# Investigation of the underlying cognitive-neurophysiological and aetiological pathways in ADHD and cross-disorder comparison with bipolar disorder

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# Investigation of the underlying cognitive-neurophysiological and aetiological pathways in ADHD and cross-disorder comparison with bipolar disorder

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**Thesis submitted to King's College London for the degree of Doctor of Philosophy (PhD)**

**2020**

# Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable neurodevelopmental disorder that is associated with a wide range of cognitive and neurophysiological impairments. This thesis uses a multi-disciplinary approach to investigate the cognitive and neurophysiological impairments, as well as their aetiology, in ADHD. A further aim is to identify cognitive markers that differentiate between ADHD and bipolar disorder (BD).

The first study examines the cognitive and neurophysiological impairments associated with remission and persistence of ADHD from childhood to young adulthood using fine-grained ex-Gaussian reaction-time distribution and electroencephalographic (EEG) brain-oscillatory measures. Detailed ex-Gaussian measures of attention-vigilance and brain-oscillatory measures of phase variability and attention allocation emerged as novel markers of ADHD remission. The second study investigates, using a polygenic risk score approach, whether genetic variants that contribute to ADHD also influence two cognitive impairments widely associated with ADHD, attention regulation and inhibition. Findings from this study show that polygenic risk for ADHD is positively associated with a measure of attention allocation, but not with response inhibition. The third study examines, in a longitudinal design of ADHD and control sibling pairs, the direction of the association between ADHD and cognitive measures, and the stability of the familial and non-familial effects that underlie the association between ADHD and such measures across time. This study shows that ADHD diagnosis is a predictor of lower IQ and working memory at follow-up and that the familial and non-familial effects influencing the associations between ADHD and cognitive measures in childhood are stable across time. The last study examines whether the cognitive impairments observed in individuals with persistent ADHD are different or overlapping compared to those observed in individuals with BD. Findings from this study, which used detailed ex-Gaussian measures across different tasks and task conditions, indicate a shared impairment between the ADHD and BD groups in occasional lapses of attention, and a BD-disorder-specific impairment

in the variability of typical reaction time responses when high cognitive control is needed. These findings, if replicated in future larger studies, may represent objective markers of these two disorders.

Overall, by using a combination of cognitive, neurophysiological, behavioural and molecular genetic approaches, this thesis furthers our understanding of the cognitive and neural profiles in children, adolescents and adults with ADHD, as well as their association with BD.

# Statement of authorship

The present thesis represents my own work, from several collaborative projects. The results in Chapters 2 and 4 include data from a follow-up project of an ADHD and control sibling-pair sample (Sibling EEG Follow-up Study [SEFOS]; PI: Prof Jonna Kuntsi). The data used in these chapters was supported by generous Grants from Action Medical Research and the Peter Sowerby Charitable Foundation (Grant Reference GN1777). Initial sample recruitment of the ADHD sample was supported by NIMH Grant R01MH062873 to Prof Stephen V Faraone, the International Multicentre ADHD Genetic [IMAGE] project; the recruitment of the control sample and initial childhood cognitive assessments of ADHD and control groups were supported by UK Medical Research Council Grant G03001896 to Prof Jonna Kuntsi.

Chapter 3 is a collaborative study using ADHD samples from several international sites with cognitive and genetic data. Chapter 3 has been conducted using Psychiatric Genomics Consortium (PGC) ADHD resources, and data funded by: UK Medical Research Council grant G03001896 (to Prof Kuntsi); NIH grants R01MH62873 and R01MH081803 (to Prof Faraone); R01MH116037 (to Prof Doyle); RO1NS054124 (to Prof Loo); Ministerio de Ciencia e Innovacion, Spain, RTI2018-100968-B-100, AGAUR, Generalitat de Catalunya, 2017-SGR-738; the Canadian Institute of Health Research MOP-93696 (to Prof Schachar); the European Commission H2020 grants 667302 (CoCA), 643051 and 728018 (to Prof Cormand), 847181 (to Prof Buitelaar); the Miguel de Servet contract from the Instituto de Salud Carlos III, Spain (CP09/00119 and CPII15/00023, to Dr Ribasés); the Instituto de Salud Carlos III (PI16/01505, PI17/00289, PI18/01788, PI19/00721 and PI19/01224), co-financed by the European Regional Development Fund (ERDF); the Agència de Gestió d'Ajuts Universitaris i de Recerca-AGAUR (2017SGR1461) and the Health Research and Innovation Strategy Plan (PERIS-SLT006/17/287), Generalitat de Catalunya, Spain.

Chapter 5 is based on data from a cross-disorder comparison study between ADHD and BD (Female Experiences and Brain Activity [FEBA]; PI: Prof Jonna Kuntsi), primarily supported by an Economics and Social Research Council (ESRC)

studentship awarded to Dr Viryanaga (formerly Glenn) Kitsune (grant reference ES/100971X/1).

Data collection for IMAGE, SEFOS, and FEBA was completed by the respective research teams before I started my PhD. For Chapter 2, I formulated new research questions for secondary analyses, processed data, programmed and ran new EEG time-frequency and ex-Gaussian analyses, and interpreted the results under the guidance of Dr Giorgia Michelini and supervisor Prof Jonna Kuntsi. For Chapter 3, I formulated the research questions, conducted analyses and interpreted the findings under the supervision of Dr Joanna Martin, Dr Anna Rommel and supervisor Prof Jonna Kuntsi. For Chapter 4, I formulated new research questions for secondary analyses, ran new statistical analyses and interpreted the results under the guidance of supervisors Prof Jonna Kuntsi, Prof Fruhling Rijsdijk and Dr Giorgia Michelini. For Chapter 5, I formulated new research questions for secondary analyses, processed data, conducted analyses and interpreted the findings under the guidance of supervisor Prof Jonna Kuntsi with further advice from Dr Nicoletta Adamo and Prof Philip Asherson.

# Publications relevant to this thesis

Chapter 2 is based on the following publication (available under the Creative Commons licence):

> **Vainieri I**,* Michelini G,* Adamo N, Cheung C, Asherson P, Kuntsi J (2020). Event-related brain-oscillatory and ex-Gaussian markers of remission and persistence of ADHD. *Psychological Medicine*.

Chapter 3 is adapted from:

> **Vainieri I,** Martin J, Rommel A, Asherson P, Banaschewski T, Buitelaar J, Cormand B, Crosbie J, Faraone S.V, Franke B, Loo S.K, Miranda A, Manor I, Oades R.D, Purves K, Ramos-Quiroga A, Ribasés M, Roeyers H, Rothenberger A, Schachar R, Sergeant J, Steinhausen H, Vuijk P.J, Doyle A.E, Kuntsi J (under review). Polygenic association between attention-deficit/hyperactivity disorder liability and cognitive impairments. *Psychological Medicine*.

Chapter 4 is adapted from the following publication:

> **Vainieri I**, Michelini G, Cheung C, Asherson P, Rijsdijk F,† Kuntsi J† (in preparation). The aetiology of the association between ADHD and cognitive impairments from childhood to young adulthood.

Chapter 5 is based on the following publication (available under the Creative Commons licence):

> **Vainieri I**, Adamo N, Michelini G, Kitsune V, Asherson P, Kuntsi J (2020): Attention regulation in women with ADHD and women with bipolar disorder: An ex-Gaussian approach. *Psychiatry Research*. 285: 112729.

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# Other publications arising from my study and collaborations during the PhD

Brunkhorst-Kanaan N, Verdenhalven M, Kittel-Schneider S, **Vainieri I**, Reif A, Grimm O (2020): The quantified behavioral test-a confirmatory test in the diagnostic process of adult ADHD? *Frontiers in Psychiatry.* 11: 216.

Du Rietz E, Barker A.R, Michelini G, Rommel A, **Vainieri I**, Asherson P, Kuntsi J (2019): Beneficial effects of acute high-intensity exercise on electrophysiological indices of attention processes in young adult men. *Behavioural Brain Research.* 359: 474–484.

Michelini G, Kitsune V, **Vainieri I**, Hosang G.M, Brandeis D, Asherson P, Kuntsi J (2018): Shared and disorder-specific event-related brain oscillatory markers of attentional dysfunction in ADHD and bipolar disorder. *Brain Topography.* 31(4): 672–689.

# Acknowledgments

First, I would like to express my sincere gratitude to my first supervisor, Professor Jonna Kuntsi, for the consistent support and guidance over the last three years. Thank you for sharing your knowledge and time with me and for giving me the opportunity to develop and improve my research and communication skills. I am grateful to have worked with you. I also wish to thank my second supervisor Professor Fruhling Rijsdijk for patiently teaching me genetic modelling and for your valuable support, thank you for sharing your expertise with me over these years. I would like to express my gratitude and appreciation for my third supervisor Dr Giorgia Michelini for her guidance, support, and encouragement; your enthusiasm for research motivated me before and throughout my PhD.

I would like to thank other experts whom I have had the pleasure of working with, particularly Dr Joanna Martin for her patience and willingness to help, and her valuable advice and guidance on statistical genetic analyses. I also want to thank Professor Philip Asheron for his useful clinical insights and fascinating chats on ADHD.

I am truly thankful to the participants from IMAGE, SEFOS, and FEBA, as this work would not have been possible without their willingness to take part, and the work of the previous students, investigators, and research assistants on these existing projects.

I also want to thank all the lovely students and researchers that were part of my team during my PhD journey at the SGDP Centre as part of the ADHD team. Thank you, Nicoletta Adamo, Anna Rommel, Ebba Du Rietz, Alessandra Carta, Adam Pawley, Talarrita Moukhtarian, Qigang Deng, and Hayley Denyer for your support and advice, but especially for our friendly chats and funny moments, I could not have imagined a better team.

I am extremely grateful to all the amazing people I have met at the SGDP centre. Special thanks to Natali Bozhilova, Georgina Krebs, Laurel Fish, Daniel Wechsler, Kunle Oginni, Megan Skelton, and Alicia Peel for being such wonderful office mates

during these years. Also, thanks to Kai Lim, Kirstin Purves, and Zeynep Nas for our amazing friendly coffee chats. I feel so lucky to have met so many wonderful people; I have created so many lovely memories that I will forever treasure with me.

Lastly, I want to acknowledge my parents and my wonderful sister, Erika, for their unconditional love and support. I am also truly grateful for my friends in Rome, especially Pandru, Alessandra, and Michela, that despite the physical distance have always been such lovely friends. Finally, the biggest thank you goes to Lele, who has always been by my side providing me with all the love and encouragement I needed to go through this journey.

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# Chapter 1

# Introduction

## 1.1 Abstract

The opening chapter of this thesis will give an overview of attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD). I will first introduce ADHD as a clinical disorder, summarising its diagnostic criteria, categorical and dimensional approaches, epidemiology and treatments. Second, I will focus on the genetic and environmental aetiology of ADHD and provide evidence on the emerging genome-wide association study (GWAS) and polygenic approaches. In the third part of this introduction, I will provide an overview of the methods used to investigate cognitive-neurophysiological impairments and brain markers in ADHD, as well as review evidence on these impairments in children and adults with the disorder. Then, I will focus on the developmental trajectories and markers of ADHD persistence and remission, reviewing evidence on case-control studies comparing children and adults with childhood ADHD and controls. This chapter will then focus on BD, introducing its similarities with ADHD at the clinical, cognitive and neurophysiological level, as well as introducing research that has investigated biomarkers that could help identify overlapping and distinct characteristics of the two disorders. Finally, I will conclude the chapter by presenting the specific aims of this thesis and discuss how the empirical chapters will address these objectives.

## 1.2 Introduction to ADHD

ADHD is a neurodevelopmental disorder characterised by developmentally inappropriate and impairing levels of inattentive and/or hyperactive-impulsive symptoms. The first record of ADHD-like behaviours in the medical literature appeared in the

late 18th century in a book chapter published in 1775, where the German physician Melchior Adam Weikard described children with attention deficits (Barkley & Peters, 2012). Further descriptions of children with hyperactive, inattentive, and impulsive symptoms followed in the eighteenth and nineteenth centuries (Lange et al., 2010). The first appearance of ADHD in a diagnostic nomenclature was in the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II) published by the American Psychiatric Association (APA), where ADHD was referred as 'Hyperactive child syndrome' (APA, 1968). In 1980, DSM-III renamed the syndrome 'Attention Deficit Hyperactivity Disorder with or without hyperactivity' (APA, 1980). The DSM-IV (APA, 1994), and later its revised version (DSM-IV-TR; APA, 2000), introduced the first distinction between ADHD subtypes (inattentive, hyperactive-impulsive and combined), giving equal emphasis to the inattentive and hyperactive-impulsive symptom dimensions. Recently, the DSM-5 (APA, 2013) revised the definition of subtypes by changing the terminology from 'types' to 'presentation', acknowledging that subtypes may not be stable across development as indicated by previous research (Willcutt et al., 2012). Furthermore, the age of onset of symptoms was raised from seven to twelve years, indicating the possible emergence of ADHD symptoms in early adolescence. The DSM-5 has also included further descriptions of ADHD in adulthood and lowered the minimum number of symptoms needed for diagnosis from six to five symptoms in the inattention or hyperactivity-impulsivity subdomains in adults. Finally, while in the DSM-IV classification ADHD could not be diagnosed in individuals with autism spectrum disorder (ASD) or other pervasive developmental disorders, the DSM-5 allowed the comorbidity between ADHD and ASD.

Another common diagnostic system is the International Classification of Diseases (ICD) by the World Health Organization (WHO) (WHO, 1992). Until very recently, the available version of this classification system (ICD-10) diverged from the DSM by referring ADHD as "hyperkinetic disorder". The ICD-10 was also considered a more stringent diagnostic tool as the hyperkinetic disorder was defined by the presence of symptoms from all three dimensions of inattention, hyperactivity and impulsivity in at least two settings (e.g. at home and at school) (Sørensen et al., 2005). In the latest version of the ICD (ICD-11), the term ADHD has replaced ICD-10 'hyperkinetic disorder' and ADHD has been moved to the grouping of neurodevelopmental disorders (WHO, 2018). ADHD can be characterised in the ICD-11 using qualifiers for predominantly inattentive, predominantly hyperactive-impulsive, or combined type, and is described across the lifespan (WHO, 2018).

### 1.2.1 Diagnostic criteria

This thesis is based on the diagnostic criteria for ADHD included in the DSM-IV-TR (APA, 2000), which was the DSM version in use during the data collection for the studies included in this thesis. The diagnostic criteria that I will therefore describe in this section are related to DSM-IV-TR. The DSM-IV-TR includes eighteen symptoms of ADHD (reported in Table 1.1). These eighteen symptoms are subdivided into nine inattentive symptoms, six hyperactive symptoms and three impulsive symptoms. A diagnosis of ADHD is given if at least six inattentive and/or six hyperactivity-impulsivity symptoms have been present for at least 6 months before the age of seven years. These symptoms must be impairing in at least two settings (e.g. at school and at home), and should not occur exclusively during the course of a pervasive developmental or psychotic disorder, or better explained by another psychiatric condition. ADHD diagnoses can be divided in different subtypes: the predominately inattentive type (ADHD-IA), if at least six inattentive symptoms (but less than six hyperactive-impulsive symptoms) are present; the predominately hyperactive-impulsive type (ADHD-HI), if at least six hyperactive-impulsive symptoms (but less than six inattentive symptoms) are present; and ADHD combined type (ADHD-C), if at least six symptoms are present on both symptom domains. According to DSM-IV-TR, adults can only be diagnosed with ADHD if they met diagnostic criteria before the age of seven, and if they still meet diagnostic criteria in adulthood.

#### 1.2.1.1 Categorical and dimensional approaches to ADHD

Diagnostic manuals, such as DSM and ICD, use a categorical classification system based on either the presence or absence of ADHD. The categorical approach reflects the nature of the binary treatment protocols in clinical practice and has the advantages of allowing clear diagnostic decisions and effective communication between professionals in health care and research settings (Coghill & Sonuga-Barke, 2012). However, ADHD, like other psychiatric disorders, reflects the extreme of a continuous distribution of quantitative traits continuously distributed throughout the general population (Demontis et al., 2019; Larsson et al., 2012; Plomin et al., 2009). This dimensional view is supported by quantitative genetic studies showing that the genetic contribution to ADHD (Chen et al., 2008; Larsson et al., 2012), as well as the cognitive and neurobiological impairments (Kuntsi et al., 2014; Kuntsi et al., 2010), are similar for categorical and dimensional approaches.

Although there have been some recent initiatives to develop a new classification of mental diseases based on a dimensional approach (Insel et al., 2010), the official

**Table 1.1:** DSM-IV-TR diagnostic criteria for ADHD

| | |
|---|---|
| | Inattention: six (or more) of the following symptoms persisting for at least 6 months to a degree that is maladaptive and inconsistent with developmental level: |
| 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 organising 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-impulsivity: six (or more) of the following symptoms persisting for at least 6 months to a degree that is maladaptive and inconsistent with developmental level: |
| 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 subjective feelings of restlessness). |
| 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'. |
| 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. |

*Note:* items replicated from the revised version of the DSM-IV (DSM-IV-TR; APA, 2000).

approach in clinical practice remains based on the categorical classification. The dimensional approach likely better reflects the complexity of mental health disorders, but it is difficult to implement in clinical practice for diagnostic and treatment decisions (Brown & Barlow, 2005). Consequently, in research settings, both categorical and dimensional approaches are recommended to study ADHD and its underlying pathophysiology (Coghill & Sonuga-Barke, 2012). As such, both approaches are employed to study ADHD in this thesis.

#### 1.2.1.2 Parent-, teacher- and self-reports

Clinical guidelines suggest that multiple informants should be used in diagnostic assessment to better establish the pervasiveness of ADHD symptoms across different settings (APA, 2013; NICE, 2018). Usually the informants are parents and teachers for children and adolescents, while, in adulthood, the diagnosis of ADHD typically relies on self-reports (NICE, 2018).

Evidence suggests that reports of ADHD symptoms and functional impairments provided by the different informants (parent vs teacher vs self), show only a modest degree of agreement in reporting ADHD symptoms in children (with correlation estimates between 0.30 and 0.50) (Achenbach Rescorla, 2001; Goodman, 2001). The modest agreement between different informant reports likely relates to different information, point of views and settings where the child's behaviour is observed. Therefore, to obtain a complete evaluation, information from multiple sources would be ideally integrated with the interviewer's perspective both in clinical and research settings (Taylor et al., 2004).

While for the assessment of children and adolescents the use of multiple-informant reports is standard practice, the diagnosis of adult ADHD often relies on self-reports alone; partly due to the difficulty in collecting multi-informant reports (Asherson, 2005). However, as shown in recent studies, adults with ADHD may sometimes lack insight into some of their difficulties and, as a result, may potentially underestimate them (Faraone & Biederman, 2016; Knouse et al., 2005). This suggests that a combination of self-reports with reports from either a parent or a significant other would be desirable in adulthood (Faraone & Biederman, 2016; Knouse et al., 2005; Kooij et al., 2008). Twin studies that show higher heritability for parent- compared to self-rated ADHD symptoms (Chang et al., 2013; Larsson et al., 2013; Merwood et al., 2013) are also consistent with the potential lower reliability of self-reports compared to parent-ratings. Specifically, low reliability leads to increased measurement error, captured in twin models by the non-shared environment component, which in turn deflates the

heritability estimates (Faraone & Biederman, 2016; Merwood et al., 2013). On the other hand, the lower heritability estimates for self-ratings of adult ADHD might stem from the use of different informants for each twin in a pair (i.e. each twin rated only themselves), rather than from a less reliable measure of behaviour (Brikell et al., 2015).

In accordance with the current diagnostic guidelines (NICE, 2018), the ADHD diagnostic status in this thesis was based on ADHD symptoms reported by parents during a structured clinical interview among samples in which ADHD symptoms were assessed during childhood and late adolescence (Chapters 2 to 4). Parent-reports were additionally chosen as primary measure to assess ADHD symptoms and impairments given the wide age range (6-27 years) of the ADHD and control samples used in this work (Chapters 2 to 4). The ADHD sample in Chapter 5 was obtained from an adult ADHD clinic where an ADHD diagnosis was established by a clinician based on self-report, in accordance with the current diagnostic guidelines.

### 1.2.2 Epidemiology and development of ADHD

#### 1.2.2.1 Prevalence

ADHD is one of the most common neuropsychiatric disorders, with a worldwide prevalence in children of approximately 5% (Polanczyk et al., 2007; Polanczyk et al., 2014). Since ADHD symptoms tend to decline, overall, with age, ADHD used to be considered a childhood-only disorder (Hill & Schoener, 1996). However, increasing recognition has been given to adult ADHD (Asherson et al., 2016) with evidence showing a prevalence of around 2-4% in the adult population worldwide (Willcutt, 2012). The somewhat lower prevalence of ADHD in adults could potentially be explained by its symptomatic remission from childhood to adulthood in a proportion of individuals. Another explanation could be related to the change in symptom manifestation in adults, leading to low recognition of ADHD in adults in clinical practice. For example, hyperactive and impulsive symptoms are often manifested with feelings of restlessness or inner tension in adults (Asherson et al., 2014; Kooij et al., 2010) which are less detectable at the behavioural level. Since until the DSM-5, the diagnostic criteria were based on behavioural descriptions developed for ADHD in children, recognition of ADHD in adults may have been underestimated. Lastly, the low recognition of ADHD in adult psychiatry centres may potentially result in under-diagnosis and consequent misdiagnosis of more typical adult psychiatric conditions, such as bipolar disorder and borderline personality disorder (Asherson, 2005; Asherson et al., 2014).

#### 1.2.2.2 Gender differences

The prevalence rate of ADHD has consistently been reported as being higher in boys than in girls (Willcutt, 2012), with an estimated gender ratio of 3:1 in population-based samples and up to 9:1 in clinical samples (Gaub & Carlson, 1997; Polanczyk et al., 2007; Staller & Faraone, 2006). This difference in prevalence rate is less prominent in adulthood, with gender ratios ranging from 1:1 to 1.6:1 (Das et al., 2012; Faraone et al., 2005; Kessler et al., 2006).

Given the discrepancies in gender ratios between clinical and population-based studies and the similar gender ratios reported in adulthood, several hypotheses have been put forward to explain the substantial lower prevalence of ADHD in girls. One possible reason for the gender discrepancy in ADHD prevalence rates can be related to the use of diagnostic tools used to detect ADHD symptoms. The current diagnostic criteria were developed based on predominantly male samples and might therefore be inadequate to ascertain ADHD in girls (Nussbaum, 2012). For instance, ADHD in boys is usually manifested with more hyperactivity and externalising symptoms compared to girls (Biederman, 2005; Thorell & Rydell, 2008; Willcutt, 2012). Since such symptoms are often the primary cause of referral from teachers and parents, girls might be underrepresented in clinical practice due to a gender-based referral bias (Biederman, 2005). In adulthood, there is a more equal balance in gender ratios of ADHD. This might be related to the fact that cases of ADHD in adulthood are usually self-referred and therefore not subject to a gender-based referral bias as in childhood, leading to a more similar number of women and men approaching mental health services (Biederman et al., 1994; Biederman et al., 2004). Alternatively, adult women with ADHD might be more likely to self-refer to mental health services, which would in turn lead to more equal prevalence rates across genders because of a possible under-diagnosis in adult men (Arcia & Conners, 1998; Biederman et al., 1994). An alternative explanation of the gender differences in ADHD in children but not in adults, is the "female protective model" of neurodevelopmental disorders (Jacquemont et al., 2014). According to this model, girls require more exposure to ADHD risk factors (e.g. higher genetic or familial burden) than boys to meet ADHD diagnostic criteria. This model has been supported by twin studies showing that co-twins of girls with ADHD had increased ADHD traits compared to co-twins of boys with ADHD, suggesting that females require greater exposure to genetic and environmental factors associated with ADHD in order to meet ADHD diagnostic criteria (Taylor et al., 2016). As such, it might be that girls require more time to be exposed to a level of risk factors sufficient to reach ADHD diagnostic criteria, leading to a later onset

than in boys (Faraone & Biederman, 2016), which is in line with the more equal gender ratio of ADHD prevalence in adults.

Overall, more research is needed to investigate the reasons for gender discrepancies in ADHD. Due to the higher rates of ADHD in boys, large scale studies have focused more on ADHD in boys than girls (Chen et al., 2008; Doyle et al., 2000; Klein et al., 2012; Kuntsi et al., 2010), while empirical evidence is more limited on girls and women with ADHD to date.

#### 1.2.2.3 Co-occurring psychiatric symptoms and disorders

Along with the inattentive and hyperactive-impulsive symptoms that define the disorder, ADHD is often associated with a wide range of psychiatric symptoms and comorbidity in both children and adults (Asherson et al., 2016; Jensen & Steinhausen, 2015; Larson et al., 2011).

In children and adolescents, ADHD frequently co-occurs with other behavioural problems and neurodevelopmental disorders. Around 10-70% of children and adolescents with ADHD present with conduct disorder or oppositional defiant disorder (Biederman et al., 1991; Larson et al., 2011). Other common comorbidities with ADHD (with rates ranging from 20% to 65%) include specific disorders of language, learning or motor development such as dyslexia, dyscalculia and dysgraphia (Biederman, 2005; DuPaul et al., 2013; Jensen & Steinhausen, 2015; Korrel et al., 2017). The comorbidity with ASD is also frequent, with evidence suggesting that around 20-50% of individuals with ADHD also display ASD symptoms (Rommelse et al., 2011).

ADHD also often co-occurs with internalising or emotional problems such as anxiety and other mood disorders as well as mood dysregulation. Anxiety disorders co-occur in 20% to 35% of individuals with ADHD across the lifespan (Biederman et al., 2013; Bloemsma et al., 2013). Co-occurring mood disorders are common comorbid diagnoses: 10% to 55% of adults with ADHD manifest with depressive symptoms and disorders, and 5% to 32% have co-occurring bipolar disorder (BD) (Angold et al., 1999; Asherson et al., 2014; Vance & Winther, 2009). The association with mood symptoms is complex, and some of the symptoms of ADHD may also resemble typical manifestations of manic and hypomanic episodes in BD, such as psychomotor restlessness, distractibility, affective lability and irritability (Asherson et al., 2014; Skirrow et al., 2012), which may in some cases lead to misdiagnosis and incorrect treatment decisions. The comparison between ADHD and BD is relevant to the research of this thesis (Chapter 5) and is discussed in further detail in this chapter in section 1.6.

### 1.2.3 Treatments for ADHD

Due to the impairing nature of ADHD across the lifespan, appropriate treatment of ADHD symptoms is often required for improving the quality of life of affected individuals. Currently, clinical guidelines recommend pharmacological intervention for children aged 5 years and over and young people only if their ADHD symptoms are still causing a persistent significant impairment in at least one domain after environmental modifications have been implemented and reviewed (NICE, 2018). When ADHD occurs in children and adolescents, non-pharmacological interventions are recommended as first line intervention (NICE, 2018).

The first-line pharmacological treatment for ADHD includes psychostimulants, such as methylphenidate and amphetamine-like agents; evidence also supports the efficacy of certain non-stimulant medications such as atomoxetine and guanfacine which are used as second-line pharmacological treatment (Coghill et al., 2013; NICE, 2018; Retz et al., 2011; Ruggiero et al., 2014; Savill et al., 2015). However, in some cases, ADHD medications are not well tolerated due to side effects, may exacerbate symptoms of comorbid conditions, or be ineffective (Biederman et al., 2004). A recent meta-analysis indicated methylphenidate in children and adolescents, and amphetamines in adults, as first-choice medications for ADHD when taking into account efficacy and tolerability of oral medications (Cortese et al., 2018).

In both children and adults, meta-analyses report moderate-to-large effects of these medication treatments on ADHD symptoms and outcomes (Chan et al., 2016; Faraone & Glatt, 2010; Gayleard & Mychailyszyn, 2017; Maneeton et al., 2014; Maneeton et al., 2015; Prasad et al., 2013). A recent meta-analysis questioned the efficacy and safety of stimulant medication for children with ADHD (Storebø et al., 2015), leading to an extensive debate amongst clinicians with several scientists highlighting flaws in this study (Banaschewski et al., 2016; Mulder et al., 2016). For instance, Storebø and colleagues used idiosyncratic methods to assess study bias and quality of evidence, which deviate significantly from standard Cochrane methodology and result in an exaggeration of study bias and excessive downgrading of the quality of the evidence (e.g. underestimation of effect sizes).

The most common non-pharmacological interventions for ADHD are psychological interventions, such as behavioural training (NICE, 2018). However, meta-analyses show that, when the outcome is rated by blinded reviewers, behavioural interventions were effective in reducing childhood conduct problems and improving parenting but not in reducing core symptoms of ADHD (Daley et al., 2014; Sonuga-Barke et al., 2013). Other interventions have been developed to treat ADHD, such as neurofeed-

back, mindfulness, cognitive training, dietary interventions and physical activity. However, strong evidence of the efficacy of these alternative non-pharmacological treatments is still lacking (Cortese et al., 2016; Halperin et al., 2014; Janssen et al., 2019; van der Oord et al., 2012) and behavioural modifications are the only interventions currently recommended by clinical guidelines (NICE, 2018).

### 1.2.4 Summary

ADHD is a neurodevelopmental disorder characterised by age inappropriate levels of inattention, hyperactivity and impulsivity. ADHD is often first diagnosed in childhood but can persist into adulthood. While tools such as the DSM and ICD define ADHD categorically, ADHD is the extreme of a continuum of symptoms that vary continuously in the population. A dimensional approach can therefore better identify subclinical expressions of ADHD symptoms. Both parents and teacher reports of ADHD symptoms are used in clinical practice for children, while self-reports are more commonly used in adults. While in childhood ADHD is more prevalent in boys, similar rates of males and females with ADHD are reported in adulthood. Individuals with ADHD are more likely to display co-occurring mental health conditions, and some overlapping diagnostic features, which may lead to misdiagnosis and incorrect treatment decisions. Overall, ADHD presents as a highly complex disorder with high clinical heterogeneity that can in turn affect treatment response and long-term outcomes.

## 1.3 Aetiology of ADHD

Similar to many other psychiatric disorders, ADHD is a multifactorial disorder with a complex aetiology, which arises from the interplay between genetic and environmental risk factors (Plomin et al., 2009). Numerous quantitative genetic studies have established the large contribution of genetic factors to ADHD, and a more limited role of individual-specific environmental influences (Burt, 2009; Burt et al., 2012; Faraone & Larsson, 2019). Given these findings, effort has been focused on investigating the genetic variants associated with ADHD (Demontis et al., 2019), as well as the environmental risk factors that can increase the risk of developing the disorder and how they interact with individual genetic predisposition (Thapar et al., 2009).

### 1.3.1 Quantitative genetic studies

Quantitative genetic studies investigate the contribution of genetic and environmental factors to individual differences in traits using twin, adoption or family (e.g. sibling data) studies, or a combination of these different designs (Rijsdijk & Sham, 2002).

The most commonly used quantitative genetic design is the twin model, which disentangles the influences of genetic and environmental factors on a trait by comparing information in monozygotic (MZ) and dizygotic (DZ) twins raised in the same family. MZ and DZ twins reared together share many aspects of their environment and are genetically identical (MZ twins) or share on average 50% of their segregating genes (DZ twins). Specifically, in twin studies the sources of genetic and environmental variation are divided into additive genetic influences (A), non-additive (or dominant) genetic influences (D), shared environmental influences among family members (C), and unique individual-specific environmental influences (E; including also measurement error). Twin studies in children and adolescents have estimated high heritability of ADHD symptoms (around 70-80%) (Burt, 2009; Faraone et al., 2005; Larsson et al., 2013) while most of the remaining variance has been attributed to individual-specific environmental factors. Similar heritability estimates have been found for inattention and hyperactivity-impulsivity symptom domains and across gender (Greven et al., 2011; Nikolas & Burt, 2010). In late adolescence and adulthood most twin studies have reported lower heritability estimates (approximately 37-44%) (Boomsma et al., 2010; Polderman et al., 2013; Reiersen et al., 2008; van den Berg et al., 2006). Given that these studies relied on self-reports, where concerns have been raised about reliability in adolescent and young adult samples, this may have contributed to the lower heritability estimates: lower reliability of measures increase measurement error (captured in E), which increases the non-shared environmental component resulting in a ceiling on the heritability estimate (Brikell et al., 2015; Faraone & Larsson, 2019; Freitag et al., 2010). Twin studies have further indicated similar contributions of genetic factors across different levels of impairment, highlighting that ADHD represents the quantitative extreme of symptoms that are continuously distributed in the population (Larsson et al., 2012).

Other common family designs are adoption and sibling studies. The adoption method investigates similarities between the adopted child and their biological and adoptive parents. Heritable genetic effect is estimated by the similarity with the biological parent, while similarity with the adoptive parent is associated with the adoptive environment. Adoption studies have shown increased rates of ADHD in the biological parents of children with ADHD compared to both adoptive parents and

parents of children without ADHD (Sprich et al., 2000). Similar to DZ twins, siblings share approximately 50% of their DNA, as well as many aspects of their environment. Using a sibling design, it is possible to decompose the variance of a trait into familial influences (combined effects of shared genetic and shared environmental effects [F]) and non-familial influences (individual-specific effects [E], including measurement error). Sibling studies have consistently reported a higher prevalence of ADHD symptoms and diagnoses in siblings of affected individuals, compared to siblings of typically developing children (Faraone et al., 2000; Faraone & Larsson, 2019), supporting the idea that familial factors play a significant role in mediating the susceptibility to ADHD. Overall, recruiting sufficiently large samples of affected twins may prove difficult, and sibling studies represent a powerful alternative to twin studies to investigate individuals with clinically diagnosed ADHD. Over the years, family and twin studies showed shared genetic and familial influences on the associations between ADHD and co-occurring traits such as bipolar disorder, schizophrenia, mood disorders, anxiety, IQ, and several cognitive impairments such as reaction time variability (RTV), working memory and short-term memory (Cole et al., 2009; Kuntsi et al., 2004; Kuntsi et al., 2010; Larsson et al., 2013; Michelini, Cheung et al., 2018; Michelini et al., 2015). The role of the aetiological influences on ADHD symptoms and cognitive impairments showed both stable and new time-specific aetiological influences emerging across development (Chang et al., 2013; Gustavson et al., 2018; Larsson et al., 2004; Tucker-Drob & Briley, 2014), thus stability in the association between ADHD and other phenotypes cannot be assumed. Further details of the sibling design can be found in Chapter 4, which uses a sibling model of the cross-lagged design to explore the contribution of familial and non-familial influences underlying the relationship between ADHD and cognitive impairments across time.

### 1.3.2 Molecular genetic studies

#### 1.3.2.1 Candidate genes studies and genome-wide association studies

Given the strong evidence from quantitative studies that genetic factors play a key role in ADHD aetiology, in the past three decades molecular genetic studies attempted to examine which genetic loci are associated with the disorder. Prior to the development of genome-wide association studies (GWAS), early molecular genetic studies used candidate gene and linkage approaches to identify candidate genes associated with ADHD. The majority of these studies targeted genes implicated

in dopaminergic, noradrenergic and serotonergic systems involved in the clinical response to ADHD pharmacotherapies (Faraone et al., 2005). While replicated associations of several candidate genes were reported (e.g. DRD4, DAT1, DRD5, 5HTT), meta-analytic evidence showed that the effect sizes of these associations were small (odds ratios below 1.5) (Bonvicini et al., 2016; Gizer et al., 2009). Importantly, given the thousands of genetic variants in the genome, hypothesis-driven candidate gene studies are likely to show false positives (Kendler, 2013).

More recent developments in molecular genetic research have led to an approach focused on testing the association between ADHD and genetic markers across the whole genome rather than specific genes (GWAS) (Neale et al., 2010). These GWAS have focused on testing associations of several hundreds of thousands of common genetic variations (or single-nucleotide polymorphisms; SNPs) across the genome. Early GWAS failed to detect SNPs that achieved the stringent genome-wide significant threshold ($p$-value $< 5 \times 10^{-8}$); this has been attributed to limited power due to inadequate sample sizes (Hinney et al., 2011; Lasky-Su et al., 2010; Mick et al., 2010; Middeldorp et al., 2016; Neale et al., 2008; Neale et al., 2010). This in turn highlighted the need for collaborative efforts with larger samples, including tens of thousands of cases and controls, to accumulate sufficient power to detect significant genome-wide associations.

Recently the international collaboration carried out by the Psychiatric Genetic Consortium (PGC) was able to significantly increase sample sizes included in the ADHD GWAS. The most recent mega-GWAS consists of more than 20 000 ADHD cases and 35 000 controls, and was able to identify, for the first time, 12 independent loci in the genome that are significantly associated with ADHD (Demontis et al., 2019). This GWAS showed that ADHD heritability can be explained by many common variants of small effect, with the heritability estimated at 0.22 based on single nucleotide polymorphisms (SNPs). However, this estimate explained only one third of the ADHD heritability derived from twin studies (Demontis et al., 2019; Faraone et al., 2005). It was therefore suggested that the 'missing' heritability could reflect the additional contribution of rare variants, such as copy number variants and single nucleotide variants (SNVs), that are not typically detected in GWAS. Several studies indicate a role for copy number variants and SNVs in contributing to ADHD risk (Martin, O'Donovan et al., 2015; Satterstrom et al., 2018; Thapar et al., 2016; Williams et al., 2012; Williams et al., 2010; Yang et al., 2013). A recent study showed that the overall mutation rate for de novo copy number variant carriers was 4.6%, suggesting that de novo copy number variants likely contribute to ADHD risk (Martin et al., 2020). Models that combine common and rare genetic variants

approaches are likely to further advance our understanding of the genetic aetiology of ADHD (Martin, O'Donovan et al., 2015).

#### 1.3.2.2 Polygenic risk score studies

The complex genetic architecture of ADHD can be explained by the contribution of many common genetic variants of very small effect that define the polygenic architecture of the disorder (Demontis et al., 2019; Sullivan et al., 2012). This complex genetic liability for psychiatric disorders can be quantified with polygenic risk scores (PRS). PRS are typically calculated for individuals by computing the sum of their risk alleles across the genome, weighted by GWAS-derived effect sizes (Choi et al., 2018). PRS derived from the new mega-GWAS could explain up to 5.5% of variance in ADHD case-control status (Demontis et al., 2019). PRS for ADHD were associated with different neuropsychiatric and psychiatric disorders, such as conduct disorder, substance use disorders, autism, schizophrenia and major depressive disorder (Jansen et al., 2020; Wimberley et al., 2020). Also, PRS for ADHD have been associated with many psychiatric and somatic traits in the general population (e.g. neuroticism, anxiety, depression, irritability, childhood internalising and externalising symptoms, obesity, IQ, smoking and school achievement (Brikell et al., 2018; Du Rietz et al., 2018; Martin et al., 2014; Riglin et al., 2017). Only a few studies explored the cognitive phenotypes associated with ADHD and have provided initial evidence for associations between PRS for ADHD, and IQ (Du Rietz et al., 2018), cognitive impairments such as working memory and alertness (Martin, Hamshere et al., 2015; Nigg et al., 2018), as well as educational outcomes (Stergiakouli et al., 2017). However, the majority of these studies have investigated the relationship between ADHD and co-occurring traits, such as cognitive traits, in population-based studies, while evidence from clinically diagnosed samples with ADHD remains more limited. Overall, PRS is a promising approach to aid in the investigation of the aetiological mechanisms underlying ADHD. Further details on PRS analyses can be found in Chapter 3, which used this approach to investigate the association between ADHD and cognitive impairments in a clinical sample of people with ADHD.

### 1.3.3 Environmental risk and gene-environment interplay

Several environmental risk factors have also been associated with ADHD. These environmental factors include preterm birth, low birth weight, smoking and consuming alcohol during pregnancy, dietary factors, psychosocial factors and family adversity (Sciberras et al., 2017; Thapar et al., 2013). However, most studies examin-

ing such environmental effects have not controlled for unmeasured confounding such as familial risk factors shared between individuals living in the same family (Thapar et al., 2009). Therefore, these individual-specific environmental factors may not necessarily reflect a role of the environmental factor per se but could instead reflect other environmental and genetic risk factors shared by the family members.

One approach that aims to disentangle such confounds is the sibling-comparison design. This approach uses a within-pair association, by comparing siblings in the same pair to estimate associations with shared and non-shared environmental effect. Using this approach, evidence shows that the association of ADHD with maternal smoking, psychosocial factors such as low socio-economic status (SES), and family adversities such as negative parenting, are explained by familial confounding factors (Skoglund et al., 2014). Instead, preterm birth may have a causal effect independent from confounding by familial factors (James et al., 2020; Skoglund et al., 2014).

Environmental risk factors may interact with an individual's genetic predisposition (Nigg et al., 2010; Thapar et al., 2013), or, vice versa, individual's genetic predisposition may increase the risk of exposure to certain environmental risks (Plomin, 2014). For instance, the environment may interact with the genetic architecture, altering DNA methylation (epigenetics) (Mill & Petronis, 2008). Emerging evidence suggests a potential role of DNA methylation and histone acetylation within genes linked to development processes associated with ADHD (van Mil et al., 2014; Walton et al., 2017). However, the investigation of the environmental risk and gene-environment interplay in ADHD is not the focus of this thesis and therefore this topic is not discussed in further detail.

### 1.3.4 Summary

This section has first provided an overview of research on ADHD aetiology. Findings from quantitative genetic research show that ADHD is a multifactorial disorder influenced by both genetic and environmental factors. These findings have guided molecular genetic research, and a recent GWAS successfully identified 12 loci that were significantly associated with ADHD. Using GWAS it is possible to perform further genetic investigations such as PRS analyses, which have shown genetic associations between ADHD PRS and a wide range of psychiatric and somatic traits. PRS analyses also provide initial evidence for an association between ADHD and specific cognitive impairments. Advanced analysis techniques, such as polygenic risk scores, may help to further define the under-

lying biology of ADHD and its co-occurrence with other traits such as cognitive impairments.

## 1.4 Cognitive and neurophysiological methods and impairments in ADHD

Cognitive and neurophysiological techniques have helped to identify alterations associated with the clinical manifestations of ADHD. In this section, I will provide an overview of the cognitive and neurophysiological assessments and measures used in this thesis, as well as review relevant studies on the cognitive and neurophysiological impairments associated with ADHD.

### 1.4.1 Cognitive assessments

General cognitive ability, measured by the intelligent quotient (IQ), and specific cognitive processes, such as working memory and short-term memory, can be assessed in clinical and research settings using standardised tests. The Wechsler scales of Intelligence were used in the studies reported in this thesis to measure IQ (vocabulary, similarities, picture completion and block design subtests). Using the Wechsler scales, it is also possible to assess working memory, measured as digit span backward (DSB), and short-term memory, measured as digit span forward (DSF). During these digits span tasks, participants see or hear a sequence of numerical digits and are tasked to recall the sequence in order of presentation (forward), or in reversed order (backwards).

A variety of cognitive computerised tasks are also employed in research settings to measure cognitive performance in ADHD. Several studies have used the continuous performance test (CPT), which requires participants to respond to certain types of stimuli (target or "Go" stimuli), while ignoring others (non-target or "No-Go" stimuli). The CPT task allows the measurement of omission errors (OE), which represent the lack of a response to a target. OE are generally used as an index of ability to maintain attention over a period of time (sustained attention) and vigilance. Other performance measures that can be obtained from the CPT are reaction time variability (RTV), measured as intra-individual fluctuations in reaction times during task performance, mean reaction time (MRT), assessing reaction time speed, and commission errors (CE), which represent incorrect responses (e.g. responses to non-target stimuli). CE are used to measure response inhibition (ability to withhold a response).

Another commonly used task is the Go/No-Go task, which, similarly to the CPT, presents both Go and No-Go stimuli. Performance measures that can be obtained from the Go/No-Go task are OE, CE and reaction time measures (RTV and MRT). Response inhibition is better assessed using a Go/No-Go task given the differences in the target-to-non-target ratios between the CPT and Go/No-Go task. In fact, the target-to-non-target ratios is low in the CPT (few targets and many distractors) and high for the Go/No-Go task (many targets and few distractors). This in turn makes the Go/No-Go task more likely to elicit CE while the CPT more suitable to detect OE (Berwid et al., 2005).

The oddball task and the Eriksen flanker task (and its variants) have also been widely used to study cognitive and neurophysiological impairments in ADHD research. The oddball paradigm (visual or auditory) requires the ability to focus attention on a given target stimuli while ignoring responses to irrelevant stimuli. In the Eriksen flanker task the target stimuli are presented with congruent or incongruent flanking stimuli, and measures of CE and reaction times can be obtained under congruent and incongruent task conditions. The Eriksen flanker task is specifically designed to measure interference control processes, which is the ability to control the interference due to competition of relevant and irrelevant stimuli (e.g. CE, under congruent and incongruent conditions).

While the aforementioned tasks are used to assess inhibition and interference control, simple reaction time (RT) tasks are used to measure the average speed of responding (MRT) and the variability in the speed of responding (RTV), the latter capturing attention fluctuations. Such tasks require participants to respond as fast as they can whenever a stimulus appears on the screen. A relevant reaction time task for this thesis is the 'fast task', a simple four-choice reaction time task under slow-unrewarded baseline and faster-rewarded conditions (Andreou et al., 2007; Kuntsi, Rogers et al., 2006). Other cognitive tasks used in this thesis are the CPT task, the Go/No-Go task, the Eriksen flanker task, and the oddball task. More details on each of these tasks can be found in the respective chapters.

In the past decade, more sophisticated metrics of RTs have been introduced to provide more detailed measures of RT performance. One such approach is the ex-Gaussian model (Luce, 1991). The ex-Gaussian approach separates the RT distribution into a normal (Gaussian) component and an exponential component, reflecting the positive skew generally observed in RT distributions (Hervey et al., 2006). In this way, ex-Gaussian analyses allow us to derive three summary parameters: mu (the mean of the Gaussian component), sigma (the standard deviation [SD] of the Gaussian component), and tau (the exponential component) (Hervey et al.,

2006; Luce, 1991). The distribution of faster responses is indexed by mu and sigma, while the infrequent, longer RTs, which lengthen the positive tail of the distribution, are indexed by tau. More details about this approach will be given in Chapters 2 and 5.

### 1.4.2 Cognitive impairments in ADHD

Cognitive impairments have been investigated to explain the underlying processes associated with ADHD. The study of such processes has provided robust evidence that ADHD is associated with impairments in several cognitive processes in both adults and children. These impairments include both higher-level, effortful cognitive functions (e.g. inhibitory control, visuo-spatial and verbal working memory, sustained attention) and lower-level, potentially more automatic cognitive processes (e.g. vigilance, intra-individual variability, reward processing, temporal information processing and timing) (Franke et al., 2018).

In children and adolescents, evidence from meta-analyses indicates moderate effect sizes (Cohen's $d = 0.46$ to 0.69) in several executive function (EF) impairments such as inhibition, working memory, sustained attention and planning (Huang-Pollock et al., 2012; Martinussen et al., 2005; Willcutt et al., 2005). Similarly, in adulthood, evidence from a meta-analysis indicates impaired response inhibition and sustained attention, measured with CE and OE with moderate effect sizes (Cohen's $d = 0.50$ to 0.75) (Hervey et al., 2004).

ADHD has further been associated with on average lower IQ scores, with a difference of 7-11 points on average between children with ADHD and controls (Frazier et al., 2004). IQ is also negatively associated with the continuum of ADHD symptoms (with moderate negative correlations between $-0.20$ and $-0.40$) (Kuntsi et al., 2004; Rommel et al., 2015).

ADHD has been also associated with slower and more variable reaction times compared to controls on cognitive tasks requiring a speeded response. Meta-analytic evidence of MRT obtained during CPT tasks suggests a modest effect size for increased MRT (Cohen's $d = 0.37$) (Huang-Pollock et al., 2012). A consistent cognitive impairment in children and adults with ADHD is increased RTV. Evidence from meta-analyses reports RTV impairments in a wide range of cognitive tasks with moderate-to-large effect sizes in children and adolescents with ADHD (Hedge's $g = 0.75$ to 0.85), and a moderate effect size in adults (Hedge's $g = 0.46$) (Huang-Pollock et al., 2012; Kofler et al., 2013).

Studies using the ex-Gaussian approach have consistently shown an increased tau

in children adolescents and adults with ADHD compared to controls (Gmehlin et al., 2014; Hervey et al., 2006; Lee et al., 2015; Leth-Steensen et al., 2000; Vaurio et al., 2009; Wolfers et al., 2015), while sigma and mu were increased in some studies (Buzy et al., 2009; Gmehlin et al., 2014; Hervey et al., 2006; Vaurio et al., 2009), but not in others (Epstein, Langberg et al., 2011; Lee et al., 2015; Leth-Steensen et al., 2000; Vaurio et al., 2009). These results indicate that the increased RTV observed in individuals with ADHD when measured with SD-RT might reflect occasional overly slow responses (tau). The use of detailed RT data analyses, such as the ex-Gaussian decomposition, has promising applications for disentangling the nature of the observed variability in responding as it can detect if this is due to high fast responses (increased mu), variability of fast responses (sigma), or infrequent slow responses (tau). Further information on the ex-Gaussian analysis is in Chapters 2 and 5.

### 1.4.3 Electrophysiological methods

In addition to the information on reaction times and response accuracy obtained from measures of cognitive performance, it is possible to investigate the neurophysiological processes underlying cognitive functions. Among neurophysiological techniques, electroencephalography (EEG) provides a non-invasive direct measure of the electrical activity of the brain from electrodes placed on the scalp with millisecond temporal resolution. This thesis focuses on EEG, which allows us to detect changes in brain activity over milliseconds and is ideally suited for measuring many of the key cognitive processes associated with ADHD, such as attention regulation, attentional selection and inconsistency of stimulus processing. Other brain imaging techniques, such as functional Magnetic Resonance Imaging (fMRI), are also used to study atypical brain processes. fMRI is an indirect measure of brain activity that measures magnetic changes associated with fluctuations in blood oxygen levels in the brain (i.e. haemodynamic response). Research using fMRI has shown that ADHD is associated with abnormalities in several but partially separate neural systems, including networks involved in EF (hypoactivation in the fronto-parietal network), as well as non-executive functions (hyperactivation in the default mode and the ventral-attentional network) (Castellanos & Proal, 2012; Cortese et al., 2012). Meta-analytic evidence from structural MRI brain scans further showed reduced volumes in several brain regions in ADHD including the hippocampus, nucleus accumbens and amygdala (Hoogman et al., 2017). Structural MRI and fMRI are useful techniques to detect brain regions and connectivity patterns implicated in cognitive processes.

While fMRI has excellent spatial resolution, it is an expensive technique and has a poor temporal resolution.

In this subsection, I will give an overview of traditional EEG approaches as well as of advanced EEG analyses.

#### 1.4.3.1 Traditional EEG methods: Quantitative EEG and event-related potentials

Quantitative EEG (QEEG) is a method that allows decomposition of EEG spectral power into its constituent frequencies using Fast Fourier Transform (FFT) spectral decomposition. Conventionally, frequency bands are measured in cycles per second (hertz [Hz]) and are divided into delta (0.1 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 12 Hz), beta (12 to 30 Hz), and gamma (>30 Hz) (Figure 1.1) (Schwilden, 2006). Delta oscillations are commonly associated with sleep and drowsiness, theta oscillations with arousal, alpha oscillations with relaxation and attentive processes, and beta oscillations with concentration and motor responses (Klimesch, 2012; Uhlhaas & Singer, 2006). Using the QEEG, it is possible to quantify the power of each frequency over a continuous recording period (lasting at least a few minutes) when brain

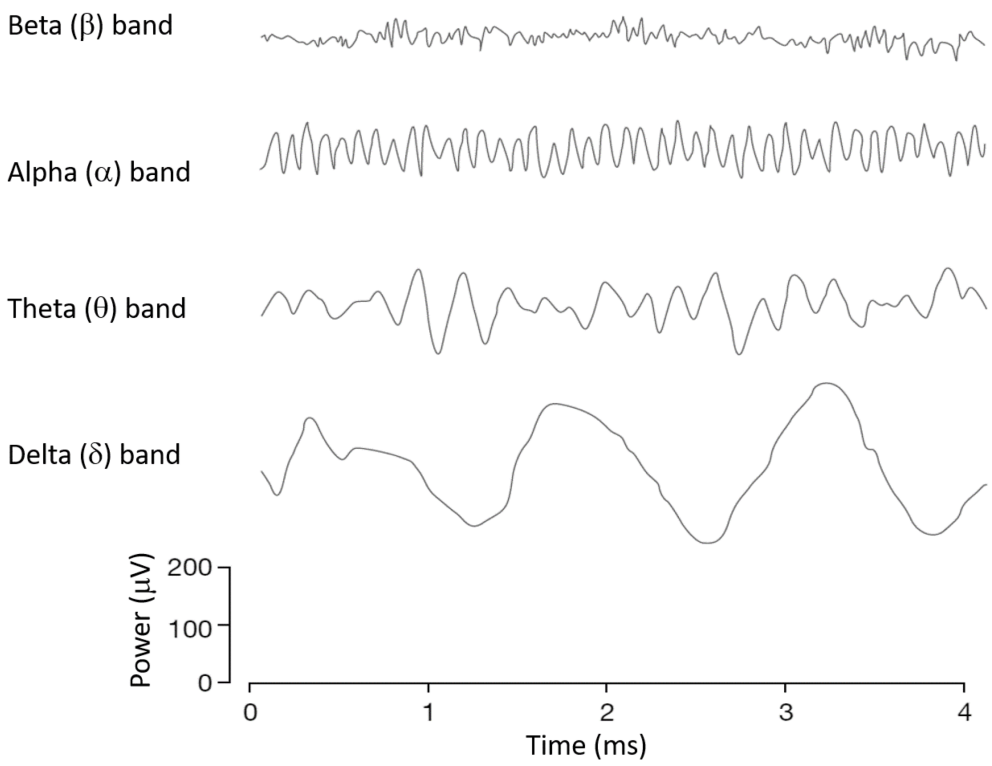


**Figure 1.1:** EEG frequency bands; adapted from Tye et al. (2011).

signals can remain stable (i.e. stationary), such as during resting state or sleep (Loo et al., 2016). Therefore, QEEG methods do not take full advantage of the excellent temporal resolution of EEG recordings and cannot capture the immediate neural responses to a stimulus.

Conversely, event-related potential (ERP) approaches capture sub-second changes in voltage that are time-locked to an event typically averaged across trials, to obtain an averaged ERP response (Figure 1.2). Averaging allows the removal of the background EEG 'noise' (oscillations unrelated to the stimulus) and allows the investigation of the emergence of the characteristic ERP waveform with alternating positive and negative peaks (Luck et al., 2011). ERP analyses allow the measurement of several overt and covert cognitive processes while performing a given task (such as CPT or Go/No-Go tasks). Different ERPs may capture different cognitive processes related to the processing of the stimuli that appear during the cognitive task. An example of an ERP is the P3, a late positive enhancement observed after stimulus presentation that index a different process depending on the stimulus under consideration. During 'Go' trials the P3 is thought to reflect response execution and attention allocation following targets, while during 'No-Go' and 'Cue' trials, the P3 reflects response inhibition processes and attentional orienting respectively (Polich & Kok, 1995; Polich, 2007). Another ERP, the contingent negative variation (CNV), is a negative

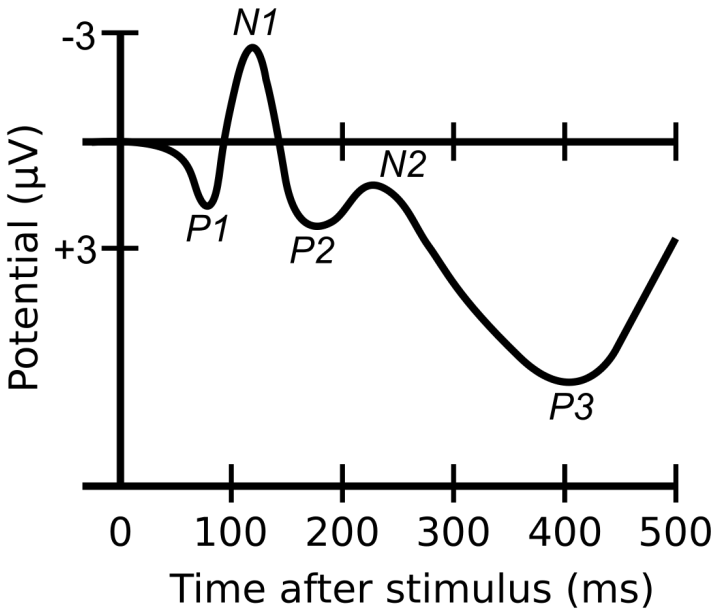


**Figure 1.2:** Simulated ERP waveform with typical components and naming conventions; adapted from Rusnakova and Rektor (2012). *Note:* negative voltage is plotted upwards.

waveform that putatively reflects response preparation. Additional ERPs can be extracted in paradigms with 'No-Go' trials and flaker task performance, such as the NoGo-N2, which measures conflict monitoring, or the error-related negativity (ERN or Ne) and error-related positivity (Pe) that measure automatic error processing and conscious error processing, respectively.

#### 1.4.3.2 Advanced EEG analyses: time-frequency

Recent advances in EEG signal processing called time-frequency analyses combine the strengths of QEEG and ERP methods by studying brain activity in the frequency and time domain (Herrmann et al., 2014) (Figure 1.3). These techniques measure changes of spectral power and phase that are time-locked to an event and can quantify event-related increases or decreases over time at each frequency band (Herrmann et al., 2014; Mathalon & Sohal, 2015). Generally, an increase in power is called event-related synchronisation (ERS), and a decrease in power is referred to as event-related desynchronisation (ERD) or suppression (Pfurtscheller & Aranibar, 1979). Additionally, time-frequency methods define indices of consistency of the phase of brain oscillations across trials, to examine whether the processing of a stimulus

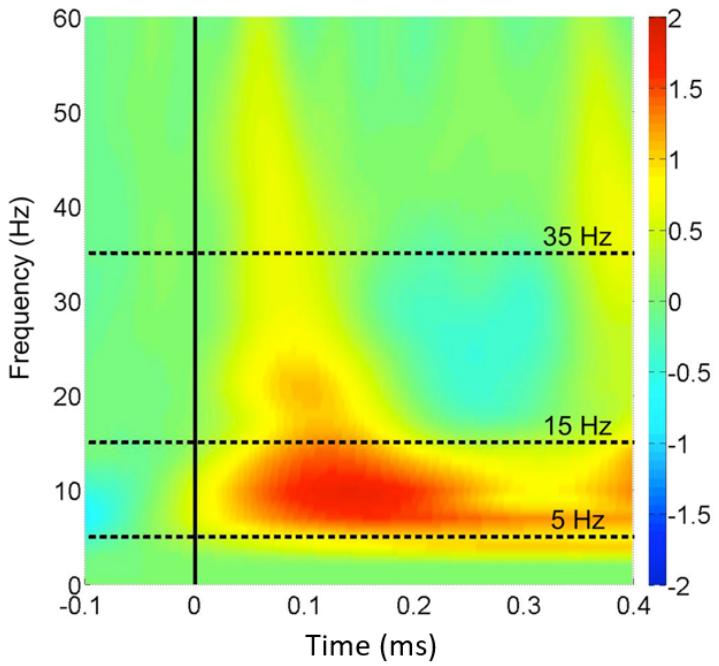


**Figure 1.3:** Time-frequency changes of power time-locked to an event; adapted from Gilbert et al. (2010).

repeated over time reflects stable or variable neural mechanisms (Makeig et al., 2004; Papenberg et al., 2013). Greater phase consistency over trials is thought to reflect an adaptive mechanism to maintain stable neural processing of a stimulus (Makeig et al., 2004; Papenberg et al., 2013). These approaches thus enable the study of detailed EEG dynamics that cannot be captured by more traditional QEEG and ERP approaches. These more sophisticated analyses are applied in Chapter 2.

### 1.4.4 EEG impairments in ADHD

#### 1.4.4.1 QEEG studies and ERPs studies

The use of traditional EEG approaches, such as QEEG and ERP analyses, can be applied to show abnormalities in brain activity during resting state and task performance (Kececi & Degirmenci, 2008). QEEG studies during resting state indicate that participants with ADHD show increased EEG power in low frequency bands (delta and theta) and decreased power in fast frequency bands (alpha and beta), compared to controls (Dupuy et al., 2013; Kitsune et al., 2015; Loo et al., 2009; Snyder & Hall, 2006; Snyder et al., 2015; Tye et al., 2012). These findings suggest a hypo-aroused brain state, which may be responsible for the low vigilance typical of ADHD. Further evidence also shows that very low frequency activity (<0.2 Hz), thought to represent a marker of the default-mode network (DMN), may be decreased in children and adults with ADHD (Helps et al., 2008; Helps et al., 2010).

Previous studies have also indicated an increased theta/beta ratio (representing imbalance in slow and fast EEG rhythms) in individuals with ADHD compared to controls. The large sample sizes and big effect sizes of these studies led to the proposal that theta/beta ratio could be used for diagnostic purposes (Snyder et al., 2015). However, several recent studies have not observed such alterations in the theta/beta ratio in individuals with ADHD (Arns et al., 2016; Loo et al., 2013; Rommel et al., 2016), which strongly questions the consistency of this suggested marker.

ERP analyses of EEG data further allow us to examine time-locked brain responses to specific task stimuli during cognitive tasks and have shown atypical brain responses underlying several cognitive processes in ADHD during a variety of cognitive tasks. For example, decreased P3 amplitudes in individuals with ADHD compared to controls, in response to target stimuli (reflecting impairments in attention allocation and response execution) (Albrecht et al., 2013; Banaschewski et al., 2003; Groom et al., 2010; McLoughlin et al., 2011), to non-target stimuli (NoGo-P3; reflecting

impaired response inhibition), and to 'cue' stimuli (Cue-P3; reflecting impaired attentional orienting). Reduced contingent-negative variation (CNV) amplitudes before a cued response, indicating impaired response preparation, have also been reported in adults with ADHD (Banaschewski et al., 2003; McLoughlin et al., 2014). ERPs of performance monitoring have also been found impaired in individuals with ADHD using the Eriksen arrow flanker task (or other adaptations of the task). For example, evidence shows reduced amplitudes in components such as the N2 (reflecting conflict-monitoring impairments) and error-related negativity (ERN; reflecting early error processing) in both children and adults with ADHD, compared to controls (Albrecht et al., 2008; McLoughlin et al., 2009; McLoughlin et al., 2014; Michelini, Kitsune, Hosang et al., 2016). Using the Go/No-Go and flanker paradigms, studies have also demonstrated attenuation of the Pe component (reflecting more conscious error processing to adapt performance) in children, adolescents and young adults with ADHD (Groom et al., 2010; Michelini, Kitsune, Hosang et al., 2016; O'Connell et al., 2009). However, N2, ERN and Pe alterations have not been consistently reported across studies (Albrecht et al., 2008; Groom et al., 2010). Recently, evidence emerged from the first meta-analysis quantitatively summarising relevant literature on cognitive ERPs in ADHD across the lifespan (Kaiser et al., 2020). This meta-analysis showed that individuals with ADHD showed, compared to controls, smaller Cue-P3-amplitudes (Cohen's $d = 0.56$), longer Go-P3-latencies (Cohen's $d = 0.52$), smaller NoGo-P3-amplitudes (Cohen's $d = 0.57$), longer NoGo-P3-latencies (Cohen's $d = 0.35$), smaller CNV-amplitudes (Cohen's $d = 0.32$), and smaller Pe-amplitudes (Cohen's $d = 0.39$). Overall the inconsistencies across studies on ERPs of performance monitoring may be partly attributed to demographic and methodological moderators of interest such as age, IQ, medications, and task related moderators (Kaiser et al., 2020).

#### 1.4.4.2 Time-frequency studies

In recent years, studies of ADHD samples have examined the synchronisation/desynchronisation of power and variability of phase of EEG oscillations during cognitive tasks using time-frequency analyses. Evidence using this method shows reductions in theta event-related phase consistency (reflecting impairment in consistency of stimuli processing) (McLoughlin et al., 2014; Michelini, Kitsune, Vainieri et al., 2018) and response-locked theta activity (Groom et al., 2010) in children, adolescents and adults with ADHD. A reduction in alpha ERD (representing impaired attentional selection) following targets (Lenartowicz, Simpson et al., 2014; Ter Huurne et al., 2017) and cue

stimuli preceding targets (Mazaheri et al., 2014) have also been reported in people with ADHD compared to controls. Further studies show reductions in target-related alpha and beta ERD (reflecting impaired motor preparation) in adults with ADHD compared to controls (Hasler et al., 2016; Michelini, Kitsune, Vainieri et al., 2018). Even though few studies have used these approaches, compared to QEEG and ERPs studies, the investigation of brain-oscillatory indices with time-frequency analyses is informative as a deeper investigation into the alterations in neural processes implicated in ADHD (Loo et al., 2016). Taken together, available time-frequency studies in individuals with ADHD indicate impairments in measures that capture fine-grained modulations in brain activity. Evidence using this approach is still scarce and replications are needed. Chapter 2 in this thesis uses this more advanced time-frequency approach to further understand the neurophysiological processes in ADHD.

### 1.4.5 Summary

In this section, I have reviewed the most commonly used cognitive and electrophysiological methods in research on cognitive and neurophysiological impairments in children and adults with ADHD. Overall, evidence shows that ADHD is associated with several alterations in cognitive and neurophysiological processes measured with more traditional approaches, such as higher delta and theta bands (reflecting low vigilance and under arousal), and decreased P3 and Cue-P3 (reflecting impaired attention allocation and attention orienting). Initial evidence using more detailed cognitive and neurophysiological approaches is emerging and suggests impairments in the consistency of stimuli processing (theta event-related phase consistency), attentional selection (reduced alpha ERD following targets) and motor preparation (reduced target-related alpha and beta ERD). By using these more detailed approaches, we can make further progress in understanding the mechanisms underlying ADHD.

## 1.5 Developmental trajectories of ADHD

### 1.5.1 Developmental presentations of ADHD

Although in the past ADHD used to be considered a childhood-limited disorder, it is now recognised as a disorder that is common also among adults (Asherson et al., 2016; Faraone et al., 2006). Prospective longitudinal studies have highlighted the persistence of the disorder from childhood into adolescence and adulthood in

a significant proportion of cases (Faraone et al., 2006; Wong et al., 2009). A meta-analysis of longitudinal studies reported that ADHD persisted in young adulthood in 15% of cases, with a further 50% of cases presenting with subthreshold but still impairing symptoms (partial remission) (Faraone et al., 2006). Recent follow-up studies of clinic-referred childhood samples have reported notably higher rates of persistent ADHD in adolescents and young adults (around 80% of cases) (Cheung et al., 2015; van Lieshout et al., 2016). In contrast, population-based studies have shown significantly lower persistence rates ranging from 1.5% to 10% (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015).

Different reasons have been suggested to explain such discrepancies in the remission-persistence rates between studies (Caye et al., 2016; Faraone & Biederman, 2016; Li et al., 2019; Sibley et al., 2016). First, clinic-based studies may have more severe cases of ADHD compared to non-clinical studies and may be less likely to remit in adulthood, leading to high persistence rates. Second, different definitions of persistence and remission along with the use of different diagnostic tools may result in different persistence rates. For example, follow-up studies of clinical samples based on self-report have found lower persistence rates of ADHD in late adolescence and young adulthood, compared to studies based on informant report (alone or in combination with self-reports) (Du Rietz et al., 2017; Klein et al., 2012).

Recent evidence from population-based studies has raised the possibility that ADHD may occur in adults who did not meet criteria for diagnosis in childhood (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015) as required by the current diagnostic guidelines. Consequently, it has been proposed that, in some cases, ADHD might emerge in adolescence or adulthood and that this adult-onset form of the disorder can represent a distinct diagnostic condition from childhood ADHD (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015), opening a controversial debate. For instance, other authors have suggested that these studies may have overestimated the prevalence of adult-onset ADHD and failed to take into account that childhood ADHD may have been missed, for example due to family scaffolding (Faraone & Biederman, 2016).

### 1.5.2 Continuity of cognitive and brain impairments from childhood to adulthood

Prospective longitudinal studies using repeated assessments of ADHD and cognitive measures have been carried out to investigate the developmental patterns from childhood to adulthood. Several of these studies have showed that working memory,

planning and response inhibition as well as general cognitive abilities (IQ), tend to persist from childhood to adulthood in individuals with persistent ADHD (individuals whose ADHD persists into late adolescence and adulthood; "persisters") (Biederman et al., 2009; Karalunas et al., 2014; van Lieshout et al., 2013; Willcutt, 2012). Studies that have focused on lower-level cognitive impairments also showed persisting impairments from middle childhood to adolescence/early adulthood in ADHD persisters compared to controls (Cheung et al., 2016; Thissen et al., 2014; Vaughn et al., 2011). Other studies that did not differentiate individuals whose ADHD remitted ("remitters") from persisters have found continuity from childhood to adulthood in visual processing, vigilance, inhibition and IQ impairments (Doehnert et al., 2013; Moffitt et al., 2015). RTV was observed to be impaired from childhood to adulthood in a small-scale study (Doehnert et al., 2013) but not in another study that found no persistence of RTV in adolescence (McAuley et al., 2014). Limited studies are available on the continuity of neurophysiological impairments in ADHD. Initial evidence showed that reduced CNV was present both in childhood and adulthood, in contrast to deficits in Cue-P3 and NoGo-P3, which were observed only in childhood (Doehnert et al., 2013). However, the sample size of this initial study was very small and could not distinguish between persistence and remission of ADHD.

Overall, evidence suggests that most cognitive impairments persist from childhood to adolescence and adulthood in individuals with persistent ADHD. While most of these studies have investigated the developmental trajectories of these cognitive impairments to adolescence or young adulthood, evidence is lacking in relation to older age groups.

### 1.5.3 Predictors of ADHD outcomes

The potential predictors of ADHD outcomes (persistence/remission) in ADHD samples based on early cognitive and neurophysiological impairments could aid in the identification of those at risk of worse long-term outcomes (van Lieshout et al., 2013). A number of studies examining such longitudinal predictions within childhood only, have shown that impairments in inhibition, working memory and IQ in early childhood predicted ADHD symptoms in later childhood (Berlin et al., 2003; Brocki et al., 2007; Campbell & von Stauffenberg, 2009; Kalff et al., 2002). Other longitudinal studies, including those incorporating follow up assessments in adolescence and adulthood, have obtained inconsistent results. Some studies showed that RTV and working memory in childhood predicted ADHD symptoms and functional impairment in adolescence (Sjöwall et al., 2015; van Lieshout et

al., 2017), while other studies found evidence that executive functions, sustained attention, inhibition, working memory and RTV in childhood were associated with ADHD remission or persistence in adolescence and adulthood (Biederman et al., 2009; Cheung et al., 2016). Yet, some evidence showed that IQ predicted later ADHD remission/persistence, while measures of attention, inhibition, working memory and RTV did not predict ADHD remission or persistence (Agnew-Blais et al., 2016; Cheung et al., 2016; Gao et al., 2015). The predictive value of IQ was, however, not replicated in other studies (Breyer et al., 2014; Francx et al., 2015). Other evidence, using cross-lagged designs, showed reciprocal associations between ADHD symptoms and IQ over time (Rommel et al., 2015). Scarce evidence is available on the predictive value of brain activity in childhood on later ADHD outcome at the neurophysiological level. One study indicates that resting-state EEG measures in the theta and beta bands in childhood predict adult ADHD remission/persistence (Clarke et al., 2011).

Overall, while some cognitive impairments in children with ADHD may predict severity of ADHD, evidence of the predictors of ADHD persistence/remission to date is limited. Further research, with repeated clinical and cognitive assessments at different time points is needed to elucidate what cognitive and neurophysiological impairments are the most predictive of ADHD persistence. One of the aims presented in Chapter 4 will be to investigate the direction of the association between ADHD diagnosis and different cognitive processes over time.

### 1.5.4 Markers of ADHD persistence and remission

Previously, it had been hypothesised that the persistence of ADHD from childhood to adulthood would be related to the degree of maturation and improvement over time in higher-level cognitive functions, while lower-level cognitive functions would be linked to the presence of ADHD in childhood irrespective of later clinical status (Halperin & Schulz, 2006). This hypothesis was initially supported by a follow-up study investigating cognitive and EEG impairments in individuals with childhood ADHD (Halperin et al., 2008). In this study, ADHD remitters did not differ from controls in higher-level cognitive functions (e.g. working memory and inhibition), but were impaired in measures associated with lower-level cognitive processes (e.g. RTV) (Bédard et al., 2010; Halperin et al., 2008).

However, several subsequent studies did not report improvements in such higher level executive functions such as response inhibition, and interference control in ADHD remission (Biederman et al., 2009; McAuley et al., 2014; Pazvantoğlu et al., 2012). In line with these studies, recent evidence suggested that cognitive processes and brain

activity of preparation-vigilance processes (reflecting lower-level cognitive functions) – instead of higher-lever functions – may be markers of ADHD remission (Cheung et al., 2016; James et al., 2016; McAuley et al., 2014; Michelini, Kitsune, Hosang et al., 2016). These studies, which used the same sample used in this thesis, showed that measures of preparation, intra-individual variability and vigilance, differentiated ADHD remitters from persisters, while remitters were indistinguishable from controls on such measures (Cheung et al., 2016; James et al., 2016; Michelini, Kitsune, Hosang et al., 2016). Instead, executive function measures (reflecting higher-level cognitive functions) did not distinguish ADHD persisters from remitters (Cheung et al., 2016).

Despite some discrepancies between studies, overall patterns regarding the cognitive and neurophysiological markers of ADHD persistence and remission are starting to emerge. Further investigation with finer-grained methods, such as time-frequency or the ex-Gaussian analyses, may further aid our understanding of cognitive and neurophysiological processes underlying the persistence or remission of ADHD, and can aid in the identification of pathways of remission. These approaches will be implemented in Chapter 2.

### 1.5.5 Summary

In this section, I reviewed results of studies that have examined the continuity of cognitive and EEG impairments from childhood to adulthood, and the prediction of ADHD outcomes. I further reviewed studies investigating cognitive and neurophysiological impairments in relation to ADHD outcomes (persistence/remission). While the identified cognitive and brain level (measured with EEG) impairments tend to persist into adulthood in individuals whose ADHD persists, when ADHD remits some of these measures may no longer be sensitive to ADHD at follow-up, representing markers of ADHD remission. Overall, some inconsistencies emerged across studies, and evidence on the prediction of ADHD outcomes and on the association between measures of brain activity and ADHD outcome remains scarce. Future longitudinal clinical studies are needed to address these questions.

## 1.6 Bipolar disorder and comparison with ADHD

According to DSM-5 criteria, bipolar disorder (BD) denotes a psychiatric condition that is distinct from ADHD (APA, 2013). Yet, the two disorders present certain areas of symptomatic overlap. In this section, I will give an overview of BD, followed by a review of research on cross-disorder comparisons between BD and ADHD at the clinical and cognitive levels.

### 1.6.1 Symptoms and epidemiology of BD

BD is a chronic, severe psychiatric disorder characterised by cyclical mood fluctuations from a major depressive episode to a manic or hypomanic state. Until the DSM-IV-TR, BD was classified as a mood disorder (APA, 2000). It was only with the DSM-5 that BD was classified in a dedicated section (APA, 2013). Depressive episodes are defined by low mood nearly every day and loss of interest in pleasurable activities for almost two weeks. Manic episodes are periods of abnormally elevated and expansive mood, and increased activity and energy, which manifest with symptoms such as talkativeness, restlessness, distractibility, and grandiosity (APA, 2013). During manic and depressive states, people with BD can experience psychotic symptoms such as hallucinations and delusional beliefs. Between these periods, people with BD manifest euthymic states, defined as periods of relatively stable mood with moderate sub-syndrome symptoms and residual impairments, although full functioning may not be reached (Müller-Oerlinghausen et al., 2002). The DSM-IV-TR and DSM-5 distinguish between different types of BD. BD type I (BD-I), characterised by the cyclic alternation of depression and manic episodes, and BD type II (BD-II), where depression alternates with episodes of hypomania (APA, 2013). Finally, cyclothymia is defined by the alternation of hypomanic episodes to episodes of mild or moderate depression, and is considered a milder but more chronic form of BD.

BD has a prevalence of around 1-2%; its onset is usually in late adolescence or early adulthood (Merikangas et al., 2011). The male to female ratio is approximately 1:1 (APA, 2013), with higher lifetime prevalence of BD-I in males than females, and greater prevalence of BD-II in females than males (Merikangas et al., 2011). BD often co-occurs with other psychiatric disorders such as anxiety (60% of BD cases), substance use disorders (40%), ADHD (20%) or conduct disorder (20%) (Merikangas et al., 2011). People with BD have high rates of mortality (2-3 times higher than in the general population), due to increased risk for harmful behavioural consequences, such as accidents or substance abuse (especially during manic periods), and suicide or fatal self-harm events (approximately 15-20% of BD individuals) (Baldessarini et al., 2006). The heritability of BD has been estimated to be between 0.58 and 0.77 based on twin studies (McGuffin et al., 2003).

### 1.6.2 Cognitive and neurophysiological impairments in BD

Cognitive impairments are a common feature in BD and seem present not only during mood episodes, but also in the euthymic phase of the disorder (with medium-to-

large effect sizes, Cohen's $d = 0.61$ to 0.83), suggesting the absence of symptoms is not necessarily bounded with cognitive recovery (Robinson & Ferrier, 2006). In participants with BD, cognitive impairments are mostly represented by executive functions such as sustained attention, working memory, and increased RTV (Bora et al., 2009; Torres et al., 2007). For example, meta-analytic evidence indicates impairments in response inhibition and sustained attention with medium-to-large effect sizes during depressive and manic episodes (Cohen's $d = 0.55$ to 1.43) and with medium-to-large effect sizes during euthymia (Cohen's $d = 0.61$ to 0.83) (Kurtz & Gerraty, 2009). Memory problems in short-term and long-term memory, spatial recognition, working memory, and verbal and visual recognition domains have been frequently reported in BD individuals during the depressive phase of the disorder (Torres et al., 2007). Impairments in executive functions have also been found in individuals before BD onset in longitudinal studies, leading to the suggestion that such impairments in BD may be state-independent (Meyer et al., 2004; Ratheesh et al., 2013). Increased RTV, suggesting fluctuations in attention, in a wide range of tasks has also been associated with BD, regardless of medication use, mood state, and comorbidity. For example, RTV has been shown to increase during CPT, especially in target sensitivity (Bora et al., 2006; Brotman et al., 2009), not only in BD participants, but also in children at familial risk for BD. Less evidence is available on cognitive impairments in BD using the ex-Gaussian approach (Geller et al., 2002; Moss et al., 2016). One study indicated that BD participants had increased tau while performing a CPT task both during euthymic and depression phases (Gallagher et al., 2015). However, another study showed individuals with BD to have increased sigma but not tau compared to controls while performing a version of the CPT task with greater cognitive demand (Moss et al., 2016). Overall, available studies on BD with these detailed analyses suggest increased tau in less cognitively demanding tasks, while increased sigma might be limited to tasks with greater cognitive demand.

EEG studies have showed abnormal QEEG and ERP profiles in individuals with BD. Resting-state studies have shown a decrease in alpha power and an increase in theta and delta power in BD participants (Clementz et al., 1994). Abnormal ERPs profiles, such as reduced P3 amplitude (reflecting attention allocation) compared to controls have been identified in participants with BD using oddball paradigms, but not while performing the visual three-stimulus oddball paradigm (Bestelmeyer, 2012) or the Go/No-Go task (Chun et al., 2013). Reduced CNV amplitudes (impaired response preparation) have further been reported in BD, indicating attentional deficits of response preparation (Li et al., 2015). Some initial evidence from time-frequency

studies further suggest increased event-related beta and delta power (Ethridge et al., 2015; Ethridge et al., 2012; Ozerdem, Güntekin et al., 2008; Ozerdem, Kocaaslan et al., 2008; Tan et al., 2016) and decreased theta and alpha power, representing reduced attention allocation and attentional selection (Atagün et al., 2013; Ethridge et al., 2015; Ethridge et al., 2012) in individuals with BD compared to controls while performing visual and auditory oddball tasks.

Overall, studies indicate cognitive and neurophysiological impairments in BD in several domains such as attention allocation, attention selection and response preparation. Initial evidence is also emerging in relation to the more detailed ex-Gaussian cognitive measures in participants with BD, highlighting the promise of this approach for future investigations.

### 1.6.3 Comparison between ADHD and BD in clinical characteristics

Although ADHD and BD represent two distinct conditions according to DSM-5 (APA, 2013), clinical overlap of some specific features is observed. For instance, some of the typical manifestations of manic and hypomanic episodes in adults with BD, such as increased energy, accelerated speech, psychomotor restlessness, and distractibility, are also seen in adults with ADHD (Geller et al., 2002; Skirrow et al., 2012). The typical mind-wandering of people with ADHD has a similar connotation of flight of ideas and racing thoughts of BD (Asherson, 2005). Mood dysregulation including affective lability and irritability, which are characteristic of BD, have also been documented in ADHD (Asherson et al., 2014; Geller et al., 2002; Skirrow & Asherson, 2013; Skirrow et al., 2012). Mood dysregulation is also a common feature of other psychiatric conditions which often co-occur with ADHD and BD, such as major depressive disorder and anxiety disorders (Skirrow & Asherson, 2013).

Despite these similarities, ADHD symptoms are manifested as chronic trait-like features that impair typical development, whereas BD symptoms are episodic and make the person markedly differ from their usual euthymic state (APA, 2000, 2013). Although BD diagnosis requires episodic symptoms, individuals with BD often show residual symptoms of distractibility and mood dysregulation during the euthymic state which significantly overlap with ADHD (Henry et al., 2013). The high degree of emotional lability shown in adults with ADHD leads to uncertainty, regarding the diagnostic boundaries between the two disorders, which may lead to incorrect treatment decisions (Asherson et al., 2014; Skirrow et al., 2012).

### 1.6.4 Cross-disorder comparisons of cognitive and neurophysiological impairments in ADHD and BD

Similarities in cognitive impairments may be identified in BD and ADHD. Both disorders present with poor accuracy in attention and inhibition tasks (Robinson & Ferrier, 2006; Torralva et al., 2011), planning and problem-solving impairments (Klorman et al., 1999), sustained attention and response inhibition, and verbal and visuospatial working memory impairments (Torralva et al., 2011). Increased RTV has been reported for both ADHD (Kuntsi & Klein, 2012) and BD patients (Adleman et al., 2014; Brotman et al., 2009). Although studies on individuals with ADHD and individuals with BD, separately, have reported that, compared to controls, both disorders show such deficits, few studies have directly compared them. Only a few cross-disorder studies have directly compared ADHD and BD. Such studies have reported that, compared to controls, participants with ADHD and euthymic participants with BD showed increased RTV, measured with SD-RT, while performing a four-choice reaction time task (Michelini, Kitsune, Hosang et al., 2016; Michelini, Kitsune, Vainieri et al., 2018).

Studies directly comparing QEEG abnormalities between adults with ADHD and adults with BD showed certain shared impairments during resting state EEG recording, such as higher theta power compared to controls (Rommel et al., 2016). ERP studies have found potentially shared and distinct features between ADHD and BD participants such as attenuation in the NoGo-N2 component (reflecting conflict monitoring) only in the BD group, and reduced CNV and NoGo-P3 responses in both clinical groups compared to controls (Michelini, Kitsune, Hosang et al., 2016). Also, Michelini and colleagues showed, using a combination of ERPs and time-frequency analyses, shared impairments in women with ADHD and women with BD while performing a four-choice reaction time task with slow-baseline and fast-incentive conditions (Michelini, Kitsune, Vainieri et al., 2018). Specifically, in this study, both ADHD and BD participants showed CNV impairments in the fast-incentive condition. Also, both women with ADHD and those with BD showed impairments in alpha suppression compared to controls from the slow-baseline to the fast-rewarded condition, indicating deficits in attentional selection (Michelini, Kitsune, Vainieri et al., 2018). Shared disorder in neural variability in theta phase consistency (theta ITC) also emerged in the fast-incentive condition of the fast task. Disorder-specific impairments for ADHD participants emerged in attention selection to target (low alpha suppression) in the fast-incentive condition, and in lower beta suppression adjustment in the change from the baseline to the fast-incentive

condition, indicating response execution impairments (Michelini, Kitsune, Vainieri et al., 2018).

Taken together, these findings suggest that shared and disorder-specific cognitive and neurophysiological impairments were detected in individuals with ADHD and BD using both traditional and more detailed brain oscillatory EEG approaches, while only shared impairments between ADHD and BD were detected at the cognitive level. However, more detailed cognitive analyses, such as the ex-Gaussian approach that has not been previously employed to directly compared people with ADHD and BD, may help in identifying further markers that distinguish between these disorders. Whereas RTV measured with SD-RT showed similar impairments in both ADHD and BD groups, the ex-Gaussian measures may be more sensitive to detect subtle differences in cognitive performance. This approach will be implemented in the investigation of disorder-specific and shared impairments between ADHD and BD in Chapter 5.

### 1.6.5 Summary

This section introduced the main clinical and cognitive features of BD. The clinical manifestation of BD presents certain overlapping features with ADHD. These overlapping features, especially in adulthood, present certain areas of overlap with ADHD when individuals present with symptoms such as distractibility, emotional lability, restlessness, which characterise both disorders. When such overlapping clinical presentations are present, more careful clinical considerations might be required to delineate between ADHD and BD, and may benefit from the development of biomarkers to aid in diagnostic decisions and treatment monitoring. Only a few cross-disorder comparisons on ADHD and BD have been carried out to date. Such studies have outlined shared cognitive impairments that characterise the two disorders. Further research with more advanced techniques is needed to further explore the cognitive profiles that may help to differentiate between the two disorders.

## 1.7 Aims and objectives

This thesis aims to further our understanding of the underlying cognitive and neurophysiological impairments in ADHD persistence and remission (Chapter 2), and to explore the aetiological association between ADHD and cognitive impairments with cutting-edge molecular genetic approaches (polygenic risk scores), and with quantitative genetic sibling design (Chapters 3 and 4). Given that ADHD in adult-

hood and BD share a degree of symptomatic and cognitive overlap, a further aim is to compare the cognitive profiles between women with ADHD, women with BD and control women, in order to identify impairments that are specific to, or shared between, ADHD and BD (Chapter 5).

ADHD persists into adolescence and adulthood, either in full or in partial remission in the majority of individuals clinically diagnosed in childhood (Faraone et al., 2006). Yet, the mechanism underlying the persistence or remission of ADHD are poorly understood. In Chapter 2 we aim to extend previous research into the cognitive and EEG markers of ADHD persistence and remission (subsection 1.5.4), using fine-grained ex-Gaussian reaction-time distribution and EEG brain-oscillatory measures, in a follow-up study of individuals with ADHD diagnosed in childhood. These novel approaches have not previously been applied to examine the processes underlying ADHD persistence and remission but could identify further cognitive and neural alterations in ADHD.

Although ADHD is associated with a wide range of cognitive impairments, evidence of their association with ADHD risk genes is very limited. Previous studies using polygenic risk score approaches show that ADHD PRS are significantly associated with several co-occurring disorders, but few studies have explored their association with the cognitive phenotypes associated with ADHD (subsubsection 1.3.2.2). In Chapter 3 we investigate, using a polygenic risk score derived from the latest ADHD GWAS, whether genetic variants that contribute to ADHD also influence specific cognitive impairments widely associated with ADHD: specifically, associations are examined between PRS for ADHD and attention regulation and response inhibition in a collaborative study using ADHD samples from several international sites.

Details on the presentation of cognitive impairments in ADHD across development, as well as the aetiological influences that underlie the association between ADHD and cognitive impairments is reported in subsections 1.3.1 and 1.5.3. As discussed in subsection 1.5.3, while some cognitive impairments may predict severity of ADHD within childhood, results are mixed for predictions later in life. Previous sibling/twin studies have shown evidence of substantial genetic and familial risk factors underlying the association between cognitive impairments and ADHD (subsection 1.3.1). In Chapter 4 we investigate longitudinally the direction of the association between ADHD diagnosis and cognitive impairments, as well as the contribution of familial and non-familial influences underlying this relationship over time.

While the above chapters focus exclusively on ADHD, it is increasingly acknowledged that some clinical symptoms and cognitive impairments – as well as genetic risks – are shared between different neurodevelopmental and psychiatric

disorders (Asherson, 2005; Asherson et al., 2014). In adult psychiatry clinics, some patients can present with certain symptoms that could either reflect ADHD and BD (Asherson et al., 2014). Cognitive comparisons between ADHD and BD are rather limited to date. Such previous studies, using traditional cognitive measures such as MRT and RTV, have detected shared cognitive impairments in participants with ADHD and those with BD (subsection 1.6.4). The use of more detailed cognitive measures, such as the ex-Gaussian approach, could be informative in further elucidating the overlap and specificity in cognitive impairments observed in ADHD and BD. The study reported in Chapter 5 examines, using ex-Gaussian decomposition across different cognitive tasks and task conditions, whether the cognitive impairments observed in individuals with persistent ADHD are different or overlapping compared to those observed in individuals with BD.

# Chapter 2

# Event-related brain-oscillatory and ex-Gaussian markers of remission and persistence of ADHD

*Psychological Medicine*

**cambridge.org/psm**

## Original Article

*These authors contributed equally.

**Cite this article:** Vainieri I, Michelini G, Adamo N, Cheung CHM, Asherson P, Kuntsi J (2020). Event-related brain-oscillatory and ex-Gaussian markers of remission and persistence of ADHD. *Psychological Medicine* 1–10. https://doi.org/10.1017/S0033291720002056

Received: 22 November 2019
Revised: 13 May 2020
Accepted: 27 May 2020

**Key words:**
ADHD; ex-Gaussian; brain oscillations; remission

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CAMBRIDGE UNIVERSITY PRESS

# Event-related brain-oscillatory and ex-Gaussian markers of remission and persistence of ADHD

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**Abstract**

**Background.** Attention-deficit/hyperactivity disorder (ADHD) often persists into adolescence and adulthood, but the processes underlying persistence and remission remain poorly understood. We previously found that reaction time variability and event-related potentials of preparation-vigilance processes were impaired in ADHD persisters and represented markers of remission, as ADHD remitters were indistinguishable from controls but differed from persisters. Here, we aimed to further clarify the nature of the cognitive-neurophysiological impairments in ADHD and of markers of remission by examining the finer-grained ex-Gaussian reaction-time distribution and electroencephalographic (EEG) brain-oscillatory measures in ADHD persisters, remitters and controls.

**Methods.** A total of 110 adolescents and young adults with childhood ADHD (87 persisters, 23 remitters) and 169 age-matched controls were compared on ex-Gaussian (mu, sigma, tau) indices and time-frequency EEG measures of power and phase consistency from a reaction-time task with slow-unrewarded baseline and fast-incentive conditions ('Fast task').

**Results.** Compared to controls, ADHD persisters showed significantly greater mu, sigma, tau, and lower theta power and phase consistency across conditions. Relative to ADHD persisters, remitters showed significantly lower tau and theta power and phase consistency across conditions, as well as lower mu in the fast-incentive condition, with no difference in the baseline condition. Remitters did not significantly differ from controls on any measure.

**Conclusions.** We found widespread impairments in ADHD persisters in reaction-time distribution and brain-oscillatory measures. Event-related theta power, theta phase consistency and tau across conditions, as well as mu in the more engaging fast-incentive condition, emerged as novel markers of ADHD remission, potentially representing compensatory mechanisms in individuals with remitted ADHD.

## Introduction

Attention-deficit/hyperactivity disorder (ADHD) often persists into adolescence and adulthood (Cheung et al., 2016; Faraone, Biederman, & Mick, 2006) and leads to several detrimental outcomes (Asherson, Buitelaar, Faraone, & Rohde, 2016). Identifying the processes underlying ADHD persistence and remission has the potential to inform the development of novel interventions to promote clinical improvement in individuals with persistent ADHD.

Longitudinal studies show that cognitive and neural impairments linked to ADHD, encompassing both higher-level executive processes (e.g. inhibition, working memory) and lower-level processes [e.g. attentional lapses measured by reaction-time variability (RTV)], tend to remain impaired in individuals whose ADHD persist ('persisters') (Franke et al., 2018). Fewer studies have examined how individuals who remit from the disorder (ADHD 'remitters') compare at the cognitive and neural levels to ADHD persisters and controls. The majority of studies to date report that most executive-functioning impairments do not distinguish ADHD remitters from persisters (Agnew-Blais et al., 2019; Franke et al., 2018), indicating that they may not be sensitive to ADHD remission. In a follow-up study of adolescents and young adults with childhood ADHD, we recently observed that cognitive-electroencephalography (EEG) measures of preparation-vigilance processes were impaired in ADHD persisters compared to remitters and controls, but comparable between remitters and controls (Cheung et al., 2016; James et al., 2017; Michelini et al., 2016). Many of these measures also showed continuous associations with ADHD severity within individuals with childhood ADHD, indicating that preparation-vigilance measures are markers of ADHD remission. For example, we found this pattern for RTV and target P3 [event-related potential (ERP) of attention allocation] during a reaction-time task under slow-unrewarded (baseline) and fast-rewarded (fast-incentive) conditions (James et al., 2017) ('Fast task'; Kuntsi et al., 2006). Notably, the

ADHD-related impairments in RTV and P3 also showed malleability and improvement under fast-incentive conditions (Cheung et al., 2017). They may thus represent compensatory processes making remitters comparable to controls in their cognitive-neurophysiological profiles.

These findings further our understanding of the cognitive and neural impairments in ADHD persisters and point to initial cognitive-neurophysiological markers of ADHD remission. However, the identified indices represent aggregate measures that may miss systematic and fine-grained aspects of the data due to averaging procedures. Rather than measuring RTV as standard deviation of reaction times (s.d.-RT), sophisticated ex-Gaussian analyses can decompose the reaction times (RTs) and separate extremely slow responses (measured by tau, the exponential component) from the mean (mu) and s.d. (sigma) of the normal RT distribution (Luce, 1991). This approach has consistently shown increased tau in individuals with ADHD compared to controls, while mixed results have been reported for sigma and mu that may reflect subtler impairments (Karalunas, Geurts, Konrad, Bender, & Nigg, 2014; Vainieri et al., 2020). While most studies have focused on children, no study to date has examined ex-Gaussian parameters in adolescents and adults with persistent ADHD. Similarly, finer-grained EEG time-frequency analyses can leverage the millisecond precision of EEG to detect stimulus-related changes in the power and in the variability of the phase (the 'timing') of brain oscillations that are not captured by more traditional ERP or quantitative EEG approaches (Loo, Lenartowicz, & Makeig, 2015; Makeig, Debener, Onton, & Delorme, 2004). The few time-frequency studies in ADHD samples to date found lower evoked theta power (reduced attention allocation) (McLoughlin, Palmer, Rijsdijk, & Makeig, 2014; Missonnier et al., 2013), alpha suppression (reduced attentional selection) (Lenartowicz et al., 2014; Ter Huurne et al., 2017), beta suppression (reduced motor preparation) (Hasler et al., 2016; Mazaheri et al., 2014), and more variable theta phase (inconsistency of stimulus processing) (Groom et al., 2010; McLoughlin et al., 2014), compared to controls. During the Fast task, we recently confirmed that adults with ADHD, compared to controls, show lower theta phase consistency, reduced alpha suppression and reduced adjustments between conditions in alpha and beta suppression (Michelini et al., 2018*b*). EEG time-frequency approaches, therefore, hold promise for identifying neural impairments in ADHD, but have not yet been employed to examine the processes underlying ADHD persistence and remission.

In the present study, we aimed to investigate the cognitive and neural processes underlying ADHD remission/persistence using detailed ex-Gaussian and time-frequency EEG measures in a follow-up of adolescents and young adults with and without childhood ADHD. First, given the paucity of previous studies, especially on finer-grained markers of brain oscillations, in adolescents and adults with ADHD, we investigate whether the measures from the baseline and fast-incentive conditions of the Fast task are impaired in ADHD persisters compared to controls (aim 1). Based on previous studies in ADHD samples, including our previous ex-Gaussian and time-frequency analyses using this task in a smaller-scale adult ADHD sample (Michelini et al., 2018*b*; Vainieri et al., 2020), we hypothesize that ADHD persisters are impaired, compared to controls, in measures of attentional fluctuations (tau and sigma), theta power and phase consistency, alpha suppression, and adjustments between conditions in alpha and beta suppression. Second, by examining ADHD remitters, we investigate whether measures that show differences between ADHD persisters and controls are markers of remission at follow-up. We examine ADHD remission with a categorical approach, by comparing remitters to persisters and controls (aim 2a), and with a dimensional approach, by examining the continuous association with ADHD symptoms and functional impairment within participants with childhood ADHD (aim 2b). We hypothesize that all measures showing ADHD persister-control differences also represent markers of remission, consistent with studies using more traditional measures (Cheung et al., 2016; James et al., 2017; Michelini et al., 2016). Third, we hypothesize a significant association between the ex-Gaussian and time-frequency measures that emerged as markers of remission (aim 3), suggestive of common underlying mechanisms.

## Methods

### *Sample*

The sample used in this study consists of 279 participants, followed-up on average 5.8 years (s.d. = 1.1) after baseline: 110 had a diagnosis of combined-type ADHD based on DSM-IV in childhood (10 sibling pairs and 90 singletons) and 169 were control participants (76 sibling pairs and 17 singletons). Participants with ADHD were recruited from specialized ADHD clinics (Kuntsi et al., 2010) and controls from schools in the UK. Clinical information (neurodevelopmental and psychiatric conditions, and medication use) were collected through neuropsychiatric screening. Exclusion criteria at both assessments included IQ < 70, autism, epilepsy, brain disorders and any medical disorder associated with externalizing behaviours that might mimic ADHD. Other comorbidities were not excluded in order to have an ADHD sample representative of the clinical population. Among participants who took part in the follow-up assessments ($N = 293$), we excluded six controls who met DSM-IV ADHD criteria based on the parent-reported Barkley Informant Rating Scale (Barkley & Murphy, 2006) and six participants with childhood ADHD with missing parent ratings of clinical impairments. Two participants with childhood ADHD, who did not meet ADHD symptom criteria but showed clinical levels of impairment at follow-up, were also excluded to minimize heterogeneity in the sample. Further details on this sample are reported elsewhere (Cheung et al., 2016; Michelini et al., 2018*a*).

Among those with childhood ADHD, 87 (79%) continued to meet clinical (DSM-IV) levels of ADHD symptoms and impairment (ADHD persisters), whereas 23 (21%) were below the clinical cut-off (ADHD remitters). Fourteen ADHD remitters displayed ⩾5 symptoms of inattention or hyperactivity/impulsivity but no functional impairment. Groups were age-matched (mean age = 18.64 across all groups). Of the total, 84% and 82% of participants in the persisters and control groups were males, while 100% of remitted participants were male, as there were no females among ADHD remitters (online Supplementary Table S1). Childhood ADHD participants on medication at follow-up (47%) showed higher ADHD symptoms ($p < 0.01$) and functional impairment ($p < 0.01$) than those not medicated. The proportion of participants on medication did not differ between ADHD persisters and remitters ($\chi^2 = 1.95$, $p = 0.16$). A 48-h ADHD medication-free period was required prior to assessments. All participants and parents provided informed consent. Study procedures were approved by the London-Surrey Borders Research Ethics Committee (09/H0806/58).

### ADHD diagnosis

The Diagnostic Interview for ADHD in Adults (DIVA) (Kooij et al., 2010) was conducted by trained researchers with parents of ADHD probands to assess DSM-IV-defined ADHD presence/persistence. Raw scores for inattention and hyperactivity/impulsivity symptoms were obtained. Functional impairment was rated from 0 (never or rarely) to 3 (very often) with items from the Barkley's Functional Impairment Scale (Barkley & Murphy, 2006) during interviews with parents. DIVA and functional impairments were used to determine ADHD status, as these were validated against objective markers (cognitive-EEG measures) in this sample, whereas the same objective markers showed limited agreement with self-reported ADHD (Du Rietz et al., 2016). Participants with childhood ADHD were classified as persisters at follow-up if they scored ⩾6 in either the inattention or hyperactivity/impulsivity domains on the DIVA and ⩾2 on at least two areas of impairments; they were classified as remitters otherwise. We defined ADHD outcome using a categorical definition of persistence based on diagnosis and a dimensional approach based on continuous levels of ADHD symptoms and functional impairments.

### IQ

IQ was measured with the Wechsler Abbreviated Scale of Intelligence vocabulary and block design subtests (Wechsler, 1999).

### Task

The task was a computerized four-choice RT task which measures performances under a slow-unrewarded and a fast-incentive condition (Kuntsi et al., 2006). The slow-unrewarded (baseline) condition consists of 72 trials, which followed a standard warned four-choice RT task (online Supplementary Fig. S1). 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 corresponded to the position of the target. 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. A comparison condition that used a fast event rate (foreperiod of 1 s) and incentives followed immediately after the baseline condition and consisted of 80 trials, with a fixed inter-trial interval of 2.5 s following the response. Participants were told to respond as quickly as possible to win smiley faces and real prizes (£5). The smiley faces appeared below the circles in the middle of the screen when participants responded faster than their own mean RT (MRT) during the baseline condition consecutively for three trials and were updated continuously.

### Ex-Gaussian analysis

We applied ex-Gaussian deconvolution to single-trial RT data employing a maximum-likelihood algorithm, implemented in the QMPE software (Heathcote, Brown, & Cousineau, 2004). This algorithm measures the mean of the normal (Gaussian) component of the RT distribution (mu) and divides the variability into its normal (sigma) and exponential (tau) components. Analyses were performed on participants with >40 RTs from correct responses with plausible RT (>150 ms), as standard procedures in ex-Gaussian analyses (Adamo, Hodsoll, Asherson, Buitelaar, & Kuntsi, 2018; Heathcote, Brown, & Mewhort, 2002).

### EEG recording, pre-processing and analyses

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 were recorded from electrodes above and below the left eye and at the outer canthi. EEG data were pre-processed using Brain Vision Analyzer 2.0 (Brain Products, Gilching, Germany). EEG recordings were down-sampled to 256 Hz, re-referenced to the average of all electrodes (turning FCz into an active channel) and filtered using Butterworth band-pass filters (0.1–30 Hz, 24 dB/octave). Electrical and movement artefacts were removed manually. Trials containing artefacts exceeding ± 100 μV or with a voltage step >50 μV were automatically rejected. Ocular artefacts were corrected using independent component analysis (Jung et al., 2000).

Time-frequency EEG analyses were performed in EEGLAB (Delorme & Makeig, 2004) following procedures adopted in our previous study (Michelini et al., 2018*b*). Modulations of power were quantified with the event-related spectral perturbation (ERSP) index (Delorme & Makeig, 2004). ERSP trials were normalized with respect to the mean log-power spectrum from the pre-stimulus period (−2000 to −1000 ms). Average ERSPs across trials produced a time-frequency representation in decibel (dB) units of increases (red) and decreases (blue) in power with respect to pre-stimulus activity. Phase consistency was calculated with inter-trial phase coherence (ITC), measuring the degree to which the phase of the evoked response is consistent across trials (Makeig et al., 2004). To allow reliable measurement of EEG indices, only participants with ⩾20 artefact-free EEG segments were included in analyses. See online Supplementary material for further details.

ERSP (event-related power) and ITC (phase consistency) were measured in time windows and at scalp locations where they were maximal, following our previous study (Michelini et al., 2018*b*) and other studies on similar attentional processes. Target-related ERSP in theta (3–7 Hz) was measured between 0 and 500 ms over fronto-central regions (average of Fz, F1, F2, FCz, FC1, FC2, Cz, C1, C2) and centro-parietal regions (average of CPz, CP1-CP6, Pz, P3, P4) (DeLosAngeles et al., 2016; Jacobs, Hwang, Curran, & Kahana, 2006), to capture differences in topography across groups and conditions (Fig. 1). Alpha (8–13 Hz) ERSP was measured in two windows (0–500 ms, 500–1000 ms), capturing the broad alpha power modulation, over parieto-occipital regions (average of Pz, P3, P4, P7, P8, POz, PO3, PO4, PO7, PO8) (Bickel, Dias, Epstein, & Javitt, 2012; Mazaheri & Picton, 2005) (online Supplementary Fig. S2). Beta (14–30 Hz) ERSP was extracted between 200 and 700 ms, to measure the shorter target-related beta power suppression over central regions (average of Cz, C1-C4, CPz, CP1-CP4) (Bickel et al., 2012; Mazaheri & Picton, 2005) (online Supplementary Fig. S3). ITC was measured only in theta, given the role of this frequency band in neural consistency (Papenberg, Hämmerer, Müller, Lindenberger, & Li, 2013), between 0 and 500 ms, where greater phase consistency was observed, over centro-parietal regions (average of CPz, CP1-CP6, Pz, P3, P4) (Fig. 2).

### Statistical analyses

For aim 1, we compared ADHD persisters and controls with random intercept linear models (multilevel regression models) investigating main effects of group (ADHD persisters *v.* control),

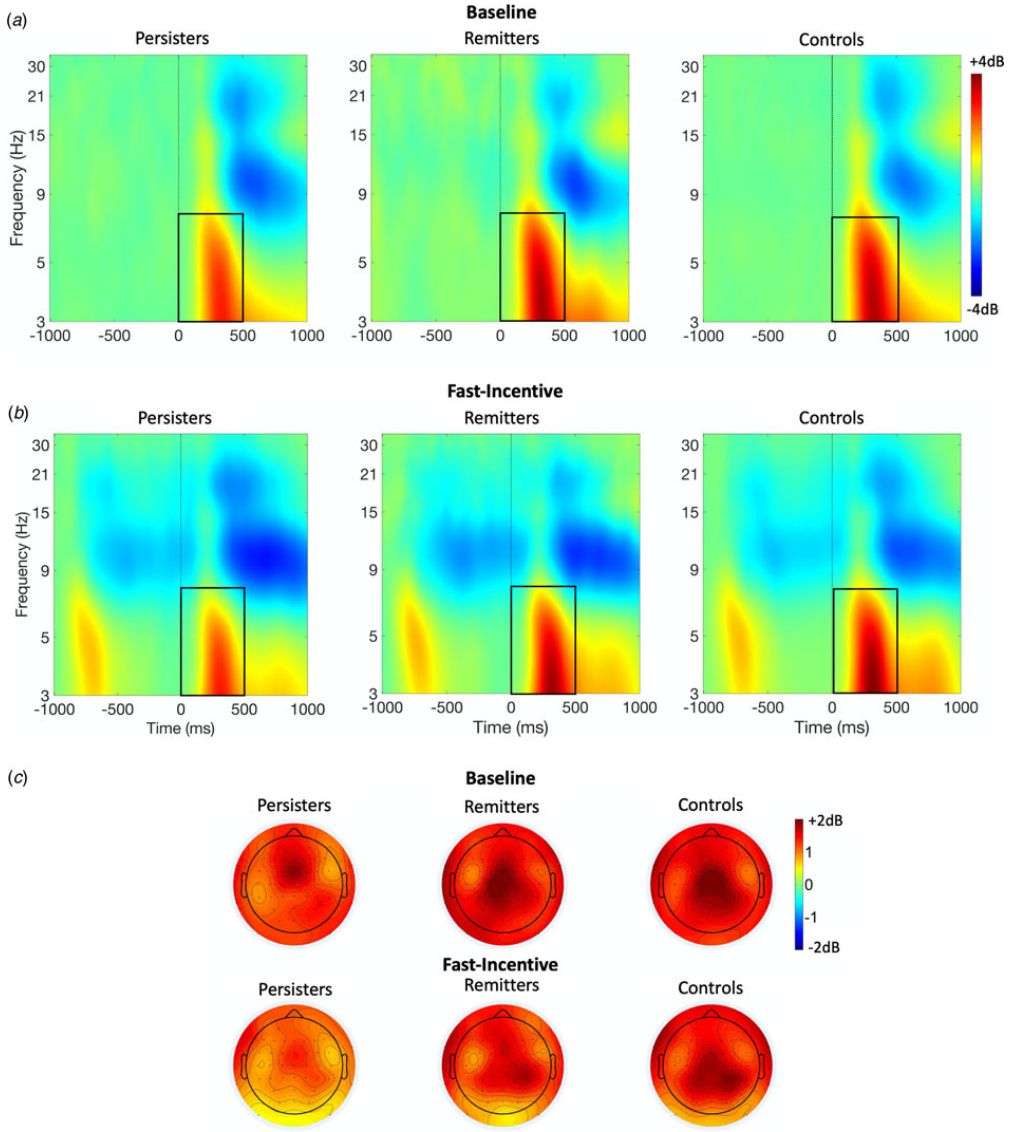


**Fig. 1.** Theta event-related spectral perturbation (ERSP) at centro-parietal regions in ADHD persisters, ADHD remitters and controls across the baseline and fast-incentive conditions of the Fast task. (*a*) ERSP in the baseline condition; (*b*) ERSP in the fast-incentive condition; (*c*) Topographic maps by the group in the 0–500 ms window at each condition.

condition (baseline *v.* fast-incentive) and group-by-condition interactions. For measures showing significant ($p < 0.05$) group-by-condition effects, we report pair-wise group comparisons in baseline and fast-incentive conditions separately. For measures showing significant main group effects but non-significant group-by-condition effects, we report pair-wise group comparisons collapsed across conditions. Additional tests followed up significant condition effects to examine within-group changes between conditions, and significant group-by-condition interactions to examine group differences on the change between conditions. Since theta and alpha ERSP indices were measured, respectively, at two scalp regions and two-time windows, we also tested three-way interactions with these additional factors. All models controlled for age and participants at the family level by including random effects to model the non-independence of observations of siblings within families in multilevel random-intercept models (Bauer, Gottfredson, Dean, & Zucker, 2013).

For measures showing ADHD persister-control differences, we ran the same random-intercept models also including ADHD

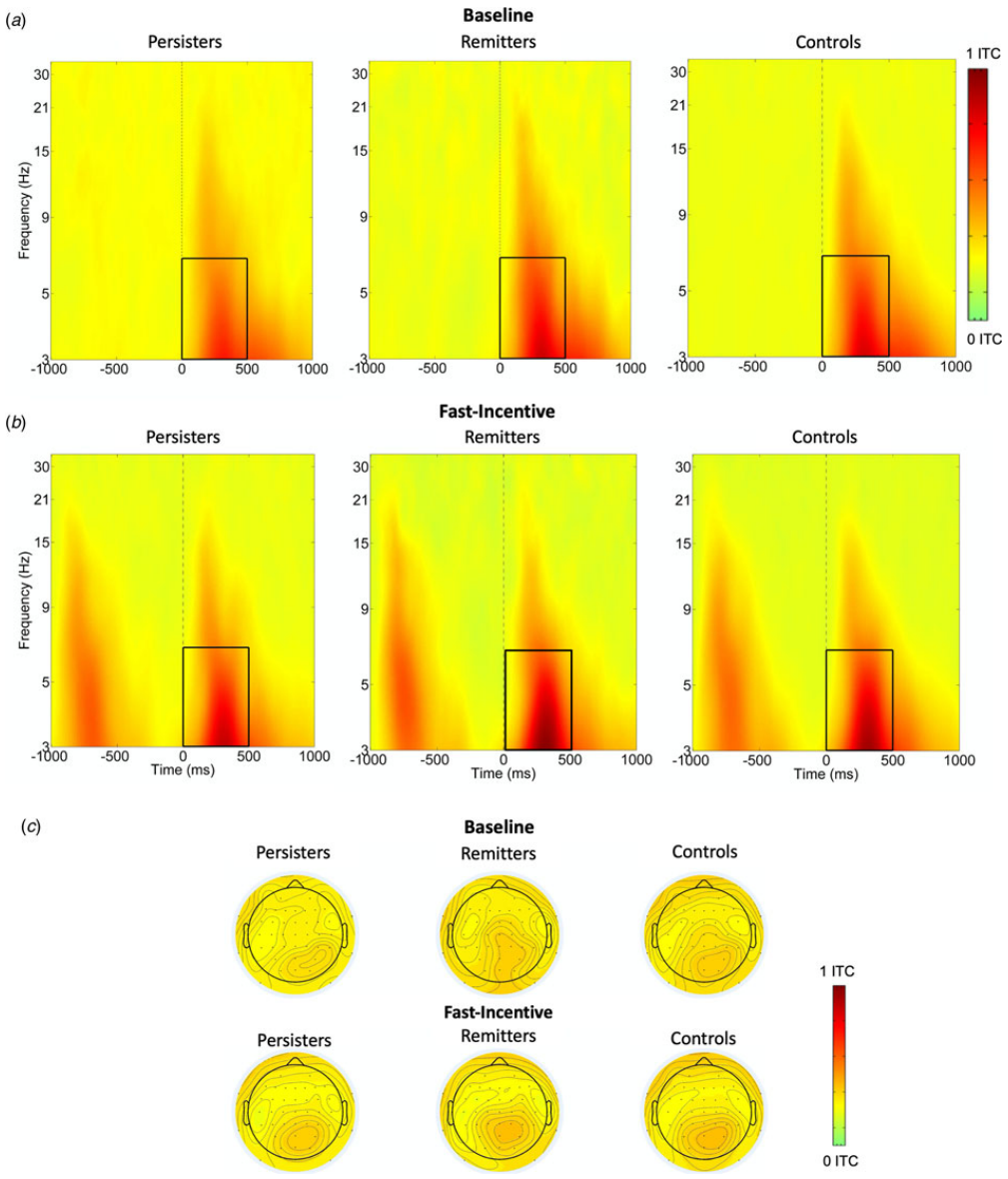


**Fig. 2.** Theta phase consistency at centro-parietal regions in the ADHD persisters, ADHD remitters and controls across the baseline and fast-incentive conditions of the Fast task. (*a*) Theta phase consistency in the baseline condition; (*b*) Theta phase consistency in the fast-incentive condition; (*c*) Topographic maps by the group in the 0–500 ms window at each condition.

remitters (aim 2a). Because ADHD persisters had a lower IQ than remitters and controls (online Supplementary Table S1), all analyses were rerun controlling for IQ. As groups were not matched on sex, group analyses were further rerun excluding females (15 persisters, 41 control). For between-group comparisons, we report both *p*-values and standardised beta coefficients, which are interpretable as Pearson's correlation coefficients, thus $\beta = 0.10$ represents a small effect, $\beta = 0.30$ represents a medium effect and $\beta = 0.50$ represents a large effect (Cohen, 1988).

We further examined ex-Gaussian and time-frequency measures in relation to ADHD remission with dimensional analyses (aim 2b). Random-intercept linear models were run in all participants with childhood ADHD to investigate the associations of ex-Gaussian and EEG measures significant in aim 1 (dependent

**Table 1.** Group comparisons on ex-Gaussian and EEG time-frequency measures in the baseline and fast-incentive conditions and across conditions

| | Baseline condition | | | | | | Fast-incentive condition | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Aim 1 | | Aim 2a | | | | Aim 1 | | Aim 2a | | | |
| | ADHD persisters *v.* controls | | ADHD persisters *v.* remitters | | ADHD remitters *v.* controls | | ADHD persisters *v.* controls | | ADHD persisters *v.* remitters | | ADHD remitters *v.* controls | |
| | *β* (95% CI) | *p* | *β* (95% CI) | *p* | *β* (95% CI) | *p* | *β* (95% CI) | *p* | *β* (95% CI) | *p* | *β* (95% CI) | *p* |
| **Mu** | 0.22 (0.01 to 0.44) | 0.043* | 0.18 (−0.19 to 0.56) | 0.332 | 0.04 (−0.32 to 0.40) | 0.823 | **0.50 (0.27 to 0.71)** | <0.001** | *0.40 (0.02 to 0.77)* | 0.037* | 0.10 (−0.26 to 0.46) | 0.583 |

| | Across condition | | | | | |
|---|---|---|---|---|---|---|
| | Aim 1 | | Aim 2a | | | |
| | ADHD persisters *v.* controls | | ADHD persisters *v.* remitters | | ADHD remitters *v.* controls | |
| | *β* (95% CI) | *p* | *β* (95% CI) | *p* | *β* (95% CI) | *p* |
| **Sigma** | *0.33 (0.15 to 0.53)* | <0.001** | *0.31 (−0.08 to 0.65)* | 0.064 | 0.01 (−0.30 to 0.34) | 0.916 |
| **Tau** | **0.74 (0.56 to 0.93)** | <0.001** | *0.42 (0.16 to 0.81)* | 0.003* | 0.26 (−0.05 to 0.57) | 0.101 |
| **Theta ERSP FC** | −0.20 (−0.44 to −0.11) | 0.003* | −0.24 (−0.51 to 0.03) | 0.081 | −0.03 (−0.30 to 0.22) | 0.784 |
| **Theta ERSP CP** | **−0.53 (−0.66 to −0.32)** | <0.001** | *−0.44 (−0.82 to −0.08)* | 0.015* | −0.08 (−0.44 to 0.27) | 0.627 |
| **Theta phase consistency** | *−0.43 (−0.67 to −0.20)* | <0.001** | *−0.42 (−0.79 to −0.04)* | 0.027* | −0.01 (−0.38 to 0.34) | 0.939 |

ADHD, attention-deficit/hyperactivity disorder; ERSP, event-related spectral perturbation; FC, fronto-central; CP, centro-parietal.
*Notes*: For aim 1, the *p*-value threshold surviving multiple testing correction was determined as 0.043 using false discovery rate (FDR). Post-hoc tests are reported by condition only for measures showing significant group-by-condition effects. For measures showing non-significant group-by-condition effects, post-hoc tests are reported across conditions. Ex-Gaussian variables were available for 86 persisters, 23 remitters and 166 controls. ERSP and theta phase consistency variables were available for 81 persisters, 23 remitters and 163 controls. $^{**}p < 0.01$, $^{*}p < 0.05$. Bold = large effect size ($\beta \geqslant 0.50$); Italics = medium effects size ($\beta \geqslant 0.30$).

variables) with parent-reported ADHD symptoms and functional impairment (independent variables). These models included symptoms-by-condition or impairment-by-condition interactions to test whether associations changed in the two conditions, and three-way interactions as appropriate for measures included in these analyses. Analyses were run clustering for family status and controlling, firstly, for age and sex and, secondly, also for IQ.

Additional random-intercept linear models examined the associations between the ex-Gaussian (dependent variables) and EEG time-frequency measures (independent variables) that emerged as markers of remission from categorical analyses (aim 3). These analyses were run in the full sample and included an interaction between group and EEG measures to investigate if the strength of the associations differed between groups.

In analyses comparing ADHD persisters and controls on all measures (aim 1), we applied multiple testing correction using the false discovery rate (FDR) to reduce type I errors. Analyses for aim 2 and 3 were only run on a restricted set of measures respectively, surviving multiple-testing correction in aim 1 and emerging as markers of remission in aim 2. We, therefore, did not apply further FDR correction and used a nominal significance level (0.05).

Statistical analyses were run in Stata 15 (Stata Corp, College Station, TX). With the exception of beta (that was normally distributed), all other variables showed skewed distributions and were transformed to normal with a logarithmic transformation. Due to technical issues during data collection, RT and EEG data were not available for one ADHD persister and three controls. All participants with RT data had sufficient responses for ex-Gaussian analyses. Six ADHD persisters and five controls were excluded from EEG analyses in the baseline condition, and one control from both conditions, due to having <20 clean EEG segments.

## Results

### *Which measures differ between ADHD persisters and controls (aim 1)?*

FDR corrections indicated a *p*-value threshold of $p < 0.043$ (see Table 1). A significant group-by-condition interaction emerged for mu, indicating that significant differences between ADHD persisters and controls were significantly greater in the fast-incentive condition than in the baseline condition (Table 1). Sigma, tau, theta ERSP, and theta phase consistency did not show significant group-by-condition effects. Compared to controls, ADHD persisters showed significantly higher sigma and tau, and significantly lower fronto-central and centro-parietal theta ERSP, as well as lower theta phase consistency, in both conditions (Table 1). No significant differences emerged in alpha and beta between ADHD persisters and controls ($p > 0.1$). All RT measures showed within-group decreases from the baseline to the fast-incentive condition ($p < 0.001$), while theta ERSP in both regions and theta phase consistency did not (all $p > 0.1$). Among measures showing the significant within-group change between condition, only mu showed a significant difference between groups in the degree of change between conditions ($p < 0.001$), with persisters changing less than controls (online Supplementary Table S2). Further details on condition and group-by-condition effects are reported in online Supplementary material.

ADHD persister-control differences in mu became non-significant in both conditions when controlling for IQ (online Supplementary Table S3) and in the baseline condition in the male-only sample (online Supplementary Table S4).

### *Which measures are markers of remission (aim 2a and 2b)?*

Analyses were restricted to measures that survived multiple testing corrections in the analysis of aim 1. In categorical analyses (aim

**Table 2.** Random-intercept linear models of ex-Gaussian and EEG time-frequency measures with parent-reported ADHD symptoms and impairment within the ADHD group only, controlling for age and sex

| | ADHD symptoms | | Functional impairment | |
|---|---|---|---|---|
| Aim 2b | *β* (95% CI) | *p* | *β* (95% CI) | *p* |
| **Mu** | <0.00 (−0.31 to 0.30) | 0.983 | – | – |
| Baseline | – | – | −0.03 (−0.21 to 0.14) | 0.701 |
| Fast-incentive | – | – | 0.20 (0.01 to 0.39) | 0.033* |
| **Sigma** | 0.13 (−0.34 to 0.60) | 0.580 | −0.06 (−0.58 to 0.46) | 0.827 |
| **Tau** | 0.27 (−0.05 to 0.59) | 0.095 | *0.37 (0.01 to 0.72)* | 0.043* |
| **Theta ERSP CP** | 0.03 (−0.13 to 0.90) | 0.147 | −0.04 (−0.60 to 0.30) | 0.523 |
| **Theta phase consistency** | 0.03 (−0.34 to 0.39) | 0.888 | −0.13 (−0.53 to 0.26) | 0.513 |

ADHD, attention-deficit/hyperactivity disorder; ERSP, event-related spectral perturbation; CP, centro-parietal.
*Notes*: Ex-Gaussian variables were available for 87 persisters, 23 remitters, and 169 controls. ERSP and theta phase consistency variables were available for 81 persisters, 23 remitters, and 163 controls. **$p < 0.010$, *$p < 0.050$. Bold = large effect size ($\beta \geq 0.50$); Italics = medium effects size ($\beta \geq 0.30$). Analyses of ADHD symptoms and impairment with all variables, as well as for mu with ADHD symptoms, were run collapsing across baseline and fast-incentive conditions, as the interactions with the condition were non-significant ($p > 0.10$).

2a) on ADHD remitters, persisters and controls, remitters did not significantly differ from controls on any other measure (Table 1). Mu, which showed a significant group-by-condition interaction, was lower in ADHD remitters compared to persisters in the fast-incentive condition, but no differences emerged in the baseline condition (Table 1). ADHD remitters further showed lower tau, as well as greater centro-parietal theta ERSP and theta phase consistency compared to persisters (Table 1, Figs 1 and 2). ADHD remitters showed significant within-group changes between conditions in all ex-Gaussian measures (all $p < 0.05$) but not in theta ERSP and phase consistency measures (all $p > 0.1$) Full details on condition and group-by-condition effects are reported in online Supplementary material.

The ADHD remitter-persister differences in mu in the fast-incentive condition became non-significant when controlling for IQ (online Supplementary Table S3) and in the male-only sample (online Supplementary Table S4).

Dimensional analyses (aim 2b) in participants with childhood ADHD, controlling for sex and age, showed non-significant associations of ADHD symptoms with all ex-Gaussian and time-frequency measures (Table 2). These associations did not differ between conditions, as indicated by non-significant interactions between ADHD symptoms and condition for all measures (all $p > 0.1$). Mu showed a significant interaction between functional impairment and condition ($p = 0.024$): functional impairment was associated with mu in the fast-incentive condition but not in the baseline condition (Table 2). Functional impairment was significantly associated with tau irrespective of condition (Table 2), as the functional impairment-by-condition interaction was non-significant. The other measures were not associated with functional impairment and the functional impairment-by-condition interactions were non-significant (all $p < 0.1$). When also controlling for IQ, the association of functional impairment with mu and tau became non-significant (online Supplementary Table S5).

### *Are ex-Gaussian and EEG time-frequency markers of remission associated with each other (aim 3)?*

We examined the association of mu in the baseline and fast-incentive condition separately and tau across conditions with centro-parietal theta ERSP and phase consistency, as these measures emerged as markers of remission in categorical analyses. Mu showed a significant negative association with theta ERSP and theta phase consistency in both conditions (online Supplementary Table S6), while the interactions between group and theta ERSP or theta phase consistency were non-significant, indicating that the groups did not differ on the strength of these associations. Similarly, tau across conditions showed a significant negative association with theta ERSP and phase consistency, while the interactions with the group were non-significant (online Supplementary Table S6).

## Discussion

In a first large-scale investigation to examine ex-Gaussian and EEG time-frequency markers in adolescents and adults with childhood ADHD, we observed widespread impairments in ADHD persisters, compared to controls, in ex-Gaussian measures of response variability (sigma and tau) and response speed (mu), and in neurophysiological markers of neural variability (theta phase consistency) and attention allocation (theta ERSP). We further identified several potential new markers of remission, on which ADHD remitters were comparable to controls but significantly different from persisters: mu, tau, centro-parietal theta ERSP and theta phase consistency. The ex-Gaussian and EEG markers of remission were significantly associated with each other, indicating they may reflect partly overlapping processes. The measures emerging as potential markers of remission represent possible compensatory mechanisms in ADHD remitters, extending our previous findings on more traditional cognitive-performance and ERP measures (Cheung et al., 2016; James et al., 2017; Michelini et al., 2016).

ADHD persisters showed increased cognitive variability compared to controls (with large effect sizes), consistent with our hypotheses and previous ex-Gaussian studies in individuals with ADHD (Buzy, Medoff, & Schweitzer, 2009; Vainieri et al., 2020; Vaurio, Simmonds, & Mostofsky, 2009). We also observed increased mu in ADHD persisters compared to controls, despite some previous studies not detecting this potentially subtler impairment (Gmehlin et al., 2014; Lin, Hwang-Gu, & Gau,

2015). In this largest time-frequency analysis of ADHD to date, we further report that individuals with persistent ADHD, compared to controls, show lower theta phase consistency and evoked theta power, reflecting lower consistency of neural stimulus processing across trials (Makeig et al., 2004) and lower attentional processing (Klimesch, Sauseng, & Hanslmayr, 2007), respectively, confirming previous evidence in smaller ADHD samples (Groom et al., 2010; McLoughlin et al., 2014; Michelini et al., 2018*b*; Missonnier et al., 2013). We did not find differences between ADHD persisters and controls on alpha suppression, nor on adjustments between conditions in alpha and beta, contrary to our predictions based on the ADHD-control differences in our previous smaller-scale time-frequency study (Michelini et al., 2018*b*). Such inconsistencies may be explained by sex differences (the current study primarily included males, while the previous one only females) or age (the current sample was younger). These findings advance our understanding of the cognitive and neural correlates of persistent ADHD in adolescence and early adulthood, showing specific RT and brain-oscillatory impairments in measures mapping onto attention-vigilance processes.

We further examined ex-Gaussian and brain-oscillatory measures in relation to ADHD remission, both categorically and dimensionally. Results for mu showed that ADHD remitters were comparable to controls and significantly different from persisters in the fast-incentive condition, but did not differ significantly from either controls or persisters in the baseline condition. ADHD remitters were also comparable to controls but different from persisters on tau across conditions. These findings suggest that tau may be considered a marker of ADHD remission in both conditions, while mu may be sensitive to remission only in the fast-incentive condition. This pattern potentially indicates residual impairments in mu in the remitted group in the baseline condition, which is more challenging for ADHD participants due to the long inter-trial interval. Conversely, the significantly lower mu in remitters than in persisters in the fast-incentive condition may suggest that compensatory processes might arise in a more engaging context. Results of dimensional analyses were consistent with these categorical findings, as tau across conditions and mu in the fast-incentive condition were continuously associated with functional impairment in individuals with childhood ADHD. For sigma, we observed no differences between remitters and the other groups or continuous associations with ADHD symptoms or functional impairments, indicating that this measure may not be a marker of remission. At the neural (EEG) level, ADHD remitters were comparable to controls but showed significantly higher centro-parietal theta power and theta phase consistency compared to persisters, suggesting that these variables are potential markers of remission. Yet, they were not dimensionally associated with ADHD symptoms or functional impairment, suggesting that the pattern of remission for these variables should be investigated further in future research. In further analyses controlling for IQ, results for tau and centro-parietal theta power were unchanged, indicating they are markers of remission independently of IQ, while results for other measures became non-significant. Taken together, the current results provide novel evidence that markers of attention-vigilance processes, including ex-Gaussian measures of response speed (mu), variability of long responses (tau) and EEG power and phase consistency in theta oscillations, may be implicated in ADHD remission, consistent with previous findings on RTV measured as S.D.-RT and P3 during this task (James et al., 2017).

In examining the association between the identified ex-Gaussian and EEG markers of remission, we found a significant association of evoked theta power and theta phase consistency with mu and tau. These results indicate that alterations in theta oscillations may partly underlie atypical response speed and variability of long responses. Future studies should replicate these associations and further investigate their possible underlying etiological processes. Of note, while all groups showed significant improvements in ex-Gaussian measures from the baseline to the fast-incentive condition, in line with previous findings on RTV (Cheung et al., 2016), no improvement emerged in theta power and phase variability. As such, these brain markers of remission may be less malleable than cognitive markers of remission.

The following limitations should be considered. First, the high ADHD persistence rate at follow-up resulted in a small group of remitters; thus, some non-significant differences between ADHD remitters and the other groups might be due to low power. Although we successfully detected medium-to-large effect sizes in markers of remission with current sample sizes and also ran dimensional analyses, future studies should include a larger remitted group. Second, groups were not matched on sex and the small number of females did not allow us to directly examine sex differences. Yet, results in the male-only sample showed comparable effect sizes to those in the full sample, indicating that reduced significance for some effects after excluding females may thus have arisen from the smaller size in the male-only sample. Third, since participants were adolescents and young adults, who may still be undergoing cortical maturation and could potentially remit at an older age, further follow-ups are required to confirm the applicability of these findings to older individuals. Fourth, although this study was conducted on the adolescent and young adult follow-up assessments of a sample of children with ADHD and controls, different cognitive-EEG batteries at the childhood and follow-up assessments precluded us from conducting formal longitudinal analyses. Our previous study on the childhood data showed no childhood differences between participants whose ADHD persisted and remitted at follow-up on cognitive measures related to those emerging here as markers of remission (e.g. RTV measured as RT-S.D.) (Cheung et al., 2015). This might suggest that the differences at follow-up reported here between remitters and persisters were likely not explained by pre-existing differences in childhood. Nevertheless, since this is a common limitation among studies of ADHD remission and persistence (Franke et al., 2018), future studies using repeated cognitive and brain measures across development are warranted.

In conclusion, our cognitive-EEG investigation shows that detailed measures of response speed emerge as potential markers of ADHD remission, under more engaging (fast-incentive) conditions, while measures of neural markers of phase variability (i.e. lower theta phase consistency) and attention allocation (cento parietal theta power), as well as attentional lapses (tau), emerged as markers of remission independently of the condition. These measures may point to potential compensatory mechanisms linked to remission of ADHD from childhood to adulthood, extending our previous findings on more traditional measures of attention-vigilance processes (Cheung et al., 2016; James et al., 2017; Michelini et al., 2016).

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S0033291720002056

**Acknowledgements.** This project was supported by generous Grants from Action Medical Research and the Peter Sowerby Charitable Foundation (Grant Reference GN1777). Initial sample recruitment of the ADHD sample

was supported by NIMH Grant R01MH062873 to Prof Stephen V Faraone; the recruitment of the control sample and initial cognitive assessments of ADHD and control groups were supported by UK Medical Research Council Grant G0300189 to Prof Jonna Kuntsi. Isabella Vainieri is supported by a 3-year PhD studentship awarded by the Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London. Dr Giorgia Michelini received a fellowship funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. We thank all who made this research possible: our participants and their families; Jessica Deadman, Hannah Collyer and Sarah-Jane Gregori. Correspondence and requests for materials should be addressed to Prof Jonna Kuntsi.

**Conflict of interest.** Prof Jonna Kuntsi has given talks at educational events sponsored by Medice; all funds are received by King's College London and used for studies of ADHD. Prof Philip Asherson has received funding for research by Vifor Pharma and has given sponsored talks and been an advisor for Shire, Janssen-Cilag, Eli-Lilly, Flynn Pharma and Pfizer, regarding the diagnosis and treatment of ADHD; all funds are received by King's College London and used for studies of ADHD. The other authors report no conflicts of interest.

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# Chapter 3

# Polygenic association between attention-deficit/hyperactivity disorder liability and cognitive impairments

## 3.1 Abstract

**Background:** A recent genome-wide association study (GWAS) identified 12 independent loci significantly associated with attention-deficit/hyperactivity disorder (ADHD). Polygenic risk scores (PRS), derived from the GWAS, can be used to assess genetic overlap between ADHD and other traits. Using ADHD samples from several international sites, we derived PRS for ADHD from the recent GWAS to test whether genetic variants that contribute to ADHD also influence two cognitive functions that show strong association with ADHD: attention regulation and response inhibition, captured by reaction time variability (RTV) and commission errors (CE).

**Methods:** The discovery GWAS included 19 099 ADHD cases and 34 194 control participants. The combined target sample included 845 people with ADHD (age 5-40 years). RTV and CE were available from reaction time and response inhibition tasks. ADHD PRS were calculated from the GWAS using a leave-one-study-out approach. Regression analyses were run to investigate whether ADHD PRS were associated with CE and RTV. Results across sites were combined via random effect meta-analyses.

**Results:** When combining the studies in meta-analyses, results were significant for RTV ($R^2 = 0.011$, $\beta = 0.088$, $p = 0.022$) but not for CE ($R^2 = 0.011$, $\beta = 0.013$,

$p = 0.732$). No significant association was found between ADHD PRS and RTV or CE in any sample individually ($p > 0.10$).

**Conclusions:** We detected a significant association between PRS for ADHD and RTV (but not CE) in individuals with ADHD, suggesting that common genetic risk variants for ADHD influence attention regulation.

## 3.2 Introduction

A recent case-control genome-wide association study (GWAS) identified, for the first time, 12 independent loci significantly associated with attention-deficit/hyperactivity disorder (ADHD) (Demontis et al., 2019). This GWAS enables further genetic investigations using polygenic risk scores (PRS), which are calculated for each individual by computing the sum of their risk alleles across the genome, weighted by effect sizes (Choi et al., 2018). PRS provide an estimate of the genetic propensity to ADHD at the individual level that can be used to investigate shared genetic aetiology between ADHD and other phenotypes.

Previous studies on general population samples show that ADHD PRS are associated with a wide range of psychiatric and somatic disorders and traits, such as depression, anxiety, neuroticism, irritability, childhood internalizing and externalizing symptoms, obesity-related phenotypes and smoking (Brikell et al., 2018; Du Rietz et al., 2018; Riglin et al., 2017). Only a few of these population-based studies explored the cognitive phenotypes associated with ADHD using polygenic approaches, but have provided initial evidence for an association between PRS for ADHD and lower general cognitive ability (Du Rietz et al., 2018; Martin, Hamshere et al., 2015), educational attainment (Stergiakouli et al., 2017) and working memory, but not inhibition impairments (measured with the Opposite Words Task (Martin, Hamshere et al., 2015)). Evidence from clinically diagnosed samples with ADHD remains even more limited. The findings reported to date indicate an association of ADHD PRS with low academic achievement (Vuijk et al., 2019) and poor working memory and arousal-alertness, measured with latent variables (Nigg et al., 2018). In contrast, no significant associations emerged between PRS for ADHD and latent variables capturing inhibition or speed of responses (Nigg et al., 2018). A recent study found that PRS for ADHD were associated with a measure of interference, the "variance of word interference time" in the Stroop test (Chang et al., 2020).

We now extend, in a sample of 845 people with ADHD, the previous PRS investigations of ADHD-related cognitive phenotypes to two cognitive measures

that have extensive evidence from phenotypic studies of a strong association with ADHD, but have not yet been investigated using PRS: increased reaction time variability (RTV) and commission errors (CE) (Kuntsi et al., 2010; Loo et al., 2009; Schachar et al., 2007; van Rooij et al., 2015). RTV captures the highly variable speed of responding that is strongly characteristic of people with ADHD across a variety of cognitive tasks requiring a speedy response (Kofler et al., 2013; Kuntsi et al., 2013), and has been linked in EEG and skin conductance studies to attention allocation and peripheral hypo-arousal (Cheung et al., 2017; James et al., 2016). CE, which represent the responses to non-target stimuli on inhibitory tasks such as the Go/No-Go task, capture failures to withhold responding.

Family and twin studies suggest a significant degree of familial/genetic sharing between ADHD and both RTV and CE (Kuntsi et al., 2014; Kuntsi et al., 2010). For example, in a large study of 1265 children and adolescents, including 464 participants with ADHD, we observed a familial correlation of 0.74 between ADHD and RTV, and 0.45 between ADHD and CE (Kuntsi et al., 2010). The analyses further indicated a significant degree of aetiological separation in the association of ADHD with RTV and CE (Kuntsi et al., 2010), with a similar conclusion emerging also from model fitting analyses in a population twin sample of 1312 children (Kuntsi et al., 2014). Family model fitting analyses also showed a high familial correlation between RTV obtained from two different tasks (a four-choice reaction time task, the Fast task, and a Go/No-Go task; $r_f = 0.75$) (Kuntsi et al., 2010), suggesting RTV can be combined across such tasks for further genetic investigations.

Using a polygenic approach, we can move beyond the inferred aetiological sharing between ADHD and RTV or CE that rely on comparisons of related individuals (in twin and family designs), to test the associations using molecular genetic data in unrelated individuals. Specifically, in this collaborative study using ADHD samples from several international sites, we derive PRS for ADHD from the recent GWAS (Demontis et al., 2019) to test whether genetic variants that contribute to ADHD also influence the cognitive impairments captured by RTV and CE in people with ADHD.

## 3.3 Methods

### 3.3.1 Discovery sample

As the discovery dataset, we used the Psychiatric Genomics Consortium (PGC) and iPSYCH Danish data analysed in the recently published GWAS of ADHD (Demontis

et al., 2019). This GWAS consists of 11 studies, with a total of 19 099 ADHD cases and 34 194 control subjects of European ancestry (full sample sizes are given in Table B.S1, Supplementary material).

### 3.3.2 Target samples and cognitive assessments

From the above discovery sample, four sub-samples from different sites were used as target samples applying a leave-one-study-out approach: International Multisite ADHD Genetics project (IMAGE-I, subdivided here to IMAGE-8 and IMAGE-Dutch that had different cognitive test batteries), University of California Los Angeles (UCLA), Toronto and Barcelona. All participants for each site completed a comprehensive protocol of cognitive tasks, which differed for each site. Participants from IMAGE-8 performed a four-choice reaction time task (Fast task) and a version of the Go/No-Go task with fast and slow conditions, while IMAGE-Dutch participants performed the Stop-Signal Task (SST). At UCLA and Barcelona, participants performed the Continuous Performance Test II (CPT-II), while the Go/No-Go task was administered in Toronto. Descriptive statistics for each sample are shown in Table 3.1. Based on previous publications, cognitive variables were selected from the tasks that showed a significant ADHD case-control difference (effect sizes ranging from 0.32 to 0.95 for RTV, and from 0.38 to 0.42 for CE; Alemany et al., 2015; Hale et al., 2014; Kuntsi et al., 2010; Schachar et al., 2007; van Rooij et al., 2015). RTV (standard deviation [SD] of reaction times) was obtained from each of the tasks. Evidence for comparability between tasks was previously obtained from model fitting analyses on the fast task and Go/No-Go task, which indicated a high familial correlation ($r_f = 0.75$) between RTVs obtained from each task, suggesting they are measuring largely the same liability (Kuntsi et al., 2010). CE was obtained from the CPT-II and Go/No-Go tasks only. The high rates of Go-stimuli in the CPT-II task makes this task comparable to a Go/No-Go task.

#### 3.3.2.1 IMAGE-I

**Sample**

IMAGE-I is a European project on ADHD familiarity using a common protocol of centralised training and data management. IMAGE-I includes data from different European sites and Israel recruited from specialist clinics in Tel-Aviv, Essen, Gottingen, Brussels, Dublin, Valencia, Zurich, London, Nijmegen and Amsterdam (Kuntsi, Neale et al., 2006; Müller et al., 2011a; Müller et al., 2011b). The full IMAGE-I

**Table 3.1:** Descriptive statistics for all samples

| Sample | | N | IQ mean (SD) | Age mean (SD) | Sex M:F (%) |
|---|---|---|---|---|---|
| IMAGE-I | IMAGE-8 | 143 | 103.78 (15.24) | 11.30 (2.67) | 119:24 (83) |
| | IMAGE-Dutch | 226 | 98.96 (11.52) | 11.50 (2.47) | 200:26 (88) |
| UCLA | | 55 | 113.33 (15.03) | 11.43 (2.98) | 30:25 (55) |
| Toronto | | 54 | 101.24 (11.40) | 9.38 (2.12) | 42:12 (78) |
| Barcelona | | 367 | NA | 33.24 (10.54) | 249:118 (68) |

*Abbreviations:* International Multisite ADHD Genetics Project, IMAGE; University of California Los Angeles, UCLA. % are reported for males only.

sample consisted of 782 individuals with DSM-IV ADHD combined type (680 with ADHD combined type probands including 102 of their siblings who also met criteria for ADHD) and 808 additional unaffected siblings aged 6 to 19 years (Kuntsi, Neale et al., 2006). All participants were recruited from specialist clinics. In IMAGE-I, parents of children were interviewed by trained researchers with the Parental Account of Childhood Symptom (PACS), a semi-structured, standardised, investigator-based interview developed as an instrument to provide an objective measure of child behaviour. Both parents and teachers completed the respective versions of the Conners' ADHD rating scales and the Strengths and Difficulties Questionnaire (SDQ). Exclusion criteria were autism, epilepsy, IQ $< 70$, brain disorders and any genetic or medical disorder associated with externalising behaviours that might mimic ADHD. Wherever possible, families withdrew stimulant medication for one week prior to research assessments to allow for more accurate ascertainment of the current level of ADHD symptoms and behaviours. Alternatively, clinical interviews were based on medication-free periods. A minimum of a 48-hour medication-free period was required for cognitive testing. All data were collected with informed consent of parents and with the approval of the site's Institutional Review Board (IRB) or Ethical Committee.

Due to differences in the protocol of the cognitive tasks, IMAGE-I can be subdivided into two subsamples: IMAGE-8 (including participants from Tel-Aviv, Essen, Gottingen, Brussels, Dublin, Valencia, Zurich, and London) and IMAGE-

Dutch (including participants from Nijmegen and Amsterdam). In the current study, we included only participants with an ADHD diagnosis who had both cognitive and genetic data available. The final sample consisted of 143 ADHD participants from the IMAGE-8 study and 226 ADHD participants from the IMAGE-Dutch study.

### Tasks: Fast-Task, Go/No-Go and SST

The Fast task is a computerised four-choice reaction time (RT) task which measures performance under a baseline (slow-unrewarded) and a fast-incentive condition (Andreou et al., 2007; Kuntsi, Rogers et al., 2006). In the current study, only data from the baseline condition was included as this condition is more sensitive to ADHD (Kuntsi et al., 2013). The baseline condition consisted of 72 trials. Four empty circles (warning signals, arranged horizontally) first appeared for 8 seconds (s), after which one of them (the target) was coloured in. Participants were asked to press the response key that corresponded to the position of the target. Following a response, the stimuli disappeared from the screen and a fixed inter-trial interval of 2.5 s followed. Speed and accuracy were emphasised equally.

The Go/No-Go task is a computerised test used to assess inhibitory control (Börger & van der Meere, 2000; Kuntsi et al., 2005; van der Meere et al., 1995). On each trial of the Go/No-Go task, one of two possible stimuli appeared for 300 milliseconds (ms) in the middle of the computer screen. The child was instructed to respond only to the Go stimuli and to withhold their response to No-Go stimuli. Participants were asked to react as quickly as possible while maintaining a high level of accuracy. The proportion of Go stimuli to No-Go stimuli was 4:1. This version of the Go/No-Go task consisted of three conditions (slow, fast and incentive). Here, we use data only from the slow condition, which show a strong association with ADHD (Andreou et al., 2007; Kuntsi et al., 2009; Uebel et al., 2010). The slow condition consisted of 72 trials that were presented with a fixed inter-stimulus interval of 8 s.

The SST is a response inhibition task, where participants had to respond as quickly as possible to a Go stimulus by left or right button press, unless shortly after presentation it was followed by a Stop signal, in which case they had to withhold their response (25% of trials) (Logan et al., 1984). The task difficulty was adaptive, meaning delays between the Go and Stop stimulus were adjusted by 50 ms after every failed or successful response, leading to an approximate 50% success rate on the Stop-trials for all participants. The task consisted of two practice blocks and four test blocks, each consisting of 60 trials.

#### 3.3.2.2 UCLA

**Sample**

At UCLA, 156 participants with ADHD were recruited as part of the PUWMa collaboration (Pfizer-funded study from the University of California, Los Angeles (UCLA), Washington University, and Massachusetts General Hospital (MGH)), which included 540 children and adolescents aged 5 to 18 years and 519 of their parents ascertained from 370 families with ADHD-affected sibling pairs. Children and adolescents were assessed according to DSM-IV-TR criteria. Families were recruited through clinical referrals, schools, and responses to advertisements (e.g. newsletters, community newspapers, or flyers distributed at parent meetings in the greater Los Angeles area). Respondents without a previous diagnosis of ADHD were screened with the parent and teacher version of the Swanson, Nolan, and Pelham Rating Scale, SNAP-IV (Swanson et al., 2012). After initial screening, children and adolescents were assessed by master's level clinical psychologists or highly trained interviewers using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL), as well as a parent-completed Child Behaviour Checklist (CBCL) and teacher report form. Participants were excluded if they were positive for any of the following: neurological disorder, head injury resulting in concussion, lifetime diagnoses of schizophrenia or autism, or estimated IQ $< 70$. Participants on stimulant medication were asked to discontinue use for 24 hours prior to their visit. The final sample with both cognitive and genetic data available consists of 55 ADHD cases.

**Task: CPT-II**

The CPT-II (Conners, 2000) is a 14-minute computerised task that consisted of 6 blocks and 3 sub-blocks. Participants were required to press the space button on the keyboard whenever any letter except the letter 'X' appeared on the computer screen. The task consisted of 360 trials, including 36 presentations of the inhibition target (X). Targets (including 'go' targets: A, B, C, D, F, I, L, O, T) were presented in randomised order for 250 ms with variable inter-trial interval of 750 ms, 1750 ms and 3750 ms. The presentation order of the different inter-trial intervals varied between blocks. The Go:No-Go ratio was 9:1.

#### 3.3.2.3 Barcelona

**Sample**

The Spanish sample included 607 adults with ADHD (age range 18-40 years), recruited and evaluated at the Hospital Universitari Vall d'Hebron in Barcelona. The diagnosis of ADHD was evaluated by clinicians with the Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID-I and SCID-II) and the Conner's Adult ADHD Diagnostic Interview for DSM-IV (CAADID Parts I and II). Exclusion criteria were IQ < 70, schizophrenia or other psychotic disorders, ADHD symptoms due to mood, anxiety, dissociative or personality disorders, adoption, sexual or physical abuse, birth weight <1.5 kg, and other neurological or systemic disorders that might explain ADHD symptoms. Cognitive and genetic data were available from 367 ADHD participants. More information about this sample can be found elsewhere (Sánchez-Mora et al., 2015).

**Task: CPT-II**

See UCLA for task description.

#### 3.3.2.4 Toronto

**Sample**

The initial Canadian ADHD sample included 248 children aged 6-16 years referred for ADHD, learning and/or behavioural problems to the Hospital for Sick Children, Toronto (Lionel et al., 2011). ADHD diagnostic information was obtained based on DSM-IV criteria from parents and teachers in semi-structured clinical interviews including the Parent Interview for Child Symptoms (PICS) and the Teacher Telephone Interview (TTI). The assessments were conducted by a social worker, a clinical nurse specialist, or a clinical psychologist and supervised by a clinical psychologist or child psychiatrist. Exclusion criteria were an IQ < 80, pervasive developmental disorder, autism, or comorbid psychiatric disorder that could better account for the disorder. Participants who were treated with stimulant medication had to be unmedicated for a minimum of 24 h before assessment and testing. Cognitive and genetic data for this study were available from 54 children with ADHD.

**Task: Go/No-Go task**

This version of the Go/No-Go task involved 128 trials of which 32 were No-Go trials and 96 were Go trials. During the Go task, one of two possible letters were presented

(an X or an O) on each trial. Participants were required to make a response to the Go task stimuli as quickly and as accurately as possible by pressing one key of a handheld response box for an X and the other for an O (Go stimuli). The No-Go task involved an auditory tone which was presented, at the same time as the stimulus (letters), at random, on 25% of trials. Participants were instructed to withhold their response when they heard the tone. The Go task stimulus was presented for 1000 ms immediately following a fixation point of 500 ms. The task included 4 blocks, each with 24 Go trials and 8 No-Go Trials. The Go:No-Go ratio was 3:1.

### 3.3.3 Data analyses

#### 3.3.3.1 Quality control of genetic and cognitive data

Quality control of genetic data was previously performed and was available for analyses (for more information see Demontis et al. (2019)).

To account for positive skewness of the cognitive data, we applied appropriate transformations to all cognitive measures for each variable prior to analyses. Square root transformations were used in all samples for CE. For RTV, we used a logarithm transformation for IMAGE-8 team, Dutch-IMAGE and UCLA, and a square root transformation for Barcelona and Toronto. There were no extreme outliers for RTV or CE (>3.5 SD).

#### 3.3.3.2 PRS analyses

The GWAS summary statistics used as the discovery sample included the four target sub-groups (IMAGE-I, Toronto, Barcelona, UCLA). For this reason, PRS were calculated from the main GWAS each time excluding one of the target samples using four leave-one-out association meta-analyses, to ensure entirely independent discovery and target samples. PRS were estimated for each target sample using the PRSice-2 software (Euesden et al., 2015) (https://www.prsice.info) and applying standard procedures (imputation quality cut-off using PRSice INFO >0.9, and minor allele frequencies cut-off using PRSice MAF >0.05) (Choi et al., 2018). PRSice computes PRS by calculating the sum of trait-associated alleles, weighted by the log odds ratio (OR) generated from the discovery GWAS. An $R^2 \geq 0.1$ (250-kb window) including all SNPs ($p^1$, $p^2 = 1$) was used for linkage disequilibrium (LD) clumping to keep a set of independent SNPs. Linear regression models were used to estimate associations between PRS and phenotypes in the target samples. PRS were calculated at a number of $p$-value thresholds for SNP inclusion to provide the

most predictive PRS. The $p$-value thresholds used were 0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5 and 1. We included age, sex, and the first five principal components (PCs) as covariates in all analyses, to control for population stratification. The number of PCs was chosen based on the cohort's sample size (all <1000) in order to avoid overfitting and to reflect the differential power to capture true population structure by PCA, as reported in Demontis et al. (2019). The estimated amount of variance explained by PRS (i.e. $R^2$ values) that we report for each study are adjusted from a baseline model including the covariates; the reported regression coefficients and standard errors (SE) were standardised to have mean = 0 and SD = 1 using the PRSice command `--score std`. For each $p$-value threshold we performed stringent permutation testing within PRSice-2 using 10 000 permutations to control for type 1 error and to prevent data overfitting. Figures B.S1 to B.S9 provide plots for the PRS prediction models for RTV and CE across all sites.

#### 3.3.3.3 Meta-analyses

For the meta-analyses, we used a random effects model using the `rma.uni` function of the `metafor` package in R, with the method set to "REML". Meta-analyses for both RTV and CE were performed across all samples at all thresholds to check the consistency of the associations between PRS and these measures (Tables B.S2 and B.S3). Combining all samples, the sample size for the meta-analysis consisted of $n = 743$ ADHD participants for RTV and $n = 679$ ADHD participants for CE.

## 3.4 Results

### 3.4.1 Polygenic risk scores in individual datasets

PRS for ADHD were not significantly associated with RTV in any of the individual datasets ($R^2 = 0.004$, empirical-$p = 0.993$, $\beta = 0.024$ for IMAGE-8; $R^2 = 0.016$, empirical-$p = 0.317$, $\beta = 0.135$ for IMAGE-Dutch; $R^2 = 0.008$, empirical-$p = 0.823$, $\beta = 0.032$ for UCLA; $R^2 = 0.031$, empirical-$p = 0.459$, $\beta = 0.112$ for Toronto; $R^2 = 0.012$, empirical-$p = 0.079$, $\beta = 0.122$ for Barcelona). All associations showed a positive direction. PRS for ADHD were not significantly associated and showed inconsistent direction of association with CE in any of the individual samples ($R^2 = 0.011$, empirical-$p = 0.217$, $\beta = -0.104$ for IMAGE-8; $R^2 = 0.036$, empirical-$p = 0.556$, $\beta = 0.101$ for UCLA; $R^2 = 0.013$, empirical-$p = 0.761$, $\beta = -0.121$ for Toronto; $R^2 = 0.006$, empirical-$p = 0.301$, $\beta = 0.083$ for Barcelona).

### 3.4.2 Meta-analyses of all datasets

Meta-analyses across all thresholds for RTV showed that the best threshold for PRS association with RTV was 0.2 (Table B.S2). At this threshold, the PRS for ADHD was significantly associated with RTV ($R^2 = 0.011$, $p = 0.022$, $\beta = 0.088$), with a positive direction. The best threshold for PRS association with CE was 0.001 (Table B.S3), but the association with CE did not reach significance ($R^2 = 0.011$, $p = 0.732$, $\beta = 0.013$). Heterogeneity tests showed low heterogeneity across studies for both measures ($Q = 3.777$, $p = 0.436$, $I^2 = 13.513\%$ for RTV; $Q = 1.195$, $p = 0.754$, $I^2 = 0\%$ for CE). Forest plots for each variable are reported in Figures 3.1 and 3.2.

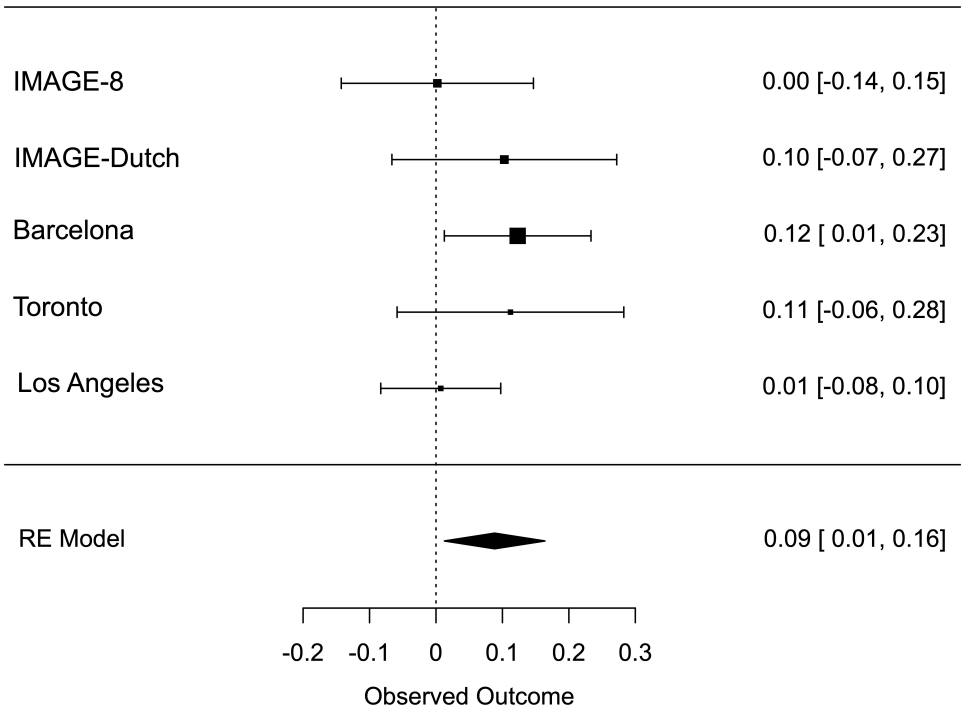


**Figure 3.1:** Forest plot of meta-analysis of reaction time variability (RTV). *Note:* overall estimate from random effects model is represented by the diamond below the individual study estimates.

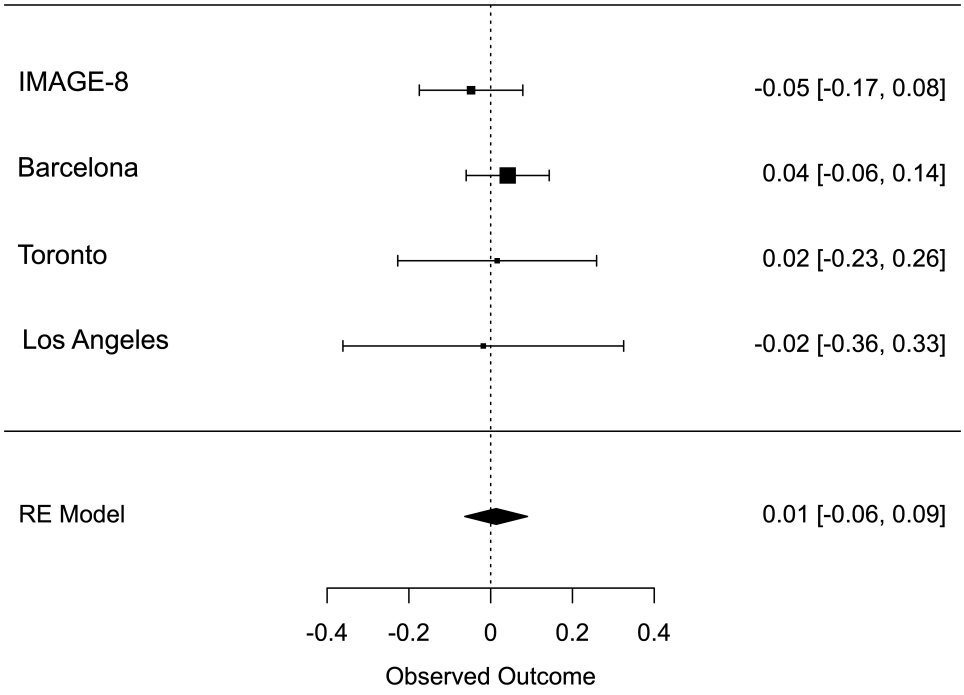


**Figure 3.2:** Forest plot of meta-analysis of commission errors (CE). *Note:* overall estimate from random effects model is represented by the diamond below the individual study estimates.

## 3.5 Discussion

This is one of the largest studies investigating the association between ADHD PRS and cognitive impairments in individuals diagnosed with ADHD. Combining our samples in meta-analyses, our results show that polygenic risk for clinically diagnosed ADHD is positively associated with higher RTV, but not with CE as measured by Go/No-Go tasks. These data suggest that common genetic variation relevant for ADHD influences attention regulation (RTV) but not response inhibition processes (CE) in a clinical ADHD sample. Whether the lack of an association with CE could reflect possible involvement of rare variants not detectable in this analysis or limited power to detect a potentially smaller association, requires further study.

Our results on RTV build on previous evidence from a smaller sample of children with ADHD showing a significant positive association between a latent variable of arousal-alertness and PRS for ADHD (Nigg et al., 2018). Of note, the association we observed between PRS for ADHD and RTV was mostly consistent across all $p$-value thresholds in the meta-analysis, with only slight fluctuations in results possibly due to low power. Similarly, our results on CE are consistent with a previous population-based study and a clinical study showing no association between polygenic risk for ADHD and other inhibition measures (Martin, Hamshere et al., 2015; Nigg et al., 2018), although a recent study did report an association between PRS for ADHD and interference when measured with the variance of word interference time in the Stroop test (Chang et al., 2020). Previous twin and sibling analyses have indicated a degree of shared genetic/familial influences on ADHD and response inhibition (Kuntsi, Rogers et al., 2006; Kuntsi et al., 2010). Further evidence from a sibling study suggested in fact two familial cognitive impairment factors for ADHD: a larger factor (85% of familial variance of ADHD) related to RTV, and a smaller factor (12.5% of familial variance of ADHD) capturing CE and omission errors (an overall measure of task accuracy) (Kuntsi et al., 2010). The findings from the sibling and twin studies (Kuntsi et al., 2014; Kuntsi et al., 2010) suggested a potential separation, at the genetic level, between attention regulation and response inhibition processes in their association with ADHD. It is possible that our current analyses detected the larger factor accounted for by RTV in the sibling analyses (Kuntsi et al., 2010) while the smaller factor (accounting for CE) could not be detected with the current sample size. Future studies should investigate the genetic correlation between ADHD and RTV or CE across the whole genome using LD score regression, when summary statistics from GWAS on the appropriate cognitive traits will be available.

While PRS capture the common risk alleles that contribute to clinically diagnosed ADHD, they do not incorporate contributions from other genetic factors, such as copy number variants (CNVs) and single nucleotide variants (SNVs) that may underlie the association of ADHD with RTV or CE. Several studies indicate a role for CNVs and SNVs in contributing to ADHD risk (Martin, O'Donovan et al., 2015; Satterstrom et al., 2018; Thapar et al., 2016; Williams et al., 2012; Williams et al., 2010; Yang et al., 2013). CNVs were showed to be associated to cognitive features in the general population such as general cognitive ability (MacLeod et al., 2012), educational and occupational attainment (Kendall et al., 2017; Männik et al., 2015), and other cognitive phenotypes such as working memory, episodic memory, speed processing, visual attention and fluid intelligence (Kendall et al., 2017). Similarly, SNVs have been implicated in intellectual disability (Satterstrom et al., 2018). Yet the extent to which CNVs and other genetic variants may contribute to cognitive impairments in individuals with ADHD is poorly understood and is an important direction for future research.

While this is the largest study to date to investigate RTV and CE with a cutting-edge polygenic risk score method in a sample of individuals with clinically diagnosed ADHD, certain limitations need to be considered. First, our individual study analyses were underpowered due to the small sample sizes available in each single study. To increase statistical power, we analysed the target studies with meta-analyses, reaching a combined sample size of $n = 743$ ADHD participants for RTV and $n = 679$ ADHD participants for CE; yet future studies, ideally with larger samples, are needed to replicate these results. Second, the age range of our participants was wide (5-40 years old). It would be informative in future larger studies to explore results separately for participants of different age groups (children, young adults and older adults). Third, our study included only participants of European ancestry; the generalisability of our findings to non-European populations requires further investigations. Fourth, the use of different tasks to reflect the two constructs of interest at different sites could have introduced heterogeneity in our data; however, we used random effects in the meta-analyses to account for between-study variation across sites. A further direction for future research is to widen the PRS investigation to additional cognitive impairments associated with ADHD.

Overall, polygenic risk associated with clinical ADHD diagnosis was associated with higher RTV in individuals with clinically diagnosed ADHD. Our results provide molecular genetic evidence that attention regulation and ADHD share common genetic factors. In other words, ADHD common variants not only contribute to risk of ADHD diagnosis but are also a marker of poorer RTV performance in the context

of having such a diagnosis. Further investigation, with bigger sample sizes, is needed to replicate these findings and to further determine the neurobiological mechanisms underlying this association. Furthermore, it is unknown whether the findings reported here are specific to ADHD or generalise to other disorders where increased RTV is also observed (such as bipolar disorder, schizophrenia and autism) (Brotman et al., 2009; Kaiser et al., 2008; Karalunas et al., 2014).

# Chapter 4

# The aetiology of the association between ADHD and cognitive impairments from childhood to young adulthood

## 4.1 Abstract

**Background:** While the association between attention-deficit/hyperactivity disorder (ADHD) and cognitive impairments is well documented in both childhood and adulthood, our knowledge about the direction and aetiology of this association over time is still limited. Here, we aim to examine the direction of the association between ADHD diagnosis and cognitive performance measures from childhood to young adulthood and to explore the familial and non-familial sources of their association over time.

**Methods:** A cross-lagged model was used in a sample of 404 participants from ADHD and control sibling pairs aged 6-17 years at baseline and 12-24 years at follow-up. Cognitive measures at both time points included IQ, digit span forward (DSF) and backward (DSB), and mean reaction time (MRT) and reaction time variability (RTV) from a reaction time task with two conditions (baseline and fast-incentive conditions).

**Results:** ADHD diagnosis at baseline predicted lower IQ and DSB at follow-up, but not RTV, MRT or DSF. None of the cognitive variables assessed at baseline predicted ADHD diagnosis at follow-up. Although time-specific familial and non-familial influences emerged for each cognitive variable, the familial and non-familial

influences involved in the association between ADHD and the cognitive variables were stable across time.

**Conclusions:** Here we provide novel evidence that childhood ADHD has direct predictive effects on IQ and working memory deficits at follow-up. Persistent familial and non-familial influences seem to underlie the aetiological influences between ADHD and the investigated cognitive measures over time. Early interventions on ADHD might help in improving future IQ and working memory impairments in individuals with ADHD.

## 4.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable disorder, characterised by developmentally-inappropriate levels of inattention and hyperactivity-impulsivity (Faraone et al., 2015). ADHD affects around 5-7% of children and adolescents worldwide (Polanczyk et al., 2007; Polanczyk et al., 2014; Willcutt, 2012) and often persists into adulthood, with significant impact on individuals' everyday lives (Cheung et al., 2016; Faraone & Biederman, 2005; Thapar et al., 2007). In addition to the symptoms of inattention and hyperactivity-impulsivity, ADHD is associated with cognitive impairments, for example decreased vigilance and increased attention fluctuations across different tasks and tasks conditions (often measured with reaction time variability [RTV]), deficits in executive functions (e.g. inhibitory control, working memory) and on average lower IQs (Franke et al., 2018). Of note, previous studies have shown that incentives and faster event rates can lead to a greater improvement in RTV in children and adolescents with ADHD than in controls (Kofler et al., 2013; Kuntsi et al., 2013; Slusarek et al., 2001; Tye et al., 2016), suggesting RTV may be a malleable cognitive process (Kuntsi et al., 2009). Cross-sectional studies indicate overall similar patterns of cognitive impairments associated with ADHD in childhood, adolescence and adulthood (Franke et al., 2018).

Longitudinal studies with clinical ADHD samples assessing the prospective association between early cognitive difficulties in childhood and future ADHD outcomes are scarce. A number of studies using non-clinical childhood samples suggest that impairments in early childhood (5-6 years) in IQ and executive functions can predict ADHD symptoms in later childhood (8-9 years) (Berlin et al., 2003; Brocki et al., 2007; Campbell & von Stauffenberg, 2009). Other studies, including follow-up studies in adolescence and adulthood, found that RTV and working memory in childhood predicted ADHD symptoms and functional impairment in adolescents and young

adults (both in a clinical and a non-clinical sample; Sjöwall et al., 2015; van Lieshout et al., 2016). A follow-up study in children diagnosed with ADHD showed that IQ was the only cognitive measure in childhood that predicted ADHD symptoms and functional impairment (but not ADHD diagnosis) in adolescence and young adulthood, while measures such as working memory, inhibition, and RTV did not (Cheung et al., 2015). Overall, findings across these studies have been mixed, possibly due to differences in study design, measures, as well as differences in the definitions of ADHD applied (Franke et al., 2018). Also, these studies have investigated the prediction of early cognitive functioning on later ADHD, but not the effect of early ADHD on subsequent cognitive impairments. Knowing the direction of the predictive effects between ADHD and cognitive functioning over time could help to identify strategies to prevent negative long-term outcomes such as cognitive difficulties or aggravation of ADHD symptoms and functional impairments.

Previous twin and sibling studies have shown evidence of substantial genetic and familial risk influences underlying the cross-sectional association between cognitive functioning and ADHD symptoms or diagnosis. Population-based twin studies in children indicate substantial overlap of genetic influences between ADHD symptoms and response speed (mean reaction time [MRT]), RTV, inhibition, working-memory performance (digit span backward [DSB]), and IQ (Kuntsi, Rogers et al., 2006; Wood et al., 2011). Similarly, evidence from clinical sibling samples shows shared familial influences between ADHD and RTV, IQ, working memory and short-term memory (measured with DSB and digit span forward [DSF]) (Michelini, Cheung et al., 2018; Wood et al., 2011). Longitudinal twin studies have further shown that the relatively high stability of both ADHD symptoms and cognitive functioning, such as IQ and working memory, is mainly due to stability of genetic influences over time (Chang et al., 2013; Gustavson et al., 2018; Larsson et al., 2004; Rommel et al., 2015; Tucker-Drob & Briley, 2014). However, new aetiological influences have also been found to emerge across development on both ADHD and cognitive functioning (Chang et al., 2013; Greven et al., 2011; Larsson et al., 2004; Pingault et al., 2015; Tucker-Drob & Briley, 2014). Given this complex interplay of stable and new aetiological effects during development, stability of the aetiological influences that account for the association between ADHD and cognitive functioning over time cannot be assumed.

A cross-lagged model allows the simultaneous examination of longitudinal influences of one variable on another, and vice versa, while also controlling for concurrent associations between variables over time. Evidence using this design in relation to ADHD and cognitive functioning is still scarce. One study showed reciprocal associ-

ations between ADHD severity and overall neuropsychological functioning, assessed using a combined score across different neuropsychological tests in pre-schoolers followed up for 3 years (Rajendran et al., 2013). Another study, that looked at the association between ADHD inattentive symptoms and rapid naming speed in a longitudinal population-based sample followed-up from pre-school (4-5 years) to fourth grade (10-11 years), showed reciprocal associations between ADHD symptoms and rapid naming speed (Arnett et al., 2012). Only one study investigated the aetiological association between ADHD symptoms and cognitive abilities, specifically focusing on IQ, in a population-based twin sample at 12, 14 and 16 years using a genetically informative cross-lagged design (Rommel et al., 2015). This study showed reciprocal associations between ADHD symptoms and verbal and performance IQ over time, and provided evidence that the aetiological factors involved in the association between ADHD symptoms and verbal and performance IQ were stable over time (Rommel et al., 2015). To our knowledge, no study to date has investigated the association between ADHD and other aspects of cognitive functioning using a cross-lagged design. Furthermore, no study has been conducted in clinically diagnosed individuals with ADHD across time, while exploring the aetiological factors involved in the association between ADHD diagnosis and cognitive processes. Investigating the stability and/or change of the aetiology of the association between ADHD diagnosis and cognitive functioning across developmental stages might help to further elucidate the sources of cognitive impairments in the disorder, as well as point to treatment strategies.

The first aim of this study is to investigate longitudinally the direction of the association between ADHD diagnosis and cognitive measures (IQ, DSF, DSB, and reaction time measures of RTV and MRT from a reaction time task with baseline and fast-incentive conditions). Using data from baseline childhood and subsequent follow-up assessment in adolescence and young adulthood of 404 individuals from ADHD and control sibling pairs, we test the predictive association between ADHD and cognitive measures across the two time points. The second aim is to explore whether latent familial and non-familial influences that underlie the association between ADHD diagnosis and each cognitive impairment are stable over time.

## 4.3 Methods

### 4.3.1 Participants

Participants who had taken part in our previous research (UK-London sub-sample of the International Multicentre ADHD Genetic (IMAGE) project (Chen et al.,

2008; Kuntsi, Neale et al., 2006; Kuntsi et al., 2010) were invited to take part in this study. During the initial study, ADHD participants aged between 6 and 17 years were recruited from specialist clinics in the UK from among those who had a clinical diagnosis of DSM-IV combined subtype ADHD during childhood. The selection criteria for the IMAGE project probands was DSM-IV combined type ADHD. Childhood ADHD was assessed based on the Parental Account of Childhood Symptoms (PACS) (Taylor, Everitt et al., 1986; Taylor, Schachar et al., 1986), a semi-structured, standardised, investigator interview with high inter-rater reliability (Taylor, Everitt et al., 1986). Closest-age siblings were also then recruited and assessed for ADHD using the same procedures. A control group, which was initially recruited from primary (ages 6-11 years) and secondary (ages 12-18 years) schools in the UK (Kuntsi et al., 2010), was also assessed at baseline and follow-up. Exclusion criteria applied at the initial childhood assessment included IQ $< 70$, autism, epilepsy, general learning difficulties, 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.

At follow-up (on average 6 years after initial assessment), participants were contacted by telephone and scheduled for a single testing session including clinical, cognitive and EEG assessments. Retention rate at follow-up was 77%. The sample retained at follow-up consisted of 404 participants, including 226 participants from ADHD sibling pairs (each including one ADHD proband and one affected or unaffected sibling), and 178 participants from control sibling pairs (both without ADHD) who had taken part in our previous research (Chen et al., 2008; Kuntsi et al., 2010). Among those with childhood ADHD at baseline, 87 continued to meet clinical (DSM-IV) levels of ADHD symptoms and impairments (ADHD persisters) and 23 were below the clinical cut-off at follow-up (ADHD remitters). Three siblings of ADHD probands were unaffected in childhood but met DSM-IV ADHD criteria at follow-up. Nine controls met ADHD criteria at follow-up based on parent-reported ADHD rating. Six siblings of ADHD probands were excluded as their diagnostic status could not be determined due to missing parent-reported data on impairment. Seven childhood ADHD probands were excluded for not having combined-type ADHD in childhood or due to equipment failure. The sample, after the exclusion of participants with missing data due to equipment failure or missing information on ADHD rating, consisted of 99 participants with ADHD and 100 of their unaffected siblings (69 full pairs, 61 singletons), 23 remitters (5 full pairs, 13 singletons), and 169 control siblings (76 full pairs, 17 singletons). There were no significant differences between

the groups in age, but they differed significantly in sex, with more males in the ADHD group compared to unaffected siblings and controls and no females among remitters (Supplementary material, Table C.S1). A 48-hour ADHD medication-free period was required prior to assessments. All participants and parents provided informed consent. Study procedures were approved by the London-Surrey Borders Research Ethics Committee (09/H0806/58).

### 4.3.2 ADHD diagnosis

This study assessed presence/absence of ADHD diagnosis based on DSM-IV criteria. At baseline the PACS interview was conducted with the parents to derive the 18 DSM-IV symptoms for ADHD index cases plus siblings who were thought, on the basis of parents' descriptions of behaviour or Conner's scores of 65 or greater, to potentially have ADHD. Situational pervasiveness was defined as some symptoms occurring within 2 or more different situations from the PACS, as well as the presence of 1 or more symptoms scoring 2 or more from the DSM-IV ADHD subscale of the teacher-rated Conner's subscale. Impairment criteria were based on the severity of symptoms identified in the PACS.

At follow-up, ADHD diagnostic status was assessed with the Diagnostic Interview for ADHD in Adults (DIVA; Ramos-Quiroga et al. (2019)), a semi-structured interview designed to evaluate the DSM-IV criteria for childhood and adult ADHD. Evidence of impairment commonly associated with ADHD was assessed with the Barkley's Functional Impairment Scale (BFIS; Barkley and Murphy (2006)), by trained researchers, along with the DIVA during face-to-face interviews with parents. Parent-report DIVA and impairments were used to determine ADHD status based on DSM-IV criteria.

### 4.3.3 IQ, digit span forward and digit span backward

At baseline, the vocabulary, similarities, picture completion and block design subtests from the Wechsler Intelligence Scale for Children third edition (WISC-III; Wechsler (1991b)) were used to obtain an estimate of the child's full-scale IQ. The digit span subtest from the WISC-III was administered to obtain digit span forward (verbal short-term memory) and digit span backward (verbal working memory) (Wechsler, 1999).

At follow-up IQ was measured with the Wechsler Abbreviated Scale of Intelligence (WASI) vocabulary and block design subtests (Wechsler, 1999). Digit span

forward and digit span backward were obtained from the digit span subtests of the WASI.

### 4.3.4 The Fast task

The task was a computerised four-choice reaction time (RT) task which measures performances under a slow-unrewarded and a fast-incentive condition (Kuntsi, Rogers 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 corresponded to the position of the target. Following a response, the stimuli disappeared from the screen and a fixed inter-trial interval of 2.5 s followed. Speed and accuracy were emphasised equally. A comparison condition that used a fast event rate (fore-period of 1 s) and incentives followed immediately after the baseline condition and consisted of 80 trials, with a fixed inter-trial interval of 2.5 s following the response. Participants were told to respond as quickly as possible to win smiley faces and real prizes (£5). The smiley faces appeared below the circles in the middle of the screen when participants responded faster than their own MRT during the baseline condition consecutively for three trials and were updated continuously. The variables obtained from the task are MRT and RTV from the baseline and fast-incentive condition.

## 4.4 Statistical analyses

### 4.4.1 Model-fitting analyses

Sibling-data model fitting was accomplished by structural equation model (SEM) fitting analyses using the `OpenMx` package in R (Boker et al., 2011). As siblings share on average 50% of their segregating genes and 100% of the common environment, we can decompose the variance/covariance of traits into contributions of familial influences (the combined effects of shared genetic and shared environmental effects) and non-familial influences (individual-specific effects and measurement error; Cheung et al., 2012; Kuntsi et al., 2010). Sibling-pair data allow us to derive: phenotypic correlations in each sibling, for example the correlation between IQ and ADHD, constrained across sibling order (first or second born); cross-sibling/within-trait correlations, for example the correlation between Sibling 1 and Sibling 2 for IQ;

and cross-sibling/cross-trait correlations, constrained such that, for example the correlations between IQ in Sibling 1 and ADHD in Sibling 2 equals the correlation of IQ in Sibling 2 and ADHD in Sibling 1. These constraints are applied in order to reflect the assumptions of the familial model that cross-sibling/cross-trait correlations are independent of sibling order and that the phenotypic correlations across traits within individuals do not vary by birth order or age. The cross-sibling/within-trait and the cross-sibling/cross-trait correlations allow to estimate, respectively, the familial variance of a trait and the familial overlap between traits.

A liability threshold model framework, which assumes that the liability of a disorder is underpinned by a normally distributed continuum of risk (Rijsdijk et al., 2005), was used as the binary ADHD affection status variable was measured as present or absent. A threshold on the liability distribution is usually estimated as a z-value and represents the cut-off point to indicate the number of affected individuals in the study population. However, given the selected nature of this sample (selection based on ADHD affection status), the threshold cannot be estimated and needs to be fixed to populations-known prevalence of 5% (Willcutt, 2012; z-score set at 1.64). This also extends to other parameters of the selection variable which are all fixed to population-known values, based on previous evidence and consistent with our previous work (Cheung et al., 2012; Frazier-Wood et al., 2012; James et al., 2016; Kuntsi et al., 2010; Michelini, Cheung et al., 2018). Specifically, the cross-sibling/within-trait correlation (correlation between siblings in each pair) was fixed to 0.40 (Chang et al., 2013; Larsson et al., 2014); the familiarity to 0.40 (representing 80% genetic variance in case of null shared environmental effects; Larsson et al., 2013), and the correlation between ADHD at time 1 and at time 2 to 0.70 (Cheung et al., 2015; Rommel et al., 2015). For further explanation of this approach, see Rijsdijk et al. (2005). Since we are using cross-sectional family data to assess relationship between data over time, possible source of errors can inflate familial and non-familial estimates. In order to address this issue, the measurement error (ME) was estimated on each predicting variable (Heath et al., 1993). ME for ADHD was fixed to 0.10 based on the high reliability of parent-reported ADHD diagnosis (Izzo et al., 2019; Zhang et al., 2005). Model-fitting analyses were performed using raw data maximum likelihood estimation incorporating all available data (thus allowing no listwise/pairwise deletion when data in sibling pairs were missing). Significance of parameters was assessed by maximum-likelihood based 95% confidence intervals. Age and sex were controlled in all analyses as standard practice for family model-fitting studies (McGue & Bouchard, 1984) and in line with our previous work on the same sample (Cheung et al., 2012; James et al., 2016; Kuntsi et al., 2010; Michelini, Cheung et al., 2018). Age and

sex were controlled by regressing out age and sex effects from continuous variables (before transforming to normality). To account for positive skewness, we applied appropriate transformations to all measures in each variable prior to analyses. MRT in the baseline and fast-incentive conditions were transformed to normality using the square root transformation, while RTV in the baseline and fast-incentive condition were log-transformed. IQ, DSF, and DSB were normally distributed. Descriptive statistics for all study variables at both time points are available in Table C.S2.

### 4.4.2 Cross-lagged model

The cross-lagged model allows the examination of the direction of the association between variables across time using partial regression coefficients (phenotypic cross-lagged and stability paths), while taking into account the pre-existing relationship between variables at baseline. The model also allows us to estimate the familial and non-familial influences on each variable at each time point (time-specific familial and non-familial influences), as well as the familial and non-familial correlations between variables at each time point (time-specific familial and non-familial correlations). Further parameters include the familial and non-familial influences over time (from baseline or time 1, to follow-up or time 2), as well as the familial and non-familial associations between ADHD and cognitive functioning over time. The time-specific familial and non-familial influences, and their effects over time, do not directly address the main aims of this study but are indispensable parts of the model which are needed to assess the aetiological influences underlying the association between ADHD and cognitive impairments over time. Estimates are defined as small (<0.30), medium (0.30-0.50) and large (>0.50). Separate analyses were conducted for each pair of variables (ADHD diagnosis with IQ, DSB, DSF, MRT in each task condition, and RTV in each task condition).

### 4.4.3 Phenotypic cross-lagged and stability paths

The cross-lagged paths (Figure 4.1) connect different measures across time points (paths *c* and *d*). The regression coefficients of the cross-lagged paths are used to examine the direction of the association between ADHD and each cognitive variable (IQ, DSF, DSB, RTV in both task conditions and MRT in both task conditions) across time. If coefficient *c* is significant, ADHD at baseline predicts the cognitive measure at follow-up. If coefficient *d* is significant, the cognitive measure at baseline predicts ADHD at follow-up. If both *c* and *d* are significant, there is a reciprocal association between

variables over time. The stability paths connect the same measure across time points ($a$ and $b$) and represent the contribution of a variable at time 1 to the same variable at time 2 (e.g. the higher the coefficient, the higher the stability of a variable over time).

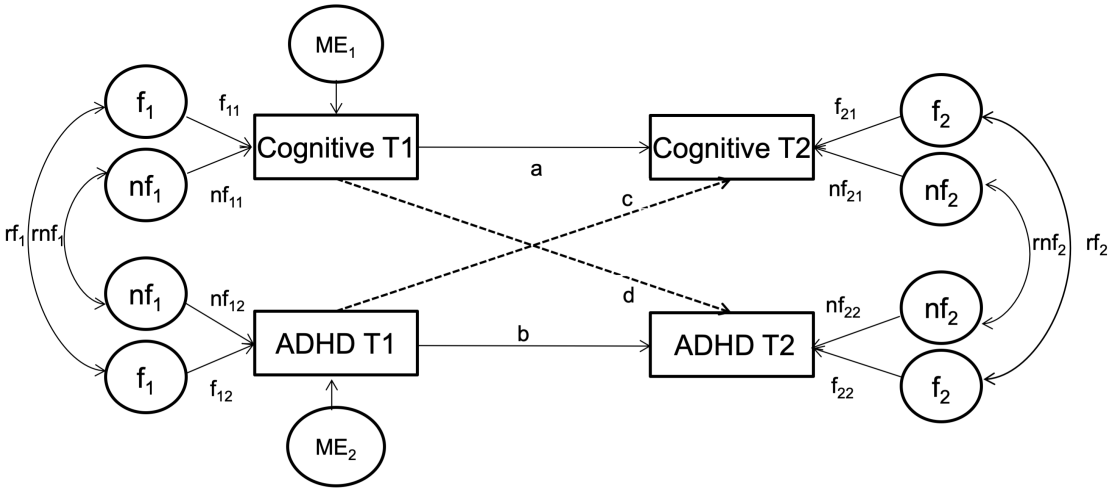


**Figure 4.1:** Cross-lagged model. *Note:* familial effects, $f$; non-familial effects, $nf$. Measurement error, ME; Attention-deficit/hyperactivity disorder, ADHD; Time 1, T1; Time 2, T2. Familial and non-familial correlations are represented by $r_f$, $r_{nf}$ respectively. Phenotypic causal path coefficients are represented by: $a$ and $b$ for stability paths and $c$ and $d$ for cross-lagged paths.

### 4.4.4 Time-specific familial and non-familial influences

At each time point, the contribution of familial and non-familial influences on DSB, DSF, MRT in both task conditions, and RTV in both task conditions are calculated, giving an estimate of the time-specific familial and non-familial influences (Figure 4.1, outer sides: $f$, $nf$). Familial and non-familial influences on ADHD diagnosis were fixed at time 1 and 2. At time 2, familial and non-familial influences on each variable are estimated as residuals, indicating the familial and non-familial contributions independent of the familial and non-familial influences transmitted from time 1 (e.g. time-specific for time 2).

### 4.4.5 Time-specific familial and non-familial correlations

Familial and non-familial correlations between ADHD and DSB, DSF, MRT in both task conditions, and RTV in both task conditions are estimated at each time point (Figure 4.1, outer sides: $r_f$, $r_{nf}$). Familial and non-familial correlations indicate the extent to which the familial and non-familial influences impacting on ADHD are the

same of those impacting on one of the cognitive variables. At time 2, familial and non-familial influences on the correlations between variables are estimated as residuals, indicating the association between the variables independent of their relationship at time 1 (time-specific for time 2).

### 4.4.6 Familial and non-familial influences over time

Variance transmitted from a variable at time 1 to one variable at time 2 will go via the stability paths (from a variable at time 1 to the same variable at time 2; $a$ or $b$), via the cross-lagged paths (from a variable at time 1 to another variable at time 2; $c$ or $d$), and via correlation paths (from the correlation between two variables at time 1 to one variable at time 2; $r_{f1}$, $r_{nf1}$). For example, for IQ at time 2 the different routes for transmitted familial effects are: $a^2 \times f_{11}^2$ divided by the total predicted variance of IQ at time 2; $c^2 \times f_{12}^2$ divided by the total predicted variance of IQ at time 2; and $2 \times (a \times f_{11} \times r_{f1} \times \sqrt{f_{12}} \times c)$ divided by the total predicted variance of IQ at time 2 (Figure 4.1). The transmitted variance due to non-familial effects follows the same logic as above and the total transmitted variance for IQ at time 2 is the sum of the three familial and three non-familial pathways. As standard procedure, we used unstandardised path coefficients to calculate these pathways or routes (e.g. Burt et al., 2005) (Table C.S3).

### 4.4.7 Familial and non-familial associations between ADHD and cognitive functioning over time

To examine the stability of familial and non-familial influences on the association between ADHD and cognitive variables over time, the covariance between ADHD and cognitive functioning was divided into covariance specific to time 2 (due to correlated residual factors; $r_{f2}$ and $r_{nf2}$) and covariance transmitted from time 1 (due to correlated familial and non-familial factors at time 1 and the causal and stability paths; $r_{f1}$, $r_{f2}$ and $a$, $b$, $c$, $d$). The transmitted covariance between ADHD and cognitive variable from time 1 (i.e. stable covariance over time) is calculated by summing all possible paths for each variable from time 1 to time 2, divided by the total covariance of ADHD and cognitive variable at time 2.

## 4.5 Results

### 4.5.1 Phenotypic cross-lagged and stability paths

Cross-lagged paths between ADHD at time 1 and IQ and DSB at time 2 were significant, as shown by the 95% confidence intervals, while cross-lagged paths between IQ and DSB at time 1 and ADHD at time 2 were non-significant (Figures 4.2 and 4.3). Cross-lagged paths between ADHD diagnosis at time 1 and all other cognitive variables at time 2, as well as between these associations in the opposite direction (cognitive variables at time 1 predicting ADHD at time 2), were non-significant (Figures C.S1 to C.S5). Stability paths for all variables were significant and moderate to large (Figures 4.2 and 4.3 and Figures C.S1 to C.S5). Stability path for ADHD was significant in each model and ranged from 0.66 to 0.73 (see Figures C.S1 to C.S5).

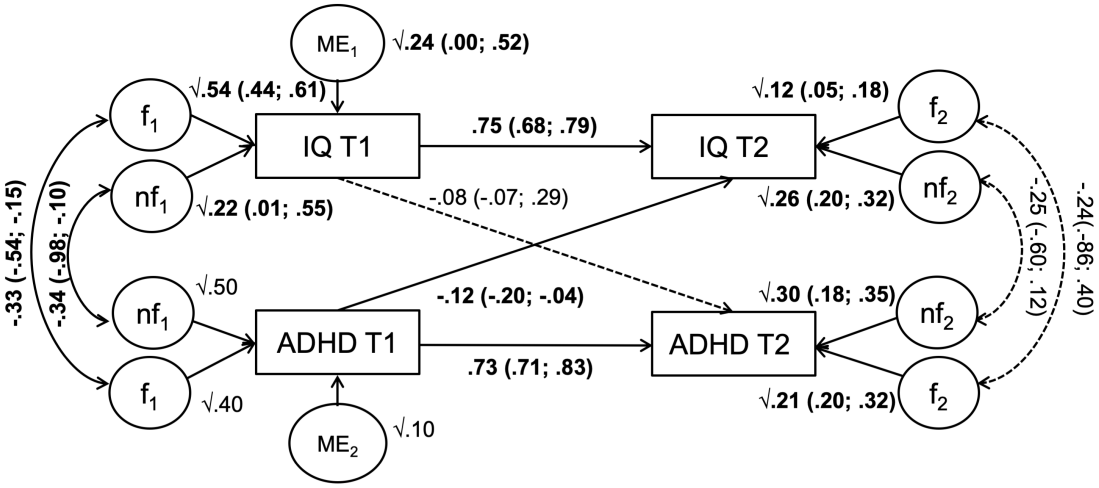


**Figure 4.2:** Path diagram with standardised effects for ADHD and IQ. *Note:* familial effects, $f$; non-familial effects, $nf$. Measurement error, ME; Attention-deficit/hyperactivity disorder, ADHD; Time 1, T1; Time 2, T2. Dotted lines represent non-significant effects; significant estimates (95% CI excluding zero) are reported in **bold**. To correct for sample selection, the $f$, $nf$ and ME effects for ADHD T1 are fixed to 40%, 50% and 10%, respectively, the stability path from ADHD T1 to T2 is fixed to 0.70, and whereas we allow the residual $f$ and $nf$ effects for ADHD at T2 to be estimated, we constrain the total (transmitted and residual) $f$ and $nf$ to be 40% and 60%, respectively.

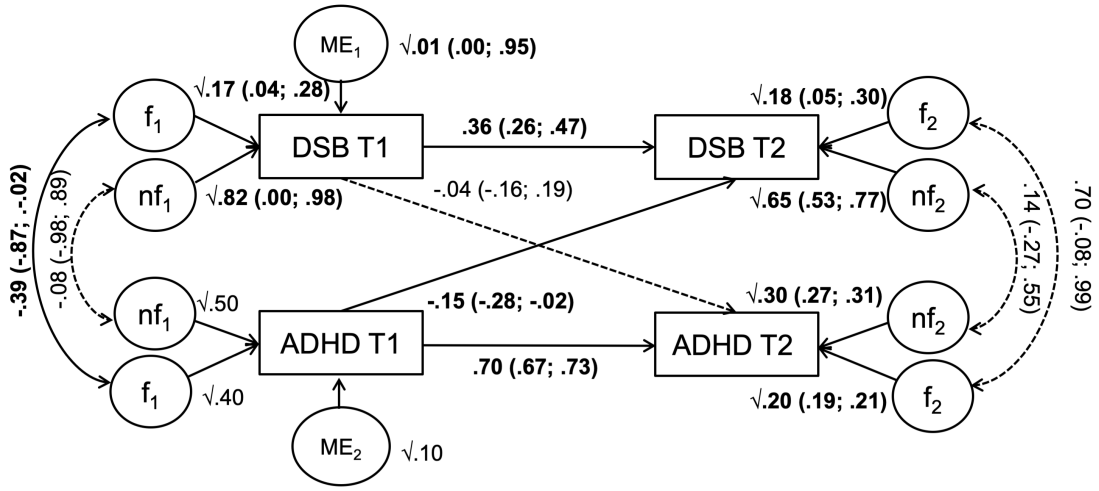


**Figure 4.3:** Path diagram with standardised effects for ADHD and Digit Span Backward (DSB). *Note:* familial effects, $f$; non-familial effects, $nf$. Measurement error, ME; Digit Span Backward, DSB; Attention-deficit/hyperactivity disorder, ADHD; Time 1, T1; Time 2, T2. Dotted lines represent non-significant estimates; significant estimates (95% CI excluding zero) are reported in **bold**. To correct for sample selection, the $f$, $nf$ and ME effects for ADHD T1 are fixed to 40%, 50% and 10%, respectively, the stability path from ADHD T1 to T2 is fixed to 0.70, and whereas we allow the residual $f$ and $nf$ effects for ADHD at T2 to be estimated, we constrain the total (transmitted and residual) $f$ and $nf$ to be 40% and 60%, respectively.

### 4.5.2 Time-specific familial and non-familial influences

Familial and non-familial influences on each variable at both time points are reported in Table 4.1. At time 1, familial influences were small for DSB, MRT in the fast incentive condition, and RTV in both conditions (ranging from 0.17 to 0.28), and moderate to large for IQ, DSF, and MRT in the baseline condition (ranging from 0.29 to 0.54). Non-familial influences were moderate to large at time 1 for all variables (ranging from 0.44 to 0.82), except for IQ which showed small non-familial influences (0.22). As reported in the methods section, familial and non-familial influences for ADHD at time 1 and for ADHD at time 2 were fixed to population-based parameters given the selected nature of this sample (40% and 60%, respectively). The total familial variance at time 2 was small for DSB, MRT and RTV both conditions (ranging from 0.18 to 0.25), while the total familial variance at time 2 for IQ and DSF was moderate (0.45 and 0.31 respectively). The total non-familial variance at time 2 was moderate to large for all variables (ranging from 0.55 to 0.82). Residual familial and non-familial influences at time 2 indicate the familial and non-familial contributions independent of the familial and non-familial influences transmitted from

time 1 (time-specific for time 2). Time-specific familial contributions for each variable at time 2 were small and ranged from 0.12 to 0.22, while time-specific non-familial contributions at time 2 were moderate to large for all variables (ranging from 0.48 to 0.70) and small for IQ (Residuals, Table 4.1). Overall, new familial and non-familial influences on cognitive impairments and ADHD emerged at time 2, which were not explained by familial and non-familial influences at time 1. The proportion of the total familial and non-familial variance at time 2 explained by time time-specific influences was high for all variables (ranging from 64% to 92% for familial influences, and from 70% to 91% for non-familial influences). Only for IQ, a small proportion of the total familial variance was explained by time-specific influences (27%), while the total non-familial variance explained by time-specific influences was moderate (47%).

**Table 4.1:** Familial and non-familial influences at both time points and proportion of total variance due to residual

| | T1 | | | T2 | |
|---|---|---|---|---|---|
| | Familial 95% CI | Non-familiar 95% CI | | Familial 95% CI | Non-familiar 95% CI |
| IQ | **0.54 (0.44; 0.61)** | **0.22 (0.01; 0.55)** **ME = 0.24** | *Total variance T2* | **0.45 (0.37; 0.52)** | **0.55 (0.47; 0.62)** |
| | | | *Residual* | **0.12 (0.05; 0.18)** **(27%)** | **0.26 (0.20; 0.32)** **(47%)** |
| DSF | **0.29 (0.17; 0.39)** | **0.49 (0.00; 0.82)** **ME = 0.22** | *Total variance T2* | **0.31 (0.18; 0.41)** | **0.69 (0.58; 0.81)** |
| | | | *Residual* | **0.22 (0.10; 0.32)** **(71%)** | **0.48 (0.38; 0.58)** **(70%)** |
| DSB | **0.17 (0.04; 0.28)** | **0.82 (0.00; 0.98)** **ME = 0.01** | *Total variance T2* | **0.22 (0.09; 0.34)** | **0.78 (0.65; 0.90)** |
| | | | *Residual* | **0.18 (0.05; 0.30)** **(82%)** | **0.65 (0.53; 0.77)** **(83%)** |
| MRT Baseline | **0.33 (0.20; 0.44)** | **0.44 (0.04; 0.79)** **ME = 0.23** | *Total variance T2* | **0.25 (0.14; 0.35)** | **0.75 (0.64; 0.85)** |
| | | | *Residual* | **0.16 (0.05; 0.27)** **(64%)** | **0.55 (0.44; 0.67)** **(75%)** |
| MRT Fast-incentive | **0.28 (0.14; 0.40)** | **0.71 (0.07; 0.85)** **ME = 0.01** | *Total variance T2* | **0.25 (0.12; 0.35)** | **0.75 (0.64; 0.87)** |

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| | T1 | | | T2 | |
|---|---|---|---|---|---|
| | Familial 95% CI | Non-familiar 95% CI | | Familial 95% CI | Non-familiar 95% CI |
| | | | *Residual* | **0.18 (0.06; 0.29) (75%)** | **0.60 (0.48; 0.72) (80%)** |
| RTV Baseline | **0.21 (0.06; 0.33)** | **0.55 (0.04; 0.92)** **ME = 0.24** | *Total variance T2* | **0.18 (0.13; 0.30)** | **0.82 (0.69; 0.93)** |
| | | | *Residual* | **0.14 (0.01; 0.27) (83%)** | **0.70 (0.58; 0.83) (87%)** |
| RTV Fast-incentive | **0.17 (0.10; 0.31)** | **0.80 (0.68; 0.99)** **ME = 0.03** | *Total variance T2* | **0.24 (0.09; 0.37)** | **0.76 (0.62; 0.98)** |
| | | | *Residual* | **0.22 (0.06; 0.36) (92%)** | **0.69 (0.56; 0.84) (91%)** |
| ADHD | 0.40 (fixed) | 0.50 (fixed) ME = 0.10 (fixed) | *Total variance T2* | 0.40 (fixed) | 0.60 (fixed) |
| | | | *Residual* | **0.20 (0.19; 0.30)** | **0.30 (0.18; 0.32)** |

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*Note:* Digit Span Forward, DSF; Digit Span Backward, DSB; Mean Reaction Time, MRT; Reaction Time Variability, RTV; Attention-deficit/hyperactivity disorder, ADHD; Measurement error, ME; Time 1, T1; Time 2, T2. Familial and non-familial influences for ADHD at T1 fixed at 0.40 (and total effects for ADHD at T2 constrained to 0.60) population values. Familial and non-familial influences for ADHD at T2 are free (here reported as the mean of the influences across models). *Residual* indicates the familial and non-familial contributions independent of the familial and non-familial contributions transmitted from T1 (time-specific for time 2). The proportion of total variance due to residual is given in brackets. **Bold** = $p < 0.05$, 95% CI not including zero.

### 4.5.3 Time-specific familial and non-familial correlations

At time 1, the familial and non-familial correlations between ADHD diagnosis and IQ, DSB, DSF, MRT in both task conditions and RTV in both task conditions are reported in Table 4.2. At time 2, the correlations between variables are estimated as residuals, indicating the association between the variables over and above their relationship at time 1 (Table 4.2). At time 1, all familial correlations between ADHD and each cognitive variable were significant and showed moderate associations (ranging from −0.39 to −0.32 for IQ, DSF, DSB; and from 0.33 to 0.48 for MRT and RTV in both task conditions) (Table 4.2). The non-familial correlation between ADHD and RTV in the fast-incentive condition was significant although small (0.25), while non-familial correlations between ADHD and IQ, MRT in both task conditions and RTV in the baseline condition were significant and showed modest to large associations (−0.34 for IQ, and ranging from 0.46 to 0.50 for MRT in both task conditions and RTV in the baseline condition). Non-familial correlations between ADHD and DSF and DSB at time 1 were non-significant.

All residual familial and non-familial correlations were non-significant at time 2. Residual non-familial correlations between ADHD at time 2 and all the investigated cognitive variables were small (ranging from −0.28 to −0.18 for IQ, DSF and MRT in the fast-incentive condition; and ranging from 0.06 to 0.14 for RTV in the fast-incentive condition, RTV and MRT in the baseline condition, and DSB). Familial correlations between ADHD at time 2, and IQ and MRT in the fast-incentive condition, were small (−0.24 and −0.02 respectively), while familial correlations between ADHD at time 2 and all the remaining variables showed moderate to large associations (−0.43 for DSF, and ranging from 0.37 to 0.70 for MRT and RTV in the baseline condition, RTV in the fast-incentive condition, and DSB). In this particular model, the fact that all residual familial and non-familial correlations at time 2 were non-significant suggests that the familial and non-familial associations between ADHD and these cognitive measures at time 2 are predominantly due to pre-existing associations at time 1 rather than to new familial and non-familial influences emerging at time 2. Non-significance of the residual familial and non-familial correlations is indicated by confidence intervals spanning zero. It should be noted that this is sometimes the case even if the point estimates are quite large (i.e. for DSB and RTV in both conditions). The fact that such large effects (e.g. 0.70) can still not have picked up as significant is due to the fact that they concern correlations between the residual variance at time 2, which is much smaller than time 1, which in turn reduces statistical power to detect significant results (e.g. illustrated by the wide confidence intervals).

**Table 4.2:** Familial and non-familial correlations between ADHD diagnosis and cognitive variables at time 1 and at time 2

| | ADHD at time 1 | | | | | |
|---|---|---|---|---|---|---|
| | Familial 95% CI | | | Non-familial 95% CI | | |
| IQ T1 | **−0.33** | **(−0.54;** | **−0.15)** | **−0.34** | **(−0.98;** | **−0.10)** |
| DSF T1 | **−0.32** | **(−0.61;** | **−0.05)** | −0.17 | (−0.89; | 0.01) |
| DSB T1 | **−0.39** | **(−0.87;** | **−0.02)** | −0.08 | (−0.98; | 0.89) |
| MRT Baseline T1 | **0.40** | **(0.14;** | **0.62)** | **0.50** | **(0.25;** | **0.80)** |
| MRT Fast-incentive T1 | **0.33** | **(0.04;** | **0.62)** | **0.30** | **(0.14;** | **0.99)** |
| RTV Baseline T1 | **0.48** | **(0.17;** | **0.90)** | **0.46** | **(0.22;** | **0.93)** |
| RTV Fast-incentive T1 | **0.43** | **(0.18;** | **0.91)** | **0.25** | **(0.10;** | **0.99)** |
| | ADHD at time 2 | | | | | |
| | Residual Familial 95% CI | | | Residual Non-familial 95% CI | | |
| IQ T2 | −0.24 | (−0.86; | 0.40) | −0.25 | (−0.60; | 0.12) |
| DSF T2 | −0.43 | (−0.69; | 0.26) | −0.18 | (−0.57; | 0.25) |
| DSB T2 | 0.70 | (−0.08; | 0.99) | 0.14 | (−0.27; | 0.55) |
| MRT Baseline T2 | 0.37 | (−0.38; | 0.97) | 0.08 | (−0.27; | 0.42) |
| MRT Fast-incentive T2 | −0.02 | (−0.79; | 0.66) | −0.28 | (−0.60; | 0.06) |
| RTV Baseline T2 | 0.59 | (−0.26; | 0.95) | 0.13 | (−0.23; | 0.47) |
| RTV Fast-incentive T2 | 0.68 | (−0.09; | 0.99) | 0.06 | (−0.31; | 0.44) |

*Note:* Digit Span Forward, DSF; Digit Span Backward, DSB; Mean Reaction Time, MRT; Reaction Time Variability, RTV; Attention-deficit/hyperactivity disorder, ADHD; Measurement error, ME; Time 1, T1; Time 2, T2. **Bold** = $p < 0.05$.

### 4.5.4 Familial and non-familial influences over time

To explore the familial and non-familial influences involved in the association between ADHD and those cognitive variables showing significant cross-lagged coefficients (IQ and DSB), we calculated the variance at time 2 due to the contribution of ADHD at time 1 (via cross-lagged path), and due to the correlation between ADHD and IQ or DSB at time 1 (via correlation path) (Table 4.3). For the other variables with non-significant cross-lagged coefficients, the familial and non-familial variance at time 2 due to the contribution of cross-lagged and correlations paths was non-significant and reported in Table C.S4.

For IQ, a high proportion of the total familial influences at time 2 was attributable to familial influences that were stable over time (73%), while 27% was due to time-specific effects that were independent of time 1 (Table 4.3). Specifically, 67% of the

**Table 4.3:** Contribution of familial and non-familial influences to IQ and DSB at time 2 via cross-lagged, stability and correlation paths

| | Familial | | Non-familial | |
|---|---|---|---|---|
| IQ total variance T2 | **0.45** | | **0.55** | |
| % of total variance due to | | | | |
| Time-specific effects at T2 | **0.12** | **(27%)** | **0.26** | **(47%)** |
| Contribution from T1 via stability path | **0.30** | **(67%)** | **0.26** | **(47%)** |
| Contribution from T1 via cross-lag path | **0.01** | **(2%)** | **0.01** | **(2%)** |
| Contribution from T1 via correlation path | **0.02** | **(4%)** | **0.02** | **(4%)** |
| Total contribution from T1* | **0.33** | **(73%)** | **0.29** | **(53%)** |
| DSB total variance T2 | **0.22** | | **0.78** | |
| % of total variance due to | | | | |
| Time-specific effects at T2 | **0.18** | **(82%)** | **0.65** | **(83%)** |
| Contribution from T1 via stability path | **0.02** | **(10%)** | **0.11** | **(14%)** |
| Contribution from T1 via cross-lag path | **0.01** | **(4%)** | **0.01** | **(1.5%)** |
| Contribution from T1 via correlation path | **0.01** | **(4%)** | 0.01 | (1.5%) |
| Total contribution from T1* | **0.04** | **(18%)** | **0.13** | **(17%)** |

*Note:* Digit Span Backward, DSB; Time 1, T1; Time 2, T2. *The total transmitted variance from time 1 for each measure, is calculated by summing the contributions via the three pathways (stability, cross-lagged and correlation paths). **Bold** = $p < 0.05$.

familial influences on IQ at time 1 contributed to the total familial variance of IQ at time 2; 2% of the familial influences on ADHD at time 1 contributed to the total familial variance of IQ at time 2; and 4% of the familial influences that accounted for the covariation between ADHD and IQ at time 1, contributed to the total familial variance of IQ at time 2. The proportion of the total non-familial influences at time 2 for IQ that was due to time-specific effects was 47%, while 53% was due to stable non-familial influences. Specifically, 47% of the non-familial influences on IQ at time 1 contributed to the total non-familial variance of IQ at time 2; 2% of the non-familial influences on ADHD at time 1 contributed to the total non-familial variance of IQ at time 2; and 4% of the non-familial influences that accounted for the covariation between ADHD and IQ at time 1, contributed to the total non-familial variance of IQ at time 2.

For DSB, a high proportion of the total familial influences at time 2 was attributable to time-specific familial influences (82%), while 18% was due to familial effects that were stable over time (Table 4.3). Specifically, 10% of the familial influences on DSB at time 1 contributed to the total familial variance of DSB at time 2; 4% of the familial influences on ADHD at time 1 contributed to the total familial variance of DSB at time 2; and 4% of the familial influences that accounted for the covariation

between ADHD and DSB at time 1, contributed to the total familial variance of DSB at time 2. A high proportion of non-familial influences at time 2 for DSB was due to time-specific effects (83%), while 17% was due to stable non-familial influences. Specifically, 14% of the non-familial influences on DSB at time 1 contributed to the total non-familial variance of DSB at time 2; 1.5% of the non-familial influences on ADHD at time 1 contributed to the total non-familial variance of DSB at time 2, and 1.5% of the non-familial influences that accounted for the covariation between ADHD and DSB at time 1, contributed to the total non-familial variance of DSB at time 2 (although the non-familial correlation between ADHD and DSB was non-significant).

### 4.5.5 Familial and non-familial associations between ADHD and cognitive variables over time

Familial and non-familial associations between ADHD and cognitive variables over time are reported in Table 4.4. At time 2, the familial covariation between ADHD and IQ showed a high proportion of stable effects (62% stable effects vs 38% time-specific effects), while the non-familial covariation between ADHD and IQ showed equal proportions of stable vs time-specific effects (49% time-specific effects vs 51% stable effects). The familial and non-familial covariation at time 2 between ADHD and DSB showed a high degree of time-specific effects (70% time-specific effects vs 30% stable effects for familial covariation, and 75% time-specific effects vs 25% stable effects for non-familial covariation). The familial and non-familial covariation at time 2 between ADHD and DSF showed a high proportion of time-specific effects (69% time-specific effects vs 31% stable effects for familial covariation, and 77% time-specific effects vs 23% stable effects for non-familial covariation). At time 2, both the familial covariations between ADHD and MRT in the baseline condition and between ADHD and MRT in the fast-incentive condition showed equal contribution of stable and time-specific effects (48% time-specific effects vs 52% stable effects for MRT in the baseline condition, and 51% time-specific effects vs 49% stable effects for MRT in the fast-incentive condition). Both the non-familial covariations between ADHD and MRT in the baseline condition and between ADHD and MRT in the fast-incentive condition showed high contribution of stable effects at time 2 (77% stable effects vs 23% time-specific effects for MRT in the baseline condition, and 67% stable effects vs 33% time-specific effects for MRT in the fast-incentive condition). An equal contribution of stable vs time-specific effects was attributable to the covariation between ADHD and RTV in the baseline condition at time 2 (57% time-specific effects vs 43% stable effects), while the non-familial covariation between

**Table 4.4:** Familial and non-familial associations between ADHD and cognitive variables specific for time 2 and transmitted from time 1

| | ADHD at time 2 | | | |
|---|---|---|---|---|
| | Familial | | Non-familial | |
| IQ T2 | | | | |
| Total covariance | 0.45 | | 0.55 | |
| Specific effects at T2 | 0.17 | (38%) | 0.27 | (49%) |
| Contribution from T1 | **0.28** | **(62%)** | **0.28** | **(51%)** |
| DSF T2 | | | | |
| Total covariance | 0.61 | | 0.39 | |
| Specific effects at T2 | 0.42 | (69%) | 0.30 | (77%) |
| Contribution from T1 | **0.19** | **(31%)** | 0.09 | (23%) |
| DSB T2 | | | | |
| Total covariance | 0.60 | | 0.40 | |
| Specific effects at T2 | 0.42 | (70%) | 0.30 | (75%) |
| Contribution from T1 | **0.18** | **(30%)** | 0.10 | (25%) |
| MRT Baseline T2 | | | | |
| Total covariance | 0.48 | | 0.52 | |
| Specific effects at T2 | 0.23 | (48%) | 0.12 | (23%) |
| Contribution from T1 | **0.25** | **(52%)** | **0.40** | **(77%)** |
| MRT Fast-incentive T2 | | | | |
| Total covariance | 0.49 | | 0.51 | |
| Specific effects at T2 | 0.25 | (51%) | 0.17 | (33%) |
| Contribution from T1 | **0.24** | **(49%)** | **0.34** | **(67%)** |
| RTV Baseline T2 | | | | |
| Total covariance | 0.47 | | 0.52 | |
| Specific effects at T2 | 0.27 | (57%) | 0.16 | (31%) |
| Contribution from T1 | **0.20** | **(43%)** | **0.36** | **(69%)** |
| RTV Fast-incentive T2 | | | | |
| Total covariance | 0.64 | | 0.36 | |
| Specific effects at T2 | 0.47 | (73%) | 0.09 | (25%) |
| Contribution from T1 | **0.17** | **(27%)** | **0.27** | **(75%)** |

*Abbreviations:* Digit Span Forward, DSF; Digit Span Backward, DSB; Mean Reaction Time, MRT; Reaction Time Variability, RTV; Attention-deficit/hyperactivity disorder, ADHD; Measurement error, ME; Time 1, T1; Time 2, T2. **Bold** = $p < 0.05$.

ADHD and RTV in the baseline condition at time 2 showed high contribution of stable effects (69% stable effects vs 31% time-specific effects). At time 2, the familial covariation between ADHD and RTV in the fast-incentive condition showed a high degree of time-specific effects (73% time-specific effects vs 27% stable effects), while

the non-familial covariation between ADHD and RTV in the fast-incentive condition showed a high proportion of stable effects (75% stable effects vs 25% time-specific effects).

Although the covariation between ADHD and cognitive variables at time 2 showed both stable and time-specific effects, the residual estimated correlations between ADHD and each cognitive variable were non-significant, suggesting that only stable effects significantly influence the association between ADHD and the cognitive measures at time 2. As reported in subsection 4.5.3, non-significance of the residual familial and non-familial correlations showing large correlation estimates (e.g. DSB and RTV in both conditions) might be due to low power.

## 4.6 Discussion

Using longitudinal assessments of ADHD diagnosis and cognitive variables in affected and control sibling pairs, we found that ADHD diagnosis in childhood and adolescence predicts lower IQ scores and impaired working memory, but not short-term memory, RTV and MRT, at follow-up six years later. None of the cognitive variables measured in childhood and adolescence predicted ADHD diagnosis at follow-up. The shared familial and non-familial effects influencing the associations between ADHD and cognitive measures in childhood showed stability over time, although time-specific familial and non-familial influences emerged for ADHD and each cognitive impairment at follow-up.

In this study, we provide evidence that ADHD diagnosis at baseline predicts impaired working memory in adolescence and young adulthood, over and above their relationship in childhood, suggesting that childhood ADHD can have a negative impact on future working memory performance. One possible interpretation might be that children with ADHD, compared to controls, have more difficulties in paying attention and suppressing distractors while performing a task, and, as a consequence, encoding, retrieval and processing of task information is more difficult, leading to impaired working memory performance (Kofler et al., 2010). We further show evidence that ADHD in childhood predicts lower IQ scores at follow-up, while childhood IQ did not predict subsequent ADHD diagnosis. This result extends a previous study which reported, using a subset of this sample (only the childhood ADHD group), that IQ at baseline predicted future continuous ADHD symptoms and impairments, but was not a predictor of future ADHD diagnosis (i.e. persistence or remission), although this latter finding was probably related to low power due

to the small number of ADHD remitters ($n = 23$) (Cheung et al., 2015). Similarly to Cheung et al. (2015), our findings that IQ at baseline was not a predictor of future ADHD diagnosis might be explained by the low number of participants whose ADHD status changed over time. Results showing a significant predictive association between ADHD diagnosis at baseline and IQ at follow-up further extend the work by Cheung et al. (2015). The evidence that IQ is a predictor of continuous symptoms of ADHD was also reported in a population-based study which showed that ADHD symptoms and verbal and performance IQ reciprocally predicted each other over time (Rommel et al., 2015). Our study did not show reciprocal associations between ADHD diagnosis and IQ over time, but only an effect from baseline ADHD diagnosis to future IQ. Since the sample used in this study is relatively smaller compared to the population-based sample used in Rommel et al. (2015) the lack of reciprocal association might be due to low power or to the use of categorical data used in this study instead of continuous ADHD symptoms as in Rommel et al. (2015).

While investigating the relationship between ADHD and cognitive variables over time, we further showed that, despite the strong phenotypic and familial association of ADHD with the further impairments on DSB, DSF, MRT and RTV in our previous cross-sectional analyses of this sample at both time points (Kuntsi et al., 2010; Michelini, Cheung et al., 2018), none of these cognitive measures in childhood and adolescence predicted subsequent ADHD diagnosis. These results are in line with previous evidence that such cognitive measures do not predict ADHD symptoms and impairments as reported in the subset of this sample used in Cheung et al. (2015). Also, here we provide further evidence that ADHD was not a predictor of DSF, MRT and RTV (in either task condition). This pattern suggests that short-term memory, MRT and RTV co-occur with ADHD without influencing its outcome over time. However, given the low number of participants whose ADHD status changed over time, our analyses might be underpowered, and those results warrant future replications. Of note, we previously showed that RTV at follow-up was comparable between those with remitted ADHD and controls but reduced compared to ADHD persisters, suggesting that RTV might be a marker of ADHD remission, while this pattern was not observed for DSF and DSB (Cheung et al., 2016; James et al., 2017; Michelini, Kitsune, Cheung et al., 2016). The latter finding, together with the findings that ADHD and RTV co-occur with no reciprocal influence over time, highlights that RTV might represent an objective measure of the attention fluctuations related to the core ADHD symptoms of inattention.

For both of the cognitive measures that showed significant negative predictive association with ADHD over time (IQ and DSB), we investigated further their

relationship with ADHD at follow-up by assessing the contribution of familial and non-familial influences attributable to ADHD and to the association with ADHD at baseline. Specifically, our results show that a small but significant proportion of the familial and non-familial influences for IQ and DSB at follow-up was accounted for by ADHD at baseline and by the association between ADHD and such cognitive impairments at baseline. Specifically, for IQ at follow-up, an equal contribution of familial and non-familial influences was attributable to ADHD (2% each), and to the relationship between ADHD and IQ at baseline (4% each). For DSB at follow-up, 4% familial and 1.5% of non-familial influences were attributable to ADHD at baseline, while 1.5% of the familial influences (but not non-familial influences) were attributable to the relationship between ADHD and DSB at baseline. Overall, these results provide evidence of ways in which the baseline association between ADHD and IQ, or between ADHD and DSB, might influence IQ or DSB over time.

We further assessed the stability or change of the familial and non-familial influences on the association between ADHD and cognitive measures over time. Our results show that the negative association between ADHD and each investigated cognitive variable at follow-up was attributable to stable familial and non-familial influences from baseline (except non-familial influences for DSB and DSF). This result was supported by the significance of the correlations at baseline and at follow-up, since only significant correlations at baseline can show stability over time, while significance of the correlations at follow-up would suggest significance of new time-specific effects at follow-up. At baseline, familial and non-familial correlations between ADHD and all cognitive variables were significant, except for the non-familial correlations between ADHD and DSB and DSF. The results for IQ, RTV and MRT replicate previous familial correlations reported in cross-sectional analyses in this sample (Wood et al., 2011). The findings for DSB and DSF are novel and indicate that these measures show significant familial correlations with ADHD, while the non-familial correlations are non-significant (and therefore could not show significant stability over time). This pattern suggests that the association between ADHD and short-term and working memory might be primarily influenced by familial effects, while non-familial effects might play a minor or negligible role. All familial and non-familial correlations became non-significant at follow-up, despite previous evidence on the same sample at follow-up showing significant familial associations between ADHD and these measures (Michelini, Cheung et al., 2018). Correlation estimates reported here at follow-up are residuals, indicating the associations between variables independently of their associations at baseline, therefore suggesting that the new aetiological influences emerging after six years might not contribute significantly to the association between

ADHD and cognitive impairments and that these associations are accountable by stable effects only. However, given the wide confidence intervals, these familial and non-familial correlations at follow-up should be interpreted cautiously. Overall, future studies using larger samples will be required to examine these associations between ADHD and cognitive impairment over time further.

The following limitations should be considered when interpreting these findings. First, given that this study focuses on sibling data only, it allowed the investigation of familial and non-familial effects, but we could not directly estimate the contribution of genetic factors. However, as previous evidence suggests a limited role of shared-environmental influences on either ADHD (Burt, 2009; Burt et al., 2012) or cognitive markers (Anokhin et al., 2008; Kuntsi et al., 2013), the familial overlap between ADHD and such markers is expected to largely reflect genetic influences. Another limitation of this study is the wide age range. Future studies using more restricted age ranges and, ideally, multiple follow-ups should replicate and extend the current results. Finally, IQ at baseline was calculated with four subtests of the WISC-III (vocabulary, similarities, picture completion and block design), while at follow-up was calculated with two subtests of the WASI (vocabulary and block design).* The WASI subtests and items parallel their counter parts in the WISC-III, so comparable constructs are measured across tests (Wechsler, 1999). Although different subtests were used to calculate IQ between time points, across the Wechsler scales, IQ measured with four subtests is highly correlated with IQ measured with two subtests (mean correlation coefficient of 0.94), and those measures are therefore comparable (Wechsler, 1999).

In conclusion, our findings indicate that childhood ADHD predicts future IQ and working memory in adolescence and young adulthood, but not measures of attention fluctuation, response speed and short-term memory. We further provide evidence of stability of familial and non-familial effects influencing the association between ADHD and cognitive measures over time, which requires replications in bigger samples. Overall, these novel results show that childhood ADHD has direct predictive effects on IQ and working memory deficits in adolescents and young adulthood, over and above the association between these measures in childhood. A potential clinical implication from these findings, which should be tested in future studies, is that early intervention strategies for childhood ADHD may help ameliorate long-term impairments in IQ and working memory.

*Note: Due to COVID-19 restrictions, access to data and materials to calculate IQ at baseline with two subtests was not available; analyses were therefore run with the data for IQ that were available at baseline.

# Chapter 5

# Attention regulation in women with ADHD and women with bipolar disorder: An ex-Gaussian approach

Psychiatry Research 285 (2020) 112729

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

# Attention regulation in women with ADHD and women with bipolar disorder: An ex-Gaussian approach

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ARTICLE INFO

*Keywords:*
Attention-deficit/hyperactivity disorder (ADHD)
Bipolar disorder (BD)
Attention
ex-Gaussian decomposition
Reaction time (RT)
Reaction time variability (RTV)

ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD) show certain overlapping features, such as increased reaction time variability. Here, we tested whether more detailed ex-Gaussian reaction time distribution measures identify shared or disorder-specific impairments in ADHD and BD. The total assessed sample consisted of 60 women (20 each in ADHD, BD and control groups). We compared the groups on ex-Gaussian measures of mu, sigma, and tau from a flanker task (congruent and incongruent conditions), an oddball task, and a four-choice reaction time task (baseline and fast-incentive conditions of the `fast task'). The ex-Gaussian measures mu and sigma reflect the speed and variability of typical responses, while tau captures variability in infrequent slow responses. Compared to controls, both ADHD and BD groups showed significantly increased tau in the fast task baseline condition. Participants with BD further showed a significantly increased sigma compared to ADHD and control groups in the flanker task incongruent condition. Our findings indicate that the ex-Gaussian approach is informative in detecting shared and disorder-specific cognitive impairments in ADHD and BD that may represent objective markers of these two disorders.

## 1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BD) are common psychiatric conditions in adults, affecting 2–4% and 1–2% of the worldwide population, respectively (Merikangas et al., 2011; Willcutt, 2012). Cross-disorder comparisons point to a degree of symptomatic overlap, such as in restlessness, accelerated speech, inability to maintain concentration and distractibility, which can lead to difficulties in the differentiation of the two disorders (Asherson et al., 2014; Kitsune et al., 2016). Cognitive measures may aid in the identification of impairments underlying both overlapping and disorder-specific symptoms.

One of the most consistently reported cognitive impairments in individuals with ADHD, across many cognitive tasks, is increased reaction time variability (RTV) (Kofler et al., 2013; Kuntsi and Klein, 2012), which is commonly measured with the standard deviation of reaction times (SD-RT) and has been linked to the neural mechanisms underlying attention allocation (Cheung et al., 2017). A number of studies have also reported increased RTV in adults with BD, compared to controls (Brotman et al., 2009; Gallagher et al., 2015; Moss et al., 2016). In a direct comparison of adults with ADHD and adults with BD, we recently reported that both clinical groups, compared to controls, showed increased RTV on a four-choice RT task (the `fast task') (Michelini et al., 2018). Yet, during a cued continuous performance task (CPT-OX), only the BD group showed a significantly increased RTV, while the ADHD group showed a marginal difference (Michelini et al., 2016). No impairments in RTV emerged in either clinical group during an arrow flanker task (Carruthers et al., under review). Overall, we detected shared impairments in participants with ADHD and those with BD when performing a less cognitively engaging task (the fast task), whereas in a more cognitively demanding task (CPT-OX) impairments emerged more clearly in the BD group. This suggests that the increased RTV in the clinical groups might be related to task differences (e.g. cognitive demand and event rates).

Despite high RTV being a common finding in ADHD, it is indeed an impairment that shows some malleability: incentives and faster event rates can lead to a greater improvement in RTV in children and adolescents with ADHD than in controls (Kofler et al., 2013; Kuntsi et al., 2013; Slusarek et al., 2001; Tye et al., 2016). Evidence of RTV malleability in individuals with BD is still scarce. In our recent study on

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https://doi.org/10.1016/j.psychres.2019.112729
Received 7 June 2019; Received in revised form 3 December 2019; Accepted 3 December 2019
Available online 06 December 2019
0165-1781/ 

adults, although RTV significantly improved from a baseline to a faster and rewarded condition of the fast task both in adults with ADHD and with BD, the improvement was not greater in ADHD or BD participants compared to controls (Michelini et al., 2018).

While the majority of the studies have investigated reaction times (RTs) using the mean (MRT) and standard deviation, which represent global indices to assess response speed and variability in task performance, RTs can be further decomposed into more detailed measures using ex-Gaussian models (Luce, 1991). The ex-Gaussian approach decomposes the RT distribution into a normal (Gaussian) component and an exponential (ex-Gaussian) component, with the latter reflecting the positive skew generally observed in RT distributions (Hervey et al., 2006). In this way, ex-Gaussian analyses allow us to derive three summary parameters: mu (the mean of the Gaussian component), sigma (the SD of the Gaussian component) and tau (the variability of the exponential component) (Hervey et al., 2006; Luce, 1991). The distribution of faster responses is indexed by mu and sigma, while the infrequent, slow RTs, which lengthen the positive tail of the distribution, are indexed by tau (Leth-Steensen et al., 2000; Luce, 1991; Vaurio et al., 2009). Overall, mu and sigma can be defined as speed and variability of typical responses, and tau as the infrequent slow responses, with the latter representing a more detailed measure to investigate lapses of attention.

Using the ex-Gaussian approach, studies using different sustained attention tasks have reported increased tau in children, adolescents and adults with ADHD compared to controls (Gmehlin et al., 2014; Hervey et al., 2006; Lee et al., 2015; Leth-Steensen et al., 2000; Vaurio et al., 2009; Wolfers et al., 2015). Only one study did not observe increased tau in ADHD children compared to controls (Geurts et al., 2008); however, the two-choice RT task lasting 3 min used in this study may have been too short to detect tau. For sigma and mu, the findings are less consistent, with some studies reporting increased sigma (Buzy et al., 2009; Gmehlin et al., 2014; Hervey et al., 2006; Vaurio et al., 2009) or decreased mu (Hervey et al., 2006; Lee et al., 2015; Wolfers et al., 2015) in participants with ADHD compared to controls, while other studies have failed to find case-control differences in sigma (Epstein et al., 2011; Lee et al., 2015; Leth-Steensen et al., 2000) and mu (Epstein et al., 2011; Lee et al., 2015; Leth-Steensen et al., 2000; Vaurio et al., 2009). These inconsistent results may relate to task differences, for example in cognitive demand (Hervey et al., 2006; Vaurio et al., 2009). Overall, the findings suggest that the increased SD-RT usually observed in individuals with ADHD is mostly explained by the infrequent slow responses measured with tau. This aligns with the effect sizes reported in a recent meta-analysis, which were significantly bigger for tau compared to sigma, but not different between SD-RT and tau (Kofler et al., 2013).

Fewer studies have examined the ex-Gaussian measures in relation to BD. One study indicated increased tau on a sustained attention task in adults with BD, compared to controls, during the euthymic phase, and increased tau and sigma during the depressive phase (Gallagher et al., 2015). However, in another study, euthymic participants with BD had increased sigma, but not tau, compared to controls, while performing a version of the CPT with high event rate and low target frequency that is considered to be more cognitive demanding (Moss et al., 2016). The inconsistent results between these two studies can be explained by differences in experimental conditions (Moss et al., 2016). Overall, whereas the studies on ADHD suggests that tau is the most sensitive measure to capture case-control differences, the studies available on BD suggest that increased tau may be limited to certain cognitive tasks only. The ex-Gaussian approach, by isolating RTs into different components, can help in the identification of more detailed processes underlying cognitive performance.

Given the overlap of increased RTV, measured with SD-RT, between ADHD and BD while performing some tasks but not others (Michelini et al., 2016, 2018; Carruthers et al., under review), we now aim to investigate whether more detailed ex-Gaussian measures help in better delineating shared or disorder-specific impairments between ADHD and BD. In order to investigate the specificity of these impairments to different tasks and task conditions, we use data from three different cognitive tasks (the flanker task, an auditory oddball task, and the fast task). We used an all-female sample to match the groups on gender; ADHD and BD in adults shows a relatively equal sex ratio (Das et al., 2012; Pini et al., 2005) .

Although we focus on `pure' groups of adults with ADHD or BD (who do not have comorbid ADHD and BD), the possibility remains of subthreshold symptoms of the other disorder; to address this, we additionally examine whether the shared cognitive impairments observed in adults with ADHD and adults with BD may be explained by subthreshold symptoms of the other disorder. For this study, we will consider shared impairments those impairments that are present in both clinical groups compared to controls, and disorder-specific impairments those that are present only in one of the two clinical groups, compared to controls, and that distinguish between the clinical groups.

## 2. Materials and methods

### 2.1. Sample

The total assessed sample consisted of 60 adult women (20 with ADHD, 20 with BD and 20 controls) aged between 20 and 52 years. Mean age and IQ did not differ by group (see supplementary material, Table S1). Participants with ADHD were recruited from the National Adult ADHD Clinic at the Maudsley Hospital, where any female cases meeting inclusion criteria were considered for potential inclusion in the study. Participants with BD were recruited from the Maudsley Psychosis Clinic from a sample that had previously taken part in another study (Hosang et al., 2012). Controls were recruited from the Mindsearch volunteer database maintained by the Institute of Psychiatry, Psychology and Neuroscience, King's College London, and randomly selected from all those meeting recruitment criteria for this study.

Diagnosis in the clinical groups was confirmed by checking medical records for details of diagnosis and psychiatric history, following DSM-IV criteria. Exclusion criteria for all groups were drug or alcohol dependency in the last 6 months, autism, epilepsy, neurological disorders, brain injury, past ECT treatment, current involvement in another research trial likely to alter symptom severity, pregnancy or a limited proficiency in English language. Individuals with ADHD and individuals with BD with a reported comorbidity of both ADHD and BD were also excluded. Individuals with BD group who were experiencing a manic episode at the time of the assessment were excluded; only participants who were euthymic at the time of participation were included in the BD group. Control participants who reported a history of psychiatric disorders or who were taking psychiatric medication, were excluded from the study. Comorbidity in the clinical groups and lack of psychiatric disorders in the control group were further assessed through gold-standard clinical evaluations when participants took part in this study. An ADHD diagnosis was excluded in the BD group after conducting the Diagnostic Interview for Adult ADHD (DIVA v. 2.0; (Ramos-Quiroga et al., 2016) and the self-rated 18-item Barkley Adult ADHD rating scale (BAARS-IV) (Barkley, Murphy, 2006). BD diagnosis was excluded in the ADHD group by checking for a history of past episodes of depression or hypomania/mania and evaluating current mood symptoms using the Altman Self-Rating Mania Scale (ASRM) (Altman et al., 1997) and the Beck Depression Inventory (BDI) (Beck et al., 1996), and current and lifetime history of mania using the Young Mania Rating Scale (YMRS) (Young et al., 1978).

Participants in the ADHD group had a current combined-type diagnosis or an inattentive-type diagnosis with sufficient symptoms of hyperactivity-impulsivity in childhood to meet a childhood combined-type diagnosis, reflecting the typical adult ADHD clinical population (Asherson et al., 2014). Participants in the BD group had a diagnosis of BD Type I, having experienced at least one manic episode lasting 1

week or more in the past, but were euthymic at the time of the assessments. Full information on clinical profiles of ADHD and BD on all clinical measures can be found in Kitsune et al. (2016), except for the BAARS-IV total scores, which are reported in supplementary material (Table S2). Briefly, the ADHD and BD groups did not differ from each other and from controls on mania symptoms (mania symptoms according to the ASRM: mean = 4.63, SD = 3.98 in the ADHD group; mean = 4.95, SD = 5.03 in the BD group; mean = 2.42, SD = 2.09 in the control group). Depression symptoms were significantly higher in the ADHD and BD groups compared to controls, with no difference between the two clinical groups (symptoms of depression according to the BDI: mean = 17.50, SD = 15.54 in the ADHD group; mean = 11.90, SD = 11.11 in the BD group; mean = 4.35, SD = 4.03 in the control group). More information on the clinical measures used for this sample is reported in supplementary material.

### 2.2. Procedure

Participants attended a single 4.5-h research session (including breaks) for cognitive-EEG assessment, IQ assessment and clinical interviews. All participants were asked to refrain from caffeinated drinks and nicotine 2 h before assessments. Participants with ADHD were asked to stop taking any stimulant medication prescribed for their ADHD 48 h prior to the assessment. On the day of the assessments, all ADHD participants who were taking stimulant medication ($n$ = 13) confirmed that they had stopped medication in the preceding 48 h. For ethical reasons, participants were not asked to stop taking mood stabilizers (70% of the BD group), anti-psychotic medication (40% of the BD group) or anti-depressants (7% of the ADHD group and 25% of the BD group) they had been prescribed. Ethical approval for the study was granted by the Camberwell St Giles Research Ethics Committee (approval number 11/LO/0438) and all participants provided informed consent.

### 2.3. Arrow flanker task

The task was an adaptation of the Eriksen flanker paradigm designed to increase cognitive load used in previous studies (Albrecht et al., 2008; McLoughlin et al., 2014, 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 the arrow pointed toward 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 pointed in either 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. Two hundred congruent and 200 incongruent trials were arranged in 10 blocks of 40 trials over 13 min.

### 2.4. Auditory oddball task

Participants completed an auditory novelty oddball task adapted from Laurens et al. (2005). The task had a total duration of 12 min and consisted of 300 frequent non-target stimuli (1000 Hz tone), 50 infrequent target stimuli (1500 Hz tones) and 50 infrequent, unique, non-repeating novel stimuli, which included digital noises (whistles, buzzes and trills). The non-target, target and novel stimuli were presented with a probability level of 0.75, 0.125, and 0.125. All stimuli had a duration of 200 ms, with 5 ms rise / 10 ms fall, and were separated with a random inter-trial interval of between 1000–1500 ms (average 1250 ms). The order of presentation was pseudorandom, while ensuring that no two low probability stimuli (target or novel) occurred consecutively. Stimuli were presented in eight blocks of 50 stimuli, with a short rest period between each block. Total task duration was approximately 12 min. Presentation of stimuli was via headphones at 90 dB sound pressure level. During recording participants were asked to sit still with their eyes-open and focused on a static fixation mark on a screen directly in front of them. Participants responded to targets by pressing a button with the thumb of their dominant hand. They were instructed to respond as quickly as possible to target stimuli, and not to respond to the infrequent novel and frequent non-target stimuli. Prior to recording, participants familiarised with the paradigm using a 35-s practice session to ensure comprehension. Responses to target stimuli within 100–1000 ms from onset were counted as correct response; failure to respond within this time window was registered as an omission error.

### 2.5. Fast task

The fast task is a computerized four-choice RT task which measures performances under a slow-unrewarded and a fast-incentive condition (Andreou et al., 2007; Kuntsi et al., 2006). In both conditions speed and accuracy were emphasized equally. The baseline (slow unrewarded) condition followed a standard warned four choice reaction-time task. A warning signal (four empty circles, arranged side by side) first appeared on the screen. At the end of the fore-period lasting 8 s (presentation interval for the warning signal), the circle designated as the target signal for that trial was filled (coloured) in. The participant 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. If the participant did not respond within 10 s, the trial terminated. First, a practice session was administered, during which the participant had to respond correctly to five consecutive trials. The baseline condition consisted of 72 trials. To investigate the extent to which a response style characterized by slow and variable speed of responding may be reduced, the task includes a comparison condition that uses a fast event rate (fore-period of 1 s) and incentives. This condition started immediately after the baseline condition and consisted of 80 trials, with a fixed inter-trial interval of 2.5 s following the response. The participants were told to respond as quickly as possible to each target, in order to win smiley faces and earn real prizes at the end. Participants won a smiley face for responding faster than their own MRT during the baseline (first) condition consecutively for three trials. The smiley faces appeared below the circles in the middle of the screen and were updated continuously. The fast-incentive condition was always administered after the baseline condition and, as such, did not involve a similar learning phase. Participants earned £5 in cash after the task battery.

### 2.6. Task performance parameters

We applied ex-Gaussian deconvolution to RT data employing a maximum-likelihood algorithm (Heathcote et al., 2004) implemented in the QMPE software (http://newcl.org/software/qmpe.htm). This algorithm measures the mean of the normal component of the RT distribution (mu) and divides the SD-RT into its normal (sigma) and exponential (tau) components. Only participants with accurate and plausible responses (> 150 ms) (Adamo et al., 2018), and who responded correctly in at least 40 trials in each task were included to ensure the correct extraction of the ex-Gaussian measures (Heathcote et al., 2002). To account for positive skewness, we applied appropriate transformations to all measures in each task prior to analyses. In the flanker task and in the oddball task we used a logarithm transformation for all variables; in the fast task we used a logarithm transformation for mu and tau and a square root transformation for sigma. For the oddball task, in addition to the ex-Gaussian variables, we report results also for MRT and RTV as these have not been reported

previously, unlike for the other two tasks (Carruthers et al., under review; Michelini et al., 2018).

### 2.7. Statistical analyses

In the arrow flanker task and in the fast task ex-Gaussian variables were investigated using random intercept linear models (i.e. multilevel regression models). Main effects of group (ADHD vs BD vs control), condition (baseline vs fast-incentive in the fast task, and congruent vs incongruent in the arrow flanker task), and group-by-condition interactions were examined. Significant ($p < 0.05$) main group effects were followed up with post-hoc comparisons between groups separately in the baseline and fast-incentive conditions of the fast task, and in the congruent and incongruent conditions of the flanker task. Additional post-hoc tests were run for measures showing a significant ($p < 0.05$) group-by-condition interaction, to examine differences between conditions within each group and differences between groups in the change between conditions (with difference scores). In the oddball task we used linear regressions to assess the main effect of group and between-group post-hoc comparisons on ex-Gaussian parameters. For all between-group comparisons, we report both p-values and Cohen's d effect sizes, calculated using the difference in the means divided by the pooled standard deviation, where $d \geq 0.20$ constitutes a small effect, $d \geq 0.50$ a medium effect and $d \geq 0.80$ a large effect . All statistical analyses were run in Stata 14 (Stata Corp, College Station, TX, USA). As this is an exploratory study, with modest sample sizes and non-independent variables derived from the same RT data, multiple-testing corrections were not applied, in line with previous publications on this sample (see also Michelini et al., 2016, 2018). Three participants were excluded from the fast task: one from the ADHD group (data on the fast-incentive condition were missing due to technical issues during the testing session), one from the control group, and one from the BD group due to the presence of outlier data (> 3.5 SD) in the baseline condition. Three participants of the BD group were excluded from the oddball task, and two participants of the ADHD group were excluded from the arrow flanker task due to lack of sufficient correct responses to fit the ex-Gaussian model. The remaining sample for each task consisted of (i) 19 participants with ADHD, 19 participants with BD and 19 controls for the fast task, (ii) 20 participants with ADHD, 17 participants with BD and 20 controls for the oddball task, and (iii) 18 participants with ADHD, 20 participants with BD and 20 controls for the arrow flanker task.

We re-ran between-group comparisons for those measures that showed both ADHD-control and BD-control differences, covarying for current self-report total symptoms of ADHD (BAARS-IV) in the BD-control comparison and for current self-report symptoms of mania (ASRM) and depression (BDI) in the ADHD-control comparison.

## 3. Results

Means and standard deviations for cognitive variables of each group are summarised in supplementary material (Table S3).

### 3.1. Arrow flanker task

Mu and tau showed significant main effects of condition (both $p < 0.001$), but no main effects of group ($p = 0.52$ and $p = 0.43$, respectively), or group by condition interaction ($p = 0.21$ and $p = 0.27$, respectively); therefore, we did not perform post hoc analyses for these variables.

Sigma showed significant main effects of group ($p = 0.04$) and condition ($p < 0.001$), but no group by condition interaction ($p = 0.10$). Post hoc tests showed a significantly higher sigma in the BD group compared to the ADHD and control groups, and a significantly increased sigma in the BD group compared to controls, in the incongruent condition (Table 1). No differences in sigma were found between the ADHD and control groups.

### 3.2. Oddball task

Given that the oddball task is a task with only one condition, we only tested the main effect of group for this task. No significant main effects of group emerged for MRT ($p = 0.98$), SD-RT ($p = 0.24$), mu ($p = 0.90$) or tau ($p = 0.46$); therefore, post hoc analyses were not performed for these variables.

Sigma showed a significant main effect of group ($p = 0.03$). Post hoc analyses revealed a significantly increased sigma in the ADHD group compared to controls (Table 1). No significant differences emerged between the BD and control groups, or between the ADHD and BD groups (Table 1).

### 3.3. Fast task

Mu showed a significant main effect of condition ($p < 0.001$) and a group by condition interaction ($p = 0.04$), but no main effect of group ($p = 0.23$). Post hoc tests in the fast-incentive condition showed a significantly increased mu in the BD group, compared to controls, but no significant differences in the ADHD group compared to controls, and between the ADHD and BD groups (Table 1). All three groups showed a within-group decrease in mu from the baseline to the fast-incentive condition (Table S4). No significant differences emerged between groups in the degree of change between conditions (Table S4).

Sigma showed a significant main effect of condition ($p < 0.001$), but no significant main effects of group ($p = 0.52$) or group by condition interaction ($p = 0.25$); therefore, we did not perform post hoc group comparisons for this variable.

Significant main effects of group ($p = 0.01$) and condition ($p < 0.001$), but not of group by condition interaction ($p = 0.62$), emerged for tau. Post hoc tests showed significantly increased tau in the baseline condition in the ADHD group compared to controls, and in the BD group compared to the control group, but no differences between the two clinical groups (Table 1). A significantly increased tau emerged in the fast incentive condition in the ADHD group compared to controls (Table 1). No differences in the fast-incentive condition emerged in tau between the BD and control groups, or between the ADHD and the BD groups.

### 3.4. Analyses controlling for symptoms of ADHD or BD

As the only shared impairment between ADHD and BD (compared to controls) was increased tau in the baseline condition of the fast task, we re-ran post-hoc comparisons, first, between ADHD and control groups covarying for symptoms of mania and depression: all results remained unchanged ($p = 0.01$, $d = 0.91$ and $p = 0.04$, $d = 0.68$, respectively). Second, we re-ran the BD-control group comparison covarying for ADHD symptoms. Also, in this case, the significance of the results did not change ($p = 0.03$, $d = 0.62$).

## 4. Discussion

Using the detailed ex-Gaussian approach, we performed a precise analysis of the nature of previously reported reaction time impairments that are shared between ADHD and BD, or that are unique to either disorder. With data from three cognitive tasks, covering a total of five task conditions, we found a shared impairment between ADHD and BD groups in occasional lapses of attention observed as rare, ultra-slow responses (tau) in the slow-unrewarded condition of the fast-task, and a BD-specific impairment in the variability of typical RT responses (sigma) in the incongruent condition of the arrow flanker task.

We previously reported, in the same sample, a shared impairment between the ADHD and BD groups that was captured by the overall RT variability measure, SD-RT, while performing the fast task

**Table 1**
Group comparisons on cognitive measures in the arrow flanker, oddball and fast tasks.

| Tasks | Measures | ADHD vs BD *d (95% CI)* | *p* | ADHD vs Control *d (95% CI)* | *p* | BD vs Control *d (95% CI)* | *p* |
|---|---|---|---|---|---|---|---|
| Arrow flanker task | Sigma congruent | 0.02 (−0.61; 0.66) | 0.94 | 0.46 (−0.18; 1.10) | 0.23 | 0.42 (−0.20; 1.05) | 0.25 |
| | Sigma incongruent | *0.57 (0.08; 1.21)* | 0.03* | 0.23 (−0.40; 0.87) | 0.42 | *0.75 (0.10; 1.39)* | 0.01** |
| Oddball task | Sigma | 0.38 (−0.28; 1.02) | 0.17 | *0.75* (0.11; 1.39) | 0.02* | 0.36 (−0.29; 1.02) | 0.48 |
| Fast task | Mu baseline | 0.07 (−0.56; 0.70) | 0.77 | 0.02 (−0.62; 0.65) | 0.96 | 0.07(−0.57; 0.69) | 0.82 |
| | Mu fast-incentive | 0.48 (−0.17; 1.12) | 0.18 | *0.64* (−0.01; 1.28) | 0.15 | **1.02** (0.33; 1.69) | 0.01** |
| | Tau baseline | 0.31 (−0.33; 0.95) | 0.27 | **0.92** (0.23; 1.57) | 0.01** | *0.72* (0.06; 1.37;) | 0.02* |
| | Tau fast-incentive | 0.24 (−0.39; 0.88) | 0.33 | *0.74* (0.08; 1.39) | 0.02* | *0.52* (−0.13; 1.16) | 0.16 |

95% CI, 95% confidence intervals around d estimates; ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; *d*, Cohen's *d*.
** $p \leq 0.01$.
* $p \leq 0.05$. Bold = large effect size ($d \geq 0.80$); Italics = medium effects size ($d \geq 0.50$). Note: between group comparisons are reported only when the main group effect is significant in the main analysis.

(Michelini et al., 2018). Applying the ex-Gaussian approach to the same task, we show that the impairment shared between the disorders is specifically related to the rare lapses of attention indexed with tau, but not to the speed or variability of typical responses (mu or sigma). The shared impairment in tau (with medium-to-large effect sizes) emerged only in the baseline condition of the fast task and not in the fast-incentive condition, where increased tau was observed in the ADHD group only, suggesting that this shared impairment might be more prominent in the slow-unrewarded condition. However, since for tau the group-by-condition interaction was non-significant, and the non-significant BD-control difference in the fast-incentive condition showed a medium effect size, we cannot exclude a possible lack of power in detecting an impairment also in the BD group in the fast-incentive condition.

In the arrow flanker task – specifically the incongruent condition of the task – we found a disorder-specific impairment in sigma in participants with BD compared to both ADHD and control groups (with medium effect size), indicating an impairment in the regulation of attention in this task condition. This evidence may suggest a BD-specific impairment when high cognitive control is needed, in line with previous evidence showing that participants with BD have increased sigma, but not tau, compared to controls when performing a task with more effortful processing (Moss et al., 2016). However, the group-by-condition interaction in the arrow flanker task was not significant, possibly because of lack of power due to the modest sample size. If future studies replicate our finding that the impairment in sigma is specific to BD and not observed in individuals with ADHD, this cognitive characteristic may aid in the differentiation of the two disorders.

We additionally examined if the shared impairments observed in the baseline condition of the fast task of increased tau in ADHD and BD, compared to controls, could be explained by symptoms of ADHD or BD. When we repeated our analyses on the shared impairments covarying for symptoms of ADHD in the BD and control groups, and for symptoms of mania and depression in the ADHD and control groups, our results did not change. This pattern suggests that the attentional lapses observed in this sample in both ADHD and BD may not be explained by symptoms of the other disorder.

The oddball task did not reveal either shared or disorder-specific impairments for any of the variables. The ADHD group differed from controls on sigma on this task, but as no difference emerged between the clinical groups for this variable, it did not fulfil our criteria for a disorder-specific impairment. Overall, our results suggest that the choice of a task is an important consideration for future studies on ex-Gaussian measures, as the tasks and conditions varied in their sensitivity to group differences.

Certain limitations should be considered while interpreting our findings. First, although between-group differences emerged with medium-to large effect sizes in this sample, larger studies are needed to confirm our results. Second, our study was conducted in a homogeneous all-female sample; and future studies are required to confirm the generalisability of our findings to adult male participants. Third, potential effects of medications must be considered on our results. Whereas participants with ADHD were asked to discontinue their stimulant medication 48 h before the assessment, participants with BD could not be asked to suspend mood-stabilizing, anti-psychotic or antidepressant medications for ethical reasons. Some studies have reported no change in cognitive performance in participants who were taking mood stabilisers (López-Jaramillo et al., 2010), or antipsychotics (Bora, 2018; Torres et al., 2010), while other studies have reported a positive association between cognitive impairments and type and dose of mood stabilisers (Pachet and Wisniewski, 2003) or antipsychotics (Arts et al., 2013; Torrent et al., 2011). As we observed significant impairments in both clinical groups compared to controls, specific confounding medication effects of mood stabilisers and antipsychotics are unlikely in this study; yet we could not directly investigate this due to the limited number of participants within each medication subgroup. Fourth, the adult participants in the clinical groups recruited for this study had slightly higher than expected IQs, which did not differ from average IQ scores in the control group. Future replication in samples with a wider range of IQs is required in order to generalise these findings to more typical clinical populations. Fifth, we did not obtain data on past psychosis in our participants with BD. Given previous evidence showing that a history of psychosis can result in more impaired or different patterns of cognitive performances in participants with BD (Bora et al., 2007; Martinez-Aran et al., 2008; Selva et al., 2007; Shin et al., 2016), future studies are needed to test the generalisability of the results to BD with psychotic features. Lastly, multiple testing corrections were not applied in this exploratory study; while the effect sizes for the main findings were, promisingly, medium-to-large, our results await replication in future larger-scale studies.

Overall, our results suggest that a fine-grained approach, such as the ex-Gaussian approach employed here across multiple tasks and conditions, is informative in elucidating overlap and specificity in cognitive impairments observed in ADHD and BD. The shared and BD-specific impairment that we identified, with moderate to large effect sizes, are potential objective cognitive markers that now await replication in future studies with larger sample sizes

## CRediT authorship contribution statement

**Isabella Vainieri:** Conceptualization, Data curation, Investigation, Methodology, Formal analysis, Writing - original draft. **Nicoletta Adamo:** Conceptualization, Data curation, Methodology. **Giorgia Michelini:** Conceptualization, Formal analysis, Methodology, Funding acquisition. **Viryanaga Kitsune:** Conceptualization, Data curation, Funding acquisition. **Philip Asherson:** Conceptualization, Investigation, Funding acquisition. **Jonna Kuntsi:** Conceptualization, Methodology, Funding acquisition, Investigation, Supervision, Writing -

review & editing.

## Declaration of Competing Interest

Professor Jonna Kuntsi has given talks at educational events sponsored by Medice; all funds are received by King's College London and used for studies of ADHD. Prof Philip Asherson has received funding for research by Vifor Pharma and has given sponsored talks and been an advisor for Shire, Janssen-Cilag, Eli-Lilly, Flynn Pharma and Pfizer, regarding the diagnosis and treatment of ADHD. All funds are received by King's College London and used for studies of ADHD. The other authors report no conflicts of interest.

## Acknowledgements

This project was supported by an Economic and Social Research Council studentship to Dr Viryanaga Kitsune (ES/100971X/1). Isabella Vainieri is supported by a 3-year PhD studentship awarded by the Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London. This project was supported by an Economic and Social Research Council studentship to Dr Viryanaga Kitsune (ES/100971X/1). Dr Nicoletta Adamo received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement no. 643051. Dr Giorgia Michelini was in receipt of a fellowship funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. Prof Asherson is supported by an NIHR senior investigator award (NF-SI-0616-10040). We thank all who made this research possible: The National Adult ADHD Clinic at the South London and Maudsley Hospital, Dr Helen Costello, Dr Georgina Hosang, Prof Sophia Frangou, Prof Anne Farmer, Jessica Deadman, Hannah Collyer, Sarah-Jane Gregori, and all participants who contributed their time to the study.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112729.

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# Chapter 6

# General discussion and conclusions

## 6.1 Abstract

In this concluding chapter, I will summarise the key findings from this thesis, and consider the clinical and research implications of this work. I will further review the strengths and limitations of the studies included in this thesis, as well as discuss future directions and final remarks.

## 6.2 Summary of aims

This thesis aimed to investigate the cognitive and neurophysiological impairments in ADHD persistence and remission and to investigate the aetiological association between ADHD and cognitive impairments with cutting-edge polygenic risk score approaches, and with quantitative genetic sibling design. A further aim was to explore disorder-specific and shared cognitive impairments between individuals with persistent ADHD and individuals with BD.

The first study of this thesis (Chapter 2) aimed to examine whether detailed measures of attention vigilance processes are markers of remission, therefore distinguishing ADHD "persisters" from "remitters" using finer-grained ex-Gaussian reaction-time distribution and brain-oscillatory measures. The second study (Chapter 3) aimed to investigate whether genetic variants that contribute to ADHD also influence attention regulation and response inhibition, which are two cognitive measures that have showed extensive evidence of association with ADHD from case-control studies (Kuntsi & Klein, 2012; Kuntsi et al., 2010; Schachar et al., 2007). The third study of this thesis (Chapter 4) used a prospective longitudinal design of siblings with ADHD and control siblings to examine the direction of the association between

ADHD and cognitive processes and to explore the aetiology of their association over time. Finally, the last study of this thesis (Chapter 5) aimed to examine whether alterations in cognitive processes identified in adults with persistent ADHD are specific to the disorder, or may be shared with BD, which often co-occurs or presents certain areas of symptomatic overlap with ADHD.

## 6.3 Key findings

### 6.3.1 Detailed measures of attention allocation and cognitive and neural variability emerge as potential markers of ADHD remission

The first study in this thesis (Chapter 2) sought to investigate detailed ex-Gaussian and time-frequency EEG measures during a reaction time task (Fast task) with slow-unrewarded baseline and fast-incentive conditions in a follow-up study of 110 adolescents and young adults with childhood ADHD and 169 age-matched control participants. Given the paucity of previous studies with these detailed measures in ADHD, the first aim was to explore whether these measures distinguished ADHD persisters from controls. A second aim was to investigate if the measures showing differences between ADHD persisters and controls were markers of remission at follow-up using both categorical and dimensional approaches. Lastly, we aimed at investigating if the ex-Gaussian and time-frequency measures that emerged as markers of remission were significantly associated with each other, suggesting they share common underlying mechanisms.

The findings showed widespread impairments in ADHD persisters, compared to controls, in the examined ex-Gaussian and brain oscillatory measures. Specifically, compared to controls, ADHD persisters showed impairments in response speed and variability (mu, sigma and tau), and in neurophysiological measures of neural variability and attention allocation (theta phase consistency and theta power). No differences between ADHD persisters and controls emerged in neurophysiological measures of attentional selection and motor preparation (alpha and beta suppression).

Further results showed that remitters did not differ from control individuals, but did significantly differ from ADHD persisters, in cognitive measures of response speed under the more engaging fast-incentive condition, and in cognitive variability (measured with tau) in both conditions. At the neurophysiological level, ADHD remitters were comparable to controls but significantly different from persisters in

neural markers of phase variability (lower theta phase consistency) and attention allocation (centro-parietal theta power), across conditions. Given this pattern of results, these cognitive and neurophysiological measures may represent markers of ADHD remission.

Results of dimensional analyses for cognitive measures were consistent with these categorical findings, as tau across conditions and mu in the fast-incentive condition were associated with the dimensional measures of functional impairment (but not with ADHD symptoms) in individuals with childhood ADHD. The identified neurophysiological markers of remission were not, however, associated with ADHD symptoms or functional impairment, highlighting the need of further investigations in future research. Lastly, in examining the association between the identified ex-Gaussian and EEG markers of remission, this study showed that alterations in theta oscillations may partly underlie atypical response speed and variability of long responses.

The findings of this study extend previous results in this sample using more traditional measures of attention-vigilance processes. In the earlier studies, measures of preparation-vigilance processes such as RTV (measured with standard deviation of reaction times) and target P3 (event-related potential of attention allocation) were markers of remission, whilst measures of executive processes (commission errors, digit span backward, NoGo-P3) were not sensitive to ADHD remission or persistence (Cheung et al., 2016; James et al., 2017; Michelini, Kitsune, Cheung et al., 2016). However, the previously identified indices represent aggregate measures that may miss systematic and fine-grained aspects of the data due to averaging procedures. Taken together, these results and previous evidence indicate that more automatic non-executive cognitive processes, such as attention-vigilance processes, at the neurophysiological level, and response speed and variability can be considered markers of ADHD remission.

### 6.3.2 Common genetic risk variants for ADHD influence attention regulation

The second study in this thesis (Chapter 3) aimed to test whether genetic variants that contribute to ADHD also influence attention regulation and response inhibition, captured by RTV and CE. In this study, we used polygenic risk scores (PRS) derived from the latest GWAS (19 099 ADHD cases and 34 194 control participants; Demontis et al., 2019). For the target sample, we used four samples from different international sites (with a combined size of 845 people with ADHD aged

5-40 years). PRS were estimated for each target sample and results were combined via meta-analyses.

Findings from the meta-analyses revealed that PRS for ADHD were positively associated with increased RTV but not CE, which suggest that common genetic variation relevant for ADHD influences attention regulation (but not response inhibition processes) in individuals with ADHD. These results expand previous evidence from a smaller sample of children with ADHD showing that PRS for ADHD were significantly associated with a latent variable of arousal-alertness (Nigg et al., 2018). No evidence of association between PRS for ADHD and inhibition had also been found in a population-based sample and a smaller clinical sample (Martin, Hamshere et al., 2015; Nigg et al., 2018), but evidence emerged of association between PRS for ADHD and a measure of interference (the "variance of word interference time" in the Stroop test) (Chang et al., 2020). These results further build on previous evidence from twin and sibling studies which showed a significant degree of familial/genetic sharing between ADHD and both RTV and CE (Kuntsi et al., 2013; Kuntsi et al., 2014). These studies showed two familial cognitive impairment factors for ADHD: a larger factor related to RTV ($r_f = 0.74$), and a smaller factor related to CE ($r_f = 0.45$), suggesting a degree of etiological separation in the association of ADHD with RTV and CE. Overall, results from this study provide molecular genetic evidence that attention regulation and ADHD share common genetic factors.

PRS capture the common risk alleles that contribute to clinically diagnosed ADHD and do not incorporate contributions from other genetic factors, such as copy number variants (CNVs) and single nucleotide variants (SNVs). Future research should explore the extent to which CNVs and other genetic variants may contribute to cognitive impairments in individuals with ADHD.

### 6.3.3 ADHD shows stable aetiology in its association with cognitive impairments over time and predicts later IQ and working memory performances but not performances in MRT, RTV and short-term memory

The third study presented in this thesis (Chapter 4) aimed to examine the direction of the association between ADHD status and cognitive performance measures (IQ, DSF, DSB, RTV and MRT) in 404 individuals from ADHD and control sibling pairs assessed in childhood and adolescence and followed-up after six years. Specifically, using a cross-lagged model we tested the simultaneous longitudinal influences of one

variable on another, and vice versa, while also controlling for concurrent associations between variables. Taking advantage of the sibling nature of the sample, we also aimed to examine the stability or change of the familial and non-familial influences that underlie the association between ADHD diagnosis and each cognitive variable across time.

Results showed that ADHD in childhood and adolescence predicted lower IQ scores and impaired working memory, but not short-term memory, RTV and MRT, at the six-year follow-up. Despite previous evidence of strong phenotypic and familial association between ADHD and the investigated cognitive impairments in this sample (Kuntsi et al., 2010; Michelini, Cheung et al., 2018), none of the cognitive measures assessed at baseline predicted ADHD diagnosis at follow-up, nor was ADHD a predictor of DSF, MRT and RTV (in either of two task conditions). Overall, the pattern of results suggests that such cognitive impairments co-occur with ADHD without influencing its outcome over time, while childhood ADHD can have subsequent negative impact on IQ and working memory. However, given the low number of participants whose ADHD status changed over time, future replications are needed to confirm such results.

For those cognitive measures showing significant predictive associations with ADHD over time (IQ and DSB), the contribution of the aetiological influences attributable to ADHD and to the association with ADHD at baseline was also investigated. Findings showed that a small but significant proportion of the familial and non-familial influences for IQ and DSB at follow-up was accounted for by ADHD at baseline and by the association between ADHD and such cognitive measures at baseline. We further showed that, although time-specific aetiological influences emerged for each cognitive variable at each time point, the familial and non-familial effects influencing the association between ADHD and different cognitive measures at follow-up showed to be attributable to stable effects from baseline. However, given the wide confidence intervals obtained from the correlation between ADHD and cognitive measures, these results warrant future replications.

Overall, results on IQ build on a previous study that, using a sub-sample of the study utilised in this chapter, reported that IQ at baseline was not a significant predictor of ADHD diagnosis per se, although it predicted future ADHD symptoms and impairments when measured as continuum (Cheung et al., 2015). However, in Cheung et al. (2015), as well as in this study, the fact that IQ at baseline did not predict ADHD diagnosis at follow-up might be explained by the low number of participants whose ADHD status changed over time and therefore limited statistical power. Our results extend the work by Cheung et al. (2015) by further showing,

using an informative cross-lagged model, a significant predictive association between ADHD diagnosis at baseline and IQ at follow-up that had not been previously investigated. Another previous study showed that ADHD symptoms and verbal and performance IQ reciprocally predicted each other over time in a population-based twin sample (Rommel et al., 2015). This reciprocal association might not have been detected here due to lack of power. Stability of the aetiological influences involved in the association of ADHD with IQ and working memory was also previously showed in population-based studies (Gustavson et al., 2018; Rommel et al., 2015), while evidence of aetiological stability for the other assessed cognitive measures is novel. Future studies using larger samples will be required to examine these associations between ADHD and cognitive impairment over time further.

### 6.3.4 Attention regulation shows shared and disorder-specific impairments in ADHD and BD across different tasks

The fourth study in this thesis (Chapter 5) investigated if detailed cognitive measures could aid in delineating shared and disorder-specific impairments between ADHD and BD. A further aim was to examine if the shared cognitive impairments observed in adults with ADHD and adults with BD could be explained by subthreshold symptoms of the other disorder. Three groups of 20 women with ADHD, 20 women with BD and 20 control women were compared on their RTs derived using the ex-Gaussian decomposition (mu, sigma and tau). The three groups performed three cognitive tasks, covering a total of five task conditions: a flanker task (congruent and incongruent conditions), an oddball task, and the 'Fast task'. For those measures showing both ADHD-control and BD-control differences (shared impairments), the between-group comparisons were re-run covarying for the symptoms of ADHD in the BD-control comparison, and for symptoms of mania and depression in the ADHD-control comparison.

The results showed a shared impairment between the ADHD and BD groups in occasional lapses of attention (tau) as, compared to controls, both ADHD and BD groups showed a significantly increased tau in the Fast task baseline condition and did not differ from each other. Furthermore, a BD-specific impairment in the variability of typical RT responses (sigma) emerged in the incongruent condition of the arrow flanker task, with participants with BD showing increased sigma compared to ADHD and control groups in this task condition. Covarying the between group differences in tau for the symptoms of the other disorder did not change results, suggesting that the attentional lapses observed

in both ADHD and BD groups may not be explained by symptoms of the other disorder.

The findings of this study extend previous evidence in the same sample that had shown shared impairment between the ADHD and BD groups as captured by the overall RT variability measure (SD-RT) while performing the Fast task. Here we show that the shared impairment between the disorders is specifically related to the rare lapses of attention measured with tau, but not to the speed or variability of typical responses (mu or sigma). Results in relation to BD are novel in this sample and suggest a BD-specific impairment in sigma but not mu or tau, when high cognitive control is needed.

Overall, examining RTs using the ex-Gaussian decomposition was informative in detecting shared and disorder-specific cognitive impairments in ADHD and BD. If replicated in future larger studies, these findings may represent objective markers of these two disorders that can aid in the differentiation of ADHD and BD.

## 6.4 Wider implications

### 6.4.1 Implications for ascertainment of ADHD remission/persistence and BD

The study in Chapter 2, using cutting-edge techniques, provides new insights into the processes that are candidate markers of remission for ADHD and that can distinguish between individuals with remitted and persistent ADHD. Cognitive and neurophysiological processes of attention-vigilance such as tau (occasional slow responses, indexing attention fluctuations), mu in the fast-incentive condition (representing response speed), evoked theta power (attention allocation), and theta phase consistency (fluctuations in neural stimulus processing) emerged as novel markers of ADHD remission. These markers may thus represent compensatory mechanisms that make remitters comparable to controls in their cognitive and neurophysiological profiles and may represent targets for non-pharmacological interventions involving cognitive training and neurofeedback.

Overall, a degree of agreement on cognitive and neurophysiological markers of ADHD persistence and remission is emerging between studies in the field. Evidence from this thesis (Chapter 2) is in line with the results obtained in the previous studies on the same sample using more traditional cognitive and neurophysiological measures (Cheung et al., 2017; James et al., 2017; Michelini, Kitsune, Cheung et al., 2016),

as well as the evidence from a number of previous independent studies (Biederman et al., 2009; McAuley et al., 2014; Pazvantoğlu et al., 2012; Roman-Urrestarazu et al., 2016). In these studies, non-executive processes, such as vigilance, preparation and attention allocation, which potentially reflect lower-level (bottom-up) mechanisms, emerged as markers of ADHD remission. On the contrary, measures related to executive (top-down) processes were not significantly related to ADHD outcomes, in line with most longitudinal studies of executive functions to date (Biederman et al., 2009; McAuley et al., 2014; Pazvantoğlu et al., 2012; Roman-Urrestarazu et al., 2016). Taken together, these findings, along with findings reported in this thesis, do not support the developmental theory of ADHD, which hypothesises that a maturation and subsequent improvement over time in prefrontally-mediated executive functions would mediate ADHD remission (Halperin & Schulz, 2006). Furthermore, according to Halperin and Schulz (2006), lower-level functions would be linked to the presence of ADHD in childhood, irrespective of later clinical status (Halperin & Schulz, 2006). Future studies should formally test the hypotheses presented here, as well as refine theoretical developmental models of ADHD based on the current available empirical evidence.

Given the persistence of ADHD and related cognitive impairments in adulthood highlighted in Chapter 2, an important aspect to consider is how some clinical and cognitive features of ADHD in adulthood may overlap or differentiate from other adulthood disorders such as BD. In clinical practice, the diagnostic procedures for both ADHD and BD are based on clinical observations and descriptions of behavioural symptoms. The identification of objective markers for psychiatric disorder could potentially aid in diagnostic and treatment decisions as well as giving more insight on the mechanisms underlying clinical symptoms and impairments (Jeste et al., 2015; Loo & Makeig, 2012; McLoughlin et al., 2014). The results reported in Chapter 5 provide evidence of shared and disorder-specific cognitive impairments between women with ADHD and women with BD, which showed also to be related to specific task conditions in relation to their cognitive engagement. If replicated in future studies with larger samples, the identified disorder-specific cognitive characteristic may aid in the differentiation of the two disorders.

### 6.4.2 Phenotypic and aetiological association between ADHD and cognitive impairments

ADHD is associated with widespread cognitive impairments across the lifespan in both higher-level cognitive functions (e.g. inhibition, working memory) and

lower-level cognitive processes (e.g. attention regulation, vigilance) (Franke et al., 2018). Yet, little is known about the genetic overlap at the molecular level between ADHD and these cognitive impairments. Polygenic analyses in Chapter 3 identified a significant association between PRS for ADHD and RTV in individuals with ADHD, suggesting that common genetic risk variants for ADHD influence attention regulation. Conversely, response inhibition was not associated with PRS for ADHD. These findings may guide further research into the specific genetic pathways and neurobiological mechanisms underlying cognitive impairments in ADHD that may be useful for clinical applications, for example by identifying targets for treatment and prevention of the development of such impairments in ADHD.

The study reported in Chapter 4 provides evidence on the predictive association between ADHD and later IQ and working memory, and showed that the aetiological influences involved in the association between ADHD and IQ, DSF, DSB, RTV and MRT are attributable to stable influences across time, which need however to be investigated in future bigger studies. These results provide novel evidence of the relationship between ADHD and cognitive impairments and the aetiological influences involved in these associations over time which, if replicated in other studies, might help for the prevention of later negative outcomes. For example, early interventions on ADHD might help in improving future working memory impairments and lower IQ, while interventions on cognitive functioning might not have an impact on later ADHD. This potential clinical implication, which should be tested in future studies, is in line with initial meta-analytic evidence showing that treatments targeting working-memory impairments have limited-to-no effects on ADHD symptoms, despite improving working memory performance (Cortese et al., 2015). However, as suggested also by Cortese et al. (2015), future studies targeting a broader range of neuropsychological deficits are required to explore the effects of cognitive training in ADHD.

Overall, results from Chapters 3 and 4 indicate novel evidence of the aetiological overlap and phenotypic relationship between ADHD and cognitive impairments. Of note, previous evidence has suggested aetiological separation of higher-level cognitive functions (e.g. response inhibition and working memory) and lower-level cognitive processes of vigilance regulation (e.g. RTV) (Frazier-Wood et al., 2012; Kuntsi et al., 2010). Results from Chapter 3 build on these previous studies by showing that ADHD PRS were associated with RTV but not with response inhibition. Similarly, evidence from Chapter 4 showed that, although persistent familial and non-familial effects influence the overlap between ADHD and the investigated cognitive impairments over time, only IQ and working memory were associated with ADHD over time

by both significant phenotypic associations and familial and non-familial effects. Overall, these results highlight how different cognitive impairments have different roles in relation to ADHD, supporting theoretical models that emphasise the role of multiple functions in the pathogenesis of ADHD (Castellanos et al., 2006; Halperin & Schulz, 2006). For example, only some impairments may represent mediators lying on the causal pathways to ADHD, while others may represent associated characteristics (Kendler & Neale, 2010).

## 6.5 Strengths and limitations

### 6.5.1 Sample sizes

The large sample sizes used in three empirical chapters of this thesis (Chapters 2 to 4) is one of the strengths of this work.

In the study reported in Chapter 2, the follow-up sample of individuals with childhood ADHD ($n = 110$) and neurotypical individuals ($n = 169$) represents one of the largest studies with detailed cognitive-electrophysiological measures. It should be mentioned that, due to the high ADHD persistence rate, the sample size of the remittent group, with 23 participants, was modest. As such, these results await replication in samples with greater numbers of remitted individuals. In Chapter 4, the use of the full ADHD and control sibling-pair samples, with 404 participants in total, makes it one of the largest longitudinal cognitive studies of ADHD with the same repeated measures across time points. Although this sample is the largest clinical sample to investigate the stability and change of the aetiological influences involved in the association between ADHD and cognitive measures over time, the sample size is still smaller compared to population-based studies. Future studies in bigger samples are needed for replication to confirm these results.

In Chapter 3, we used as discovery sample data from the largest, and therefore most powerful, GWAS on ADHD to date. The target sample used ($n = 845$), derived from an international collaboration across different sites in Europe, Canada and USA, although among the largest clinical samples to date used to investigate the association between PRS for ADHD and cognitive impairments, was modest for PRS analyses and therefore these results also await replication in future research.

Lastly, the cross-disorder comparison analyses of ADHD and BD in Chapter 5, focused on a small sample ($n = 60$ participants: 20 with ADHD, 20 with BD, 20 controls), as this project was originally designed as a pilot study to inform larger-scale investigations. Future larger-scale investigations are required to confirm its results.

### 6.5.2 Effects of medications

In all the studies included in this thesis, participants with ADHD were asked to suspend stimulant medications 48 h before the testing sessions, as standard procedure in cognitive and neurophysiological studies of ADHD (Cheung et al., 2016; McLoughlin et al., 2009). As such, the findings reported in this thesis cannot be attributed to ADHD medications and the short-term carry-over effects of such medications on the investigated measures. Yet, potential long-term effects of ADHD medication use cannot be ruled out. In Chapters 2 and 4, individuals from the remitted and persistent ADHD groups were taking ADHD medication at follow-up in a comparable proportion. In the cross-disorder comparison between ADHD and BD (Chapter 5), it was not possible, for ethical reasons, to ask participants to stop taking mood-stabilising, anti-psychotic or antidepressant medications. Furthermore, due to the limited number of medicated subgroups, it was not possible to directly test the effect of medication on cognitive impairments, which represents a limitation of this study. As there were significant impairments in both clinical groups compared to controls, specific confounding medication effects are unlikely in this study.

### 6.5.3 Generalisability

The age ranges of the follow-up samples included in Chapter 2 was restricted to adolescence and early adulthood. Results from this chapter may therefore not generalise to age groups outside those studied due to maturational effects on cognitive and neurophysiological indices (Liechti et al., 2013; Michels et al., 2013; Poil et al., 2014; Valko et al., 2009). The samples included in Chapter 3 had a wide age range from childhood to adulthood (5 to 40 years) and the analyses accounted for age effects. When larger samples will be available, future studies might explore the results separately for different age groups. The age range of participants included in the longitudinal sample used in Chapter 4 was wide at each time point (6-17 at baseline and 12-27 at follow-up); age was therefore included as covariate within time point to account for age effects. Results from this chapter might not be generalisable outside of these age ranges. Participants included in the last chapter (Chapter 5) were all in early or middle adulthood; thus, further studies are needed to compare ADHD and BD groups earlier or later in the lifespan. The majority of participants in the samples for the studies in the first three chapters were males, thus providing limited information on the generalisability of these results in females, warranting future research. Conversely, the sample used for the last chapter was an all-female sample,

in order to match groups on sex in this smaller-scale study. Future investigations should explore if these results would generalise to adult men.

### 6.5.4 Advanced cognitive and EEG approaches

In this thesis, recent and advanced cognitive and brain oscillatory techniques were used. The time-frequency analyses applied in Chapter 2 examined changes in power and phase variability of stimuli processing, which provided fine-grained information of the neurophysiological processes involved in ADHD remission and persistence. Of note, the examination of the inter-trial coherence (ITC), which provided an index of neural variability in the processing of a stimulus, showed that it parallels cognitive variability (RTV), previously observed as a marker of ADHD remission. The more detailed ex-Gaussian measures, applied in Chapters 2 and 5, allowed to disentangle the nature of the cognitive variability into variability of fast responses (sigma), or infrequent slow responses (tau). The use of this approach allowed to detect subtle differences in cognitive performances and to distinguish between ADHD and BD, as well as point at novel markers of ADHD remission.

## 6.6 Future directions

### 6.6.1 Replication

Given the novelty of the studies reported in this thesis, especially related to the use of novel cognitive and neurophysiological techniques, future studies in independent samples are needed before firm conclusions can be drawn. The study in Chapter 2 is the first using time-frequency brain oscillatory measures and ex-Gaussian decomposition in individuals with remitted and persistent ADHD, and future studies are needed to confirm the results and conclusions. Results reported in Chapter 4 are also novel and will benefit from comparable analyses on twin samples to further establish the genetic and environmental influences on the association between ADHD and cognitive measures over time. Future studies should include samples at different developmental stages, including late adulthood, to have a complete picture of the developmental trajectories of ADHD across the lifespan. Similarly, the study reported in Chapter 3, showing genetic associations between ADHD and attention regulation but not response inhibition, should be replicated when larger GWAS for ADHD will be available. Lastly, results from Chapter 5, included a relatively small sample compared to the studies in the previous

chapters. As such, replication in large samples will be especially important for this study.

### 6.6.2 Examining other definitions of ADHD

In all chapters included in this work, ADHD was defined based on diagnostic criteria from the DSM-IV (APA, 2000), which was the DSM version in use at the time of setting up the data collection for the samples included in this thesis. It would be informative if future studies replicate these findings using the current DSM-5 criteria for ADHD. Recommendations from clinical guidance state the need of different informant sources to ascertain ADHD symptoms and impairments at different stages of development. Given the wide age range (11-27 years) of the ADHD and control sibling-pair sample (Chapters 2 and 4), ADHD diagnosis was achieved by using parent-report symptoms and impairments in all participants to have consistency in informants. Future studies should investigate further the reliability and value of different informant accounts. A wide age range (5-40 years) from different independent samples was included for Chapter 3. Here, parent reports were used for childhood sample while self-informant reports were used for adult samples, in line with current clinical guidelines. In Chapter 5, ADHD diagnosis was based on self-reported ADHD symptoms and impairment, as all participants in this cross-disorder study were adults (age range 20-52 years), and self-report is also commonly used for BD in adulthood. Future studies may, however, benefit from the collection of clinical information also from co-informants.

### 6.6.3 Persistence and remission of ADHD in middle and late adulthood

In Chapters 2 and 4, the clinical follow-up of the participants with ADHD was completed in adolescence and early adulthood. Evidence shows that young adolescents and young adults are still undergoing cortical maturation (Castellanos & Tannock, 2002; Shaw et al., 2006) and therefore, their clinical presentation may further change in later ages (i.e. may still remit at later stages). Longitudinal studies of cognitive and neurophysiological processes in ADHD samples are limited to date. Evidence from longitudinal studies using structural MRI show that prefrontal brain areas continue to develop until young adulthood (Shaw et al., 2006). As such, lack of differences between ADHD persisters and remitters in executive functions (largely prefrontally-mediated) might be related to the young age of participants at follow-

up, as these processes may continue to develop into adulthood, and potentially improve in remitters later in life. Future research should carry out additional follow-up assessments of the ADHD and control sibling-pair sample in middle and late adulthood.

A further future direction could extend the investigation to a new follow-up with cognitive and EEG assessments when all the participants have reached adulthood in order to provide new data on markers of remission and persistence of cognitive and neurophysiological profiles later in life. Using identical cognitive-EEG measures between follow-up assessments would allow to examine differences between ADHD remitted and persistent groups while controlling for baseline assessments.

## 6.7 Overall conclusions

Overall, by using a multidisciplinary approach including a combination of cognitive, neurophysiological, molecular and quantitative genetic approaches, the work presented in this thesis furthers our understanding of impairments in cognitive and brain function in adolescents and adults with ADHD and gives new insight on the familial-genetic association between ADHD and cognitive impairments. The research reported in this thesis shows that fine-grained ex-Gaussian reaction-time distribution and EEG brain-oscillatory measures of attention-vigilance processes are sensitive to ADHD outcomes of persistence and remission. The identification of cognitive and neurophysiological measures linked to the varied clinical outcomes of ADHD, reported in Chapter 2, provides new evidence of neural markers that may underlie remission of symptoms and impairments, but also of neural alterations that may not be sensitive to developmental outcomes of remission or persistence. At the genetic level, this thesis further provides new insights into the relationship between ADHD and cognitive impairments showing a significant association between attention regulation (RTV) and ADHD liability. The PRS study showed that the genetic variants that contribute to ADHD also influence attention regulation, widely associated with ADHD and linked to ADHD remission in Chapter 3. Furthermore, the analyses reported in Chapter 4 furthers our understanding on the predictive relationship between ADHD diagnosis and IQ and working memory, as well as novel evidence on the aetiological stability of familial and non-familial sources of influence between ADHD and cognitive impairments over time. Finally, the cross-disorder examination of ADHD in comparison with BD, reported in Chapter 5, provides novel evidence of overlap in cognitive impairments, but also a distinct alteration distinguishing ADHD from BD.

Overall, individuals with ADHD showed consistent impairments across the different studies reported in this thesis in relation to the measures of cognitive and neural variability while using the same task (Fast-task) (Table 6.1). For instance, in the studies reported in Chapters 2 and 5, people with ADHD showed consistent impairments in tau compared to controls. In the study reported in Chapter 3, cognitive variability, measured with the aggregate measure RTV, was the only cognitive measure associated with ADHD liability. Similarly, in the study reported in Chapter 4, we showed stability of the familial and non-familial effects influencing the association between ADHD and RTV across time. In addition, measures of cognitive and neural variability were markers of ADHD remission in the study reported in Chapter 2. The latter finding, together with findings on the phenotypic and aetiological association between measures of cognitive variability and ADHD, suggest that cognitive variability might represent an objective measure of the attention fluctuations related to the core ADHD symptoms of inattention. Despite the above-mentioned similarities, findings from mu and sigma seem to be less consistent across the different studies reported in this thesis (Table 6.1). Specifically, sigma and mu were impaired in ADHD persisters compared to controls in the study reported in Chapter 2 but not in Chapter 5, where mu and sigma were not impaired in women with ADHD compared to controls. These inconsistent results between the studies reported in Chapters 2 and 5 in relation to mu and sigma might be due to age or sex, being the study reported in Chapter 2 predominantly on male adolescents while the study reported in Chapter 5 focused on adult women. Overall, findings suggest that tau and the aggregate measure RTV consistently differentiate between people with ADHD and controls, while findings from mu and sigma are less consistent. These results align with meta-analytic evidence showing bigger effect sizes for tau and RTV compared to sigma and mu in case-control differences (Kofler et al., 2013).

To conclude, the findings and implications presented in this final chapter highlight the value of combining multiple methodological approaches and levels of analysis to gain a deeper understanding of the cognitive processes in ADHD and their comparability with the cognitive impairments observed in BD. The use of cutting-edge EEG analysis approaches further allowed the investigation of various aspects of neural processes such as brain oscillatory processes not previously identified in ADHD persistence/remission. The use of the ex-Gaussian decomposition helped in better define the nature of attention regulation processes involved in ADHD remission as well as identifying disorder specific impairment for BD. By using the PRS approach with the latest GWAS, it was possible to identify the molecular genetic basis of the association between ADHD and attention regulation. Lastly, the use of a cross-lagged

**Table 6.1:** Comparison of results across chapters on cognitive and neurophysiological measures on the Fast-task

| Results | Chapters | Consistency (yes/no) |
|---|---|---|
| Increased tau in ADHD persisters compared to controls | 2 and 5 | yes |
| Aetiological association between ADHD and RTV | 3 and 4 | yes |
| Increased neurophysiological variability in ADHD persisters compared to controls | 2 | yes |
| Increased mu in ADHD persisters compared to controls | 2 and 5 | no |
| Increased sigma in ADHD persisters compared to controls | 2 and 5 | no |

*Note:* Reaction Time Variability, RTV; Attention-deficit/hyperactivity disorder, ADHD.

model in siblings, which allowed to model familial and non-familial influences between ADHD and cognitive impairments across time, was informative in providing novel evidence for the predictive relationship between ADHD and cognitive impairments and the stability of the aetiological influences involved in these associations over time. Future longitudinal studies integrating repeated assessments of cognitive measures and neurophysiological indices at various developmental stages will be particularly useful in further characterising the developmental trajectories of the cognitive and neurophysiological processes in relation to the course of ADHD into adulthood. Further research efforts should also aim to examine the neurobiological mechanisms that may be specific to ADHD or shared with other disorders, such as BD.

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# Appendix A

# Chapter 2 supplementary material

## A.1 Further details on the event-related spectral perturbation (ERSP) analysis

Time-frequency analyses were conducted using the ERSP index calculated in the EEGLAB toolbox. Specifically, ERSP values were computed from −2 to 2 s centred around target onset with a Morlet wavelet decomposition of frequencies between 3 and 30 Hz, with linearly increasing number of cycles (frequency step of 0.80 Hz) from 2 cycles for the lowest frequency (3 Hz) to 24.60 cycles for the highest frequency (30 Hz). The modulations of EEG frequency components in response to a stimulus are normalised with respect to spectral power in a pre-defined pre-stimulus period. Specifically, the post-stimulus power at each time-frequency point is divided by the mean spectral power in the pre-stimulus period (typically reflecting spontaneous EEG) at the same frequency. The normalised post-stimulus signal is scaled in decibel (dB), a logarithmic unit that represents the ratio of two signals. When comparing the ERSPs in two conditions, it is necessary to match the pre-stimulus period used to normalise the post-stimulus ERSPs (Herrmann et al., 2014). Phase consistency was calculated with inter-trial phase coherence (ITC), measuring the degree to which the phase of the evoked response (derived from the Morlet wavelet used for ERSPs) is consistent across trials (Delorme & Makeig, 2004; Makeig et al., 2004; Tallon-Baudry et al., 1996). ITC is independent of power and ranges from 0 (no phase consistency) to 1 (perfect phase consistency).

Consistent with our previous time-frequency publication using this task (Michelini, Kitsune, Vainieri et al., 2018), to compare the ERSPs in the baseline and fast-incentive conditions, we matched the timing of the pre-stimulus window across the two conditions (−2 to −1 s) with respect to the appearance of the target stimulus

Figure A.S1). In the fast-incentive condition, this window represents the 1 s period during a 2.5-s fixed inter-trial interval between the end of a trial and the subsequent warning, appearing 1 s before the target. During the −2 to −1 s period in this condition, participants are inactive (i.e., waiting for the target) while viewing a "+" fixation and as many smiley faces as they have accumulated over the course of the fast-incentive condition. The same corresponding −2 to −1 s window was used as the pre-stimulus period in the baseline condition, which similarly represents an inactive period during the long fore-period (8 s) between the appearance of the warning and of the target. This window in the baseline condition was chosen instead of a pre-warning window in the baseline condition (−9 to −8 s) in order to use pre-stimulus periods with identical time lags before the target onset (−2 to −1 s) in both conditions.

## A.2 Further details on categorical analyses

### A.2.1 Which measures differentiate between ADHD persisters and controls (aim 1)?

Significant group, condition and group-by-condition interaction (all $p < 0.001$) effects emerged for mu. ADHD persisters showed greater mu than controls in both conditions (Table 2.1). Mu was greater in both groups in the baseline conditions compared to the fast-incentive condition ($p < 0.001$), but the degree of change was greater in controls compared to ADHD persisters (Table A.S2). Significant group and condition effects (both $p < 0.001$), but non-significant group-by-condition interactions (both $p > 0.10$), emerged for sigma and tau. Sigma and tau were significantly increased in ADHD persisters compared to controls across conditions (Table 2.1). Both measures were higher in the baseline condition compared to the fast-incentive condition.

Theta ERSP showed a significant effect of group ($p < 0.001$) and region ($p < 0.001$), but no effect of condition ($p = 0.347$) or group-by-condition-by-region interaction ($p = 0.298$). After removing the three-way interaction, theta in both regions showed a significant group effect ($p < 0.001$), but no significant condition effect ($p = 0.229$ at fronto-central site and $p = 0.745$ at centro-parietal site) or group-by-condition interaction ($p = 0.698$ and $p = 0.469$, respectively). Theta ERSP across regions was significantly decreased in ADHD persisters compared to controls (Table 2.1).

Alpha ERSP showed a significant condition effect ($p < 0.001$), but no group effects ($p = 0.799$) or group-by-condition-by-time interaction ($p = 0.511$). After removing

the three-way interaction, in both time windows there was a significant condition effect ($p < 0.001$), but no group effect ($p = 0.585$ and $p = 0.853$, respectively) or group-by-condition interaction ($p = 0.856$ and $p = 0.395$, respectively), indicating no differences between ADHD persisters and controls on this measure. In both groups, alpha suppression was greater in the fast-incentive condition compared to the baseline condition.

Beta ERSP showed a significant main effect of condition ($p < 0.001$), but no significant main effect of group ($p = 0.051$) and group-by-condition interaction ($p = 0.968$), indicating no differences between ADHD persisters and controls on this measure. In both groups, beta suppression was greater in the fast-incentive condition compared to the baseline condition.

A significant group effect ($p < 0.001$), but no condition effect ($p = 0.455$) or group-by-condition interaction ($p = 0.758$), emerged for theta phase consistency. Theta phase consistency was significantly lower (i.e., greater phase variability) in ADHD persisters than controls across task conditions (Table 2.1, Figure 2.2).

### A.2.2 Which measures are markers of remission (aim 2a and 2b)?

Mu showed significant group ($p < 0.001$), condition ($p < 0.001$) and group-by-condition interaction ($p = 0.032$) effects. Sigma and tau showed significant group and condition effects (both $p < 0.001$), but non-significant group-by-condition interactions (both $p > 0.10$). Pair-wise comparisons for mu in the baseline condition and sigma across conditions between ADHD remitters and persisters, as well as between ADHD remitters and controls, were not significant (Table 2.1). Tau across conditions showed a significant difference between ADHD remitters and persisters and a non-significant difference between ADHD remitters and controls (Table 2.1). In the fast-incentive condition, ADHD remitters showed significantly lower mu than persisters. Remitters did not differ from controls on any ex-Gaussian measure (Table 2.1). ADHD remitters showed a significant decrease in all ex-Gaussian measures from the baseline to the fast-incentive condition (all $p < 0.001$). For mu, the degree of change between conditions in ADHD remitters did not differ from either persisters or controls (Table A.S2).

Theta ERSP showed a significant effect of group ($p < 0.001$) and region ($p = 0.003$), but no effect of condition ($p = 0.675$) or group-by-condition-by-region interaction ($p = 0.485$). After removing the three-way interaction, theta in both regions showed a significant group effect ($p < 0.001$), but no significant condition effect ($p = 0.331$ and $p = 0.798$, respectively) or group-by-condition interaction

($p = 0.916$ and $p = 0.601$, respectively). ADHD remitters did not differ on centro-parietal theta from controls, but showed a significant difference from persisters in the post-hoc analyses across conditions (Table 2.1, Figure 2.1), while remitters did not differ from controls or persisters on fronto-central theta (Table 2.1, Figure 2.1).

A significant group effect ($p < 0.001$), but no condition effect ($p = 0.328$) or group-by-condition interaction ($p = 0.398$), emerged for theta phase consistency. ADHD remitters showed significantly higher theta phase consistency than persisters but did not differ from controls when performing post-hoc analyses across conditions (Table 2.1, Figure 2.2).

## A.3 Results covarying for IQ

ADHD persisters in this sample had a lower IQ than ADHD remitters and controls, and childhood IQ predicted ADHD outcome at follow up (Cheung et al., 2015). To examined whether group differences on IQ contributed to the results on ex-Gaussian and time-frequency analyses, we re-run all analyses controlling for IQ (Tables A.S3 and A.S5).

### A.3.1 Which measures differentiate between ADHD persisters and controls covarying for IQ (aim 1)?

Controlling for IQ, effects of condition and group-by-condition interaction on mu, sigma and tau were unchanged ($p < 0.001$ and $p = 0.009$ respectively for mu; $p < 0.001$ and $p = 0.629$ respectively for sigma; $p < 0.001$ and $p = 0.475$ respectively for tau), but main group effects became non-significant for mu and sigma ($p = 0.392$ and $p = 0.173$, respectively). Group differences on tau between ADHD persisters and controls remained unchanged across conditions ($p < 0.10$). In both groups, the within-group change between conditions for all measures, as well as the degree of change between conditions in mu, remained unchanged (all $p < 0.001$) (Table A.S2).

The main effects of group, condition and group-by-condition interaction did not change in theta ERSP at fronto-central regions ($p = 0.001$, $p = 0.202$ and $p = 0.646$) or centro-parietal regions ($p < 0.001$, $p = 0.759$ and $p = 0.454$). Group differences between ADHD persisters and controls remained unchanged across conditions for theta ERSP in both regions (Table A.S3).

The main effects of group, condition and group-by-condition interaction at both time windows did not change for alpha ERSP ($p = 0.518$, $p < 0.001$, $p = 0.852$ respectively; and $p = 0.867$, $p < 0.001$, $p = 0.392$ respectively). In both groups, the

within-group change between condition also did not change in either time window (all $p < 0.001$).

For beta ERSP, the main effect of group, condition and group-by-condition interaction remained unchanged ($p = 0.057$, $p < 0.001$ and $p = 0.829$ respectively). Within-group change between condition also remained unchanged in both groups (all $p < 0.001$).

Main effects of group, condition, and group-by-condition interaction did not change in theta phase consistency when covarying for IQ ($p = 0.003$, $p = 0.463$ and $p = 0.735$ respectively). Group differences in theta phase consistency between ADHD persisters and controls remained unchanged across conditions (Table A.S3).

### A.3.2 Which measures are markers of remission covarying for IQ (aim 2a and 2b)?

In categorical analyses (aim 2a), controlling for IQ, effects of condition and group-by-condition interaction on mu and sigma were unchanged ($p < 0.001$ and $p = 0.032$ respectively for mu; $p < 0.001$ and $p = 0.852$ respectively for sigma), but the main group effect for mu and sigma became non-significant ($p = 0.293$ and $p = 0.512$, respectively). For tau, the group, condition and group-by-condition interaction effects were unchanged ($p < 0.001$, $p < 0.001$ and $p = 0.416$ respectively). Group differences in mu between ADHD persisters and remitters became non-significant in the fast-incentive condition (Table A.S3). Since the effect of group and group-by condition interaction was not significant for sigma, pair-wise group comparisons in each condition separately were not run for this variable (Table A.S3). For tau, group differences between ADHD persisters and remitters, and between ADHD remitters and controls remained unchanged (Table A.S3). The within-group change between conditions in ADHD remitters for all measures (all $p < 0.001$), as well as the degree of change between conditions in ADHD remitters compared to persisters and controls, remained unchanged (Table A.S3).

The main effects of group, condition and group-by-condition interaction did not change in theta ERSP at fronto-central regions when controlling for IQ ($p < 0.002$, $p = 0.672$ and $p = 0.497$ respectively). Group differences between ADHD persisters and remitters in theta at the centro-parietal regions remained unchanged (Table A.S3).

Main effects of group, condition, and group-by-condition interaction did not change in theta phase consistency when covarying for IQ ($p = 0.047$, $p = 0.379$ and $p = 0.615$ respectively). Group differences on theta phase consistency ADHD persisters and remitters became non-significant across conditions (Table A.S3).

In dimensional analyses (aim 2b), when controlling for IQ, results remained mostly unchanged except for the post-hoc test for mu in the fast-incentive condition and the association between tau and impairment (both of which became non-significant; Table A.S5).

## A.4 Categorical analyses in the male-only sample

The majority of individuals in our sample (80%) were males. Since groups were not fully matched on sex, analyses were repeated with females (15 ADHD persisters, 41 controls) removed (Table A.S4).

### A.4.1 Which measures differentiate between ADHD persisters and controls in the male-only sample (aim 1)?

Effects of group, condition and group-by-condition interaction on mu, sigma and tau were unchanged ($p = 0.003$, $p < 0.001$ and $p = 0.04$ respectively for mu; $p < 0.001$, $p < 0.001$ and $p = 0.636$ respectively for sigma; $p < 0.001$, $p < 0.001$ and $p = 0.476$ respectively for tau). Group differences on mu between ADHD persisters and controls became non-significant in the baseline condition, while differences on sigma and tau between ADHD persisters and controls remained unchanged across conditions (Table A.S4). The within-group change between conditions for both groups, as well as the degree of change between conditions in ADHD persisters compared to controls in mu, remained unchanged (Table A.S2).

The main effects of group, condition and group-by-condition interaction did not change for theta ERSP at fronto-central regions ($p = 0.001$, $p = 0.229$ and $p = 0.697$ respectively) or centro-parietal regions ($p < 0.001$, $p = 0.745$ and $p = 0.469$ respectively). Group differences between ADHD persisters and controls remained unchanged across conditions (Table A.S4).

The main effects of group, condition and group-by-condition interaction at both time windows did not change for alpha ERSP ($p = 0.956$, $p < 0.001$, $p = 0.393$ respectively; and $p = 0.570$, $p < 0.001$, $p = 0.676$ respectively). The within-group change between condition in both groups also did not change in either time window (all $p < 0.001$).

For beta ERSP, the main effect of group, condition and group-by-condition interaction remained unchanged ($p = 0.469$, $p < 0.001$ and $p = 0.859$ respectively). The within-group change between conditions remained unchanged for both groups (both $p < 0.001$).

Main effects of group, condition and group-by-condition interaction did not change for theta phase consistency in the male-only sample ($p = 0.002$, $p = 0.956$ and $p = 0.740$ respectively). Group differences on theta phase consistency between ADHD persisters and controls remained unchanged (Table A.S4).

### A.4.2 Which measures are markers of remission in the male-only sample (aim 2a and 2b)?

Group and condition effects did not change for mu, sigma or tau when repeating the analyses in the male-only sample ($p < 0.001$, $p < 0.001$ and $p > 0.10$, respectively, for all measures), while group-by-condition interaction effect became non-significant for mu only ($p = 0.115$). The significant differences in mu between ADHD persisters and remitters became non-significant in the fast-incentive condition (Table A.S4). The significant differences in tau between ADHD persisters and remitters remain unchanged. The within-group change between conditions remained unchanged in ADHD remitters for all measures (all $p < 0.001$).

Main effects of group, condition and group-by-condition interaction did not change for theta ERSP in either region when repeating the analyses in the male-only sample ($p < 0.05$, $p > 0.10$ and $p > 0.10$ respectively). The differences between persisters and remitters in theta ERSP for both regions remained unchanged across conditions (Table A.S4).

Main effects of group, condition and group-by-condition interaction did not change in theta phase consistency in the male-only sample ($p = 0.004$, $p = 0.373$, and $p = 0.487$ respectively). Group differences on theta phase consistency between ADHD remitters and persisters, and between ADHD remitters and controls remained unchanged across conditions (Table A.S4).

**Table A.S1:** Sample demographics divided by group, with test for group differences

| | ADHD persisters | ADHD remitters | Controls | Group comparison | | | |
|---|---|---|---|---|---|---|---|
| | | | | | ADHD persisters vs controls | ADHD persisters vs remitters | ADHD remitters vs controls |
| | | | | $p$ | $p$ | $p$ | $p$ |
| Male | 84% | 100% | 81% | 0.02* | 0.24 | 0.03* | <0.01** |
| Age | 18.27 (3.03) | 18.89 (3.06) | 18.77 (2.19) | 0.15 | - | - | - |
| IQ | 96.20 (15.33) | 104.57 (13.63) | 109.98 (12.42) | <0.01** | <0.01** | 0.02 | 0.10 |
| ADHD symptoms | 14.13 (2.82) | 9.17 (4.16) | - | - | - | <0.01** | - |
| Functional impairment | 16.44 (5.31) | 5.56 (3.64) | - | - | - | <0.01** | - |

*Abbreviations:* ADHD, attention-deficit/hyperactivity disorder. Group differences on gender were tested via Chi-square test; group differences on age and IQ were tested with regression models. Group differences in gender, age and IQ were reported in previous papers on this sample (Cheung et al., 2016; Michelini, Kitsune, Cheung et al., 2016). Since diagnostic interviews were not conducted in controls, descriptive statistics and group comparisons are provided for the ADHD persisters and remitters only. *Notes:* $^{**}p < 0.01$, $^{*}p < 0.05$.

**Table A.S2:** Within-group analyses and between-group comparisons of condition effects for mu

| Measures | Within-group differences from the baseline to the fast-incentive condition | | | Between-group comparisons of changes between conditions | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ADHD persisters | ADHD remitters | Controls | Aim 1 | | Aim 2a | | | |
| | | | | ADHD persisters vs controls | | ADHD persisters vs remitters | | ADHD remitters vs controls | |
| | *p* | *p* | *p* | *β (95% CI)* | *p* | *β* (95% CI) | *p* | *β* (95% CI) | *p* |
| Mu | <0.001** | <0.001** | <0.01** | *−0.49 (−0.48; 0.14)* | 0.009* | 0.21 (−0.14; 0.57) | 0.249 | 0.05 (−0.28; 0.40) | 0.733 |
| Mu covarying for IQ | <0.01** | <0.01** | <0.01** | *−0.48 (−0.49; −0.07)* | 0.009* | 0.21 (−0.14; 0.57) | 0.249 | 0.06 (−0.28; 0.40) | 0.733 |
| Mu in the male-only sample | <0.01** | <0.01** | <0.01** | *−0.32 (−0.54; −0.11)* | 0.003* | - | - | - | - |

*Abbreviations:* ADHD, attention-deficit/hyperactivity disorder. *Notes:* $^{**}p < 0.01$, $^{*}p < 0.05$. *Italics* = medium effects size ($\beta \geq 0.30$).

**Table A.S3:** Group comparisons on ex-Gaussian and EEG time-frequency measures in the baseline and fast-incentive conditions and across conditions covarying IQ

| | Baseline condition | | | | | | Fast-incentive condition | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Aim 1 | | Aim 2a | | | | Aim 1 | | Aim 2a | | | |
| | ADHD persisters vs controls | | ADHD persisters vs remitters | | ADHD remitters vs controls | | ADHD persisters vs controls | | ADHD persisters vs remitters | | ADHD remitters vs controls | |
| | $\beta$ (95% CI) | $p$ | $\beta$ (95% CI) | $p$ | $\beta$ (95% CI) | $p$ | $\beta$ (95% CI) | $p$ | $\beta$ (95% CI) | $p$ | $\beta$ (95% CI) | $p$ |
| Mu | 0.05 (−0.27; 0.18) | 0.685 | 0.05 (−0.30; 0.41) | 0.772 | −0.09 (−0.44; 0.24) | 0.582 | 0.22 (0.03; 0.45) | 0.053 | 0.26 (−0.09; 0.62) | 0.145 | −0.03 (−0.38; 0.30) | 0.833 |

| | | Collapsed across condition | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Aim 1 | | | | Aim 2a | | | | | | |
| | | ADHD persisters vs controls | | | | ADHD persisters vs remitters | | | | ADHD remitters vs controls | | |
| | | $\beta$ (95% CI) | | | $p$ | $\beta$ (95% CI) | | | $p$ | $\beta$ (95% CI) | | | $p$ |
| Tau | | **0.57** | **(0.35;** | **0.77)** | <0.001** | *0.40* | *(0.07;* | *0.71)* | 0.014* | 0.17 | (−0.13; | 0.47) | 0.263 |
| Theta ERSP | FC | −0.23 | (−0.42; | −0.04) | 0.013* | −0.22 | (−0.49; | 0.05) | 0.117 | −0.01 | (−0.28; | 0.25) | 0.918 |
| | CP | *−0.40* | *(−0.65;* | *−0.15)* | <0.001** | *−0.38* | *(−0.74;* | *−0.02)* | 0.037* | −0.02 | (−0.37; | 0.33) | 0.901 |
| Theta phase consistency | | *−0.34* | *(−0.54;* | *−0.03)* | 0.026* | −0.28 | (−0.72; | 0.26) | 0.069 | −0.05 | (−0.30; | 0.42) | 0.748 |

*Abbreviations:* ADHD, attention-deficit/hyperactivity disorder; ERSP, event-related spectral perturbation; FC, fronto-central; CP, centro-parietal. *Notes:* for aim 1, the $p$-value threshold surviving multiple testing correction was determined as 0.026 using false discovery rates (FDR). Post-hoc tests are reported by condition only for measures showing significant group-by-condition effects. For measures showing non-significant group-by-condition effects, post-hoc tests are reported across conditions. Ex-Gaussian variables were available for 86 persisters, 23 remitters, and 166 controls. ERSP and theta phase consistency variables were available for 81 persisters, 23 remitters, and 163 controls. $^{**}p < 0.01$, $^{*}p < 0.05$. **Bold** = large effect size ($\beta \geq 0.50$); *Italics* = medium effects size ($\beta \geq 0.30$).

**Table A.S4:** Group comparisons on ex-Gaussian and EEG time-frequency measures in the baseline and fast-incentive conditions and across conditions in the male participants only

| | | Baseline condition | | | | | | Fast-incentive condition | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Aim 1 | | Aim 2a | | | | Aim 1 | | Aim 2a | | | |
| | | ADHD persisters vs controls | | ADHD persisters vs remitters | | ADHD remitters vs controls | | ADHD persisters vs controls | | ADHD persisters vs remitters | | ADHD remitters vs controls | |
| | | $\beta$ (95% CI) | $p$ | $\beta$ (95% CI) | $p$ | $\beta$ (95% CI) | $p$ | $\beta$ (95% CI) | $p$ | $\beta$ (95% CI) | $p$ | $\beta$ (95% CI) | $p$ |
| Mu | | 0.21 (−0.03; 0.45) | 0.092 | 0.12 (−0.26; 0.51) | 0.523 | 0.08 (−0.28; 0.45) | 0.654 | *0.43 (0.22; 0.67)* | <0.001** | *0.40 (−0.03; 0.73)* | 0.075 | 0.09 (−0.27; 0.46) | 0.614 |

| | | Collapsed across condition | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Aim 1 | | | | Aim 2a | | | | | | | |
| | | ADHD persisters vs controls | | | | ADHD persisters vs remitters | | | | ADHD remitters vs controls | | | |
| | | $\beta$ (95% CI) | | | $p$ | $\beta$ (95% CI) | | | $p$ | $\beta$ (95% CI) | | | $p$ |
| Sigma | | *0.33* | *(0.10;* | *0.42)* | 0.003* | *0.32* | *(−0.01;* | *0.68)* | 0.060 | −0.01 | (−0.34; | 0.32) | 0.943 |
| Tau | | **0.69** | **(0.49;** | **0.89)** | <0.001** | *0.40* | *(0.07;* | *0.73)* | 0.016* | 0.19 | (−0.02; | 0.20) | 0.079 |
| Theta ERSP | FC | −0.28 | (−0.44; | −0.11) | <0.001** | −0.22 | (−0.40; | 0.04) | 0.065 | −0.04 | (−0.30; | 0.22) | 0.751 |
| | CP | **−0.50** | **(−0.76;** | **−0.24)** | <0.001** | *−0.37* | *(−0.75;* | *−0.24)* | 0.022* | −0.12 | (−0.49; | 0.23) | 0.494 |
| Theta phase consistency | | *−0.42* | *(−0.47;* | *−0.13)* | <0.001** | *−0.40* | *(−0.79;* | *0.01)* | 0.043* | −0.01 | (−0.39; | 0.35) | 0.925 |

*Abbreviations:* ADHD, attention-deficit/hyperactivity disorder; ERSP, event-related spectral perturbation; FC, fronto-central; CP, centro-parietal. *Notes:* for aim 1, the $p$-value threshold surviving multiple testing correction was determined as 0.003 using false discovery rates (FDR). Post-hoc tests are reported by condition only for measures showing significant group-by-condition effects. For measures showing non-significant group-by-condition effects, post-hoc tests are reported across conditions. Ex-Gaussian variables were available for 86 persisters, 23 remitters, and 166 controls. ERSP and theta phase consistency variables were available for 81 persisters, 23 remitters, and 163 controls. $^{**}p < 0.01$, $^{*}p < 0.05$. **Bold** = large effect size ($\beta \geq 0.50$); *Italics* = medium effects size ($\beta \geq 0.30$).

**Table A.S5:** Random-intercept linear models of ex-Gaussian and EEG time-frequency measures with parent-reported ADHD symptoms and impairment within the ADHD group only, controlling for age and sex and IQ (top half) and without covariate (bottom half)

| Aim 2b | | ADHD symptoms | | | Impairment | | | |
|---|---|---|---|---|---|---|---|---|
| | | $\beta$ | | $p$ | $\beta$ | | | $p$ |
| Covarying for sex, age, and IQ | | | | | | | | |
| Mu | | −0.07 | (−0.36; | 0.23) 0.671 | | - | | - |
| | Baseline | | - | - | −0.09 | (−0.27; | 0.08) | 0.304 |
| | Fast-incentive | | - | - | 0.08 | (0.09; | 0.26) | 0.355 |
| Sigma | | 0.07 | (−0.39; | 0.54) 0.766 | −0.12 | (−0.65; | 0.39) | 0.636 |
| Tau | | 0.22 | (−0.09; | 0.54) 0.175 | *0.31* | *(0.04;* | *0.67)* | 0.087 |
| Theta phase consistency | | 0.09 | (−0.26; | 0.45) 0.611 | −0.06 | (−0.47; | 0.33) | 0.513 |
| Without covariates | | | | | | | | |
| Mu | | −0.01 | (−0.15; | 0.21) 0.751 | | - | | - |
| | Baseline | | - | - | −0.01 | (−0.18; | 0.17) | 0.943 |
| | Fast-incentive | | - | - | 0.22 | (0.03; | 0.41) | 0.019* |
| Sigma | | 0.07 | (−0.35; | 0.22) 0.647 | −0.06 | (−0.27; | 0.39) | 0.740 |
| Tau | | 0.04 | (−0.23; | 0.14) 0.645 | −0.09 | (−0.29; | 0.11) | 0.385 |
| Theta phase consistency | | −0.03 | (−0.26; | 0.18) 0.746 | −0.06 | (−0.24; | 0.33) | 0.994 |

*Abbreviations:* ADHD, attention-deficit/hyperactivity disorder; ERSP, event-related spectral perturbation. *Notes:* ex-Gaussian variables were available for 86 persisters, 23 remitters, and 166 controls. ERSP and theta phase consistency variables were available for 81 persisters, 23 remitters, and 163 controls. $^{**}p < 0.01$, $^{*}p < 0.05$. **Bold** = large effect size ($\beta \geq 0.50$); *Italics* = medium effects size ($\beta \geq 0.30$). Analyses of ADHD symptoms and impairment with all variables, as well as for mu with ADHD symptoms, were run collapsing across baseline and fast-incentive conditions, as the interactions with condition were non-significant ($p > 0.10$).

**Table A.S6:** Associations of mu and tau with centro-parietal theta ERSP and theta phase consistency, with interactions between group (ADHD persisters, remitters, controls) and theta ERSP or theta phase consistency

| Aim 3 | Mu Baseline | | | | Mu Fast-incentive | | | | Tau collapsed across conditions | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Main effect | | Interaction | | Main effect | | Interaction | | Main effect | | Interaction | |
| | $\beta$ | $p$ | $\beta$ | $p$ | $\beta$ | $p$ | $\beta$ | $p$ | $\beta$ | $p$ | $\beta$ | $p$ |
| Theta ERSP CP | −0.22 (0.11; 0.33) | <0.001** | −0.02 (−0.16; 0.10) | 0.664 | *−0.32 (0.20; 0.43)* | <0.001** | −0.06 (−0.06; 0.19) | 0.343 | −0.10 (0.02; 0.18) | <0.001** | −0.03 (−0.11; 0.05) | 0.479 |
| Theta phase consistency | *−0.30 (−0.41; −0.20)* | <0.001** | −0.07 (−0.03; 0.19) | 0.185 | *−0.32 (−0.46; −0.17)* | <0.001** | −0.05 (−0.06; 0.18) | 0.374 | *−0.31 (−0.39; −0.24)* | <0.001** | −0.01 (−0.08; 0.07) | 0.881 |

*Abbreviations:* ERSP, event-related spectral perturbation; CP, centro-parietal. *Notes:* the $p$-value threshold surviving multiple testing correction was determined as 0.001 using false discovery rates (FDR). Ex-Gaussian variables were available for 86 persisters, 23 remitters, and 166 controls. ERSP and theta phase consistency variables were available for 81 persisters, 23 remitters, and 163 controls. Post-hoc tests examining the association between measures within each group were run only when the interaction with group was significant, thus for none of the variables. $^{**}p < 0.01$, $^{*}p < 0.05$. **Bold** = large effect size ($\beta \geq 0.50$); *Italics* = medium effects size ($\beta \geq 0.30$).

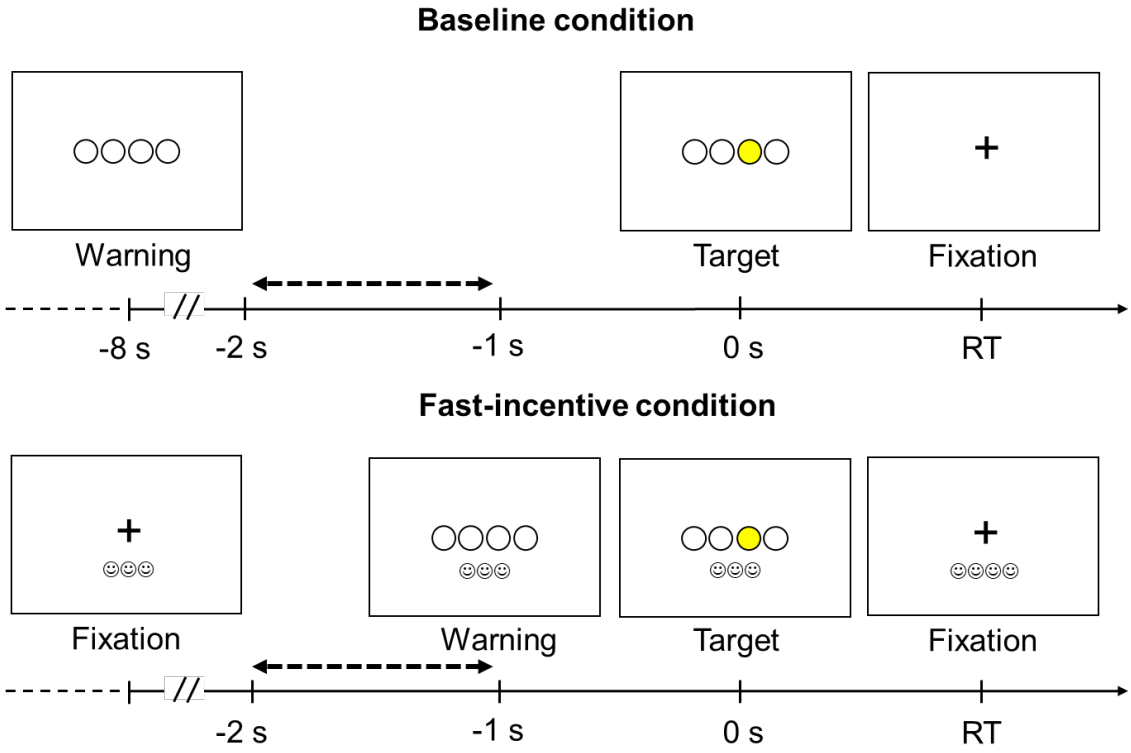


**Figure A.S1:** A schematic illustration of the temporal sequence of events in the baseline and fast-incentive conditions of the Fast task. *Notes:* in both conditions, the warning remained on the screen until target onset. The target remained on the screen up to 10 s until a response (response time [RT]), followed by a fixed 2.5 s inter-trial interval. The double-headed dashed window corresponds to the pre-stimulus baseline window ($-2$ to $-1$ s) used to normalise the event-related spectral perturbations (ERSPs).

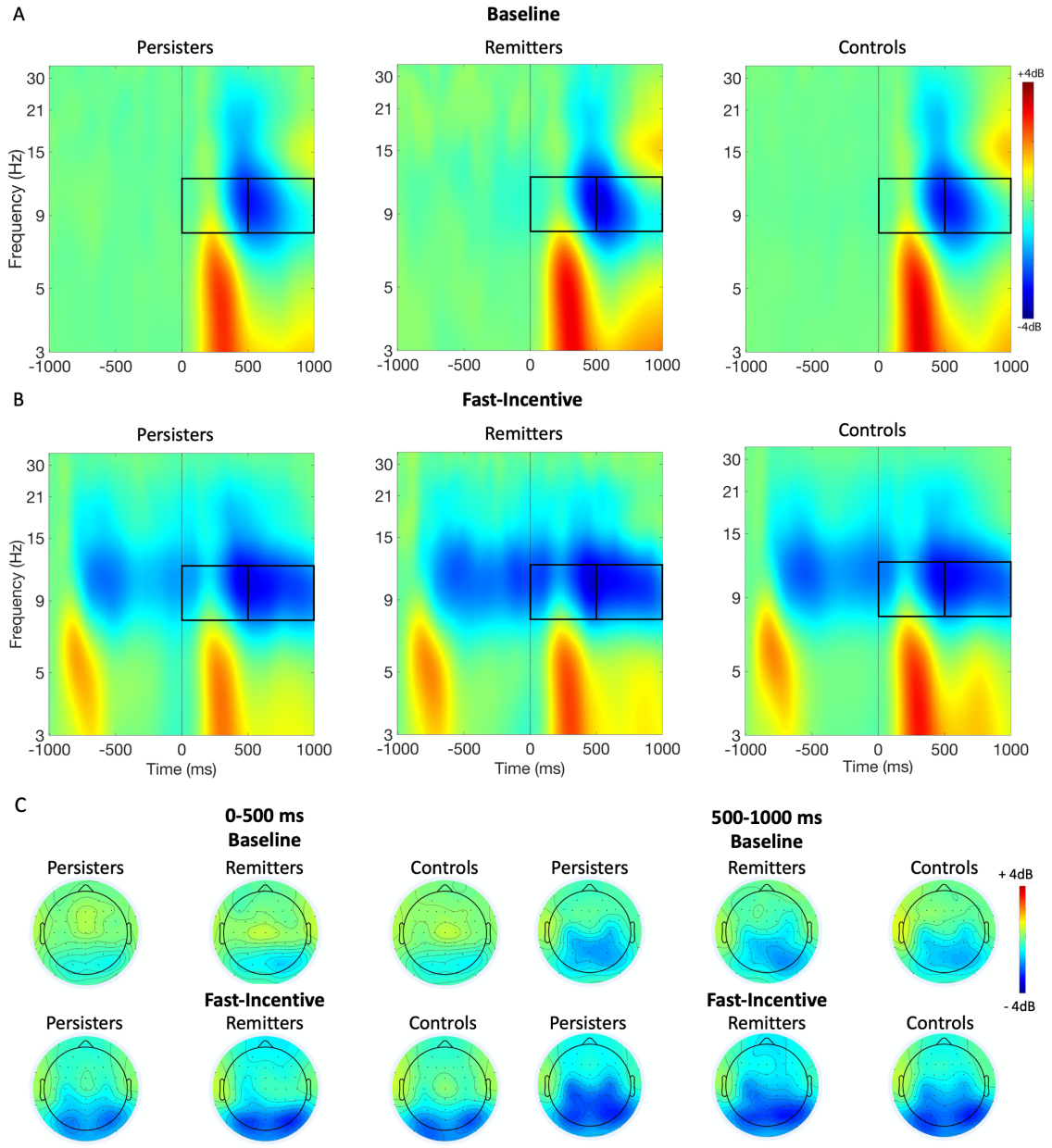


**Figure A.S2:** Alpha event-related spectral perturbation (ERSP) at parieto-occipital regions in the ADHD persisters, ADHD remitters, and control groups in the baseline and fast-incentive condition of the Fast task. A. ERSP in the baseline conditions; B. ERSP in the fast-incentive condition; C. Topographic maps by group in the 0 - 500 ms and 500 - 1000 ms windows at each condition.

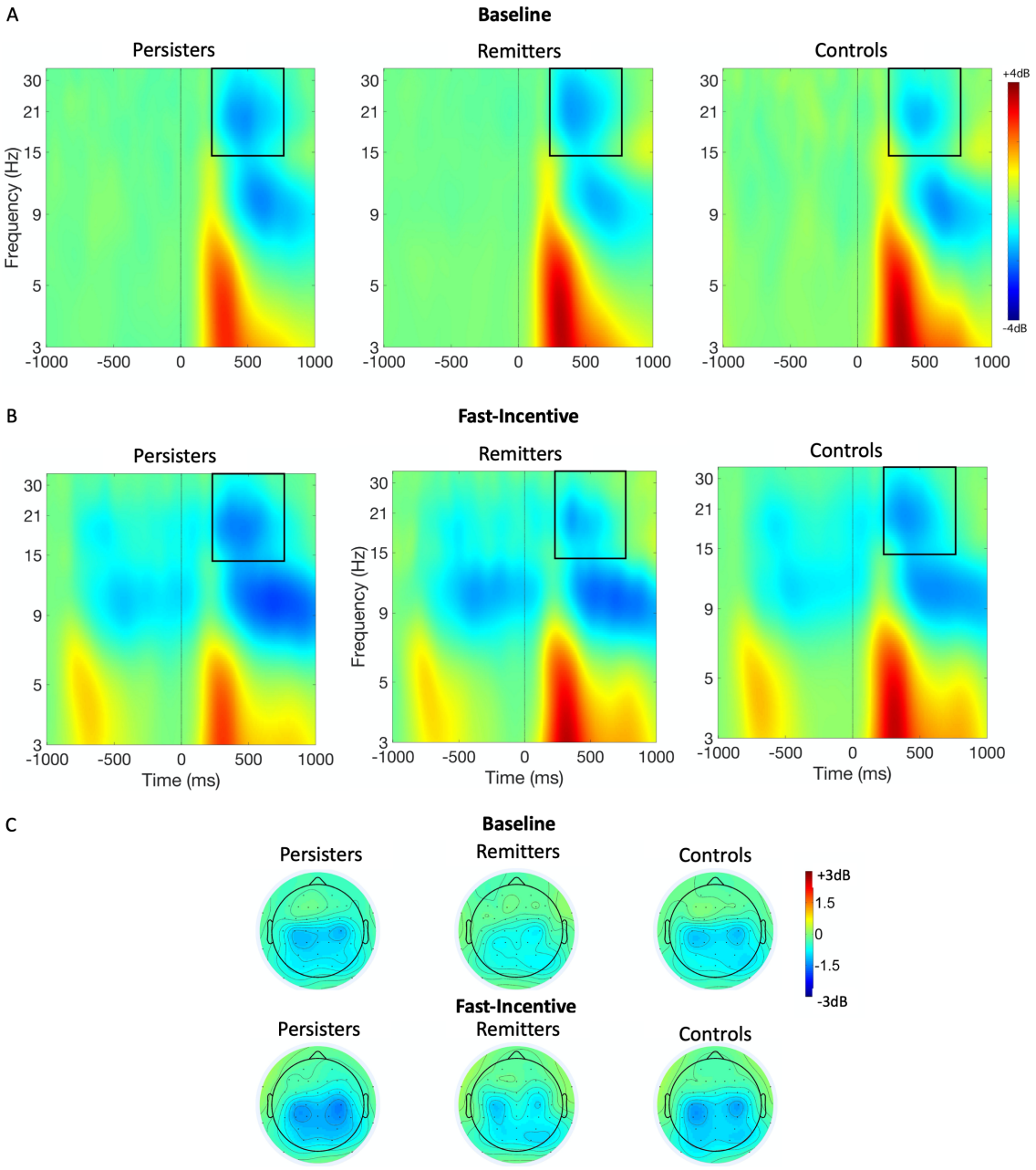


**Figure A.S3:** Beta event-related spectral perturbation (ERSP) at central regions in the ADHD persisters, ADHD remitters, and control groups in the baseline and fast-incentive conditions of the Fast task. A. ERSP in the baseline condition; B. ERSP in the fast-incentive condition; C. Topographic maps by group in the 200 - 700 ms.

## A.5 References


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Tallon-Baudry, C., Bertrand, O., Delpuech, C. & Pernier, J. (1996). Stimulus specificity of phase-locked and non-phase-locked 40 hz visual responses in human. *The Journal of Neuroscience*, *16*(13), 4240–4249. https://www.ncbi.nlm.nih.gov/pubmed/8753885

# Appendix B

# Chapter 3 supplementary material

## B.1 Supplementary tables

**Table B.S1:** Total sample sizes for each of the PGC and iPSYCH studies of European Ancestry

| Study | Number of cases | Number of controls |
|---|---|---|
| Bergen | 295 | 202 |
| Canada | 109 | 109 |
| Cardiff | 721 | 5081 |
| CHOP | 262 | 262 |
| Germany | 487 | 1290 |
| IMAGE-1 | 700 | 700 |
| IMAGE-2 | 624 | 1755 |
| PUWMa | 563 | 563 |
| Spain | 572 | 425 |
| Yale-Penn | 182 | 1315 |
| iPSYCH Danish | 14 584 | 22 492 |

*Abbreviations:* CHOP, Children's Hospital of Philadelphia; IMAGE, International Multisite ADHD Genetics Project; PUWMa, Pfizer-funded study from the University of California, Los Angeles (UCLA), Washington University, and Massachusetts General Hospital (MGH).

**Table B.S2:** Meta-analysis results across all thresholds in all target samples for reaction time variability (RTV) controlling for age and sex

| Threshold | SNP | $R^2$ | $\beta$ | $p$ | CI (95%) | SE | i2 | Q | Q-$p$ |
|---|---|---|---|---|---|---|---|---|---|
| 0.001 | 1069 | 0.006 | 0.082 | 0.025 | 0.010; 0.153 | 0.036 | 7.055 | 4.001 | 0.405 |
| 0.05 | 14 361 | 0.005 | 0.068 | 0.062 | 0.002; 0.140 | 0.036 | 0 | 1.146 | 0.886 |
| 0.1 | 22 858 | 0.006 | 0.063 | 0.083 | −0.008; 0.135 | 0.036 | 0 | 2.065 | 0.724 |
| 0.2 | 35 793 | 0.011 | 0.088 | 0.022 | 0.012; 0.163 | 0.038 | 13.513 | 3.777 | 0.436 |
| 0.3 | 45 909 | 0.003 | 0.074 | 0.062 | −0.003; 0.151 | 0.039 | 18.269 | 3.844 | 0.427 |
| 0.4 | 54 170 | 0.004 | 0.064 | 0.085 | −0.008; 0.136 | 0.037 | 8.231 | 3.366 | 0.498 |
| 0.5 | 61 172 | 0.001 | 0.066 | 0.078 | −0.007; 0.149 | 0.037 | 8.329 | 3.314 | 0.506 |
| 1 | 80 663 | 0.004 | 0.069 | 0.056 | −0.002; 0.141 | 0.036 | 2.796 | 3.023 | 0.553 |

*Abbreviations:* single nucleotide polymorphisms, (SNPs); confidence intervals, (CI); standard errors, (SE).

**Table B.S3:** Meta-analysis results across all thresholds in all target samples for commission errors (CE) controlling for age and sex

| Threshold | SNP | $R^2$ | $\beta$ | $p$ | CI (95%) | SE | i2 | Q | Q-$p$ |
|---|---|---|---|---|---|---|---|---|---|
| 0.001 | 1069 | 0.011 | 0.013 | 0.732 | −0.063; 0.089 | 0.039 | 0 | 1.195 | 0.754 |
| 0.05 | 14 361 | 0.009 | 0.005 | 0.886 | −0.076; 0.088 | 0.041 | 0 | 2.575 | 0.461 |
| 0.1 | 22 858 | 0.010 | 0.009 | 0.869 | −0.099; 0.117 | 0.055 | 28.527 | 3.567 | 0.312 |
| 0.2 | 35 793 | 0.012 | 0.012 | 0.833 | −0.120; 0.149 | 0.068 | 49.137 | 5.823 | 0.123 |
| 0.3 | 45 909 | 0.017 | 0.012 | 0.869 | −0.118; 0.139 | 0.065 | 46.002 | 5.271 | 0.152 |
| 0.4 | 54 170 | 0.011 | 0.011 | 0.863 | −0.119; 0.142 | 0.066 | 46.621 | 5.381 | 0.145 |
| 0.5 | 61 172 | 0.010 | 0.004 | 0.948 | −0.125; 0.133 | 0.065 | 44.953 | 5.104 | 0.164 |
| 1 | 80 663 | 0.009 | 0.005 | 0.936 | −0.128; 0.139 | 0.068 | 47.217 | 5.378 | 0.146 |

*Abbreviations:* single nucleotide polymorphisms, (SNPs); confidence intervals, (CI); standard errors, (SE).

## B.2 Supplementary figures

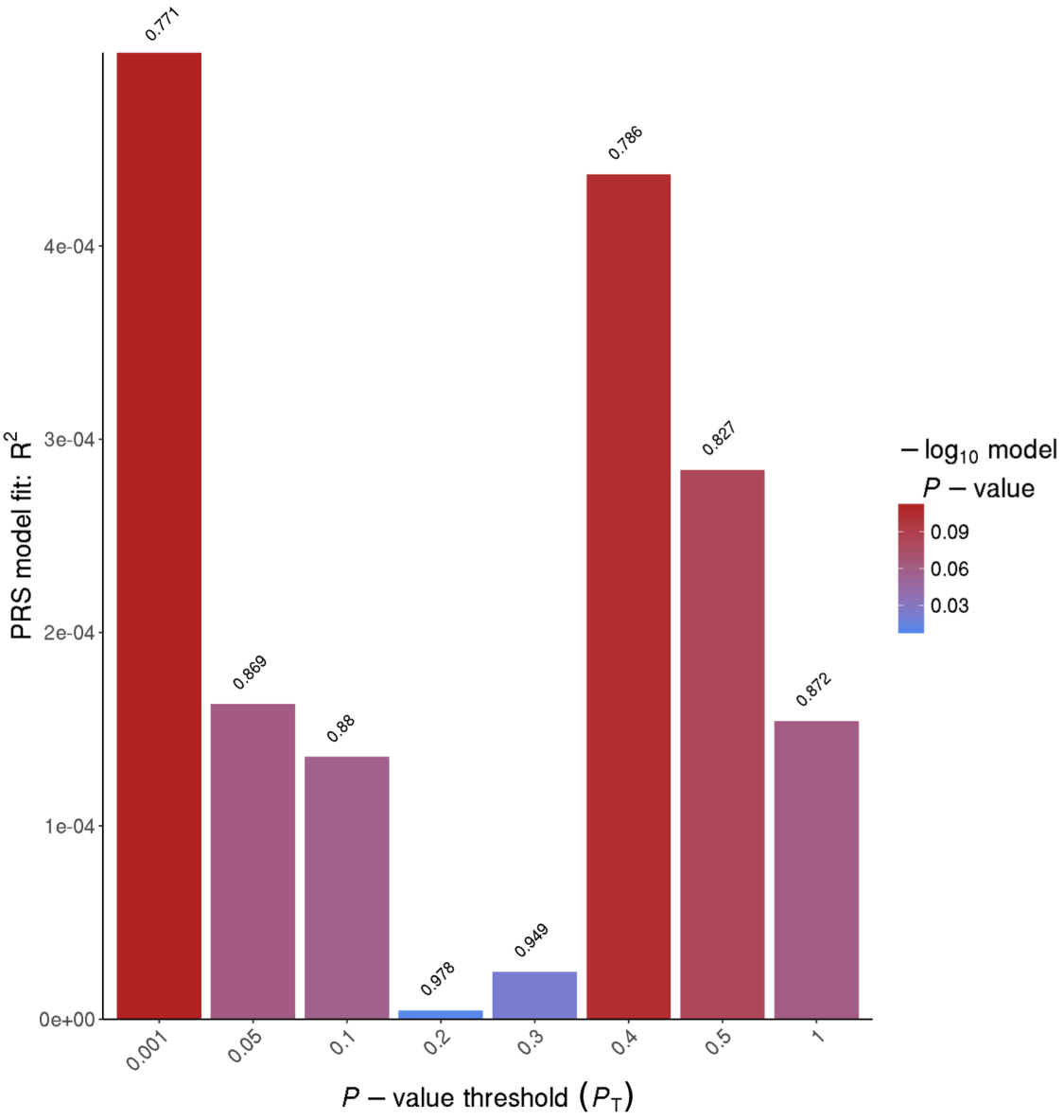


**Figure B.S1:** Plot for reaction time variability (RTV) for the International Multisite ADHD Genetics Project (IMAGE) – 8

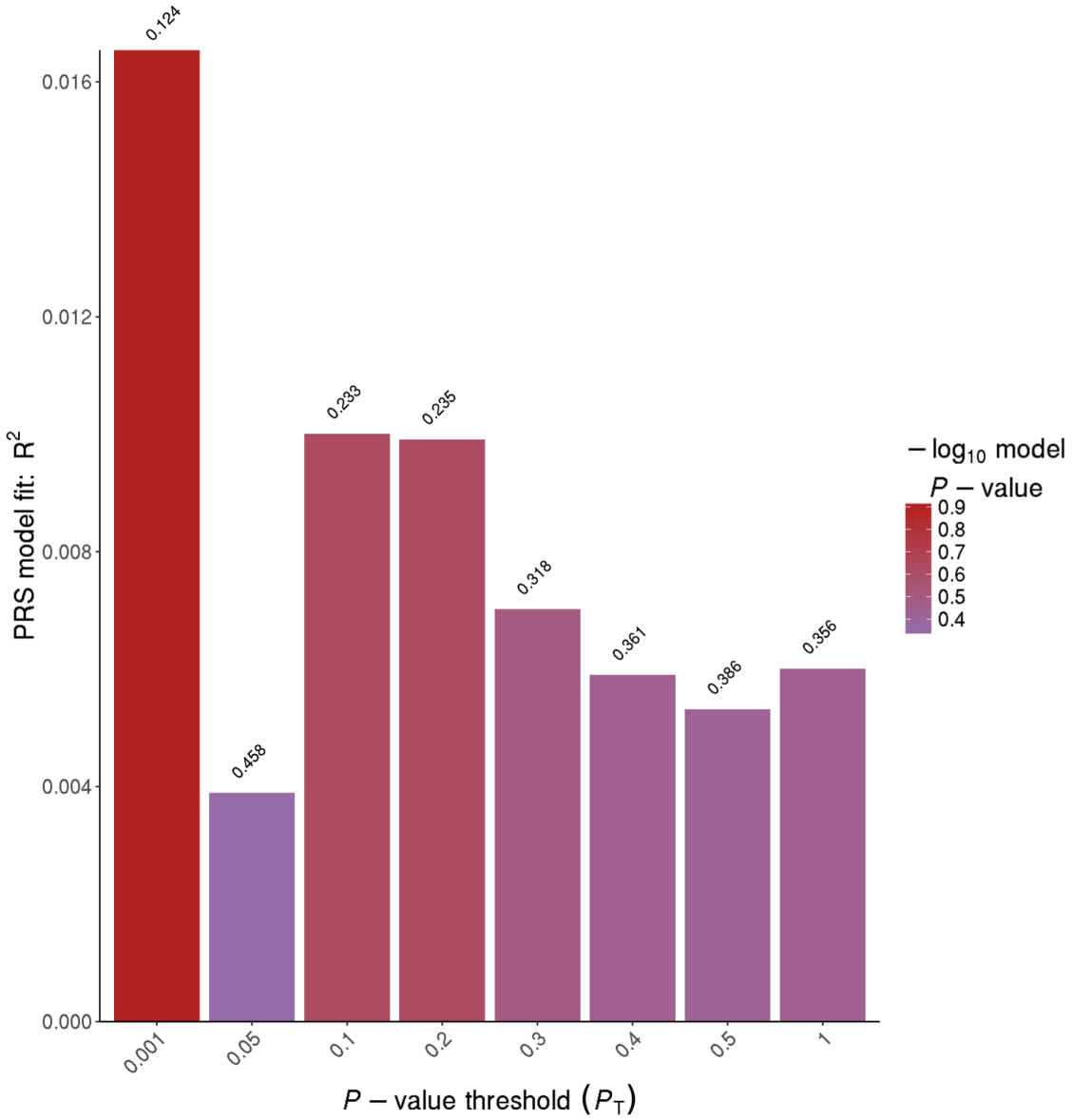


**Figure B.S2:** Plot for reaction time variability (RTV) for the International Multisite ADHD Genetics Project (IMAGE) – Dutch

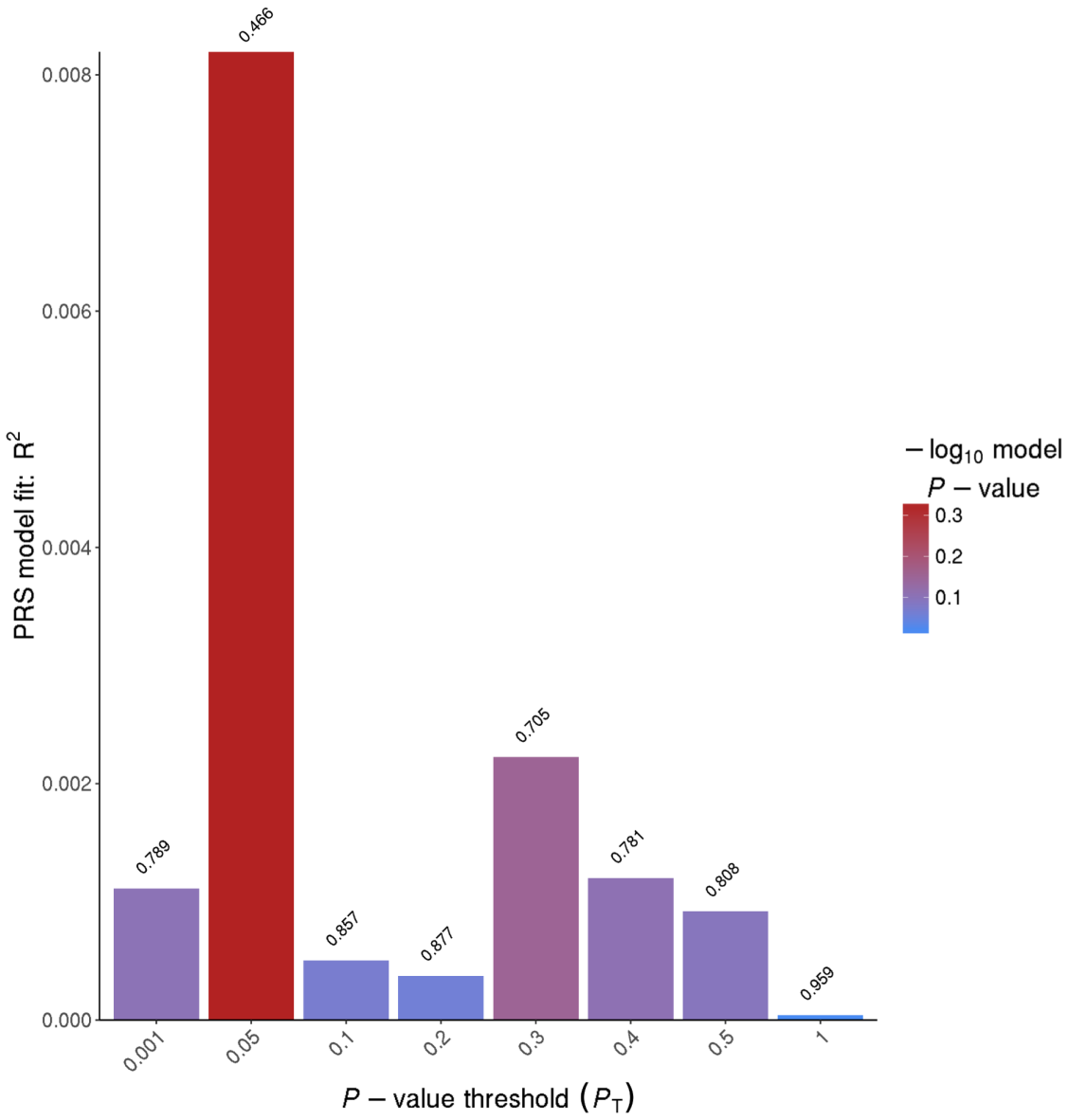


**Figure B.S3:** Plot for reaction time variability (RTV) for Los Angeles

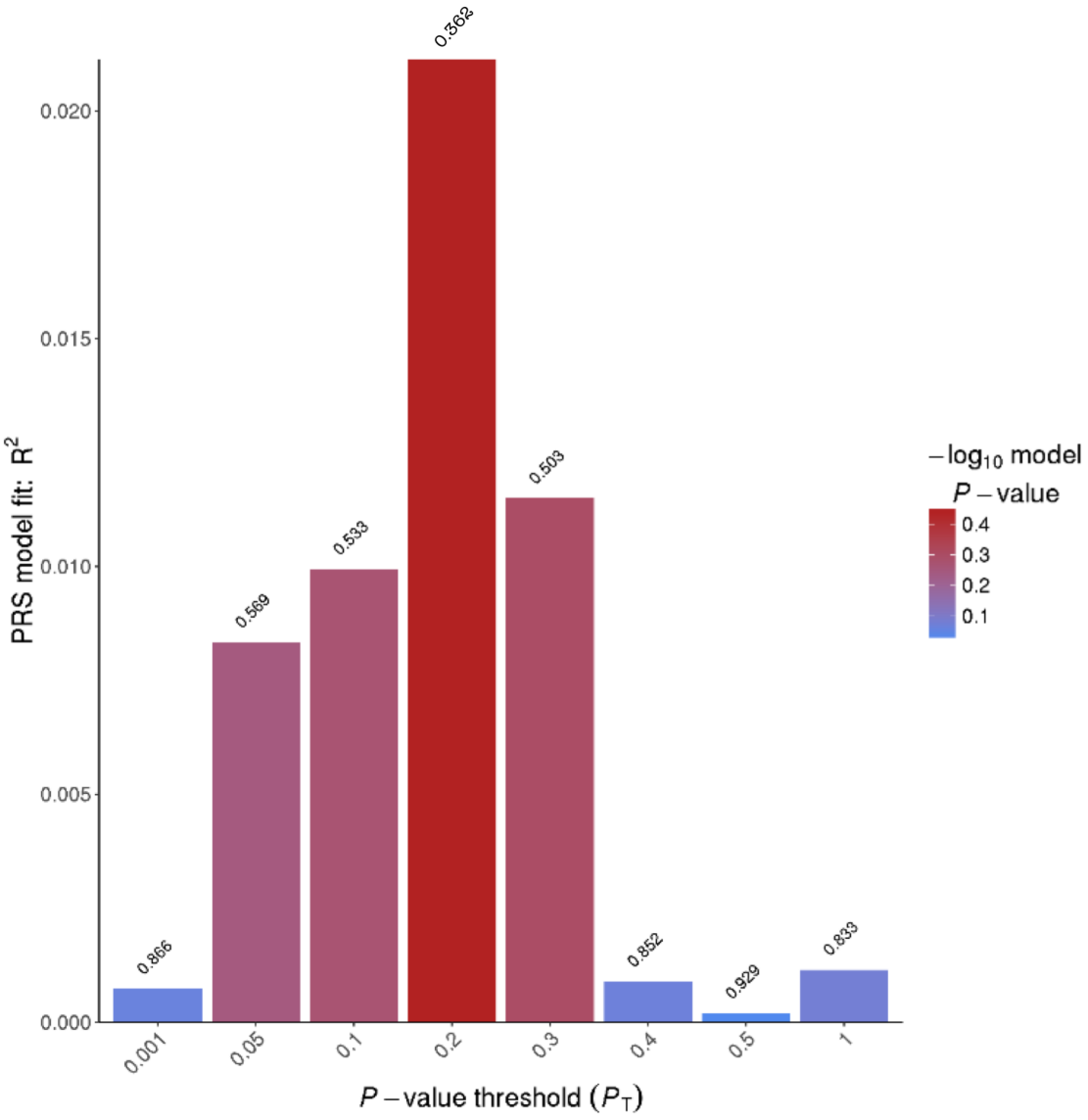


**Figure B.S4:** Plot for reaction time variability (RTV) for Toronto

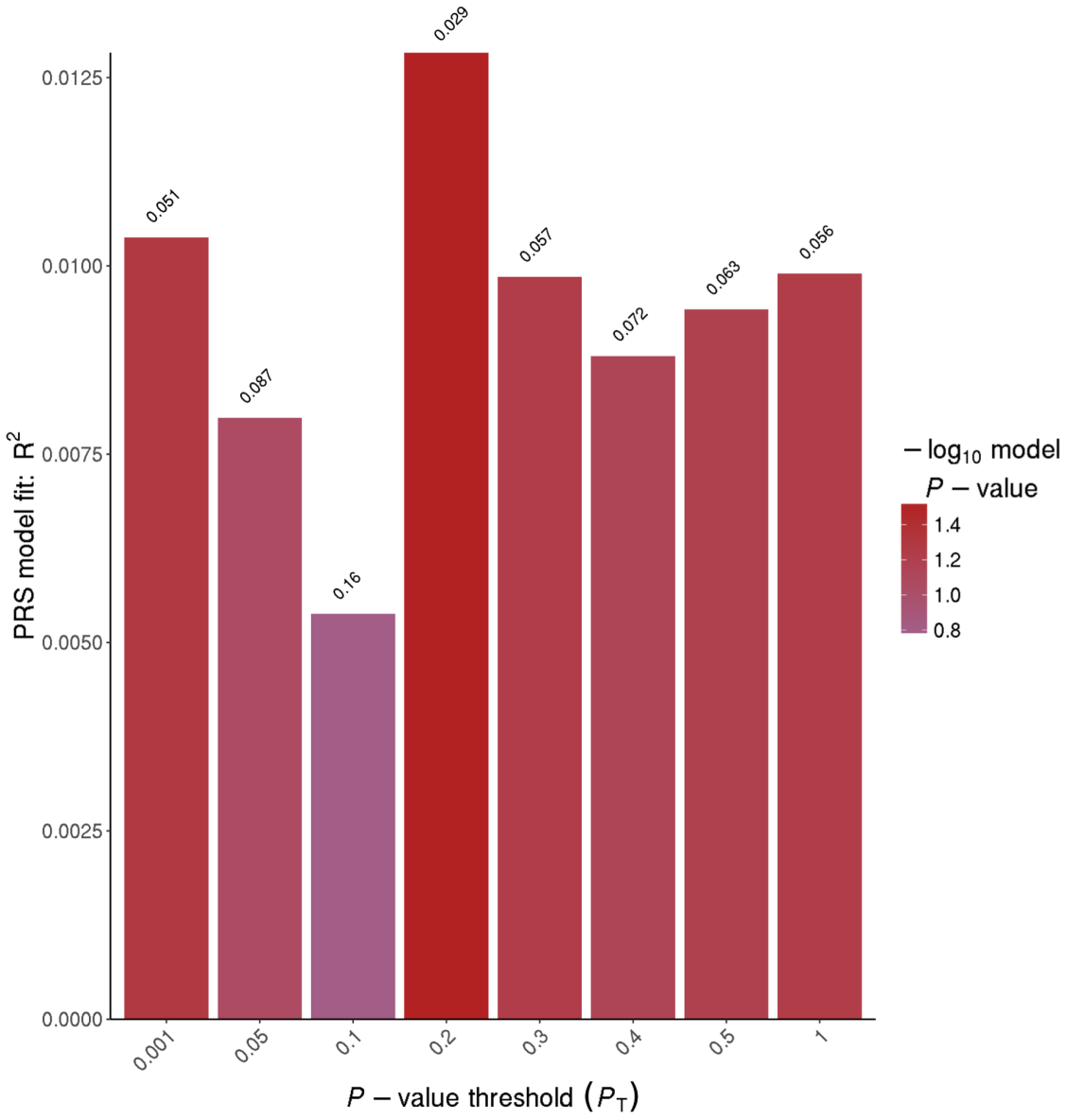


**Figure B.S5:** Plot for reaction time variability (RTV) for Barcelona

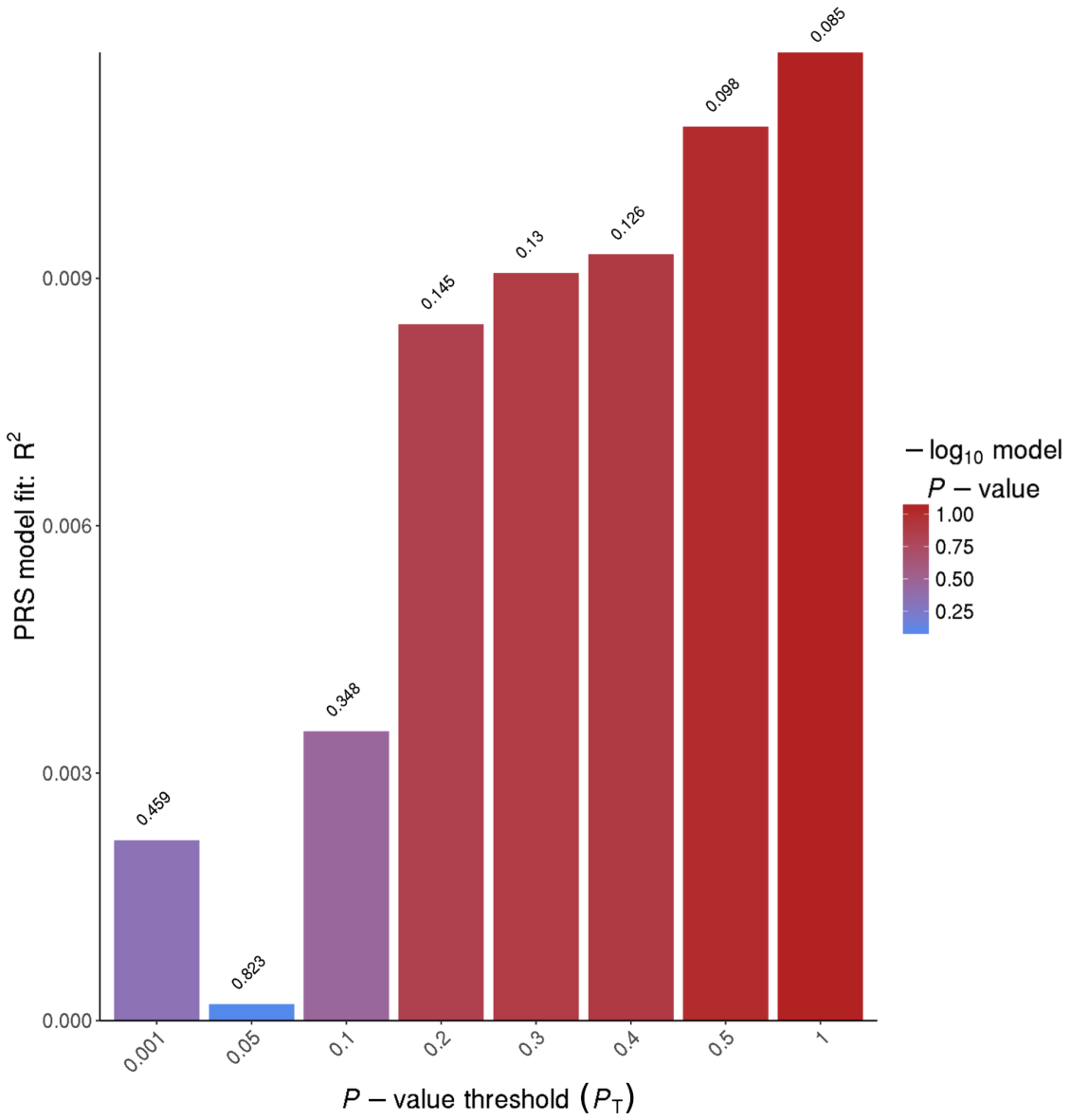


**Figure B.S6:** Plot for commission errors (CE) for the International Multisite ADHD Genetics Project (IMAGE) – 8

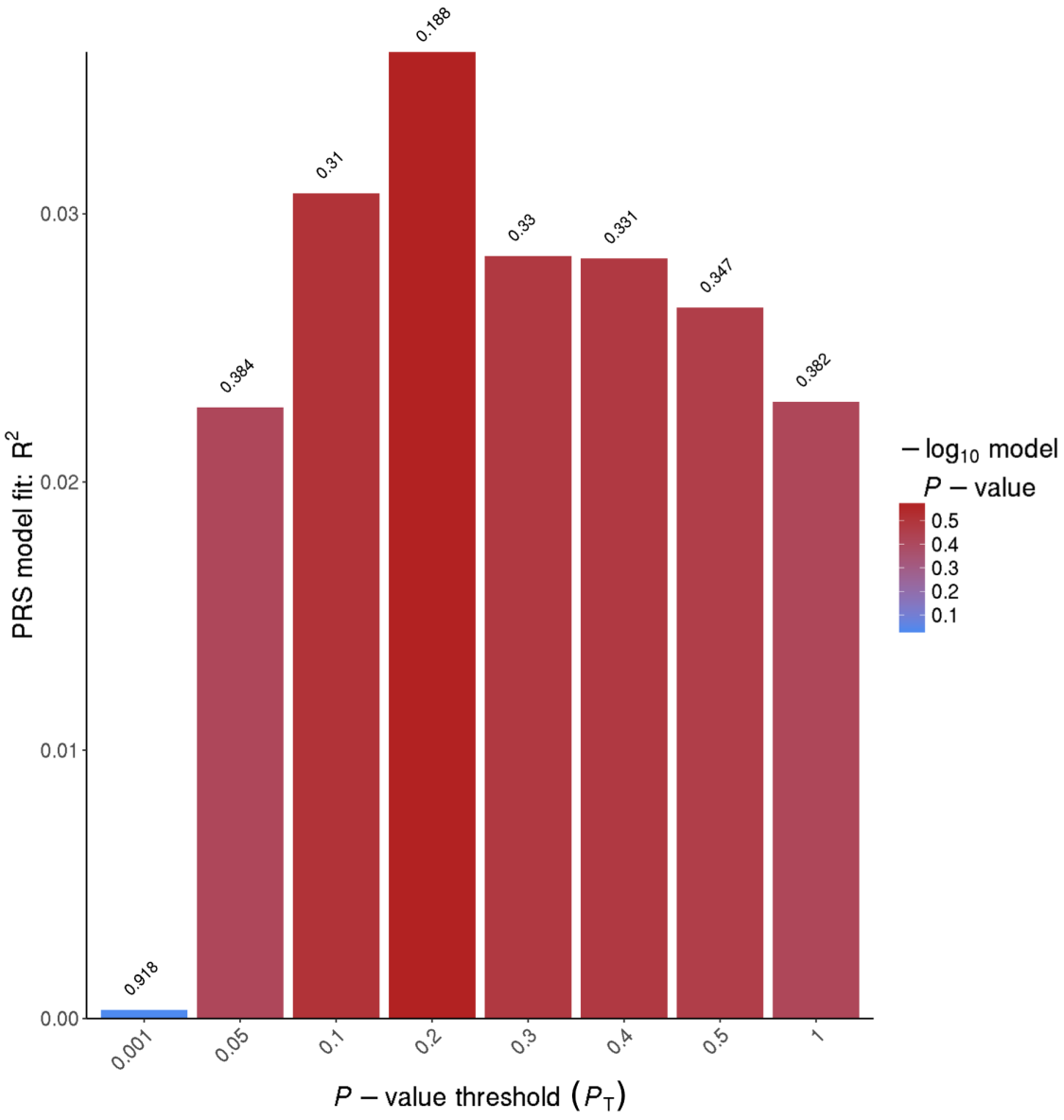


**Figure B.S7:** Plot for commission errors (CE) for Los Angeles

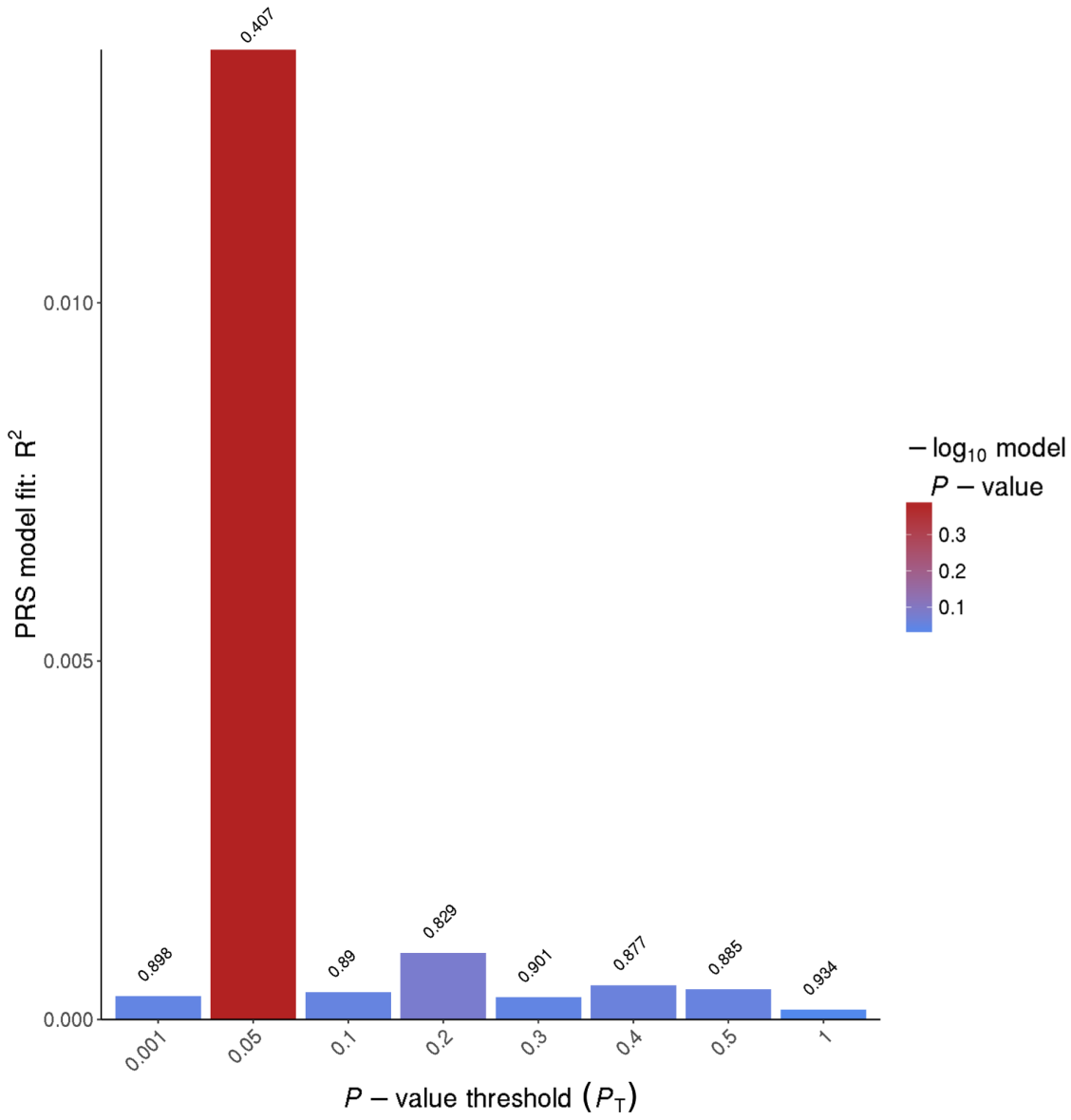


**Figure B.S8:** Plot for commission errors (CE) for Toronto

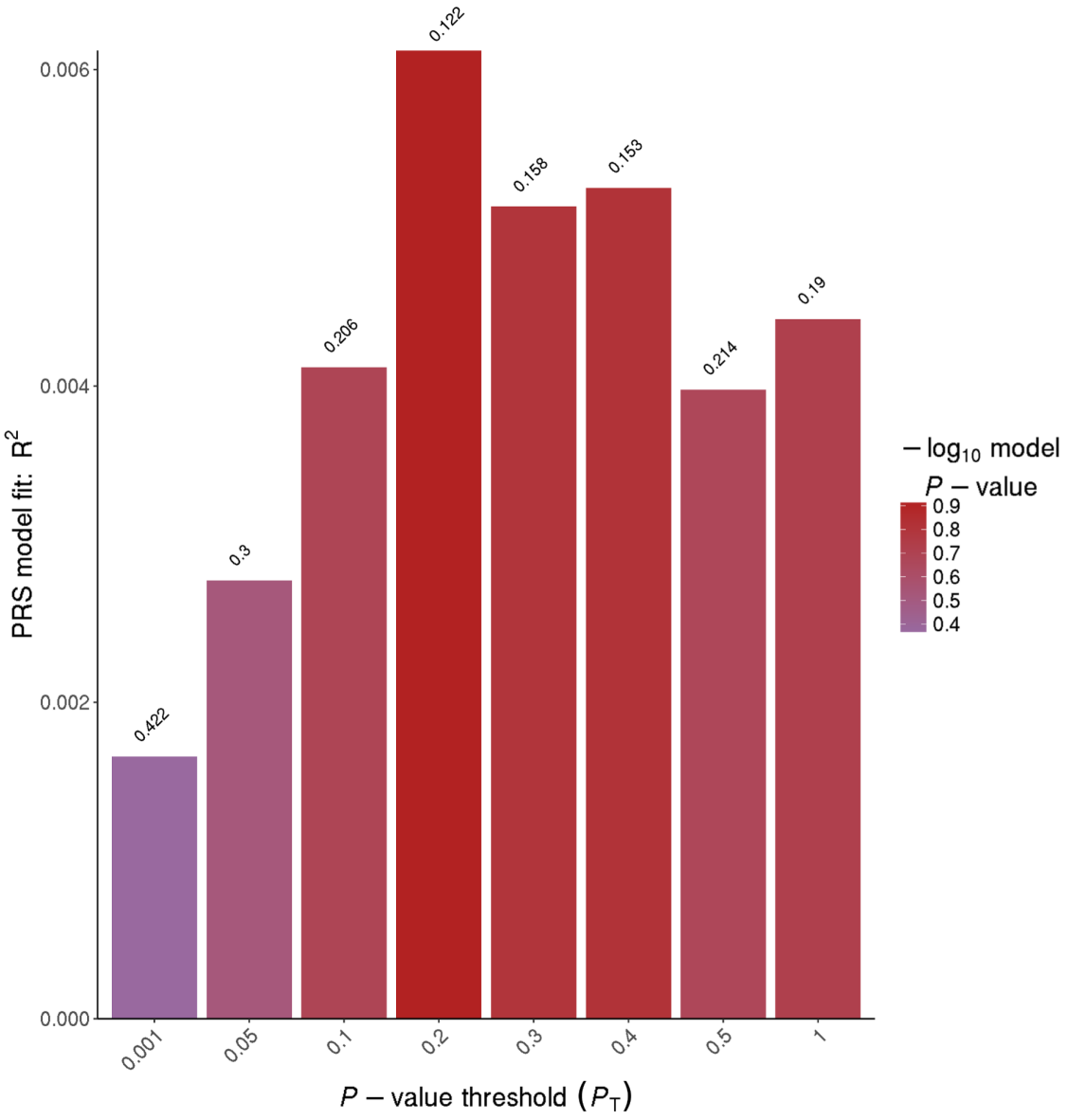


**Figure B.S9:** Plot for commission errors (CE) for Barcelona

# Appendix C

# Chapter 4 supplementary material

## C.1 Supplementary tables

**Table C.S1:** Sample demographics divided by group, with test for group difference

| | ADHD probands ($n = 99$) | Unaffected siblings ($n = 100$) | Remitters (n = 23) | Controls ($n = 169$) | $p$ |
|---|---|---|---|---|---|
| SEX (M:F) | 84:15 | 43:47 | 23:0 | 129:40 | **0.02** |
| Age | 18.34 (3.03) | 18.56 (3.33) | 18.89 (3.06) | 17.75 (2.17) | 0.07 |

*Note:* group differences on gender were tested via Chi-square test; group differences on age were tested with regression models. **Bold** = $p < 0.05$.

**Table C.S2:** Descriptive statistics for all study variables at both time points

| | ADHD | | | | non-ADHD | | | |
|---|---|---|---|---|---|---|---|---|
| | T1 | | T2 | | T1 | | T2 | |
| | Mean | (SD) | Mean | (SD) | Mean | (SD) | Mean | (SD) |
| IQ | 99.88 | (14.84) | 96.56 | (15.54) | 106.29 | (13.81) | 104.04 | (13.52) |
| DSF | 8.29 | (2.13) | 9.27 | (2.08) | 9.13 | (2.15) | 10.18 | (2.13) |
| DSB | 4.90 | (1.99) | 6.29 | (2.43) | 5.51 | (2.01) | 7.48 | (2.53) |
| MRT Baseline | 822.18 | (267.66) | 637.99 | (177.85) | 686.52 | (243.34) | 553.71 | (130.79) |
| MRT Fast-incentive | 587.21 | (162.03) | 483.36 | (105.66) | 524.06 | (159.84) | 427.17 | (63.98) |
| RTV Baseline | 403.35 | (330.18) | 208.88 | (245.75) | 220.02 | (217.95) | 116.37 | (108.02) |
| RTV Fast-incentive | 183.85 | (123.29) | 100.11 | (94.05) | 131.88 | (119.46) | 63.93 | (46.82) |

*Note:* Digit Span Forward, DSF; Digit Span Backward, DSB; Mean Reaction Time, MRT; Reaction Time Variability, RTV; Time 1, T1; Time 2, T2. DSF and DSB are reported as raw scores.

**Table C.S3:** Unstandardised coefficients of the cross-lagged model of ADHD with IQ and ADHD and DBS

| | IQ | | DSB | |
|---|---|---|---|---|
| $f_{11}$ | 1.041 | | 0.748 | |
| $f_{12}$ | 0.400 | (fixed) | 0.400 | (fixed) |
| $nf_{11}$ | 0.661 | | 1.665 | |
| $nf_{12}$ | 0.600 | (fixed) | 0.600 | (fixed) |
| $rf_1$ | −0.338 | | −0.392 | |
| $rnf_1$ | −0.340 | | −0.080 | |
| $a$ | 0.722 | | 0.481 | |
| $b$ | 0.060 | | 0.412 | |
| $c$ | −0.169 | | −0.383 | |
| $d$ | −0.723 | | −0.022 | |
| ME | 0.707 | | −0.003 | |
| Total variance T2 | 1.890 | | 6.410 | |

*Note:* Digit Span Backward, DSB; Measurement error, ME. Familial and non-familial influences for ADHD at T1 fixed to population-based values.

**Table C.S4:** Familial and non-familial influences on cognitive variables specific for time 2 and transmitted from time 1 via cross-lagged, stability and correlation paths

| | Familial | | Non-familial | |
|---|---|---|---|---|
| DSF total variance T2 | **0.31** | | **0.69** | |
| % of total variance due to | | | | |
| Time-specific effects at T2 | **0.22** | **(71%)** | **0.48** | **(70%)** |
| Contribution from T1 via stability path | **0.09** | **(29%)** | **0.21** | **(30%)** |
| Contribution from T1 via cross-lag path | <0.001 | (0%) | <0.001 | (0%) |
| Contribution from T1 via correlation path | <0.001 | (0%) | <0.001 | (0%) |
| MRT Baseline total variance T2 | **0.25** | | **0.74** | |
| % of total variance due to | | | | |
| Time-specific effects at T2 | **0.16** | **(64%)** | **0.56** | **(75%)** |
| Contribution from T1 via stability path | **0.09** | **(36%)** | **0.18** | **(24%)** |
| Contribution from T1 via cross-lag path | <0.001 | (0%) | <0.001 | (0%) |
| Contribution from T1 via correlation path | <0.001 | (0%) | 0.01 | (1%) |
| MRT Fast-incentive total variance T2 | **0.24** | | **0.75** | |
| % of total variance due to | | | | |
| Time-specific effects at T2 | **0.18** | **(75%)** | **0.60** | **(80%)** |
| Contribution from T1 via stability path | **0.06** | **(25%)** | **0.13** | **(17%)** |
| Contribution from T1 via cross-lag path | <0.001 | (0%) | 0.01 | (1%) |
| Contribution from T1 via correlation path | <0.001 | (0%) | 0.02 | (2%) |
| RTV Baseline total variance T2 | **0.18** | | **0.82** | |
| % of total variance due to | | | | |
| Time-specific effects at T2 | **0.15** | **(83%)** | **0.71** | **(87%)** |
| Contribution from T1 via stability path | **0.02** | **(11%)** | **0.08** | **(10%)** |
| Contribution from T1 via cross-lag path | <0.001 | (0%) | 0.01 | (1%) |
| Contribution from T1 via correlation path | 0.01 | (6%) | 0.02 | (2%) |
| RTV Fast-incentive total variance T2 | **0.24** | | **0.76** | |
| % of total variance due to | | | | |
| Time-specific effects at T2 | **0.22** | **(92%)** | **0.69** | **(91%)** |
| Contribution from T1 via stability path | **0.02** | **(8%)** | **0.05** | **(7%)** |
| Contribution from T1 via cross-lag path | <0.001 | (0%) | 0.01 | (1%) |
| Contribution from T1 via correlation path | <0.001 | (0%) | 0.01 | (1%) |

*Note:* Digit Span Forward, DSF; Mean Reaction Time, MRT; Reaction Time Variability, RTV; Attention-deficit/hyperactivity disorder, ADHD; Measurement error, ME; Time 1, T1; Time 2, T2. **Bold** = $p < 0.05$.

## C.2 Supplementary figures

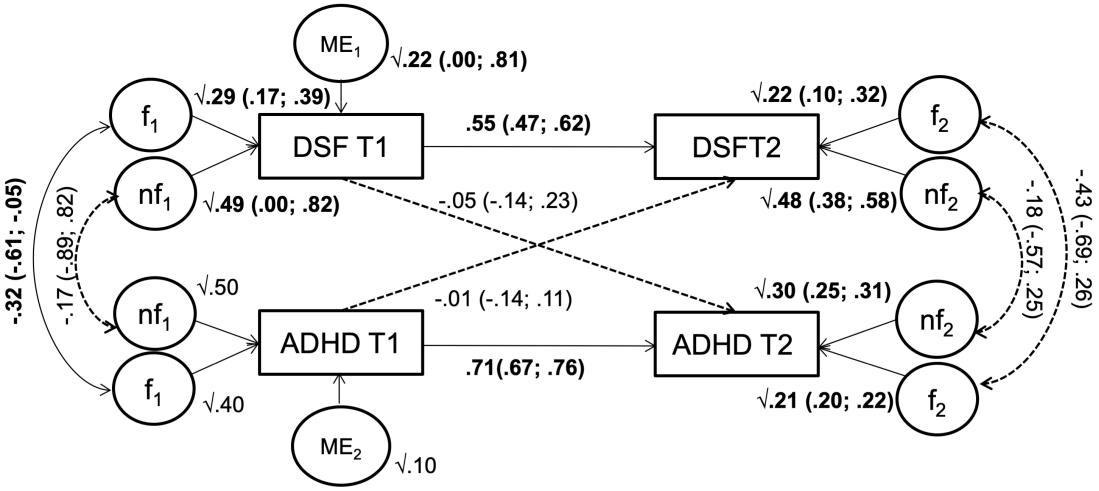


**Figure C.S1:** Path diagram with standardised effects for ADHD status and Digit Span Forward (DSF). *Note:* familial effects, $f$; non-familial effects, $nf$. Measurement error, ME; Attention-deficit/hyperactivity disorder, ADHD; Time 1, T1; Time 2, T2. Dotted lines represent non-significant estimates; significant estimates (95% CI excluding zero) are reported in **bold**.

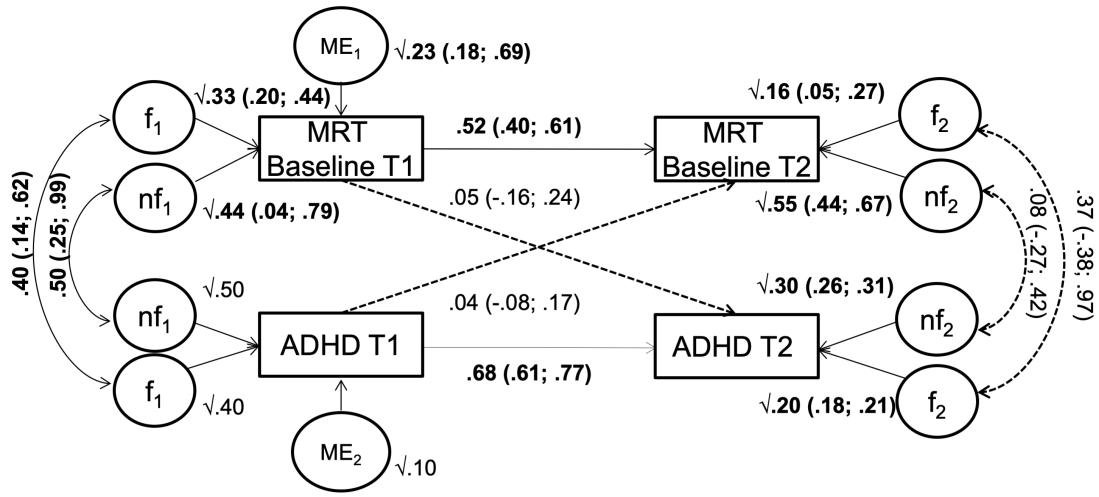


**Figure C.S2:** Path diagram with standardised effects for ADHD status and Mean Reaction Time (MRT) in the Baseline condition of the Fast task. *Note:* familial effects, $f$; non-familial effects, $nf$. Measurement error, ME; Attention-deficit/hyperactivity disorder, ADHD; Time 1, T1; Time 2, T2. Dotted lines represent non-significant results and thick lines represent significant estimates; significant estimates (95% CI excluding zero) are reported in **bold**.

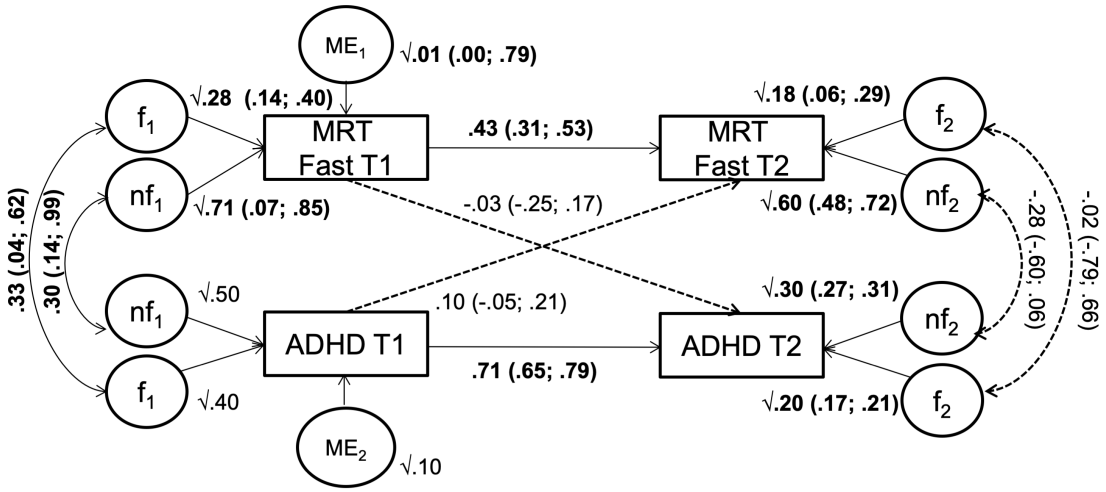


**Figure C.S3:** Path diagram with standardised effects for ADHD status and Mean Reaction Time (MRT) in the Fast-incentive condition of the Fast task. *Note:* familial effects, $f$; non-familial effects, $nf$. Measurement error, ME; Attention-deficit/hyperactivity disorder, ADHD; Time 1, T1; Time 2, T2. Dotted lines represent non-significant results and thick lines represent significant estimates; significant estimates (95% CI excluding zero) are reported in **bold**.

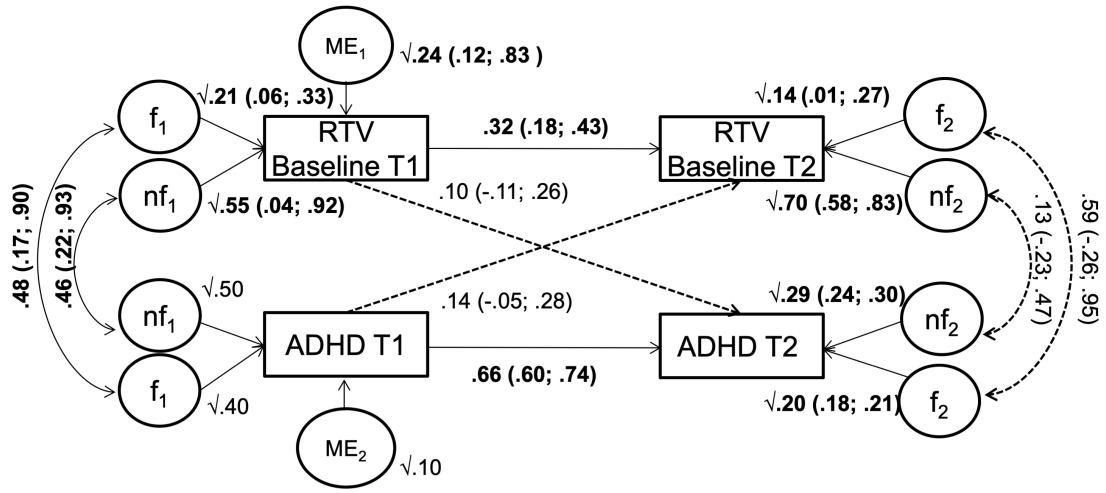


**Figure C.S4:** Path diagram with standardised effects for ADHD status and Reaction Time Variability (RTV) in the Baseline condition of the Fast task. *Note:* familial effects, $f$; non-familial effects, $nf$. Measurement error, ME; Attention-deficit/hyperactivity disorder, ADHD; Time 1, T1; Time 2, T2. Dotted lines represent non-significant results and thick lines represent significant estimates; significant estimates (95% CI excluding zero) are reported in **bold**.

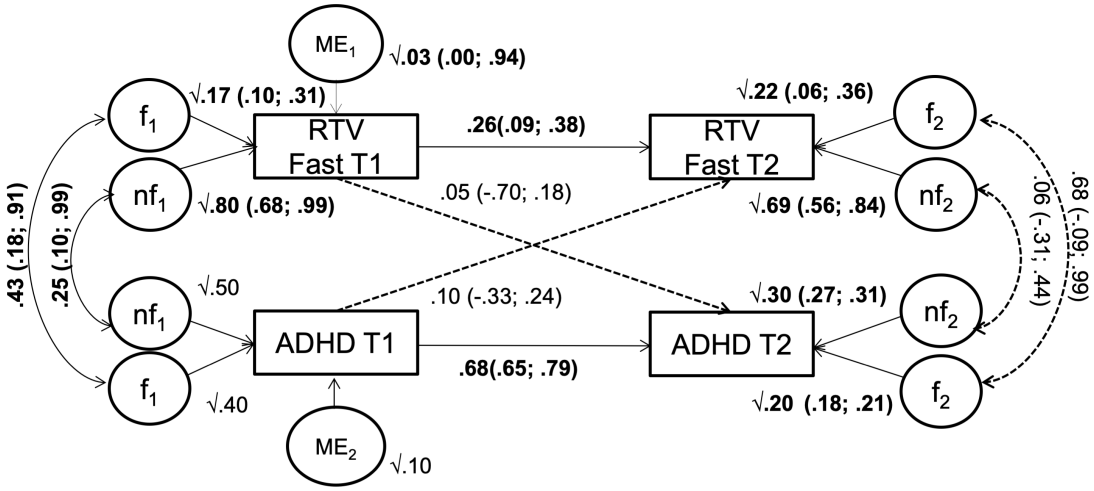


**Figure C.S5:** Path diagram with standardised effects for ADHD status and Reaction Time Variability (RTV) in the Fast-incentive condition of the Fast task. *Note:* familial effects, $f$; non-familial effects, $nf$. Measurement error, ME; Attention-deficit/hyperactivity disorder, ADHD; Time 1, T1; Time 2, T2. Dotted lines represent non-significant results and thick lines represent significant results; estimates; significant estimates (95% CI excluding zero) are reported in **bold**.

# Appendix D

# Chapter 5 supplementary material

## D.1 Further information on clinical measures

### D.1.1 ADHD symptoms

Measures of ADHD symptoms were obtained using the self-rated BAARS-IV (Barkley & Murphy, 2006), which consists of the DSM-IV items related to inattention and hyperactivity-impulsivity. Respondents indicated how frequently they experienced behaviours on a scale of 0 to 3 (never or rarely, sometimes, often, very often) during the past 6 months. Total score of ADHD symptoms was used as covariate.

### D.1.2 Mania and depression symptoms

The BDI (Beck et al., 1996) was included as a self-rated measure of depression symptoms. The scale has 21 questions, rated 0-3 based on the severity of symptoms, during the past two weeks. Total score was used as covariate.

The self-report ASRM (Altman et al., 1997) was used to measure mania symptoms in the past week. This is a 5-item measure scored 0-4 based on the strength of the behaviour. Total score was used as covariate.

**Table D.S1:** Sample demographics divided by group, with ANOVA test for group differences

| | ADHD Mean (SD) | BD Mean (SD) | Control Mean (SD) | F | $p$ |
|---|---|---|---|---|---|
| Age | 37.4 (7.7) | 40.3 (7.7) | 36.7 (4.3) | 1.63 | 0.21 |
| IQ | 104 (17.9) | 108 (12.5) | 112 (14.2) | 1.37 | 0.26 |

*Note:* group differences on age and IQ were tested with univariate ANOVAs. *Abbreviations:* ADHD, Attention-deficit/hyperactivity disorder; BD, bipolar disorder; F, ANOVA statistic; $p$, $p$-value from the ANOVA.

**Table D.S2:** Descriptive statistics and group differences on the BAARS-IV total score

| | ADHD | BD | Control | ADHD vs BD | ADHD vs Control | BD vs Control |
|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | Mean (SD) | $p$ | $p$ | $p$ |
| BAARS-IV | 35.1 (11.1) | 16.2 (8.2) | 9.9 (5.1) | <0.01 | <0.01 | 0.07 |

*Abbreviations:* ADHD, Attention-deficit/hyperactivity disorder; BD, bipolar disorder; BAARS-IV, Barkley ADHD Adult Rating Scale; $p$, $p$-value from the ANOVA.

**Table D.S3:** Non-transformed mean (SD) for each cognitive variable in each group in all tasks

| Tasks | Measures | ADHD mean (SD) | BD mean (SD) | Control mean (SD) |
|---|---|---|---|---|
| Arrow flanker task | MRT congruent | 374.0 (39.3) | 375.5 (47.6) | 359.3 (44.1) |
| | MRT incongruent | 463.8 (57.1) | 467.5 (57.3) | 449.4 (45.3) |
| | SD-RT congruent | 95.1 (31.2) | 87.4 (28.9) | 81.2 (31.3) |
| | SD-RT incongruent | 84.7 (28.8) | 83.1 (32.1) | 85.1 (36.1) |
| | Mu congruent | 293.3 (29.3) | 298.2 (39.9) | 293.3 (31.7) |
| | Mu incongruent | 393.6 (39.8) | 400.2 (39.3) | 382.6 (31.1) |
| | Sigma congruent | 32.9 (8.9) | 32.7 (9.2) | 28.8 (9.1) |
| | Sigma incongruent | 34.7 (10.9) | 42.3 (14.3) | 31.5 (12.3) |
| | Tau congruent | 80.8 (29.4) | 74.1 (26.6) | 67.2 (23.4) |
| | Tau incongruent | 70.3 (23.1) | 67.1 (27.3) | 68.8 (27.4) |
| Oddball task | MRT | 450.8 (57.9) | 508.9 (79.1) | 451.7 (59.6) |
| | SD-RT | 107.1 (30.7) | 115.8 (21.2) | 101.1 (19.6) |
| | Mu | 362.5 (49.2) | 394.3 (65.6) | 362.8 (67.6) |
| | Sigma | 69.4 (40.9) | 55.1 (36.1) | 44.1 (23.3) |
| | Tau | 80.7 (42.8) | 91.4 (37.1) | 88.9 (22.9) |

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| Tasks | Measures | ADHD mean (SD) | BD mean (SD) | Control mean (SD) |
|---|---|---|---|---|
| Fast task | MRT baseline | 806.5 | 814.6 | 843.1 |
| | | (233.1) | (280.7) | (290.5) |
| | MRT fast-incentive | 581.5 | 577.9 | 513.1 |
| | | (155.2) | (140.8) | (87.6) |
| | SD-RT baseline | 374.4 | 289.3 | 232.4 |
| | | (288.2) | (275.8) | (240.2) |
| | SD-RT fast-incentive | 176.9 | 132.8 | 114.8 |
| | | (145.3) | (68.8) | (79.1) |
| | Mu baseline | 541.5 | 551.4 | 542.3 |
| | | (106.8) | (19.6) | (108.1) |
| | Mu fast-incentive | 432.2 | 466.1 | 400.8 |
| | | (53.6) | (80.1) | (47.2) |
| | Sigma baseline | 59.6 | 58.5 | 61.4 |
| | | (31.8) | (33.8) | (43.9) |
| | Sigma fast-incentive | 30.9 | 44.1 | 35.6 |
| | | (16.5) | (16.9) | (14.6) |
| | Tau baseline | 290.8 | 231.3 | 165.5 |
| | | (187.3) | (146.2) | (132.8) |
| | Tau fast-incentive | 131.7 | 112.7 | 84.7 |
| | | (78.7) | (62.3) | (54.6) |

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*Abbreviations:* ADHD, Attention-deficit/hyperactivity disorder; BD, bipolar disorder; MRT, mean reaction time; SD-RT, standard deviation of reaction times. Descriptive statistics and group differences in MRT and SD-RT in the arrow flanker task and fast-task were previously reported in other papers on this sample (Michelini, Kitsune, Vainieri et al., 2018).

**Table D.S4:** Within-group analyses and between groups comparison of condition effects in the fast task

| Measures | Within-group differences | | | Between group differences | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ADHD | BD | Control | ADHD vs BD | | ADHD vs Control | | BD vs Control | |
| | $p$ | $p$ | $p$ | $d$ (95% CI) | $p$ | $d$ (95% CI) | $p$ | $d$ (95% CI) | $p$ |
| Mu | <0.01** | <0.01** | <0.01** | 0.25 (−0.40; 0.89) | 0.52 | 0.33 (−0.32; 0.97) | 0.19 | *0.60 (−0.04; 1.25)* | 0.07 |

*Abbreviations:* 95%, CI 95% confidence intervals around $d$ estimates; ADHD, Attention-deficit/hyperactivity disorder; BD, bipolar disorder; Ctrl, control group; $d$, Cohen's $d$. $^{**}p < 0.01$, $^{*}p < 0.05$. **Bold** = large effect size ($d \geq 0.80$); *Italics* = medium effects size ($d \geq 0.50$).

## D.2 References


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