 100ms, before the target arrowhead also appeared for 150ms between the flankers. Subjects had to press response buttons with the index-finger of their hand corresponding to the direction indicated by the target (Supplementary Figure 7.3). On congruent trials, flanker and target arrowheads pointed in the same and on incongruent trials into opposite directions (Supplementary Figure 7.3). A trial was presented every 1650ms, and total task duration was approximately 13 min. The features congruent vs. incongruent and target pointing to the left vs. right were balanced and randomized. Written feedback was given at the end of each block. If more than 10% errors on congruent or more than 40% errors on incongruent trials were made, it was instructed to be more accurate. In case of less than 10% errors in the congruent and less than 40% errors in incongruent trials, it was stressed to respond faster; otherwise it was told to go on the same way. Feedback was introduced in order to control for accuracy, which may influence error processing.

Supplementary Material 7.2. Data processing steps

9.1.1.4 Skin conductance (SC) processing steps.



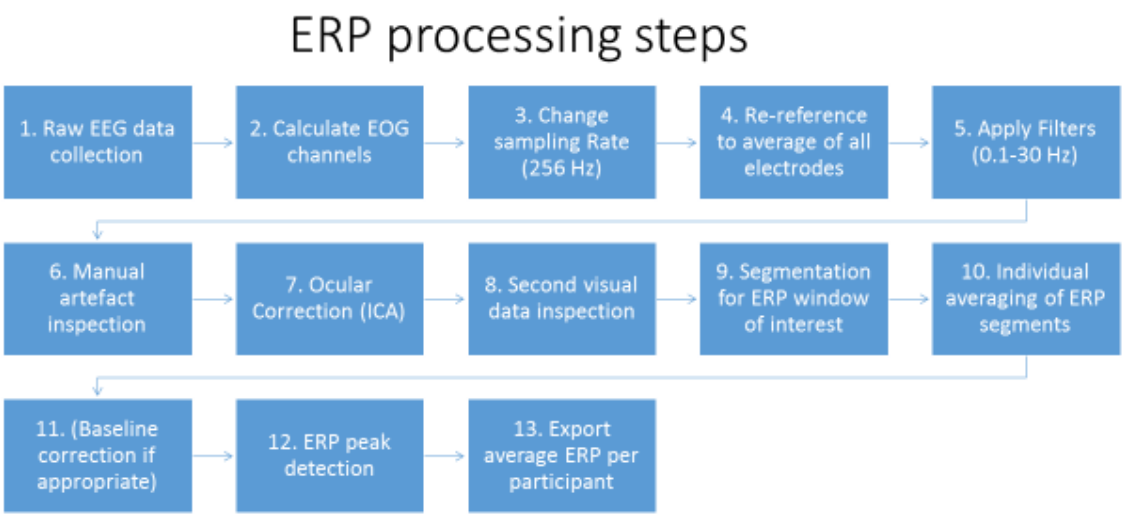
Data processing steps:

1. SC data were measured with a sampling rate of 32 Hz by attaching a pair of reusable 8mm diameter silver-silver chloride electrodes on the thenar eminence and hypothenar eminence of participant's non-dominant hand at the start of the testing session. A non-saline gel was used to increase impedance and help establish an electrical signal. A constant imperceptible voltage (0.5 V) was applied. SC was recorded using PSYCHLAB SC5 24 bit equipment system, which has an absolute accuracy of +/- 0.1 microsiemens (µS) (PSYCHLAB, UK). The SC5 was connected to a computer to run the PSYCHLAB software, where data were monitored and recorded in real time. Stimulus onset and participant response events were recorded on a common timeline, which enabled SC activity to be stimulus-locked. 2.
2. The data were semi-auto inspected for obvious artefacts.
3. SC data values were calculated using a skin conductance system which is based on a SC sigmoid-exponential model that allows the tonic measure of SC level (SCL) to be disentangled from phasic, stimulus-associated, SC responses (SCR), and further allows

the decomposition of overlapping SCRs (Boucsein, 1992; Figner & Murphy, 2011; Lim et al., 1997; Williams et al., 2001).

4. The data were segmented for the window of interest.
5. The SCL and SCR was averaged across the participant.
6. SCL and SCR amplitude was exported per participant.

9.1.1.5 Event related potential (ERP) processing steps



Data processing steps:

1. The EEG was recorded from 62 channels DC-coupled recording system (extended 10–20 montage), with a 500 Hz sampling rate, impedances kept under 10 kΩ, and FCz as the recording reference electrode. The electro-oculograms (EOGs) were recorded from electrodes above and below the left eye and at the outer canthi. The EEG data were collected using Brain Vision Recorder, and analysed using Brain Vision Analyzer (2.0) (Brain Products, Germany).
2. EOG channels were calculated: Vertical EOG was calculated using Fp1 and the electrode below the left eye; Horizontal EOG was calculated from the lateral outer canthi electrodes.
3. The data were down-sampled to 256 Hz.
4. The data were re-referenced to the average from all electrodes.
5. The data were filtered offline with digital band-pass (0.1 to 30 Hz, 24 dB/oct) Butterworth filters.
6. The data were manually inspected for electrical artefacts and obvious movement.
7. Ocular artifacts were identified from the data using Independent Component Analysis (ICA) (Jung et al., 2000). Only components associated with ocular artefacts were

removed, allowing ocular artefacts correction by back projection of all components except the ocular components.

8. A second visual inspection with additional automatic artefact rejection (activity +/- 100μV) was carried out to allow removal of residual artefacts.
9. The data were segmented into latency windows for the ERP window of interest (based on the literature).
10. The ERP segment of interest was averaged across each individual.
11. Baseline correction was applied to the individual average if applicable for the ERP of interest.
12. ERP peaks of interests were identified within pre-defined latency windows (based on the literature and grand average ERPs of all participants).
13. ERP amplitude/area was exported per participant if they at least 20 accepted sweeps.