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Lukito, Steve Daniel Adji Widjoyo

Awarding institution:
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Neurocognitive and MRI Correlates of Attention-Deficit/Hyperactivity Symptoms in Autism Spectrum Disorder (ASD)

Steve Lukito

Institute of Psychiatry, Psychology and Neuroscience
King's College London

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Abstract

Attention deficit and hyperactivity symptoms occur at high rates among individuals with ASD, resulting in a substantial proportion of people in the population meeting the dual diagnoses of ASD+ADHD. The current study aims to investigate the similarities and differences of the neurocognitive and neural underpinnings of ADHD symptoms in the ASD and ADHD populations and explore the mechanisms underlying the co-occurrence of both disorders. The thesis contains five studies. **Study I** explored the relationships among executive function (EF), theory of mind (ToM), and ASD and ADHD symptoms in a population-based sample of adolescents with ASD from the Special Needs and Autism Project (SNAP) using structural equation modelling. The study revealed that EF was specifically associated with ADHD symptoms while ToM was specifically associated with ASD symptoms in this population. **Study II** compared the cognitive performance of young adults with diagnoses of ASD, ADHD, or ASD+ADHD, and typically developing controls on a range of EF and social cognition (SC) tasks. The results of this study showed that individuals with ADHD and ASD+ADHD were predominantly impaired in EF relative to the pure ASD and control groups. The pure ASD group was more impaired than the pure ADHD and control groups in SC although this seemed to be IQ-dependent. **Study III** was a comparative meta-analysis of neural abnormalities in ASD and ADHD relative to typically developing controls. The study compared the disorder-specific and shared abnormalities in neural functions related to inhibition and structural grey matter volume in ASD and ADHD. The study showed that ASD and ADHD were largely distinct disorders with few overlapping abnormalities, suggesting that phenocopy might be one explanation for the difficulties in inhibitory function among individuals with ASD. **Study IV and V** compared the neural underpinning of response inhibition, error monitoring, and selective attention and duration discrimination among young adults with ASD, ADHD, and ASD+ADHD and typically developing controls. The findings from **Study IV** suggested that individuals with ASD+ADHD was the most impaired among the four groups during error monitoring, and they showed reduced activations in the bilateral inferior frontal, anterior insula, thalamus and parahippocampal gyrus typically associated with error monitoring. Both people with ASD+ADHD and with ASD shared impairments in the right precuneus during selective attention. **Study V** showed that individuals with ASD+ADHD also display impairments in the right inferior frontal gyrus during duration discrimination. The impairments in the ASD+ADHD group resembled those found in previous studies of children with ADHD, possibly suggesting persisting impairments. The overall findings of this study suggested that there were several pathways that lead to the increased ADHD symptoms among individuals with ASD.

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Declarations

Some of the works completed in this thesis were carried out in collaboration with other researchers. The data in Study I were collected by the SNAP team from the first two waves of investigations, funded by the Medical Research Council. The analyses on the data in this thesis were carried out by the candidate under the supervision of Professor Emily Simonoff. The data were kindly provided by Dr Catherine Jones from University of Reading and Dr Susie Chandler at the IoPPN. Additional guidance for the statistical analyses were provided by Professor Andrew Pickles from the IoPPN.

Study III, a neuroimaging meta-analysis, was a collaborative effort with fellow PhD students Luke Norman and Christina Carlisi, under the supervision of Professor Katya Rubia. The candidate's roles were to set out inclusion and exclusion criteria for the studies, to screen, assess the eligibility of fMRI studies in ASD, ADHD, and OCD, and to finally identify suitable articles with the other two students. The candidate conducted the meta-analyses of the data from the ASD and ADHD perspective, under the guidance of Dr Joaquim Radua from FIDMAG Research Foundation in Barcelona.

Study II, IV, and V used the newly collected data from young adults with diagnoses of ASD, ADHD, and ASD+ADHD. The data were collected with the support of funding from the Biomedical Research Centre (BRC) and the Autism Speaks and the study was nested in the Wave 3 investigation of the SNAP cohort about the outcomes of children with ASD in young adulthood. The candidate was supervised jointly by Professors Emily Simonoff and Katya Rubia. The roles of the candidate were to seek ethical approval for the project, plan the investigations, to program and set up several neurocognitive tasks, run a small pilot for the study, conduct the day-to-day organisation of the project, liaise with the clinicians and ASD and ADHD support organisations on recruitment matters, liaise with radiographers and administrative staff at the neuroimaging centre, manage all data including the behavioural, neurocognitive, and neuroimaging data, and run quality control for the data. The candidate conducted all data analyses and processing, including the neuroimaging data, for this thesis. The candidate follows guidance from Dr Owen O'Daly and Professor Katya Rubia for conducting the neuroimaging analyses.

List of Abbreviations

General terms

ADHD	Attention-deficit/hyperactivity disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS, ADOS-G	Autism Diagnostic Observation Schedule, ADOS-Generic
AIC	Akaike information criterion
ALE	Activation-likelihood estimation
ANCOVA, MANCOVA	Analysis of covariance, multivariate analysis of covariance
ANOVA, MANOVA	Analysis of variance, multivariate analysis of variance
APA	American Psychological Association
ASD	Autism spectrum disorder
AT	Animated triangle
AUC	Area under the curve
BIC	Bayesian information criterion
BOLD	Blood-oxygen-level dependent
CAARS	Conners' Adult ADHD Rating Scales
CAPA, YAPA	Child and Adolescent Psychiatric Assessment, Young Adult Psychiatric Assessment
CC	Central coherence
CD	Conduct disorder
CFI	Comparative fit index
CPT, CPT-AX, CPT-OX	Continuous Performance Task
CST	Card sort task
DSM	Diagnostic and Statistical Manual of Mental Disorders
EF	Executive function
EFA	Exploratory factor analysis
EPI	Echo planar image
ERN	Error-related negativity
FER	Facial emotion recognition
FEW	Family-wise error
fMRI	Functional magnetic resonance imaging
FSIQ, VIQ, PIQ	Full-scale IQ, verbal IQ, performance IQ
GNG	Go/no-go
HFA	High-functioning autism
HKD	Hyperkinetic disorder
HRF	Haemodynamic response function
ICC	Intraclass correlation

ICD	International Classification of Diseases
ISI	Interstimulus interval
MARS	Maudsley Attention and Response Suppression
MNI	Montreal Neurological Institute
MOOSE	Meta-analysis of Observational Studies in Epidemiology
MPH	Methylphenidate
NB	Number backwards
OCD	Obsessive compulsive disorder
ODD	Oppositional defiant disorder
OW	Opposite worlds
PD	Planning/drawing task
PDD	Pervasive developmental disorder
PDD-NOS	Pervasive developmental disorder-not otherwise specified
PES	Post-error slowing
PET	Positron emission tomography
PHG	Penny hiding game
PONS	Profile of Neuropsychiatric Symptoms
POP	Preparing to Overcome Prepotency
PRI	Perceptual reasoning index
RCT	Randomised controlled trial
RME	Reading the Mind in the Eyes Task
RMSEA	Root mean square error of approximation
ROI	Regions of interests
RRB	Repetitive behaviours
RT, MRT, SDRT	Response time, mean RT, standard deviation RT
SC	Social cognition
SCI	Social communication/interaction
SDM	Seed-based <i>d</i> Mapping
SDQ, SDQ17+	Strengths and Difficulties Questionnaire, 17+ version
SEM	Structural equation modelling
SNAP	Special Needs and Autism Project
SPM	Statistical Parametric Mapping
SRS	Social responsiveness scale
SSD	Stop-signal delay
SSRI	Selective serotonin response inhibitor
SSRT	Stop-signal reaction time
TEA-Ch	Test of Everyday Attention for Children
TLI	Tucker-Lewis Index
TMT	Trail making test
ToM	Theory of mind
VBM	Voxel-based morphometry

VCI	Verbal comprehension index
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler's Abbreviated Scale of Intelligence
WCST	Wisconsin Card Sort Task
WHO	World Health Organisation

Brain regions

ACC, rACC, rdACC	Anterior cingulate cortex, rostral ACC
AI, Ins	Anterior insula, insula
BA	Brodmann area
BG	Basal ganglia
DMN	Default mode network
FFG	Fusiform gyrus
GMV	Grey matter volume
IFG	Inferior frontal gyrus
IPL, IPC	Inferior parietal lobule, inferior parietal cortex
ITL	Inferior temporal lobe
MFG	Middle frontal gyrus
MTG, MTL	Middle temporal gyrus, middle temporal lobe
OFC	Orbitofrontal cortex
PCC	Posterior cingulate cortex
PFC, dl/dm/vl/vmPFC, mPFC	Prefrontal cortex, dorsolateral/dorsomedial/ ventrolateral/ventromedial PFC, medial PFC
PHGy	Parahippocampal gyrus
PMC	Premotor cortex
Pre-CG	Precentral gyrus
SFG	Superior frontal gyrus
SMA	Supplementary motor area
SPL	Superior parietal lobe
STG, STL	Superior temporal gyrus,
STN	Subthalamic nucleus
STS	Superior temporal sulcus
Th	Thalamus
TPJ	Temporo-parietal junction

1 ASD, ADHD and Their Co-occurring Presentation

1.1 Overview

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are common neurodevelopmental conditions with lifelong consequences. The two disorders are characterised by distinct sets of symptoms (APA, 2013) but studies have suggested high rates of co-occurrence between the two disorders (Gjevik, Eldevik, Fjæran-Granum, & Sponheim, 2011; Salazar et al., 2015; Simonoff et al., 2008). Findings from twin studies have suggested that both disorders have underlying shared and disorder-specific genetic influences (Reiersen, Constantino, Grimmer, Martin, & Todd, 2008; Ronald, Larsson, Anckarsäter, & Lichtenstein, 2014; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008). Several models, based on the framework of genetic risk factor and neurocognitive intermediate phenotype (Kendler & Neale, 2010; Neale & Kendler, 1995), have been formulated to explain the co-occurrence of these two disorders (Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). In this introductory chapter I briefly describe the clinical presentation of and the neurocognitive deficits and their neuroimaging correlates in ASD and ADHD. I also review the clinical presentations of the individuals with combined ASD and ADHD, referred to in this thesis as the ASD+ADHD group. Various models of comorbidity proposed in the current literature will be discussed. This chapter concludes with an outline of the general aims of this thesis and several research questions the thesis aims to answer.

1.2 ASD: Clinical Presentation, Neurocognitive and Neuroimaging Correlates

1.2.1 Prevalence and Diagnostic Criteria

Once thought a rare disorder affecting only five in 10,000 children (Lotter, 1966; Wing & Gould, 1979), ASD has been reported at increasingly higher rates. The current global estimate for the prevalence of ASD is at least 1% and rates approaching 2% have been reported in a few countries in the Western Pacific (Elsabbagh et al., 2012). Earlier studies showed higher prevalence in males who were affected 4-5 times more than females among those with IQ in the normal range, and up to twice more in males among those with intellectual disability (Fombonne, 2005). However, recent epidemiological studies suggest a male-to-female ratio of 3:1 regardless of IQ (Idring et al., 2012; Mattila et al., 2011).

The present classification systems and diagnostic criteria of mental disorders are described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013) and the International Classification of Diseases (ICD-10; WHO, 1992). In both systems, ASD is described as a childhood-onset condition characterised by marked and persistent impairment which, according to the more up-to-date DSM-5 (APA, 2013), falls in two broad domains: (1) reciprocal social communication and interaction across multiple contexts and (2) restricted or repetitive patterns of behaviour. Individuals with ASD have difficulties in conversational turn-taking, reduced amount of information sharing, poorer quality and quantity of social overtures, and difficulties in maintaining social interactions once started. Atypical language development such as delayed comprehension and expression is a common feature, although it is not a criterion for diagnosis (Lai, Lombardo, & Baron-Cohen, 2014), as well as repetitive or unusual use of language. Nonverbal communications for social purposes are also reduced among individuals

with ASD, and where present, their elements such as facial expression, gestures and eye contact appear to be poorly integrated. Understanding of social relationships may be limited to immediate familial relationships, with little insights into the subtleties of other type of relationships like acquaintances, friendships, or spousal relationships, and their own possible roles in them. These may lead to difficulties in making and keeping friends or developing relationships with intimate partners (Howlin, Moss, Savage, & Rutter, 2013; Mendelson, Gates, & Lerner, 2016).

Classic accounts of children with autism describe their “obsessive desire for the maintenance of sameness” (Kanner, 1943, p. 245). These can range from having ritualised behaviour such as doing activities in a specific sequence, using the exact same route when travelling, arranging objects in a specific order, to having rigid ways of thinking. Families of children with autism often need to accommodate or adapt to these rigid behaviours (e.g., Marquenie, Rodger, Mangohig, & Cronin, 2011) due to the extreme distress the children experience when encountering changes. Stereotyped movements are usually evident in children with autism. This can include simple motor movements such as hand flapping or more complex whole body movements such as rocking, although this might be more limited in adulthood (Chowdhury, Benson, & Hillier, 2010; Howlin et al., 2013). Other behaviours that can manifest in individuals with ASD include unusually restricted interests in certain objects or topics, with high intensity and strong attachment to such preoccupations. Finally, individuals with autism may have unusual sensory responses. This could be in the form of extreme sensitivity to smell, touch or sounds, or indifference to pain, or temperature (see Table 1-1 for the complete diagnostic criteria). Given the range of possible symptoms, heterogeneous presentations with differing severity, type and frequency are not uncommon in ASD (S. E. Levy, Mandell, & Schultz, 2009). For

this reason, the present DSM-5 introduces severity specifiers and modifiers to acknowledge the heterogeneity of the condition.

Table 1-1: DSM-5 diagnostic criteria for ASD

- A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested, by the following, currently or by history (examples are illustrative, not exhaustive):
1. **Deficits in social-emotional reciprocity**, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
 2. **Deficits in nonverbal communicative behaviours used for social interaction**, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
 3. **Deficits in developing, maintaining, and understanding relationships**, ranging, for example, from difficulties adjusting behaviour to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behaviour.

- B. Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):
1. **Stereotyped or repetitive motor movements, use of objects, or speech** (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
 2. **Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behaviour** (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
 3. **Highly restricted, fixated interests that are abnormal in intensity or focus** (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
 4. **Hyper- or hypo-reactivity to sensory input or unusual interests in sensory aspects of the environment** (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity:

Severity is based on social communication impairments and restricted, repetitive patterns of behaviour.

- C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
- D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
- E. These disturbances are not better explained by intellectual disability (intellectual developmental

disorder) or global developmental delay.

Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:

With or without accompanying intellectual impairment

With or without accompanying language impairment

Associated with a known medical or genetic condition or environmental factor

Associated with another neurodevelopmental, mental, or behavioural disorder

With catatonia

Note. The current diagnostic criteria for ASD according to the DSM-5 (APA, 2013). Major changes in the current criteria for ASD include the elimination of diagnostic subtypes, the merging of communication and social interaction difficulties as a defining domain, elimination of age-of-onset criterion, and the introduction of specifiers and modifiers to acknowledge the heterogeneity of ASD.

Also relevant is the ICD-10 criteria (WHO, 1992), which is adhered to by clinicians worldwide. The criteria and classification system of ASD in the ICD-10 differ from the DSM-5 in several core features, primarily in the classification of the disorder. The ICD-10 describes autism within the umbrella term of pervasive developmental disorders (PDD), which consists of several subdivisions similar to those previously described in the DSM fourth edition (APA, 2000). These categories are (1) childhood autism, (2) atypical autism, (3) Rett's syndrome, (4) other childhood disintegrative disorder, (5) over-active disorders associated with mental retardation and stereotyped movements, (6) Asperger's syndrome, (7) other PDD, and (8) PDD unspecified. The current ASD category of the DSM-5 consists of a subset of these ICD-10 categories. Thus, only descriptions pertaining to these ICD-10 PDD subcategories will be given here.

Childhood autism is a category defined by abnormal development in three domains of impairments of social interaction, communication and restricted or

repetitive behaviour, apparent before the age of 3 years. Children with childhood autism, which also includes those given the diagnoses of autistic disorder, infantile autism or Kanner's autism may have normal IQ. In such case, the children are described as having high-functioning autism (HFA). However, approximately three quarters of the childhood autism cases in fact have intellectual disability, that is, IQ below 70 (e.g., Charman et al., 2011; Postorino et al., 2016). Individuals with atypical autism differ from those the previous category in that they do not fulfil the onset criteria, that is, showing symptoms before the age of 3 years, or are not impaired in all three domains. Children with Asperger's syndrome are characterised by the same difficulties as those with childhood autism. However, they differ from the latter by not having an additional language or cognitive impairment and by reaching normal expressive language milestones. Furthermore, individuals with Asperger's syndrome are mostly of normal intelligence.

Some distinctions between the two diagnostic criteria and classification systems are worthy of discussion. First, the DSM-5 reduces the number of domains of impairment by merging the social interaction and communication domains presently separated in the ICD-10. Deficits in communication are closely related to difficulties in social interaction. Studies have shown that symptoms underlying these separated domains load into a single factor representing social behaviour and verbal and nonverbal communication (T. Frazier et al., 2012; Mandy, Charman, & Skuse, 2012). Therefore, by separating these symptoms into two domains, clinicians would run the risk of counting the same symptoms twice. Second, the DSM-5 merges the subcategories of PDD to reflect the recent consensus that autism is best viewed as a spectrum "with variable manifestations across life span, gender, and intellectual level and/or language ability" (Happé, 2011, p. 540). Evidence suggests that the subcategories of the autism spectrum were poorly defined, particularly for individuals with Asperger's syndrome who often received the

diagnosis of HFA (Klin, Pauls, Schultz, & Volkmar, 2005; Mayes, Calhoun, & Crites, 2001). In addition, the inter-rater agreements between the subcategories of autism were weak (Klin, Lang, Cicchetti, & Volkmar, 2000; Mahoney et al., 1998; van Daalen et al., 2009). This was probably because clinicians relied more on their idiosyncratic systems when assigning diagnostic subgroups, rather than using the characteristics of the children, as findings from a multisite study recently suggested (Lord, 2012).

1.2.2 Outcomes of Individuals with ASD

ASD is commonly regarded as a lifelong condition with no cure. Research has shown that almost all individuals with ASD retain their diagnoses from childhood to adolescence/young adulthood (Louwerse et al., 2015), and to adulthood (Billstedt, Gillberg, & Gillberg, 2005; Cederlund, Hagberg, Billstedt, Gillberg, & Gillberg, 2008; Farley et al., 2009). Although symptoms persist for the majority, there have been some contrasting findings. Improvements of overall symptoms have been reported in some individuals in adulthood (Cederlund et al., 2008; Farley et al., 2009; Gray et al., 2012; Piven, Harper, Palmer, & Arndt, 1996), as well as specific improvements in the domain of stereotyped and repetitive behaviour or interests (Chowdhury et al., 2010; Howlin et al., 2013). Improvements of symptoms are modest on average although considerably heterogeneous across individuals, with higher IQ and early language status among predictors of better outcomes in adulthood (Seltzer, Shattuck, Abbeduto, & Greenberg, 2004). Most recently, a few studies have reported a minority of individuals with an early history of ASD who reached an “optimal outcome” and no longer met the diagnostic criteria at the time of the report (Fein et al., 2013; Mukaddes, Tutkunkardas, Sari, Aydin, & Kozanoglu, 2014; Troyb et al., 2014). A series of studies on a group of these individuals, aged 8-21 years, reveal performance on par with their typically developing peers in adaptive behaviours, facial recognition, language, and academic ability (Fein et al., 2013;

Troyb et al., 2014), although difficulties in social insights, attention and self-control ability are still evident (Orinstein et al., 2015).

Regardless of these positive findings, the general outcomes remain poor for most adults with ASD. Adults with ASD encounter more difficulties in further education and gainful employment compared to their typically developing peers or people with disability other than autism (Howlin et al., 2013; Roux et al., 2013; Shattuck et al., 2012; S. W. White et al., 2016). Interpersonal difficulties and social exclusion (Baldwin, Costley, & Warren, 2014; Howlin et al., 2013; Roux et al., 2013), as well as difficulties in managing competing demands (S. W. White et al., 2016) might just be few factors that contribute to these difficulties. Many adults with ASD, even those with average nonverbal IQ in childhood, have poor adaptive skills and will need continuous supports from their parents (Cederlund et al., 2008; Chamak & Bonniau, 2016; Howlin et al., 2013) and for the parents, meeting the support needs of their sons and daughters may become an increasing burden as they themselves age (Chamak & Bonniau, 2016; Howlin et al., 2013).

1.2.3 Neurocognitive deficits and associated neuroimaging findings in ASD

From the neurocognitive perspectives, individuals with ASD are thought to have deficits in three domains of cognitive functions: theory of mind (ToM), i.e., the ability to “mentalise” or attribute and infer mental states such as beliefs, intentions, or emotions of others (Baron-Cohen, Leslie, & Frith, 1985); executive function (EF), i.e., the ability to maintain goal-directed behaviour and self-control (Banich, 2009); and central coherence, i.e., a detail-focused cognitive style (Happé & Frith, 2006). Evidence shows that these neurocognitive deficits do not always manifest together in an individual with ASD (reviewed in Happé & Ronald, 2008; Happé, Ronald, & Plomin, 2006), hence a recent conceptualisation of “fractionable” cognitive deficits in ASD (Brunsdon & Happé, 2014). As this thesis encompasses only two of these

cognitive domains, i.e., ToM and EF, the scope of this brief review is limited to these two domains only.

The ToM deficits among children with autism were found in landmark study by Baron-Cohen et al. (1985). In this study, children with autism aged 6-16 years were compared to age-matched children with Down's syndrome and neurotypical children age 3-5 years. While approximately 85% children with Down's syndrome and controls passed the ToM test "False-Belief" task, 80% of the autistic children failed, suggesting common ToM deficits in this population. Subsequent replication of these findings (Brent, Rios, Happé, & Charman, 2004; Kaland, Callesen, Møller-Nielsen, Mortensen, & Smith, 2008) alongside findings of reduced joint attention, i.e., shared attention on object or events (Dawson et al., 2002; Hurwitz & Watson, 2015), and in recognising emotional expressions on faces (Hobson, 1986a, 1986b) indicate an extensive social cognition (SC) impairment in the ASD population. Meta-analytic studies suggest a large effect size of impairment in facial emotion recognition (FER; Lozier, Vanmeter, & Marsh, 2014; Uljarevic & Hamilton, 2013) and ToM difficulties (Yirmiya, Erel, Shaked, & Solomonica-Levi, 1998), although significant variation is apparent across studies for the FER deficits. Of particular relevance to this thesis, a meta-analysis comparing ToM performance on separate samples of IQ-matched individuals with ASD and ADHD indicated significantly poorer performance in the former relative to the ADHD group with a medium effect size (Bora & Pantelis, 2015). To date, it is unclear whether ToM difficulties in individuals with ASD follow a pattern of delayed or atypical development. Many adults with ASD perform worse than typically developing controls on the ToM task (Heavey, Phillips, Baron-Cohen, & Rutter, 2000; Rogers, Dziobek, Hassenstab, Wolf, & Convit, 2007; Spek, Scholte, & Van Berckelaer-Onnes, 2010; S. J. White, Coniston, Rogers, & Frith, 2011), suggesting a persistent difficulty. However, a recent study of nearly 120 adults with ASD aged 20-79 years showed comparable

ToM performance among older (> 50 years old) participants relative to those with no ASD (Lever & Geurts, 2015). Interpretations based on these cross-sectional findings are constrained, however, as age-dependent changes may differ between the ASD group from the typical developing controls. Long-term longitudinal studies will be required one day to shed some light on the development of ToM in ASD.

Neuroimaging studies of typically developing individuals show that ToM tasks are associated with activations in the frontal-posterior network, particularly the bilateral temporo-parietal junction (TPJ), posterior cingulate cortex (PCC), and medial prefrontal cortex (mPFC), as well as precuneus and bilateral middle temporal gyrus (see meta-analyses Van Overwalle, 2009; van Veluw & Chance, 2014). In addition, tasks that elicited self-awareness activated superior temporal gyrus (STG), the right parahippocampal gyrus (PHGy), the right inferior frontal gyrus (IFG), anterior cingulate cortex (ACC) and the left IPL. An example of a ToM task within the fMRI environment is the Frith-Happé animated triangle, which contrasts an individual's mental states attribution towards geometric objects during movements portraying complex mental states, e.g., persuasion or pretence, against random motion (e.g., Kana, Keller, Cherkassky, Minshew, & Just, 2009). Studies in children with ASD have shown reduced activations in the mPFC, the left anterior paracingulate and rostral anterior cingulate cortex (rACC), and the left inferior orbitofrontal cortex (OFC). They have also found the insula and TPJ to be under-activated and functionally under-connected during tasks involving mentalising (Kana et al., 2015, 2009). In adults with ASD, a PET study has shown similarly reduced activations in the basal temporal, superior temporal sulcus (STS; a neighbouring area to the TPJ) and mPFC during a mentalising task (Castelli, Frith, Happé, & Frith, 2002). A recent sophisticated study in adults with ASD has investigated judgements about the mental or physical states of the *self* or *familiar* others. The study, which contrasted the participants' reflective mentalising to questions such as

“How likely are *you* to think that keeping a diary is important?” and “How likely is the *Queen* to have bony elbows?” (Lombardo, Chakrabarti, Bullmore, & Baron-Cohen, 2011, pp. 1833–1834), revealed hypoactivation in the right TPJ in the ASD group compared to age- and IQ-matched controls. Specific impairments of the TPJ thus appear to be associated with mentalising difficulties among people with autism.

In addition to SC deficits, individuals with ASD often demonstrate executive dysfunction (E. L. Hill, 2004; Pennington & Ozonoff, 1996). The findings from several reviews and meta-analyses, however, point out substantial inconsistencies across studies (e.g., Geurts, Corbett, & Solomon, 2009; Geurts, Sinzig, Booth, & Happé, 2014; Kuiper, Verhoeven, & Geurts, 2016; Landry & Al-Taie, 2016). Meta-analyses of neurobehavioural studies show that findings of response inhibition (e.g. Geurts, van den Bergh, & Ruzzano, 2014; Kuiper et al., 2016), as well as cognitive flexibility among people with ASD (reviewed in Geurts et al., 2009; Landry & Al-Taie, 2016) demonstrate significant heterogeneity across studies. Mixed findings have been attributed to differences in autism severity, age and IQ across samples, but some researchers also suggest that EF deficits might be mediated by other factors such as comorbid psychopathology like ADHD (Geurts et al., 2009; J. M. J. van der Meer et al., 2012), or even the primary deficits of mentalising (S. J. White, 2013). Other executive deficits that have been found to be impaired in studies of individuals with ASD include planning (see, e. g., R. Booth, Charlton, Hughes, & Happé, 2003; Ozonoff & Jensen, 1999; Van Eylen, Boets, Steyaert, Wagemans, & Noens, 2015; D. Williams & Jarrold, 2013), visuospatial working memory (reviewed in Barendse et al., 2013; see also Fried et al., 2016; Merchán-Naranjo et al., 2016), and also generativity and verbal fluency (Kenworthy et al., 2013; Turner, 1999).

Several fMRI findings suggest prefrontal functional impairments as the underpinning of EF deficits in autism, although variations effect size, regions recruited by the cognitive task, and the hemispheric laterality of the effect are

apparent across studies. For instance, adults with ASD showed not only under-activated key inhibitory regions in right inferior frontal gyrus (IFG), thalamus (Daly et al., 2014) and right insula (Kana, Keller, Minshew, & Just, 2007; Shafritz, Bregman, Ikuta, & Szeszko, 2015), during motor response inhibition tasks, but also *over-activated* IFG (Duerden et al., 2013), and under-activated regions unrelated to motor inhibition such as the PCC, lingual and middle occipital gyri (Solomon et al., 2014). Individuals with ASD demonstrate reduced activation in the ACC (Fan et al., 2012; Shafritz, Dichter, Baranek, & Belger, 2008; Vaidya et al., 2011) during cognitive switching tasks, and reduced activation in the right dorsolateral prefrontal cortex (dlPFC) during the n-back working memory task (Chantiluke, Barrett, Giampietro, Brammer, Simmons, & Rubia, 2015). Unusual recruitment of brain regions may be related to compensatory mechanisms. For instance, some children with ASD seemed to rely on the middle occipital gyrus and FFG during a working memory task, because these regions were up-modulated in response to increased working memory load (Vogan et al., 2014). Furthermore, during sustained attention, a left cerebellar activation, instead of the typical dlPFC activation, were found among boys with ASD compared to controls, which was associated with less severe performance deficits (Christakou et al., 2013). These examples show that recruitment of brain regions other than those typically activated during a task might be needed to compensate for cognitive performance.

The heterogeneity of ASD is also reflected in the findings of structural neuroimaging studies (e.g., Katuwal, Baum, Cahill, & Michael, 2016; Lenroot & Yeung, 2013; Salmond, Vargha-Khademl, Gadian, de Haan, & Baldeweg, 2007; Sussman et al., 2015). Reviews of structural imaging studies suggest alterations in several grey matter regions including the amygdala, cerebellum and fusiform gyrus, and also findings of abnormalities of the white matter and cortical thickness (Amaral, Schumann, & Nordahl, 2008; R. Chen, Jiao, & Herskovits, 2011; Salmond et al.,

2007). Meta-analyses of grey matter volume (GMV) find abnormalities in the temporo-parietal regions, including MTG, precuneus and the posterior cingulate and lateral frontostriatal areas, as well as ACC, caudate and the opercular areas (Cauda et al., 2011; Nickl-Jockschat et al., 2012). Although the findings may change across ages in atypical manner relative to typically developing individuals, as the brain of individuals with autism undergo rapid overgrowth in early years and accelerated decline from late adolescence to middle age (Courchesne, Campbell, & Solso, 2011). Other factors such as age, IQ, autism severity and sex, most likely influence the heterogeneity of brain deficits in individuals with ASD as well because stratifying samples by these variables may improve the detection of cases (Katuwal et al., 2016; Lai et al., 2013).

1.3 ADHD: Clinical Presentation, Neurocognitive and Neuroimaging Correlates

1.3.1 Prevalence and Diagnostic Criteria

With a prevalence rate of 5-7% in children (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014; Willcutt, 2012), ADHD is considered one of the most common neurodevelopmental disorders. Similar to ASD, boys are more likely to have the diagnosis of ADHD than girls, with a ratio of 2.5:1 approximated from a mixture of clinical and population-based studies (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). The ADHD prevalence rates among adults based on meta-analyses are 2.5-3.4% with the data suggesting approximately equal ratios between males and females (Fayyad et al., 2007; Simon, Czobor, Bálint, Mészáros, & Bitter, 2009).

The DSM-5 classification (APA, 2013) defines ADHD as a persistent pattern of inattention and/or hyperactivity and impulsivity that is developmentally inappropriate and interferes with functioning or development. Individuals meeting

the diagnostic criteria of ADHD may display one of three possible presentations formerly known as “subtypes” (APA, 2000). These presentations are: (1) combined inattention and hyperactivity/impulsivity, (2) predominantly inattentive presentation, and (3) predominantly hyperactive/impulsive presentation. The use of the term presentation instead of subtype reflects the recognition that symptoms of individuals with ADHD are changeable across their lifespan and not a stable trait as implied by the term subtype (Epstein & Loren, 2013). To fulfil the diagnosis criteria of ADHD children must demonstrate at least six symptoms of inattention and/or six symptoms of hyperactivity and impulsivity while the threshold of symptoms is reduced to five in adults. For both age groups, symptoms must have been present before the age of 12 years in more than one setting. Briefly, typical symptoms of inattention may include being careless and not paying attention to details, having difficulties in sustaining attentions in tasks or activities, not listening when spoken to directly, and being easily distracted and forgetful in day-to-day activity. Meanwhile, symptoms of hyperactivity and impulsivity can include being fidgety, being unable to stay seated or be still, having excessive energy, having difficulties in doing things quietly, being “on the go”, talking excessively, intruding on or interrupting others, and in adulthood, spending impulsively or starting and stopping new jobs or relationships abruptly (Kooij et al., 2010; Table 1-2).

The equivalent diagnostic category for ADHD in the ICD-10 classification system is called the “hyperkinetic disorder” (HKD). The disorder is described as early onset with symptoms of inattention, over-activity and poorly modulated behaviour, as well as lack of persistence in tasks which are apparent from before the age of 6 years for long duration. Clinically, hyperkinetic disorder is more severe in presentation than ADHD. This is so because its diagnostic criteria require symptoms to be present in all three domains of hyperactivity, impulsivity, and inattention (Swanson et al., 1998). Therefore, only individuals with ADHD combined

presentation based on the DSM criteria can meet the fundamental diagnostic requirement of HKD. Striving for one single diagnosis for every person, the ICD-10 system also applies a more stringent exclusionary criterion for co-occurring psychiatric disorders for HKD than the DSM's ADHD. Diagnoses are not to be given in the presence of internalising symptoms of affective disorders. A special provision is given to individuals with HKD and conduct disorders, who will be given the specific diagnosis of "hyperkinetic conduct disorder" diagnosis (WHO, 1992). Finally, the diagnostic criteria for HKD require higher level of cross-situational pervasiveness than the ADHD. For these reasons, epidemiological studies of prevalence rates of the HKD, which is 1-2%, is lower than the prevalence rates of ADHD (Swanson et al., 1998).

Table 1-2: DSM-5 diagnostic criteria for ADHD

- A. Persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development as characterized by (1) and/or (2)
1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
Note: The symptoms are not solely a manifestation of oppositional behaviour, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
 - a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
 - b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
 - c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
 - d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily side tracked).
 - e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
 - f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
 - g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
 - h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).

- i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

2. **Hyperactivity and Impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

Note: The symptoms are not solely a manifestation of oppositional behaviour, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

- a. Often fidgets with or taps hands or feet or squirms in seat.
- b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
- c. Often runs about or climbs in situations where it is inappropriate (**Note:** In adolescents or adults may be limited to feeling restless).
- d. Often unable to play or engage in leisure activities quietly.
- e. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experience by others as being restless difficult to keep up with).
- f. Often talks excessively.
- g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
- h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
- i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more setting, (e.g., at home, school, or work; with friends or relatives; in other activities).

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

E. The symptoms do not occur only during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.

Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.

Predominantly hyperactive/impulsive presentation: If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Specify if:

In partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.

Moderate: Symptoms or functional impairment between "mild" and "severe" are present.

Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning

Note. The current diagnostic criteria for ADHD, taken from the DSM-5 (APA, 2013). Noted changes in the current criteria for ADHD include onset age before 12 years instead of 7 years, having symptoms instead of impairments in more than one settings, the addition of descriptions appropriate for adults, and a threshold of minimum five symptoms for adolescents and adults aged 17 years and older, the use of the term presentation rather than subtype, and the introduction of severity specifiers (see also text). Importantly, ASD no longer precludes the diagnosis of ADHD and a dual diagnosis is now permitted.

The onset criteria for ADHD and hyperkinetic disorder, which are 12 years and 6 years, respectively, are one major difference between the two diagnostic systems. The relaxed onset criterion adopted by the DSM-5 is expected to improve recognition of certain groups (e.g., those with high intelligence or predominant inattention) whose symptoms are only evident upon increased demands for self-organisation, for instance during middle school or older years. It is also expected to better detect individuals whose symptoms are not recognised until adulthood and who may no longer remember many of their childhood symptoms (Epstein & Loren, 2013). In support to these new criteria, studies have shown that individuals with either age onsets have similar features as would be expected from an arbitrary criterion for distinction. Both groups of individuals demonstrate similar symptom severity and functional impairments, patterns of comorbidity, and neuropsychological deficits (e.g., Faraone et al., 2006; Guimarães-da-Silva et al., 2012; Karam et al., 2009; Y. J. Lin, Lo, Yang, & Gau, 2015; Vande Voort, He, Jameson, & Merikangas, 2014). It is uncertain whether the older onset threshold will be similarly adopted in the next revision of the ICD but this recommendation has been made by some researchers (Todd, Huang, & Henderson, 2008).

1.3.2 Outcomes of Individuals with ADHD

The notion that children grow out of their ADHD during puberty was popular until the 1990s (Barkley, 2006). Indeed, evidence suggests that hyperactivity becomes less obvious in adulthood while inattention is relatively more persistent (Kooij et al., 2010). Consequently, many children with a combined ADHD presentation turn to have the inattentive presentation as adults (Biederman, Mick, & Faraone, 2000;

Cheung et al., 2015; van Lieshout et al., 2016). Nevertheless, there is also evidence that ADHD symptoms persist in adulthood in many individuals diagnosed in childhood. In a previous study, at least 15% of children met ADHD criteria at 25 years of age, with a further 25 to 45% described as having significant impairments (Faraone, Biederman, & Mick, 2005). More recent studies have suggested increasing rates of ADHD diagnosis retainers among adults, possibly due to improved diagnostic criteria for adults. A 10-year follow-up study of over 100 males with childhood ADHD showed that a third of cases still met the diagnostic criteria in adulthood, and 78% continued to exhibit symptoms and other persistent problems such as having additional psychiatric comorbidities, low educational attainment, and interpersonal problems (Biederman, Petty, Evans, Small, & Faraone, 2010). Approximately between 33% and 84% ADHD diagnosis retainers have been reported among 600 adults across 10 countries (Lara et al., 2009). Furthermore, two recent follow-up studies of children seen in paediatric mental health clinics in southeast England and the Netherlands have found approximately 80% ADHD diagnosis retainers in young adulthood (Cheung et al., 2015; van Lieshout et al., 2016).

Like those with ASD, individuals with ADHD often have poor outcomes in adulthood. Reports suggest that young adults with ADHD are less likely to attend higher education, more likely to drop out, and have lower grades compared to their peers (Advokat, Lane, & Luo, 2011; Barkley, 2002; Blase et al., 2009; DuPaul, Weyandt, O'Dell, & Varejao, 2009). Psychosocial and psychiatric difficulties (which include antisocial behaviour, mood and anxiety disorders, familial conflicts, nicotine dependence, and alcohol and drug addictions) are present at higher rates in adults with ADHD compared to typically developing controls (Biederman et al., 2012). Adults with ADHD are less likely to be in employment, more likely to be financially dependent on their parents (Gjervan, Torgersen, Nordahl, & Rasmussen, 2012),

more likely to have job changes, less satisfied with their professional lives and have lower socioeconomic status compared with their typically developing peers (Biederman, Faraone, et al., 2006). Findings have also suggested that employees with ADHD experience more workplace injuries, have reduced work performance and are often out of work, which might be compounded by additional problems of depression and anxiety (Halmøy, Fasmer, Gillberg, & Haavik, 2009; Kessler, Lane, Stang, & Van Brunt, 2009).

Evidence have suggested, however, that ADHD symptoms can be managed effectively with pharmacotherapy, using either stimulants such as methylphenidate (MPH) and dexamphetamine or nonstimulant medications such as atomoxetine (Biederman, Mick, et al., 2010; T. Spencer et al., 2005). Response rates to stimulant medications are particularly high with 70 to 90% children and adult patients responding to first- or second-choice stimulants (Biederman, Mick, et al., 2010; Fridman, Hodgkins, Kahle, & Erder, 2015; T. Spencer et al., 2005; Wigal, 2009). Treatments also typically result in large effect-sizes in symptom reductions (Faraone & Buitelaar, 2010; Fridman et al., 2015; Wigal, 2009). Effective treatments in children are associated with improved on-task behaviour and increased completion of academic work (Prasad et al., 2013) and also better outcomes in adulthood (e.g., Adler et al., 2013; Asherson et al., 2015; M. Shaw et al., 2012; Sobanski, Schredl, Kettler, & Alm, 2008). An analysis of over 40 studies has shown that treatments in children and adults led to better self-esteem, social and academic function, and driving behaviour in the long-term compared to those untreated (M. Shaw et al., 2012). Some findings have also suggested that effective treatment enhance sleep quality (Boonstra et al., 2007; Kooij, Middelkoop, van Gils, & Buitelaar, 2001; Sobanski et al., 2008), emotional control, and overall quality of life (Adler et al., 2013; Asherson et al., 2015).

1.3.3 Neurocognitive deficits and associated neuroimaging findings in ADHD

Recent neurocognitive models of ADHD have undergone rapid evolution, expanding from the earlier model that focused on the “core” cognitive deficit of inhibition and EF (Barkley, 1997). When compared to typically developing controls, people with ADHD often demonstrate deficits in response inhibition, sustained attention, working memory, planning (reviewed by Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008), timing (reviewed by Noreika, Falter, & Rubia, 2013), and temporal reward discounting (Solanto et al., 2001; Sonuga-Barke, Dalen, & Remington, 2003). Results across studies appear consistent, possibly more so than in ASD based on formal analyses of heterogeneity in several meta-analyses, especially in inhibition, sustained attention, and working memory (Alderson, Kasper, Hudec, & Patros, 2013; Alderson, Rapport, & Kofler, 2007; Kasper, Alderson, & Hudec, 2012; Lipszyc & Schachar, 2010; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Across *individuals* with ADHD, however, there is considerable variation of findings. That is, some individuals may have difficulties in one set of cognitive tasks but not in others. Approximately 75 to 80% of individuals in the ADHD group (vs. 40 to 50% controls) are characterised by at least one impaired EF task performance beyond the 90th percentile (Coghill, Seth, & Matthews, 2014; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). The current model of ADHD hypothesises that there are multiple independent pathways towards the disorder, which include deficits in temporal reward discounting, inhibition, and timing (de Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012; Sonuga-Barke, Bitsakou, & Thompson, 2010). These deficits, occurring singly or in combinations in an individual, are thought explain the individual differences of cognitive findings in ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008; see also Fair, Bathula, Nikolas, & Nigg, 2012; Mostert, Hoogman, et al., 2015 for the latest conceptualisation of the multiple-pathway model).

Findings have suggested persistent EF deficits in many adults with ADHD diagnosed in childhood (Bédard, Trampush, Newcorn, & Halperin, 2010; Biederman et al., 2007, 2009; M. Miller, Ho, & Hinshaw, 2012; Nigg, Butler, Huang-Pollock, & Henderson, 2002), despite reports of reduced behavioural symptoms in the population (Bédard et al., 2010; Kooij et al., 2010). Compared to age-matched controls, college students with combined ADHD presentation in childhood and persistent symptoms in adulthood have deficits in effortful motor inhibition (Nigg et al., 2002). Furthermore, Biederman et al. (2007) have found that a large proportion of individuals displaying at least two impaired EF tests in childhood (i.e., performance 1.5 standard deviation away from controls) continue to do so in adulthood. Importantly, adults who demonstrated impaired performance of EF, based on the above definition of impairment, were found to have lower educational and occupational attainment, and adaptive social and leisure functioning than those who did not, suggesting that individuals with EF impairments also have more severe impairment (Biederman, Petty, et al., 2006). Recent investigations have extended these findings by showing that EF deficits persisted even in adults with ADHD who already reached a partial remission status (Bédard et al., 2010). This finding suggests that EF deficits are a stable trait among those with childhood ADHD regardless of their diagnostic status in adulthood.

EF deficits in ADHD were traditionally linked with abnormalities in the lateral frontostriatal circuitries. However, recent findings have shown that the impairments also extended into the orbito-fronto-striatal and frontocerebellar circuitries (Cubillo, Halari, Smith, Taylor, & Rubia, 2012; Durston, van Belle, & de Zeeuw, 2011). The lateral frontostriatal circuitries and the dorsal ACC are associated with higher order function such as response inhibition, working memory, and attentional control (see e.g., Arnsten & Rubia, 2012; Aron, 2011). A meta-analysis of 55 EF studies of individuals with ADHD have revealed consistent under-activation in the fronto-

striato-temporo-parietal regions in children, and in the right central sulcus, precentral gyrus (pre-CG), and middle frontal gyrus (MFG) in adults with ADHD relative to controls (Cortese et al., 2012). In the context of the neural correlates of response inhibition, recent meta-analyses have shown predominant under-activations in the right IFG/insula, supplementary motor area (SMA)/dmPFC and basal ganglia (BG) among individuals with ADHD (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Norman et al., 2016).

The vmPFC and OFC mediate top-down control of affect and motivation through their interactions with the amygdala and striatum (Dolan, 2007; Kringelbach, 2005). The orbito-fronto-striatal circuitries are implicated in ADHD during delayed reward task (Plichta & Scheres, 2014). Specifically, reduced activations are found in the striatum during reward anticipation (Kappel et al., 2015; Plichta & Scheres, 2014) and increased activations in this region are observed instead during reward receipt (Furukawa et al., 2014; Stroehle et al., 2008; Von Rhein et al., 2015). The cerebellum, traditionally implicated in the planning and execution of movement, is now thought to also play role in higher order processes including language processing, spatial processing, emotional processing, working memory, inhibition, vigilance, and timing (Baumann et al., 2015; Stoodley, 2012; Strick, Dum, & Fiez, 2009). Correspondingly in ADHD, abnormal cerebellar activation has been observed, mostly in the lateral and medial parts, in conjunction with frontostriatal deficits during sustained attention (Cubillo et al., 2012; Rubia, Halari, Cubillo, et al., 2009) and inhibition (Cubillo et al., 2014; Hart, Chantiluke, et al., 2014; Rubia, Halari, Mohammad, Taylor, & Brammer, 2011). Findings from a meta-analysis of fMRI studies in finger tapping, temporal foresight or perceptual timing tasks have suggested that the right cerebellar under-activations, left IFG/insula, left supramarginal gyrus/STG and right dlPFC were neural correlates of poor interval timing among ADHD patients (Hart, Radua, Mataix-Cols, & Rubia, 2012).

Furthermore, abnormal functional connectivity between cerebellum and prefrontal, striatal, and parietal regions were found during attention and working memory performance (Massat et al., 2012; Rubia, Halari, Cubillo, et al., 2009).

Findings of functional impairment in the frontal lobe of people with ADHD are consistent with the maturational delay hypothesis (El-Sayed, Larsson, Persson, Santosh, & Rydelius, 2003; Rubia, 2007; P. Shaw et al., 2007; Sripada, Kessler, & Angstadt, 2014). First suggested by Kinsbourne (1973), who noticed the behavioural resemblance of children with ADHD with younger children, the delayed maturation hypothesis has provided an explanation for the frontal-lobe reliant EF performance deficits among individuals with ADHD (see e.g., Berger, Slobodin, Aboud, Melamed, & Cassuto, 2013). The hypothesis might also explain the symptom decline among adults with ADHD, which could be suggestive of a developmental “catch-up” (El-Sayed et al., 2003). Cortical maturation takes place in a “back-to-front” manner (Gogtay et al., 2004), occurring first in the primary sensory areas such as the somatosensory and visual cortices and last in higher order association areas such as the dlPFC, inferior parietal, cingulate cortex, and STG (Giedd et al., 2015; Gogtay et al., 2004; P. Shaw et al., 2008). P. Shaw et al. (2007) have shown that peak cortical thickness is reached on average 2 to 5 years later in ADHD than in typically developing adolescents, with the greatest delay observed at the middle frontal (5 years) and superior temporal cortices (4 years). Analyses of cortical surface areas and gyrification have also suggested similar delay in the ADHD group by approximately 2 years compared to the typically developing controls (P. Shaw et al., 2012), providing direct neuroanatomical support for the delayed maturational theory in ADHD.

1.4 The Co-occurrence of ASD and ADHD and Models of Comorbidity

1.4.1 Prevalence, Clinical Characteristics, and Treatments

Despite their distinctive clinical presentations, symptoms of ASD and ADHD frequently co-occur (Gjevik et al., 2011; Grzadzinski et al., 2011; Kochhar et al., 2011; Leyfer et al., 2006; Salazar et al., 2015; Simonoff et al., 2008). It might seem difficult at first to picture the co-occurrence of ADHD symptoms such as “boisterousness” and “impulsivity” together with ASD symptoms such as “social aloofness” and “insistence on sameness”. However, ASD has a highly heterogeneous presentation and not everyone with the condition conforms to the socially-uninterested stereotype. An early epidemiological study described a substantial proportion (43%) of ASD children as “active but odd” (Wing & Gould, 1979). These socially motivated children were described as having over-bearing social overtures consisting of “pestering”; sometimes revolving around their circumscribed interests (Wing & Gould, 1979).

An early study using a multivariate analyses of ADHD symptoms among 166 ASD children showed that these symptoms were distributed among two groups thought to represent children with the Asperger’s and HFA (Eaves, Ho, & Eaves, 1994), which made up 25% of the entire sample. This rate is consistent with to the lowest estimate of ADHD diagnoses among clinically referred ASD in subsequent studies, that is, 23 to 83% (J. Frazier et al., 2001; Ghaziuddin, Weidmer-Mikhail, & Ghaziuddin, 1998; Kaat, Gadow, & Lecavalier, 2013; Mattila et al., 2010; Mukaddes, Hergüner, & Tanidir, 2010; van Steensel, Bögels, & de Bruin, 2013), although these estimates may be inflated by referral biases. In community samples of children with ASD, approximately 30 to 60% children meet the criteria for ADHD diagnosis (Gjevik et al., 2011; Leyfer et al., 2006; Salazar et al., 2015). Importantly, an estimated 28% of children with ASD in their middle childhood meet the criteria for

ADHD diagnoses according to epidemiological study of a small but representative population cohort “the Special Needs and Autism Project” (SNAP; Simonoff et al., 2008), confirming that ADHD occurs in the ASD population at rates above what is expected by chance. Interestingly, estimates of co-occurring ASD in the ADHD (10 to 40%), are lower than in the ASD populations (e.g., Carpenter Rich, Loo, Yang, Dang, & Smalley, 2009; Grzadzinski et al., 2011; Kochhar et al., 2011; A. Mulligan et al., 2009). These figures were not estimated rigorously, however, since they were derived from the number of cases of people with ADHD scoring beyond cut offs on single questionnaires, which is an inadequate method for diagnosing ASD (Risi et al., 2006). Nevertheless, the lower rates are not unexpected given the relatively higher base prevalence of ADHD compared to ASD.

In the absence of longitudinal studies following individuals with ASD+ADHD, the stability of ADHD symptoms in among adult population with ASD is presently unknown. Simonoff et al. (2013) have observed that the ADHD symptoms among 81 children with ASD seen in the SNAP cohort persisted into mid-adolescent years, although the issue of persistence has not been thoroughly investigated in this sample now that the children are reaching their young adulthood. In clinical samples of adults, approximately 37 to 46% of individuals of ASD meet the for current ADHD diagnosis, which were not different compared to ADHD diagnostic rates among non-ASD clinical referrals (Hofvander et al., 2009; K. Johnston et al., 2013; Joshi et al., 2013; A. J. Russell et al., 2016). A finding from one study contrasting the lifetime and current (68 versus 42%) ADHD diagnoses among adults with ASD suggested decreasing number of ADHD prevalence with age (Joshi et al., 2013). These findings may suggest that ADHD symptoms are not in fact overrepresented among adults with ASD, although clinical estimates are unlikely to be accurate due to sample biases. Nevertheless, the fact that ADHD symptoms are present in a

substantial proportion of adults with ASD warrants further investigation in this age group.

One way to understand the phenomenology of ADHD symptoms in the ASD+ADHD group is by exploring the similarities or differences in symptoms compared to those in the “pure” ADHD cases. Findings from past studies have suggested that the presentation and severity of ADHD symptoms in the ASD+ADHD are largely similar those found in the pure ADHD population (S. Goldstein & Schwebach, 2004; K. Johnston et al., 2013; Joshi et al., 2014). Similar profiles of ADHD symptoms are found between individuals with PDD+ADHD, combined or inattentive, and their pure ADHD counterparts in a thorough investigation involving retrospective chart reviews of developmental, psychosocial, and neuropsychological functioning (S. Goldstein & Schwebach, 2004). In addition, clinical ADHD presentations (i.e., combined, inattentive, and hyperactive) do not seem to be associated with any particular subcategories of the PDD according to a clinical study (K. Johnston et al., 2013). Where differences were detected, these were subtle. For instance, adults with PDD-NOS were found to have significantly more symptoms of inattention and hyperactivity/impulsivity than those with Asperger’s syndrome although the diagnostic rates among the PDD subgroups in this study did not differ from one another (Hofvander et al., 2009). More recently, youths with HFA+ADHD were found to show less carelessness, less tendency for not listening, but more problems waiting their turn and intruding on others than the pure ADHD group (Joshi et al., 2014).

ASD symptoms in the ASD+ADHD group are also similar to those found in the pure ASD group (Holtmann, Bölte, & Poustka, 2007; Salley, Gabrielli, Smith, & Braun, 2015; Yerys et al., 2009) when assessed using gold-standard measures such as the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) or the Autism Diagnostic Observation Schedule (ADOS; Lord et al.,

2000). Studies have suggested that children with ASD and with ASD+ADHD demonstrate the same number of social interaction, communication, and repetitive behaviour symptoms (Holtmann et al., 2007; Yerys et al., 2009) on the ADI-R or the ADOS. In contrast, autistic traits as judged on Social Responsiveness Scale (SRS; Constantino, 2011) are found increased in the ASD+ADHD relative to the ASD group (Yerys et al., 2009), although the difference in findings might be because SRS is designed for assessing broad spectrum of autistic traits in the general population. Most recently, a large study of over 200 children and youth with ASD, ADHD, ASD+ADHD and typically developing controls shows that communication and social interaction judged on the ADOS are similarly impaired in the ASD and ASD+ADHD groups, and substantially less impaired in the ADHD and controls, which do not differ from one another (Salley et al., 2015). These findings led the authors to suggest that ADOS could be used as an instrument to distinguish youth ADHD alone from those with ASD alone or with ASD+ADHD.

Despite the similarities between ASD and ADHD symptoms in the ASD+ADHD group compared to the pure groups, those with dual diagnoses are often reported to have more severe additional problems. Studies have shown that children with ASD+ADHD have more externalising behaviour, for example delinquencies, aggressive behaviours or conduct problems than children with ASD alone (F. Craig et al., 2015; Holtmann et al., 2007; Jang et al., 2013; Yerys et al., 2009) and those with ADHD alone (Goldin, Matson, Tureck, Cervantes, & Jang, 2013; Jang et al., 2013). Individuals with ASD+ADHD also display increased internalising symptoms than the pure groups, for instance, symptoms of withdrawal, anxiety and depression (Holtmann et al., 2007; Yerys et al., 2009). They demonstrate poorer adaptive skills in daily living (Rao & Landa, 2014; Sikora, Vora, Coury, & Rosenberg, 2012; Yerys et al., 2009), and socialisation and/or communication skills expected for their level of cognitive ability compared to those

with ASD or ADHD alone (Ashwood et al., 2015). Evidence also suggests that individuals with ASD+ADHD have poorer quality of life, judged from psychosocial and physical functioning (Sikora et al., 2012), as well as more emotional, behavioural and peer problems than those with ASD (S. Thomas, Sciberras, Lycett, Papadopoulos, & Rinehart, 2015).

Finally, conventional pharmacological treatments for ADHD symptoms given to children with ASD+ADHD appear to result in modest outcomes with lower response rates and effect size and more unfavourable side effects than those found in children with ADHD alone (Harfterkamp et al., 2012; Pearson et al., 2013; Posey et al., 2007; RUPP Autism Network, 2005). One double-blind randomised controlled trial (RCT) cross-over study reported a response rate of 49% to immediate release MPH among 66 children with ASD (RUPP Autism Network, 2005) and 20% to atomoxetine after an 8-week trial (Harfterkamp et al., 2012). The effect sizes of improvement for the optimal dose of MPH and atomoxetine are similarly lower in magnitude (Harfterkamp et al., 2012; Posey et al., 2007; RUPP Autism Network, 2005) when given to individuals with ASD+ADHD than in those with pure ADHD. Note that strict comparison cannot be made between these separate studies because of the variety of outcome measures used across investigations. Nevertheless, the somewhat different effect of ADHD medication among individuals with ASD+ADHD compared to those with ADHD alone might suggest that ADHD symptoms in ASD+ADHD have different underlying biology from those found in ADHD alone. The evidence based on these pharmacological trials is circumstantial, however, and the similarities or differences in ADHD phenotypes between the ASD+ADHD and the pure ADHD group must be directly investigated using a range of methodologies, including genetics, neurocognitive and neuroimaging studies.

1.4.2 Genetic Findings and the Conceptualisation of the Intermediate Phenotypes

Findings of molecular and behavioural genetic have shown influences that link ASD and ADHD (e.g., Polderman, Hoekstra, Posthuma, & Larsson, 2014; Ronald et al., 2014, 2008; N. M. Williams et al., 2010). Both autistic and ADHD traits are highly heritable (Chang, Lichtenstein, Asherson, & Larsson, 2013; Holmboe et al., 2014), thus the role of shared genetic risk factors in explaining the high phenotypic correlations is within the expectation. Twin studies in the general population have shown substantial genetic influences in the overlapping phenotypes of ASD and ADHD, as well as specific genetic influences for each disorder (Polderman et al., 2014; Reiersen et al., 2008; Ronald et al., 2014, 2008). Also interesting is the evidence from molecular genetic genome wide analysis studies that have shown that ADHD is associated with enriched copy number variants, i.e., large and rare deletions and repeats of chromosomes, in loci that have previously been reported in autism and intellectual disability (Langley et al., 2011; N. M. Williams et al., 2010).

Despite these compelling findings, the mechanism that leads to the co-occurring of the two disorders remains unclear. This is so because there are a myriad of biological and cognitive processes and thus multiple routes from genes to observable behavioural symptoms (Viding & Blakemore, 2007). In recent years, researchers have conceptualised the “endophenotypes”, which can be either mediating or moderating influences between genes and psychopathology (Kendler & Neale, 2010; Rommelse et al., 2011; Viding & Blakemore, 2007). The endophenotypes are “simpler clues to genetic underpinnings than the disease syndrome itself” (Gottesman & Gould, 2003, p. 636). Therefore, they are supposed to be stable and simpler phenotypes of syndromes that could facilitate investigation of their genetic roots. In the context of psychiatric disorders, one recent formulation of endophenotypes is as mediators, that is, the intermediate phenotypes, between

genes and symptoms (Banaschewski, Neale, Rothenberger, & Roessner, 2007; see also other models in Rommelse et al., 2011). Domains of cognitive functions such as EF, error processing, social cognition, temporal foresight, and sustained attention were among the candidate intermediate phenotypes, and several models of comorbidity involving some these intermediate phenotypes are discussed further below.

1.4.3 Alternative Explanations for the Co-occurrence of ASD and ADHD

1.4.3.1 Some Unlikely Explanations

In the current literature, several possible explanations have been evaluated for the increased co-occurrence of ASD and ADHD. Some of these explanations are unlikely and can be ruled out immediately based on the available findings. Firstly, the elevated co-occurrence ASD and ADHD is not an “artefactual” phenomenon (Caron & Rutter, 1991; Neale & Kendler, 1995) due to biased estimation or due to “nosological confusion” (Caron & Rutter, 1991, p. 1067). The classification of psychiatric disorders is often characterised by ambiguous boundaries, that can be partly caused by the presence of “nonspecific symptoms” (e.g. restlessness) which index for several psychopathologies.

The conservative estimate of the co-occurrence of ASD and ADHD is 28% according to the only epidemiological study by Simonoff et al. (2008). From the base rates for ASD and ADHD estimated by epidemiology studies of each disorder, the co-occurrence rate estimated by the epidemiological study is several-hundred times the rate of co-occurrence by chance. With respect to the nosological boundary issue, factor analyses of symptoms of ASD and ADHD among samples of children with ASD, with ADHD or a large population-based sample have shown little evidence for overlapping diagnostic criteria that could influence the number of comorbid cases (Ghanizadeh, 2010, 2012; J. Martin, Hamshere, O'Donovan, Rutter,

& Thapar, 2014). In these studies, symptoms of ADHD and ASD are typically separable into two-factor solutions of each disorder's symptoms (Ghanizadeh, 2012), or several factors representing the subdomains of symptoms such as social difficulties, repetitive behaviour, hyperactivity and inattention (Ghanizadeh, 2010; J. Martin et al., 2014).

Another explanation that seems unlikely is that ASD or ADHD gives rise to the other disorder or be its "pre-comorbid disorder" (Taurines et al., 2010). In this model, the manifestation of one disorder increases the risk of the other like a "domino effect" (Banaschewski et al., 2007), although their risk factors are uncorrelated. In this case, the role of pre-comorbid disorder in the co-occurrence of ASD and ADHD is likely to be taken by the ASD, particularly the childhood autism subcategory. This is so because childhood autism is apparent at earlier age of onset (< 3 years) and, thus hypothetically, should be the "cause" for the ADHD and not the other way around (Taurines et al., 2010). Yet reports of children with early ASD diagnosis who become primarily ADHD at later age are rare (see Fein, Dixon, Paul, & Levin, 2005 for few exceptions) and in fact up to 50% of children with diagnoses of ASD and ADHD, receive their ADHD diagnoses first before being diagnosed with ASD in later years (Davidovitch, Levit-Binnun, Golan, & Manning-Courtney, 2015; Frenette et al., 2013; Jensen, Larrieu, & Mack, 1997; Miodovnik, Harstad, Sideridis, & Huntington, 2015).

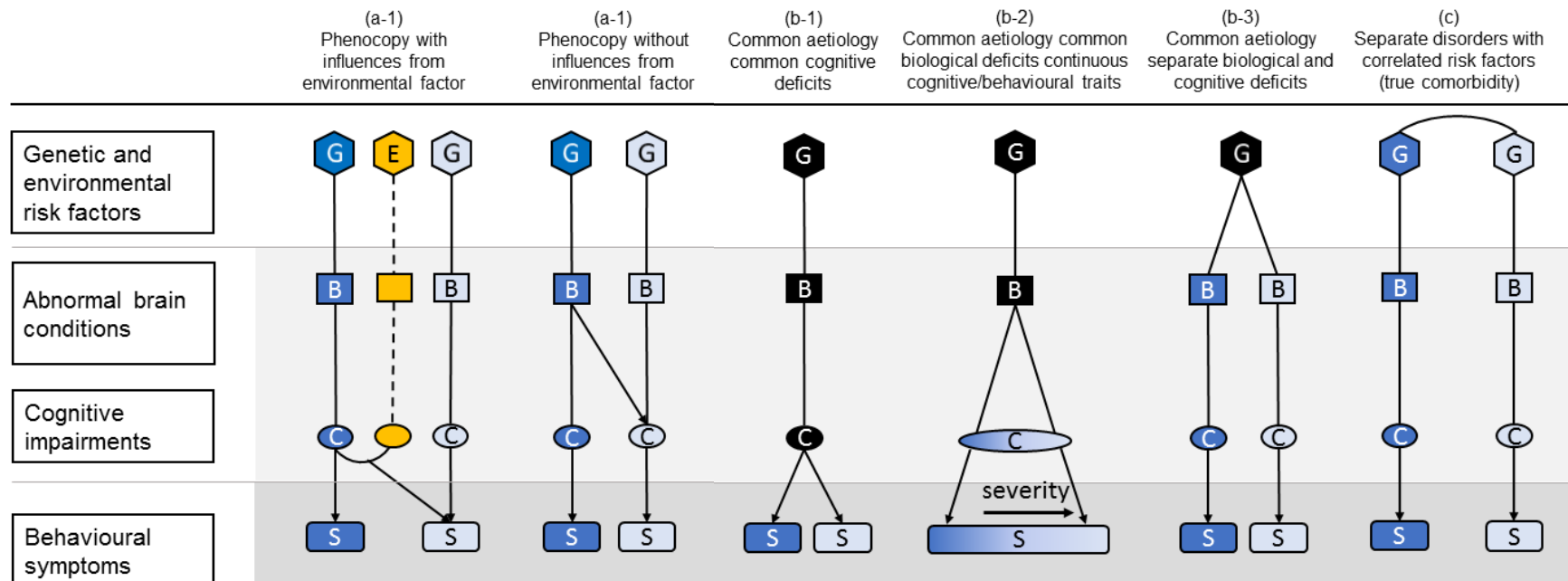
Equally unlikely is the argument that the cases where ADHD is recognised before ASD can represent instances where ADHD traits lead to ASD symptoms. There is very little evidence to suggest that treatments of ADHD have a major effect on the autistic traits in individuals with ASD+ADHD presentation (Harfterkamp et al., 2014; Pearson et al., 2013; Posey et al., 2006, 2007; RUPP Autism Network, 2005; Troost et al., 2006), which was expected if those autistic traits were rooted in the primary ADHD diagnosis. The largest effect of ADHD medication on the ASD-like

trait reported so far are in reducing the amount of inappropriate speech (Harfterkamp et al., 2014; Posey et al., 2006) which may reflect ADHD-related excessive talking (Harfterkamp et al., 2014). Further no study has reported the effects of these medications on reciprocal social behaviour, the cornerstone of ASD symptoms.

1.4.3.2 Possible Models for the Co-occurrence of ASD and ADHD

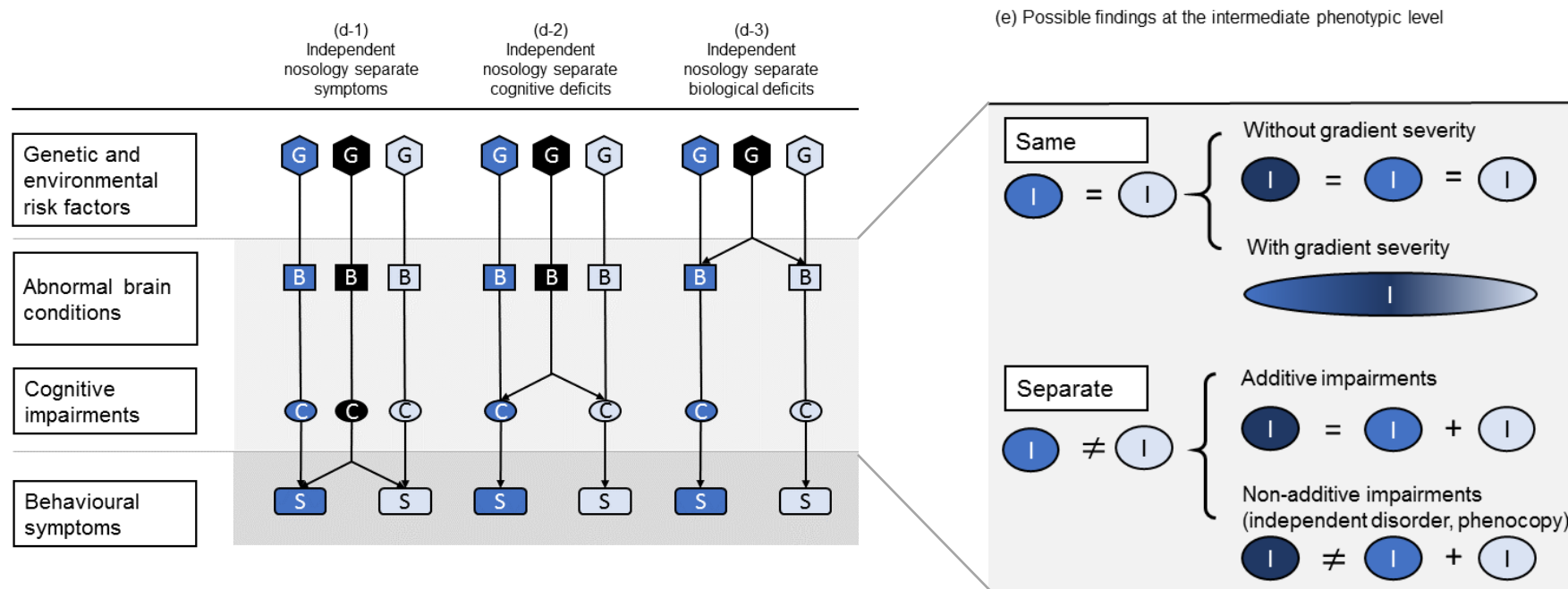
The cartoon on Figure 1-1 (p. 53) depicts four models of comorbidity adapted from the multifactorial model of comorbidity (Neale & Kendler, 1995), with the paths connecting the risk factors to behavioural symptoms mediated by the intermediate phenotypes, distinguished at the brain and neurocognitive levels (Banaschewski et al., 2007). Other more sophisticated models that do not assume this mediated path organisation can be seen in a recent publication by Rommelse et al. (2011). The co-occurrence of two disorders could be because: (a) one disorder is symptomatic phenocopy or a multiform of the other, (b) the two disorders are alternate forms of the same underlying condition, (c) the two disorders are independent disorders but have correlated risk factors and (d) there is third separate disorder that lead to the expression of both disorders at symptomatic level. If ASD and ADHD were the same disorder they will have the same underlying intermediate phenotypes as the ASD+ADHD group, or in a specific case that will be described further below, they will present a gradient of severity in their intermediate phenotype. If the two disorders are separate, impairments seen in the ASD+ADHD cases might be a linear combination of the pure condition. Findings otherwise will point towards a third independent disorder or a symptomatic phenocopy.

Figure 1-1: Possible models for the co-occurrence of ASD and ADHD and possible findings at cognitive and brain levels



Note. (a-d) Four models of comorbidity adapted from the multifactorial model (Neale & Kendler, 1995), but with path from genetic and environmental risk factors to behavioural symptoms mediated by intermediate phenotypes distinguished at the brain and neurocognitive levels (Banaschewski et al., 2007). List abbreviations: G = genetics risk factors, E = environmental risk factors, B = brain conditions, C = cognitive impairments, S = symptoms. The elements coloured blue is ADHD-related and the elements coloured light blue is ASD-related. The elements coloured black represents a third condition. The models represent (a) the symptomatic phenocopy or multifactorial, where one disorder mimics the presentation of another through its interaction with environmental factor or in the absence of interaction with environment, e.g., when two different neural impairments produce similar neurocognitive performance and overlapping behavioural presentation from the two pure disorders within an individual, (b) the alternate forms, when one underlying genetic risk factor, i.e., a pleiotropic gene gives rise to both disorders presentation, depicted here at range of different phenotypic levels, and leading to either co-manifesting of the two disorders or temporally alternating presentation of the two disorders. Included in type of comorbidity is the a specifically hypothesised "gradient overarching disorder" (Rommelse et al., 2011; J. M. J. van der Meer et al., 2012) where the behavioural and cognitive phenotype of ASD and ADHD were thought to be distributed continuously to express increasing social communication severity from ADHD (the least severe) to ASD (the most severe). The next model (c) expresses two independent disorders with correlated risk factors, i.e., a form of true comorbidity where the two separate disorders in an individual co-occurs above chance because they have correlated liability (Please turn over).

Figure 1-1 (cont.): Possible models for the co-occurrence of ASD and ADHD and possible findings at cognitive and brain levels



Note. List abbreviations: G = genetics risk factors, E = environmental risk factors, B = brain conditions, C = cognitive impairments, S = symptoms, I = intermediate phenotype. The elements coloured blue is ADHD-related and the elements coloured light blue is ASD-related. The elements coloured black represent a third condition. The elements coloured navy blue represent the ASD+ADHD phenotype. The model (d) expresses a comorbidity model where the apparent co-occurrence of the two disorders in fact a manifestation of a third disorder of independent nosology. Here the effect of the third set of genes are not assumed to manifest only at the behavioural level but could also be in the brain or cognitive level. The test for this would involve investigating the comorbid form of the disorders at a genetic level. The figure (e) depicts the possible outcome for the intermediate phenotypes when they are representing the same or separate disorders. The fact that ASD and ADHD are the same disorder would be revealed by the same intermediate phenotype (brain/cognitive abnormality). In the absence of gradient severity individuals with ASD+ADHD will have the same phenotype of as those with ASD or ADHD, in the case of gradient severity, cognitive impairments will follow the trend $ADHD < ASD+ADHD < ASD$. The figure below depicts possible findings when if the two disorders are separate. In this case the impairments seen in the ASD+ADHD cases will be a function of the added impairment of each pure condition. If this is not the case, the comorbid case might well be an independent disorder or a phenocopy.

Phenocopy

As shown in Figure 1-1a, the elevated co-occurrence of ASD and ADHD can be a manifestation of symptomatic phenocopy, i.e., where symptoms of one disorder mimic the others. The important feature of this model is that ASD and ADHD are influenced by two separate genetic influences therefore it can be considered a “true comorbidity” (Banaschewski et al., 2007). One variant of the phenocopy is where an individual in a certain environment develops an identical phenotype to a person whose phenotype is determined by their genes. Hypothetically, a child who is genetically predisposed to ADHD but is brought up in a family with strong ASD traits may develop ASD traits through social learning or mimicking behaviour, as well as ADHD symptoms from genetic influences (Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010). Children with ASD perhaps can develop traits consistent with ADHD when the incentive to self-regulate behaviours is lacking or because the children lack in social motivation. Studies have shown that certain styles of parenting, that is the permissive and authoritarian styles, are typically associated with increased disruptive behaviour, aggressiveness and reduced delayed gratification among children (Baumrind, 1966; DeVito & Hopkins, 2001; Mauro & Harris, 2000; Underwood, Beron, & Rosen, 2009). More permissive parenting styles have been reported among parents towards children with ASD compared to unaffected siblings (van Steijn et al., 2013), although the relationships between parenting styles and ADHD traits in these children were not explored.

Another variant of phenocopy independent from environmental factor is also a possible model (Neale & Kendler, 1995). For instance, it is well-established that performance deficits in response inhibition task in ADHD is underpinned by functional under-activations in the ventrolateral prefrontal areas such as the opercular frontal, IFG and insula, as well as subcortical regions such as the BG (Hart et al., 2013; Norman et al., 2016). However, it is also known that the

performance on a specific cognitive task often relies on wider brain networks other than those crucial for the cognitive function the task is used to tap in. The performance on motor inhibition task may rely on the capacity for maintaining response sets and salience detection (e.g., M. Hughes et al., 2014; Ray Li, 2006). An individual may therefore have difficulties in maintaining a set of responses (between responding and non-responding in a motor inhibition task for instance) due to impairments in the dlPFC regions instead of the IFG, but demonstrate deficit on a motor inhibition task on par to those with ADHD.

ASD and ADHD as Alternate Forms of One Disorder

An interesting model considered by some researchers is where ASD and ADHD are alternate forms of the same underlying disorder (Rommelse et al., 2011; J. M. J. van der Meer et al., 2012; see Figure 1-1b). Anecdotal observation of children admitted in clinics with ASD or ADHD suggest fluid presentation throughout the development as if a “common symptomatology runs through these disorders like a continuous thread” (Rommelse et al., 2011, p. 1368). Indeed, both disorders demonstrate similar range of cognitive difficulties particularly in the EF domain (briefly reviewed above) with preliminary evidence suggesting that individuals with ADHD are also impaired in social cognition (Bora & Pantelis, 2015; Uekermann et al., 2010). Based on these observations, the two disorders may be part of a continuum with same underlying neurocognitive and genetic influences. One specific hypothesis that has been suggested is that the behavioural symptoms of individuals with ASD or ADHD would follow a graded severity in social communication, ranging from the least severe presentation in ADHD, to the most severe in ASD, i.e., the following pattern: ADHD < ASD+ADHD < ASD. A latent class analysis by van der Meer et al. (2012) on the parental reports of ADHD and ASD symptoms of a large sample of children allows differentiation of four types of “classes” of children, i.e., typically developing, children with pure ADHD, with dominant ADHD traits and secondary ASD traits, and

with dominant ASD and secondary ADHD traits. Their symptoms support the gradient severity hypothesis, with the group with ADHD alone having the least overall impairments compared to those with co-occurring symptoms ASD and ADHD. However cognitive comparisons using a set of tasks assessing separate EF and social cognition domains also demonstrate specific deficits across classes (J. M. J. van der Meer et al., 2012). No pure ASD group was found in the study, however, which could pose a limitation to the findings. This might be due to the recruitment participants from a specialist ASD and ADHD clinic that could increase the comorbid cases, and also due to the participant ascertainment, which was based on statistical classification of parental ratings of symptoms, and not by clinical diagnosis. A further investigation into this hypothesis involving individuals with ASD, ADHD and ASD+ADHD diagnoses will thus be useful to explore its validity.

Separate Disorders with Correlated Liability

Like the symptomatic phenocopy model, this model rests on the fundamental assumption that the two disorders have separate risk factors and therefore also expresses a true comorbidity (Banaschewski et al., 2007). The co-occurrence of the disorders in this model is explained by shared, overlapping, or correlated risk factors. In line with this model, the co-occurring ASD and ADHD will produce a hybrid condition with combined impairments of the pure disorders. The impairment observed in the ASD+ADHD group is expected to follow an “additive” pattern (e.g., Sinzig, Morsch, Bruning, Schmidt, & Lehmkuhl, 2008; Tye, Asherson, et al., 2014). As a possible explanation for the co-occurrence of ASD and ADHD, this model receives the most support to date at least from specific cognitive domains. Findings from neurocognitive studies suggest that EF difficulties increase among individuals with ASD+ADHD compared to individuals with ASD alone (e.g., Adamo et al., 2014; Andersen, Hovik, Skogli, Egeland, & Øie, 2013; Buehler, Bachmann, Goyert, Heinzl-Gutenbrunner, & Kamp-Becker, 2011; Corbett, Constantine, Hendren,

Rocke, & Ozonoff, 2009; Sinzig, Morsch, Bruning, et al., 2008; Yerys et al., 2009). Several studies using electrophysiological methodology also show patterns of additive impairments for the underlying electrophysiological marker, i.e., event-related potential (ERP) that underpin attention, inhibition as well as gaze and face processing (Tye, Asherson, et al., 2014; Tye, Battaglia, et al., 2014; Tye et al., 2013). These studies will be reviewed later in the relevant chapters.

The Co-occurring Condition as a Third Distinct Disorder

Finally, ASD+ADHD can also be a manifestation of a third independent disorder. In this case a phenotype of the ASD+ADHD arises from separate genotype from the pure group, resulting in distinct cognitive or neurobiological impairments compared to the pure ASD or ADHD form. Evidence for this comorbidity pattern exists. For instance, Tye et al.'s (2014) electrophysiology findings among individuals with ASD+ADHD suggest a mostly additive pathology of the pure groups in attention and inhibition. However, a closer examination into the ASD and the ASD+ADHD groups reveals disorder-specific mechanism in their stopping preparation. That is, individuals with ASD, but not ASD+ADHD, exhibited enhanced marker of stopping preparation, which is found associated with enhanced electrophysiological marker of inhibitory processes. These ASD-specific cognitive processes suggest a distinctive resource allocation for preparing to stop, which is lacking in the comorbid group and may indicate a separate genetic influence. Another evidence of ASD+ADHD-specific impairment was provided by a neuroimaging study by Chantiluke et al. (2014) that shows that neural impairments in the ASD+ADHD group does not follow an additive pathology or phenocopy of the pure groups during a temporal reward discounting. The ASD+ADHD group display the weakest brain-behaviour association in brain regions associated with reward and decision making, i.e., vmPFC, ACC, and ventral striatum, as well as severe abnormalities in the inferior

and superior frontal areas and the temporal lobe, compared to the pure groups. This suggests that they may have a different underlying neuropathology.

1.5 The Aims of This Thesis

The overarching aim of this thesis is to explore further evidence that will shed additional light on the mechanisms underlying the co-occurrence of ASD and ADHD. Advancing further from the current literature, this study involves behavioural, neurocognitive and neuroimaging data. Several data sources were used in this investigation, ranging from a dataset of a population-based sample of adolescents with ASD previously collected from the Special Needs and Autism Project (SNAP), the neuroimaging data of ASD and ADHD related impairment that are already published in the literature, and three sets of newly collected data of neurocognitive performance and neuroimaging data from convenience samples of young adults meeting the criteria of ASD, ADHD and ASD+ADHD. The latter datasets are important since the co-occurring symptoms of ASD and ADHD change over the lifespan (Hartman, Geurts, Franke, Buitelaar, & Rommelse, 2016; Taurines et al., 2010). Since few studies compare adults with ASD, ADHD, and ASD+ADHD, the findings from last three datasets will contribute to the understanding of comorbidity patterns of ASD and ADHD in adulthood.

This thesis examines several research questions: (1) Are ADHD symptoms in ASD associated with the heterogeneous EF impairments, if so how? (2) How do groups of individuals with ASD, ADHD and ASD+ADHD compare in separate neurocognitive subdomains of EF and SC? (3) How do people with “pure” ASD and ADHD compare in their brain structures and functions? (4) How do the neural correlates of response inhibition in people with ASD, ADHD, and ASD+ADHD compare? (5) How do the neural correlates of timing in people with ASD, ADHD,

and ASD+ADHD compare? Ultimately, (6) what comorbidity models fit the findings of these studies?

1.5.1 Are ADHD Symptoms Associated with EF Impairments in ASD?

EF is a candidate endophenotype for both ASD and ADHD. Its association with ADHD is much more consistent than with ASD, however. One possible reason for the inconsistent finding among individuals with ASD is that it is associated with the co-occurring ADHD symptoms (Geurts et al., 2009; J. M. J. van der Meer et al., 2012). In Chapter 2, I will explore the relationships among EF and ToM deficits and ASD and ADHD symptoms in a population-based sample of 100 adolescents with ASD using structural equation modelling (SEM). The study explores whether ASD and ADHD symptoms among adolescents with ASD share neurocognitive bases in the domains of EF and ToM. The data used in this study were collected from the earlier waves of the SNAP study (Baird et al., 2006; Simonoff et al., 2008).

1.5.2 How Do Groups of Individuals with ASD, ADHD and ASD+ADHD Compare in Separate Neurocognitive Subdomains of EF and SC?

The constructs of EF and SC are thought to be the common factors underlying separate neurocognitive functions, such as response inhibition, sustained attention, visuospatial working memory, cognitive flexibility, temporal reward discounting, and ToM and emotion recognition (Bulgarelli, Testa, & Molina, 2015; Friedman et al., 2015; Miyake & Friedman, 2012). Exploring the performance of these neurocognitive tasks as separate cognitive subdomains is as important as exploring the underlying common factors across groups, however, because each cognitive subdomain may depend on the underlying EF ability as well as other subdomain specific cognitive processes. In Chapter 3, I present new data from a study of young adult males with diagnoses of ASD, ADHD, and ASD+ADHD recruited from the SNAP cohort, local communities, support organisations, and specialist clinics

compared to a group of typically developing young adults. Performance of subdomains of EF and SC as mentioned above were contrasted in four-way comparisons.

1.5.3 How Do People with “Pure” ASD and ADHD Compare in Their Brain Structures and Functions?

Investigations based on neurocognitive performance alone are insufficient for characterising the similarities or differences between disorders such as ASD and ADHD. Multiple underlying biological and cognitive processes lead to observable phenotypes (Viding & Blakemore, 2007); thus tapping the underlying neural correlates of the neurocognitive performance can be highly important. Chapter 4 reports the findings of a comparative multimodal meta-analysis of voxel-wise functional MRI studies of inhibition function and structural MRI grey matter volume (GMV) abnormalities in ASD and ADHD. The aim of the study was to explore shared and disorder-specific neural underpinning of the two conditions. The study made use of published data on whole-brain functional BOLD activation impairments associated with inhibition function and whole-brain comparisons of voxel-based morphometry (VBM), i.e., voxel-wise comparisons of brain structure, in children and adults with ASD or ADHD relative to typically developing controls.

1.5.4 How Do the Neural Correlates of Response Inhibition in People with ASD, ADHD, and ASD+ADHD Compare?

Deficits of performance on a stop-signal task are the most consistent cognitive symptom among children and adults with ADHD (Alderson et al., 2007; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Lipszyc & Schachar, 2010; Willcutt et al., 2008). Therefore, the neural correlates underlying the performance of the stop-signal task could be a useful index for assessing similarities and differences of the neural underpinning of response inhibition in people with ADHD and ASD, and

those with dual diagnosis. In Chapter 5, I report findings from the newly collected sample described above including functional neuroimaging data of performance of a modified stop-signal task among young adults with ASD, ADHD, ASD+ADHD relative to typically developing controls. Performance of a stop-signal task depends on several cognitive functions including response inhibition, error-monitoring, and selective attention. The neural correlates of all these functions were compared across groups in a single study.

1.5.5 How Do the Neural Correlates of Interval Timing in People with ASD, ADHD, and ASD+ADHD Compare?

Timing function is an established area of impairment among people with neurodevelopmental condition, especially in ADHD (Barkley, Murphy, & Bush, 2001; Falter & Noreika, 2011; Noreika et al., 2013). Difficulties in getting ready and turning up on time, estimating time to go somewhere, and difficulties in waiting are indices of the core behavioural symptoms in children and adults with ADHD, which could be related to the ability to perceive time and make temporal judgement. Behavioural studies also suggests disturbances of timing among individuals with ASD (Allman, DeLeon, & Wearden, 2011; Bhatara, Babikian, Laugeson, Tachdjian, & Sininger, 2013; Falter, Noreika, Wearden, & Bailey, 2012; Maister & Plaisted-Grant, 2011; J. S. Martin, Poirier, & Bowler, 2010), although no fMRI studies of interval timing have taken place to examine the neural correlates of such deficits in the ASD population. Therefore, an fMRI study comparing individuals with ASD, ADHD, and ASD+ADHD would elucidate the underpinning of the ASD group, clarify the correlates of timing deficits in adults with ADHD, and ultimately be useful for assessing the neuropathology of ASD+ADHD group. In this study I used the duration discrimination task that has been previously used in studies in people with ADHD (Smith et al., 2011, 2013).

1.5.6 What Models of Comorbidity Suit the Co-occurrence of ASD and ADHD?

Taking the results from Chapter 2 to 6 altogether, I discuss the findings in the context of the different models that may explain the co-occurrence of ASD and ADHD as a general discussion in Chapter 7. In this chapter I summarise each study and its findings briefly. I then discuss these results from the perspective of the comorbidity models outlined in the present Chapter. The strengths and limitations of the present study are briefly discussed again in the context of the comorbidity model and finally the implications of the findings and future research directions are discussed as a closing remark.

2 Study I: Modelling the Neurocognitive Functions and ASD and ADHD Symptoms in Adolescents with ASD

2.1 Introduction

Children with ASD often meet the diagnostic criteria for ADHD. The rate of ADHD is approximately 30-60% in community samples of children with ASD (Gjevik et al., 2011; Leyfer et al., 2006; Salazar et al., 2015; Simonoff et al., 2008) compared to 5-7% for ADHD in the general population (Polanczyk et al., 2014; Willcutt, 2012). Both ASD and ADHD have been linked to deficits in EF and ToM (see e.g., Bora & Pantelis, 2015; Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008); thus, a cognitive model of ASD and ADHD symptoms might be useful for elucidating the mechanisms that underlie the co-occurrence of the two conditions. While the broad overlap of EF and ToM deficits between the two conditions are evident in the literature; these findings are limited by the fact that many studies in ASD or ADHD, especially those conducted prior to the DSM-5, often did not account for symptoms of the other disorder (J. M. J. van der Meer et al., 2012). For this reason, an investigation of the cognitive basis for ASD and ADHD symptoms in individuals with ASD, which takes account of the relationships between the cognitive domains and the two sets of symptoms, is an important step towards understanding the mechanisms underlying the occurrence of ADHD symptoms in ASD.

2.1.1 Cognitive Deficits in ASD

ToM is the ability to attribute and infer mental states of others, e.g., beliefs, intentions, or emotions (Baron-Cohen et al., 1985). ToM ability is thought to be a specific aspect of broader social cognition, which includes social perception and

attribution and emotion processing, among others (Adolphs, 1999; Green et al., 2008). Failures in ToM have been shown among 80% children with autism, as opposed to 15% children with Down's syndrome, in a landmark study using a simple false-belief test that required the children to take the perspective of a story character (Baron-Cohen et al., 1985). As children with a mental age of approximately 6 years pass this test (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997), other tasks such as the "strange-stories task" (Happé, 1994), which require decoding of more complex mental states such as double bluff and persuasion, have been used in older children or adults with ASD. Also employed for studies of ToM in adults is the "reading the mind in the eyes" task (Baron-Cohen et al., 1997), which requires inference of others' mental state from pairs of eyes. Studies using these tasks have consistently shown that individuals with ASD have difficulties in ToM (Brent et al., 2004; Kaland et al., 2008; Spek et al., 2010; S. J. White et al., 2011). Although poor ToM ability is also associated with intellectual disability, which in turn often co-occurs in individuals with ASD (Centers for Disease Control and Prevention, 2014; Charman et al., 2011; Postorino et al., 2016); the findings suggest that IQ variation only partially accounts for ToM performance among people with ASD (Dyck, Ferguson, & Shochet, 2001; Yirmiya et al., 1998). Finally, ToM deficits among children with ASD have also been found to correlate with social interaction and communication difficulties (Frith, Happé, & Siddons, 1994; Nagar Shimoni, Weizman, Yoran, & Raviv, 2012; San José Cáceres, Keren, Booth, & Happé, 2014).

Executive dysfunction is also observed among individuals with ASD (E. L. Hill, 2004; Ozonoff, Pennington, & Rogers, 1991; J. Russell, 1997). EF enables goal-directed behaviour and self-control (Banich, 2009; Jurado & Rosselli, 2007). As a construct, the ability of EF is not directly measurable, although it underlies a variety of cognitive functions, including prepotent response inhibition, cognitive interference, working memory and cognitive flexibility, among others. EF ability is

typically inferred from performance of tasks that assess these subdomain functions (Friedman et al., 2015; Miyake & Friedman, 2012). Poor cognitive performance among individuals with ASD as assessed on tasks for inhibitory function (see meta-analyses by Geurts, van den Bergh, & Ruzzano, 2014; Kuiper, Verhoeven, & Geurts, 2016) and cognitive flexibility (reviewed in Geurts et al., 2009; Landry & Al-Taie, 2016), as well as planning (see e.g., Booth, Charlton, Hughes, & Happé, 2003; Van Eylen, Boets, Steyaert, Wagemans, & Noens, 2015; Williams & Jarrold, 2013) and visuospatial working memory (reviewed in Barendse et al., 2013; see also Friedman et al., 2016; Merchán-Naranjo et al., 2016), can thus indicate an underlying EF impairment among people with ASD. However, findings across studies are highly heterogeneous and it is not fully clear what factors lead to the mixed findings among individuals with ASD.

Further, it is unclear how EF might explain the core ASD symptoms. EF is thought to be vital for the initiation and maintenance of social interactions (Brunsdon & Happé, 2014) and, in the context of inhibition, for suppressing inappropriate social behaviour (Geurts, van den Bergh, et al., 2014). Several studies have demonstrated the associations between EF deficits and social interaction or communication problems although such studies are rare in the literature (Ames & White, 2011; Joseph & Tager-Flusberg, 2004; Kenworthy, Black, Harrison, della Rosa, & Wallace, 2009; Pellicano, 2013). Joseph & Tager-Flusberg (2004) found for instance that planning difficulties, over and above ToM, predicted communication symptoms in a community sample of school-aged children with ASD. Further, based on archival data of nearly 90 children with ASD, Kenworthy et al. (2009) found that divided attention performance, was associated with socialisation symptoms, independently from category fluency and after controlling for age. Reduced inhibitory ability has also been found among children with ASD with greater social interaction impairment (Ames & White, 2011). Finally, a longitudinal study following

up children aged 4-7 years found that better EF, and not ToM skills, predicted fewer socio-communicative difficulties three years later (Pellicano, 2013).

Links between EF and another domain of ASD difficulties, i.e., stereotyped and repetitive behaviours are also observed. On a reversal learning task, where individuals are taught to associate a stimulus location with the probability of winning a reward before this association is reversed without warning, D'Cruz et al. (2013) found that people with ASD were more likely to erroneously revert to a previous reward-behaviour association than controls, and their errors were correlated with restricted and repetitive behaviour. Reed et al. (2013) extended these findings by showing that perseverative errors on a card sort adapted for low functioning children, were correlated with stereotyped behaviours among children with low-functioning autism. Further, using a variant of the switch task, Mostert-Kerckhoffs et al. (2015) showed that the switch cost accuracy among children and young adults with ASD and also predicted their ADOS repetitive behaviour scores (see also Lopez, Lincoln, Ozonoff, & Lai, 2005; Yerys et al., 2009).

2.1.2 Are EF and ToM Deficits Associated with ADHD Symptoms in ASD?

Several explanations have been offered for the mixed findings of EF deficits among individuals with ASD. As S. J. White (2013) suggested, rather than considering task performance in relation to EF failures, the inconsistent EF performance among children with ASD could be a by-product of poor mentalising instead. That is, the lack of spontaneous ability to infer an experimenter's mental state, could lead to poor awareness of the task's implicit instructions. This could then moderate EF performance, especially during tasks with open-ended instructions such as the card sort task, but may also occur when arbitrary task rules are imposed on the participants such as in response inhibition tasks (S. J. White, 2013). Task performance might also be moderated by stress or arousal, induced by task

parameters such as rates of stimulus presentation or stimulus characteristics (Kuiper et al., 2016). However most importantly, EF performance variability among individuals with ASD might be associated with additional psychiatric problem such as ADHD symptoms in the population (Corbett, Constantine, et al., 2009; Geurts et al., 2009; J. M. J. van der Meer et al., 2012).

How would EF be associated with ADHD symptoms in ASD? In an early study, Corbett et al. (2009) found inhibitory impairments among children with ASD or ADHD relative to controls; however, when those with additional ADHD were excluded from the analysis, this significance association fell to trend level only, indicating a specific relationship between ADHD symptoms and inhibition deficits among children with ASD (Corbett, Constantine, et al., 2009). Another study involving individuals with ASD+ADHD and pure ADHD and ASD groups reported comparable impairments of inhibition the first two groups (Buehler et al., 2011). Other studies have reported greater number of omission errors on the Go/No-Go (GNG) task, believed to be an attentional index and visuospatial or verbal working memory in the ASD+ADHD relative to the ASD group (Andersen et al., 2013; Sinzig, Morsch, Bruning, et al., 2008; Yerys et al., 2009). Note also that among several studies reporting EF impairments in individuals with ASD relative to those with ADHD, some included a substantial proportion of individuals with high ADHD traits or even diagnoses among the ASD group (Fried et al., 2016; Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004; Johnson et al., 2007). Overall, there is sufficient evidence to suggest that EF deficits among individuals with ASD could be associated with *increased* ADHD symptoms in this population (more extensive reviews are provided in Chapter 3).

EF deficits may not be the only explanation for ADHD symptoms in ASD. Deficits in EF and ToM are often correlated in ASD (Ames & White, 2011; Harris et al., 2008; Joseph & Tager-Flusberg, 2004; Ozonoff et al., 1991). It is generally

believed that EF and ToM are developmentally related (S. E. Miller & Marcovitch, 2012; Perner & Lang, 1999; J. Russell, 1997). In one model, ToM was thought of as a prerequisite for EF (Perner & Lang, 1999), and in an alternative model EF was a precursor for ToM instead (C. Hughes, 1998; J. Russell, 1997). Perner (1999) believed that a successful undertaking of the false-belief task and inhibitory tasks rested on a “common mental factor”, i.e., an awareness of the need to overcome prepotent wrong responses and an understanding that internal mental states could influence goal-directed actions (Perner & Lang, 1999). J. Russell (1997) argued instead that executive controls especially inhibition and working memory are needed for ToM task performance. The latter perspective was supported by studies that have shown a predictive relationship between earlier EF performance and later success on ToM tasks. For instance, Hughes (1998) showed that inhibition task performance among 4-year old typically developing children predicted false-belief performance a year later, irrespective of verbal ability and baseline ToM task performance, while the opposite relationship was non-significant. Among 3-year-old typically developing toddlers, Flynn et al. (2004) also observed that most children performed inhibition tasks well if they were able to correctly perform a false-belief test. Importantly, Pellicano (2007, 2010) showed that the development of EF among children with ASD as young as 4 years old predicted ToM ability 3 years later suggesting similar developmental pattern of EF and ToM for children with and without ASD. Therefore, a link between ToM deficits and ADHD symptoms, whether it is mediated or unmediated by EF deficits might exist, and must also be considered.

2.1.3 The Aims of This Study

This study aimed to model the relationship among deficits in EF, and ToM, and symptoms of ASD and ADHD in a sample of adolescents with ASD, using a multi-measure and multi-informant approach. Specifically, we explored the neurocognitive

correlates of ADHD symptoms in individual with ASD using an SEM approach. EF deficits were expected to be associated with ADHD and ASD symptoms, whereas ToM deficits were expected to be associated with ASD symptoms only. The study made use of already collected data from a well-characterised, population-based cohort of young people with ASD. To my knowledge this is the first attempt to model the relationships among the variables in a population derived sample of ASD.

2.2 Methods

2.2.1 Participants

SNAP is a population-based cohort of people with ASD who were first ascertained and characterised at the age of 10-12 years (Wave 1; see Baird et al. [2006] for details). The children received ICD-10 research diagnoses of ASD as assessed using the ADI-R parental interview (Lord et al., 1994), ADOS-G (Lord et al., 2000) and measures of IQ, language, and adaptive behaviour. Of the original cohort, 100 adolescents ($n = 9$ females) with a full-scale intelligent quotient (FSIQ) ≥ 50 estimated using the Wechsler Intelligence Scale for Children (WISC-III-UK; Wechsler, 1992) were followed up at the age of 14-16 years (Wave 2) and were the subjects of this study. The latter research assessment was conducted in two sessions completed on average in 29 days ($SD = 36$ days; Range = 1-259 days) apart. The study was approved by the South-East London Research Ethics Committee (05/MRE01/67). Informed consent was given by the young people's parents.

2.2.2 Measures

Measures used in this study fall in the domains of ADHD and ASD symptoms, EF and ToM, and are described below. All measures were collected from the young

people or parent/teacher informants across Wave 1 and 2 of the SNAP investigations, when the young people were between 10 and 16 years of age. The measures and timing (Wave 1 or 2) are presented in Table 2-1.

2.2.2.1 Cognitive Measures

Table 2-1: Measures, completers and wave of investigations

Domains	Measures	Completed by	Wave
Cognitive	WASI	child	2
ASD symptoms	ADI-R	parent	1
	ADOS-G	child	1
	SRS	parent	2
	SDQ	parent, teacher	parent (2), teacher (1)
ADHD symptoms	PONS	parent	2
	CAPA ^a	parent	1
	Card sorting task	child	2
	Luria hand game		
EF	Trail making		
	Planning/drawing		
	Opposite worlds		
	Numbers		
	Reading the mind in the eyes	child	2
ToM	Penny hiding game		
	Animated triangle		
	Strange stories		
	False-belief		

Note. Wave 1 investigation took place when the children were 10-12 years old whereas Wave 2 investigation took place when they were 14-16 years. ^aThe CAPA interviews were conducted with parents when the children were 10-14 years. List of abbreviations: WASI = Wechsler's abbreviated scale of intelligence. ADI-R = Autism Diagnostic Interview-Revised, ADOS-G = Autism Diagnostic Observation Schedule-Generic, SRS = Social Responsiveness Scale, and SDQ = Strengths and Difficulties Questionnaire, PONS = Profile of Neuropsychiatric Symptoms, CAPA = Child and Adolescent Psychiatric Assessment

Wechsler's Abbreviated Scale of Intelligence (WASI)

The WASI (Wechsler, 1999) was chosen as a brief but reliable measure of general intellectual ability. The scale consisted of four subtests, two each generating verbal and nonverbal IQ, and all contributing to an estimate of FSIQ.

2.2.2.2 ASD measures

ADI-R

The ADI-R is a semi-structured interview for caregivers of individuals who may have ASD. Scores are given for each item by the interviewer according to the behaviour described by parents/carers about the children in their early development, at the age of four to five years and at the time of the interview (current). The composite score uses an algorithm with established cut-offs for the diagnosis of autism (Lord et al., 1994), according to the criteria set by the ICD-10 (WHO, 1992) and the DSM-IV (APA, 2013).

ADOS-G

The ADOS-G is a semi-structured observation-based assessment for individuals with possible ASD. The instrument consists of tasks or social presses which are designed to elicit social-communicative behaviours. It also includes questions to evaluate the individual's understanding of social relationships and emotions. Responses and behaviours of the participants are coded on individual items that index characteristics of communication, social interaction and other behaviours relevant for ASD. The ADOS has established cut-offs for autism cases and other ASDs (Lord et al., 2000).

SRS

The SRS (Constantino, 2011) is a 65-item questionnaire for measuring reciprocal social behaviour, of which overall difficulties are represented by a standardised total score. The questionnaire also has normative scores for difficulties in the two autistic trait subdomains, i.e., social communication interaction and repetitive behaviour. The scores are moderately correlated with total scores of ADI-R and ADOS-G ($r = 0.48-0.59$) and it differentiates children aged 9-13 years with special needs, with or

without ASD, with sensitivity and specificity of 78% and 67%, respectively (Charman et al., 2007). Raw parent-rated total scores about the young people were used as continuous measure of ASD symptoms in this study, where higher score indicated more symptoms.

2.2.2.3 ADHD Measures

Strengths and Difficulties Questionnaires (SDQ)

The SDQ (R. Goodman, Ford, Simmons, Gatward, & Meltzer, 2003) is a brief psychiatric screening questionnaire comprising 25 items in five domains for assessing emotional symptoms, conduct problems, hyperactivity/inattention (ADHD) symptoms, peer relationship problems and prosocial behaviour. The sensitivity of parent and teacher SDQs ratings for detecting children with hyperkinetic or ADHD symptoms in a sample of over 3200 children aged 11–15 years from the general population was 85% and 75%, depending on whether the ICD-10 or DSM-IV criteria for diagnosis was used (R. Goodman et al., 2003). Scores of the SDQ ADHD domain range from 0 – 10 with higher scores indicating higher symptoms. There are presently no ASD-specific psychometric evaluations of the SDQ. Although a recent study involving a large sample of birth cohort of nearly 20,000 children and over 170 children with ADHD and over 200 children with ASD aged 6-8 years showed a sensitivity of 91% and specificity of 90% for the hyperactivity subscale for detecting ADHD, and a sensitivity and specificity of 79% and 93% using all the scales except peer relations for detecting ASD (G. Russell, Rodgers, & Ford, 2013).

Profile of Neuropsychiatric Symptoms (PONS)

The PONS (Santosh, Gringras, Baird, Fiori, & Sala, 2015) is 60-item measure of psychiatric symptoms in children and adolescents, with special application to those with developmental disorders. Items evaluate both the frequency and the impact of individual symptoms. There are six items concerning ADHD symptoms, divided into

symptom domains of attention, hyperactivity and impulsivity. Each domain asks about the symptom's frequency (one item) and its impact on everyday functioning (one item) and each item is rated on a Likert scale (0-6). The sensitivity and specificity of the PONS was 92% and 91%, respectively, for screening children with neuro-developmental disability (ASD or ADHD) among 147 children aged 5-18 years with neuropsychiatric disorders, including (n = 111) with ADHD, (n = 96) with ASD, (n = 59) with oppositional defiant disorder or conduct disorder, (n = 31) with bipolar or psychosis, (n = 80) with anxiety or depressive disorder, (n = 38) with developmental coordination disorder, (n = 36) with obsessive compulsive disorder and/or tics (the children may meet several psychiatric disorders); and over 900 typically developing children from the general population. There are no ASD-specific psychometric evaluations of the PONS currently. An early version of the PONS was used in this study (Santosh, Baird, Pityaratstian, Tavaré, & Gringras, 2006) where item scores ranged from 0 to 5, yielding a total score ranging from 0 to 30.

Child and Adolescent Psychiatric Assessment (CAPA)

The CAPA (Angold & Costello, 2000) is a semi-structured interview for children aged 9-18 years and their parents. For the parent, CAPA interview of clinically referred children has a 1-week test-retest intraclass correlation (ICC) was .82 for ADHD symptoms, .79 for hyperactivity symptoms and .77 for inattention respectively (Angold & Costello, 1995). Although CAPA has not been used widely in the population of children with autism and their parents, the interview has been used with adolescents and adults with intellectual disability prior to the study (Baker & Skuse, 2005). The interview assesses the presence of psychiatric symptoms and disorders judged from behavioural descriptions of symptoms in the last 3 months, accompanied by onset and duration, to elicit information necessary for ICD-10 and DSM-IV diagnoses. The parent CAPA interview was used in the current study. The

hyperactivity section of the CAPA was used to derive DSM-IV symptoms of ADHD used in the present analyses.

2.2.2.4 EF Measures

Card Sorting Task

The card sorting task (Tregay, Gilmour, & Charman, 2009) is a child-friendly adaptation of the Wisconsin Card Sort Task (Grant & Berg, 1948). In this task, participants were introduced to three characters and were given a deck of 64 cards illustrating single objects varying in colour (red/blue; yellow/green; black/pink), shape (squares/hearts; stars/moons; and smiley faces/lightning) and size (small/large). At the start of the game, the participants were told that each character favoured some cards over others with a specific rule the participants must solve. The experimenter picked one card at a time and asked the participants if it was the character's favourite card. The experimenter gave feedback (i.e., "right" or "wrong") for each answer provided by the participants, and then put the character's favourite card face down on one pile and the disliked cards on another. After six consecutive correct sorts or after 20 sorts elapsed, another character was introduced to the participants and the sorting rule changed without explicit mention of a rule switch. The rules for the card sorting were counterbalanced and the participant's decision on the first sort was always taken as the correct answer. Error scores were used to indicate deficits in cognitive flexibility.

Luria Hand Game

The Luria hand game (Luria, Pribram, & Homskaya, 1964) consists of three stages: a pre-test, a practice run and a test. In this game, the experimenter displayed two types of hand shape with their right hand, a fist or, alternatively, a finger-pointing shape. Participants responded with an identical or the alternate hand shape (i.e., by showing a fist when the experimenter showed a finger-pointing shape) depending

on the experimental block. In the pre-test, identical hand shape was required for six consecutive trials. In the practice run, the alternative hand shape was requested instead, and this trial stops after four consecutive correct responses. During the test, the experimenter showed a sequence of 15 trials of either hand shapes, and the participants were instructed to show the alternative hand shape in response. Between trials, the participants and experimenter hide their hands behind their back. The order of the sequence was fixed across participants. The number of correct responses on a first attempt indexed the inhibitory function ability. We used reversed scores in this study to operationalise inhibitory deficits.

Trail Making Test

Trail making (Reitan, 1958) is a measure of switching or cognitive flexibility. It is a pen-and-paper task that requires a participant to draw a path connecting circles labelled with numbers 1-25 and letters A-Y in a specific order. The experimenter administered this task in three blocks. In the first block, the participant was asked to join circles in numerical order (i.e., 1-2-3 and so on), then in alphabetical order (i.e., A-B-C and so on) for the second, and in alternating order of numbers and letters (i.e., 1-A-2-B-3- and so on) for the third. The difference between the time taken to complete the last and the first trials indexed switching ability and higher scores indicated poorer performance.

Planning/drawing Task

The planning/drawing task (R. Booth et al., 2003) consists of several blocks of copy-drawing and “modification” drawing trials. In the first trial, the participants were given an illustration to copy fully. In the following trial the participants were required to do the same drawing with some additional features. For instance, in the first trial the participants were asked to copy a drawing of a snowman with an open mouth whereas in the second trial, they were asked to draw it again and with teeth in the

snowman's mouth. To complete this task successfully, the participants must plan prior to the task, e.g., increasing the size of key parts such as the snowman's mouth, to accommodate some teeth. Evidence of advance planning earned the participants the "allowance scores", judged from the comparison between drawings from the copy-drawing and the modification-drawing trials (see R. Booth et al., 2003 for scoring rules). Scores were reversed so that higher allowance scores indexed poorer planning corresponding to an EF deficit.

Opposite Worlds

This task is part of the Test of Everyday Attention for Children (TEA-Ch; Manly et al., 2001) and is a measure of inhibition. During this task, participants followed a trail consisting of the numbers "1" and "2" on a piece of paper and they were instructed to call out "one" or "two" as they passed each number. There were two task conditions, which were "same worlds" and "opposite worlds" to be completed twice each. In the same-world condition, the verbal call outs corresponded to the numbers, while in the opposite-world condition the call outs were reversed. The difference of RT to complete the opposite-world versus the same-world condition is a measure of inhibitory function, where a higher score indexed poorer performance.

Numbers

Numbers is a subtest of the Children's Memory Scale (Cohen, 1997). In this task, the experimenter gave a sequence of one-digit numbers verbally to the participants at a rate of one number per second. The participants must then recall and repeat these sequences as accurately as possible. The experimenter started by giving two-digit sequences, then adding one digit in the next trial either until the participants failed to repeat the correct sequences twice within the span, or until the maximum nine-digit sequences were completed. The task was then repeated, but now the

participants must repeat the digits in reversed order (digit spans ranging from 2-8). To capture EF difficulties, we used the reversed scores.

2.2.2.5 ToM measures

Reading the Mind in the Eyes

This task (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) involves 28 photos of the eye regions of various individuals in different social contexts. Each photo was presented with four choices of adjectives, one of which was consistent with the feelings reflected in the pair of eyes. Each correct answer was given a score of one thus the participants could earn a maximum score of 28. A reversed score was used to operationalise the ToM deficits.

Penny Hiding Game

The penny hiding game (Baron-Cohen, 1992) is a naturalistic and non-verbal deception task. In this task, the experimenter hid a penny in one fist with both hands obscured behind their back. The experimenter then presented both fists to the participants who had to guess where the penny was hidden. The game commenced with a training phase where the experimenter hid the penny six consecutive times from the participants. Then, the participant took his turn to hide the penny for the next six trials and deceive the experimenter. Error scores were given for failures to carry out the deception, for instance, if the participants failed to keep hands out of sight when hiding the penny, or told the experimenter where the penny was. These errors were systematically coded into five categories which were given a score each, resulting in a total score ranging from 0-30, where higher score reflected increased ToM difficulties.

Strange Stories Test

The strange stories test (Happé, 1994) consists of several short stories depicting several complex interactions involving lies, double bluffs or persuasion. The stories were read to the participants and were also presented in written form with illustrations. Four stories involving ToM and two “physical” stories were included in this test. The scoring system described by Happé (1994) was used where a score zero was given to incorrect or “don’t know” responses and a score of two was given to children who gave fully and explicitly correct answers. The total score ranging from zero to eight from the four ToM items indexes ToM ability. Reversed score was used as indicator of ToM deficits.

Frith-Happé Animated Triangle

This animated task (Castelli et al., 2002) consists of six video clips depicting two triangles moving in a goal-directional manner (two clips) or in an interaction involving mental state attribution with one another (four clips). Participants were instructed to give verbal accounts of triangles action for each clip while being audio-recorded by the experimenter. The participants’ attributions of mental states towards the triangles were rated as the “intentionality scores”, ranging from zero to five, whereas the correct identification of the animation’s contents was rated as the “appropriateness scores”, ranging from zero to two, averaged across the number of clips (see details in Jones, Swettenham, et al., 2011). Seventy-two of 129 verbal descriptions (56%) were coded by two raters independently, where high intraclass correlations (.82-.98) were found, indicating good reliability. The sum of average intentionality and appropriateness scores for each scenario were used in this study as measure of ToM ability. Scores were reversed to index ToM deficits.

Combined False-Belief Story

This task ("The Chocolate Story") was developed by Rhonda Booth (Institute of Psychiatry, London) and was based on previous first-order and second-order false belief tasks (Baron-Cohen, 1989; Bowler, 1992). During the task, the experimenter presented a story with an accompanying cartoon to the participants. In the story Mary and John hid some chocolate in a fridge together, but John then removed the chocolate in Mary's absence. The experimenter asked the participants where they think Mary would look for the chocolate, followed by a "justification question" where the experimenter asked why Mary looked for the chocolate there, and a "control question" asking where John hid the chocolate. In the second part of the task, the experimenter added that Mary had in fact watched John removed the chocolate into the bag although John did not see her watching. In the same manner as the first part of the test, the participants were asked questions about where John thought Mary would look for the chocolate followed by a justification and control questions. A maximum score of five were given in the first part and a maximum score of three was given in the second part. Scores were reversed so that higher scores indicated poorer ToM ability.

2.2.3 Analytical Plan

Data preparation and descriptive analyses were undertaken in STATA 11 (StataCorp, 2009). Raw scores for each measure were visually inspected to verify that they were correlated in the same directions, that is, higher scores indicated more neurocognitive impairments and higher level of symptoms. Box-Cox transformations were used to normalise skewed data (see Table 2-2). Structural equation modelling (SEM) was used to model the relationship among the latent, underlying factors of EF and ToM deficits, and ASD, and ADHD symptoms. The analysis was divided into four steps. In Step 1, the structure of the latent factors for

EF and ToM were investigated using an exploratory factor analysis (EFA) with all indicators entered, employing Geomin rotation and contrasting one and two-factor structure. An EFA was thought more suitable than a confirmatory factor analysis for two reasons: (a) the factor structures of the cognitive domains indexed by EF and ToM measures were not fully clear as the two cognitive domains were usually explored separately (see e.g., Bulgarelli et al., 2015; Friedman et al., 2015) and (b) individual neurocognitive measures are known not to be “process pure” and are likely to involve both domains of cognitive function (Brunsdon & Happé, 2014, p. 18). The model fit between one- and two-factor structure models was evaluated using χ^2 statistics. A two-factor structure fit the EF and ToM factors better and was chosen. To improve the “purity” of the factors, indicators that cross-loaded, i.e., significantly loaded to both the EF and ToM factors, or to the factor expected a priori, and those or with factor loadings ≤ 0.4 were excluded.

In Step 2, the first SEM model (Model 1) was built to assess the relationships among the neurocognitive (ToM and EF) and behavioural (ASD and ADHD) latent factors. The data were modelled with the cognitive factors, EF and ToM, predicting the symptom domain factors (see Figure 2-1A, p. 88) because a model with reciprocal paths in both directions was likely not identified. However, the aim was not to test the strong hypothesis that cognitive factors causally underpin symptom domains, but rather to understand better the pattern of relationships between the cognitive and behavioural constructs. EF and ToM latent factors were allowed to correlate to take into account the known relationship between the two factors (Joseph & Tager-Flusberg, 2004; Ozonoff et al., 1991; Pellicano, 2007; Perner & Lang, 1999). For the same reason, ASD and ADHD latent factors were permitted to correlate in the model (see e.g., Ames & White, 2011; Holtmann et al., 2007; Sprenger et al., 2013; Tureck, Matson, Cervantes, & Turygin, 2013; Yerys et

al., 2009). The EFA and SEM modelling was conducted in Mplus (Muthén & Muthén, 2000).

Table 2-2: Descriptive statistics of measures used in this study

	Mean (SD)	Range
<i>IQ measures</i>		
FSIQ	84.3 (18.0)	50 – 119
VIQ	80.8 (18.0)	55 – 120
PIQ	90.4 (18.6)	53 – 126
<i>EF indicators</i>		
Card sort task (98/100) ^a	7.2 (6.6)	1 – 36
Luria hand game (97/100) ^{a, b}	12.2 (3.3)	0 – 15
Trail making (88/100) ^{a, c}	63.4 (44.0)	13.4 – 257.1
Planning/drawing (98/100) ^{a, b}	3.6 (1.7)	0 – 6
Opposite worlds (98/100) ^{a, b}	8.4 (7.5)	-3.7 – 47.4
Numbers (99/100) ^{a, b}	4.7 (2.5)	0 – 12
<i>ToM indicators</i>		
RME (94/100) ^b	17.0 (4.4)	6 – 25
Penny hiding game ^b	2.3 (2.7)	0 – 14
Strange stories (88/100) ^b	3.4 (2.1)	0 – 8
Animated triangle (98/100) ^{a, b}	3.5 (1.3)	0 – 6.5
False belief (99/100) ^b	3.3 (1.7)	0 – 5
<i>ADHD symptom indicators</i>		
Parent SDQ hyperactivity(93/100) ^a	5.8 (2.5)	0 – 10
Teacher SDQ hyperactivity (80/100)	5.7 (2.3)	1 – 10
Parent PONS ADHD (89/100) ^a	10.7 (6.6)	0 – 27
DSM-IV ADHD symptoms (73/100)	6.0 (3.6)	0 – 14
<i>ASD symptom indicators</i>		
Parent SRS total raw score (92/100) ^c	92.5 (29.3)	21 – 153
ADI-R total (90/100)	21.6 (7.8)	7 – 41
ADOS total (90/100)	11.8 (6.2)	1 – 27

Notes. Descriptive statistics reported here are based on raw (non-transformed) data. IQ measures were taken from all participants. The numbers of measure completers are denoted in parentheses after each measure. Abbreviations FSIQ = Full-scale IQ, RME = Reading the Mind in the Eye Tasks, SDQ = Strengths and Difficulties Questionnaire, PONS = Profile of Neuropsychiatric Symptoms, SRS = Social Responsiveness Scale, ADI-R = Autism Diagnostic Interview-Revised, ADOS = Autism Diagnostic Observation Schedule. Indices a = Box-Cox transformed, b = reverse score, and c = scores rescaled to conform to the dimension of variances of other measures during the formation of latent factors.

In Step 3, an additional step to improve the fit of the initial model in Step 2 was introduced by adding a latent factor representing a parental-reporting effect to account for shared informant influences (Model 2). The parental-reporting factor was indexed by all measures of ADHD and ASD symptoms reported by parents and hence excluded the ADOS and the teacher SDQ report. Furthermore, to assess the specificity of relationships between the cognitive deficits and behavioural symptoms, I compared Model 2 against alternative models (Model 3 & 4). Model 3 retained all

paths between cognitive deficits and the behavioural symptoms in Model 2 but held the coefficients fixed to ones, thus expressing non-specific relationships between the predictors and outcomes. Model 4 explored alternative relationships where the paths from EF to ASD and from ToM to ADHD remained but the counterpart paths from each cognitive domain to behaviour were dropped. As a final consideration, I investigated in Step 5 whether accounting for the covariance between FSIQ and EF or ToM performance would change the relationships among the variables. In this model (Model 5), FSIQ was included within the model, upon which the EF and ToM factors were regressed on.

For each model, maximum-likelihood (ML) estimation was implemented and model fit was evaluated using the comparative fit index (CFI) and the Tucker-Lewis Index (TLI; acceptable fit for both indices $\geq .90$, Bentler & Bonett [1980]), the root mean square error of approximation (RMSEA; acceptable fit $\leq .08$, Browne & Cudeck [1993]) for nested models, while the Bayesian Information Criterion (BIC) and the Akaike Information Criterion (AIC) were used to help evaluate non-nested model with the same manifest variables. Each model was compared against nested models where non-significant pathways were left out to yield more parsimonious models.

2.3 Results

2.3.1 Descriptive Statistics

The mean age of participants was 15.5 years (SD = 0.5 years; range = 14.7 – 16.8 years), with mean FSIQ of 84.3 (SD = 18.0; range = 50 – 119). Descriptive statistics of neurocognitive performance are presented in Table 2-2.

Table 2-3: Bivariate correlations among neurocognitive and symptom measures

	EF measures						ToM measures					ADHD measures				ASD measures	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Card sort task (1)	-																
Luria hand game (2)	.28**	-															
Trail-making (3)	.36***	.26*	-														
Opposite worlds (4)	.31**	.17	.38***	-													
Numbers (5)	.51***	.35***	.47***	.37***	-												
Planning/drawing (6)	.36***	.20†	.17	.18†	.17†	-											
Animated triangle (7)	.34**	.12	.05	.16	.26*	.05	-										
Penny hiding game (8)	.27**	.45***	.17	.26*	.30**	.14	.40***	-									
RME (9)	.22*	.39***	.25*	.21*	.39***	.06	.41***	.47***	-								
Strange stories (10)	.29**	.22*	.18	.23*	.37***	.25*	.22*	.29**	.29**	-							
False belief (11)	.62***	.46***	.32**	.32**	.45***	.27**	.36***	.52***	.41***	.43***	-						
pPONS ADHD (12)	.16	.10	.21†	.23*	.26*	.21†	.09	.24*	.11	.01	.03	-					
pDSM ADHD (13)	.27*	.16	.20	.19	.25*	.30**	.02	.10	.09	.09	.13	.55***	-				
pSDQ ADHD (14)	.17	.22*	.31**	.21*	.28**	.14	.13	.19†	.25*	.08	.08	.56***	.46***	-			
tSDQ ADHD (15)	.21†	.28*	.13	.12	.32**	.08	.02	.29**	.08	-.18	.15	.40***	.50***	.40***	-		
pADI-R (16)	.20†	.16	-.01	-.04	.05	.17	.25*	.30**	-.00	.11	.27*	.25*	.35**	.20†	.20†	-	
ADOS (17)	.13	.29**	.06	.01	.11	.17	.36**	.45***	.32**	.30**	.33**	-.02	-.17	-.06	.08	.33**	-
pSRS (18)	.17	.28**	.27*	.14	.18	.12	.17	.25*	.29**	.20†	.20†	.52***	.36**	.38***	.05	.44***	.16

Notes Abbreviations of neurocognitive measures EF=Executive Function, ToM=Theory of Mind, RME=Reading the Mind in the Eye Tasks. Abbreviations for ASD or ADHD measures: ADOS =Autism Diagnostic Observation Schedule Total Score, ADI-R=Autism Diagnostic Interview-Revised, SRS=Social Responsiveness Scale, DSM ADHD = Diagnostic and Statistical Manual of Mental Disorders ADHD symptom numbers, SDQ ADHD=Strengths and Difficulties Questionnaire ADHD domain, PONS ADHD =Profile of Neuropsychiatric Symptoms ADHD domain. The prefix *p* on the measures indicates parent reports whereas the prefix *t* indicates a teacher report. Significant levels † $p < .1$, * $p < .05$, ** $p < .01$, and *** $p < .001$.

2.3.2 Model Fitting

Bivariate correlations among the neurocognitive tasks and symptom measures are presented in Table 2-3. Significant correlations among the neurocognitive tasks ranged from .21 to .62. Correlations among ASD and ADHD symptoms ranged from .25 to .56 and correlations between the tasks and ASD or ADHD symptoms ranged from .21 to .45; all uncorrected for multiple comparisons.

Table 2-4: Loading of the measures on factors EF and ToM

	With cross-loading indicators		Without cross-loading indicators	
	EF	ToM	EF	ToM
Card sort task	.74*	.00	.57*	.15
Trail making	.73*	-.09	.81*	-.12
Opposite worlds	.49*	.02	.54*	.03
Luria hand game ^a	.21	.43*	--	--
Numbers	.68*	.03	.70*	.00
Planning/drawing	.45*	-.07	.35*	.06
Animated triangles	.01	.77*	-.01	.93*
Penny hiding game	-.10	.85*	.10	.65*
RME	.10	.60*	.24	.50*
Strange stories ^a	.40*	.24	--	--
False belief ^a	.49*	.40*	--	--

Notes. ^a Measures which cross loaded on factors expected a priori. We excluded these measures from the final model to increase the independence of the predictors. Abbreviation: RME = Reading the Mind in the Eyes Task.

2.3.3 Step 1: EFA

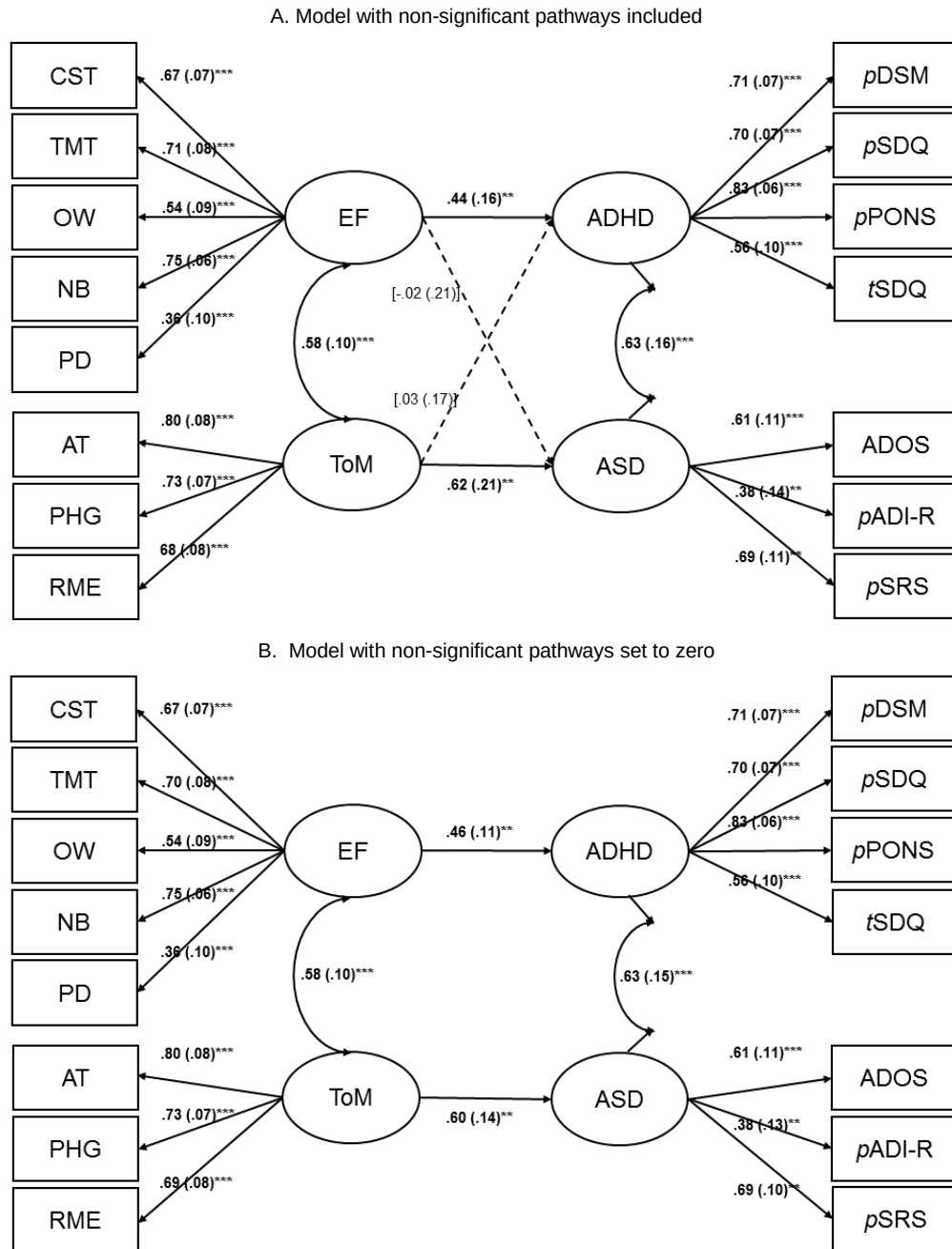
The EFA of the ToM and EF indicators showed that they better fitted a two-factor, $\chi^2(34) = 41.3$, $p = .18$; CFI = .97; TLI = .96; RMSEA = .05, than a one-factor model, $\chi^2(44) = 73.8$, $p = .003$; CFI = .89; TLI = .86; RMSEA = .08; $\Delta\chi^2(10) = 32.5$, $p < .001$. The geomin factor correlation between ToM and EF was significant, $r = .61$, $p < .05$. The factor loadings for the indicators of each latent factor are listed in Table 2-4. Several tasks showed cross-loadings with respect to the *a priori* expected loadings on ToM and EF; The Luria hand game cross-loaded on the ToM factor (factor

loading = .43) and similarly the False Belief and Strange Stories tasks cross-loaded on the EF factor (factor loadings = .49 and .40, respectively). Because these measures were less 'pure' in the present sample, they were excluded as indicators in the SEM model. The model of the predictors with no cross-loading indicators still fit well to a 2-factor model, $\chi^2(13) = 15.2$, $p = .30$; CFI = .99; TLI = .97; RMSEA = .04. Removing these indicators did not change the model fit significantly, $\Delta\chi^2(24) = 26.1$, $p = .20$, but the correlation between factors was reduced from .61 to .45.

2.3.4 Step 2: The Relationships among EF, ToM, and ASD and ADHD Symptoms (Model 1)

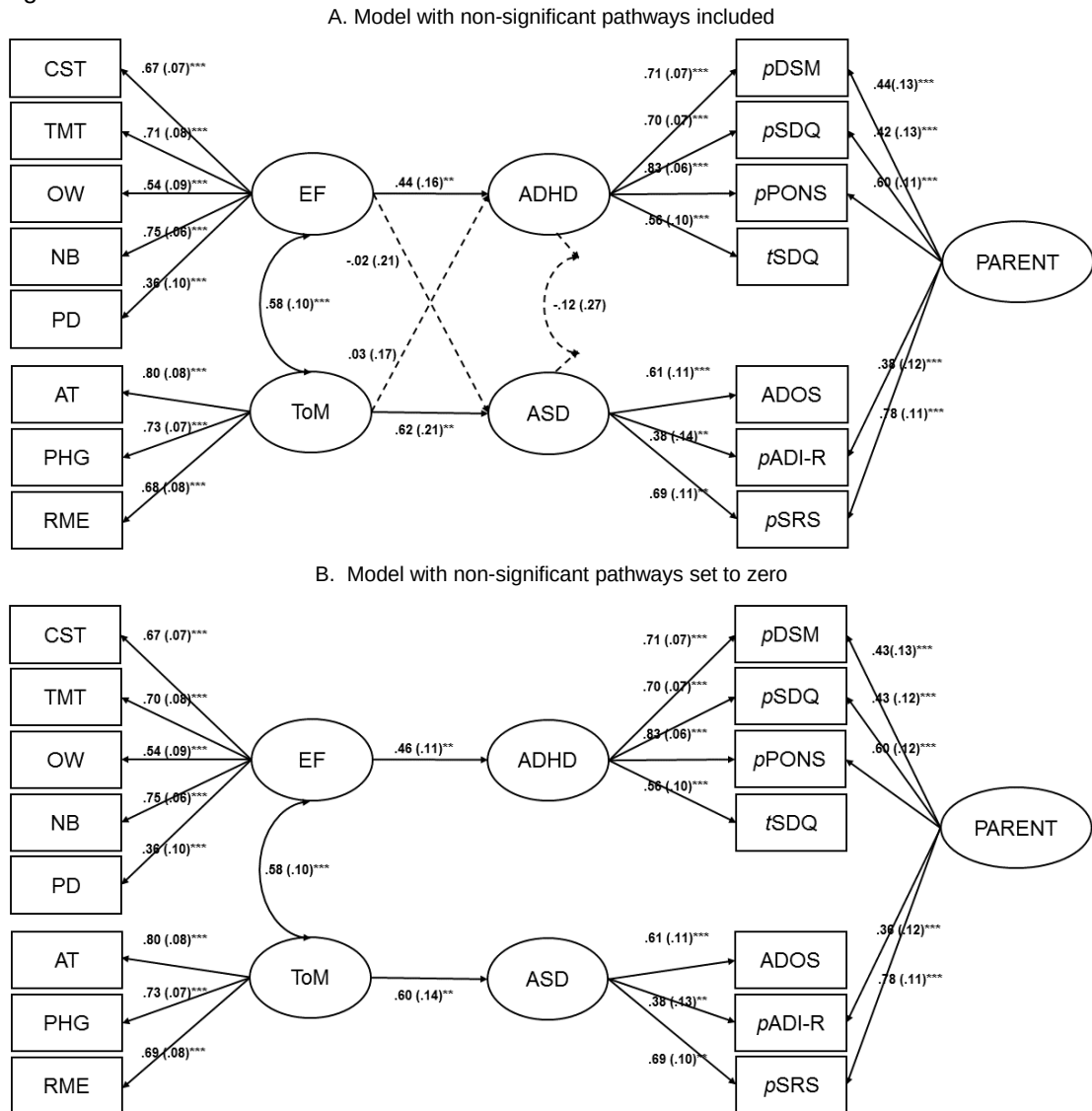
The fit of Model 1 as shown in Figure 2-1A approached an acceptable fit threshold, $\chi^2(84) = 131.8$, $p = .001$; CFI = .86; TLI = .82; RMSEA = .075; AIC = 6078.1; BIC = 6210.9. Non-significant paths between EF and ASD (standard coefficient = -.02, $p = .09$) and between ToM and ADHD (standard coefficient = .03, $p = .88$) were identified and removed. The model did not significantly, $\Delta\chi^2(2) = .1$, $p = .95$, alter the previous fit, $\chi^2(86) = 131.9$, $p = .001$; CFI = .86; TLI = .84; RMSEA = .07; AIC = 6074.1; BIC = 6074.1, rendering it the more parsimonious of the two models considered. The model fit was below the threshold of acceptability, however the model suggested that individual differences in EF were associated with the latent ADHD factor (standard coefficient = .46, $p < .001$), while variations in ToM performance were associated with the latent ASD factor (standard coefficient = .60, $p < .001$). There were significant correlations between the EF and ToM factors (standard coefficient = .58, $p < .001$) and between the ASD and ADHD factors (standard coefficient = .63, $p < .001$).

Figure 2-1: SEM Model 1



Note. Figures show the Model 1A with non-significant pathways shown in dotted pathways and Model 1B after setting the non-significant pathways to zero to obtain a more parsimonious model. List of abbreviations CST=card sort task, TMT= Trail-Making Test, OW= Opposite Worlds, NB = Number Backward, PD = planning task, AT = animated triangle, PHG = penny hiding games, RME=Reading the Mind in the Eye tasks, EF=executive function, ToM=theory of mind. Abbreviations for ASD or ADHD measures: ADOS =Autism Diagnostic Observation Schedule, ADI-R=Autism Diagnostic Interview-Revised, SRS=Social Responsiveness Scale, DSM = Diagnostic and Statistical Manual of Mental Disorders, SDQ=Strengths and Difficulties Questionnaire, PONS=Profile of Neuropsychiatric Symptoms. The prefix p on these behavioral measures indicates parent-based reports whereas the prefix t on the SDQ indicates a teacher-based report. Adding the latent factor Parent isolates the parental-reporting effect resulting in increased loadings of ADOS on the ASD factor and tSDQ ADHD on the ADHD factor, and reduces the correlation between ASD and ADHD symptoms to non-significance. The significant levels * $p < .05$, ** $p < .01$, and *** $p < .001$.

Figure 2-2: SEM Model 2



Note. Model 2 includes a latent factor controlling the shared sources of information from parents on ADHD and ASD symptoms. Adding the parent latent factor appeared to diminish the correlation between ADHD and ASD symptoms previously observed in Model 1 to a non-significant level. Non-significant pathways were included in Model 2A, shown in dotted pathways, whereas Model 2B present the model after setting the non-significant pathways to zero to obtain a more parsimonious model. List of abbreviations CST=card sort task, TMT= Trail-Making Test, OW= Opposite Worlds, NB = Number Backward, PD = planning drawing task, AT = animated triangle, PHG = penny hiding games, RME=Reading the Mind in the Eye tasks, EF=executive function, ToM=theory of mind. Abbreviations for ASD or ADHD measures: ADOS =Autism Diagnostic Observation Schedule, ADI-R=Autism Diagnostic Interview-Revised, SRS=Social Responsiveness Scale, DSM = Diagnostic and Statistical Manual of Mental Disorders, SDQ=Strengths and Difficulties Questionnaire, PONS=Profile of Neuropsychiatric Symptoms. The prefix p on these behavioral measures indicates parent-based reports whereas the prefix t on the SDQ indicates a teacher-based report. Adding the latent factor Parent isolates the parental-reporting effect resulting in increased loadings of ADOS on the ASD factor and tSDQ ADHD on the ADHD factor, and reduces the correlation between ASD and ADHD symptoms to non-significance. The significant levels * $p < .05$, ** $p < .01$, and *** $p < .001$.

2.3.5 Step 3: Adding Parental Latent Factor (Model 2)

To account for shared sources of information, a parental-reporting factor was added to the Model 1 (see Figure 2-2A). The fit of Model 2 met the threshold of

acceptability, $\chi^2(79) = 99.2$, $p = .06$; CFI = .94; TLI = .92; RMSEA = .05; AIC = 6055.5; BIC = 6201.3, and retained the specific relationships between EF and ADHD symptoms (standard coefficient = .40, $p = .028$) and ToM and ASD symptoms (standard coefficient = .91, $p < .001$). The correlation between ASD and ADHD was no longer significant (standard coefficient = -.12, $p = .68$), reflecting that the overlap in the symptom ratings was accounted for by shared variance in the parent rating factor. Removing non-significant paths between EF and ASD, between ToM and ADHD, and between ASD and ADHD did not change the model fit significantly, $\Delta\chi^2(3) = 2.8$, $p = .43$. The final model fit was acceptable, $\chi^2(82) = 102.0$, $p = .07$; CFI = .94; TLI = .93; RMSEA = .049; AIC = 6052.2; BIC = 6190.3. In this model, EF deficits were associated with increased ADHD symptoms (standard coefficient = .47, $p < .001$), ToM deficits were associated with ASD symptoms (standard coefficient = .73, $p < .001$), and EF and ToM were significantly correlated (standard coefficient = .56, $p < .001$).

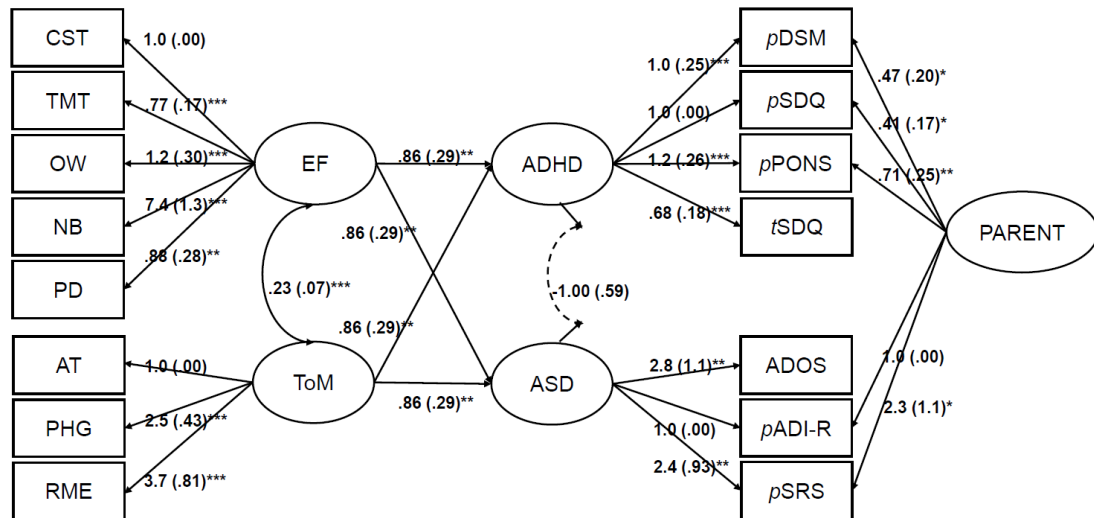
2.3.6 Step 4: Testing the Specificity of Relations between Cognitive Factors and Behavioural Symptoms

The specific relationships between the cognitive and behavioural factors were tested by comparing Model 2 against alternative Models 3 and 4 (Figure 2-3). Model 2 had significantly better fit, $\Delta\chi^2(3) = 14.5$, $p = .002$, than the alternative Model 3, where all paths between cognitive factors and behavioural symptoms were constrained to be equal in magnitude, $\chi^2(82) = 113.7$, $p = .011$; CFI = .90; TLI = .88; RMSEA = .062; AIC = 6064.0; BIC = 6202.1. The fit of Model 4, which could not be compared against Model 2 directly as they were non-nested models, also indicated poorer fit as observed from the direction of changes in model fit parameters, $\chi^2(83) = 131.0$, $p = .0006$; CFI = .86; TLI = .82; RMSEA = .076; AIC = 6079.3; BIC = 6214.8. These results showed that there was specificity in the relations between EF

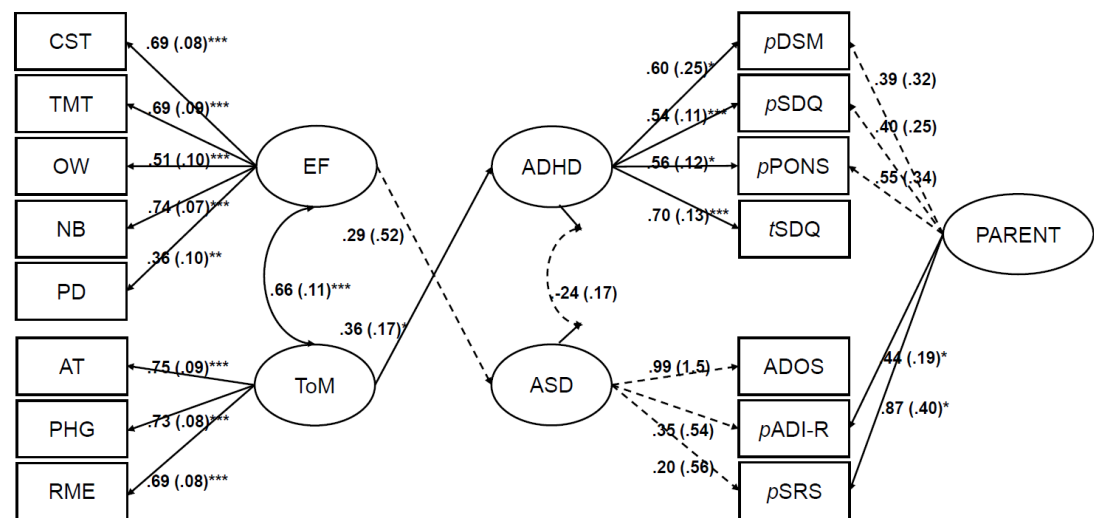
deficits and ADHD symptoms and between ToM deficits and ASD symptoms in the model.

Figure 2-3: SEM Model 3 and 4

A. Model 3 applies equality constraint to paths from cognition to symptoms



B. Model 4 included non-significant paths from cognition to symptoms only

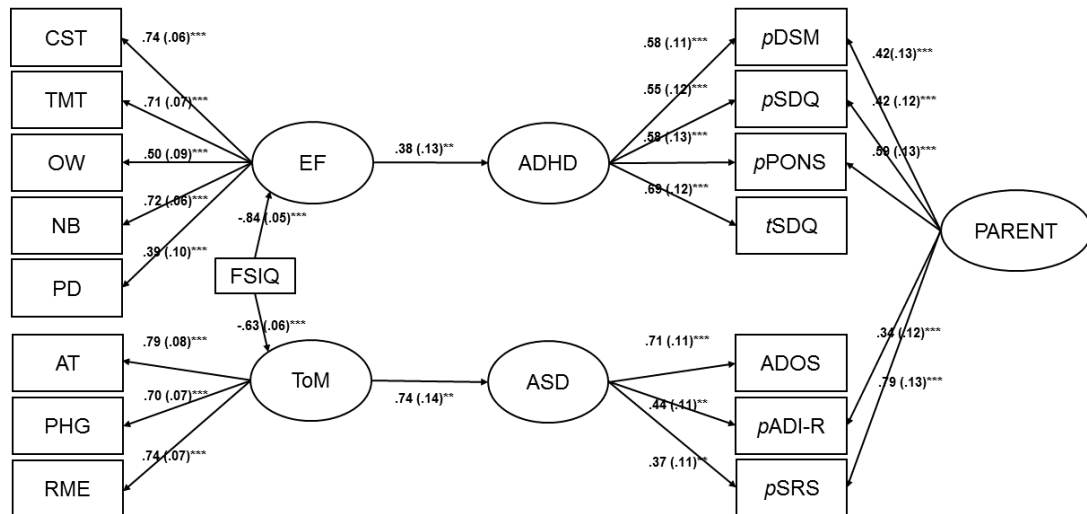


Note. Model 3 and 4 were compared against Model 2 to confirm the specificity of relationships between the neurocognitive and symptom factors. In Model 3, each path from the neurocognitive to the behavioural factors is constrained to equal magnitude (non-standardized coefficients are shown here to demonstrate the equality constraint). Non-standardized coefficients, instead of standardized coefficients, are shown in this model to demonstrate the equality constraint applied on the paths between the cognitive and the symptom factors. In Model 4, paths from EF to ADHD and from ToM to ASD were dropped from the model, which was opposite to the specific paths which are part of the final Model 2 in Figure 2-2B. Non-significant paths are represented by the dotted lines. List of abbreviations CST = card sort task, TMT = Trail-Making Test, OW = Opposite Worlds, NB = Number Backward, PD = planning drawing task, AT = animated triangle, PHG = penny hiding games, RME = Reading the Mind in the Eye tasks, EF = executive function, ToM = theory of mind. Abbreviations for ASD or ADHD measures: ADOS = Autism Diagnostic Observation Schedule, ADI-R=Autism Diagnostic Interview-Revised, SRS = Social Responsiveness Scale, DSM = Diagnostic and Statistical Manual of Mental Disorders, SDQ=Strengths and Difficulties Questionnaire, PONS=Profile of Neuropsychiatric Symptoms. The prefix p on these behavioural measures indicates parent-based reports whereas the prefix t on the SDQ indicates a teacher-based report. Adding the latent factor Parent isolates the parental-reporting effect resulting in increased loadings of ADOS on the ASD factor and tSDQ ADHD on the ADHD factor, and reduces the correlation between ASD and ADHD symptoms to non-significance. The significant levels * $p < .05$, ** $p < .01$, and *** $p < .001$.

2.3.7 Step 5: Does Controlling for FSIQ Change the Relationships Among Factors (Model 5)?

Finally, the influence of FSIQ in the relations among factors seen in Model 2 (Figure 2-4) was assessed in Model 5. The model including IQ resulted in a near-acceptable model fit, $\chi^2(95) = 123.3$, $p = .027$; CFI = .94; TLI = .92; RMSEA = .055; AIC = 6609.1; BIC = 6757.6. As in Model 2, the paths between EF and ADHD factors (standard coefficient = .38, $p = .004$), and ToM and ASD (standard coefficient = .74, $p < .001$) were significantly associated. When FSIQ was included to account for the covariance in EF and ToM, the correlation between these factors diminished to non-significance (standard coefficient = .02, $p = .54$). FSIQ was significantly associated with EF (standard coefficient = -.84, $p < .001$) and ToM (standard coefficient = -.63, $p < .001$).

Figure 2-4: SEM Model 5



Note. Figures shows Model 5 which tested the effect covarying for IQ has on the relationships from each neurocognitive domain to the symptom domains. Covarying for IQ appeared to reduce the magnitude of associations between the factors EF and ADHD symptoms, and ToM and ASD symptoms. List of abbreviations CST=card sort task, TMT= Trail-Making Test, OW= Opposite Worlds, NB = Number Backward, PD = planning drawing task, AT = animated triangle, PHG = penny hiding games, RME=Reading the Mind in the Eye tasks, EF=executive function, ToM=theory of mind. Abbreviations for ASD or ADHD measures: ADOS =Autism Diagnostic Observation Schedule, ADI-R=Autism Diagnostic Interview-Revised, SRS=Social Responsiveness Scale, DSM = Diagnostic and Statistical Manual of Mental Disorders, SDQ=Strengths and Difficulties Questionnaire, PONS=Profile of Neuropsychiatric Symptoms. The prefix p on these behavioural measures indicates parent-based reports whereas the prefix t on the SDQ indicates a teacher-based report. Adding the latent factor Parent isolates the parental-reporting effect resulting in increased loadings of ADOS on the ASD factor and tSDQ ADHD on the ADHD factor, and reduces the correlation between ASD and ADHD symptoms to non-significance. The significant levels * $p < .05$, ** $p < .01$, and *** $p < .001$.

2.4 Discussion

The aim of this study was to explore how the difficulties in EF and ToM are related to ADHD and ASD symptoms in a community sample of adolescents with ASD. The primary findings are the specific associations among these variables, i.e., the results show that poor EF and not ToM is associated with ADHD symptoms, whereas difficulties in mentalising, and not EF, are associated with ASD symptoms, which in turn indicate that symptoms of ADHD and ASD among individuals with ASD have distinct neurocognitive correlates. The secondary findings are that the observed relationship between ASD and ADHD symptoms in the sample can be explained by a parent reporting effect. The specific relationships between EF deficits and ADHD symptoms, and ToM deficits and ASD symptoms remain even after covarying for FSIQ. However, the correlation between the EF and ToM deficits, which were observed in earlier models became non-significant when the variance of EF and ToM related to IQ was controlled. To my knowledge this is the first study to investigate the relationships among these factors using a structural equation modelling approach.

2.4.1 EF was Associated with ADHD Symptoms and ToM was Associated with ASD Symptoms in Adolescents with ASD

With regard to the relationship between EF and ADHD symptoms, the present model shows that that an underlying deficit in EF among individuals with ASD is associated with increased ADHD symptoms in the population. This finding is in line with previous findings based on group comparisons that have shown increased EF difficulties among individuals with ASD+ADHD compared to those with ASD alone (Ames & White, 2011; Andersen et al., 2013; Buehler et al., 2011; Geurts et al., 2004; Johnson et al., 2007; Sinzig, Morsch, Bruning, et al., 2008; Yerys et al., 2009). The specific link between EF deficits and ADHD symptoms is not entirely

unexpected. EF difficulties strongly characterise individuals in the ADHD population. EF has consistently been associated with ADHD in studies comparing groups of individuals with this condition against controls (see meta-analyses by Alderson et al., 2013; Kasper et al., 2012; Lipszyc & Schachar, 2010; Willcutt et al., 2008). Further, longitudinal studies have also demonstrated the stability of EF deficits in individuals with ADHD throughout development and their associations with diagnostic status in adulthood among those receiving ADHD diagnosis in childhood (Biederman et al., 2007; Halperin, Trampush, Miller, Marks, & Newcorn, 2008). It is thus conceivable that EF is associated with ADHD symptoms in the ASD population.

Note, however, that many previous neurocognitive studies were conducted on relatively small clinical or convenience samples often with greater severity and increased level of co-occurring symptoms (S. H. Goodman et al., 1997), which could contribute to inconsistent findings across studies. Further, most group comparison studies involved groups of individuals with $IQ > 70$, thus were not fully representative of the ASD population. Given the context, the current results show that, firstly, the associations between EF deficits and ADHD symptoms found in studies based on convenience samples (e.g., Ames & White, 2011; Andersen et al., 2013; Buehler et al., 2011; Sinzig, Morsch, Bruning, et al., 2008), in fact generalised to population-based cohort of children with ASD including those with lower IQ (> 50). Secondly, the association between EF deficits and ADHD symptoms in the model, which was robust even after controlling for the covariances of EF and ToM that were attributable to IQ, could suggest a shared neurocognitive underpinning between ADHD symptoms in ASD and those found in ADHD alone.

The findings are also consistent with previous results of the associations between mentalising abilities and social reciprocity and communication symptoms in studies of children with ASD alone, with and without co-occurring intellectual disability (Ames & White, 2011; Joseph & Tager-Flusberg, 2004; Nagar Shimoni et

al., 2012; San José Cáceres et al., 2014), which have supported the view of ToM as an explanatory factor for social problems in ASD. However, there have also been studies that reported no significant relationships between performance on ToM tasks and social behaviour (Fombonne, Siddons, Achard, Frith, & Happé, 1994; Pellicano, 2013; Travis, Sigman, & Ruskin, 2001). One explanation offered for the null findings in previous studies is the reliance upon single measures such as the false-belief test, that do not fully capture the range of social cognitive and perceptual processes that might be associated with ToM (Bloom & German, 2000; Pellicano, 2013; Tager-Flusberg, 2007). In the present study, these limitations were addressed by applying a multi-measure approach to better capture the different processes underlying the capacity for ToM. The current study also controlled the overlapping cognitive demands that ToM and EF tasks might have imposed during the task performance (Brunsdon & Happé, 2014; Carlson, Moses, & Breton, 2002). By removing several tasks that cross-loaded onto the cognitive domain expected a priori, the EF and ToM latent factors may be “purer” than those reported in other studies. In addition, we found little evidence of an association between EF and ASD symptoms; therefore, the relationship between ToM deficits and ASD symptoms was unlikely to be mediated by deficits in EF.

Contrary to reports of associations between EF and ASD symptoms (Ames & White, 2011; D’Cruz et al., 2013; Joseph & Tager-Flusberg, 2004; Kenworthy et al., 2009; Lopez et al., 2005; Mostert-Kerckhoffs et al., 2015; Pellicano, 2013), no relationship between the EF latent factor and ASD symptoms was found in this study. There are two possible reasons for this lack of finding. First, the apparent relationships between EF task performance and ASD symptoms in previous studies could be an epiphenomenon of other unrelated factors. One concrete example for this explanation was observable in the present study. Bivariate correlation analyses have shown that performance of Luria hand game was correlated significantly with

ASD symptoms measures on the ADOS and SRS. However, the correlation could be explained by the fact that the task game's performance loaded primarily on the ToM domain, which is associated with ASD symptoms. Second, EF performance might be only weakly associated with ASD symptoms and only specifically associated with repetitive behaviour as has been suggested by findings from some studies. It is possible that this study, which is moderate to large in size for statistical modelling purposes, was underpowered to detect this relationship.

2.4.2 Correlations between Autistic and ADHD Traits were Explained by Shared Parental Rating Factor

The relationship between autistic trait severity and the level of co-occurring ADHD symptoms have been subject to mixed findings. Previous studies, mostly based on parent-rated social withdrawal and social problems on questionnaires such as the Child Behaviour Checklist (Achenbach & Rescorla, 2001) and the SRS typically showed increased autistic trait severity among individuals with ASD+ADHD relative to those with ASD alone (see e.g., Holtmann et al., 2007; Sprenger et al., 2013; Yerys et al., 2009) suggesting that those with additional ADHD symptoms also had more severe ASD traits. This is in contrast to comparisons of autistic symptoms based on gold standard measures such as ADI-R and ADOS, which more consistently show comparable levels of ASD symptoms in the ASD+ADHD group and the pure ASD group (Holtmann et al., 2007; Salley et al., 2015; Yerys et al., 2009), which is further supported by several clinical and population-based studies that fail to find an association between symptoms of ASD and ADHD in individuals with ASD (see e.g., Louwerse et al., 2015; Simonoff et al., 2008, 2013).

Several explanations for these discrepant findings have been offered in the past. Sprenger et al. (2013) pointed out the qualitative differences among the SRS, ADOS, and ADI-R in an attempt to explain these contrasting findings. For instance,

while the ADOS and SRS assess current symptoms, the ADI-R also includes symptoms from age 4-5 years as a severity index. In addition, the ADOS might be vulnerable to interviewer bias as autistic symptoms could be under-rated when they were thought to be ADHD-related (Sprenger et al., 2013). Also considered was the fact that the SRS, as a broad measure for traits in the general populations, might be insensitive to the distinction between the ASD+ADHD and the ASD groups or tap more than just autism-specific traits (Yerys et al., 2009). The latter explanation is consistent with the observed positive association between parent-rated SRS scores and non-ASD behaviour problems, as well as other parent-rated measures of ASD symptoms and social development among a very large sample of children with ASD; and the poor specificity of the SRS total score among another large sample of children with a mixture of externalising and internalising psychopathology and ASD (Hus, Bishop, Gotham, Huerta, & Lord, 2013; Moul, Cauchi, Hawes, Brennan, & Dadds, 2015).

In contrast to the studies by Sprenger (2013) and Yerys (2009), participants were not categorised into groups of individuals with ASD or ASD+ADHD *a priori*. Rather, all assessments were conducted within a single sample of children already characterised with primary research diagnoses of ASD. Therefore, interviewer bias in the form of underrated autistic symptoms because they were thought to be manifestations of ADHD were unlikely to occur in this study. Other measurement issues, such as the inclusion or exclusion of past symptoms in the severity index, and the specificity of measures such as the SRS for ASD could indeed have played role in producing an association between the two factors in the initial model (with poorer fit). However, the fact that the correlation was lost upon the inclusion of latent factor controlling for the shared information source from parents, suggested that the ASD and ADHD symptom correlation in the initial model was attributable to the fact that the information was given by the same source, i.e., parents.

There are several possible reasons for this. Parents might have a specific response style, e.g., tendency to rate all behaviours as high or low, that influence their responses across measures (De Los Reyes & Kazdin, 2005). Further, children's behaviour might differ at home, when they spend time with their parents, from that in other settings (Kanne, Abbacchi, & Constantino, 2009; D. W. Murray et al., 2007). Due to the limited availability of measures from other sources, it was not possible to explore the matter further in the current study, e.g., by contrasting models where symptom information was derived from parents compared to other sources. Nonetheless, the findings underline the importance of obtaining multiple sources of information and accounting for their shared characteristics when examining the relationships between factors in the ASD population (Risi et al., 2006).

2.4.3 Explaining the Co-occurrence of ADHD Symptom Among ASD Children

The findings of this study show that symptoms of ASD and ADHD among children with ASD have separate neurocognitive basis. While the cognitive-behaviour relationships between EF-ADHD symptoms and ToM-ASD symptoms in the ASD population are specific, the neurocognitive bases for these relationships are moderately correlated (.56), thus there is a possibility for EF and ToM deficits to both occur among children with ASD, which could explain why ADHD symptoms frequently co-occur in this population. The correlation of the EF and ToM factors is consistent with past findings (Ames & White, 2011; Harris et al., 2008; Joseph & Tager-Flusberg, 2004; Ozonoff et al., 1991; Pellicano, 2007). As discussed previously, EF and ToM are generally believed to related developmentally (S. E. Miller & Marcovitch, 2012; Perner & Lang, 1999; J. Russell, 1997), although it is unclear from the present literature whether social cognition is a precursor for EF (Perner & Lang, 1999) or whether the opposite relationships is valid (C. Hughes, 1998; J. Russell, 1997). The relationships between EF and ToM is measurable in

typically developing children as young as 3-4 years of age (Flynn et al., 2004; C. Hughes, 1998; Pellicano, 2007), and it is possible that the precursor of such functions are existing in infancy (see e.g., Marcovitch, Clearfield, Swingler, Calkins, & Bell, 2016; Moll & Tomasello, 2007). The model presented in the present study also points to IQ as a possible moderating influence between EF and ToM. Therefore, the co-occurrence of ADHD symptoms in children with ASD appears to have a strong organic influence.

Without the ADHD group as a comparison, the findings from this study are of insufficient use for examining the suitable comorbidity model for the co-occurrence of the two disorders. However, the current model may help to judge the likelihood of several models. First, based on the similarity of the neurocognitive underpinning of ADHD symptoms in ASD and in ADHD alone, compared indirectly between the present findings and past studies of ADHD, we can suggest that two conditions are possibly not symptomatic phenocopy from the neurocognitive perspective. The IQ-moderated relationship between EF and ToM suggest strongly that the ADHD symptoms in ASD are not environmentally driven therefore a model such as the environmentally-influenced phenocopy is possibly less likely according to the present model's findings. This is not say that the two conditions are not *neurocognitive phenocopies* which is entirely possible if the EF deficits in ADHD and ASD have different underlying neural correlates. Second, the separated neurocognitive underpinning of ASD and ADHD symptoms may support the gradient overarching manifestations of a single condition (Rommelse et al., 2011; J. M. J. van der Meer et al., 2012), i.e., those with high severity of ASD trait may have higher severity EF deficits mediated by the severity of the ToM deficit (J. M. J. van der Meer et al., 2012). Furthermore, the specific association between EF and ADHD symptoms could reflect an additive impairment of the two disorders, that is, individuals with ASD with *additional* ADHD symptoms are those with more severe

EF deficits (Banaschewski et al., 2007; Sinzig, Morsch, Bruning, et al., 2008). However, the absence of ADHD comparison group in this study prevents us from putting forward this idea strongly.

2.4.4 Strengths and Limitations

The strengths of this study include the use of a well-characterised sample of individuals with ASD. Furthermore, the sample was population-based (although not population-representative at the second timepoint as it excluded individuals with FSIQ < 50 by design). Therefore, the findings are not subject to the biases in clinical samples, which often reflect the more severe end of disorders with higher rates of co-occurring disorders (S. H. Goodman et al., 1997). The inclusion of multiple sources of information using a variety of well-validated and/or well-replicated neurocognitive and symptom measures produces more robust findings than studies relying on single measures. The use of SEM enabled modelling of multiple relationships among the latent factors simultaneously. Finally, the model describes how variations in EF and ToM relate to dimensional measures of ASD and ADHD symptoms, thus the model captures individual differences within the ASD population.

The study also has some limitations. Importantly, the estimation of latent factors in this investigation is constrained by the selection of the measures employed in the study, which were not primarily designed to fully explore the aetiology of ADHD symptoms in ASD. Measures such as the SDQ and PONS are screening instruments which do not probe the full range of ADHD symptoms. Only one measure, i.e., the CAPA, explores all ADHD symptoms among the participants. Therefore, the latent ADHD symptom factor derived in this model may not have captured the full extent of ADHD-related difficulties in the sample. Nevertheless, with the present approach meaningful relationships between EF and ADHD

symptoms were found in this sample and the use of multiple source of information may have mitigated the use of less comprehensive screening tools in this study. Furthermore, factors were modelled with EF and ToM “predicting” the ADHD and ASD symptoms to conform with the assumption that EF and ToM were the underpinning of behavioural symptoms. This was partly a statistical necessity and was also conforming to the conventional model asserting EF and ToM as an endophenotype for behavioural symptoms (e.g., Banaschewski et al., 2007; F. Craig et al., 2015; Rommelse et al., 2011). Arguably, a model where ADHD and ASD symptoms predicting EF and ToM should also be considered but was not tested in this study.

An additional limitation is the modelling of associations between factors estimated with measures collected over a four-year period, i.e., when the children were 10 to 16 years. Changes in behaviour or traits may have occurred within this time span. However, having previously found considerable persistence in ADHD symptoms in this sample over this time frame (Simonoff et al., 2013), a reasonable estimate of the ADHD factor was expected using the present approach. Similarly, ASD symptoms among the participants were expected to be reasonably stable over the four-year follow up to mid-adolescence. This is so because studies have indicated stability of diagnosis from childhood to young adulthood (Billstedt et al., 2005; Cederlund et al., 2008). Furthermore, in a seven-year prospective study in 72 adolescents with ASD, the ADHD symptom score was found to be largely stable with a substantial number of participants showing an increased (40%) or stable (40%) symptom profile over time (Louwerse et al., 2015). Finally, the sample size of this study can be considered moderate to large for modelling purposes. However weaker relationships may still be undetected. Therefore, replication of findings using a similar approach in a larger sample is crucial to confirm the reliability of these results.

2.4.5 Implications and Future Directions

This study has several empirical and clinical implications. First, it adds to the growing literature that explores the cognitive underpinnings of ADHD symptoms in the ASD population. The findings show that ADHD symptoms in this group have cognitive correlates that are distinctive from those associated with ASD symptoms. Within the clinical context, exploring the neurocognitive underpinnings of ADHD symptoms in ASD and investigating further their similarities and differences to those seen in individuals with ADHD alone, might cast some light on the findings of the decreased effectiveness of standard interventions such as MPH for treating ADHD symptoms in people with ASD compared to in ADHD alone (RUPP Autism Network, 2005). The relationships between EF and ADHD symptoms found in this study might suggest some similarities in the cognitive basis between ADHD symptoms found in both disorders. Further, previously noted similar profiles of EF deficits in both ADHD and ASD (Rommelse et al., 2011) could be due to the presence of ADHD symptoms in the latter. In the context of the comorbidity debate, the model shows that the presence of ADHD symptoms could constitute an additional feature among children with ASD. Consequently, these findings might suggest that ADHD is distinct from ASD although this opinion is asserted with caution as the study lacked an ADHD comparison sample. Therefore, to understand further the association between cognitive deficits and the co-occurrence of ADHD and ASD, further studies comparing participants with ADHD, ASD, and ASD+ADHD, utilising broad sets of social cognition and executive function measures, are needed. Also useful are studies that would extend our knowledge of the neurobiological basis of the co-occurrence of the two conditions.

3 Study II: Neurocognitive Deficits in Young Adults with ASD, ADHD and ASD+ADHD

3.1 Introduction

ADHD symptoms co-occur among individuals with ASD in adulthood (Joshi et al., 2013; A. J. Russell et al., 2016) although the mechanisms underlying this co-occurrence are still unclear. Understanding the patterns of neurocognitive abilities such as EF and social cognition (SC) among individuals with ASD, ADHD, and ASD+ADHD can be a useful strategy to disentangle the specific and shared difficulties in these populations. Among individuals with ADHD diagnosed in childhood, longitudinal studies have shown that EF deficits persist into adulthood (Bédard et al., 2010; Biederman et al., 2007, 2009; M. Miller et al., 2012; Nigg et al., 2002). Studies of adults with ASD similarly suggest lifelong difficulties in ToM (Heavey et al., 2000; Rogers et al., 2007; Spek et al., 2010; S. J. White et al., 2011). The SEM model presented in Chapter 2 showed specific relationships between the underlying EF deficits and ADHD symptoms; and between ToM deficit and ASD symptoms in a population-based sample of adolescents with ASD. However, EF underlies independent cognitive constructs such as inhibition, sustained attention, working memory, and cognitive flexibility (Friedman et al., 2015; Happé, Booth, Charlton, & Hughes, 2006; Miyake & Friedman, 2012). It is thus important to explore the differences of each subdomain of cognitive function across groups of individuals with ASD, ADHD and ASD+ADHD and typically developing controls. Few studies compared these groups in four-way comparisons in both SC and EF domains (Sinzig, Morsch, Bruning, et al., 2008; Sinzig, Morsch, & Lehmkuhl, 2008; J. M. J. van der Meer et al., 2012) and only one study was among adults (Nydén et al.,

2010). To address this gap in the literature, I conducted an EF and SC comparison among adults with ASD, ADHD, and ASD+ADHD.

3.1.1 Neurocognitive Difficulties in ASD, ADHD and ASD+ADHD

Early cognitive comparisons among children with neurodevelopmental conditions have explored the discriminant validity of measures across conditions. Among SC research in ASD, an ADHD group was typically included as a psychiatric control to determine the specificity of deficits in the former (Buitelaar, van der Wees, Swaab-Barneveld, & van der Gaag, 1999a; Muris et al., 1999). Increasingly, however, number of studies has reported mixed findings and similar deficits across the two disorders. Therefore, in this section I would review further the findings of cognitive deficits in the ASD, as well as the pure ADHD and the ASD+ADHD population.

In comparison to healthy controls several studies reported that people with ADHD had poor face emotion recognition (Corbett & Glidden, 2000; Da Fonseca, Segulier, Santos, Poinso, & Deruelle, 2009; Pelc, Kornreich, Foisy, & Dan, 2006; L. J. Rapport, Friedman, Tzelepis, & Van Voorhis, 2002), and others found poor ToM as judged on tasks such as the False Belief and Faux Pas tests (Caillies, Bertot, Motte, Raynaud, & Abely, 2014; Mary et al., 2015; Shuai, Chan, & Wang, 2011; Sjöwall, Roth, Lindqvist, & Thorell, 2013). SC deficits are traditionally linked to ASD, but its presence among individuals with ADHD might partly explain problems in social interactions (Uekermann et al., 2010) and related difficulties such as lack of empathy, poor peer relationships, communication deficits (Clark, Feehan, Tinline, & Vostanis, 1999) and lack of social reciprocity previously reported in the population (Kochhar et al., 2011; A. Mulligan et al., 2009; Santosh & Mijovic, 2004). These findings could indicate that SC difficulties are shared deficits in ASD and ADHD, although inferring the similarities or differences in these domains between ASD or ADHD based on independent comparisons of each group against healthy controls

would be inappropriate as the studies utilised different measures, sample characteristics and have varying magnitude of effect sizes. More importantly, these studies typically did not account for cross-disorder traits despite the frequent co-occurrence of the two conditions (Geurts et al., 2009; Rommelse et al., 2011; J. M. J. van der Meer et al., 2012).

Recent studies have taken up this methodological concern by directly comparing SC in the ASD and ADHD groups and controlling for IQ, age, and cross-disorder traits statistically or through group matching (see Table 3-1). These studies showed greater SC deficits in the ASD than ADHD group especially in ToM (Baribeau et al., 2015; Demurie, De Corel, & Roeyers, 2011; Dyck et al., 2001; Gonzalez-Gadea et al., 2013; Muris et al., 1999; J. M. J. van der Meer et al., 2012; J. Yang, Zhou, Yao, Su, & McWhinnie, 2009). In terms of ToM studies, a group of children with autism and PDD-NOS performed more poorly on a ToM task compared to children with ADHD and children with anxiety (Muris et al., 1999), and further regression analyses showed greater deficits in ToM with increasing severity of ASD diagnostic subcategories, i.e., autism versus PDD-NOS, even when IQ and age discrepancies were controlled for. Interestingly, comparing a large sample of children with autism and Asperger's against non-ASD psychiatric controls with anxiety, ADHD, intellectual disability (ID), and typically developing controls, Dyck et al. (2001) found that only children with ASD were impaired relative to typically developing controls after covarying for IQ.

In another study of children in mainland China involving a battery of three ToM tasks, i.e., the Chinese adaptation of the Appearance-Reality test (Flavell, Flavell, & Green, 1983), the Sally-Anne task (Baron-Cohen et al., 1985) and the Smarties task (Perner & Lang, 1999), Yang et al. (2009) showed greater overall ToM impairment in children with autism compared to children with ADHD, relative to typically developing controls matched for non-verbal IQ. A subsequent small study

by Demurie et al. (2011) found that adolescents with ASD were selectively more impaired and responded with slower response time (RT) than age- and IQ-matched controls and children with ADHD on the RME task. Also using the RME task, Baribeau et al. (2015) showed in a large study involving over 250 children and adolescents that those with ASD and with ADHD performed more poorly than children with OCD and typically developing controls. Interestingly, while the group differences remained after covarying for ADHD and OCD traits, as well as IQ, age and sex, they became non-significant upon covarying for SCQ scores, suggesting a specific association between ToM and ASD traits. Among adults, Gonzalez-Gadea et al. (2013) found that participants with Asperger's were more impaired on the Faux-Pas task in comparison to age-, sex-, education- and IQ-matched groups of adults with ADHD and typically developing controls, who did not differ from each other.

With respect to face emotion recognition (FER), Downs and Smith (2004) found impairments in a small sample of children with autism relative to children with ADHD *with* comorbid oppositional defiant disorder (ODD) and controls, even though the ASD group demonstrated better verbal understanding than the ADHD children regarding the emotion an individual would experience in a variety of contexts. In another study using a data-driven latent class analysis of parent reports of ASD and ADHD trait severity, Van der Meer et al. (2012) separated more than 600 children recruited from into five classes, including two groups considered typically developing, one group with ADHD alone, one with predominant ADHD and secondary ASD traits, that is, the ADHD (+ASD) group, and one with predominant ASD with secondary ADHD traits, that is the ASD (+ADHD) group. FER difficulties across these groups increased with ASD traits. Thus, children with ASD (+ADHD) had greater difficulties than those with ADHD (+ASD) or ADHD alone. Another large study involving more than 550 children by Demopoulos et al. (2013) showed that

children with ASD had deficits in facial and vocal emotion recognition as well as social pragmatic judgement and problem solving with effect size larger (.62-1.55) than age-matched children with ADHD (.18-.55), although these effects diminished when covarying for FSIQ, which was 10 points higher in the ADHD group.

Contrasting with the results of these studies are findings from a few studies that showed that SC was similarly or more impaired in groups with ADHD as in those with ASD (Buitelaar et al., 1999a; Dyck et al., 2001; Kuijper, Hartman, & Hendriks, 2015; Sinzig, Morsch, & Lehmkuhl, 2008). A study by Buitelaar et al. (1999a) showing that similar level of ToM difficulties in children with ASD compared to nine ADHD children was probably underpowered. In addition, Dyck et al. (2001) reported that a composite score of “emphatic ability” (Dyck et al., 2001, p. 106), assessed by using several tasks including a FER task, were equally impaired in autism, ADHD and ID groups relative to controls. FER deficits in children with ADHD and with ASD+ADHD, but not in matched-age and IQ group with ASD, were reported by Sinzig et al. (2008). However, the study included a large proportion (37-53%) of children with conduct disorder (CD) or oppositional defiant disorder (ODD) across the clinical groups but particularly in the ADHD group, which might confound their findings. Lastly, Kuijper et al. (2015) reported that children with ASD and with ADHD were similarly impaired relative to controls on the first and second order False-Belief task. Note that some of these studies did not adequately control the presence of co-occurring symptoms or ASD or ADHD in their samples (see Table 3-1 for a summary of these findings).

Turning into the executive subdomains, comparisons of individuals with ASD against those with ADHD, and occasionally including an ASD+ADHD group, have been made in the domains of inhibition, sustained attention, working memory/planning, cognitive flexibility and reward responses (e.g., Andersen et al., 2013; Buehler et al., 2011; Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2012;

Table 3-1: Direct comparisons of SC in ASD and ADHD

Authors	Participants	Group matching	Co-occurring ADHD or ASD	SC sub-domain / tasks	Summary findings
Studies in children:					
Baribeau et al. (2015)	ASD (n = 118), ADHD (n = 71), and TD (n = 34), aged 6-19 years	Age but not IQ (mean IQ TD > ADHD > ASD), covaried	Co-occurring ASD/ADHD traits were covaried.	ToM / RMET	Correct responses: ASD < ADHD, TD (covarying IQ), group differences remained after controlling for ADHD, but not ASD, traits.
Bühler et al. (2011)	ASD (n = 86), ADHD (n = 84) and ASD+ADHD (n = 52) aged 4-22 years	Age but not FSIQ (ASD highest), covaried	Formed the ASD+ADHD group	Emotion / Face emotion task	Correct responses: ASD < ADHD (<10 years) ASD = ADHD (> 10 years)
Buitelaar et al. (1999)	ASD (n = 18), ADHD (n = 9) and TD (n = 20), aged 8-18 years	Not matched in age or IQ, subgroup analysis matching both	n/a	ToM / FB1, FB2 tasks Emotion / Face emotion task	FB1 scores: n.s. FB2 scores: ADHD < TD; ASD < TD Correct emotion: ASD < TD
Demopoulos et al. (2013)	ASD (n = 115) and ADHD (n = 276), mean age 10.5 years	Age but not FSIQ (ADHD>ASD)	ADHD traits did not differ between groups.	Emotion / DANVA Face & vocal affect task	DANVA standardised scores: ASD < ADHD
Demurie et al. (2011)	ASD (n = 13), ADHD (n = 13) and TD (n = 13), aged 11-17 years	Age and FSIQ	ASD+ADHD cases were excluded	ToM / RMET	Correct responses: ASD < TD Response time: ASD > ADHD, TD
Downs & Smith	ASD (n = 10), ADHD+ODD (n = 16) and TD (n = 10), aged 5-9 years	Age and FSIQ	n/a	Emotion / Face emotion task	Emotional recognition on face photos: ASD < ADHD+ODD < TD Emotional understanding total scores: ASD, ADHD+ODD < TD
Dyck et al. (2001)	ASD (n = 48), ADHD (n = 35), and TD (n = 36), aged 9-16 years	Age and FSIQ	No ASD+ ADHD cases	ToM / Strange stories Emotion / Face emotion task	Strange stories task scores: ASD < ADHD, TD Composite scores including the face emotion task: ASD, ADHD < TD
Kuijper et al. (2015)	ASD (n = 46), ADHD (n = 37) and TD (n = 38) aged 6-12 years.	Age but not IQ (ASD, ADHD < TD), not covaried	n/a	ToM / FB1 and FB2	FB1 scores: n.s. FB2 scores: ASD, ADHD < TD

Muris et al. (1999)	ASD (n = 20) and ADHD (n = 14), aged 5-12 years.	Age and FSIQ	n/a	ToM / FB	FB scores: PDD < ADHD
Sinzig et al. (2008)	ASD (n = 19), ADHD (n = 30), ASD+ADHD (n = 21) and TD (n = 29), aged 6-18 years	Age and FSIQ	Formed the ASD+ADHD group	Emotion / FEFA task (faces and pairs of eyes)	Correct responses (faces): ADHD < TD Correct responses (eyes): ADHD, ASD+ADHD < TD
Van der Meer et al. (2012)	Children (5-7 years) with ASD[+ADHD] (n = 41-56), ADHD [+ASD] (n = 45-59), ADHD (n = 64-108) and TD (n = 234-416)	Non-matching age (TD, ADHD < ADHD[+ASD], ASD[+ADHD]) and IQ (TD > ADHD [+ASD])	ASD+ADHD differentiated between predominant ASD (with ADHD trait) and predominant ADHD (with ASD trait)	Emotion / Face emotion task	Speed: ASD [+ADHD] < ADHD, TD ADHD [+ASD] < TD Accuracy: ASD [+ADHD] < ADHD, TD
Yang et al. (2009)	ASD (n = 20) ADHD (n = 26), and TD (n = 30), aged 3-15 years	Age but not NVIQ (ASD < TD), covaried	n/a	ToM / FB	FB scores: ASD < ADHD, TD
Studies in adults:					
Gonzales-Gadea et al. (2013)	ASD (n = 23), ADHD (n = 22), and TD (n = 36), mean age 33-38 years	Age and IQ	n/a	ToM / Faux pas, RMET	Faux pas scores: ASD < ADHD, TD RMET scores: n.s.
Nydén et al. (2010)	ASD (n = 55), ADHD (n = 73), and ASD+ADHD (n = 33), mean age 31-33 years	Age and FSIQ	Formed the ASD+ADHD group	ToM / Strange stories (cartoon)	RT on mentalising condition vs physical condition: n.s.

Note. ASD = autism spectrum disorder, ADHD = attention-deficit/hyperactivity disorder, TD = typically developing, Cognitive tests: FB1 = first order false belief, FB2 = second order false belief, DANVA = diagnostic analysis of nonverbal Accuracy, ToM = theory of mind, NVIQ = nonverbal IQ, VIQ = verbal IQ, FSIQ = full scale IQ, ODD = oppositional defiant disorder, RMET = reading the mind in the eyes, RT= response time, n/a = not available, n.s. = not significant.

Happé, Booth, et al., 2006; Kado et al., 2012; Sinzig, Morsch, Bruning, et al., 2008; J. M. J. van der Meer et al., 2012; Yerys et al., 2009). These studies reveal a similarly mixed pattern of findings as observed in the SC studies (see Table 3-2). There may be a couple of reasons for this inconsistency. Measures may have unexpected ceiling or floor effects. For instance, Happé et al. (2006) were unable to distinguish the inhibitory performance across older adolescents but not younger children under the age of 10 years with ASD, ADHD, and controls on a GNG task, suggesting an age-related floor effect in the task. Furthermore, as has been shown in the previous chapter, an underlying EF impairment, associated with additional ADHD traits among individuals with ASD, could contribute to heterogeneity of findings among individuals with ASD (e.g., Corbett et al., 2009; Geurts et al., 2004; Johnson et al., 2007; Johnston, Madden, Bramham, & Russell, 2011).

Nevertheless, studies of EF directly comparing individuals with ASD or ADHD, as well as those with ASD+ADHD, have collectively revealed interesting patterns of findings. Inhibition is the function most frequently investigated, which has been the hallmark of cognitive deficits in ADHD (Lipszyc & Schachar, 2010; Willcutt et al., 2008). Studies have found difficulties in inhibitory function among children and adults with ADHD relative to individuals with ASD and typically developing controls (Buehler et al., 2011; Happé, Booth, et al., 2006; K. Johnston, Madden, Bramham, & Russell, 2011; Sinzig, Morsch, Bruning, et al., 2008). Happé et al. (2006) found that children with ADHD, especially those in their early to mid-teens, performed more poorly than children with ASD and control groups, judged from the number of commission errors and task sensitivity on the GNG task taken from the Maudsley Attention and Response Suppression battery (Rubia, Smith, & Taylor, 2007). Sinzig et al. (2008) similarly reported more commission errors on a GNG task among ADHD children, compared to children with ASD, ASD+ADHD and TD controls. Furthermore, Corbett et al. (2009) showed that although children with either ASD or

ADHD appeared to be impaired in inhibitory measures relative to controls, the impairment among children with ASD dropped to trend level when those with co-occurring ADHD in the sample were removed from the analysis, suggesting that findings of inhibitory deficits among individuals with ASD could be partly attributable to the additional presence of ADHD symptoms in the sample (Sinzig, Morsch, Bruning, et al., 2008).

In a study involving individuals of a wide age-range up to young adulthood (5-22 years), Buehler et al. (2011) reported greater inhibitory difficulties on the GNG task among large groups of participants with ADHD and with ASD ($n > 80$ each). An additional group of approximately 50 individuals with ASD+ADHD demonstrated performance on a par with the ADHD group. Due to the lack of typically developing controls in the study, however, it was unclear what threshold of performance would constitute the norm. Johnston et al. (2011) found that adults with ADHD (50% of who scored beyond threshold on ASD symptom measures) demonstrated greater distractibility on the Stroop task than either controls or adults with ASD. Interestingly, among studies comparing ASD and ADHD groups, those reporting inhibition difficulties in ASD include a non-negligible number of ASD subjects with high ADHD traits (Fried et al., 2016; Geurts et al., 2004; Johnson et al., 2007). Twenty-five percent children in the ASD group in Geurts et al.'s (2004) study had substantial symptoms or diagnoses of ADHD; In Johnson's (2007) study, 57% of the ASD children had above the cut-off ratings of Conner's Parent Rating Scale for ADHD symptoms; while the majority of adults (81%) in the ASD sample of the study by Fried et al.' (2016) meet the criteria for ADHD or subthreshold ADHD. Altogether, these reports were consistent with the suggestion that inhibitory deficits among people with ASD might be related to co-occurring ADHD symptoms in the population.

With respect to vigilance or sustained attention, previous studies in ASD, including one with more than 100 participants, did not reveal impairments relative to controls (e.g., Bogte, Flamma, Van Der Meere, & Van Engeland, 2009; G. Goldstein, Johnson, & Minshew, 2001; Pascualvaca, Fantie, Papageorgiou, & Mirsky, 1998). In contrast, large studies involving people with ADHD consistently showed impaired performance (e.g., Epstein, Johnson, Varia, & Conners, 2001; Fischer, Barkley, Smallish, & Fletcher, 2005; K. R. Murphy, Barkley, & Bush, 2001; Rubia, Smith, & Taylor, 2007; Silva et al., 2013). These results are consistent with recent findings of primary sustained attention deficits among individuals with ADHD relative to the ASD group (Happé, Booth, et al., 2006; Johnson et al., 2007) and findings of similar patterns of deficits between the ADHD and the ASD+ADHD groups (Adamo et al., 2014; Sinzig, Morsch, Bruning, et al., 2008), judged from omission errors and RT variability on the GNG task. Both Happé et al. (2006) and Johnson et al. (2007) found that children with ADHD made more omission errors than controls or the ASD group, which did not differ from one another, despite a high proportion of individuals with ADHD symptoms in the ASD group. Further, Sinzig et al. (2008) showed that children with ADHD or ASD+ADHD omitted more responses than children with ASD alone or controls. Using a novel frequency domain analysis, Adamo et al. (2014) showed similar pattern of behavioural response among the ADHD and the ASD+ADHD groups compared to the controls on the GNG task even though they did not demonstrate overt differences on omission errors.

In the domains of working memory and planning, studies typically reveal poor performance in children and adults with ADHD or ASD relative to controls and such difficulties become more pronounced in tasks with higher executive demands (Alderson et al., 2013; Barendse et al., 2013; Kasper et al., 2012). Among studies comparing both clinical groups, deficits in working memory and planning were

typically found in both the ASD and ADHD groups compared to controls (Andersen et al., 2013; R. Booth et al., 2003; Goldberg et al., 2005; Sinzig, Morsch, Bruning, et al., 2008), although some studies showed more pronounced difficulties in the ADHD group possibly due to variation in the tasks used in these studies. (Fried et al., 2016; Gonzalez-Gadea et al., 2013; Happé, Booth, et al., 2006; Nydén et al., 2010; J. M. J. van der Meer et al., 2012). Among studies that have assessed working memory in an ASD+ADHD group (Andersen et al., 2013; J. M. J. van der Meer et al., 2012; Yerys et al., 2009), individuals with ASD+ADHD were typically found to be more impaired than individuals with pure ASD or ADHD. Yerys (2009), for instance, showed that young children with ASD+ADHD performed significantly worse on the backward digit span task than those with ASD alone who performed at the same level as controls, but no ADHD comparison group was included in this study. In a large study with over 150 children, Andersen (2013) showed that both children with HFA and those with pure ADHD were impaired on measures of verbal working memory and a delayed recall test relative to controls. Further, a subset of the ASD individuals with co-occurring ADHD were more impaired than those with ADHD or ASD alone, who showed impairment relative to controls. Finally, van der Meer et al. (2012) showed that individuals with predominant ADHD(+ASD) or pure ADHD were impaired on visuospatial and verbal working memory relative to controls, with individuals with ASD+(ADHD) performing in between these groups and the controls. The findings suggest that working memory difficulties were associated with ADHD symptom severity.

Impairments in cognitive flexibility were traditionally associated with ASD and were thought to explain patterns of rigid behaviours in the population (see e.g., Ozonoff & Jensen, 1999). Evidence suggests that individuals with ASD are consistently impaired in set-shifting tasks such as WCST or Trail-Making Test (Geurts et al., 2009). The specificity of this impairment for ASD relative to ADHD

has been questioned before. However, the effect sizes of cognitive flexibility impairments in individuals with ADHD were among the lowest of all domains (Willcutt et al., 2005, 2008). Further, recent studies using the WCST and trail-making in individuals with pure ASD and with pure ADHD supported the idea that the cognitive flexibility impairments were ASD-specific (e.g., Fried et al., 2016; Geurts et al., 2004; Gonzalez-Gadea et al., 2013; Kado et al., 2012; Winsler, Abar, Feder, Schunn, & Rubio, 2007). Both Geurts et al. (2004) and Winsler et al. (2007) found that individuals with HFA uniquely demonstrated higher perseverative errors on the WCST than controls, although in the latter, the ADHD group appear to have some deficits with performance in between the ASD and the TD groups. Most interesting are the findings of Kado et al. (2012) who presented the Japanese adaptation of the WCST in two steps, in children with pure PDD, pure ADHD and controls. In the first step, the task was administered using its typical open-ended instructions and prior to the administration of the task in the second step, the children were told that the rule of this task would occasionally change without warning. Both the ASD and the ADHD group showed significantly higher perseverative errors than controls after the first step. However, after the second step only the PDD group demonstrated the perseverative errors relative to controls while the ADHD group's performance improved to a level between the PDD and the control group, suggesting a specific relationship between perseveration and ASD.

Two studies in children found the opposite pattern of findings and demonstrated flexibility impairments in children with ADHD but not in those with ASD (see Nydén, Gillberg, Hjelmquist, & Heiman, 1999; J. Yang et al., 2009). However, one of these studies, consisting of 10 people per group would be underpowered and most likely vulnerable to Type I error (Nydén et al., 1999). In the other study (J. Yang et al., 2009), children seemed to complete varying number of trials, which could suggest compliance issues. Among adults, findings appeared to

be weaker and less consistent than in children. Gonzales-Gadea et al. (2013) found a trend for impaired performance on the modified WCST among adults with ASD relative to the ADHD group although not on the trail-making task. The authors attributed the lack of significance to the reduced sensitivity of these measures for assessing adults with ASD. Furthermore, Fried et al. (2016) showed that performance on the trail-making was significantly impaired among adults with ASD but not ADHD, who performed as well as controls, although most individuals in the ASD group met the criteria for ADHD which confounded the findings.

Finally, children and adults with ADHD show difficulties with temporal discounting, i.e., they discount future rewards at much steeper rates compared to present rewards, demonstrating a preference for immediate over prospective gratification (Mostert, Onnink, et al., 2015; Sjöwall et al., 2013; Solanto et al., 2001; Sonuga-Barke et al., 2008). The deficits were thought to represent choice impulsivity conceptualised as motivationally driven or “hot” EF (Castellanos et al., 2006; Rubia, 2011). Only a few studies have compared ASD and ADHD groups, with varying results (Chantiluke et al., 2014; Demurie et al., 2012). A large study involving nearly 120 children, showed steep monetary discounting over time delay was characteristic of individuals with ADHD and not those with ASD, who performed similarly to controls (Demurie et al., 2012). A subsequent smaller neuroimaging study involving over 60 boys with pure ASD, pure ADHD, with ASD+ADHD and controls reported a different pattern; there was steeper discounting over time in the ASD+ADHD and ASD groups compared to the ADHD and control groups, suggesting that ASD and not ADHD traits were associated with the impulsive choice behaviour (Chantiluke et al., 2014). The relatively small sample gathered for the latter study may reduce its power, however. Taken together these findings indicate that reward discounting can potentially differentiate ADHD from ASD group.

Table 3-2: Direct comparisons of EF between ASD and ADHD

Authors	Participants	Matching	Co-occurring ADHD or ASD	EF sub-domains/ tasks	Summary findings
Studies in children					
Adamo et al (2014)	ASD (n = 46), ADHD (n = 46) and TD (n = 36), aged 7-11 years.	Age and FSIQ	n = 17 ASD have ADHD diagnosis, identified as ASD+ADHD in a post-hoc analysis	Inhibition / SART GNG	MRT, SDRT and commission errors = all n.s. Restricted IS-SDRT in the frequency domain: ASD+ADHD is similar to ADHD
Andersen et al. (2013)	ASD (n = 22), ADHD (n = 79), ASD+ ADHD (n = 16) and TD (n = 50), aged 8-17 years.	Age but not FSIQ (ADHD < TD), covaried.	Formed the ASD+ADHD group	WM / WISC-IV LNS	Verbal WM score ASD+ADHD < ASD, ADHD < TD
Booth et al. (2003)	ASD (n = 30), ADHD (n = 30) and TD (n = 27), aged 8-16 years	Age and FSIQ	ASD+ADHD cases were excluded	Planning / Planning drawing task	Allowance score: ASD, ADHD < TD
Bühler et al. (2011)	ASD (n = 86), ADHD (n = 84), ASD+ ADHD (n = 52), predominantly children aged 4-22 years	Age but not FSIQ (ASD highest), covaried	Formed the ASD+ADHD group	Inhibition / TAP GNG	Commission errors: ASD+ADHD, ADHD > ASD
Corbett et al. (2006)	ASD (n = 15), ADHD (n = 15) and TD (n = 15), aged 7-12 years	Age but not FSIQ (TD > ASD)	n/a	Inhibition / IVA-CPT (GNG) VRCQ and ARCQ	Visual response control: ASD < ADHD, TD Auditory response control: ASD < ADHD < TD
Corbett et al (2009)	ASD (n = 18), ADHD (n = 18) and TD (n = 18), aged 7-12 years	Age but not FSIQ (TD, ADHD > ASD), covaried	n=8 ASD met the criteria for ADHD	Inhibition / IVA-CPT (GNG) VRCQ and ARCQ D-KEFS naming	Visual response control: ASD < ADHD, TD Auditory response control: ASD, ADHD < TD Naming interference control: ASD < ADHD, TD
				Flexibility / CANTAB ID/ED, D-KEFS T-switch, CCTT2	Total errors at advance stage: n.s. Task category switching score: ASD < ADHD, TD CCTT2 interference score: n.s.
				Planning / CANTAB SoC	Minimal moves, thinking time: n.s.
				WM / CANTAB SWM	Spatial Span: ASD, ADHD < TD SWM between errors: ASD > ADHD, TD SWM strategy score: ASD > ADHD, TD
Geurts et al (2004)	ASD (n = 64), ADHD (n = 42) and TD (n = 41), aged 6-12 years	Age but not FSIQ (ASD, ADHD < TD)	11 ASD have ADHD-c type characteristics, and a further 5 have clinical diagnosis of ADHD.	Inhibition / Change task, Circle drawing, TEA-Ch OW	SSRT: ADHD, ASD > TD, SDRT: ASD > TD Circle time difference: ASD < TD OW time difference: n.s.

				Flexibility / Change task, WCST	Change MRT: ASD > TD Change errors: n.s. WCST perseverative errors: ASD > ADHD, TD
				Planning / ToL	ToL beta score & decision time: n.s. ToL beta execution time: ASD > ADHD, TD
				WM / SoP	SoP beta errors: n.s.
				Inhibition / Stroop	Interference: n.s.
Goldberg et al. (2005)	ASD (n = 17), ADHD (n = 21) and TD (n = 32), aged 8–12 years	Age but not FSIQ (ASD < TD, ADHD)	ASD+ADHD cases were excluded	Flexibility / CANTAB ID/ED	Trials to criterion: n.s.
				Planning / CANTAB SoC	Number of extra moves: n.s.
				WM / CANTAB SWM	Total between-search errors: ASD, ADHD > TD
				Inhibition / GNG	Commission Errors: ADHD > ASD Omission Errors: ADHD > TD
Happé et al. (2006)	ASD (n = 32), ADHD (n = 30) and TD (n = 32), aged 8–16 years	Age and FSIQ	ASD+ADHD cases were excluded	Flexibility / CANTAB ID/ED	Trials to criterion: n.s.
				Planning / CANTAB SoC	Number of extra moves: n.s.
				WM / CANTAB SWM	Between search errors: ADHD > TD
				Inhibition / GNG (fixed and random ISI)	Commission errors (fixed): ADHD > ASD, TD Commission errors (random): ADHD, ASD > TD Omission errors (fixed and random): ADHD > ASD, TD
Johnson et al (2007)	ASD (n = 21), ADHD (n = 23), and TD (n = 18), mean age 10–12 years	Age and FSIQ	n = 12 ASD scored > cut-off on CPRS	Flexibility / k-WCST	1 st Step: <i>Implicit rule</i> Categories achieved: ASD, ADHD < TD Total errors: ASD, ADHD < TD Perseverative error: ADHD < TD 2 nd Step: <i>Explicit rule</i> Categories achieved: ASD, ADHD < TD Total errors: ASD, ADHD < TD Perseverative error: ASD < TD
Kado et al. (2012)	ASD (n = 52), ADHD (n = 46) and TD (n = 52), aged 5-15 years	Age and FSIQ	ASD+ADHD cases were excluded	Inhibition / Stop-signal task	SSRT: n.s.
Kuijpers et al (2015)	ASD (n = 46), ADHD (n = 37) and TD (n = 38), aged 6-12 years.	Age but not IQ (ASD, ADHD < TD), not covaried	n/a	WM / 2-back task	Number correct n.s.
Nydén et al. (1999)	ASD (n = 10), ADHD (n = 10) and TD (n = 10), aged 8-11 years	Age and FSIQ	n/a	Inhibition / GNG	MRT auditory task (conflict): ASD, ADHD > TD MRT visual task (conflict): ASD, ADHD > TD MRT auditory task (sustain): ASD, ADHD > TD MRT visual task (sustain): ASD, ADHD > TD

				Flexibility / WCST	Categories: ADHD < ASD, TD
Ozonoff et al. (1999)	ASD (n = 40), ADHD (n = 46) and TD (n = 29), aged 6-18 years	Age but not FSIQ (TD > ASD)	n/a	Inhibition / Stroop task	Colour-word test score: ADHD < ASD, TD
				Flexibility / WCST	Perseverative responses: ASD > ADHD, TD
				Planning / ToH	Planning strategy: ASD < ADHD, TD
Sinzig et al (2008)	ASD (n = 20), ADHD (n = 20), ASD+ ADHD (n = 20) and TD (n = 20), aged 6-18 years	Non-matching age and IQ	Formed the ASD+ADHD group	Inhibition / GNG	Commission errors: ADHD > ASD+ADHD, ASD, TD Omission errors: ADHD, ASD+ADHD > ASD, TD
				Flexibility / CANTAB ID/ED	Stages: ASD+ADHD > TD Errors: n.s.
				Planning / CANTAB SoC	Initial thinking time: ASD < ADHD Subsequent thinking time: ASD < TD Problem solved: n.s.
				WM / CANTAB SWM	Errors: ADHD, ASD > TD Strategies: ADHD < ASD+ADHD, TD
Unterrainer et al (2015)	ASD (n = 18), ADHD (n = 42), ASD+ ADHD (n = 23) and TD (n = 42), aged 6-13 years		Formed the ASD+ADHD group	Planning / ToL	Problem solved: n.s. Initial thinking time: n.s.
Van der Meer et al. (2012)	ASD[+ADHD] (n = 41-56), ADHD [+ASD] (n = 45-59), ADHD (n = 64-108) and TD (n = 234-416), aged 5-17 years	Non-matching age (TD, ADHD < ADHD[+ASD], ASD[+ADHD]) and IQ (TD > ADHD [+ASD])	ASD+ADHD differentiated between predominant ASD (with lesser ADHD) and predominant ADHD (with lesser ASD)	Inhibition / Switch task	Inhibition speed: n.s. Inhibition accuracy: n.s.
				Flexibility / Switch task	Switching errors: n.s. Switching accuracy: n.s.
				WM / Backward visuospatial attention and backward verbal DS	Visuospatial WM performance: ADHD[+ASD] < TD Verbal backward DS performance: ADHD < TD
Winsler et al (2007)	ASD (n = 33), ADHD (n = 21) and TD (n = 28), aged 7-18 years.		n/a	Flexibility / WCST	Perseverative errors: ASD > TD
Yang et al. (2009)	ASD (n = 20) ADHD (n = 26), and TD (n = 30), aged 3-15 years	Age but not NVIQ (ASD < TD), covaried	n/a	Inhibition / Stroop task	Count of interference trials: n.s.
				Flexibility / WCST	Perseverative errors: n.s.
				WM / Corsi block task	Sum of longest recalled sequence number: n.s.
Yerys et al (2009)	ASD (n = 28), ASD+ ADHD (n = 21) and TD (n = 21), aged 6-13	Age and FSIQ	Formed the ASD+ADHD group	WM / WISC-IV Backward DS, CANTAB SWM	Backward DS: ASD+ADHD < ASD < TD Between search errors: n.s.

	years.			Inhibition / TEA-Ch Walk Don't Walk	Total score: n.s.
Studies in adults:					
Bramham et al (2009)	ASD (n = 45), ADHD (n = 53), TD (n = 41), mean age 31-32 years	Age and FSIQ	n/a	Planning / Zoo map test	Accuracy and execution time: n.s. Planning time: ADHD < TD < ASD Total time: ADHD, TD < ASD
Fried et al. (2016)	ASD (n = 26), ADHD (n = 52), TD (n = 52) aged 18-40 years	Age and FSIQ	n = 16 ASD meet the criteria for ADHD, and a further n = 5 had subthreshold ADHD	Inhibition / D-KEFS Stroop inhibition score	Inhibition score: ASD < ADHD < TD
				Flexibility / D-KEFS TMT, DKEF Stroop switching score	TMT-B: ASD < ADHD, TD Switching score ASD < ADHD, TD
				WM / WAIS-III Working memory	WM score: ASD < ADHD, TD
Gonzales-Gadea et al. (2013)	ASD (n = 23), ADHD (n = 22) and TD (n = 21), mean age 33-38 years	Age and IQ	n/a	WM / Letters and numbers, backward DS	Backward DS recall score: ADHD < ASD, TD Letters and numbers recall score: ADHD < ASD, TD
				Flexibility / TMT, WCST	TMT-B: n.s. WCST Perseverative errors: n.s.
				Planning / Hotel task	
Johnston et al. (2011)	ASD (n = 24), ADHD (n = 24), and TD (n = 14), aged 18-55 years	Age and VIQ (FSIQ was not interpretable in some cases)	n = 12 ADHD scores >100 on SRS, n = 1 ASD scored above ADHD cut-off on Barkley	Inhibition / Stroop test, Hayling test	Colour-word standard score: ADHD < ASD, TD Hayling inhibition time scaled score; n.s.
Nydén et al (2010)	ASD (n = 55), ADHD (n = 73) and ASD+ADHD (n = 33), mean age 31-33 years	Age and FSIQ	Formed the ASD+ADHD group	WM / WAIS-R digit span	Digit span: ADHD < population norm
				Planning / ToL	Planning total number of moves: n.s. Planning total reaction times: n.s.

Note. Abbreviations GNG = Go/no-go, SART = Sustained-attention to response task, WM = Working memory, WISC-IV LNS = Wechsler Intelligence Scale for Children 4th version Letter–Number Sequencing (working memory domain), FSIQ = Full-scale IQ, IVA-CPT = Integrated Visual and Auditory Continuous Performance Task, A/VRCQ = Audio/visual response control quotient, D-KEFS = Delis-Kaplan Executive Function System, CANTAB = Cambridge Neuropsychological Test Automated Battery, ID/ED = Internal/External Dimension shift task (part of CANTAB), SoC = Socks of Cambridge (part of CANTAB), SWM = spatial working memory (part of CANTAB), SoP = Self-order pointing task, CCTT2 = Children's Color Trails Test 2nd edition, WCST = Wisconsin Card Sort Task, k-WCST = Keio-WCST, a Japanese adaptation of the WCST, ToL = Tower of London task, Backward DS = Digit Span, TMT = Trail-Making Test, WAIS-III = Wechsler Adult Intelligence Scale 3rd version, VIQ = Verbal IQ, NVIQ = Nonverbal IQ, TEA-Ch = Test of Everyday Attention for Children, n/a = not available, n.s. = not significant.

3.1.2 The Aims of This Study

Findings from studies in EF and SC among individuals with ASD and ADHD suggest both shared and specific neurocognitive difficulties in these conditions. Few studies have been undertaken in adults with ASD and ADHD, and even fewer included adults with ASD+ADHD to offer the lifespan perspective needed to understand the role of cognitive function in ASD and ADHD and their co-occurrence. This study therefore explored the neurocognitive similarities and differences in both EF and SC domains among adults with ASD, ADHD, and ASD+ADHD. The study took the perspective of fractionable cognitive function (Happé, Ronald, et al., 2006; E. L. Hill, 2004) and therefore a range of cognitive subdomains of EF and SC were included. EF domains included response inhibition, sustained attention, working memory, cognitive flexibility, and delayed reward while SC components included ToM and FER. The aim of the study was to address the following questions: (1) what kinds of EF and SC difficulties are present in young adults with ASD relative to ADHD? (2) How would the cognitive difficulties in the ASD+ADHD group compare to those in the ASD and ADHD groups? And lastly (3) how would the difficulties in EF and SC relate to ASD or ADHD symptoms in adulthood? Based on previous studies impairments in EF were expected to be present in the ADHD group and not in the ASD group. An exception to the case is within the subdomain of cognitive flexibility, for which deficits were expected primarily in the ASD group. SC deficits were expected to occur in the ASD group but not in the ADHD group. The ASD+ADHD group was expected to display similar difficulties in the EF domain as the ADHD group and similar SC difficulties as the ASD group.

3.2 Methods

3.2.1 Participants

One hundred and twelve young-adult males aged 20-27 years took part in this study, a subset of whom (N = 107) met the study criteria and were included in one of four diagnostic groups: ASD (n = 26), ADHD (n = 28), ASD+ADHD (n = 27), and typically developing (TD) controls (n = 26). The study was approved by the Camberwell – St. Giles NHS Research Ethics Committee (13/LO/0373) and each participant gave informed consent to take part in this study. The general inclusion criteria for all participants were male with full-scale IQ (FSIQ) ≥ 70 . The general exclusion criteria were neurological disorders such as epilepsy, personality disorder, active substance abuse or dependence, lifetime history of bipolar disorder or schizophrenia, or past head injury resulting in loss of consciousness ≥ 5 minutes. The participants in the ASD, ADHD and ASD+ADHD groups were recruited from several sources: (1) the South London and Maudsley Adult ASD and ADHD clinics; (2) the SNAP cohort, an epidemiological sample consisting of individuals characterised at the age of 10-12 years (see Baird et al. [2006] and Chapter 2 for details) and (3) through advertisements in newsletters of ASD and ADHD support organisations, social media networks, and universities. The individuals in the SNAP cohort took part in this study as a part of a wider follow-up study focusing on the adult outcome of individuals with ASD.

The majority (n = 22) of individuals in the ASD group, including several who were part of the SNAP cohort, had clinical diagnoses of ASD. The remaining participants with no clinical diagnoses (n = 4) received research diagnoses as part of the SNAP cohort. All but one individuals' diagnosis, be it in form of research diagnoses through SNAP or clinical diagnoses through specialist clinics, were supported by gold-standard research diagnostic instruments the ADOS and/or the

ADI-R (both the ADOS and the ADI-R [$n = 24$] and the ADOS only [$n = 1$]). The only participant with no history of assessments using the ADOS or ADI-R received a clinical diagnosis from a paediatric service in South London specialising in neurodevelopmental disorders. In terms of the time point of the diagnosis, most participants ($n = 20$) received research or clinical diagnoses of ASD in childhood and the remaining ($n = 6$) were diagnosed in adulthood through the South London and Maudsley adult ASD clinics. None of the participants in this group was on any psychotropic medications at the time of the study.

The majority ($n = 27$) of participants from the ADHD group had ADHD diagnoses. Most of diagnoses ($n = 21$) were supported by research instruments the Diagnostic Interview for Adult ADHD (DIVA 2.0; Kooij, 2013) and two diagnoses were supported with the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID; Conners, Erhardt, & Sparrow, 1999), all conducted by the clinicians in the specialist ADHD clinics; thus, the participants met criteria for ADHD specified by the DSM-IV or DSM-5. Four participants received their ADHD diagnoses in childhood which was subsequently confirmed in the specialist adult ADHD clinics but did not go through research assessments using the above research instruments. One remaining participant did not have ADHD clinical diagnosis but was referred by his GP to an adult ADHD specialist clinic. This participant was assessed by the researcher using the DIVA 2.0 interview conducted with the participant and his elder brother and an assessment of the participant's childhood ADHD symptoms was obtained from the participant's parents prior to the study using the CAARS and SDQ17+, confirming that he met the criteria for ADHD. Approximately half ($n = 13$) of the participants received their diagnoses in adulthood. The participants met criteria for combined ADHD ($n = 18$), followed by inattentive ($n = 9$), and hyperactive presentations ($n = 1$). Several participants ($n = 5$) were on current stimulant medication but withdrew for 48 hours prior to the study. Individuals taking non-

stimulant medications such as atomoxetine were excluded due to its prolonged wash-out period (up to 1 week). Three people with comorbid affective disorder were included in the study. These individuals were taking the selective serotonin response inhibitors (SSRIs) at the time of the study.

The majority ($n = 15$) of participants in the ASD+ADHD group had clinical diagnoses of ASD in childhood. Few ($n = 4$) received research diagnosis in childhood through the SNAP study and the remaining ($n = 8$) received diagnosis in adulthood. Most of the individuals' ASD diagnoses were supported by assessments on gold-standard diagnosis instruments the ADOS and/or the ADI-R (both the ADOS and the ADI-R [$n = 24$], the ADOS only [$n = 1$], the ADI-R only [$n = 3$]). Three participants received clinical diagnoses in childhood from specialist paediatric clinics in London. One participant was assessed using the Diagnostic Interview for Social and Communication Disorders (DISCO; Wing, Leekam, Libby, Gould, & Larcombe, 2002) but the other two had no record of having received gold-standard assessments using the ADI-R, ADOS or DISCO. Most ($n = 21$) of these participants had current clinical ADHD diagnoses. A further five had a significant history of ADHD in childhood and met the current research diagnoses for ADHD based on the DSM-5, assessed by researcher in the SNAP team using the Young Adult Psychiatric Assessment (YAPA; Angold, Cox, Prendergast, Rutter, & Simonoff, 2009). One participant was at the time of the study referred by his GP to an adult ADHD clinic, thus an interview using the DIVA 2.0 conducted by the researcher took place with the young adult and his parents prior to placing him into the ASD+ADHD group. Most ($n = 13$) participants were first diagnosed with ADHD in childhood while fewer than half of the participants ($n = 8$) were first diagnosed with ADHD in adulthood. As in the ADHD group, some participants were on psychostimulant medication ($n = 10$) and withdrew for 48 hours prior to the study. Four people took

SSRIs, three of whom took the medication for affective disorder and one for ASD-related ritualistic behaviour.

Table 3-3: Recruitment sources for this study

Participant groups	Recruitment source	n	Total (N = 107)	With ADI/ADOS	With clinical diagnosis of ASD	With clinical diagnosis of ADHD
TD	Universities	17	26	--	--	--
	Community	9				
ASD	SNAP cohort	21	26	25	22	--
	SLaM ASD/ADHD clinics	3				
	Community	2				
ADHD	SLaM ASD/ADHD clinics	18	28	--	--	27
	Other ADHD / CMH clinics	3				
	Universities	3				
	Community	4				
ASD+ADHD	SLaM ASD/ADHD clinics	14	27	23	23	21
	SNAP cohort	9				
	Community	4				

Note. Abbreviations TD = Typically developing group, SNAP = Special Needs and Autism Project, SLaM = South London and Maudsley, CMH = Community mental health

Typically developing controls were recruited from the local community, London universities and adult community colleges. In addition to the general inclusion criteria (male and FSIQ ≥ 70), a specific exclusion criterion for these individuals was having diagnoses of ASD, ADHD or any other psychiatric disorders, taking any psychotropic medication at the time of the study, and having self-ratings higher than thresholds for clinical concern on any domains of attention, hyperactivity, impulsivity, or reciprocal social behaviour on the Conners' Adult ADHD Rating Scales or the Social Responsiveness Scale-2 (see descriptions of measures in section 3.2.2.2).

3.2.2 Measures

3.2.2.1 Cognitive Measures

Wechsler Abbreviated Scale of Intelligence-II (WASI-II)

The WASI-II (Wechsler, 2011) is an abbreviated measure of intelligence. It consists of two non-verbal, i.e., the block design and matrix reasoning, and two verbal tests, i.e., vocabulary and similarities, the total scores of which are used respectively to derive a perceptual reasoning index (PRI), a domain measure of nonverbal abilities and visuomotor/coordination skills, and a verbal comprehension index (VCI) a domain measure of crystallised abilities. The combination of all these measures, or a combination of the vocabulary and matrix reasoning tests only, were used estimate full-scale intelligent quotient (FSIQ-4 or FSIQ-2). The WASI-II was chosen over other measures as it is easily administered within the time constraints of the study. In general, the IQ estimates from WASI-II have high test-retest reliability (.88-.92) and the measure has been tested in special group studies including in individuals with mild and moderate intellectual disability and ADHD (Wechsler, 2011). Most participants (n = 102) completed all four subtests. Four participants completed only the two subtests due to the constraints of time so in these participants FSIQ-2 was used as an estimate of intelligence. Finally, one participant who was due to complete a full cognitive clinical assessment did not complete the WASI to prevent any interference with his assessment in the clinic. The PRI and VCI scores from the participant's clinical assessment were used with his permission to impute and FSIQ score. These scores were originally estimated using the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2008).

3.2.2.2 Behavioural Symptom Measures

Conners' Adult ADHD Rating Scales (CAARS)

The CAARS was used to assess the level of ADHD symptoms in the samples. The scales are available in screening, long and short versions; each with separate informant- and self-report forms (Conners et al., 1999). The scale has not been validated in adults with ASD; however, surveys of the general population indicate internal reliability ranging from .64 to .89, and test-retest reliability of .80-.91 for scores of ADHD symptom domains among males aged 18-29 years, as specified in the manual (Conners et al., 1999). The long scale consists of 66 items and produces eight domain scores, e.g., DSM-IV inattentive symptoms, DSM-IV hyperactivity-impulsivity symptoms, DSM-IV ADHD symptom numbers, and the ADHD index, which were used to conduct group comparison of ADHD symptom severity in this study. The short scale consists of 26 items, which are a subset of items from the long scale, and yields the first five domain scores, e.g., inattention/memory problems, hyperactivity/ restlessness, impulsivity/emotional lability and ADHD index. The ADHD index is derived using the same items and algorithms in both scales. Each item of the CAARS is given a rating “not at all, never”, “just a little, once in a while”, “pretty much, often” or “very much, very frequently”. Informant reports, especially from parents, are more diagnostically sensitive compared to self-report possibly because the young adults tend to underreport their symptoms (Kooij et al., 2008; Sibley et al., 2012). Therefore, the long-version of CAARS were collected from each young adult and an informant, a person who knows the young adult well, whether they are parent, sibling or partner. Only short scales of the CAARS were completed by participants in the SNAP cohort (n = 30) and their parents as part of their battery of psychiatric assessments. Efforts were made to collect these additional data from parents of young adults in the

SNAP cohort; however, few participants ($n = 4$) had missing data, therefore relevant scores were imputed from the short scale to replace these missing values.

Social Responsiveness Scale-2 (SRS-2)

The SRS-2 (Constantino & Gruber, 2012) is a measure of reciprocal social behaviour and autistic traits. The questionnaire contains 65 items, which produce a total score reflecting the overall autistic traits. This overall score can be divided into separate domain scores of social communication/interaction (SCI) and repetitive behaviours (RRB). Among adults with ASD, typically developing adults and mixed psychiatric samples, high internal consistency was found in the different domain scores (.71-.89), with the highest index of internal consistency was found among individuals in the ASD group (Bölte, 2012). In the current study, the SRS t -scores were used as an index of autistic symptom severity. Social functioning rating discrepancy has been observed between youth with autism and their parents, attributed to difficulties in self-perceptions in ASD (Lerner, Calhoun, Mikami, & De Los Reyes, 2012). For this reason, self-ratings were collected from all young adults and informant ratings were gathered for the young adults in the clinical group from people who know the individual well, e.g., parent, sibling or partner.

Strengths and Difficulties Questionnaires (SDQ17+)

The SDQ17+ is an adaptation of the SDQ for adolescents and adults aged 17 years and above. The questionnaire is a subtle modification of the child measure, leaving out references to school, parents, teacher or homework (kindly provided by Professor Robert Goodman from the Institute of Psychiatry, Psychology and Neuroscience, King's College London). As with the child SDQ, this questionnaire consists of 25 items, each to be rated "not true", "sometimes true", or "certainly true", which produce five domain scores of emotional symptoms, conduct problems, hyperactivity/ inattention, peer relationship problems, and prosocial behaviour (R.

Goodman et al., 2003). The child questionnaire is widely recognised as a screening measure of children's mental health with good reliability and validity although this has not been specifically validated in adults or in an ASD population. However, the measure has been used in a previous study involving adolescents with ASD (Simonoff et al., 2013). This measure was collected from all young adults, and additional informant-ratings were collected from the parent, sibling, or partner, of the participants in the clinical groups.

3.2.2.3 EF Measures

GNG

This task is part of the Maudsley Attention and Response Suppression (MARS; Rubia, Smith, & Taylor, 2007) neurocognitive task battery and is a measure of inhibition to prepotent response. This task requires participants to respond continuously to stimuli and to withdraw their responses occasionally. Variants of this task is known to differentiate adults with ADHD from TD with moderate to large effect size (e.g., Fischer et al., 2005; K. R. Murphy et al., 2001; Silva et al., 2013). The MARS GNG consists of 150 trials comprising green airplanes, i.e., the "Go" cues, and exploding planets, i.e., the "No-Go" cues, with a ratio of 11:4, presented in a pseudorandomised sequence. Each stimulus appears for 300 ms and is followed by a constant interstimulus interval (ISI) of 700 ms. Participants were instructed to respond to the Go cue and inhibit their response when the No-Go cue appeared. The task was run in two blocks of approximately 2.5 minutes each, to be completed once with each hand. The key measures of inhibitory function from this task were commission and premature response errors, while mean response time (MRT) to go signals, intra-subject standard deviation of response time (SDRT) to go signal, and omission errors indexed inattention (Bezdjian, Baker, Lozano, & Raine,

2009; Trommer, Hoeppe, Lorber, & Armstrong, 1988). Higher values in these variables indexed greater difficulties.

Continuous Performance Task (CPT-AX)

The CPT-AX is also from the MARS battery and is a measure of sustained attention. During the task, a sequence of letters from the alphabet “A” to “L”, and the letters “O” and “X” were presented on a screen for 300 ms followed by an ISI of 700 ms. Participants were instructed to respond to the letter “X” or “O” if it was immediately preceded by the letter “A”, and not respond if it was preceded by any other letter. There were 60 target sequences among 480 letter trials and the task lasted for 8 minutes. Omission errors, i.e., not responding when supposed to, MRT and SDRT, computed from the correctly executed trials, were the primary variables indexing inattention. Secondary variables were commission errors and premature errors, thought to index inhibitory difficulties (Epstein et al., 2003; Huang-Pollock, Karalunas, Tam, & Moore, 2012). Higher values on these variables indicated increased difficulties on the task.

Dot-in-the-Box Task

This task taps visuospatial working memory and has been used in several recent studies comparing children and adults with ADHD to healthy controls (Alderson et al., 2013; M. D. Rapport et al., 2008). The task design takes into account storage of memory, maintenance, and manipulation of information, i.e., the executive demand (Baddeley, 2003). It also has high executive demands and assesses performance in incremental load of memory, thus has greater sensitivity for distinguishing the ADHD group from controls (Kasper et al., 2012). This computerised task was presented on Superlab 4.5. The task consisted of four approximately 5-minute blocks of 24 trials. In each trial a sequence of coloured dots (one red and the remaining black) was presented one at a time among nine equally sized adjacent

squares or “boxes”. Each dot remained for 800 ms with an ISI of 200 ms and no dots appeared in the same square. At the end of each trial, the participants were prompted to reproduce the sequence by clicking on the boxes, leaving the red dot last. The blocks became progressively more difficult as the sequence length was increased by adding one black dot. Each participant completed this task using his non-dominant hand. Only valid responses, where the mouse click was inside a square, were used to score performance. The mean number of correct responses per trial was used in a previous study as a measure of working memory ability (M. D. Rapport et al., 2008). The number of errors for each block was used to operationalise difficulties and the number of errors within each block were analysed to assess the influence of difficulty levels on performance. Also indexing the performance were the MRT and the SDRT. Poorer performance would be reflected by greater values on these variables.

Wisconsin Card Sort Task (WCST)

The WCST measures cognitive flexibility, i.e., the ability to engage and disengage from one set of rules to another (Berg, 1948). A computerised WCST (PAR Inc., Florida; Heaton, 2003) was used in this study. In this task, participants were required to match a card from a “deck” of 64 cards displayed at the bottom of the screen, against four “key” cards shown on the top. Each card from the deck displayed symbols that could be sorted by shape, colour, or number, although the participants were not given any explicit rules. Participants matched the card from the deck against the four key cards by clicking on a box displayed under each key card. Feedback was given by the computer about the correctness of matching and participants were told to try to match the next card correctly when a mistake occurred. When the participants correctly sorted 10 cards in successions, the sorting-rule changed following a predetermined order. The correct sorting count reset to zero when the participants made a sorting mistake. Persistence in using the

same rule for sorting the cards once the new rule commenced was scored as “perseverative error”, the key variable in this study. This task was completed in 5-10 minutes.

Temporal Reward Discounting Task

This task taps reward discounting over time, i.e., the rate at which reward devalues over a period of time (Myerson, Green, & Morris, 2011). Participants were given the option of receiving a hypothetical sum of money “now” or £100 after a fixed delayed timespan (a week, a month, a year, and two years). The task was completed in four blocks. Each block corresponded to one of the time frames, in randomised order, and consisted of 25 binary choices. The reward offered varied according to an algorithm that took into account previous choices, thus allowing the choices to converge to an “indifference point” considered as the reward equivalent for the time delay according to the participants. Delay discounting was measured using the area under the curve (AUC), considered appropriate for investigations with quantitative inferential statistics (Myerson et al., 2011). Smaller AUC indicated steeper discounting rates or increased choice impulsivity.

3.2.2.4 SC Measures

Emotional Multi-Morph Task

This task assesses emotion recognition and sensitivity to emotional expression in faces and is a variant of a previously published task (Wallace et al., 2011). The task was modified to be fully computerised using the Superlab 4.5 software. It used 24 pairs (emotional/neutral) of face photos of individuals taken from the NimStim set (Tottenham et al. [2009]; <http://www.macbrain.org/resources.htm>). Each emotional face displayed one of six categories of emotion (happy, sad, angry, frightened, disgusted, and surprised) and there were four different individual faces for each emotion category. The task consisted of three blocks of eight runs and each run

consisted of 20 trials showing morphed images of the same individual presented in order of affective strength from neutral to reveal one of the emotions. Each trial started with a 500 ms fixation cross followed by the face image which lasted for 1250 ms, and was concluded by a forced choice event for the participant to either identify the emotional expression, or to request for the next slide. The participants could revise their answers if they thought they had made a mistake. The sensitivity to emotion was derived from the affective strength of the image required to gain a response, averaged over the correct trials only. Emotion recognition difficulties were judged according to the total number of errors. Higher scores on both variables indicated greater difficulties in recognising emotion in faces.

Strange Stories Test

This task was designed to tap ToM or mentalising abilities (Happé, 1994; S. White, Hill, Happé, & Frith, 2009) and consisted of short stories about a character committing lies, double-bluffs, or emotional manipulation. In the current study, all stories were presented as text on a computer screen (presented using Superlab 4.5) accompanied by a pre-recorded story. To minimise memory load, both text and questions continued to appear on the screen once the voice-over ended and participants could re-read the story when necessary. The probe question required verbal responses within a one-minute window. The key variable was the mentalising attributional ability, coded zero to two for each question, according to the degree of correctness and explicitness of the answer. Higher scores here represented better ToM ability and were reversed for analysis to operationalise impairments.

3.2.3 Procedure

Participants in this study took part in an extensive examination investigating the behavioural and neural correlates of ADHD symptoms in individuals with ASD. The study involved the measures described above, i.e., questionnaires, IQ and the

battery of neurocognitive assessments. Further, some neuroimaging investigations (described in Chapters 5 and 6) were also undertaken with the participants. This entire battery extended over two sessions of approximately 2.5 hours each. The entire assessment was completed within one day or on two separate occasions within the same week, depending on the participants' preference. Participants who completed the study in one day conducted the two sessions separated with a lunch break. Participants were given £50 in return for their time upon completion of the study.

Table 3-4: Neurocognitive domains, tasks and variables used in this study

EF/SC Domain	Task	Key variables	Parametric characteristics
Inhibition	GNG	Commission errors* Premature errors*	Parametric Non-parametric
	CPT	Commission errors Premature errors	Non-parametric Non-parametric
Attention	GNG	Omission errors SDRT* MRT*	Non-parametric Parametric Parametric
	CPT	Omission errors* SDRT* MRT*	Parametric Parametric Parametric
Working memory	Dot in the box	Total errors* SDRT* MRT*	Parametric Parametric Parametric
Cognitive flexibility	WCST	Perseverative errors*	Parametric
Temporal foresight	Delay discounting task	AUC*	Parametric
Emotion recognition	Emotional multi-morph task	Total errors* Mean sensitivity to emotion*	Parametric Parametric
ToM	Strange stories task	Mentalising scores* Physical scores	Parametric Non-parametric

Note. Abbreviations: EF= executive function, GNG = go/no-go task, CPT = continuous performance task, SDRT = standard deviation of response time, i.e., intra-subject response time variability, MRT = mean response time, WCST = Wisconsin card sort task, and ToM = theory of mind. * denoted the primary task variables for the task.

3.2.4 Statistical Analysis

3.2.4.1 Analyses of Demographic Data and Behavioural Reports

Statistical analyses were performed using IBM SPSS Statistics for Windows version 22 (IBM Corp., 2013). Group differences on continuous data of sample characteristics such as age and IQ were assessed using the univariate ANOVAs, while discrete variables such as medication use and diagnosis status were all analysed using Chi-square tests. Group differences in related domain scores such as ADHD traits were analysed in the first instance using the MANOVA. This step of analysis is introduced to protect against Type I error associated with multiple comparisons using univariate ANOVAs. Once group differences were established through the MANOVA, univariate ANOVAs were used to investigate the effect of group on each domain score. As the emotional/behavioural domain scores of SDQ17+ represent independent psychiatric construct, they were analysed separately using the univariate ANOVAs. The group differences on the univariate ANOVAs were further assessed using multiple pairwise comparisons, Dunn-Sidak corrected for independent groups.

3.2.4.2 Analyses of Neurocognitive Performance

Analyses were conducted separately for the EF and SC sets of variables as these two domains represent independent constructs. The independent variable here was the group with four levels: (1) ASD, (2) ADHD, (3) ASD+ADHD and (4) TD, while the dependent variables were key variables derived from the neurocognitive measures. To control for multiple testing, MANOVA was conducted in the first instance. As the power of MANOVA is reduced upon inclusion of variables not meeting the parametric assumption, only a subset of 14 of 19 variables in Table 3-4 (11 EF and three SC) were included. The remaining variables were analysed on a univariate basis using non-parametric statistics as supporting information. The 14 variables

were normalised where necessary and standardised into Z-scores. Outliers were detected using multivariate strategies outlined by Tabachnick and Fidell (2014). Briefly, Mahalanobis distance within the domains of EF and SC was computed within group and compared against the critical χ^2 values of 31.3 and 16.3, corresponding to the $df = 11$ and 3 (and $p = .001$ cut-off), i.e., the number of variables within the EF and SC domains, respectively. Outliers were excluded from this point of the analysis onward.

Analyses of variance, covarying for IQ were chosen to explore the differences across groups. IQ is thought to be an inherent confounder among people neurodevelopmental conditions and acceptable in cases where groups do not inherently differ in IQ (Dennis et al., 2009; G. M. Miller & Chapman, 2001). In cases where individuals with the neurodevelopmental conditions were compared against typically developing controls, IQ does not meet the definition for covariate. However, the comparisons of interest in this study were across three clinical groups with differing mean IQ, two of which (ASD, ADHD) often associated with reduced IQ (e.g., Charman et al., 2011; Kuntsi et al., 2004; Postorino et al., 2016; Rommel, Rijdsdijk, Greven, Asherson, & Kuntsi, 2015). For this reason, MANCOVAs with FSIQ as a covariate were favoured in this study to allow the comparison between the different clinical groups. As reported in the next sections, IQ influenced the group effect in EF, and the effect remained significant once IQ was covaried. To explore the group effect in each subdomain of EF, a series of univariate ANCOVAs was carried out on each variable with IQ covaried. Multiple pairwise comparisons, Dunn-Sidak corrected for independent groups, were conducted to see the pairwise differences between groups.

Although no omnibus group differences in the SC domain were found having controlled for IQ, group effects were explored on SC without covarying for IQ. The reason for this was that IQ has been thought to be inherently confounded in

individuals with neurodevelopmental conditions and these findings might be representative of difficulties found in the samples (Dennis et al., 2009; J. M. J. van der Meer et al., 2012), therefore reporting these group differences could be important for comparison against other investigation. Multiple comparisons were also carried out to explore the pairwise differences between groups in the SC domain, Dunn-Sidak corrected. In both EF and SC domains, the group effects among variables that did not meet the parametric assumption were explored using Kruskal-Wallis ANOVAs. Finally, as typically explored in previous investigations (Happé, Booth, et al., 2006; Sinzig, Morsch, Bruning, et al., 2008), the associations between cognitive deficits and symptoms over and above those accounted by the diagnostic status were investigated. Multivariate regression tests including key parametric variables in the EF and SC domains as outcome variables were carried out when group effects were significant. In these additional analyses, IQ, group, and self-rated ADHD or ASD symptoms (ADHD index or SRS total score) were entered as predictors for the key cognitive variables.

3.3 Results

3.3.1 Participant Demographics and Behavioural Characteristics

Two multivariate outliers were detected in the SC domain; none was found in the EF domain. These outliers were one TD participant and another with ADHD. Their data were rejected from the final analyses therefore resulting in a participant pool comprising of 25 controls, 26 individuals with ASD, 27 individuals with ASD+ADHD and 27 individuals with ADHD. The participants' demographic and behavioural characteristics are presented in Table 3-5. Group comparisons indicated no significant difference in age, $F(3, 100) = .71, p = .63$. However, there were

significant differences in FSIQ, $F(3, 100) = 5.78, p = .001$, with individuals in the TD and ADHD groups having significantly higher IQ than the ASD group ($ps < .001$).

3.3.1.1 CAARS

The MANOVA analyses on self- and informant-ratings using the CAARS t -scores showed significant group effects, $F(12, 257) = 13.3, p < .001$; Wilk's $\Lambda = .28, \eta_p^2 = .35$, and, $F(8, 142) = 12.7, p < .001$; Wilk's $\Lambda = .34, \eta_p^2 = .42$, respectively. Group effect on the self-rating of symptoms of inattention, $F(3, 100) = 39.4, p < .001$, hyperactivity, $F(3, 100) = 27.9, p < .001$, impulsivity, $F(3, 100) = 19.4, p < .001$, and overall ADHD index, $F(3, 100) = 35.1, p < .001$, were all significant, with most ratings of symptom domains higher in the ADHD and ASD+ADHD groups compared to the TD and ASD groups (all $ps < .001$), while comparisons between TD and ASD pairs, and between ADHD and ASD+ADHD pairs did not differ significantly (most $ps > .43$ except the hyperactivity ratings between ASD+ADHD and ADHD, $p = .08$). Analyses of the informant-ratings of ADHD symptoms supported the self-rating findings in the clinical groups. Significant group differences were found for informant-ratings on DSM-IV inattention symptoms, $F(2, 75) = 40.0, p < .001$, hyperactivity/impulsivity symptoms, $F(2, 75) = 13.4, p < .001$, number of symptom, $F(2, 75) = 33.2, p < .001$, and ADHD index, $F(2, 75) = 29.0, p < .001$, with higher endorsement of ADHD symptoms in the ADHD and ASD+ADHD groups than the ASD alone (all $ps \leq .001$).

3.3.1.2 SRS-2

Univariate ANOVAs showed significant differences on the SRS-2 total t -scores across groups according to self-ratings, $F(3, 100) = 20.1, p < .001$, and informant-ratings, $F(2, 75) = 11.5, p < .001$. Young adults across all clinical groups rated themselves as having more ASD symptoms than the TD group ($ps < .001$), and no significant pairwise differences were found among the clinical groups ($ps > .14$,

except between ASD and ASD+ADHD, $p = .071$). Informants for the young adults in the ASD and the ASD+ADHD groups rated them as having higher levels of ASD symptoms than informants in the ADHD groups ($p = .046$ and $p < .001$), whereas the difference between ASD and ASD+ADHD was not significant ($p = .068$).

3.3.1.3 SDQ17+

Significant group effects on self-ratings of difficulties were found for all domains, i.e., hyperactivity/inattention, $F(3, 100) = 47.1$, $p < .001$, where ratings of difficulties were higher in the ASD+ADHD and ADHD than ASD and TD (all $ps < .001$); emotional problems, $F(3, 100) = 13.0$, $p < .001$, where all three clinical groups had higher ratings than the TD group, $ps < .001$; conduct problems, $F(3, 100) = 8.4$, $p < .001$, where higher ratings were found in the ASD+ADHD and ADHD relative to ASD and TD; and lastly problems with peers relation, $F(3, 100) = 3.4$, $p = .022$, although post-hoc comparisons did not find significant pairwise differences across groups. Informant-ratings mostly supported the findings from the self-ratings. Significant group effects in hyperactivity/inattention, $F(2, 74) = 40.8$, $p < .001$, conduct, $F(2, 74) = 11.8$, $p < .001$, and peer problems, $F(2, 74) = 9.7$, $p < .001$, were found and marginal group effect was observed for emotional problems, $F(2, 74) = 2.6$, $p = .08$. Post-hoc comparisons showed that informants of young adults with ASD+ADHD or ADHD rated the participants to have hyperactivity/inattention and conduct problems than informants of participants with ASD or TD ($ps \leq .001$). Emotional problems were marginally higher in the ASD+ADHD than in ASD ($p = .078$). Finally, peer relationship problems were rated higher in the ASD group and the ASD+ADHD than the ADHD groups ($ps < .05$ and $< .001$) and all other pairwise differences were non-significant ($p > .15$).

Table 3-5: Participants characteristics for the neurocognitive study.

	TD (n = 25)		ASD (n = 26)		ADHD (n = 27)		ASD+ADHD (n = 27)		Group comparison			Post-hoc
	M	SD	M	SD	M	SD	M	SD	F	df	p	
Age	23.3	1.5	22.8	.9	23	1.9	23.1	1.3	.62	3, 101	n.s.	--
FSIQ	117.2	12.3	101.6	18.4	115.2	14.3	106.8	15.7	5.9	3, 101	.001	ADHD, TD > ASD
ADHD DX in adult (%)	--	--	--	--	48.1	--	40.7	--	.79*	1, 54	n.s.	--
CAARS self (t-scores)^a												
Inattention	44.6	6.9	46.4	11.7	65.4	9.0	63.1	10.4	39.4	3, 100	<.001	ADHD, ASD+ADHD > ASD, TD
Hyperactive	45.3	8.5	45.6	6.8	64.9	10.1	58.5	11.4	27.9	3, 100	<.001	ADHD > ASD+ADHD > ASD, TD
Impulsive	41.3	5.9	43.7	11.0	57.0	9.8	54.9	10.9	19.4	3, 100	<.001	ADHD, ASD+ADHD > ASD, TD
ADHD index	42.3	8.4	44.9	11.6	64.6	8.5	59.9	11.5	35.1	3, 100	<.001	ADHD, ASD+ADHD > ASD, TD
CAARS informant (t-scores)^b												
DSM-IV inattention	--	--	57.4	12.4	77.2	20.2	80.6	17.9	40.0	2, 75	<.001	ADHD, ASD+ADHD > ASD
DSM-IV hyperactive	--	--	47.7	10.6	67.7	18.0	67.2	17.9	13.4	2, 75	<.001	ADHD, ASD+ADHD > ASD
DSM-IV symptom number	--	--	52.3	13.1	74.5	21.7	77.5	21.6	33.2	2, 75	<.001	ADHD, ASD+ADHD > ASD
ADHD index	--	--	48.4	7.4	61.5	16.3	65.2	16.5	29.0	2, 75	<.001	ADHD, ASD+ADHD > ASD
SRS-2 self (t-scores)												
Total SRS score	48.8	5.9	61.0	8.5	61.8	7.8	67.2	11.7	20.1	3, 100	<.001	ASD, ASD+ADHD, ADHD > TD
SRS-2 informant (t-scores)												
Total SRS score	--	--	64.1	8.3	57.1	10.9	70.7	11.5	11.5	2, 75	<.001	ASD, ASD+ADHD > ADHD
SDQ17+ self												
Hyperactivity	2.5	1.8	3.4	2.1	7.4	1.4	6.9	1.9	47.1	3, 100	<.001	ADHD, ASD+ADHD > ASD, TD
Emotion	1.2	1.4	4.3	2.5	4.3	2.4	4.6	2.5	13.0	3, 100	<.001	ASD, ASD+ADHD, ADHD > TD
Conduct	1.3	1.2	1.6	.9	2.9	2.0	2.9	1.8	8.4	3, 100	<.001	ADHD, ASD+ADHD > ASD, TD
Peer relations	2.6	1.9	3.5	1.7	2.2	1.5	3.5	2.0	3.4	3, 100	.02	--
SDQ17+ informant^c												
Hyperactivity	--	--	3.3	1.9	7.5	2.0	7.2	1.7	40.8	2, 74	<.001	ADHD, ASD+ADHD > ASD
Emotion	--	--	3.3	2.0	4.2	2.5	4.8	2.7	2.6	2, 74	.08	--
Conduct	--	--	1.2	.8	3.4	2.3	3.6	2.3	11.8	2, 74	<.001	ADHD, ASD+ADHD > ASD
Peer relations	--	--	3.5	1.5	2.3	1.8	4.5	2.1	9.7	2, 74	<.001	ASD, ASD+ADHD > ADHD

Note. Abbreviations M = mean, SD = standard deviation, FSIQ = full-scale IQ, DX = diagnosis, CAARS = Conners Adult ADHD Rating Scale, SRS = Social Responsiveness Scale version 2, SDQ17+ = Strengths and Difficulties Questionnaires for age 17 years and above, n.s. = not significant. Self-rated symptoms were indicated by 'self', while informant-rated symptoms (filled in by parents, partner, relatives or childhood friend) were indicated by 'informant'. ^{a,b}CAARS-self questionnaires were rated on the short form, whilst CAARS-informants were rated on the long versions thus generating different domain scores. ^cAn SDQ17+ questionnaire was not returned by the participant's parents thus the degree of freedom was fewer by one.

3.3.2 Multivariate Group Comparisons on EF and SC

Table 3-6: Raw descriptive data across groups on variables of EF/SC tasks

Task/ variable	CON (n = 25)	ASD (n = 26)	ADHD (n = 27)	ASD+ADHD (n = 27)
<i>GNG</i>				
Commission errors (%)	14.8 (11.4)	24.4 (17.3)	34.6 (18.6)	32.0 (14.9)
Go SDRT	58.8 (16.3)	67.5 (22.3)	75.9 (27.5)	79.0 (38.6)
Go MRT	298.4 (39.3)	297.3 (37.9)	305.8 (34.3)	296.8 (34.2)
Premature errors (%)	.60 (1.2)	1.4 (1.9)	2.6 (3.2)	4.7 (9.2)
Omission errors (%)	.36 (.49)	.77 (1.1)	1.5 (2.3)	2.3 (4.1)
<i>CPT-AX</i>				
Omission errors (%)	2.1 (2.2)	6.2 (8.4)	9.5 (7.3)	6.5 (9.7)
Target SDRT	86.2 (29.5)	90.2 (31.9)	113.9 (38.9)	90.4 (28.2)
Target MRT	448.7 (67.3)	461.0 (65.4)	475.1 (57.2)	441.8 (84.6)
Premature errors (%)	.06 (.21)	.10 (.37)	.18 (.29)	.12 (.48)
Commission errors (%)	.16 (.22)	.70 (1.4)	.73 (.76)	1.1 (2.3)
<i>Dot in the box task</i>				
Overall Errors	61.3 (37.0)	124.5 (89.0)	102.8 (60.6)	131.7 (79.5)
Overall SDRT	401.1 (150.1)	469.1 (205.6)	551.9 (198.3)	515.5 (182.3)
Overall MRT	855.4 (151.3)	945.1 (172.4)	916.7 (182.7)	895.4 (179.4)
<i>WCST</i>				
Perseverative Errors	6.8 (3.4)	8.9 (7.0)	8.0 (4.2)	7.8 (4.1)
<i>Delay discounting</i>				
AUC	44463.9 (12657.5)	41957.0 (14039.0)	38751.4 (11139.6)	41595.2 (15169.0)
<i>Emotional Multi-Morph Task</i>				
Sensitivity	.49 (.08)	.55 (.10)	.48 (.09)	.50 (.08)
Recognition errors	1.3 (1.2)	3.1 (2.7)	1.9 (1.5)	2.2 (1.4)
<i>Strange Stories</i>				
Attribution errors	.64 (.76)	2.62 (2.4)	.85 (1.1)	1.67 (1.7)

Note. Abbreviations EF = executive function, SC = social cognition, GNG = go/no-go task, CPT-AX = continuous performance task-AX, SDRT = standard deviation of response time, MRT = mean response time, AUC = area under the curve.

Descriptive data for neurocognitive performance across participant groups are presented in Table 3-6. Omnibus MANOVA tests on EF variables indicated differences across groups, $F(33, 266) = 2.04$, $p = .001$; Wilk's $\Lambda = .51$, $\eta_p^2 = .20$. Subsequent MANCOVAs revealed significant main effects for both FSIQ, $F(11, 89) = 5.44$, $p < .001$; Wilk's $\Lambda = .60$, $\eta_p^2 = .40$, and group, $F(33, 263) = 1.89$, $p = .003$, Wilk's $\Lambda = .53$, $\eta_p^2 = .19$, indicating that the group differences were robust after covarying for IQ. In the SC domain, the omnibus MANOVA revealed an overall

significant group difference, $F(9, 241) = 2.94, p = .002$; Wilk's $\Lambda = .78, \eta_p^2 = .08$. However, these differences appeared to be IQ-dependent as the MANCOVA yielded a significant effect of IQ, $F(3, 98) = 15.1, p < .001$; Wilk's $\Lambda = .68, \eta_p^2 = .32$, but not group, $F(9, 239) = 1.31, p = .23$; Wilk's $\Lambda = .89, \eta_p^2 = .04$, on the SC performance.

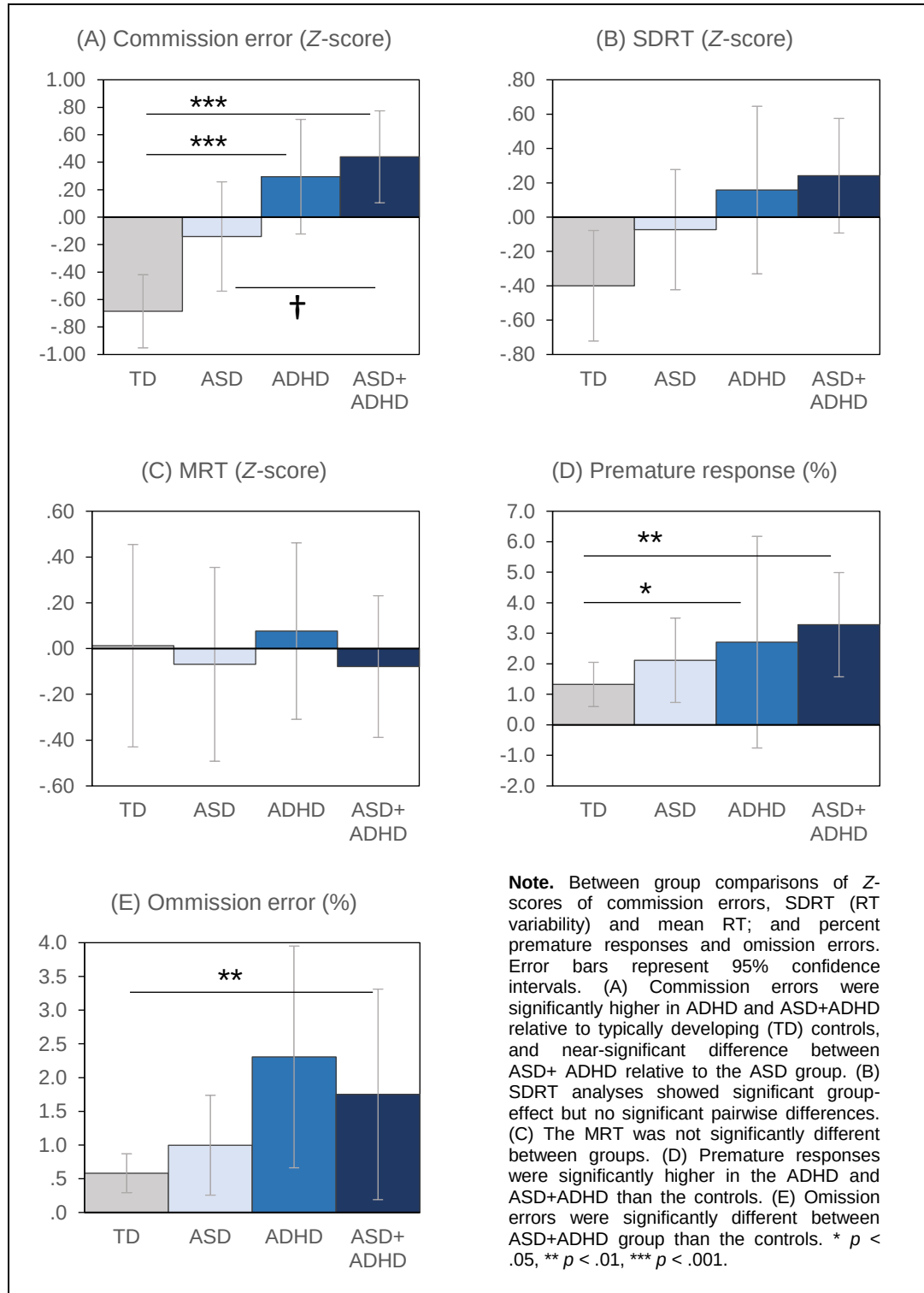
3.3.3 Univariate Analyses on Performance Indices on Each Task

3.3.3.1 GNG

Univariate ANCOVAs showed differences across groups on commission errors, $F(3, 101) = 7.77, p < .001, \eta_p^2 = .19$. Post-hoc analyses revealed higher commission errors by ADHD and ASD+ADHD groups relative to TD, $ps \leq .001$, and higher commission errors by ASD+ADHD relative to the ASD group, approaching significance, $p = .054$. The ASD group performed between the TD and ADHD groups. Differences in SDRT among groups were significant, $F(3, 101) = 2.72, p = .049, \eta_p^2 = .08$, however pairwise group comparisons were not significant. The MRT did not differ between groups. Secondary variable analyses using Kruskal-Wallis ANOVA, revealed group effect on the number of premature response, $H(3, N = 105) = 2.5, p = .005$, with more premature errors committed by the ADHD, $p = .016$, and ASD+ADHD group, $p = .009$, than the TD group. A group effect was also found for omission errors, $H(3, N = 105) = 7.1, p = .016$, where more errors were committed by individuals in the ASD+ADHD group than the TD group, $p = .01$ (see Figure 3-1). Regression analyses suggested that the influence of ADHD symptoms on commission errors over and above diagnostic status was not significant, $\beta = .16, t(100) = 1.30, p = .20$. While increased ADHD symptoms appeared to be associated with significant increase of SDRT, $\beta = .32, t(100) = 2.69, p = .008$, the associations merely replaced the effect of diagnostic status found in a model including diagnostic group and FSIQ, $\beta = .24, t(101) = 2.71, p = .008$. Therefore, self-rated ADHD

symptoms did not predict key variables of the GNG task over and above what already accounted by the diagnostic status and IQ.

Figure 3-1: Group comparison of variables from the GNG task



3.3.3.2 CPT-AX

ANCOVA showed that omission errors differed across groups, $F(3, 100) = 6.89$, $p < .001$, $\eta_p^2 = .17$. Pairwise comparison showed that the ADHD group omitted more responses than the TD ($p < .001$) and the ASD group ($p = .016$). Likewise, intra-subject SDRT to target stimuli differed across groups, $F(3, 100) = 3.74$, $p = .014$, $\eta_p^2 = .10$. The ADHD group's SDRT was higher than that for the TD ($p = .026$) and ASD group ($p = .049$) and the ASD+ADHD appeared to be an intermediate group that did not differ from the TD, ASD pairs and from the ADHD group. The MRT did not differ across groups, $F(3, 100) = 1.04$, $p = .38$. A group effect was observed in the number of commission errors, $H(3, N = 104) = 16.3$, $p = .001$, with the ASD+ADHD and the ADHD group making more commission errors than the TD group ($ps \leq .003$), while the group effect in the number of premature responses was not significant, $H(3, N = 104) = 6.6$, $p = .07$ (Figure 3-2). ADHD symptoms did not influence the number of omission errors, $\beta = .09$, $t(99) = .65$, $p = .52$, or the SDRT, $\beta = .14$, $t(99) = 1.09$, $p = .28$, over and above the influence of the diagnostic status.

3.3.3.3 Dot-in-the-Box

Figure 3-3 shows the global performance on the working memory task across groups. A significant group effect was found in the overall number of errors, $F(3, 100) = 4.06$, $p = .009$, $\eta_p^2 = .11$, and the SDRT, $F(3, 100) = 2.95$, $p = .036$, $\eta_p^2 = .08$, but not the MRT, $F(3, 100) = .84$, $p = .47$. Post-hoc pairwise comparisons indicated that individuals with ASD+ADHD and ADHD made more errors than TD ($ps = .022$ and $.023$). With respect to total errors, the ASD group between TD and ASD+ADHD as it did not differ pairwise from either group ($ps > .5$). No pairwise group differences were found for the SDRT ($ps > .1$). The influence of ADHD symptoms was not significant on the number of total errors, $\beta = .14$, $t(100) = 1.3$, $p = .20$, or the SDRT, $\beta = .09$, $t(100) = .65$, $p = .52$, over the diagnostic status.

Figure 3-2: Group comparison of variables from the CPT-AX task

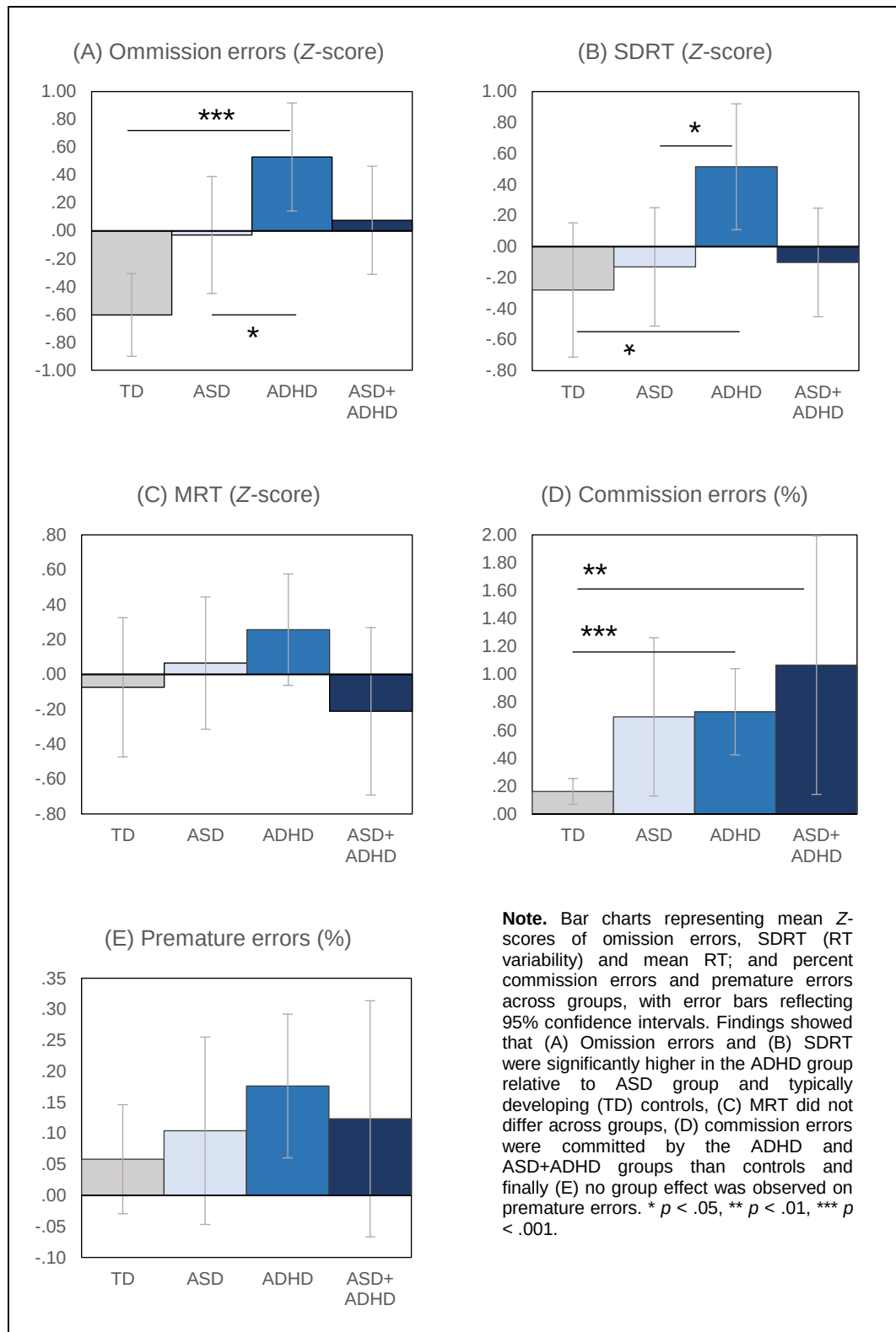
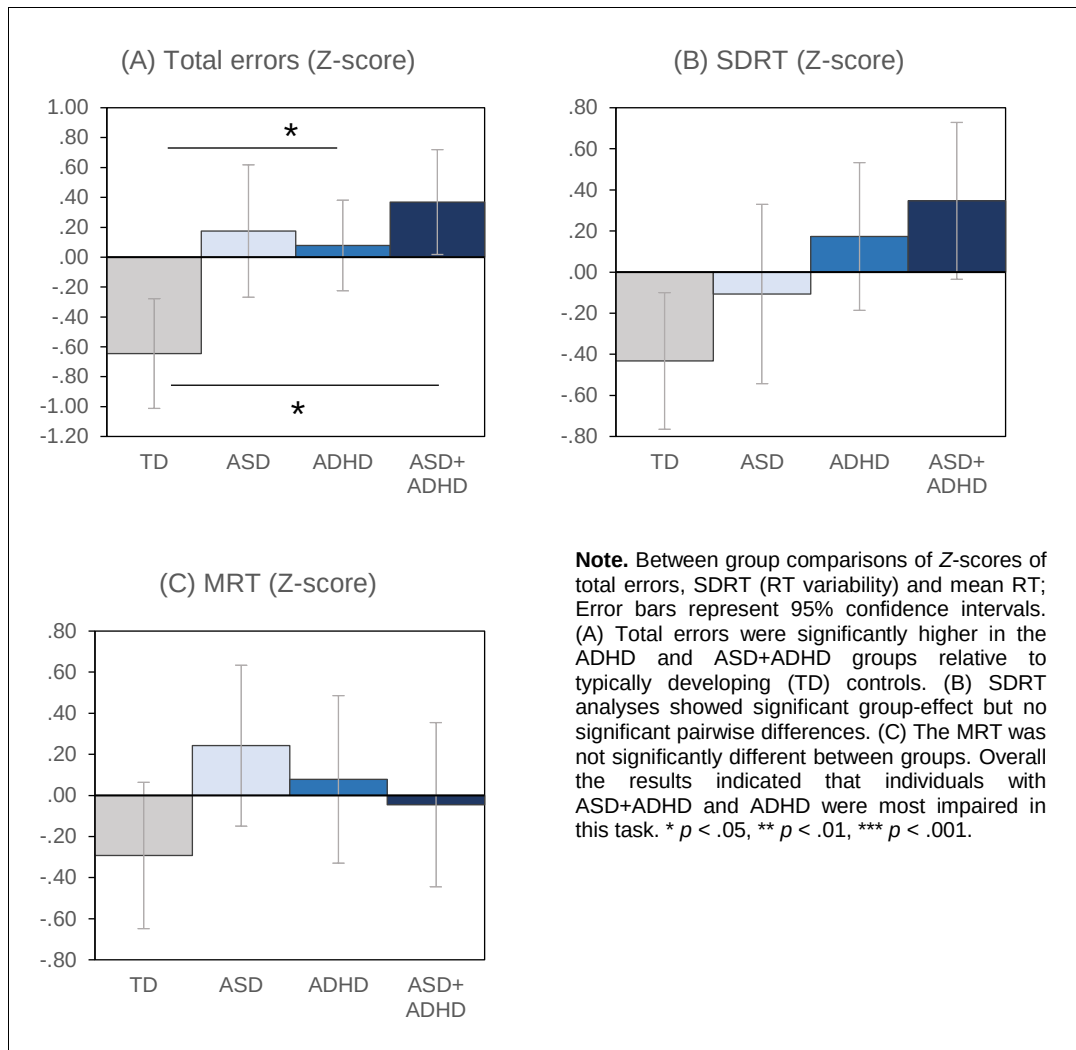


Figure 3-3: Group comparison of variables from the dot-in-the-box task



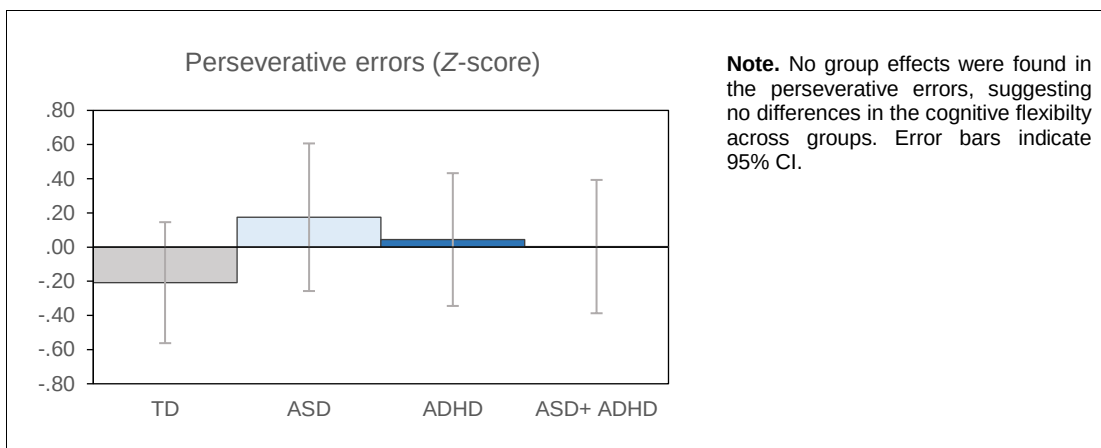
As the task was designed with four levels of difficulty, it was interesting to see if the group differences in the performance were modulated by difficulty level. A 4×4 (group $\times$ difficulty) repeated ANOVA, separating the errors and SDRT by difficulty level and covarying for IQ. A significant main effect of group on errors was found when covarying for IQ, $F(3, 100) = 3.87$, $p = .011$, $\eta_p^2 = .10$, IQ, $F(3, 100) = 10.7$, $p < .001$, $\eta_p^2 = .27$, and difficulty, $F(3, 264) = 10.2$, $p < .001$, $\eta_p^2 = .09$, but no interaction of group $\times$ difficulty, $F(9, 264) = 1.46$, $p = .16$. Equivalent analyses on SDRT revealed a near-significant effect of group, $F(3, 100) = 2.57$, $p = .059$, and a significant effect of IQ, $F(1, 100) = 4.72$, $p = .03$, but not difficulty, $F(3, 100) = .99$, $p = .40$. Likewise no group $\times$ difficulty interaction was found, $F(9, 290) = .41$, $p = .90$.

Finally, no significant effects of group, IQ, difficulty and group $\times$ difficulty interaction were found on the MRT (all p s $> .19$).

3.3.3.4 WCST

Univariate ANCOVAs indicated no group difference in perseverative errors, $F(3, 100) = .35$, $p = .79$, $\eta_p^2 = .01$ (see Figure 3-4). To assess the hypothesis that individuals with ASD would have greater difficulty on this task, a multiple regression analysis including only the TD and ASD groups, with FSIQ as a covariate, was also conducted but did not reveal a significant difference between group, $\beta = .10$, $t(48) = .66$, $p = .51$, or a significant effect of IQ, $\beta = -.20$, $t(48) = -1.25$, $p = .22$.

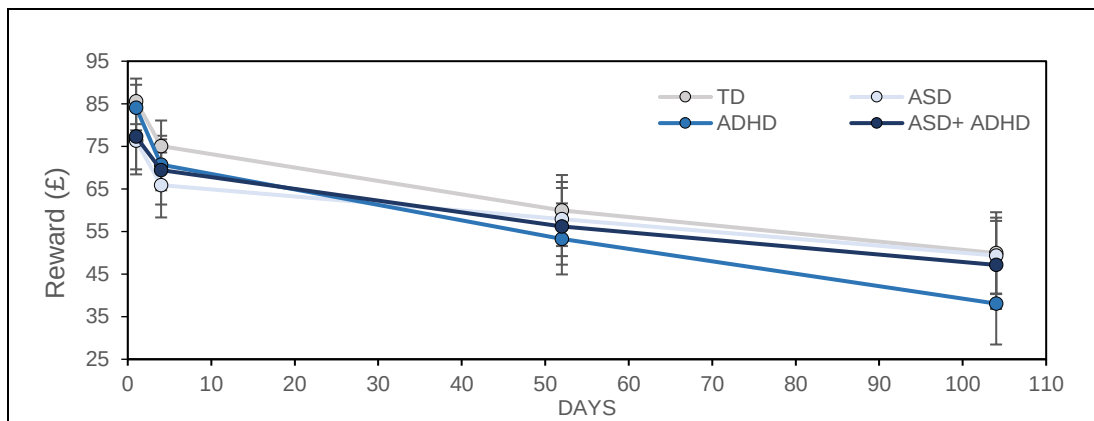
Figure 3-4: Cognitive flexibility across groups



3.3.3.5 Temporal Reward Discounting

Univariate ANCOVA indicated no group effect on the AUC, $F(3, 100) = 2.10$, $p = .11$, $\eta_p^2 = .06$ (see Figure 3-5, p. 148). To test the hypothesis that individuals with ADHD would show greater discounting on this task, a multiple regression was conducted between the TD and ADHD group with IQ as a covariate; this revealed a significant group difference, $\beta = -.31$, $t(49) = -2.24$, $p = .029$, $\eta_p^2 = .09$ but no effect of IQ, $\beta = .003$, $t(49) = .02$, $p = .98$. Self-rated ADHD symptoms did not influence the group effect over and above the diagnostic status, $\beta = -.06$, $t(49) = -.25$, $p = .80$.

Figure 3-5: Plots of indifference points overtime across groups

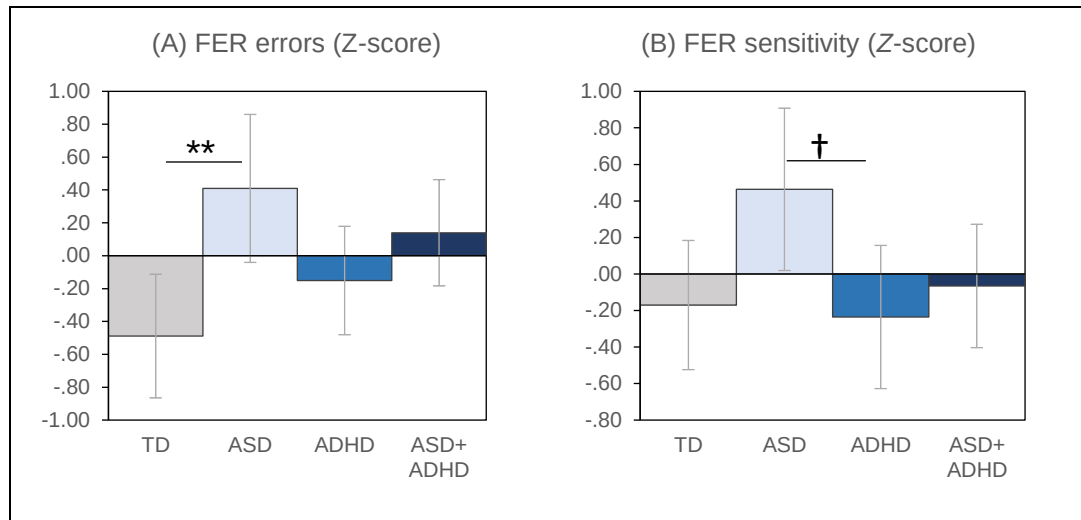


Note. Error bars indicate 95% CI. Indifference points are the reward a participant is willing to wait for the amount of time he waited. The area under the curve (AUC) is the trapezoid area formed under the linear lines between two indifference points

3.3.3.6 FER

Univariate ANOVA revealed a significant group effect in recognition errors, $F(3, 101) = 4.20$, $p = .008$, with the ASD group committing more emotion recognition errors than TD, $p = .006$. The ADHD and ASD+ADHD groups performed at an intermediate level between the ASD and TD groups. Consistent with the MANCOVA analyses, covarying for IQ in the univariate ANOVA demonstrated a significant main effect of IQ, $F(1, 100) = 11.2$, $p < .001$, and reduced the group effect to a non-significant level, $F(3, 100) = 1.68$, $p = .18$. An initial ANOVA also suggested group differences in emotion sensitivity, $F(3, 100) = 2.73$, $p = .048$, where individuals with ASD appeared less sensitive to emotion in faces than the ADHD group at near-significant level ($p = .065$) although no other pairwise differences were detected. The significant effect of IQ, $F(1, 100) = 14.9$, $p < .001$, again reduced the group effect to a non-significant level, $F(3, 100) = 1.02$, $p = .39$ (see Figure 3-6). Self-rated ASD symptoms did not influence the group effect over and above the diagnostic status on facial emotion recognition errors, $\beta = -.01$, $t(100) = -.10$, $p = .92$, or sensitivity towards facial emotion, $\beta = .17$, $t(100) = 1.63$, $p = .11$.

Figure 3-6: Face emotion recognition error and sensitivity across groups

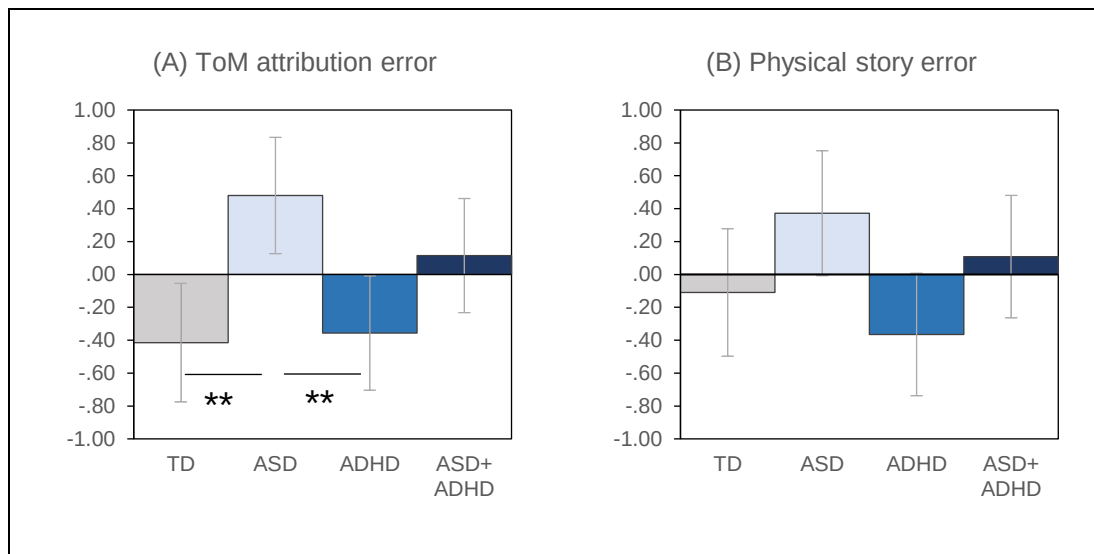


Note. Group effects were found in facial emotion recognition or FER (A) and sensitivity (B) before FSIQ was covaried, and pairwise comparisons suggested that the ASD group was the most impaired among the four groups. The group effect was fully accounted for by FSIQ differences. Error bars indicate 95% CI. † $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$.

3.3.3.7 ToM

Figure 3-7 shows the difficulties in ToM differences across groups. Univariate ANOVA revealed a group effect in the ToM attribution errors for mentalising stories, $F(3, 101) = 5.67$, $p = .001$, $\eta_p^2 = .14$, and pairwise comparisons showed that individuals in the ASD group performed more poorly than the TD, $p = .004$, and ADHD groups, $p = .006$, while individuals in the ASD+ADHD were intermediate in their performance and did not differ any of the other groups. Self-rated ASD symptoms did not influence the group effect over and above the diagnostic status on ToM attribution errors, $\beta = .003$, $t(100) = .03$, $p = .98$. Using a Kruskal-Wallis ANOVA test, a near-significant group differences was also for answers to questions for the physical stories, $H(3, 101) = 7.7$, $p = .053$, although no pairwise group differences were found. The pattern of performance suggested that individuals with ASD had the most impairment in this task too, not taking into account IQ differences across groups.

Figure 3-7: Comparison of ToM difficulties across groups



Note. Group effects were found in ToM attribution error (A) but not physical story error (B) before FSIQ was covaried, and pairwise comparisons suggested that the ASD group had the most ToM impairment among the four groups. The group effect was fully accounted for by FSIQ differences. Error bars indicate 95% CI. † $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$.

3.4 Discussion

The overarching aim of this study was to explore the similarities and differences of EF and SC difficulties in young adult males meeting the criteria for ASD, ADHD, or ASD+ADHD compared to typically developing controls. To measure dimensional ASD and ADHD traits among the participants, self-ratings of ASD traits on the SRS and ADHD traits on the CAARS and SDQ hyperactivity were collected from all participants. In addition, informant-ratings on these measures were collected from parent, sibling or partner of individuals in the clinical group. In line with the participants' diagnostic status, self-rated ADHD symptoms on the CAARS and the SDQ hyperactivity were significantly greater in the ASD+ADHD and ADHD groups, relative to other two groups. Informant ratings of the ADHD and the ASD+ADHD groups were also significantly higher than the ASD group. This indicated that ratings of ADHD symptoms distinguish the ASD+ADHD and the ADHD groups the non-ADHD group well. In contrast, self-rated autistic traits on the SRS did not seem to differentiate the clinical groups from one another although they were higher than the

TD self-ratings. Informants however rated individuals in the ASD+ADHD and ASD groups as having higher autistic traits on this measure, although the difference of less than 10 points between the autistic traits in the ADHD and the ASD group was surprisingly subtle.

More importantly, findings from the neurocognitive study showed that EF impairments appeared to be specifically associated with ADHD symptoms. Deficits were typically found among individuals with ADHD and/or ASD+ADHD relative to the ASD and TD groups even after covarying for IQ. Deficits in EF were found in the subdomain of response inhibition, where individuals with ADHD and ASD+ADHD were most impaired, the subdomains of sustained attention and temporal discounting, where individuals with ADHD appeared to be most impaired, and in the subdomain of working memory, where individuals with ADHD and ASD+ADHD appeared to be more impaired relative to the TD group. No differences across groups were found in perseverative errors, which was unexpected. Unexpectedly in the SC domain, group effects were only found when IQ was not covaried, which suggested that the variation of group performance across SC tasks was IQ-dependent. Interestingly without covarying for IQ group differences were in the direction as expected, i.e., the ASD group made more emotion identification error compared to the TD group on the FER task and showed trend-wise decrease of sensitivity to emotional expression on faces than the ADHD group. In addition, the ASD group also displayed poorer ToM than the TD and the ADHD groups. The EF findings are discussed first in the following section.

3.4.1 EF Findings across Groups

Regarding inhibitory function, the ADHD and ASD+ADHD groups displayed increased inhibitory deficits relative to controls, while the ASD group's performance was midway between the ADHD and the TD groups, as judged from their

commission and premature errors on the GNG and CPT-AX tasks. Further, the ASD+ADHD also group displayed poorer inhibitory deficits than the ASD group. This was similar to previous results (Buehler et al., 2011; Corbett, Constantine, et al., 2009) and may represent the additive pattern of impairment suggested in previous studies (Sinzig, Morsch, Bruning, et al., 2008; Tye, Asherson, et al., 2014). However, these results were inconsistent with Sinzig et al.'s (2008) findings of comparable commission errors among individuals with ASD, ASD+ADHD, and controls; and among the ASD, ADHD, ASD+ADHD, and controls in Adamo et al.'s (2014) study. One potential explanation for the discrepant results is the differences in the tasks employed in these studies.

The GNG task used by Sinzig et al. (2008) presented the stimulus at a lower frequency (0.33 Hz vs. 0.5-1.0 Hz) than other studies (Buehler et al., 2011; Corbett, Constantine, et al., 2009) including the present. Further, Sinzig et al. (2008) used a variant of the GNG task with equal numbers of Go and No-Go cues which would decrease the prepotency of response. According to the cognitive-energetic model of ADHD (Sanders, 1983), stimulus presentation of low frequency is associated with increased inattention and omission errors. This was supported by findings from a recent meta-analysis that has shown that slower stimulus rate presentation is associated with reduced commission errors (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012). Therefore, the GNG task employed by Sinzig et al. (2008) was possibly not adequately sensitive for measuring inhibition. In line with this reasoning, Adamo et al.'s (2014) "fixed" SART GNG was more suitable for assessing inattention. In this task a fixed sequence of number, i.e., one to nine, is presented to a participant who responds to every number except the "No-Go" number three. Although the stimuli were presented approximately at 0.70 Hz, the No-Go stimuli appear at a fixed and extremely slow rate of around 0.08 Hz and the study did not find increased omission errors across groups using this task. This

explanation is supported by the finding by Johnson et al. (2007) who showed that children with ADHD, ASD, and typically developing controls showed no difference on the index on commission errors on this task, while those with ADHD specifically demonstrated inattention by omitting responses on the task compared to the two comparison groups.

Difficulties in sustained attention as indicated by the number of omission errors and the SDRT were found predominantly in the ADHD group. Individuals with ADHD appeared to have increased omission errors and SDRT compared with the controls on the CPT-AX task, consistent with prior findings (e.g., Fischer et al., 2005; Rubia, Smith, & Taylor, 2007; Slama, Fery, Verheulpen, Vanzeveren, & Van Bogaert, 2015). They also performed more poorly than the ASD group. The mean omission error rate for the ADHD group on the GNG task, which was higher than the controls (although fell to non-significant level after multiple comparison correction), was also in line with past studies (e.g., Epstein et al., 2001; K. R. Murphy et al., 2001; Silva et al., 2013). Further, the lack of sustained-attention deficits in the ASD group compared to controls was consistent with results of previous studies using the CPT-AX and the GNG tasks (e.g., Bogue et al., 2009; G. Goldstein et al., 2001; Pascualvaca et al., 1998).

Individuals with ASD+ADHD appeared to have significantly higher rates of omission errors and greater SDRT overall on the GNG task; they showed similarities with the ADHD group on these two variables, as found in two previous studies (Adamo et al., 2014; Sinzig, Morsch, Bruning, et al., 2008). However, on the CPT-AX, they performed in between the TD and the ADHD groups with average omission errors closer to the ASD group and controls than the ADHD group. This is inconsistent with the finding from the GNG task. Furthermore, this finding also contradicts a previous finding by Tye et al. (2014), who found similarly increased omission errors and SDRT in children with ASD+ADHD and with ADHD relative to

the TD and ASD group, on a hybrid CPT-AX/Flanker task called the CPT-OX. Since the present study is the first to test sustained attention among adults with ASD, ADHD, and ASD+ADHD, using attentional indices from both the GNG and the CPT-AX tasks it is also the first to show that the conclusions regarding sustained attention in the ASD+ADHD group might also depend on the task type.

The GNG, the CPT-OX, and the CPT-AX differ from one another. Both the GNG and the CPT-OX have greater inhibitory load than the CPT-AX task. The GNG task requires continuous responses towards frequently presented Go cues and occasional withholding of responses when a No-Go cue appears. Consequently, the participants were predisposed to respond and would have difficulties in withdrawing their action. Similarly, inhibitory response is evoked during the CPT-OX task but not in common sustained-attention tasks such as the CPT-AX used in the present study. The task, involves presentation of a sequence of letters, flanked by the letters “X” or “O” on each side, providing “a flanker effect on every trial” (see McLoughlin et al., 2010, p. 67). Flanker effects elicit conflict and one interpretation of such conflict, supported by findings from imaging studies, is that they evoke downstream inhibitory processes (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Eriksen & Eriksen, 1974; Takezawa & Miyatani, 2005). Therefore, measures such as omission errors or SDRT on these tasks are influenced by prepotent responses and are also confounded by conflicts (Albrecht, Uebel-von Sandersleben, Wiedmann, & Rothenberger, 2015; Huang-Pollock et al., 2012). Nevertheless, these findings altogether offer an interesting insight into the ASD+ADHD group. That is, under the condition where conflicts or inhibitory load are concurrent with the target detection, individuals in the ASD+ADHD, based on the literature and the current findings, appear to have difficulties in sustaining attention and demonstrate performance closer to the ADHD groups, while under an alternative condition where target

detection is the sole task demand, their performance appear to improve and closer to the ASD group.

An intriguing but speculative interpretation of the sustained attention finding in the present study is that ASD traits might down-moderate the performance of individuals with ASD+ADHD during the CPT-AX task. Sensory hypersensitivity is a common feature among individuals with ASD, presenting in one in five individuals according to one population-based study (Jones et al., 2009). Evidence from electrophysiological and fMRI studies suggest that a number of individuals with ASD demonstrate atypically enhanced perception during a target detection task that could be associated with their hypersensitivity to stimulus changes (e.g., Cléry et al., 2013; Gomot, Belmonte, Bullmore, Bernard, & Baron-Cohen, 2008; Karhson & Golob, 2016). This interpretation may explain the result from the only electrophysiology study to date that has compared children with ADHD to a group of children with autism on an oddball task, which showed an absence of impairment on the P3 ERP component, an index of attention, in the ASD group relative to the ADHD children (Kemner, Verbaten, Koelega, Camfferman, & van Engeland, 1998). The CPT-AX is similar to a target detection task with the addition of a cue prior to targets, designed for tapping the response preparation stage (Albrecht et al., 2015). It is thus possible that co-occurring sensory sensitivity among individuals with ASD+ADHD could moderate the CPT-AX performance in this group. Given the absence of prior investigations the relationship between performance on sustained attention using the CPT-AX task and sensory perception sensitivity in these four groups, however, the present interpretation is tentative.

Poor visuospatial working memory was found primarily in the ASD+ADHD and ADHD groups compared to the controls, with individuals with ASD showed intermediate performance between the controls and the ASD+ADHD groups but closer in their performance to the ADHD group. The direction of these results was

consistent with previous findings of working memory, verbal and visuospatial, among children (Andersen et al., 2013; J. M. J. van der Meer et al., 2012; Yerys et al., 2009). In investigating verbal working memory Andersen et al. (2013) found that the difficulties in children with ASD+ADHD and ADHD were related to impairments during memory acquisition, as well as delayed recall, while the ASD group was characterised by memory acquisition difficulty only. The compounded effect of memory acquisition and delayed recall difficulties in the ASD+ADHD and the ADHD groups could explain why visuospatial working memory performance in these groups was the most impaired in the present study. This interpretation should be taken cautiously given the limited scope other investigation in the visuospatial domain, which excluded assessments of memory acquisition and delayed recall. Future studies should investigate whether the findings of Andersen et al. (2013) can be extended into the young adult population to explain the visuospatial working memory difficulties in individuals with ADHD and ASD+ADHD.

No differences were detected on the cognitive flexibility across the four groups, although the average perseverative errors were greater in the ASD group, i.e., in the direction expected from the literature. The finding is not consistent with the majority of previous studies that have shown large effect size deficits of in cognitive flexibility in children and adults with ASD relative to typically developing controls (see Geurts et al., 2009; Landry & Al-Taie, 2016). Note however, that cognitive flexibility deficits were absent in several previous studies involving children, adults and older adults with ASD (see e.g., Ambery, Russell, Perry, Morris, & Murphy, 2006; Barnard, Muldoon, Hasan, O'Brien, & Stewart, 2008; Geurts & Vissers, 2012; E. L. Hill & Bird, 2006; Minshew, Goldstein, Muenz, & Payton, 1992). Particularly pertinent to the finding from the present study is the idea that a computerised task could increase the accessibility, and therefore reduce the apparent deficits, in individuals with ASD due to the limited social demand it

imposes (Kenworthy, Yerys, Anthony, & Wallace, 2008; Ozonoff, 1995). However as Landry and Al-Taie (2016) reported, the magnitude of cognitive flexibility deficits reported in studies using the computerised or manual WCST among people with ASD did not differ significantly, negating the supposed benefit of the computerised version of the task for the population. Using a series of regression analyses involving age, autism severity judged on the ADI-R, and IQ as predictors for perseverative errors, Landry and Al-Taie (2016) found instead that younger children with lower IQ had increased deficits in cognitive flexibility. It is thus possible that adults are less likely to exhibit perseverative tendencies on the WCST. However, it is unclear whether this is related to development or due to decreasing task sensitivity to detect the deficits in adulthood (Geurts & Vissers, 2012). Therefore, future studies may consider using a range of tasks with greater sensitivity for investigating this cognitive subdomain among adults with ASD and ADHD.

The difficulties in temporal reward discounting among individuals with ADHD have been consistently reported (e.g., Sjöwall et al., 2013; Solanto et al., 2001; Sonuga-Barke et al., 2008), including in a recent large study involving over 130 adults with ADHD relative to controls (Mostert, Onnink, et al., 2015). The latter found that individuals with ADHD displayed steeper reward discounting relative to controls, especially at longer time delays of 100 days. In the present study, using a similar task and an equivalent outcome measure, that is, the AUC of reward discounting, the ADHD group was found to have significantly steeper temporal discounting compared to controls, and IQ variation did not influence the results, therefore replicating previous findings in ADHD. However, no effect of group was found when all groups were included in the comparison, which conflicted with previous findings on this task (Demurie et al., 2012). Compared to the present study, Demurie et al.'s (2012) investigation, which found an ADHD-specific monetary reward discounting impairment, included 30-40 children in each of the

ASD, ADHD, and TD group. Given that studies in adults appear to have lower effect sizes and variable findings overall, it is possible that the present study was underpowered to detect group differences.

3.4.2 SC Findings across Groups

The primary finding from the present study is that young adults with ASD, ADHD, and ASD+ADHD did not differ in SC when differences in IQ across groups were covaried. The finding is most unexpected for the ASD group, where the difficulty in ToM and FER were often reported in previous studies. From the current finding in young adults and past findings of SC difficulties among children with ASD (Brent et al., 2004; Kaland et al., 2008; Spek et al., 2010; S. J. White et al., 2011), one may suggest that the lack of ToM and FER deficits among individuals with ASD is both age- and IQ-dependent. Nevertheless, many adults with ASD are perform poorer on ToM tasks than typically developing controls (Heavey et al., 2000; Rogers et al., 2007; Spek et al., 2010; S. J. White et al., 2011). Thus, age may not be the best explanation for the current findings. In individuals with ASD, both IQ and ASD traits are suggested to be independent contributors to poor performance on SC including the ToM task (Buitelaar, van der Wees, Swaab-Barneveld, & van der Gaag, 1999b) and a variety of emotion recognition tasks (Jones, Pickles, et al., 2011), thus IQ remains the possible explanation for the current finding.

Putting to one side the IQ-dependence of the group effects, the findings in relation to social cognition from this study among individuals with ASD or ADHD alone were very much in line with results from a recent meta-analysis (Bora & Pantelis, 2015) that has concluded that emotion recognition and ToM abilities were impaired in individuals with ADHD to much lesser degree than in individuals with ASD, and the additional findings indicate that the deficits in *adults* with ADHD were subtle for emotion recognition and non-significant for ToM. The present findings are

also consistent with results from a number of previous comparative studies of ToM and FER in people with ASD compared to ADHD group (Baribeau et al., 2015; Demurie et al., 2011; Dyck et al., 2001; Gonzalez-Gadea et al., 2013; Muris et al., 1999; J. M. J. van der Meer et al., 2012; J. Yang et al., 2009), which strongly suggest a specific association between SC difficulties and ASD. Furthermore, the study in the previous chapter has also shown a specific association between ToM deficits and ASD symptoms among adolescents with ASD.

Individuals with ASD+ADHD appear to perform FER and ToM task in midway between the TD and the ASD groups. This was unexpected findings when compared to results from the previous literature. Only a handful of studies have reported the FER performance among children with ASD+ADHD (Tye, Battaglia, et al., 2014; Tye et al., 2013; J. M. J. van der Meer et al., 2012). Most findings suggested that individuals with ASD+ADHD would display more FER and ToM difficulties than the pure ADHD counterpart. Van der Meer et al. (2012) showed that increased FER difficulties is associated with increased ASD traits by demonstrating that individuals in the ASD+ADHD group. Tye et al. (2014; 2013) specifically demonstrated that the electrophysiological underpinnings of SC such as FER, and face and gaze processing in children in the ASD+ADHD group followed an additive impairment of the pure ASD and ADHD children, which differed from one another.

Following the findings by van der Meer et al. (2012) and Tye et al. (2014; 2013), one expects the ASD+ADHD group to display level of deficits closer to the ASD group during FER and ToM tasks than were currently found. The inconsistencies of findings could be due to several reasons. However, IQ difference is most probably not one of them since pairwise comparison between the ASD+ADHD and the ASD group showed non-significant difference of IQ. One possible explanation for the contrasting findings between this study and Tye et al.'s (2014; 2013) is that the impairments of SC behavioural performance in the

ASD+ADHD group are not as unambiguously additive as suggested by their electrophysiology markers, presumably because those temporally rapid electrophysiological markers can be moderated by other factors before manifesting as behaviours. Another potential explanation is that the ASD+ADHD group consists of individuals with heterogeneous presentations including those with predominant ASD traits and others with predominant ADHD traits as shown in van der Meer et al.'s (2012) study, which could reduce the presentation of ASD-associated SC deficits. However, bimodal distributions were not detected during exploratory analyses of behavioural symptoms, ToM, and FER performance rendering this explanation unlikely.

A final consideration would be that ADHD traits might moderate SC difficulties in the ASD+ADHD group. Studies in children with ASD and ASD+ADHD typically shows that they demonstrate the same number of symptoms on ADI-R and ADOS (Holtmann et al., 2007; Salley et al., 2015; Yerys et al., 2009), although these analyses were all conducted at global domain level. A recent study in approximately 50 school-age children with ADHD and over 150 verbally fluent children ASD, all referred due to ASD concerns, demonstrate that the two groups of children were differentiable from their ADOS (not from the ADI-R scores), particularly on four items, which were their quality of social overtures, amount of reciprocal social communication, amount of unusual eye contact, and amount of facial expressions directed to examiner, endorsed >66% in children with ASD *and* <33% of those with ADHD (Grzadzinski, Dick, Lord, & Bishop, 2016). This seems to be consistent to previous findings demonstrating that school-aged children with ASD were poorer than age-matched group of ADHD children on the use of context, non-verbal communication, and their social relationships quality, although both have more difficulties than TD controls (Geurts & Embrechts, 2008). In addition, an unpublished study based on the Dutch Sample of Children and Adolescents (Scheres,

Oosterlaan, & Sergeant, 2001) with ASD, hyperkinetic disorder (HKD), and ASD+HKD and controls showed that co-occurring HKD in the ASD population was associated with increased verbal fluency and cognitive flexibility (Santosh et al., 2006). The key question here is whether children with ASD+ADHD, might have similar qualities shown by children with ADHD that might set them at better footing for developing social relationships, social cognition and ToM as they grow up, resulting in the group to have milder SC deficits than the ASD group in adulthood. These potential explanations could be explored further in future studies.

3.4.3 Findings in the Context of the Comorbidity Debate

Two hypotheses have been proposed to explain the ASD+ADHD condition in relation to the pure groups in previous studies. One hypothesis proposes the ADHD and ASD as two manifestations of the same underlying disorder. The specific form of this comorbidity model predicts that individuals with ADHD, ASD+ADHD and ASD form a continuum of neurocognitive and behavioural characteristics, i.e., a gradient overarching disorder, with neurocognitive impairments and social difficulty symptoms increasing in the direction of increasing ASD traits (e.g., Rommelse et al., 2011; J. M. J. van der Meer et al., 2012). This hypothesis predicts that individuals with ASD will demonstrate more impairment than individuals with ASD+ADHD which demonstrate more impairment than individuals with ADHD alone. Another hypothesis proposes that individuals with ASD+ADHD would demonstrate additive impairments of the ASD and the ADHD groups (e.g., Sinzig, Morsch, Bruning, et al., 2008; Tye et al., 2013). This is so because the two pure groups are essentially distinct disorders, and their combined form will simply have the aggregate deficits of the pure forms (Banaschewski et al., 2007).

Only partial support for the gradient overarching disorder model was observed from the current findings. For instance, ToM ability appeared to be most

impaired in the ASD group relative to the ADHD and the TD group, while individuals with ASD+ADHD showed an intermediate level of impairment. However, neither informant- nor self-ratings on the SRS-2 confirmed that the ASD group had more severe autistic traits compared to the ASD+ADHD group as the gradient overarching disorder model had predicted. In fact, in the context of behavioural symptoms and EF performance, most of the findings provided support for the additive impairment model. The ASD+ADHD group appeared to have a similar level of autistic traits as individuals with ASD, and a similar level of ADHD traits as the ADHD group. Furthermore, in the response inhibition, sustained attention (measured on the GNG task), and working memory subdomains, the ASD+ADHD group appeared as impaired or more impaired than the ADHD group depending on the EF subdomain examined, while the ASD group tend to be in between the TD and the ASD+ADHD or the ADHD groups.

Did the findings suggest that ASD and ADHD were distinct disorders? As mentioned above, the neurocognitive findings were not as clear as Tye et al.'s (2014; 2013) which demonstrated clear phenotypic separation of the ASD from the ADHD group. While overall the findings appeared to show that EF deficits were associated more strongly with ADHD than ASD, and that SC deficits were associated more strongly with ASD than ADHD (neglecting the IQ influence), subtle deficits of EF in ASD and SC, especially FER, in ADHD might also exist since they tend to show a level of performance in between the TD and the counterpart pure disorder group respectively. This might suggest that each disorder had a variation of cognitive impairments of the other.

3.4.4 The Associations between EF or SC Deficits with ADHD or ASD Symptoms

In each subdomain of EF and SC, associations between EF or SC deficits and indices of ADHD or ASD symptoms were explored. In this study, no associations

were found between ADHD or ASD symptoms and SC or EF subdomain deficits beyond what has been accounted by diagnostic status. Moderate correlations between symptoms and neurocognitive performance among ADHD groups were previously reported in studies involving population representative or sufficiently large samples (Epstein et al., 2003; Kuntsi, Andreou, Ma, Börger, & Van Der Meere, 2005; Wood et al., 2011). The present study was designed to primarily find differences among groups defined by their diagnostic status and, by definition, their ADHD or ASD symptoms. Individuals within these convenience samples might represent the more severe end of the distribution (S. H. Goodman et al., 1997), with insufficient variation in autistic or ADHD traits within group to regress against EF or SC performance.

3.4.5 Strengths and Limitations

The strength of this study was the inclusion of individuals with well-characterised diagnostic status, supported by self-rated behavioural symptoms, as well as ratings by informants for participants in the clinical groups. The study used a range of neurocognitive tests that, although not all standardised, have been considered good indices of cognitive functions and have produced well-replicated findings among individuals with ADHD or ASD. Most measures, except the ToM task, produced data with no floor and ceiling effects thus not constraining their variability.

One weakness to the study is the significant IQ difference across groups which may influence the findings across groups. IQ differences between groups in studies involving people with neurodevelopmental condition were typically covaried during the analyses, although this analytical strategy has been a subject of debate of late. This is so because individuals with neurodevelopmental disorders typically have lower IQ than typically developing controls, which is a defining characteristic of the former (Dennis et al., 2009; G. M. Miller & Chapman, 2001). Researchers have

advocated several approaches for this problem including one that partially removed the variance of neurocognitive performance in the clinical groups according to the relationship between the performance and IQ of the control group (e.g., Brunsdon & Happé, 2014; M. S. C. Thomas et al., 2009). Others opted to not covary for IQ at all (Dennis et al., 2009; J. M. J. van der Meer et al., 2012). It should be noted that the pure ADHD and the control groups in this study were those with IQ beyond the normal range in this study, thus they might be unrepresentative to their population. As there seem to be no satisfactory solution for the present example, I opted for covarying for IQ in this study. The findings still suggest that the difficulties of inhibition, sustained attention, and working memory were characteristics of individuals with ADHD, despite their higher IQ compared to the other clinical groups, which showed the strong association between EF deficits and the condition.

Another limitation is over the subtle difference of autistic traits across the participant groups as judged on the SRS-2. Recent studies suggest that ratings of the SRS were influenced by non-ASD specific behaviour problems (Hus et al., 2013) and had reduced specificity for among children with emotional and behavioural problems (Moul et al., 2015). Based on these findings, it is possible that such issues extend to the adult population and causes the specificity of the questionnaires to be low people with ADHD, ASD and ASD+ADHD. The grouping of the ASD and ADHD participants in this study were however based on diagnostic status provided by clinicians. Most diagnoses were also supported by assessment on gold-standard research instruments such as the ADOS and the ADI-R and therefore were independent of the SRS-2 scores. Thus, it is unlikely that the findings of this study were confounded by misdiagnoses of ASD due to insensitive instrument.

In the interest of gaining as many participants as possible who were medication-naïve or not on current medication, the study was opened to adults who

have received their first-time diagnosis of ADHD in adulthood. These participants made up a significant proportion (~40%) of individuals in the ADHD and the ASD+ADHD groups. Although the process of diagnosing these participants required that symptoms were present in childhood, the participants may represent a subset of individuals with less severe cases, with less pronounced difficulties in childhood, and higher IQ (Antshel et al., 2010; Barkley, Murphy, & Fischer, 2008; Kolar et al., 2008). Thus, the EF difficulties demonstrated by the participants in this study might be an underestimation of the difficulties that many individuals in the ADHD population have.

Finally, another limitation to this study was insufficient exploration of other psychiatric difficulties in the clinical groups. Individuals with ADHD, for instance, demonstrate additional problems in adulthood such as conduct problems and antisocial personality, anxiety, and substance abuse disorders (Biederman et al., 1993; Kessler et al., 2006; Molina & Pelham, 2014), some of which were exclusion criteria for the study. Phone screening was conducted prior to inviting individuals into the study to rule out those meeting the exclusion criteria and with significant additional problems. However, mean SDQ scores in the clinical samples still showed higher levels of emotional, conducts, and peer relationships problems in the clinical groups compared to controls, although to what extent these observations are clinically significant is unknown. Additional structured interview would be recommended in future studies either to control for additional psychiatric difficulties in the clinical groups or to allow investigating the influence of those additional problems in the findings.

3.4.6 Implications and Future Directions

Comparing participant groups on a wide range of measures across the lifespan is critical to understanding the role of EF in autism (E. L. Hill, 2004). Likewise, studying

ADHD and its associated comorbidities in adulthood is important as the form of psychiatric disorders may change throughout ages due to influences of biological and sociocultural factors (Taurines et al., 2010). The findings from this study are consistent with those reported in previous studies, i.e., adults with ASD displayed primarily SC difficulties, including in ToM and FER while individuals with ADHD displayed primarily EF difficulties instead including in inhibition, sustained attention working memory and temporal reward discounting. However, the specificity of the findings is undermined by the fact that individuals with ASD or ADHD tend to have level of performance in between the typically developing and the counterpart groups. Adults with ASD+ADHD appeared to have similar EF difficulties as adults with ADHD particularly in response inhibition and working memory, and possibly in sustained attention, although the latter finding appear to be moderated by task types. Individuals with ASD+ADHD appeared to perform SC tasks at the level in between the TD and ASD groups. The findings did not lend support a gradient overarching disorder. The difficulty asserting the two groups as independent disorder at this neurocognitive level also prevent us from firmly concluding that ASD+ADHD follows an additive impairment shown by the pure groups. Instead, the findings appear to suggest that from the neurocognitive perspective the groups are variations of one another, although the addition of co-occurring ADHD symptoms among individuals with ASD appears to be associated with increased EF deficits in the latter. The findings of this study appear to highlight the limitation of the neurocognitive methodology for discerning the underpinning of the similar or different symptoms between individuals with ASD, ADHD, and ASD+ADHD. Other more sensitive methods such as electrophysiology or functional neuroimaging might be a better option for investigating the underlying group similarities or differences in these clinical populations.

4 Study III: Meta-analyses of Functional Impairments during Inhibitory Control and Brain Structure Abnormalities in ASD and ADHD

4.1 Introduction

Inhibitory control is one of the most investigated cognitive functions among individuals with ASD and ADHD, both in neurocognitive (Geurts, van den Bergh, et al., 2014; Kuiper et al., 2016; Lipszyc & Schachar, 2010; Willcutt et al., 2008) and neuroimaging studies (Hart et al., 2013; Norman et al., 2016). Inhibition deficits in ADHD are highly consistent across studies, suggesting that the deficits are strongly associated with the condition (Nigg et al., 2005; Willcutt et al., 2005). The deficits in ADHD are associated with abnormal lateral frontostriatal functions, encompassing brain regions such as the IFG, SMA and BG (e.g., Cortese et al., 2012; Hart et al., 2013); possibly underpinned by structural deficits in these areas (Nakao, Radua, Rubia, & Mataix-Cols, 2011; e.g., Norman et al., 2016; Seidman et al., 2011; Valera, Faraone, Murray, & Seidman, 2007).

Difficulties of inhibition have also been reported among individuals with ASD (see, e.g., Raymaekers, van der Meere, & Roeyers, 2004; Verté, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006), although findings have not been as consistent across studies as was the case for ADHD. Different demographic characteristics were typically suggested as possible explanations for the heterogeneity of findings. However, a most recent meta-analysis has shown that neither age nor IQ moderated these findings (Kuiper et al., 2016). Another possible explanation of the heterogeneity could be the co-occurring ADHD symptoms in the ASD population, which has been shown to be associated with EF deficits in previous studies

(Buehler et al., 2011; Corbett, Constantine, et al., 2009) and in Chapter 2 of this thesis. Whether such findings signify a common neuropathology between ASD and ADHD must be further explored neurobiologically. Neuroimaging studies in people with ASD have shown abnormal function in brain regions within the lateral frontostriatal networks similar to ADHD (Daly et al., 2014; Shafritz et al., 2008; Vaidya et al., 2011), although mixed findings are common (see e.g., Duerden et al., 2013; Solomon et al., 2014; Yerys, Antezana, et al., 2015). Exploring brain structures or functions that are consistently abnormal among individuals with ASD or ADHD relative to controls, and comparing these abnormalities across the disorder groups will enable us to find the underlying neural similarities or differences that are associated with response inhibition in both disorders.

4.1.1 Inhibition and Its Neural Correlates

Inhibition is a deliberate override of dominant or prepotent response, including motor actions or higher-order cognitive responses (Miyake & Friedman, 2012; Nigg, 2000). It is typically investigated in laboratory setting using tasks involving withholding, cancelling, or switching of actions, or overcoming cognitive interference. In the GNG task, subjects are required to withhold prepotent frequent responses when rare no-go stimuli appear in a stream of highly frequent go trials. In the stop-signal task subjects are required to cancel a motor response triggered by frequent go stimuli, after the arrival of an unexpected, infrequent stop-signal (Aron & Poldrack, 2006; Rubia et al., 2001). The switch task requires individuals to disengage from previously valid stimulus-response association and engage with a newly defined response mode (Smith, Taylor, Brammer, & Rubia, 2004); whereas interference inhibition tasks such as the Simon, Stroop, and flanker tasks entail suppression of prepotent response tendencies that are conflicting with the primary intended action (Liu, Banich, Jacobson, & Tanabe, 2004).

Across these tasks, a range of brain activations were observed during response inhibition, although findings have converged in showing the involvement of extensive networks in the fronto-striato-thalamo-parietal regions (Cai, Ryali, Chen, Li, & Menon, 2014; Congdon et al., 2010; B. J. Levy & Wagner, 2011; Nee, Wager, & Jonides, 2007). As has been demonstrated by Nee et al. (2007), inhibition performance across Stroop, GNG, Flanker and Simon tasks elicited activations in the medial frontal/anterior cingulate, right dlPFC, left premotor cortex (PMC), bilateral inferior frontal/insula and IPL. Levy and Wagner (2011), having combined the stop-signal task and GNG data across 49 studies, also showed similar activations in the frontal areas and also in the right STN region during action cancellation. Pooling data from five separate fMRI studies involving the stop-signal task performance resulting in over 120 healthy adult participants, Congdon et al. (2010) also showed that successful inhibition, judged from the contrast of successful Stop against Go, elicited activations largely from similar areas in the right inferior frontal/insular cortices reaching to the frontal pole, right mPFC and precentral gyri (pre-CG), and medial pre-SMA and PMC, as well as bilateral activation in the AI, posterior cingulate, and BG, predominantly in the caudate, right thalamus, supramarginal and angular gyri. Finally, the largest meta-analysis of stop-signal task performance to date involving 70 studies identified the right IFG and the AI as foci of action stopping, with the right IFG playing the key role of implementing inhibitory control (Cai et al., 2014).

4.1.2 Functional and Structural Neuroimaging Findings in ASD and ADHD

Two meta-analyses have been conducted in fMRI studies involving individuals with ASD. None of these studies focused solely on inhibitory function, however, response inhibition studies made up a substantial proportion of those studies included (Dickstein et al., 2013; Philip et al., 2012). By separating studies on EF from other studies, Philip et al. (2012) revealed that people with ASD showed over-

activation in a cluster in the left MFG, and under-activated clusters in the right MFG, left lentiform nucleus, insula, IPL, and right posterior cingulate during executive control. Relatedly, Dickstein et al. (2013) distinguished fMRI studies in ASD into those in social versus non-social cognition domain and found that non-social tasks elicited greater activations in the bilateral insula and the right MFG and under-activations in the right caudate and SFG in children with ASD against typically developing children. Adults with ASD were found to demonstrate significant over-activations in the right and left MFG, inferior occipital gyrus, and ACC relative to controls. Note that by further differentiating studies in adults and children, Dickstein et al. (2013) had fewer than ten studies representing each age group which would reduce their analytical power and increase the probability for false positives. Furthermore, the reported functional impairments were not specific to inhibitory function, rather they were correlates of a broad variety of cognitive functions including working memory and attentional processes.

Response inhibition or cognitive interference studies among adults and children with ASD tend to show mixed findings, possibly due to their small sample sizes. Over-activations in the mPFC and precuneus during the Stroop task (Kennedy, Redcay, & Courchesne, 2006). Also reported were over-activated insula during the Stroop task and over-activated left MFG/IFG/OFC during the GNG (Schmitz et al., 2006). In children with ASD, under-active inferior right MFG and over-active IFG on a GNG task involving face stimuli (Duerden et al., 2013) were found, as well as under-active PCC, lingual and middle occipital gyri (Solomon et al., 2014), and over-active ACC/SFG, left MFG, and right IFG (Yerys, Antezana, et al., 2015) on variants of switch tasks. However, ADHD-like lateral frontostriatal under-activation during motor inhibition has also been found in several studies involving patients with ASD. Reduced activations in the right insula/IFG, left inferior temporal gyrus, and PMC for instance, were reported by Kana et al. (2007) in adults

with ASD during the GNG task, whereas Shafritz et al. (2008) found under-activation in the left dlPFC, ACC, BG, and insula in ASD adults using a switch task. Interference inhibition was found to be associated with reduced ACC activation (Fan et al., 2012) and also an under-active left MFG and right caudate in children with ASD (Vaidya et al., 2011), concomitant with poorer behavioural performance in the patient group relative to controls. Using variants of GNG tasks, involving oddball trials to control for selective attention (Daly et al., 2014) and involving emotional stimuli (Shafritz et al., 2015), studies found reduced activation in right IFG, and left thalamus, and also in the insula, ACC and dlPFC respectively. Despite the heterogeneous impairments, lateral frontostriatal under-functioning, particularly in the right IFG that have been reported among individuals with ASD and ADHD, might be a shared basis for poor inhibition in these populations.

Functional impairment in ASD could be underpinned by the presence of structural deficits. Activation-likelihood estimation (ALE) meta-analyses of studies of grey matter volume (GMV) in ASD patients relative to typically developing controls have suggested the presence of wide-ranging structural abnormalities in the population (Cauda et al., 2011; Nickl-Jockschat et al., 2012). In one meta-analysis involving 16 VBM studies comprising 350 ASD patients, enhanced GMV in the cerebellum, MTG, right ACC, insula, caudate head, FFG, left lingual gyrus, precuneus and PCC and reduced GMV in the cerebellar tonsil, right amygdala, IPL, insula, MTG, caudate tail, precuneus and pre-CG were found in patients relative to controls (Cauda et al., 2011). In addition, using a somewhat different set of 16 studies comprising 277 ASD patients, Nickl-Jockschat et al. (2012) found increased GMV in temporo-occipital clusters, right precuneus, and right cerebellum; and reduced volume of bilateral putamen, cerebellar vermis, left hippocampus/amygdala, left operculum and superior MFG, right MTG and pre-CG.

Several VBM studies documenting structural abnormalities among people with ASD have been published since the above meta-analyses. There were mixed findings as studies frequently reported an increase and decrease of GMV particularly in fronto-parieto-temporo-cerebellar regions. Of the more consistently reported findings were reduced GMV in the ACC/SMA/mPFC (e.g., Mengotti et al., 2011; Greimel et al., 2013), which is consistent with previous results (Abell et al., 1999; M. Craig et al., 2007; Kwon, Ow, Pedatella, Lotspeich, & Reiss, 2004) and reduced GMV in the cerebellar regions (D'Mello & Stoodley, 2015; Ecker et al., 2012; Foster et al., 2015; Retico et al., 2016). There were also reports of increased volume of superior and middle frontal areas including SFG/MFG and dlPFC (D'Mello & Stoodley, 2015; Ecker et al., 2012; Foster et al., 2015; H. Y. Lin, Ni, Lai, Tseng, & Gau, 2015). Clusters of increased GMVs in frontal regions are interesting findings since frontal lobe overgrowth has been reported among children with ASD (Courchesne et al., 2011; Stanfield et al., 2008). In addition to these findings, striatal GMV enhancement has been reported albeit in a few studies (Bonilha et al., 2008; Foster et al., 2015; Toal et al., 2010), in line with previous reports of enhanced striatal volume by Langen et al. (2009, 2014) who used a manual tracing method in their investigations. Given the variety of deficits and enhanced volume reported in these individual studies, it is likely that several clusters of GMV abnormalities would be found among individuals with ASD in the present meta-analysis.

In ADHD, the abnormalities in the prefrontal cortex and its connectivity implicate wide-ranging networks from the PFC and the OFC to the striatum, parietal cortex and the cerebellum (Cubillo et al., 2012; Durston et al., 2011). An early meta-analysis showed that people with ADHD had under-activated medial superior frontal, inferior frontal, and middle frontal gyri, SMA, right STG, left inferior occipital gyrus, right thalamus and the midbrain, and over-activation in the right parieto-occipital cortices and intermediate frontal sulcus during inhibition (Cortese et al.,

2012). In a meta-analysis of fMRI studies specific to motor inhibition and interference inhibition, Hart et al. (2013) found consistent under-activations in the bilateral SMA, ACC, right IFG/anterior insula (AI), left caudate/putamen/AI and right thalamus across 21 studies involving 287 patients with ADHD. The largest meta-analysis to date, involving 33 studies and comprising 489 ADHD patients (Norman et al., 2016), showed that under-activations in bilateral IFG/AI, caudate and putamen as well as the SMA/dmPFC and the STL were the most consistent across studies. A large-scale study missed in the latter meta-analysis also revealed under-activations in the IFG albeit in the left hemisphere, SFG, as well as under-activated supramarginal and post-CG gyri and the TPJ, in a group of 185 children and young adults with ADHD performing the stop-signal task (van Rooij et al., 2015). Interestingly while the brain activation in the left IFG is correlated with stop-signal in the control group, such association is non-significant in the ADHD group.

In structural MRI studies, reduced GMV in the frontostriatal networks and cerebellum were reported in several studies focusing on specific regions of interest (Valera et al., 2007) as well as in exploratory studies involving the whole brain (e.g., Bhajiwala et al., 2014; Lim et al., 2015; Roman-Urrestarazu et al., 2016). Several previous meta-analyses assessing GMV deficits in ADHD revealed reduced volume of the right lentiform nucleus and caudate nucleus, as well as enhanced GMV in the PCC/precuneus (Nakao et al., 2011). Reduction of the GMV in the BG was found in children while frontal reduction such as the ACC was found in adults when studies involving participants of these two age groups were analysed separately (Frodal & Skokauskas, 2012). The latest meta-analysis by Norman et al. (2016) including 27 VBM datasets of 931 ADHD patients is the largest to date. It revealed reduced GMV in the right putamen/pallidum/insula, bilateral caudate, vmOFC/rACC, right cerebellum in children and reduced GMV in the vmOFC, right PCC and putamen among adults with ADHD. There have been several studies of GMV among people

with ADHD since, and their results are largely consistent with Norman et al.'s (2016) meta-analysis. For instance, Bonath et al. (2016) reported GMV reduction in the ACC and bilateral cerebellum (as well as occipital cortex and bilateral hippocampus/amygdala), while Shimada et al. (2015) found reduced striatal volume among adolescents with ADHD. Bralten et al. (2016), who conducted a large-scale study involving 307 children and adults with ADHD, also identified reduced GMV clusters in the left OFC, right frontal pole, paracingulate/cingulate cortices, and medial frontal/ACC/subcallosal cortices, and the left pre-CG robust to variations of age, sex, and medication use. Controlling for IQ differences between groups revealed an additional cluster in the cuneus, which was reduced in the ADHD subjects relative to controls.

Findings of GMV abnormalities in precuneus and PCC in both ASD (Ecker et al., 2012; Foster et al., 2015; Kaufmann et al., 2013; H. Y. Lin et al., 2015) and ADHD (L. Chen et al., 2015; Kappel et al., 2015; McAlonan et al., 2007), correspond to the anatomical location of the default mode network (DMN), a network of nodes including the vmPFC/ACC, inferior temporal lobe and posterior cingulate/precuneus. This network is typically decreased in activity during task engagement and is anti-correlated with task-relevant networks (Raichle, 2015). Its activation during rest reflects self-referential mental activity or mind wandering (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Weissman, Roberts, Visscher, & Woldorff, 2006). Evidence from resting state studies also suggest that both the ASD and ADHD groups are associated with reduced connectivity of the DMN (Di Martino et al., 2013; Ray et al., 2014; Sripada et al., 2014).

4.1.3 Direct Neuroimaging Comparisons Between ASD and ADHD

A handful of fMRI studies have compared individuals with ASD and with ADHD in a single investigation. Previous studies in sustained attention, reversal learning,

working memory, and inhibition comparing the two patient groups showed disorder-specific as well as shared functional impairments (Chantiluke, Barrett, Giampietro, Brammer, Simmons, Murphy, et al., 2015; Chantiluke, Barrett, Giampietro, Brammer, Simmons, & Rubia, 2015; Chantiluke et al., 2014; Christakou et al., 2013). During sustained attention, Christakou et al. (2013) reported ASD-specific increased activations in the cerebellum, and shared reduced activation in the left dlPFC, anti-correlated activation in the precuneus among ASD and ADHD boys with no comorbidities relative to typically developing boys, and shared reduced activations in the thalamus and caudate and in pre- and post-central gyrus. In a study primarily investigating the acute effect of the selective serotonin reuptake inhibitor (SSRI) fluoxetine during reversal-learning, Chantiluke et al. (2015) reported ASD-specific under-activations in the mPFC and shared reduced activation in the precuneus in ASD and ADHD boys relative to controls during reward reversal with placebo administration. However, these findings could be attributed to reward-related processing inherent to the reversal-learning task.

Using the n-back task and analysing brain activation during the 3-back condition, which involved the highest working memory load during the task, Chantiluke et al. (2015) reported increased deactivation in the PCC region among 17 ASD boys, compared to 17 ADHD boys and 20 typically developing controls, which did not differ to each other. In addition, shared reduction of right dlPFC activation was found in both clinical groups relative to controls, which was correlated with commission errors among the ASD group. Finally, in the only fMRI study to date comparing ASD and ADHD subjects, Chantiluke et al. (2015) found ADHD-specific under-activation in the OFC and BG, which was correlated with omission errors, using the contrast successful against unsuccessful inhibition trials on the stop-signal task. A bilateral over-activation was reported in the IFC in the ASD group relative to the controls and trend-wise significant relative to the ADHD boys.

Again, both studies primarily investigated the acute effect of single dose fluoxetine in performance and brain activation during these EF task, therefore only findings from the placebo condition are reviewed here.

Finally, with respect to brain structures, two studies have compared GMV deficits in ASD against ADHD and healthy controls (Brieber et al., 2007; Lim et al., 2015). An early VBM study involving modest sample sizes of 15 ADHD and 15 ASD children, revealed ASD-specific GM increase in the supramarginal gyrus relative to controls and the ADHD group, and shared GM reduction in the MTL and increase in the left IPL in the ASD and ADHD groups relative to controls, uncorrected for multiple comparisons (Brieber et al., 2007). Similarly using the VBM data, Lim et al. (2015) found overall group GM differences among 33 typically developing children, 19 children with ASD and 44 with ADHD in the posterior cerebellum and left MTG/STG areas, whereas ADHD-specific reduction of right posterior cerebellar GMV were observed in the ADHD group compared to controls and ASD boys. Children with ASD had enhanced GM at the left MTG/STG relative to controls and, at more lenient threshold, to the ADHD boys.

4.1.4 The Aims of This Study

The aim of this study was to conduct a voxel-based meta-analytic comparison of the brain function and structure abnormalities associated with ASD and ADHD. The study aims to use all published whole-brain fMRI studies of inhibitory function and all published whole-brain VBM studies in ADHD and ASD. The objective of the study is to find the most consistent similarities or differences in neural abnormalities between these two conditions. Inhibitory control was chosen because it is a key impairment in both disorders based on neurocognitive studies. Multimodal analyses were used to find regions that were impaired both structurally and functionally within

each disorder. Furthermore, conjunction analyses were used to find regions where functions or structure similarly deviated in ASD or ADHD groups from controls.

Both ASD and ADHD were expected to be associated with functional impairments and structural abnormalities in frontostriatal regions. Specifically, I hypothesised that the ASD group relative to their controls would be characterised by reduced activations in the ACC and medial and lateral frontal areas such as the dlPFC, IFG and insula during inhibition. Based on several common findings of GMV studies, however, clusters of enhanced GMV were expected in the middle and superior frontal areas including the MFG/SFG and dlPFC and reduced GMV in medial frontal areas (e.g., Mengotti et al., 2011; Greimel et al., 2013; Abell et al., 1999; M. Craig et al., 2007; Kwon et al., 2004), and cerebellum (e.g., D'Mello & Stoodley, 2015; Ecker et al., 2012; Retico et al., 2016). In ADHD, similar findings to a previous meta-analysis by Norman et al. (2016) were anticipated, including the under-activations of the striatal regions, such as the caudate and putamen, and of the lateral frontal regions such as the IFG, insula, and the SMA during inhibition, accompanied by reduced GMV in the caudate, putamen, vmOFC, ACC, and PCC.

With regard to the comparison between the abnormalities associated with the two disorder groups, I hypothesised an ADHD-specific reduced activation relative to ASD in the BG, as has been shown in Chantiluke et al.'s (2015) study. With respect to the striatal volume, individuals with ASD were expected to have increased GMV, as has been found by Langen et al. (2009, 2014) and few other studies (Bonilha et al., 2008; Foster et al., 2015; Toal et al., 2010) while individuals with ADHD were expected to show reduced striatum and insula volumes (Norman et al., 2016). Finally, in keeping with findings by Christakou et al. (2013), shared increased activations in the precuneus, in both the ASD and ADHD groups relative to controls, were anticipated.

Table 4-1: Sample characteristics of fMRI studies in ASD

Source	Age group	Task type	Patients						Controls				Summary findings	
			N (% male)	Age, y	Range, y	IQ	Stim. Exp. %	Com. ADHD %	N (% male)	Age, y	Range, y	IQ	ASD < TD	ASD > TD
Ambrosino et al. (2014) ^a	Child	GNG	19 (100)	11.5	9-12	112	26	0	19 (100)	11.1	9-14	120	--	--
Chantiluke et al. (2015)	Child	Stop	19 (100)	14.7	10-17	112	0	0	25 (100)	13.4	10-17	109	L IPL	R IFC, L IFG, L MFG
Daly et al. (2014)	Adult	GNG	14 (100)	31	n/a	115	0	n/a	14 (100)	31	n/a	123	R IFG, L thalamus	R caudate, R cerebellum
Duerden et al. (2013) ^b	Adult	GNG	16 (69)	27.2	19-39	112	0	0	17 (71)	30.7	20-43	114	R MFG	R IFG, L FFG
Fan et al. (2012)	Adult	Flanker	12 (75)	30	n/a	115	0	n/a	12 (83)	28	n/a	120	ACC	--
Kana et al. (2007)	Adult	GNG	12 (92)	26.8	n/a	110	n/a	n/a	12 (92)	22.5	n/a	117	L ITG, R parahippocampal gyrus, R calcarine sulcus, R PMC, R mid CC, L/R post-CG, R insula/IFG, L lingual gyrus	--
Kennedy et al. (2006)	Adult	Stroop	15 (100)	25.5	16-44	96	n/a	n/a	14 (100)	26.1	n/a	n/a	--	mPFC, Precuneus
Schmitz et al (2006) ^c	Adult	GNG, Switch, Stroop	10 (100)	38	18-52	105	n/a	n/a	12 (100)	39	18-52	106	--	L M/IFG, OFC (GNG), insula (Stroop), and IPL, mesial parietal lobe (Switch)
Shafritz et al. (2008)	Adult	Switch	18 (89)	22.3	n/a	103	6	n/a	15 (87)	24.3	n/a	111	L dlPFC, ACC, L intraparietal sulcus, L BG, L insula	--
Shafritz et al. (2015) ^b	Mixed	GNG	15 (80)	18.1	13-23	102	13	0	15 (80)	18.4	12-23	115	R IFG/insula	--
Solomon et al. (2014) ^d	Child	POP	27 (19)	15.4	12-18	108	11	55	27 (19)	16.1	12-18	113	PCC, lingual gyrus, middle occipital gyrus	--
Vaidya et al. (2011)	Child	Stroop	11 (100)	10.8	7-12	114	47	n/a	14 (100)	11.0	n/a	119	ACC, L MFG, R caudate	--
Yerys et al. (2015)	Child	Switch	20 (80)	11.3	7-14	115	5	n/a	19 (68)	11.4	7-13	120	--	L MFG/ pre-CG, L SFG/ mid-dorsal ACC, R IFG

Note. Thirteen independent fMRI datasets, comparing 208 people with ASD against 215 controls, during response inhibition are listed on this table. a = ADHD was screened using DISC, b = co-occurring ADHD was an exclusion criterion, c = The study by Schmitz et al (2006) produced three datasets and were combined together with variance adjustment as specified in Norman et al (2016), and d = ADHD comorbidity was estimated using Conners' Parent Rating Scale. List of abbreviations: GNG = Go/No-Go task, POP = 'Preparing to Overcome Prepotency', a variation of a switch task, y = year, n/a = information not available, stim exp = stimulant exposure, i.e., present or past use of psychostimulant medication, com. ADHD = comorbid ADHD, R/L = right/left, IPL = inferior parietal lobe, IFC/G = inferior frontal cortex/gyrus, MFG = middle frontal gyrus, FFG = fusiform gyrus, ACC = anterior cingulate cortex, ITG = inferior temporal gyrus, PMC = premotor cortex, CC = cingulate cortex, pre-/post-CG = pre-/post-central gyrus, mPFC = medial prefrontal cortex, OFC = orbitofrontal cortex, dlPFC = dorsolateral prefrontal cortex, BG = basal ganglia, PCC = posterior cingulate cortex.

Table 4-2: Sample characteristics of VBM studies of GMV abnormalities in ASD

Source	Adult /child	ASD						TD				Summary findings	
		N (% male)	Age, y	Range, y	IQ	Stim. Exp. %	Com. ADHD %	N (% male)	Age, y	Range, y	IQ	ASD < TD	ASD > TD
Abell et al. (1999)	Adult	15 (80)	28.8	n/a	n/a	n/a	n/a	15 (80)	25.3	n/a	n/a	R paracingulate, L IFG, L occipito-temporal junction	L amygdala, L/R anterior cerebellum, L MTG, R ITG
Boddaert et al. (2004)	Child	21 (76)	9.3	7-15	n/a	0	n/a	12 (58)	10.8	7-15	n/a	L/R STS	--
Bonilha et al. (2008)	Child	12 (100)	12.4	8-15	n/a	0	n/a	16 (100)	13.2	n/a	n/a	--	L/R IFG, L/R cuneus, CG, precuneus, L/R thalamus, L/R ITG/MTG, L/R SFG, L/R SPL, L insula, L putamen, L/R FFG, L/R occipital, L lingual gyrus, L cerebellum, L pre-/post-CG, L PHGy
Brieber et al. (2007) ^a	Child	15 (100)	14.2	10-16	106.8	0	0	15 (100)	13.3	10-16	107.7	--	--
Cheng et al. (2011) ^a	Child	25 (100)	13.7	10-18	101.6	0	0	25 (100)	13.5	11-18	109.0	R IFG, R pre-CG, L post-CG, cuneus, thalamus, lingual gyrus, STG	ACC, paracentral lobule, SPL, precuneus, MFG, FFG, subcallosal gyrus
Craig et al. (2007)	Adult	14 (0)	37.9	n/a	103.4	n/a	n/a	19 (0)	35.0	n/a	111.2	Cuneus, L ITG/STG, R MTG, R ACC	--
D'Mello et al. (2015)	Child	35 (86)	10.4	8-13	n/a	n/a	n/a	35 (60)	10.4	8-13	n/a	R lingual gyrus, R cerebellum, R angular gyrus	L PCC/precuneus, R SFG, L middle occipital gyrus
Ecker et al. (2012)	Adult	89 (100)	27.0	18-43	110	n/a	n/a	89 (100)	28.0	18-43	113.0	R Occipital/ITG/ MTG/ cerebellum/posterior FFG/ lingual gyrus/ inferior and superior occipital gyrus/ cuneus/ precuneus/PCC	L /R anterior temporal/I/M/STG/ FFG/PHGy/insula, L/R dIPFC/ MFG/pre- and post-CG
Foster et al. (2015)	Child	38 (100)	12.4	6-17	102.5	n/a	n/a	46 (100)	12.6	7-17	113.1	STG, IPL, cerebellum	M/I/SFG, pre-/post- CG, pre-SMA, ACC, OFC, I/M/STG, FFG, lingual gyrus, PCC, precuneus, IPL, inferior occipital, striatum
Freitag et al (2008) ^a	Child	15 (87)	17.5	n/a	101.2	n/a	0	15 (87)	18.6	n/a	112.1	R intraparietal sulcus	--
Greimel et al. (2013)	Mixed	47 (100)	18.3	10-50	107.5	0	13	51 (100)	21.4	8-47	112.5	ACC, L/R posterior STS/MTG	--
Groen et al. (2011)	Child	17 (82)	14.4	12-18	98.0	0	n/a	25 (88)	15.5	12-18	105.0	--	--
Hyde et al. (2010)	Adult	15 (100)	22.7	14-33	100.4	6.7	n/a	15 (100)	19.2	14-34	106.6	Post-/pre-CG	Brainstem/midbrain, reticular, medial FG/OFG/ MFG
Itahashi et al. (2015) ^a	Adult	46 (100)	30.2	19-50	106.0	0	0	46 (100)	30.5	19-47	109.2	--	--
Kaufmann et al. (2013)	Child	10 (80)	14.7	n/a	102.3	n/a	n/a	10 (80)	13.8	n/a	109.5	Lateral portion of R precuneus	L medial FG, R precuneus,
Ke et al. (2008)	Child	17 (82)	8.9	6-14	108.8	n/a	n/a	15 (80)	9.7	6-14	109.8	R PHGy	L/R IPL, post-CG, R MFG, R cerebellum
Kosaka et al. (2010)	Adult	32 (100)	23.8	17-32	101.6	n/a	n/a	40 (100)	22.5	18-34	109.7	R insula, IFG, IPL	--

Kurth et al. (2011)	Child	52 (73)	11.2	5-20	102.2	n/a	n/a	52 (73)	11.1	6-19	106.0	Hypothalamus	--
Kwon et al. (2004)	Child	20 (100)	13.5	10-18	n/a	n/a	n/a	13 (100)	13.6	10-18	n/a	R ITG, ACC, R FFG	--
Langen et al. (2009)	Child	99 (92)	12.9	7-24	107.6	0	n/a	89 (92)	12.4	6-24	110.0	--	--
Lin et al. (2015) ^b	Child	28 (100)	10.7	7-12	106.9	n/a	n/a	43 (100)	10.6	7-12	115.2	R Post-CG, precuneus, L middle occipital gyrus	L Subcallosal gyrus, L/R sub-lobar
	Adol	40 (100)	14.7	13-17	101.5	n/a	n/a	18 (100)	15.5	13-17	108.7	--	--
	Adult	18 (100)	22.2	18-29	99.6	n/a	n/a	29 (100)	23.4	18-29	116.8	--	L/R SFG, L MFG
Lim et al. (2014) ^a	Child	19 (100)	14.9	11-17	113.0	0	0	33 (100)	14.9	11-17	110.0	--	L MTG/STG, L medial FG
McAlonan et al. (2002)	Adult	17 (90)	32.0	18-49	96.0	n/a	n/a	24 (92)	33.0	18-49	114.0	L cerebellum, R lenticular nucleus, R CG, R MFG/SFG, precuneus	--
McAlonan et al. (2008) ^a	Child	33 (82)	11.6	7-16	113.2	0	0	55 (86)	10.7	7-16	117.1	L dlPFC, L/R BG, L/R inferior cerebellar vermis, L STS, PCC	--
Mengotti et al. (2011) ^a	Child	20 (90)	7.0	4-14	n/a	0	0	22 (91)	7.7	4-11	n/a	L SMA, R IFG	R IPL, L/R ITG, L SPL, R superior occipital gyrus, precuneus
Mueller et al. (2013)	Adult	12 (75)	35.5	n/a	111.3	n/a	n/a	12 (67)	33.3	n/a	110.8	L MTG, ITG	--
Poulin-Lord et al. (2014)	Adult	23 (87)	19.8	14-30	100.3	0	n/a	22 (86)	22.6	15-35	107.3	--	--
Poustka et al. (2012)	Child	18 (89)	9.7	6-12	111.0	n/a	n/a	18 (89)	9.7	6-12	112.8	--	--
Radeloff et al. (2014) ^a	Mixed	34 (91)	19.1	14-33	105.7	14.7	0	26 (85)	19.5	14-27	107.8	--	--
Retico et al (2016)	Child	38 (50)	4.6	3-7	90	0	n/a	38 (50)	4.6	2-7	94	L posterior MTG, L cerebellum, L/R temporal pole	L precuneus, L PCC, R posterior STG, R MTG/ITG, R medial FG, L SPL, mid-CC
Rojas et al. (2006)	Mixed	24 (100)	20.8	7-44	94.8	n/a	n/a	23 (100)	21.4	7-44	118.7	--	--
Schmitz et al. (2006) ^a	Adult	10 (100)	38.0	18-52	105.0	0	0	12 (100)	39.0	18-52	106	--	--
Toal et al. (2010)	Adult	65 (88)	31.0	16-59	98.0	n/a	n/a	33 (91)	32.0	19-58	105	L cerebellum, R ITG/ PHGy/ STG, L STG/ITG/MTG	R brain stem/ PHGy/thalamus/ caudate/CG/ MFG/ pre-CG/CG/ putamen/thalamus, post-CG
Waiter et al. (2004)	Child	16 (100)	15.4	12-20	100.4	n/a	n/a	16 (100)	15.5	12-20	99.7	R thalamus	L SFG, R FFG, L/R MTG, R PCC, L/R STG, L lingual gyrus, L IFG, L MFG, L inferior occipital gyrus, L PHGy
Wilson et al. (2009)	Adult	10 (80)	30.1	22-47	91.5	n/a	n/a	10 (70)	29.4	21-43	127.2	--	--

Note. Thirty-seven independent ASD VBM datasets, comprising 1059 people with ASD and 1077 controls, are listed on this table. ^a = In these studies, participants underwent psychiatric interview to determine and exclude those with co-occurring psychiatric disorders, ^b = In this study, five participants had co-occurring ADHD diagnoses and five used psychostimulants, however, no additional information was given by the authors as to which age groups these participants belonged. List of abbreviations: VBM = voxel-based morphometry, GMV = grey matter volume, y = year, n/a = information not available, stim exp = stimulant exposure, i.e., present or past use of psychostimulant medication, com. ADHD = comorbid ADHD, R/L = right/left, IFC/G = inferior frontal cortex/gyrus, MTG = middle temporal gyrus, ITG = inferior temporal gyrus, STS = superior temporal sulcus, CG = cingulate gyrus, SFG = superior frontal gyrus, SPL = superior parietal lobe, pre-/post-CG = pre-/post-central gyrus, FFG = fusiform gyrus, ACC = anterior cingulate cortex, STG = superior temporal gyrus, MFG = middle frontal gyrus, PCC = posterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, SMA = supplementary motor area, OFC = orbitofrontal cortex, BG = basal ganglia, mid-CC = mid-cingulate cortex, PHGy = Parahippocampal Gyrus.

Table 4-3: Sample characteristics of fMRI studies in ADHD

Source	Age group	Task type	ADHD						Controls				Summary findings	
			N (% male)	Age, y	Range, y	IQ	Stim. Exp. %	Com orbid ASD	N (% male)	Age, y	Range, y	IQ	ADHD < TD	ADHD > TD
Banich et al. (2009)	Adult	Stroop	23 (61)	20.0	n/a	116	61	n/a	23 (57)	19.0	n/a	113	L IPL	R MFG, cuneus
Bhajiwal et al. (2014) ^a	Child	Stop	12 (58)	13.8	9-18	n/a	100	0	12 (50)	15.4	9-18	n/a	R MFG, R MTG, L cerebellum	R MFG/SFG
Booth et al. (2005)	Child	GNG	12 (67)	11.0	9-12	n/a	100	n/a	12 (58)	11.7	9-12	n/a	R SFG, IFC, ACC, B MFG; pre-CG, amygdala, fusiform, thalamus, caudate; L GP, cuneus	--
Carmona et al. (2012)	Adult	GNG	19 (100)	33.6	n/a	110.9	0	n/a	19 (100)	29.4	n/a	111.7	--	--
Chantiluke et al. (2015)	Child	Stop	18 (100)	14.3	10-17	95	61	0	25 (100)	13.4	10-17	109	L OFC, STL/putamen/ GP, L IPL	--
Chou et al. (2015)	Child	Stroop	42 (81)	10.5	7-17	108.5	0	n/a	20 (80)	12.0	8-17	106.5	R MFG/IFG, L IFG, L SPL	L/R SPL Pre-CG, L dlPFC, ACC, Post-CG
Congdon et al. (2010)	Adult	Stop	35 (54)	30.9	21-50	n/a	29	n/a	62 (45)	30.8	21-50	n/a	--	--
Cubillo et al. (2011) ^c	Adult	Stop, Switch	11 (100)	29.0	26-30	92	0	n/a	14 (100)	28.0	26-30	106	R IFC, insula, thalamus, putamen, caudate	--
Cubillo et al. (2014)	Child	Stop	19 (100)	13.1	10-17	92	0	0	29 (100)	13.8	10-17	110	L/R IFG, L M/ITG/IPL, R cerebellum/FFG	L cerebellum, L/R PCC/occipital gyri, R STG/post-CG/posterior insula/putamen
Cubillo et al. (2011) ^c	Adult	Simon	11 (100)	29.0	26-30	92	0	n/a	15 (100)	28.0	26-30	112	L OFC, IFC, MFC, ACC, caudate, pre-CG	--
Dibbets et al. (2010) ^d	Adult	GNG	16 (100)	28.9	21-42	n/a	88	n/a	13 (100)	28.1	21-41	n/a	--	--
Dibbets et al. (2010) ^d	Adult	Switch	15 (100)	28.8	21-42	n/a	80	n/a	14 (100)	28.6	21-41	n/a	R Putamen, R CG, L MFG/IFG, R thalamus, L post-CG	R MTG, ACC, precuneus, lingual gyrus, L pre-CG, insula
Durston et al. (2006)	Child	GNG	11 (100)	14.0	8-20	100	55	n/a	11 (100)	15.3	8-20	106	--	--
Iannaccone et al. (2015)	Child	GNG/ Flanker	18 (50)	14.5	12-16	108.5	72	n/a	18 (61)	14.8	12-16	114.4	R MFG/dlPFC/SFG	L/R MTG/STG, L insula/putamen/pre-CG, L ITG/FFG/ PHGy/MTG, L pons, L amygdala/ hippocampus, L FFG/ lingual gyrus, L post-CG/IPG, R brainstem/ pons/cerebellum
Janssen et al. (2015)	Child	Stop	21 (90)	10.6	8-13	98.6	90	n/a	17 (76)	10.3	8-13	108.7	--	--
Konrad et al. (2006)	Child	Flanker	16 (100)	10.2	8-12	103	0	0	16 (100)	10.3	8-12	105	L Pre-CG, R Putamen	L medial SPL

Kooistra et al. (2010)	Adult	GNG	11 (100)	21.5	18-25	110	0	n/a	11 (100)	10.1	18-25	125	--	R ACC, supramarginal gyrus
Ma et al. (2012)	Child	GNG	15 (53)	9.8	8-12	100.2	0	n/a	15 (53)	22.3	8-12	102.6	--	R ITF, R midbrain, R pre-CG, R calcarine, R inferior occipital, R middle occipital gyri, L/R cerebellum, L post-CG, L IFG, R hippocampus
Passarotti et al. (2010)	Child	Stop	11 (55)	13.1	10-18	107.6	0	n/a	15 (48)	9.9	10-18	101.2	R MFG, SFG	Caudate, L cerebellar vermis
Peterson et al. (2009)	Child	Stroop	16 (81)	14.1	7-18	101.2	0	n/a	20 (60)	14.1	7-18	118.5	L ACC, insula R, precuneus, thalamus, caudate	R SFG, hippocampus, L ACC
Rubia et al. (2005)	Child	Stop	16 (100)	13.2	9-16	100	0	0	21 (100)	13.4	9-16	95	R IFC, OFC, pre-CG, STL	--
Rubia et al. (2011) ^b	Child	Simon	12 (100)	13.0	10-15	90	0	0	13 (100)	14.0	11-16	102	R IFC, SMA/ACC/PCC/SPL/IPL, L vmPFC/BG/thalamus, L STL/ MTL, occipital	--
Rubia et al. (2011) ^b	Child	Stop	12 (100)	13.0	10-15	90	0	0	13 (100)	13.0	11-16	102	B IFC, insula, ACC, pre-SMA; thalamus; R MTL, occipital, IPL, precuneus, PCC, cerebellum	--
Schulz et al. (2004)	Mixed	GNG	10 (100)	17.9	14-18	88.4	0	0	9 (100)	13.0	14-16	91.9	R pre-CG, R ITG, L hippocampus, R lingual gyrus, L/R cerebellum	L/R MFG, L/R IFG, ACC, L/R IPL, precuneus
Sebastian et al. (2012)	Adult	GNG Stroop Stop	20 (55)	33.3	n/a	115.3	0	n/a	24 (46)	17.5	n/a	115.7	R Caudate (GNG), R GP (Stop), R post-CG, L para-central lobule/mid-CC, L STG/MTG, R temporal pole, R GP (Stroop)	--
Siniatchkin et al. (2012) ^c	Child	GNG	12 (83)	9.3	7-13	n/a	n/a	0	12 (75)	30.3	7-13	n/a	ACC, R dlPFC, R caudate	--
Smith et al. (2006) ^b	Child	GNG	17 (100)	12.8	n/a	n/a	0	0	18 (100)	9.3	n/a	n/a	L MFG	--
	Child	Stroop	19 (100)	12.9	n/a	n/a	0	0	24 (100)	12.8	n/a	n/a	--	--
	Child	Switch	14 (100)	13.3	n/a	n/a	0	0	27 (100)	12.9	n/a	n/a	L STG/IFG/pre-CG/insula, R MTG/IFG, IPL/STG	--
Spinelli et al. (2011)	Child	GNG	13 (69)	10.6	8-13	109.2	15	n/a	17 (47)	13.3	8-13	108.8	--	R pre-CG, MFG
Tamm et al. (2004) ^c	Child	GNG	10 (100)	16.0	14-18	109.2	50	0	12 (100)	10.6	14-16	111.6	R ACC, SMA, SFG, MFG	L MTL/ITL/STL
Van Rooij et al. (2015) ^a	Child	Stop	108 (64)	15.1	8-17	92.7	75	0	77 (49)	16.0	9-17	109.2	L STG, pre-CG	L SMA
	Adult	Stop	77 (78)	20.3	18-25	99.1	79	0	45 (33)	14.6	18-23	106.4	L SFG, R hippocampal gyrus	--

Note. Twenty-eight independent ADHD fMRI datasets, comprising 623 people with ADHD and 607 controls, are listed on this table. ^a = In this study, ASD diagnosis was part of the exclusion criteria. ^b = In these studies, participants were screened for ASD using a structural clinical interview for DSM disorders (SCID) conducted in the Maudsley hospital, London. ^c = In these studies, participants were screened for developmental disorders. List of abbreviations: GNG = Go/No-Go task, y = year, n/a = information not available, stim exp = stimulant exposure, i.e., present or past use of psychostimulant medication, com. ASD = comorbid ASD, R/L = right/left, IPL = inferior parietal lobe, MFG = middle frontal gyrus, MTG = middle temporal gyrus, SFG = superior frontal gyrus, IFC/G = inferior frontal cortex/gyrus, ACC = anterior cingulate cortex, pre-/post-CG = pre-/post-central gyrus, GP = globus pallidus, OFC = orbitofrontal cortex, STL = superior temporal lobe, SPL = superior parietal lobe, dlPFC = dorsolateral prefrontal cortex, FFG = fusiform gyrus, PCC = posterior cingulate cortex, STG = superior temporal gyrus, vmPFC = ventromedial prefrontal cortex, CG = cingulate gyrus, IPG = inferior parietal gyrus, SMA = supplementary motor area, BG = basal ganglia, MTL = middle temporal lobe, ITL = inferior temporal lobe, ITG = inferior temporal gyrus, and mid-CC = mid-cingulate cortex.

Table 4-4: Sample characteristics of VBM studies of GMV abnormalities in ADHD

Source	Adult /child	ADHD						TD				Summary findings	
		N (% male)	Age, y	Range, y	IQ	Stim. Exp. %	Comor bid ASD	N (% male)	Age, y	Range, y	IQ	ADHD < TD	ADHD > TD
Ahrendts et al. (2011)	Adult	31 (65)	31.2	18-55	n/a	0	n/a	31 (65)	31.5	19-52	n/a	L/R occipital lobe	--
Almeida Montes et al. (2010)	Adult	20 (50)	29.0	25-35	102.9	0	n/a	20 (50)	27.6	25-35	100.2	R caudate	--
Amico et al. (2011)	Adult	20 (75)	33.6	n/a	n/a	30	n/a	20 (75)	34.7	n/a	n/a	--	--
Bonath et al. (2016)	Child	18 (100)	13.6	11-17	106.8	56	n/a	18 (100)	14.1	11-17	108.1	L/R cerebellum, occipital cortex, L/R hippocampus, L ACC	--
Bralten et al. (2016) ^a	Mixed	307	17.1	8-30	97.1	87	0	196	16.7	8-30	106.6	L pre-CG, L OFC, R frontal pole, L paracingulate/ cingulate cortex/ frontal pole, bilateral medial frontal/ paracingulate/ cingulate/ subcallosal cortices	--
Brieber et al. (2007)	Child	15 (100)	13.1	10-16	104.1	67	0	15 (100)	13.3	10-16	107.7	--	--
Carmona et al. (2005)	Child	25 (84)	10.8	6-16	n/a	100	n/a	25 (84)	11.2	6-16	n/a	L pre-/post-CG, R OFG, L/R cerebellum	--
Depue et al. (2010)	Adult	31 (61)	20	n/a	114.2	77	n/a	21 (65)	19.3	n/a	112.6	--	--
He et al. (2015)	Child	37 (100)	9.9	7-16	n/a	0		35 (100)	10.7	8-15	n/a	R OFC, R PMC, L PCC, L posterior midcingulate cortex	--
Iannaccone et al. (2015)	Child	18 (50)	14.5	12-16	114.5	72	n/a	18 (61)	14.8	12-16	108.5	R medial SFG/ACC/SFG, L SMA/CG, L cerebellum	R pre- and post-CG
Johnston et al. (2014)	Child	34 (100)	12.5	n/a	99.8	29	n/a	34 (100)	13.2	n/a	103.7	Brainstem, putamen	--
Kappel et al. (2015)	Child	14 (71)	9.8	8-12	104.6	0	n/a	10 (80)	11.0	8-12	111.9	R STG, R heschls gyrus, R rolandic operculum	L paracentral lobule, L/R middle orbital gyrus, R FFG, L rectal gyrus
	Adult	16 (94)	23.5	19-31	97.8	0	n/a	20 (100)	23.7	19-31	108.4	R supramarginal gyrus, R precuneus, L OFG, R hippocampus, L rectal gyrus	--
Kobel et al. (2010)	Child	14 (100)	10.4	9-13	n/a	100	n/a	12 (100)	10.9	9-13	n/a	--	--
Li et al. (2015) ^b	Child	30 (100)	10.3	8-14	121.7	0	0	30 (100)	10.3	8-14	107.1	R insula, R OFC	--
Lim et al. (2015)	Child	44 (100)	13.6	10-18	92.2	18	0	33 (100)	14.3	10-18	110	L/R cerebellum, L IPL, pre-/post-CG	--
Maier et al. (2015) ^a	Adult	131 (48)	34.5	18-58	113.1	0	0	95 (47)	37.7	n/a	121	--	--
McAlonan et al. (2007)	Child	28 (100)	9.9	6-13	109.9	100	n/a	31 (100)	9.6	6-13	116.5	R MFG, L/R SFG, R GP, precuneus, L IPL, occipital gyrus, R cerebellum vermis	--
Onnink et al. (2014)	Adult	119 (39)	36.3	n/a	107.5	69	n/a	107 (42)	36.9	n/a	110.2	--	--
Overmeyer et al.	Child	18 (83)	10.4	8-13	99	94	n/a	16 (94)	10.3	7-14	n/a	R PCC, R SFG, L/R putamen	--

(2001)													
Ramesh & Rai (2013)	Child	15 (26)	16.8	11-20	n/a	n/a	n/a	15 (26)	16.7	11-20	n/a	L CG, R mid-CG, L SFG, L/R medial SFG, L temporal lobe, L middle occipital gyrus, L cuneus, L STG, L supramarginal gyrus	--
Roman-Urrestarazu et al. (2016) ^a	Adult	49 (76)	22.2	20-24	96.6	2	0	34 (50)	22.9	20-24	112.2	L/R caudate	--
Sasayama et al. (2010)	Child	18 (72)	10.6	6-16	90	72	0	17 (71)	10.0	6-14	n/a	L/R amygdala/temporal pole/OFC, L/R occipital cortex, R STS, L parietal cortex, L MFG, L temporal pole, R rectal gyrus, L PHGy	--
Seidman et al. (2011)	Adult	74 (51)	37.3	18-59	116	28	n/a	54 (46)	34.3	18-59	115.8	--	--
Shimada et al. (2015)	Child	17 (88)	10.3	n/a	95.3	n/a	n/a	15 (73)	12.8	n/a	104.1	L putamen	--
Stevens & Haney-Caron (2012)	Child	24 (67)	15.7	12-18	n/a	n/a	n/a	24 (70)	16	12-18	n/a	--	--
Van Wingen et al. (2013)	Adult	14 (100)	32	22-50	104	0	n/a	15 (100)	37	22-50	99	R putamen, R cerebellum	L/R midbrain, R pre-CG
Villemonteix et al. (2015)	Child	33 (55)	10.3	7-13	105.6	0	n/a	24 (50)	10	7-13	109.7	R insula, R MTG,	--
Villemonteix et al. (2015)	Child	20 (80)	10.4	7-13	107.4	100	n/a	24 (50)	10	7-13	109.7	R MFG, R pre-CG	--
Wang et al. (2007)	Child	12 (100)	13.4	n/a	n/a	0	n/a	12 (100)	13.5	n/a	n/a	L parietal lobe, R PFC, R MTG, R BG	R occipital lobe, L posterior lateral ventricle
Yang et al. (2008)	Child	57 (61)	11.1	7-17	196.6	86	n/a	57 (60)	11.7	7-17	n/a	L/R caudate, L/R cerebellum, R calcarine sulcus, L cuneus	--

Note. Thirty independent ADHD VBM datasets, comprising 1283 people with ADHD and 1054 controls, are listed on this table. ^a = In these studies, ASD are exclusion criteria. ^b In this study, children were screened for severe language developmental delay and communication problem with parental interview, clinical history, and clinical observation. List of abbreviations: VBM = voxel-based morphometry, GMV = grey matter volume, y = year, n/a = information not available, stim exp = stimulant exposure, i.e., present or past use of psychostimulant medication, com. ASD = comorbid ASD, R/L = right/left, ACC = anterior cingulate cortex, pre-/post-CG = pre-/post-central gyrus, OFC/G = orbitofrontal cortex/gyrus, PMC = premotor cortex, PCC = posterior cingulate cortex, SFG = superior frontal gyrus, SMA = supplementary motor area, CG = cingulate gyrus, STG = superior temporal gyrus, IPL = inferior parietal lobe, FFG = fusiform gyrus, PHGy = parahippocampal gyrus, MFG = middle frontal gyrus, mid-CG = mid-cingulate gyrus, STS = superior temporal sulcus, MTG = middle temporal gyrus, and BG = basal ganglia.

4.2 Methods

4.2.1 Publication Search

A comprehensive literature search was conducted on the databases PubMed, ScienceDirect, Scopus, and Web of knowledge for studies published up to March 2016 using the search terms related to: (1) ASD, i.e., autism OR autistic OR Asperger OR ASD OR autism spectrum disorder OR pervasive developmental disorder; (2) ADHD, i.e., hyperkinetic OR ADHD or attention-deficit/hyperactivity disorder; (3) VBM; (4) inhibitory function, i.e., inhibition OR stop OR Stroop OR flanker OR go/no-go OR Simon OR interference OR executive function OR switch; and (5) neuroimaging, i.e., fMRI OR MRI. Also reviewed were past meta-analyses to acquire additional publications not identified by the original search. Publications based on whole-brain grey-matter VBM and fMRI data, as opposed to those based on regions of interests (ROI) specified *a priori*, were included. This is so because the latter method would inappropriately bias the present meta-analysis towards particular brain anatomy or functionality (Friston, Rotshtein, Geng, Sterzer, & Henson, 2006). For the functional MRI studies, contrasts comparing inhibitory function (i.e., stop, no-go, incongruent or switch trials) against control conditions (i.e., go, oddball, failed stop, congruent or repeated trials) were included. Excluded were studies that: (1) involved fewer than ten participants, deemed as having insufficient power in neuroimaging investigations (Cubillo et al., 2014; Desmond & Glover, 2002; Nakao et al., 2011); (2) included duplicate data already reported in other publications; (3) focused on individuals with IQ outside the normal range, i.e., studies exclusively involving individuals with intellectual disability or IQ above norm; (4) lacked patient-group or typically developing controls; (5) did not report information for the peak coordinates in the relevant contrasts. The present meta-

analysis observed the “Meta-analysis of Observational Studies in Epidemiology” (MOOSE) guidelines (Stroup et al., 2000).

4.2.2 Materials

The seed-based *d* Mapping (SDM) software package was used to meta-analyse the differences in the regional GMV or BOLD activation abnormalities reported across studies (www.sdmproject.com; see Radua et al., 2012 for details). SDM combines both the image-based and coordinate-based meta-analytic approaches and accommodates either the statistical parametric map of the MRI/fMRI contrasts of interest or the peak coordinates and effect size (*t*-scores) as input data. This method is more advantageous than approaches that rely exclusively on peak coordinates (e.g. the activation likelihood estimation [ALE] see <https://www.brainmap.org/ale/>) since the effects observed from maps across the brain are more accurate than those estimated from discrete peaks. SDM can also integrate findings from different modalities, e.g., structural and functional neuroimaging, which is desirable for investigating psychiatric disorders (Radua, Romeo, Mataix-Cols, & Fusar-Poli, 2013). In cases where statistical parametric maps are not available, SDM will compute effect size and activation variance maps for the contrasts of interest from the peak coordinate and *t*-scores specified, by convolving an anisotropic kernel (i.e., a distribution function). This kernel should be centred at the peak, such that its neighbouring voxels are assigned values close to the peak and the values reduce as they are further away from the centre. The use of anisotropic kernel allows the estimation of activation at each voxel, adjusted by its correlation with the peak, i.e., the voxels are assigned larger effect size when they are highly correlated with the peak. A novel feature of SDM enables adjustment for correlated datasets (Norman et al., 2016). The latter is especially useful for analysing studies that employ a within-subject design, or investigate equivalent

underlying cognitive functions, through several fMRI tasks using largely overlapping groups of participants.

4.2.3 Statistical Methods

The population characteristics of participants included in this meta-analysis were explored using STATA 14 (StataCorp, 2015). Distributions of sex, age, and IQ amongst ASD, ADHD, and their respective control groups, were compared using sample-size weighted *F*-tests to examine differences in IQ, age, and sex. Pairwise comparisons between the ASD and ADHD group were conducted using sample-size weighted *t*-tests. “Within-disorder” meta-analyses were first conducted using SDM to find the consistent GM volume and functional abnormalities associated with ASD or ADHD relative to controls. In the next step, comparative “between-disorder” meta-analyses were conducted using a linear model for examining differences of GM or functional activations abnormality between the ASD and ADHD samples, each relative to healthy controls, incorporating the sex and IQ as covariates to account for their differences in the ASD and ADHD samples. To reduce the effect of these demographic confounders in the findings, these comparative meta-analyses were repeated in a subset of samples matched in age, sex, and IQ. These matched samples were identified using an algorithm that iteratively computed group differences for the above factors in all possible combinations of $n-k$ studies (where k started from 1) and selected one combination of those differences that had the largest *p*-value below a threshold of .05. Throughout the iteration process, the number of ASD and ADHD studies was kept balanced, and the exclusion of studies incorporating continuous *t*-maps were avoided as they were more powered to detect differences between groups compared to data relying on discrete peak coordinates.

Conjunction analyses were used to investigate regions with overlapping or mutually exclusive GM volume and functional activations abnormalities. These

analyses were used within each disorder group relative to controls, and between the disorder groups. Meta-regressions were conducted to analyse the relationships between GM volume or functional activations, and the proportion of participants exposed to psychostimulant medication. A statistical threshold of $p < .005$ (with a cluster extent of 20 voxels) was used in the meta-analysis while a threshold of $p < .0005$ was used for the meta-regressions. A jack-knife sensitivity analysis (where analyses were repeated leaving one dataset out and replaced in the next run each time) was completed to assess the replicability of findings. The analyses identified whether the clusters differentiating the ASD or ADHD samples from their control groups remained significant when one of the studies taken of the set. The Egger's tests were computed within each significant cluster that differentiated cases from controls to assess potential publication bias in the findings.

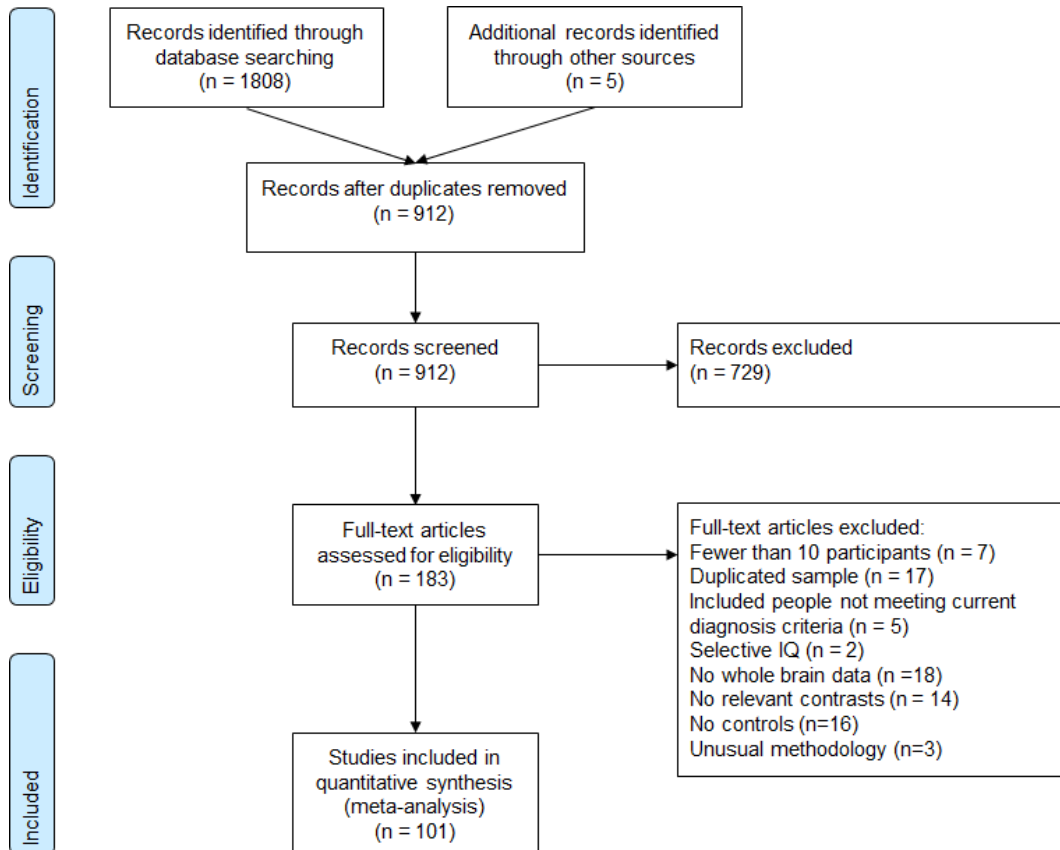
4.3 Results

4.3.1 Search Results and Sample Characteristics

From the database searches, 1808 records were retrieved, and five further records were identified from past meta-analyses. After duplicates were removed, 912 records remained and were screened, resulting in 183 full-text articles assessed for eligibility, and 101 included in the meta-analysis. Of the full-text articles excluded: seven consisted of publications with fewer than ten participants (Epstein et al., 2007; Karch et al., 2010; Langleben et al., 2006; Pironti et al., 2014; Schulz, Tang, et al., 2005; Schulz, Newcorn, Fan, Tang, & Halperin, 2005; Zang et al., 2005); 17 included samples already used in other publications (Almeida Montes et al., 2011; Burgess et al., 2010; Calderoni et al., 2012; Depue, Burgess, Bidwell, Willcutt, & Banich, 2010; Dibbets, Evers, Hurks, Marchetta, & Jolles, 2009; Durston et al., 2003; Ecker et al., 2010; Gori et al., 2015; Lim et al., 2013; Rubia, Cubillo, et al.,

2010; Rubia et al., 2008; Rubia, Halari, et al., 2010; Rubia, Halari, Smith, et al., 2009; Solomon et al., 2009; D. van der Meer et al., 2015; van Rooij & Buitelaar, 2015; Villemonteix, De Brito, Slama, et al., 2015); five with individuals in remission

Figure 4-1: Flow diagram of literature search and study selection process



Note. This literature search included the databases PubMed, ScienceDirect, Scopus and Web of knowledge for studies published up to 16 March 2016. See text for further details.

or not meeting the criteria for current ADHD (Godinez et al., 2015; Schneider et al., 2010; Schulz et al., 2014; van 't Ent et al., 2007, 2009); two were selective of IQ, that is, including individuals with delayed development only (Riva et al., 2013) or individuals with above average IQ only (Riedel et al., 2014); 18 did not provide whole brain data (Belle et al., 2015; Bledsoe, Semrud-Clikeman, & Pliszka, 2009; Braet et al., 2009; Chiu et al., 2008; de Mello et al., 2013; Dillo et al., 2010; Fitzgerald et al., 2015; Garrett et al., 2008; Goddard, Swaab, Rombouts, & van Rijn,

2015; Makris et al., 2015; Padmanabhan et al., 2015; Pironti et al., 2014; Pliszka et al., 2006; Richter et al., 2015; Salmond et al., 2005; Schwerdtfeger et al., 2013; Vaidya, Bunge, Dudukovic, & Zalecki, 2005; Wolfe, Auzias, Deruelle, & Chaminade, 2015); 14 did not provide relevant contrasts (Beacher et al., 2012; Bush et al., 1999; Dichter & Belger, 2007; Durston et al., 2007; Goldberg et al., 2011; R. C. Mulligan et al., 2011; Posner et al., 2011; Salmond, de Haan, Friston, Gadian, & Vargha-Khadem, 2003; Semrud-Clikeman et al., 2000; Spinelli, Vasa, et al., 2011; Suskauer et al., 2008; Vaidya et al., 1998; Vasic et al., 2014; S. Wang et al., 2013) and 16 did not include typically developing controls (Beauregard & Levesque, 2006; Bédard et al., 2003, 2015; Brown et al., 2010; Bush et al., 2008, 2013; Hoekzema et al., 2010; Lee, Han, Lee, & Choi, 2010; Lévesque, Beauregard, & Mensour, 2006; Parks et al., 2009; Proal et al., 2011; Rasmussen et al., 2015; Salmond et al., 2007; Schulz et al., 2012; Solanto, Schulz, Fan, Tang, & Newcorn, 2009; Sotnikova et al., 2012). Three other studies used methods outside the inclusion criteria, i.e., using the GNG preceded by emotional induction (Hwang et al., 2015) and using a primarily target detection task modified to include response inhibition element (Cerullo et al., 2009). One structural investigation not using the VBM method was also excluded (Sowell, Thompson, et al., 2003).

The 101 selected articles produced 13 independent ASD fMRI datasets (208 people with ASD and 215 controls), 37 ASD VBM datasets (comprising 1059 people with ASD and 1077 controls), 28 ADHD fMRI datasets (623 people with ADHD and 607 controls), and 30 ADHD VBM datasets (1283 people with ADHD and 1054 controls). Demographic information such as sex, age, and IQ are presented on Table 4-5. Sample-size weighted univariate ANOVAs applied to the fMRI inhibition studies indicated no group difference in age, $F(3, 37) = .72, p = .54$ or sex, $F(3, 37) = 2.0, p = .13$, but IQ differed across groups significantly, $F(3, 31) = 10.9, p < .0001$. Post-hoc comparisons showed that the ASD had higher IQ, $t(33) = 2.9, p = .007$

than the ADHD. Equivalent analyses of the VBM studies indicated similarly no group differences in age, $F(3, 63) = .63$, $p = .60$, although there were differences in sex, $F(3, 62) = 7.1$, $p = .0003$, and, based on the available data, in IQ, $F(3, 51) = 20.9$, $p < .0001$. Post-hoc comparisons indicated that there were more males in the ASD than the ADHD samples, $t(65) = 4.3$, $p < .001$, although the difference in IQ was not apparent between the ASD and the ADHD VBM samples, $t(53) = .04$, $p = .97$ (see Table 4-5). To account for these differences, all analyses were covaried in the first instance for sex and IQ.

Table 4-5: Characteristics of overall samples and IQ-, sex-, and age-matched subsamples

	ASD	ADHD	ASD con	ADHD con
(A) Overall study samples				
fMRI – inhibition				
<i>N</i>	208	623	215	607
% males	88	78	87	69
Mean age (range), y	20.4 (7-52)	17.4 (7-50)	20.4 (7-52)	17.9 (7-50)
Mean FSIQ (SD)	109 (6.0)	102 (8.3)	116 (5.1)	104 (24.1)
VBM				
<i>N</i>	1059	1283	1077	1054
% males	90	68	89	65
Mean age (range), y	18.3 (3-58)	21.3 (6-59)	18.0 (2-59)	21.5 (6-59)
Mean FSIQ (SD)	104 (8.1)	103 (5.7)	110 (5.8)	110 (5.4)
(B) Matched subsamples				
fMRI – inhibition				
<i>N</i>	208	390	215	406
% males	88	84	87	82
Mean age (range), y	20.4 (7-52)	16.4 (7-42)	20.4 (7-52)	16.5 (7-41)
Mean FSIQ (SD)	109 (6.0)	103 (8.2)	116 (5.1)	108 (17.5)
VBM				
<i>N</i>	554	652	600	602
% males	83	79	81	79
Mean age (range), y	16.3 (3-52)	15.8 (6-55)	16.5 (2-52)	16.3 (6-52)
Mean FSIQ (SD)	102 (7.0)	102 (7.9)	109 (6.7)	106 (6.3)

Note. *N* = overall number of subjects, ASD con = mean characteristics of controls in the ASD studies, ADHD con = controls in the ADHD studies, VBM = voxel-based morphometry, fMRI = functional Magnetic Resonance Imaging, % males = proportion of males among the samples, y = year, FSIQ = full scale IQ, and SD = standard deviation.

4.3.2 Differences in Brain Activations during Inhibition

4.3.2.1 ASD fMRI

During inhibition, individuals with ASD relative to controls showed decreased activation in several clusters, including the ACC/midcingulate/dmPFC, left dlPFC, left parahippocampal gyrus/FFG reaching into the cerebellum, right AI/IFG, left IPL, and right PMC areas. Enhanced activation was observed relative to controls in the precuneus/paracentral lobule, right inferior occipital/FFG, and right dlPFC. Increased age was associated with increased activation in the precuneus (Montreal Neurological Institute [MNI] coordinates: -4, -40, 52; $Z = 2.17$, $p < .0001$, 141 voxels), and reduced activation in the left dmPFC/SMA (BA32, 6; MNI coordinates: -8, 20, 46; $Z = -1.37$, $p < .0005$, 73 voxels).

4.3.2.2 ADHD fMRI

Individuals with ADHD, relative to controls, showed decreased activation in several clusters consisting of the right AI and putamen reaching into the IFG and STL, the left MTG, the right caudate and the left pre-CG. Increased activation in the ADHD group relative to typically developing controls was found at the anterior SMA. Exposure to stimulant was associated with increased activation in the right MTL/STL (BA22) regions (MNI coordinates: 58, -16, -10; $Z = 1.57$, $p < .0005$, 27 voxels) and the right IFG (BA47; MNI coordinates: 44, 24, -10; $Z = 1.58$, $p < .0005$, 16 voxels). Increased age was associated with increased activations in the right caudate nucleus (MNI coordinates: 8, 10, 6; $Z = 1.09$, $p < .0001$, 198 voxels) and reduced activations in the right STG/MTG (BA22; MNI coordinates: 56, -18, -4; $Z = -1.99$, $p < .0001$, 198 voxels).

Table 4-6: Brain activations abnormalities during inhibition in ASD, ADHD, and their comparisons

Contrasts	MNI coord. x, y, z	SDM Z	p-value	Voxels No	Brodmann areas
A. ASD vs. TD					
ASD < TD					
ACC/midcingulate/dmPFC	-2, 34, 22	1.82	<.00005	1895	24, 32, 9
L dIPFC/IFG	-44, 32, 26	1.79	<.0001	571	46, 9
L parahippocampal gyrus/FFG/ cerebellum	-14, -46, -10	1.39	<.005	288	19, 36, 37
L IPL	-34, -46, 52	1.33	<.005	205	40
R PMC	42, 12, 46	1.51	<.0005	185	6, 8
R AI/IFG	40, 16, -6	1.27	<.005	59	13, 47
ASD > TD					
Precuneus/paracentral lobule	-4, -40, 54	1.34	<.00005	793	4, 5, 7
R occipital lobe/FFG	36, -66, -10	1.51	<.00005	413	19, 18, 37
R IFG triangular part/MFG	42, 26, 20	1.20	<.001	150	45, 46
B. ADHD vs. TD					
ADHD < TD					
R AI/putamen/pallidum/STL	32, 16, 0	1.44	<.001	586	--
L MTL/STL	-50, -18, -10	1.85	<.0005	404	21, 22, 38
R caudate nucleus	8, 10, 6	1.24	<.005	77	--
L pre-CG	-48, -10, 56	1.24	<.005	17	4
R IFG	42, 28, -14	1.15	<.005	14	47
ADHD > TD					
L medial SFG	-8, 2, 52	1.11	<.005	116	6/8
C. ASD (vs. TD) vs ADHD (vs. TD)					
ASD (vs. TD) < ADHD (vs. TD)					
<i>ACC/midcingulate/dmPFC*</i>	0, 32, 22	1.76	<.00005	2009	32, 24, 8, 9
<i>L IPL/SPL*</i>	-32, -46, 54	1.40	<.0005	638	40, 7
<i>L dIPFC/IFG*</i>	-40, 34, 28	1.08	<.005	228	46, 9
<i>R PMC*</i>	40, 12, 48	1.03	<.005	112	6
L lingual gyrus	-28, -68, 6	1.06	<.005	22	17
ASD (vs. TD) > ADHD (vs. TD)					
R MTG	54, -16, -8	1.19	<.001	913	21
<i>Precuneus*</i>	2, -44, 48	1.11	<.005	439	7
<i>R occipital lobe/FFG*</i>	36, -70, -8	1.33	<.0005	275	19, 37
<i>R IFG triangular part/MFG*</i>	44, 22, 18	1.13	<.005	142	45, 44

Note. * Italic and bold print = Differences survived subgroup meta-analysis involving samples matched in age, sex, and IQ.

4.3.2.3 Comparisons of fMRI in ASD Versus ADHD

Covarying for sex and IQ, individuals with ASD displayed disorder-specific reduced activation in comparison to the ADHD group, both relative to controls, in the ACC/dmPFC, and left dIPFC, as well as in the left IPL and right PMC. Reduced activations in the left lingual gyrus and right MTG did not survive subgroup analyses. People with ADHD showed disorder-specific reduction relative to ASD in

the right IFG triangular part. Conjunction analyses revealed shared under-activations between the ASD groups and the ADHD groups, relative to TD controls, in the right insula reaching into the right IFG orbital part (BA47; MNI coordinates: 36, 16, 0; 110 voxels). Conjunction analyses also suggested “disjunctive” relationship in the left medial SFG, where over-activations are associated with the ADHD groups, but under-activations are associated with the ASD groups relative to controls (MNI coordinates: -4, 36, 38; 19 voxels). This finding should be taken cautiously, however, as there was no indication of ASD- or ADHD-specific abnormalities in that region.

4.3.3 Regional Differences in GMV

4.3.3.1 ASD VBM

Relative to controls, individuals with ASD showed reduced GMV in the ACC/mPFC, right parahippocampal gyrus/uncus, left cerebellum and thalamus. Enhanced GMV was found in the left temporal lobe, in the middle/inferior/superior temporal area and the temporal pole, right IPL, left precuneus, left vmPFC/caudate, and left PCC, and a cluster at the left superior frontal gyrus (SFG; Table 4-7[A]). Age did not influence the findings of GMV deficits in ASD.

4.3.3.2 ADHD VBM

Individuals with ADHD showed decreased GMV relative to control in a large cluster comprising of vmOFC/vmPFC/rdACC extending deep into the right caudate, in the right putamen/pallidus/posterior insula, left IFG reaching into the left STG, left occipital gyrus/cuneus, a cluster in the left precuneus and right MFG. No GMV increase was found among individuals with ADHD with respect to controls (Table 4-7[B]). Meta-regression analyses revealed positive associations between psychostimulant exposure and GMV in a cluster at the vmPFC (MNI coordinates: -2,

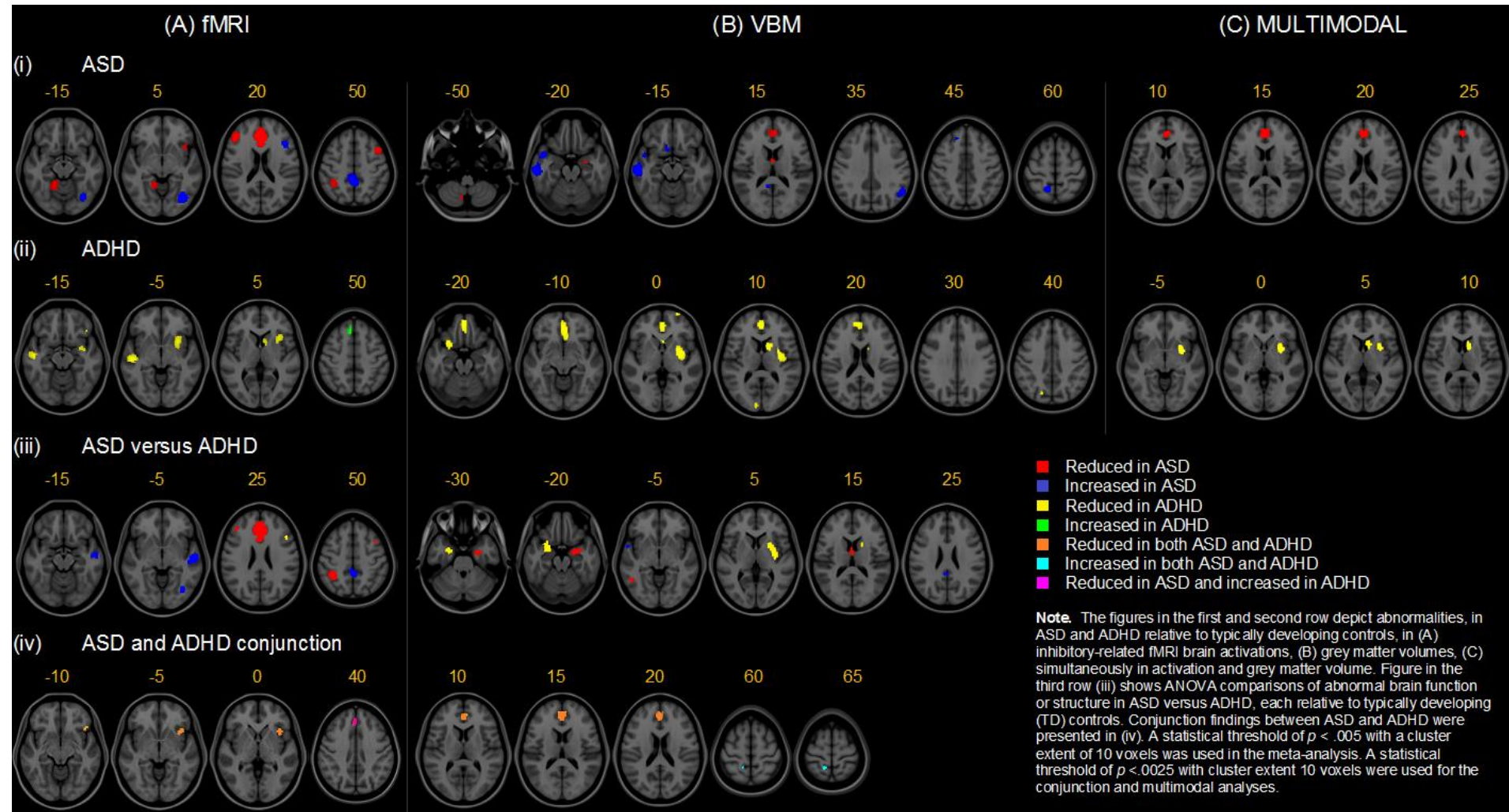
52, -26; $Z = 2.11$, $p < .000005$, 326 voxels) and negative associations at the left IFG (BA 47; MNI coordinates: -26, 16, -22; $Z = -2.11$, $p < .0005$, 32 voxels) and at the right olfactory cortex (BA 25; MNI coordinates: 2, 20, -2; $Z = -2.03$, $p < .0005$, 19 voxels). Increased age was associated with decreased GMV in the vmOFC regions (MNI coordinates: -4, 54, -26; $Z = -1.38$, $p < .0001$, 93 voxels).

Table 4-7: Abnormalities of GMV in ASD, ADHD, and their comparisons

Contrasts	MNI Coord. x, y, z	SDM Z	p-value	Voxels no	Brodmann areas
A. ASD vs. TD					
ASD < TD					
rdACC/dmPFC	4,42,18	1.44	<.005	168	9, 24, 32
R parahippocampal gyrus/uncus	24, -8, -22	1.35	<.005	51	28, 34
L cerebellum hemispheric lobule VIII/IX	-8, -66, -48	1.28	<.005	30	--
Thalamus	0, -6, 16	1.34	<.005	20	--
ASD > TD					
L MTL/ITL/STL/temporal pole	-60, -22, -16	2.42	<.000005	893	21, 20, 38
R angular gyrus/IPL	52, -58, 34	1.72	<.001	306	39, 40
L precuneus	-12, -54, 62	1.89	<.0005	146	5, 7
L vmPFC/caudate	-12, 18, -8	1.68	<.001	126	25
L PCC	-6, -48, 20	1.65	<.001	106	23, 29, 30
L SFG	-16, 34, 42	1.56	<.005	27	8
B. ADHD vs. TD					
ADHD < TD					
vmOFC/vmPFC/rdACC/ R caudate nucleus	0, 50, -22	1.97	<.001	1636	11, 10, 32, 9
R Putamen/pallidus/posterior insula	30, -4, 4	2.24	<.0005	716	13
L IFG/STG	-26, 16, -22	2.14	<.0005	170	47, 38
L occipital gyrus/cuneus	-10, -94, 12	1.60	<.005	37	18
L precuneus	-18, -72, 38	1.67	<.005	27	7
R MFG/dIPFC	28, 66, 0	1.78	<.005	20	10
ADHD > TD					
NIL	--	--	--	--	--
C. ASD (vs. TD) vs ADHD (vs. TD)					
ASD (vs. TD) < ADHD (vs. TD)					
R hippocampus/uncus	24, -6, -22	1.21	<.0005	227	28, 34
Thalamus*	-2, -4, 16	1.12	<.001	94	--
L posterior ITG	-50, -56, -6	1.04	<.005	71	37
ASD (vs. TD) > ADHD (vs. TD)					
R putamen/pallidus/posterior insula*	28, -4, 8	2.23	<.0001	465	--
L STG/IFG/uncus/hippocampus	0, 48, -20	1.75	<.005	242	38, 47, 28, 34
L STG/temporal pole	-24, -6, -26	1.53	<.005	34	22
R caudate nucleus*	18, 8, 14	1.79	<.001	32	--
L PCC*	-4, -44, 24	1.52	<.005	35	23, 30

Note. * Italic and bold print = Differences survived subgroup meta-analysis involving samples matched in age, sex, and IQ.

Figure 4-2: Summary of functional, structural, and multimodal abnormalities in the ASD and ADHD groups relative to TD



4.3.3.3 Comparisons of GMV Deficits in ASD versus ADHD

Table 4-7(C) presents the findings of the ANCOVA analysis covarying for sex and IQ. Disorder-specific reduction of GMV was found in the ASD relative to the ADHD group in the thalamus, each clinical group relative to their controls. Disorder-specific GMV reductions in ADHD relative to ASD samples were found in the right putamen/pallidus/posterior insula, right caudate nucleus, and left PCC. Differences in the GMV in the left and right temporal and IFG regions between ASD and ADHD did not survive the subgroup meta-analysis matched for age, sex and IQ (Table 4-7[C]). Conjunction analyses revealed shared reduction of the GMV between ASD and ADHD in the rACC (MNI coordinates: 0, 42, 16; 292 voxels) and increased GMV in a cluster in the precuneus (MNI coordinates: -14, -48, 66; 25 voxels).

4.3.4 Multimodal VBM and fMRI Analyses

An overlapping cluster of reduced GMV and functional under-activation during inhibition tasks was found among individuals with ASD in the rdACC/mPFC (MNI coordinates: 4, 42, 18; 390 voxels). In participants with ADHD, co-occurring reduced GMV and functional under-activation were found in two clusters, i.e., in the right putamen/AI (MNI coordinates: 30, 4, 0; 240 voxels) and the right caudate nucleus (MNI coordinates: 10, 10, 8; 194 voxels). There were no shared abnormalities in the GMV, and functional activations in the ASD relative to the ADHD, both compared to their respective controls (Figure 4-2[C]).

4.3.5 Jack-knife Reliability Analyses

The jack-knife reliability analyses showed that fMRI under-activations in the rACC/dmPFC and left dlPFC/mPFC regions among ASD studies were fully replicable in all 13 study combinations (Table 4-8). The fMRI findings among ADHD studies were mostly replicable in 25-27 of the 28 possible combinations in the right

insula/ putamen/STL, left MTL/STL, right caudate, left precentral gyrus, and left medial SFG (Table 4-9). The findings of enlarged GMV in left MTL, left precuneus, and left PCC among ASD was highly replicable as they were preserved throughout all 37 combinations of studies, whereas findings of enlarged GMV in the right IPL, left PCC and left SFG were replicable in 34 to 36 possible study combinations (Table 4-10). Among the ADHD studies, reduced GMV in the right putamen/pallidum/insula, vmOFC/vmPFC/rACC/ right caudate and right SFG were most replicable and were preserved throughout all 30 combinations of studies (Table 4-11). The reduced GMV in the left IFG and precuneus were preserved in 29 combinations of studies, while the reduced GMV in the cuneus/middle occipital gyrus were retained in the 28 study combinations.

Table 4-8: Jack-knife analyses of anomalous clusters in the ASD fMRI studies

Study excluded	Under-activation						Over-activation		
	rACC/ dmPFC	L dlPFC /MFC	L HG/ FFG/ cereb ellum	L IPL	R PMC/ MFC	R IFG/ AI	Precune us	R occipital lobe	R dlPFC/ MFC
	0, 32, 22	-44, 34, 26	-14, - 46, - 10	-34, - 46, 52	42, 12, 46	40, 16, -6	-4, -40, 54	36, -66, - 10	42, 26, 20
Ambrosino et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chantiluke et al. (2015)	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes
Daly et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Duerden et al. (2013)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Fan et al. (2012)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kana et al. (2007)	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes
Kennedy et al. (2006)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Schmitz et al. (2006)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Shafritz et al. (2008)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Shafritz et al. (2015)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Solomon et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vaidya et al. (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yerys et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Note. List of Abbreviations L = left, R= right, rdACC = rostradorsal anterior cingulate cortex, dmPFC = dorsomedial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex, HG = hippocampal gyrus, MFC = middle frontal cortex, FFG = fusiform gyrus, IPL = inferior parietal lobe, PMC = premotor cortex, IFG = inferior frontal gyrus, AI = anterior insula.

Table 4-9: Jack-knife analyses of anomalous clusters in the ADHD fMRI studies

Study excluded	Under-activation					Over-activation
	R insula/ putamen/S TL	L MTL/STL	R caudate nucleus	L pre-CG	R vlPFC	L medial SFG
	32, 16, 0	-50, -18, - 10	8, 10, 6	-48, -10, 56	42, 28, -14	-8, 2, 52

Banich et al. (2009)	Yes	Yes	Yes	Yes	Yes	Yes
Bhajibwala et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes
Booth et al. (2005)	Yes	Yes	No	Yes	Yes	Yes
Carmona et al. (2012)	Yes	Yes	Yes	Yes	Yes	Yes
Chantiluke et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes
Chou et al. (2015)	Yes	Yes	Yes	Yes	No	Yes
Congdon et al. (2010)	Yes	Yes	Yes	Yes	Yes	Yes
Cubillo et al. (2011)	Yes	Yes	Yes	Yes	No	Yes
Cubillo et al. (2014)	Yes	Yes	Yes	Yes	No	Yes
Dibbets et al. (2010)	Yes	Yes	Yes	Yes	Yes	Yes
Durston et al. (2006)	Yes	Yes	Yes	Yes	Yes	Yes
Iannaccone et al. (2015)	Yes	Yes	Yes	Yes	No	Yes
Janssen et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes
Konrad et al. (2006)	No	Yes	Yes	Yes	Yes	Yes
Kooistra et al. (2010)	Yes	Yes	Yes	Yes	Yes	Yes
Ma et al. (2012)	Yes	Yes	Yes	Yes	No	Yes
Passarotti et al. (2010)	Yes	Yes	Yes	Yes	No	Yes
Peterson et al. (2009)	Yes	Yes	No	Yes	Yes	No
Rubia et al. (2005)	Yes	Yes	Yes	Yes	No	Yes
Rubia et al. (2011)	Yes	Yes	Yes	Yes	No	Yes
Schulz et al. (2004)	Yes	Yes	Yes	No	Yes	Yes
Sebastian et al. (2012)	Yes	Yes	Yes	Yes	No	Yes
Siniatchkin et al. (2012)	Yes	Yes	No	Yes	Yes	Yes
Smith et al. (2006)	Yes	Yes	Yes	Yes	Yes	Yes
Spinelli et al. (2011)	Yes	Yes	Yes	Yes	No	Yes
Tamm et al. (2004)	Yes	Yes	Yes	Yes	Yes	Yes
Van Rooij et al. (2015) *	Yes	No	Yes	No	Yes	No
Van Rooij et al. (2015) *	Yes	Yes	Yes	Yes	Yes	Yes

Note. List of Abbreviations L = left, R= right, STL = superior temporal lobe, MTL = middle temporal lobe, pre-CG = precentral gyrus, vIPFC = ventrolateral prefrontal cortex, SFG = superior frontal gyrus; * Van Rooij et al. (2015) = datasets were separated between children and adults.

Table 4-10: Jack-knife analyses of anomalous GMV clusters in the ASD studies

Study excluded	Reduced GMV				Enlarged GMV					
	rACC / mPFC	R HG/uncus	L cerebellum	Thalamus	L MTL	R IPL	L pre-cuneus	L vmPFC/caudate	L PCC	L SFG
	4,42, 18	24, -8, -22	-8, -66, -48	0, -6, 16	-60, -22, -16	52, -58, 34	-12, -54, 62	-12, 18, -8	-6, -48, 20	-16, 34, 42
Abell et al. (1999)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Boddaert et al. (2004)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bonilha et al. (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Brieber et al. (2007)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cheng et al. (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Craig et al. (2007)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
D'Mello et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Ecker et al. (2012)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Foster et al. (2015)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Freitag et al. (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Greimel et al. (2013)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Groen et al. (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hyde et al. (2010)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Itahashi et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kaufmann et al. (2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ke et al. (2008)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kosaka et al. (2010)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kurth et al. (2011)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Kwon et al. (2004)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Langen et al. (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lim et al. (2015)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lin et al. (2015) *	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Lin et al. (2015) *	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lin et al. (2015) *	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McAlonan et al. (2002)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McAlonan et al. (2008)	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mengotti et al. (2011)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Mueller et al. (2013)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Poulin-Lord et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Poustka et al. (2012)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Radeloff et al. (2016)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Retico et al. (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Rojas et al. (2006)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schmitz et al. (2006)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Toal et al. (2010)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Waiter et al. (2004)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wilson et al. (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Note. List of Abbreviations L = left, R= right, rACC = rostral anterior cingulate cortex, mPFC = medial prefrontal cortex, HG = hippocampal gyrus, MTL = middle temporal lobe, IPL = inferior parietal lobe, vmPFC = ventromedial prefrontal cortex, PCC = posterior cingulate cortex, SFG = superior frontal gyrus. * Lin et al. (2015) = datasets were separated between children, adolescents, and adults.

Table 4-11: Jack-knife analyses of reduced GMV clusters in the ADHD studies

Study excluded	vmOFC/ vmPFC/ rACC/R caudate	R putamen/ insula	L IFG (BA47)	L cuneus/ middle occipital gyrus (BA18)	L precuneus (BA7)	R SFG
	0, 50, -22	30, -4, 4	-26, 16 -22	-10, -94, 12	-18, -72, 38	28, 66, 0
Ahrendts et al. (2011)	Yes	Yes	Yes	Yes	Yes	Yes
Almeida Montes et al. (2010)	Yes	Yes	Yes	Yes	Yes	Yes
Amico et al. (2011)	Yes	Yes	Yes	Yes	Yes	Yes
Bonath et al. (2016)	Yes	Yes	Yes	Yes	Yes	Yes
Bralten et al. (2016)	Yes	Yes	No	Yes	No	Yes
Brieber et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes
Carmona et al. (2005)	Yes	Yes	Yes	Yes	Yes	Yes
Depue et al. (2010)	Yes	Yes	Yes	Yes	Yes	Yes
He et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes
Iannaccone et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes
Johnston et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes
Kappel et al. (2015) *	Yes	Yes	Yes	Yes	Yes	Yes
Kappel et al. (2015) *	Yes	Yes	Yes	Yes	Yes	Yes
Kobel et al. (2010)	Yes	Yes	Yes	Yes	Yes	Yes
Li et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes
Lim et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes
Maier et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes
McAlonan et al. (2007)	Yes	Yes	Yes	Yes	Yes	Yes
Onnink et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes
Overmeyer et al. (2001)	Yes	Yes	Yes	Yes	Yes	Yes
Ramesh et al. (2013)	Yes	Yes	Yes	No	Yes	Yes
Roman-Urrestarazu et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes
Sasayama et al. (2010)	Yes	Yes	Yes	Yes	Yes	Yes
Seidman et al. (2011)	Yes	Yes	Yes	Yes	Yes	Yes
Shimada et al. (2016)	Yes	Yes	Yes	Yes	Yes	Yes
Stevens et al. (2012)	Yes	Yes	Yes	Yes	Yes	Yes
Van Wingen et al. (2013)	Yes	Yes	Yes	Yes	Yes	Yes
Villemonteix et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes
Wang et al. (2007)	Yes	Yes	Yes	Yes	Yes	Yes
Yang et al. (2008)	Yes	Yes	Yes	No	Yes	Yes

Note. List of Abbreviations L = left, R= right, vmOFC = ventromedial orbital prefrontal cortex, vmPFC = ventromedial prefrontal cortex, rACC = rostral anterior cingulate cortex, IFG = inferior frontal gyrus, SFG = superior frontal gyrus. * Kappel et al. (2015) = datasets were separated between children and adults.

4.3.6 Egger Tests for Publication Bias

Egger test revealed publication bias for one cluster found in the fMRI meta-analysis of the ASD samples at the rACC/dmPFC ($p = .0012$) although no publication bias was observed in any other clusters or in the clusters of ASD-related GMV abnormalities. Publication bias among the ADHD fMRI studies was detected for one brain activation cluster in the left medial SFG ($p = .045$), although no publication bias was found with respect to the ADHD-related GMV abnormalities. The publication bias would indicate underreporting of non-significant finding in these clusters.

4.4 Discussion

During inhibition, people with ASD displayed disorder-specific under-activation relative to the ADHD group in ACC/midcingulate/dmPFC, left MFG/dlPFC, left IPL/SPL, right PMC, and disorder-specific increased activation in the precuneus, and right occipital lobe/FFG. People with ADHD showed disorder-specific decreased activation in the right IFG triangular part/MFG during inhibition relative to the ASD group, both with respect to typical developing controls. Conjunction analyses of fMRI data revealed shared under-activations between ASD and ADHD relative to controls in a cluster in the right insula reaching into the IFG orbital part (BA 47). Structurally, ASD-specific GMV reductions were found in the thalamus relative to ADHD and an ADHD-specific reduction was observed relative to ASD, both with respect to controls, in the right putamen/caudate/posterior insula, right caudate nucleus and left PCC. Conjunction analyses of VBM data revealed shared GMV reduction between ASD and ADHD relative to controls in the mPFC/ACC area, and shared GMV increase in the precuneus. Within group, the multimodal analyses showed that GMV reduction in the mPFC/ACC among individuals with ASD coincided with functional under-activation in the same region, whilst among

individuals with ADHD, GMV reduction coincided with functional under-activation in the right caudate and right putamen/insula.

4.4.1 Disorder-specific and Shared Deficits during Inhibition

Among the regions functionally impaired in ASD, only the rdACC/dmPFC and the PMC are typically activated during inhibition (Cai et al., 2014; Swick, Ashley, & Turken, 2011). The roles of the dmPFC/dACC, including regions such as the pre-SMA during inhibition are not fully clear, although it is thought that the dmPFC and the IFG, including the opercular, triangular, and some of the orbital parts (BA44, 45, and 47), work together to send a “stop command” via the BG that inhibits the activation of the motor cortex (Aron, 2011, p. e56). The activation of dmPFC/dACC during the inhibitory task could also partly reflect responses to stimulus change during the motor response inhibition task (Botvinick et al., 1999; Braver, 2001; Grahn & Manly, 2012). The dorsal division of the ACC is part of the salience network and is typically activated during detections of salient stimuli, such as conflicts during Stroop task (Botvinick et al., 1999), and low-frequency stimulus presentation in the GNG, target detection, and forced-choice tasks (Braver, 2001), and error processing (Garavan, Ross, Kaufman, & Stein, 2003; Rubia et al., 2005). In ASD, abnormal dACC/dmPFC function is associated with core symptoms of autism, including in social impairment (Monk et al., 2009; Ohnishi et al., 2000) and repetitive behaviour (Shafritz et al., 2008), rendering the conceptualisation of ASD-related difficulties open to either deficits in inhibition, or self-monitoring.

The dlPFC, IPL and precuneus are often activated during inhibition as well as during the attention task (Nee et al., 2007; Swick et al., 2011). The dlPFC, as well as regions such as the vlPFC, dmPFC, and insula are known as the “task-positive” regions, and are typically active during goal-directed tasks. Resting state studies have shown that the dlPFC is part of the executive control network, and its

activation is thought to be related to coordinating responses towards inhibitory sets or task rules (Arnsten & Rubia, 2012; Aron, 2011). The IPL is activated during tasks requiring different aspects of attention including sustained attention (Foucher, Otzenberger, & Gounot, 2004), target or novel stimuli detection (Gur et al., 2007; L. M. Williams et al., 2007), and phasic orienting (Fan, Mccandliss, Fossella, Flombaum, & Posner, 2005). The IPL is also currently thought to bridge the divide between the dorsal and ventral attention networks and serve to both maintain and orient attention (Singh-Curry & Husain, 2009). Finally, the precuneus is one of the main nodes of the DMN, together with the vmPFC, dmPFC, PCC, and the lateral parietal cortex (Raichle, 2015). It is functionally connected to both the DMN and the fronto-parietal network regions such as the dlPFC and the IFG, but activates in an anti-correlated manner relative to these task-positive regions. Reduced deactivation in the DMN during task was found among people with ASD during the Stroop task (Kennedy et al., 2006); during a visual search task, which was found shared with unaffected siblings (M. D. Spencer et al., 2012); and during a sustained-attention task, concomitant to reduced activation in the left dlPFC (Christakou et al., 2013). Overall these findings suggest that ASD-specific increase of self-referential thoughts, or attentional lapses during tasks, may influence the performance of motor and interference inhibition in the population.

The ADHD-specific reduced activation in the right IFG relative to ASD (BA 44/45) is consistent with previous meta-analytic findings (Hart et al., 2013; McCarthy, Skokauskas, & Frodl, 2014; Norman et al., 2016). The IFG is important for inhibition as well as cognitive control (Arnsten & Rubia, 2012). Meta-analytic studies have shown that action cancellation or restraint are most prominently associated with the right IFG activation (Cai et al., 2014; Criaud & Boulinguez, 2013; B. J. Levy & Wagner, 2011), while interference control is associated with bilateral IFG (Derrfuss, Brass, Neumann, & von Cramon, 2005). The right IFG is thought to

implement a “brake” during inhibition (Aron, Robbins, & Poldrack, 2014), since permanent damage or temporary cortical disruption by transcranial magnetic stimulation in this region was able to impair stopping (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Chambers et al., 2006). Recent findings have also suggested that the IFG played role in the early stage of the inhibitory process because its activation predicted individuals’ variations of stop-signal response time (SSRT) but not accuracy during a stop-signal task (Cai et al., 2014). The IFG impairment has also been found to be specific to ADHD relative to OCD in a meta-analysis of inhibition tasks (Norman et al., 2016). It is also ADHD-specific relative to conduct disorder during attention and cognitive control tasks (Rubia, 2011; Rubia, Smith, Halari, et al., 2009). Furthermore the IFG impairment is ADHD-specific relative to paediatric bipolar disorder (Passarotti & Pavuluri, 2011). The present meta-analysis shows that the specificity of reduced activation in IFG, triangular part, may also extend relative to ASD.

The pattern of right-lateralized IFG impairments in ADHD during inhibition is consistent with the view of right-dominant IFG specialisation during inhibition (Aron et al., 2014; Cai et al., 2014; Criaud & Boulinguez, 2013; B. J. Levy & Wagner, 2011). In contrast, this meta-analysis result suggests that during inhibition ASD is specifically associated with reduced activation in the left dIPFC/IFG (among other regions). Atypical hemispheric lateralisation has been reported among individuals with ASD or those with autistic traits. It has been found not only in the context of language where the lack of left-lateralisation of language function such as verbal fluency and language processing has been shown (see, e.g., Floris, Lai, et al., 2016; Kleinhans, Müller, Cohen, & Courchesne, 2008; Saban-Bezelel & Mashal, 2015), but also in the context of motor function deficits (Floris, Barber, et al., 2016), reinforced by findings of marked increase of left-and mixed-handedness among individuals with autism (reviewed by Lindell & Hudry, 2013). In the cognitive domain,

atypical lateralisation have been observed during face and gaze perception (Keehn, Vogel-Farley, Tager-Flusberg, & Nelson, 2015; Tye et al., 2013), spatial attention (English, Maybery, & Visser, 2015), and attention orienting and executive tasks (Rinehart, Bradshaw, Brereton, & Tonge, 2002). The present meta-analysis adds inhibitory control among the variety of cognitive functions that may be atypically lateralised in individuals with ASD.

The conjunction analyses of the fMRI data have shown a shared reduced activation in a small cluster in the right AI, reaching into the orbital part of the IFG (BA47) between the ASD and the ADHD groups. Functionally, the AI has an established role in salience detection (Menon & Uddin, 2010). It is intrinsically connected with the dACC and form the salience network (Seeley et al., 2007; Taylor, Seminowicz, & Davis, 2009), and is also activated in response to internal bodily state and subjective feelings, such as emotional awareness (Picard, Scavarda, & Bartolomei, 2013), pain perception (Ostrowsky, 2002), and empathy (Singer et al., 2006). Therefore, the AI is thought to play a crucial role in interoceptive or self-awareness (A. Craig, 2009; Critchley, Eccles, & Garfinkel, 2013). The AI's role during inhibition is not entirely clear (Aron, 2011), although a previous meta-analysis has shown that activation of the AI and that of the dmPFC (pre-SMA), maximally overlapped during performance of the GNG and the stop-signal tasks (Swick et al., 2011; see also Dambacher et al., 2014), suggesting its importance during both action restraint and cancellation. Significant correlations between the activation in the insula and the stop-signal task SSRT and accuracy are found among children with ADHD. This suggests that the AI activation exerts direct influence on inhibition (Boehler, Appelbaum, Krebs, Hopf, & Woldorff, 2010). Furthermore, a recent structural study has also shown that AI volume is negatively correlated with commissions on the CPT task among children with ADHD, suggesting its association with increased impulsivity in the population (Lopez-

Larson, King, Terry, McGlade, & Yurgelun-Todd, 2012). Most importantly, both AI and the IFG, orbital part, are implicated in motor and interference inhibition deficits in ADHD (Hart et al., 2013; Norman et al., 2016). Therefore, one possible interpretation to the present meta-analytic finding is that the overlapping of impairments in this small cluster reflects common difficulties in salience detection or motor and interference inhibition among individuals in the ASD and ADHD groups.

4.4.2 Disorder-specific and Shared GMV Deficits

Most interesting is the finding of ASD-specific reduced thalamic GMV relative to ADHD. In the first ever neuroanatomic model of ASD, Damasio and Maurer (1978) hypothesised a link between the dorsomedial and anterior nuclei of the thalamus and autism to explain the reduced facial expressiveness in the population. Several studies have indicated that a range of structural features of the thalamus differed between people with ASD relative to controls. For instance, reduced thalamic volume has been found in people with ASD (Tamura, Kitamura, Endo, Hasegawa, & Someya, 2010; Tsatsanis et al., 2003) and the thalamic volume in children and adults with ASD appear not to follow a linear relationship with the total brain volume as is usually observed in the typically developing controls (Hardan et al., 2006, 2008). In studies with much larger ($n \geq 100$) samples of people with ASD, however, thalamic volume was found to not differ relative to controls (Lange et al., 2015; Schuetze et al., 2016), although further analyses of thalamic surface by Schuetze et al. (2016) revealed greater surface area in the left and right thalamus and more concave surface in the right medio-dorsal nucleus in the ASD relative to controls. The thalamus is traditionally seen as a sensory relay. However, observations of patients with thalamic lesions also suggest other roles in social cognition, mood regulation, as well as EF (Carrera & Bogousslavsky, 2006; Ioannidis et al., 2013). In autism, the role of the thalamus is not well-understood. However, Schuetze et al. (2016) have shown recently that the left thalamic surface area among individuals

with ASD was associated with symptom severity. Consistent with these findings, the current meta-analysis shows that thalamic GMV deficit is present in ASD and furthermore, that this deficit is disorder-specific to ADHD.

Enlarged GMV in the left ventral PCC was found in the ASD relative to the ADHD group. This is an important finding in the light of the ASD-specific increased activation in the precuneus during inhibition and the enlarged GMV in the left precuneus in the ASD group relative to controls (see below). Post-mortem studies in individuals with autism show altered PCC cytoarchitecture, reduced γ -aminobutyric acid-A (GABA-A) receptors and benzodiazepine binding sites (Oblak, Gibbs, & Blatt, 2011; Oblak, Rosene, Kemper, Bauman, & Blatt, 2011), which suggest a local inhibitory processing abnormality. As discussed previously, the PCC GMV and precuneus abnormalities in the ASD may point to DMN impairment related to poor attention. This is supported by past findings of failure to deactivate during cognitive tasks (Christakou et al., 2013; Kennedy et al., 2006). The DMN is also thought to be central to the socio-cognitive difficulties in ASD (Murdaugh et al., 2012; Yerys, Gordon, et al., 2015), reinforced by findings of atypical activations in these regions during ToM, emotional awareness, and social processing (Kana et al., 2015; Murdaugh et al., 2012; Salmi et al., 2013; Silani et al., 2008). Further, classifications based on regions implicated in the DMN differentiate individuals with autism from controls with high accuracy (Murdaugh et al., 2012; Uddin et al., 2011). By applying multivariate “searchlight” pattern analysis on VBM data in the ventral PCC, Uddin (2011) classified 24 autistic individuals and 24 controls with 92% accuracy and the region discriminated children with severest communication symptoms from the mildest as judged on the ADI-R. Likewise, Murdaugh (2012) found that the DMN connectivity patterns and its reduced deactivation after ToM task allowed discrimination of 13 individuals with HFA from 14 controls with 96% accuracy. This

suggests a strong association between ASD and DMN structural and functional impairments.

Unlike in previous studies in children and young adults with ASD (Langen et al., 2009, 2014) using manual tracing method of the striatal structures, no increase in the caudate or putamen GMV was found in the present meta-analysis. These conflicting results might be attributed to methodological differences as those studies used manual tracing to delineate the striatal structure in people with ASD before comparing them against controls. While increased striatal volume has also been reported in a few VBM whole-brain studies (Bonilha et al., 2008; Foster et al., 2015; Toal et al., 2010), such a structural difference is lost in the present study. This could be attributed to the lack of power for finding subtle difference in this subcortical structure.

ADHD was associated with disorder-specific GMV reduction relative to ASD in right caudate, putamen and insula. Structural abnormalities in the right caudate/putamen in ADHD have been found in previous meta-analyses (Frodl & Skokauskas, 2012; Nakao et al., 2011). The dorsal BG and insula are part of the ventrolateral frontostriatal saliency and EF networks (Arnsten & Rubia, 2012), which is implicated in sustained attention and inhibitory control frequently impaired in ADHD (Lipszyc & Schachar, 2010; Willcutt et al., 2008). More recently the dorsal striatum is also thought to play a critical role during “proactive” or selective stopping, that is, self-generated inhibitory control (Aron, 2011; Majid, Cai, Corey-Bloom, & Aron, 2013; Zandbelt & Vink, 2010), in contrast to “reactive” stopping that is typically studied in ADHD. Although not often discussed in the ADHD literature, proactive inhibition may be as relevant as reactive inhibition to the condition. Many aspects of inhibitory action in everyday life involve deliberately selective as well as reactive inhibition. For instance, distancing oneself from distracting activities such as checking emails or browsing one’s phone, and reducing instead of picking up speed

at the traffic lights, depend on proactive stopping. Research in proactive stopping in ADHD could further our understanding of the inhibitory mechanism associated with condition. Finally, Norman's (2016) meta-analysis has shown that the GMV in this region is disorder-dissociated between ADHD and OCD where it was reduced in structure in ADHD and enhanced instead in OCD. The current meta-analysis extends these findings by showing that right striatal and insula GMV reductions are also disorder-specific relative to ASD.

Reduced GMV in the rdACC/dmPFC and enhanced GMV in the precuneus were found shared between ASD and ADHD in this meta-analysis. Reduced GMV in dACC, and also bilateral insula, are interestingly shared among patients with schizophrenia, major depression, bipolar disorder, addiction, and obsessive-compulsive disorders (Goodkind et al., 2015), as well as among children with disruptive behaviour (Alegria, Radua, & Rubia, 2016). In this context, the present meta-analysis results might suggest that reduced dACC GMV features transdiagnostically among a wider range of psychiatric conditions including ASD and ADHD. Most interestingly, multimodal analyses of structural and functional data in ASD showed that functional under-activation in the dACC/dmPFC was conjunctive with reduced GMV, suggesting that the functional abnormalities in this region in ASD might be underpinned by structural deficits. As discussed above reduced dACC GMV might affect response monitoring ability, which can negatively influence EF and attention task performances (see Goodkind et al., 2015). Furthermore, reduced GMV in the rdACC/mPFC in ASD and ADHD might be associated with poor top-down regulation of emotion (Bush, Luu, & Posner, 2000; Etkin, Egner, & Kalisch, 2011), which could lead to the unregulated emotionality and temper outbursts typically observed in these populations (Goldin et al., 2013; Mazefsky et al., 2013; Skirrow et al., 2014; Surman et al., 2013).

Shared increase in the precuneus GMV between ASD and ADHD relative to controls is partly in line with the hypothesised shared DMN impairment, although the inhibitory study meta-analysis has shown that functional impairment in this region was ASD-specific, rather than shared with the ADHD group. The current finding of enhanced precuneus GMV in the ADHD groups is consistent with results from previous meta-analyses (Frodl & Skokauskas, 2012; Nakao et al., 2011). The abnormalities of the DMN in ADHD are generally thought to be related to attentional lapses and mind wandering (Christoff et al., 2009; Weissman et al., 2006), as resting-state functional connectivity studies in individuals with ADHD have consistently shown reduced inverse connectivity between the DMN and the frontal regions (Cao et al., 2009; Castellanos et al., 2008; Hoekzema et al., 2014), presumably reflecting a failure in the brain's intrinsic ability for modulating the DMN during a task.

Despite shared structural abnormalities in precuneus between both disorders, DMN abnormalities during inhibition were not found consistently in the ADHD studies. The reason for this finding is unknown given that reduced DMN deactivation has been observed in children and adults with ADHD during a variety of task-based and resting state studies (Dibbets et al., 2010; Liddle et al., 2011; Schulz et al., 2004), shared in some studies with children with ASD (Chantiluke, Barrett, Giampietro, Brammer, Simmons, Murphy, et al., 2015; Christakou et al., 2013; Di Martino et al., 2013). One possible reason could be that the DMN abnormalities in the two disorders are qualitatively different. The meta-analysis results suggested that the reduced DMN suppression was more apparent during inhibitory state in people with ASD, while for people with ADHD this phenomenon might be non-inhibitory specific. Note that only a small proportion of studies in ADHD found reduced precuneus suppression specifically during inhibition trials (e.g., Dibbets et al., 2010; Schulz et al., 2004). In a recent study, Liddle et al. (2011) has shown that

attenuated DMN deactivation in children with ADHD, although reversed by methylphenidate, was in fact non-differentiated across the trial types of a GNG task, suggesting that the phenomenon was associated with a task-positive condition rather than specifically to an inhibitory state. Another possible explanation could be that some tasks are more sensitive to precuneus deactivation than others, given that different inhibitory tasks tap brain activations from slightly different areas (Criaud & Boulinguez, 2013; Nee et al., 2007; Swick et al., 2011). It is possible that the apparent precuneus abnormalities in the ASD samples were a by-product of unequal proportion of studies utilizing specific tasks. Stratifying the analyses according to task types can be done in future meta-analytic studies, although it was not possible to do this in the present analysis due to the limited number of ASD studies. Finally, the relatively small number of ASD studies could have led to low statistical power and, in turn, increased probability of false positive findings in the precuneus. It is thus important to repeat these analyses using larger number of inhibitory studies in ASD samples in the future.

The present findings of abnormalities in ASD and ADHD suggest that they are mostly disorder-specific with relatively few shared abnormalities, at least from the point of view of their inhibitory-related brain function and structural GMV abnormalities. The findings pose the possibility that the two conditions are distinctive and separate, despite being similarly impaired in inhibition according to behavioural studies (Geurts, van den Bergh, et al., 2014; Kuiper et al., 2016). This interpretation is consistent with the distinctive phenomenology of each disorder, as discussed in the literature. ADHD has been thought of as primarily a disorder of inhibitory function with delayed brain structure and function maturation (P. Shaw et al., 2007, 2012; Sripada et al., 2014), affecting the frontal part of the brain as well as subcortical regions such as BG. The GMV in the BG, particularly, has been shown to be age-dependent in a previous meta-analysis. Thus, only ADHD children were

impaired but not older ADHD patients were not (Nakao et al., 2011). Other meta-analytic findings were also suggestive of greater decreases of inhibitory-related activation in the BG in children compared to adults (Hart et al., 2013; Lei et al., 2015), which was confirmed by a meta-regression analysis in the present meta-analysis. ASD on the other hand is conceptualised as atypical brain development. It is characterised by abnormal acceleration of brain growth in the first 2 years especially in the frontal lobe, related to excess cortical neurons, aberrant pattern of connectivity, and belated synaptic pruning (Courchesne et al., 2011; Redcay & Courchesne, 2005). This is supported by post-mortem findings of active neurogenesis in some individuals with autism as well as dysregulated neuronal migration and maturation (Wegiel et al., 2010).

Unlike in ADHD, the impairment of inhibition among individuals with ASD is heterogeneous across neurocognitive studies, neither accounted for by variations of IQ nor age (Kuiper et al., 2016). Two possible explanations can be tentatively offered based on the present meta-analytic findings. First, inhibitory response difficulties among individuals with ASD might be underpinned by a range of neurofunctional impairments, associated with e.g. inhibition, monitoring, set maintenance, sustained and selective attention, or even self-referential thinking, which singularly or in combination has produced variable outcomes of inhibitory performance, including an impaired one. Conversely, the inhibitory difficulties in ADHD are specifically related to under-active right IFG, a key region of action inhibition (Cai et al., 2014; Criaud & Boulinguez, 2013; B. J. Levy & Wagner, 2011). Thus, poor task performance among people with ASD that is mediated by neurofunctional deficits in areas not typically impaired in ADHD would constitute a neurocognitive phenocopy. Second, poor inhibitory performance observed among individuals with ASD as well as ADHD could be associated with common impairments in the right AI and inferior frontal area (orbital part), and possibly in the

precuneus, although the latter was not sufficiently conclusive due to the discrepancy between the structural and the functional findings in the meta-analyses. Implicated in both motor inhibition and interference in ADHD (Hart et al., 2013; Norman et al., 2016), AI and IFC impairment among individuals with ASD might characterise shared impairment and, therefore, reflecting a pleiotropic influence for both disorders.

4.4.3 Meta-analytic Findings within Each Disorder Relative to Controls

In addition to the above disorder-specific and shared findings, several other differences were noted between each disorder group relative to controls. Left cerebellar GMV deficits were found in ASD relative to controls, which were consistent with previous meta-analyses (Cauda et al., 2011; Nickl-Jockschat et al., 2012; Stoodley, 2014). Observations of cerebellar abnormalities among individuals with autism included the hypoplastic cerebellar vermian lobules, judged from MRI scans (Courchesne et al., 1994; Hashimoto, Tayama, Miyazaki, Murakawa, & Kuroda, 1993; Levitt et al., 1999). This was supported by post-mortem findings of reduced number and density of cerebellar Purkinje cells and profound disruption to the olivofloccular circuits (Skefos et al., 2014; Wegiel et al., 2013; Whitney, Kemper, Bauman, Rosene, & Blatt, 2008), which, given the latter's contribution to eye movement control, might explain the atypical gaze in autism (Wegiel et al., 2013). Focal GMV reduction in several cerebellar regions, including the lobule VIII and IX, and anterior lobules I-V have also been found and they correlate with impairments in social interaction among individuals with autism (D'Mello et al., 2015; Hodge et al., 2010; Rojas et al., 2006). These findings suggest that cerebellar deficit is part of the characteristic neuropathology of autism.

The functional and structural findings in ADHD relative to controls showed predominantly reduced activation in the executive networks in the frontal and striatal

regions, which is consistent with the hypothesis of delayed brain maturation (P. Shaw et al., 2007, 2012; Sripada et al., 2014). In addition to the ADHD-specific reduced activations in right IFG relative to ASD during inhibition, reduced activations in left MTL/STL and right AI/putamen/pallidum/STL and right caudate nucleus were also found relative to controls. Interestingly, the multimodal analyses showed that the inhibitory-related striatal impairment coincided with ADHD-specific reduced GMV in these regions, indicating a possible link between the functional impairment and structural deficits of the striatum.

Relative to controls, the ADHD groups also displayed significantly reduced GMV in the vmOFC, which, together with the ventral striatum, were key regions for the top-down motivation control network (Plichta & Scheres, 2014). Studies consistently found under-activated reward-sensitive limbic regions such as ventral and dorsal striatum, during the anticipation of rewards (Kappel et al., 2015; Plichta & Scheres, 2014). Reward receipt was associated with the opposite pattern of increased activation in the ventral or dorsal striatum (Furukawa et al., 2014; Stroehle et al., 2008; Von Rhein et al., 2015), but mixed findings with respect to the vmOFC. With respect the latter, studies have shown under-activated vmOFC among children and adults with ADHD (Cubillo et al., 2012; Dibbets et al., 2009) and also increased activations (Rubia, Halari, Cubillo, et al., 2009; Stroehle et al., 2008; Von Rhein et al., 2015). A possible confounding factor is the co-occurrence of conduct disorder (CD) among individuals with ADHD, rarely controlled in these studies (reviewed by Rubia, 2011). Indeed, in a study comparing boys with pure CD and pure ADHD, impairment in the vmOFC, associated with the hot EF, was found CD-specific while boys with ADHD showed specific under-activation in the IFG bilaterally and enhanced activation in the cerebellum/hippocampus/PCC associated with the cool EF element of the task (Rubia, Smith, Halari, et al., 2009).

Surprisingly no cerebellar GMV deficits or functional impairments were observed in ADHD relative to controls in the findings, which is inconsistent with a previous finding of ADHD-specifically reduced right posterior cerebellum relative to ASD in a direct comparison between the two groups (Lim et al., 2015). Reduced cerebellar GMV has been found in one previous meta-analysis, based on ten ADHD studies (Stoodley, 2014), but not in several others (Frodl & Skokauskas, 2012; Nakao et al., 2011; Norman et al., 2016). Differences in the included studies were presumably one factor that has produced these mixed findings. Stoodley's meta-analysis (2014) showed reduced cerebellar GMV in the cerebellar lobule IX, although previous evidence of cerebellar structures alteration ranged from reduced cerebellar volumes, cerebellar vermis, and posterior inferior vermis VIII-X in children with ADHD (e.g., Bussing, Grudnik, Mason, Wasiak, & Leonard, 2002; Mostofsky, Reiss, Lockhart, & Denckla, 1998; Valera et al., 2007). In adults with ADHD, reduced overall cerebellar volume (Hove et al., 2015) and right posterior cerebellum lobules VIII and IX (Makris et al., 2015), were associated with posture control difficulties. Other than during motor inhibition tasks (Bhajiwal et al., 2014; Cubillo et al., 2014; Rubia, Halari, Cubillo, et al., 2011; Suskauer et al., 2008), reduced cerebellar activations in the left posterior lobes have been found during working memory tasks (Valera, Faraone, Biederman, Poldrack, & Seidman, 2005; Wolf et al., 2009). Reduced activations have also been found in the right anterior vermis during a variety of timing tasks (see meta-analysis by Hart et al., 2012). Thus, it appears that cerebellar deficits in ADHD are heterogeneous across studies. This could be the reason for the lack of finding in cerebellar deficits in this meta-analysis.

Meta-regression analyses showed that exposure to psychostimulants in ADHD was associated with enhanced GMV in a large cluster at the vmOFC, and reduced GMV in small clusters in the left IFG and right olfactory cortex; and functionally with increased activation of small clusters in the right IFG and right

MTG. These findings are partly consistent with a previous meta-analysis (Norman et al., 2016) and extend previous fMRI meta-analytic findings of increased activation in these areas during acute psychostimulant use among children with ADHD (Rubia et al., 2014). In the present study, right IFG is disorder-specifically reduced in ADHD relative to ASD, and is found to be increased in ADHD patients with long-term stimulant use. This finding suggests that stimulant medication is unlikely to confound any disorder-comparison findings as a medication-naïve ADHD group, as it will likely have shown an even increased reduction in IFG activation. The structural disorder-specific findings in ADHD were also unlikely to be confounded by medication as long-term medication had no effect on these structures.

4.4.4 Limitations, Implications and Future Directions

The interpretations of the present findings should be viewed with several limitations. Some limitations are inherent to meta-analyses of neuroimaging studies, that is, most available data are in discrete peak coordinates rather than in the form of continuous statistical parametric map that the SDM can accommodate, and the application of stringent statistical corrections to protect against false positives within each study, may limit the number of peaks reported and conceal differences between groups.

Other limitations are dependent upon the available data. First, it is unknown to what extent the findings of this study were confounded by co-occurring cases of ASD and ADHD, which were often reported in the clinical literature (Gjevick et al., 2011; Salazar et al., 2015; Simonoff et al., 2008). The co-occurring cases were insufficiently controlled in most neuroimaging research in spite of several exceptions (e.g., McAlonan et al., 2008; Mengotti et al., 2011; Radeloff et al., 2014; Rubia, Halari, Cubillo, et al., 2011; Smith et al., 2006). Cases of ASD+ADHD in the ASD or ADHD samples could affect the disorder-specific and shared findings in the study.

For instance, common impairments or deficits may perhaps reflect the fact that a proportion of individuals in each group have significant traits of the counterpart condition, rather than representing an overlap of neural underpinnings of the two disorders. Since little information about this possible confound was provided by each study, however, its effect could not be determined in the present study. Second, relatively few fMRI studies in inhibitory function were found in ASD in comparison to ADHD studies and there were predominantly far more independent datasets with adult participants among ASD studies than in ADHD. Relatedly, stratification by tasks type and contrasts used across studies was not possible due to the insufficient number of published fMRI inhibition studies, particularly in the ASD group. Third, some conclusions of this study, specifically those related to findings of reduced activations in the rACC/dmPFC among individuals with ASD during inhibition might be vulnerable to publication bias as indicated by the Egger tests.

To conclude, people with ASD display wide-ranging functional impairments in brain regions often related to inhibition and salience monitoring (ACC/dmPFC), set-maintenance or working memory (dlPFC) and attention (IPL, precuneus), while individuals with ADHD display specific decreases in the key region for stopping actions in the right IFG. A small cluster in the orbital part of the IFG (BA47) extending to the right AI appeared to be impaired functionally in both ASD and ADHD, which is thought to be important for action stopping and salience detection. Structurally, ASD is associated with a disorder-specific GMV deficit in the thalamus, a gateway of sensory information that is also implicated in social cognition and mood regulation. Individuals with ASD also demonstrate PCC enhancement, which might be associated DMN abnormalities, whereas ADHD is associated with striatal/insula GMV deficit, which is a host of many functions including sustained attention and inhibition. Both conditions share reduced GMV in the rdACC/dmPFC.

This might be a transdiagnostic feature across several psychiatric disorders associated with cognitive control, salience detection, and emotional control. Both disorders also share enhanced left precuneus GMV, possibly associated with DMN abnormalities that lead to lapses of attention or increased mind wandering, although functional abnormalities in this region was found ASD-specific in this study.

Neuroimaging studies in ASD and ADHD often did not take account the co-occurrence between the two disorders and little information was provided by each study on this potential issue. However, the findings from the present meta-analysis suggest that ASD and ADHD inhibition-related brain function and structure abnormalities are mostly disorder-specific, with relatively few shared abnormalities. This poses the intriguing possibility that inhibition difficulties in ASD are a symptomatic phenocopy with different neural underpinnings from those found typically in ADHD. Evidence for shared neural underpinning for the two disorders also exist in this study although it is unclear if the evidence reflects a true overlap between two otherwise separate and distinct conditions, or whether it is an influence of undetected comorbid cases in the ASD and ADHD samples. To answer this question, future neuroimaging studies in ASD or ADHD, especially in children where the co-occurrence of both symptoms appeared most prevalent (Gjevik et al., 2011; Salazar et al., 2015; Simonoff et al., 2008), should systematically examine the influence of traits of both disorders in their disorder-specific findings, or apply the stringent criteria of excluding or separately grouping individuals with co-occurring ASD and ADHD. Finally, to better understand the disorder-specific and shared impairments, future meta-analyses should consider stratifying studies by task types, especially when sufficient numbers of studies are published in individuals with ASD.

5 Study IV: An fMRI Study of Inhibition and Error Monitoring in Young Adults with ASD, ADHD, and ASD+ADHD

5.1 Introduction

Deficits of EF are frequently observed among individuals with ADHD and often co-occur in individuals with ASD albeit less consistently (Alderson et al., 2013; Geurts et al., 2009; Willcutt et al., 2008). Among such deficits are the difficulties in motor response inhibition and attention (Lijffijt et al., 2005; Lipszyc & Schachar, 2010; Willcutt et al., 2008) found among individuals with ADHD to be associated with underperforming network of regions including, primarily, the ventrolateral and frontal opercular regions IFG/insula and subcortically in the dorsal BG, as well as regions such as the SMA in the case of inhibition, and the dlPFC and precuneus for attention (Hart et al., 2013; Norman et al., 2016). Individuals with ASD also display inhibition (Geurts et al., 2009) and sustained attention difficulty (see e.g., Bodner, Beversdorf, Saklayen, & Christ, 2012; Corbett, Constantine, et al., 2009; but see G. Goldstein et al., 2001; Johnson et al., 2007) although typically there is significant heterogeneity across studies, independent from variation of demographic characteristics such as age and IQ (Kuiper et al., 2016). Several neurobehavioural findings, including those reported in Chapter 3 of this thesis, have indicated that co-occurring ADHD symptoms might be one factor that has augmented the inhibitory and sustained attention difficulties among individuals with ASD (Adamo et al., 2014; Buehler et al., 2011; Corbett, Constantine, et al., 2009; Sinzig, Morsch, Bruning, et al., 2008). Findings from Chapter 4 suggest little overlaps in the neural underpinning of response inhibition among individuals with ASD or ADHD. Therefore, the key

question now is how similar the inhibitory and attention deficits are in ASD+ADHD and ADHD at the neural level. A neuroimaging study comparing the neural correlates of these cognitive deficits in individuals with ASD, ADHD and ASD+ADHD will further our knowledge about the similarities and differences among these groups.

5.1.1 Investigating Response Inhibition and Error Monitoring Using the Modified Stop-Signal Task

Given its consistency in tapping inhibitory deficits (Alderson et al., 2007; Lijffijt et al., 2005; Lipszyc & Schachar, 2010) and its frequent use in neuroimaging studies of ADHD (see e.g., Chantiluke, Barrett, Giampietro, Santosh, Brammer, Simmons, et al., 2015; Congdon et al., 2014; Sebastian et al., 2012; van Rooij et al., 2015), a variant of the stop-signal task was chosen for this investigation. The stop-signal task requires cancellation of already initiated motor responses evoked by “Go” stimuli, upon the arrival of an unexpected infrequent “Stop” signal (Logan, Cowan, & Davis, 1984; Verbruggen & Logan, 2009a). It is known however that the infrequent presentation of the Stop cue in would elicit attentional capture, possibly activating the salience networks overlapping with the inhibitory processes and associated with deactivated DMN (Aron, 2011; Duann, Ide, Luo, & Li, 2009; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). To control for these attentional capture, past studies have contrasted successful against failed Stop trials (see e.g., Padmala & Pessoa, 2010; Rubia, Smith, & Taylor, 2007; Vink et al., 2005), which was a conservative approach given both trials activate inhibitory functions, although in the case of failed Stop, the Stop processes fell behind the Go processes (Aron & Poldrack, 2006; Boehler et al., 2010). In the present study a modified stop-signal task was favoured as in previous studies where Oddball trials were embedded in the Simon task (Cubillo et al., 2011; Rubia, Halari, Cubillo, et al., 2011) or the GNG task (Daly et al., 2014).

Response inhibition, investigated by contrasting the successful Stop against Go trials during the stop-signal task, typically activates an extensive network of regions involved in EF and salience detection, such as the right IFG/insula, the SMA, the thalamus and subthalamic nucleus (STN), BG, temporo-parietal regions, and premotor areas (Aron & Poldrack, 2006). The right IFG is considered vital for motor response inhibition as revealed in an ALE meta-analysis of 70 motor inhibition studies (Cai et al., 2014). Clinical studies have shown that the extent of damage in the right IFG was selectively correlated with SSRT ($>.8$), and focal lesions in this region increased RT variability (Aron et al., 2003; Picton et al., 2006). These results were consistent with findings of significant reduction in the probability of inhibition after a temporary neural disruption in the region (Chambers et al., 2006, 2007), induced using transcranial magnetic stimulation (TMS). The precise roles of the IFG and the whole fronto-basal ganglia system during the stop-signal task performance are still under investigation. However, the influence of their activations in the inhibition of downstream motor areas has been observed in several studies (see Aron et al., 2014). For example, the strength of the functional and structural connection of the IFG with the pre-SMA was found to be associated with the speed of stopping (Duann et al., 2009; Madsen et al., 2010). Furthermore, the deactivation of the motor cortex during the stop-signal task was found to be a function of the striatum activation during successful inhibition (Aron & Poldrack, 2006; Zandbelt & Vink, 2010). The striatum activations were found to link with SMA activations and parametrically enhanced with increased probability of stopping, suggesting that it could be crucial for both stopping and stopping preparation (Vink et al., 2005; Zandbelt & Vink, 2010).

Performance on the stop-signal task also depends upon cognitive functions other than response inhibition, such as the ability to monitor one's own errors or stopping failures, and the capacity for sustaining attention (Ray Li, 2006). Error

monitoring can be investigated on the stop-signal task by contrasting failed Stop against Go trials (Ray Li, 2006; Rubia, Smith, Brammer, & Taylor, 2003; Sharp et al., 2010). Typically, awareness of having made an error resulted in post-error behavioural adjustments including post-error slowing (PES). Errors during inhibitory tasks evoke activations in regions such as the bilateral insula, IFG, dACC/mPFC and also the bilateral IPL (Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Klein et al., 2007; Rubia, Halari, Mohammad, et al., 2011), while the awareness to error is associated with activation in the insular region (Klein et al., 2007; Klein, Ullsperger, & Danielmeier, 2013). Unsurprisingly, the majority of these regions, including AI, IFG, and dACC, are part of the salience network (Menon & Uddin, 2010; Seeley et al., 2007), which are activated during bottom-up attentional captures. The experience of committing an error is a salient occurrence that captures one's attention and recruits similar brain regions as those activated during target detection tasks (Harsay, Spaan, Wijnen, & Ridderinkhof, 2012; Klein et al., 2013).

5.1.2 Neural Correlates of Inhibition Task Performance in ADHD, ASD, and ASD+ADHD

Most ADHD studies using the stop-signal task are typically conducted in children and usually find under-activation in the IFG, insula, and striatum in whole-brain investigations (e.g., Cubillo et al., 2014; Rubia, Halari, Cubillo, et al., 2011). The few studies using the stop-signal task in adults with ADHD demonstrated less consistent findings than in children (Cubillo & Rubia, 2010). Some studies of adults showed lateral frontostriatal impairments similar to those found in children, in the right IFG/insula/PMC, BG, and thalamus in a modest sample of medication-naïve adults with childhood-diagnosed ADHD (Cubillo et al., 2010), and in the right pallidum and left IFG, the latter at an uncorrected threshold (Sebastian et al., 2012). Others found no neural impairments even among a moderate large sample of 35 adults (Congdon et al., 2014). However, nearly a third of participants in the latter study were on

psychostimulants and did not stop taking them throughout the investigation which could confound the findings. The largest study to date by van Rooij et al. (2015), conducted in a mixed group of 185 children and adults with ADHD aged 8-25 years, found reduced activation in the left IFG, SFG, supramarginal gyrus, right post-CG and right TPJ during inhibition. The latter three clusters were also found impaired in their unaffected siblings. Among 77 adults, the only impairments were found in the left SFG and right hippocampal gyrus (van Rooij et al. [2015], personal communication, June 9, 2016).

Other studies of response inhibition among individuals with ADHD using the GNG tasks typically demonstrated impairments in the frontal areas, even among underpowered studies with ten participants or fewer (Karch et al., 2010; Kooistra et al., 2010). These studies have shown impairments in the lateral and medial regions (Karch et al., 2010) as well as the orbitofrontal, posterior parietal, and anterior temporal regions when contrasting activation from the fast versus slow GNG task (Kooistra et al., 2010). Slightly larger studies showed under-activations in the right frontal eye field, pre-SMA, bilateral IPL, and left pre-CG and precuneus (R. C. Mulligan et al., 2011), as well as left IFG (Vasic et al., 2014). Moderate-sized studies, with approximately 20 participants per group, showed the more typical impairment of inhibition in key regions such as the right MFG/IFG using an ROI approach (Morein-Zamir et al., 2014), which were found negatively correlated with ADHD symptoms, even after controlling for selective attentional processes, and also the right caudate, thalamus, right supramarginal gyrus/SPL/angular gyrus and bilateral precuneus (Rasmussen et al., 2015). While there has been heterogeneity in findings in terms of effect-sizes and hemispheric laterality across studies, the evidence suggests that lateral frontostriatal abnormalities during motor inhibition are expected in adults with ADHD.

In ASD, only one fMRI study using the stop-signal task has been carried out to date (Chantiluke, Barrett, Giampietro, Santosh, Brammer, Simmons, et al., 2015). This study, which was conducted with 19 boys with ASD and 18 age-matched boys with ADHD, found a disorder-specific increased activation in the bilateral IFG in ASD relative to ADHD, and an ADHD-specific under-activation in the OFC and BG during inhibition, extending previous findings of over-activated left MFG/IFG during inhibition on the GNG task in an underpowered study (Schmitz et al., 2006). Other studies have shown mixed findings in the effect and directionality of inhibitory-related activation across studies. This is possibly associated with the heterogeneous nature of ASD, and the small sample sizes and variation of tasks (e.g., Daly et al., 2014; Duerden et al., 2013; Kana et al., 2007; Shafritz et al., 2015). The varying findings included: over-activated right IFG and fusiform gyrus during inhibition on a GNG task involving emotional faces among 13 adults with ASD (Duerden et al., 2013); reduced activation in the right IFG in a study involving 15 adults with two GNG tasks involving emotional faces and neutral letter stimuli; and reduced activation in the right IFG, as well as the right insula, cingulate gyrus and PMC using a conventional GNG task in 13 adults with ASD (Kana et al., 2007). Using a GNG task with Oddball trials to control for salience detection, Daly (2014) revealed reduced activation in the right IFC and the left thalamus, as well as enhanced activation in the caudate and right cerebellum.

Importantly, the meta-analysis of response inhibition conducted in Chapter 4 found ASD-specific under-activations relative to ADHD during response inhibition in ACC/dmPFC, left MFG/dlPFC, left IPL/SPL, right PMC, and over-activations in the precuneus and right occipital lobe/FFG relative to the ADHD group during response inhibition. Furthermore, ADHD-specific under-activations were found in the right IFG triangular part/MFG during inhibition relative to the ASD group. Shared under-activations were observed in the right insula and the IFG orbital part which may

reflect impairments that could potentially be found among the individuals with ASD+ADHD.

During error monitoring, several studies reported reduced activation among children with ADHD relative to controls in the right IFG, AI, thalamus, and striatum (Cubillo et al., 2010), posterior cingulate, precuneus and primary motor areas (Rubia et al., 2005). Reduced activations have also been reported in the dmPFC and left vPFC, thalamus, cingulate, and parietal regions in ADHD boys, which was normalised under methylphenidate (Rubia, Halari, Mohammad, et al., 2011). In a mixed sample of 185 children and adults with ADHD, Van Rooij et al. (2015) detected reduced activation in the left IFG, bilaterally in the TPJ, left SFG, ACC/mPFC and supramarginal gyrus, whereas Chen et al. (2015) found reduced activation in the right IFG orbital part, having applied a small volume correction in this ROI. Finally, employing the Flanker/GNG combined task, Vasic et al. (2014) found reduced activation during error detection among 12 adults with ADHD similarly in the orbital part of the IFG, although lateralised in the left hemisphere. To my knowledge, only one fMRI study has tested error monitoring in ASD using a motor inhibition paradigm (Goldberg et al., 2011). This study, which was conducted with 11 HFA children using the GNG task, showed an increased activity in the mPFC, left STG, and in the right insula during error processing.

The neural correlates of stop-signal task performance have not been investigated among individuals with ASD+ADHD. To date, the one fMRI study related to inhibition involving the ASD+ADHD group was conducted by Chantiluke et al. (2014), who investigated impulsive choice among children with ASD, ADHD, and ASD+ADHD using the delay discounting task. Inhibition of impulsive choice differs from response inhibition measured on the stop-signal task, in that it involves both temporal foresight and the inhibition of immediate reward (Cooper, Kable, Kim, & Zauberman, 2013; Luhmann, 2009; Noreika et al., 2013; Rubia, Smith, Halari, et al.,

2009), specifically “immediate gratification ... over delayed advantages” (Bari & Robbins, 2013, p. 64). Therefore, the delay discounting task typically activates reward and motivational-related brain regions such as the vmPFC, OFC and the ventral striatum, which were often dysregulated during reward anticipation and receipt among people with ADHD (Furukawa et al., 2014; Kappel et al., 2015; Plichta & Scheres, 2014; Von Rhein et al., 2015; Wilbertz et al., 2012). Chantiluke’s (2014) study revealed that boys with ASD+ADHD displayed the weakest brain-discounting association in vmPFC, ACC, ventral striatum, right superior frontal cortex and also left IFG/STL compared to groups of children with pure ASD, ADHD and controls, suggesting most pronounced neural impairments in the comorbid group.

5.1.3 The Aims of This Study

No fMRI studies involving individuals with comorbid ASD+ADHD in the context of inhibition or error monitoring has been conducted to date. Several cognitive studies using the GNG task (Adamo et al., 2014; Buehler et al., 2011; Corbett, Constantine, et al., 2009) have shown that individuals with ASD+ADHD and those with ADHD alone shared deficits in performance on motor inhibition task (see Chapter 3 for review). The aim of this study was thus to explore the neural correlates of inhibitory function and error monitoring, in groups of young adults with diagnoses of ASD, ASD+ADHD, and ADHD. The study used a modified stop-signal task that controls for the attentional oddball effect of the low frequency appearance of stop signals. Of interest was whether those with ADHD, that is, the ASD+ADHD and pure ADHD groups, have similar profile of neural impairments given that they displayed similar behavioural performance during neurocognitive testing reported in Chapter 3. Understanding the neural underpinning of the ADHD symptoms in ASD would help answer the question of which model of comorbidity, as discussed in Chapter 1, can apply to the ASD+ADHD group.

During response inhibition, under-activations in the ACC/dmPFC, left MFG/dlPFC, left IPL/SPL, right PMC and possibly over-activations in the precuneus, were expected in the ASD group relative to the ADHD group based on the meta-analytic findings in Chapter 4. On the other hand, ADHD-specific under-activations were expected in the left and right IFG triangular part/MFG, based on the meta-analysis and also previous motor response inhibition studies in adults with ADHD (Cubillo et al., 2010; Morein-Zamir et al., 2014; Rasmussen et al., 2015; Sebastian et al., 2012; van Rooij et al., 2015). During error monitoring, under-activations in the ACC/mPFC, IFG, AI, thalamus, and striatum and the parietal regions such as the IPL, PCC and precuneus were expected among individuals with ADHD (Cubillo et al., 2010; Rubia, Halari, Mohammad, et al., 2011; van Rooij et al., 2015; Vasic et al., 2014). Individuals with ASD were expected to show increased activity in the mPFC, left STG, and in the right insula, according to findings from a previous study (Goldberg et al., 2011). Since there has not been a study in young adults with ASD+ADHD using the stop-signal task, no strong hypothesis can be formed with respect the neural impairments associated with response inhibition and error monitoring in this group. However, based on the finding by Chantiluke et al. (2014), of a more severe neurofunctional impairment pattern in the combined relative to the pure groups during temporal discounting, I anticipated the combined group to have the most severe neural pathology than the pure groups and controls.

5.2 Methods

5.2.1 Participants

Participants of this study were 107 young-adult males, aged 20-27 years with diagnoses of ASD, ADHD, ASD+ADHD, and typically developing controls with neither ASD nor ADHD (see Chapter 4 for full details of recruitment and full

participant characteristics). Data from four participants with ASD, one with ADHD, two with ASD+ADHD and four healthy controls were rejected from the final analysis as they responded to fewer than 70% Go trials. Two further participants with ADHD and one with ASD+ADHD were excluded due to excessive head movement beyond 3 mm. One participant's data from the ASD group was lost due to technical error, while another from the ASD+ADHD group was not used due to an incidental finding. The final sample comprised of 22 controls, 21 individuals with ASD, 25 with ADHD, and 23 with ASD+ADHD.

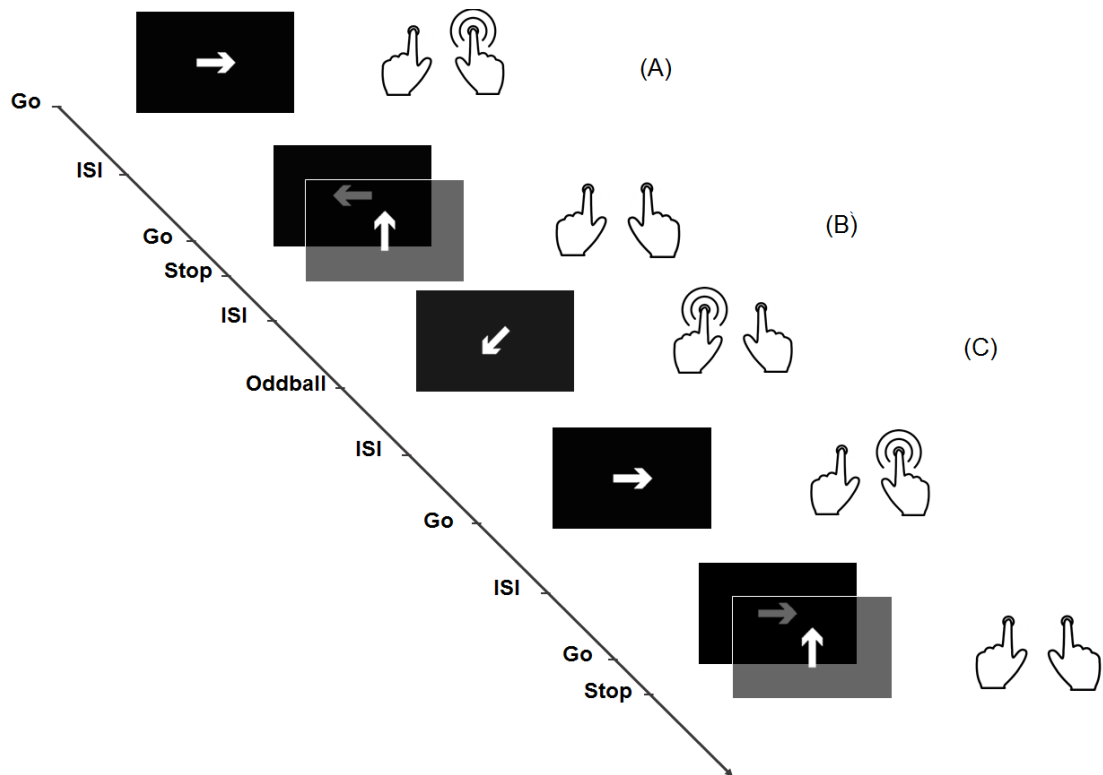
5.2.2 Measures

Behavioural measures taken during the study included a measure of IQ (WASI-2), social reciprocity (SRS-2), a measure of ADHD symptoms (CAARS), and a screening questionnaire on general psychiatric difficulties (SDQ17+), all described in Chapter 4. An additional measure, the Edinburgh Handedness Inventory (Oldfield, 1971), was used in this study to compare handedness across groups.

5.2.3 The Modified Stop-Signal Task

This study used a modified stop-signal task incorporating Oddball trials in the stimulus sequence to control for selective attentional processes associated with the infrequent presentation of the stop cue. This additional control approach has been implemented in previous investigations using the Simon task (Cubillo et al., 2011; Rubia, Halari, Cubillo, et al., 2011) and the GNG task (Daly et al., 2014). This 9-minute task consisted of 300 trials, comprised of 200 Go trials, 40 Oddball trials and 60 Stop trials. In each Go trial, a left- or right-pointing Go arrow was presented for 1000ms, with an ISI jittered between 700-1000 ms, to be responded to by pressing the left and the right key, respectively, on the button box. The Oddball trials were equivalent to the Go trials in its presentation and they required equivalent responses. However, they were much less frequent and consisted of arrows that

Figure 5-1: Schematic illustration of the modified stop-signal task



Note. All stimuli were presented against a black background. The Go trials (A) consisted of arrows pointing horizontally to the left or right to be responded by left or right button press respectively. The Stop trials (B) consisted of a Go signal followed by a Stop signal, presented here on transparent background for clarity, arriving between 50 and 900ms after the Go signal, started from 250ms in the first trial. Participants were instructed to cancel their initiated response as best as they can in these trials. The Oddball trials (C) were arrows pointing diagonally downward to the left or right and participants were instructed to respond by pressing the left or right button, respectively. Each trial was followed by an ISI jittered between 700-1000ms. The blue and red coloured arrow on the left indicated the time line of the events. Abbreviations. Go = Go cue, ISI = interstimulus interval, Stop = Stop signal, and Oddball =Oddball cue.

were pointing diagonally downward to the left or right. Each Stop trial consists of a Go signal followed by a Stop signal, which lasted for 300 ms, arriving after a stop-signal delay (SSD) of few hundred ms, signalling the participants to cancel their already initiated response. In the first Stop trial the Stop signal is presented 250ms after the Go signal. Thereafter, its onsets were adjusted according the participant's performance, by a tracking algorithm that computed the overall probability of inhibition each time a stop trial had been completed. These adjustments followed a staircase procedure, moving forward or backward by 50ms steps (within the range of 50-900 ms) when the probability of inhibition was over or under 50%, respectively, therefore allowing the participants to successfully stop their responses at 50% probability (see e.g., Chantiluke et al., 2015; Ray Li, 2006). There were equal numbers of left- and right-pointing Go and Oddball arrows.

Prior to completing this task in the scanner, the participants went through a 6-minute practice run under the supervision of the researcher. All participants achieved the 50% threshold during this practice. The main outcome measure of the task was the SSRT, i.e., the optimum SSD for which a cancellation of response was just feasible, which was computed by subtracting the mean SSD from the mean response time (MRT) during the Go trials. High SSRT indicated inhibitory difficulties and impulsivity (Aichert et al., 2012; Congdon et al., 2012; Logan, Schachar, & Tannock, 1997). Other measures such as omission errors and intra-subject variability of RT (SDRT) to Go trials were thought of as indices of inattention during the task (Castellanos et al., 2005; J. I. Lake & Meck, 2013; Tamm et al., 2012). In addition, PES or post-error slowing, were computed by subtracting the MRT of the trial immediately after a successful Stop, from the MRT after failed Stop.

5.2.4 fMRI Acquisition

Neuroimaging data were acquired on a General Electric (GE) MR750 3.0T MR scanner (General Electric, Milwaukee, WI, USA) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology, and Neuroscience, at King's College London, UK. An 8-channel head coil was used for RF transmission and reception. The echo planar image (EPI) gradient-echo pulse sequence (TR/TE = 1800/27ms, flip angle = 75°, FOV = 21cm x 21cm, 64 x 64 matrix, in-plane resolution = 3mm, slice thickness = 3mm with gap of 0.3mm) was used to acquire 40 slices of T2*-weighted MR images parallel to the inter-commissural plane, depicting BOLD contrast and covering the entire brain. The 9-minute scan resulted in 303 volumes in time series. A whole-brain high resolution structural T1 scan (Enhanced Fast Gradient Echo 3-Dimensional/EF-GRE3D), co-registered with individual activation maps during pre-processing, was also acquired in the inter-commissural plane with TE = 3.016 ms, TR = 7.312s, flip angle = 11°, 196 slices, FOV = 27cm x 27cm, 256 x 256 matrix, and slice thickness of 1.2mm and gap of 1.2mm.

5.2.5 Analysis of the fMRI Data

All fMRI data went through standard pre-processing steps including slice-time correction, realignment, co-registration to the individual structural T1 scan, segmentation, normalisation and smoothing. Each participant's EPI data were normalised to the Montreal Neurological Institute (MNI) EPI template and smoothed using the 8-mm Gaussian kernel. Statistical analyses were conducted using the Statistical Parametric Mapping version 8 (SPM8). The analyses were done in two steps to ease the computational load. At the subject-level analyses, blood-oxygen-level-dependent (BOLD) responses to the experimental blocks were predicted using a vector of onsets and durations convolved with the canonical haemodynamic response function (HRF). Three contrasts were defined for each participant: (1) successful Stop versus correct Oddball, which probes response inhibition while controlling for attentional processes; (2) failed Stop versus correct Oddball, which probes error monitoring; and to assess the different effect of the Oddball trials across groups, an additional contrast (3) Oddball versus Go were analysed. Seven nuisance regressors were included to control the effects of volume-to-volume head movement and abrupt movement above 1 mm. A high-pass filter was applied at the cut-off (128s) and a first-order autoregressive model was used to correct for time series correlation.

Within-group activations were reported with a cluster extent threshold at $p < .05$ with family-wise error (FWE) correction and a voxel threshold of $p < .001$. At the group level, the three contrasts were analysed with univariate ANCOVAs on SPM8 with group as independent factor, covarying for volume-to-volume total movement (Power et al., 2014). Between-group activations are reported at corrected cluster size ≥ 396 voxels, corresponding to a cluster defining threshold of .001 and FWE-corrected alpha level of .05 (http://blogs.warwick.ac.uk/nichols/entry/spm5_gem_6/). The effect size of brain activity for each individual subject was

extracted from significant clusters using the MarsBaR toolbox (Brett, Anton, Valabregue, & Poline, 2002) and subsequently analysed in the IBM SPSS Statistics for Windows, version 22 (IBM Corp., 2013). Post-hoc analyses were conducted pairwise with Dunn-Sidak correction and further ANCOVAs were conducted on SPSS covarying for IQ, and excluding individuals on medications. In addition, correlations between brain activity and relevant behavioural and trait measures in the groups showing impairments were contrasted against the findings in the control group.

5.2.6 Analysis of Behavioural Data

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., 2013). Analyses of the demographic data, behavioural reports, and performance during tasks on key variables were completed with univariate ANOVAs, while categorical variables such as medication use and diagnosis status were all analysed using Chi-square analyses. The direction of group differences on the univariate ANOVAs were assessed using multiple pairwise comparisons, Dunn-Sidak corrected for independent groups.

5.3 Results

5.3.1 Group Characteristics

The participant characteristics are summarised in Table 5-1. The sample did not differ in age and handedness although, FSIQ differed and was found highest in the ADHD and the TD group, where the difference reached significance in comparison to the ASD group, $F(3, 87) = 5.2, p < .002$. As found in the full sample (see Chapter 3), individuals in the ASD+ADHD or ADHD rated themselves as having higher inattention, hyperactivity and impulsivity, and overall ADHD index on CAARS than

Table 5-1: Characteristics of participants in the study

	TD (n=22)	ASD (n=21)	ADHD (n=25)	ASD+ ADHD (n=23)	Group comparison		
					<i>F</i> (3,87)	<i>p</i>	Post-hoc
Age (SD)	23.0 (1.3)	22.8 (.9)	23.1 (2.0)	23.1 (1.3)	.22	.89	--
FSIQ (SD)	118.5 (12.1)	102.0 (19.8)	116.0 (13.2)	109.2 (14.8)	5.2	.002	ADHD, TD > ASD
Handedness (Range)	60.9 (-100-100)	57.1 (-100-100)	65.2 (-95-100)	54.6 (-100-100)	.10	.97	--
Left-handed	4	4	4	5	--	--	--
Current stimulant	--	--	5	6	--	--	--
Current SSRI	--	--	3	1	--	--	--
CAARS self (t-scores)^a							
Inattention	44.1 (7.4)	46.6 (6.3)	66.1 (7.9)	61.8 (10.2)	41.3	<.001	ASD+ADHD, ADHD > ASD, TD
Hyperactive	44.9 (8.8)	45.4 (6.7)	65.1 (10.1)	57.8 (9.8)	27.2	<.001	ADHD > ASD+ADHD > ASD, TD
Impulsive	41.2 (6.3)	45.2 (6.8)	57.2 (9.5)	53.6 (10.1)	17.7	<.001	ASD+ADHD, ADHD > ASD, TD
ADHD index	42.1 (9.1)	45.7 (7.7)	65.2 (7.7)	58.4 (10.7)	34.0	<.001	ASD+ADHD, ADHD > ASD, TD
CAARS informant (t-scores)^b							
DSM-IV inattention	--	57.0 (12.7)	79.3 (13.6)	82.9 (8.4)	30.4	<.001	ASD+ADHD, ADHD > ASD
DSM-IV hyperactive	--	47.3 (10.9)	66.1 (17.8)	65.7 (18.5)	9.5	<.001	ASD+ADHD, ADHD > ASD
DSM-IV symptom no	--	51.9 (13.7)	76.3 (16.3)	79.1 (11.7)	24.4	<.001	ASD+ADHD, ADHD > ASD
ADHD index	--	47.8 (7.3)	63.0 (18.4)	66.5 (10.3)	22.7	<.001	ASD+ADHD, ADHD > ASD
SRS self (t-scores)							
Total SRS score	48.2 (6.5)	61.8 (9.1)	62.7 (6.9)	65.0 (10.4)	18.4	<.001	ASD+ADHD, ADHD, ASD > TD
SRS informant (t-scores)							
Total SRS score	--	63.4 (8.2)	56.9 (10.5)	69.4 (11.5)	8.7	<.001	ASD+ADHD > ADHD
SDQ17+ self							
Hyperactivity	2.5 (1.8)	3.2 (2.0)	7.4 (1.5)	7.0 (1.9)	44.6	<.001	ASD+ADHD, ADHD > ASD, TD
Emotion	1.1 (1.5)	4.2 (2.7)	4.2 (2.4)	4.3 (2.6)	9.8	<.001	ASD+ADHD, ADHD, ASD > TD
Conduct	1.2 (1.3)	1.6 (.9)	2.8 (1.9)	2.8 (1.9)	6.4	.001	ASD+ADHD, ADHD > TD
Peer relations	2.7 (2.0)	3.7 (1.7)	2.1 (1.5)	3.2 (2.0)	3.0	.036	ASD > ADHD
SDQ17+ informant							
Hyperactivity	--	3.0 (1.6)	7.4 (2.0)	7.3 (1.8)	41.1	<.001	ASD+ADHD, ADHD > ASD
Emotion	--	3.3 (2.0)	4.0 (2.4)	4.4 (2.6)	1.2	.299	--
Conduct	--	1.1 (.8)	3.2 (2.1)	3.4 (2.3)	9.9	<.001	ASD+ADHD, ADHD > ASD
Peer relations	--	3.4 (1.6)	2.4 (1.8)	4.4 (2.1)	6.3	.003	ASD+ADHD > ADHD

Note. Abbreviations M = mean, SD = standard deviation, FSIQ = full-scale IQ, DX = diagnosis, CAARS = Conners Adult ADHD Rating Scale, SRS = Social Responsiveness Scale version 2, SDQ17+ = Strengths and Difficulties Questionnaires for age 17 years and above. Self-rated symptoms were indicated by 'self', while informant-rated symptoms (filled in by parents, partner, relatives or childhood friend) were indicated by 'informant'.

^{a,b} CAARS-self questionnaires were rated on the short form, whilst CAARS-informants were rated on the long versions thus generating different domain scores.

controls or the ASD group, all $F_s(3, 86) \geq 17.7$, all $ps < .001$. Multiple comparisons also suggested that individuals with ADHD rated themselves to have higher hyperactivity than those with ASD+ADHD ($p < .001$). Informant scores of DSM-IV inattention, hyperactivity/impulsivity, symptom numbers and ADHD index, obtained from among the clinical groups, were likewise significantly higher in the ADHD and the ASD+ADHD groups than the ASD group, all $F_s(3, 86) \geq 9.5$, all $ps < .001$. All individuals in the clinical groups reported higher difficulties in social reciprocity as measured on the SRS, $F(3, 86) = 18.4$, $p < .001$, than controls (all $ps < .001$); although ratings of informants suggested that the ADHD group had the lowest difficulty, with rating against the ASD+ADHD group reaching significance level. The SDQ hyperactivity ratings were consistent with the CAARS, whereby the ASD+ADHD and the ADHD groups rated themselves with higher ADHD symptoms than controls and the ASD group (all $ps < .001$).

5.3.2 Behavioural Data

Table 5-2: Behavioural data from the modified stop-signal task

	TD (n=22)	ASD (n=21)	ADHD (n=25)	ASD+ ADHD (n=23)	Group comparison	
					<i>F</i> (3,87)	<i>p</i>
SSRT (SD)	124.5 (115.0)	138.6 (115.6)	179.1 (59.4)	179.3 (98.2)	1.86	.14
Go MRT (SD)	646.2 (147.1)	589.1 (117.4)	606.4 (141.1)	572.4 (106.7)	1.33	.27
Go SDRT (SD)	166.6 (49.4)	160.0 (56.6)	152.0 (42.7)	150.5 (47.2)	.53	.66
SSD (SD)	521.7 (200.5)	450.5 (160.2)	427.3 (144.1)	393.2 (146.8)	2.48	.07
% Omission errors to Go (SD)	11.8 (7.7)	12.1 (6.1)	12.5 (6.1)	11.5 (7.2)	.09	.96
% Omission errors to Oddball (SD)	9.55 (6.5)	11.3 (7.7)	10.4 (5.4)	9.9 (8.2)	.26	.86
% Correct Stop (SD)	48.9 (2.8)	49.1 (2.0)	49.1 (2.9)	49.1 (3.9)	.03	.99
PES (SD)	25.2 (55.0)	24.2 (71.3)	32.4 (41.1)	26.6 (65.8)	.09	.97

Note. Group comparison of measures during the modified stop-signal task indicated no difference in performance. SSRT, MRT, and SDRT are presented in seconds, whereas the rates of omission errors and correct Stop are presented in percentages. The correct stop rate is not strictly an outcome measure as the stop-signal task is design so that this score converges to approximately 50%. Abbreviations: SSRT = Stop-signal response time, MRT= Mean response time, SDRT = intrasubject standard deviation of response time, a measure of response time variability, PES = Post-error slowing and SD = standard deviation.

The proportion of failed Stop trials was approximately 50% and did not differ among groups, indicating that the tracking algorithm was successful in balancing the number of successful and unsuccessful response inhibition. No differences were found in the performance indices of the stop-signal task among groups, including in the primary response inhibition index SSRT and attentional indices such as Go MRT, intrasubject SDRT and omission errors. PES also did not differ across groups (see Table 5-2 below). Since individuals with ADHD usually had difficulties in this task, additional pairwise *t*-test analyses were conducted to compare the SSRT of the clinical groups against controls. The findings indicated that the ADHD group had significantly higher SSRT than controls, $t(45) = 2.08$, $p = .04$, while the individuals with ASD+ADHD and ASD did not differ from controls, $t(43) = 1.72$, $p = .09$ and $t(41) = .40$, $p = .69$, respectively.

5.3.3 Neuroimaging Data during Inhibition and Response Monitoring

5.3.3.1 Motion

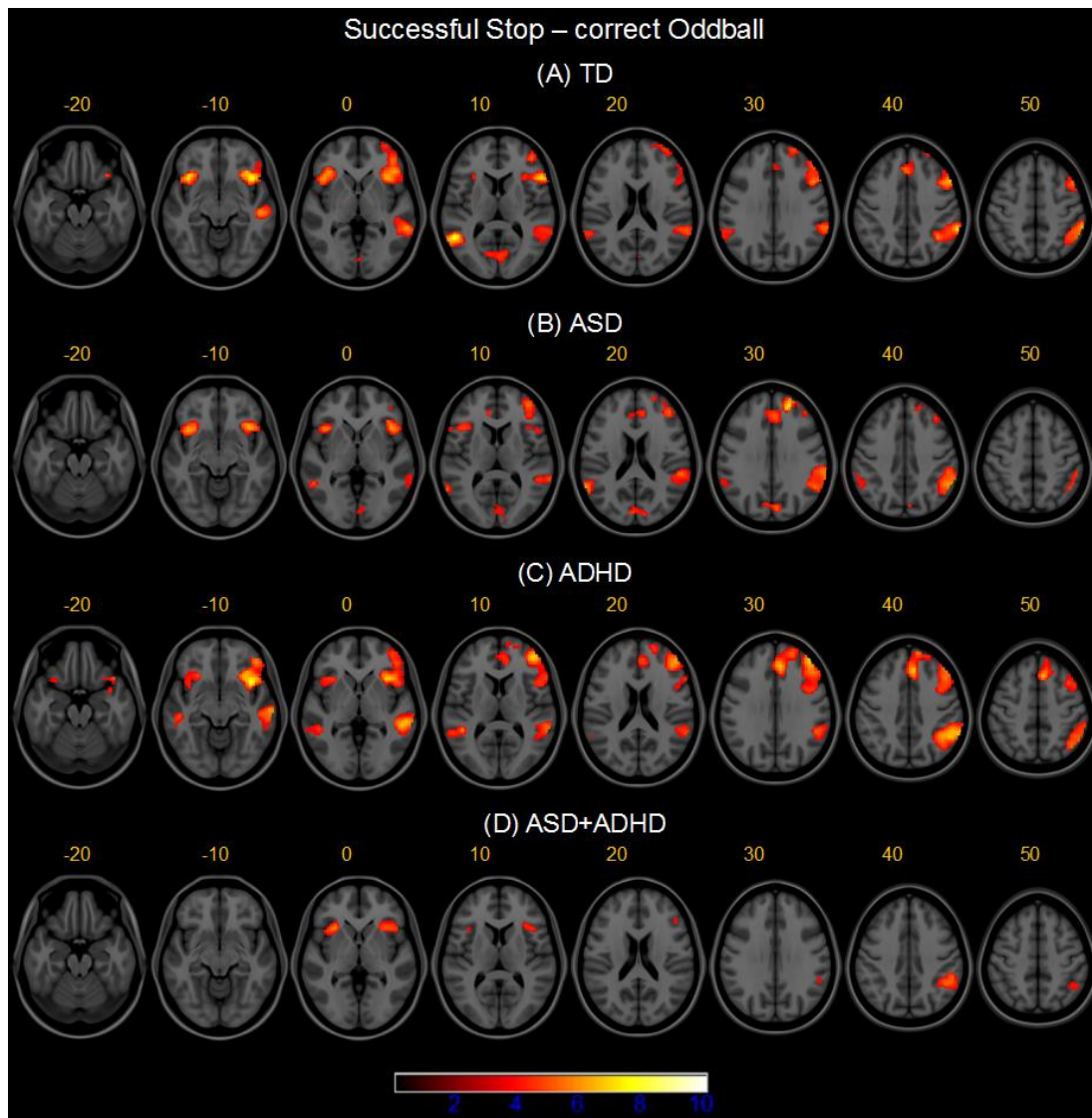
No group differences were observed among movement in the x, y and z rotation and x, y and z translation, $F(3,87) = 1.34$, $p = .27$. However, total volume-to-volume movement would still be covaried at the group-level analyses of BOLD activation as they could contribute to unwanted variation of signal within group.

5.3.3.2 Inhibition Contrast Successful Stop – Correct Oddball

Within-group Brain Activations

Figure 5-2 shows within-group brain activations for the contrast of successful Stop against correct Oddball trials. The control group displayed activation in the bilateral AI (BA13) and IFG (BA47), reaching up to the right dlPFC (BA8, 9) areas, bilateral supramarginal gyrus/angular gyrus (BA39, 37), and the STG/MTG (BA21, 24), reaching into the ITG in the left hemisphere, also the mPFC/dACC (BA8, 32), and

Figure 5-2: Within-group brain activations during response inhibition



Note. Within-group brain activation clusters revealed during successful Stop-correct Oddball contrast corresponding to response inhibition in the TD group (A), ASD group (B), ADHD group (C) and ASD+ADHD group (D). The clusters were obtained at a threshold cluster extent $k \geq 396$ voxels, corresponding to $p < .05$ FWE. Only increased activations are presented in the figure. Images' left is the participants' left side.

the cuneus (BA18). The ASD group showed activation at the right IFG/MFG (BA46, 10) and left IFG/MFG (BA44, 46) reaching into AI (BA13) bilaterally, and at the dACC/ mPFC (BA8, 32). Activation was also seen in the cuneus (BA17,18), and bilaterally in the IPL/supramarginal gyrus/angular gyrus (BA39, 40), reaching into the STG/MTG (BA21, 22), more dominantly, on the right hemisphere. The ADHD group displayed activation in a large cluster comprising right AI/IFG/MFG/dlPFC/SFG (BA 13, 47, 45, 44, 46, 10, 9, 6) and dACC/mPFC, (BA24, 32), left IFG/AI (BA13, 47), right SPL/IPL/ supramarginal gyrus/angular gyrus (BA7,

40, 39), reaching deep into the right STG/MTG (BA21, 22), in the left STG/MTG (BA21, 22), and in the left premotor cortex (BA6). The ASD+ADHD group displayed the least activation during successful inhibition, with activation observed in the IPL (BA40) and bilateral AI (BA13), reaching into the IFG (BA44, 47) on the right.

Between-group Brain Activations

The univariate ANOVA test showed no significant group effect for the whole-brain analysis using the Stop – Oddball contrasts. The more traditional contrasts of Stop-Go were also tested and yielded no group differences. Finally, as there was the possibility of having limited power to detect effects with four groups of participants, pairwise independent *t*-tests were conducted between controls and each clinical group. This also revealed no clusters of group differences in brain activations. The conclusions remained when individuals with medication were excluded from the analysis.

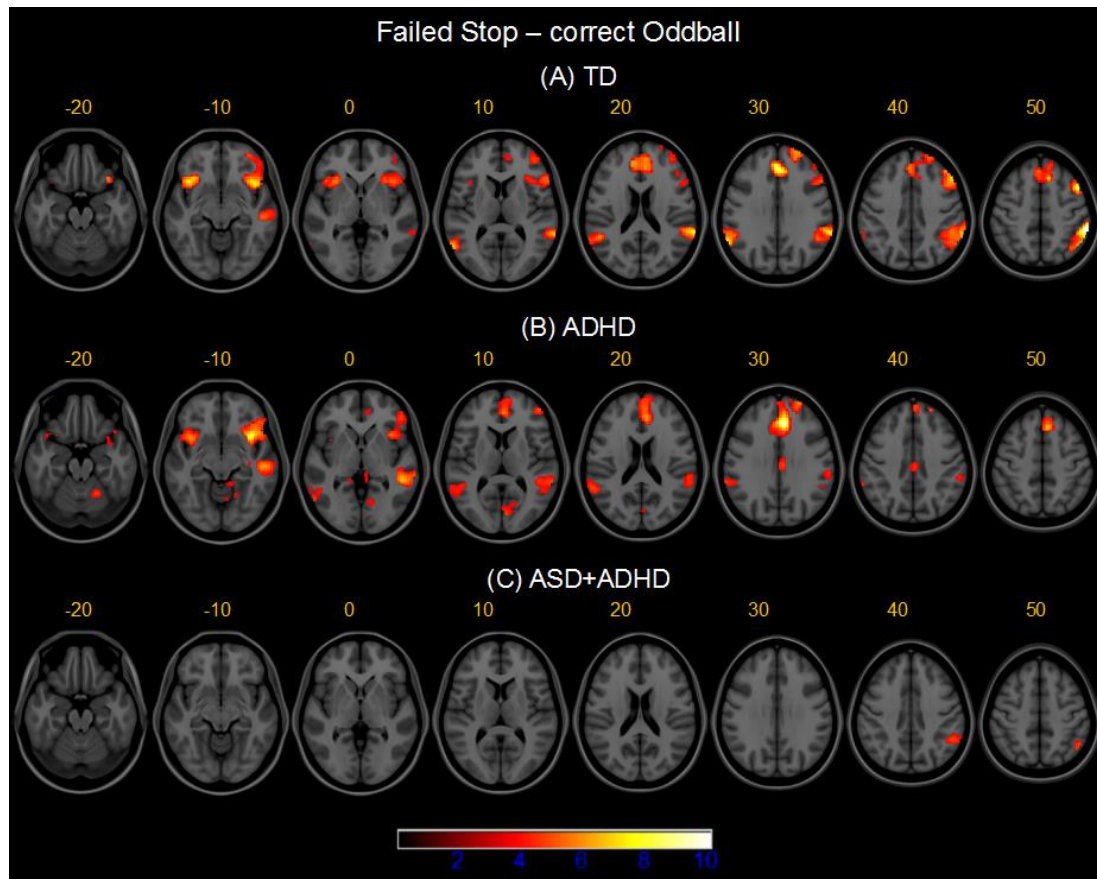
5.3.3.3 Error-monitoring Contrast Failed Stop – Correct Oddball

Within-group Brain Activations

Within-group brain activations during failed Stop against correct Oddball are presented on Figure 5-3. In the TD group, activations were seen in right SPL/IPL/supramarginal gyrus/angular gyrus (BA7, 40, 39) reaching into STG/MTG (BA22, 21), right AI/IFG (BA13, 47, 44, 46), reaching up to the right MFG/dIPFC/SFG (BA9, 6), the mPFC/dACC (BA24, 32), the left AI/IFG (BA13, 47), and the left IPL/supramarginal gyrus/angular gyrus/posterior STG/MTG (BA40, 39, 21, 22). No significant cluster was observed in the ASD group in this threshold. In the ADHD group, activations were found in right AI/IFG (BA13, 47, 45, 46), left AI/IFG/MFG (BA13, 47), mPFC/dACC (BA24, 32), SFG (BA8, 9, 10), bilateral IPL/supramarginal gyrus/angular gyrus/ STG/ MTG (BA40, 39, 21, 22), ventral cingulate cortex (BA24),

and right cuneus/cerebellum (BA17). In the ASD+ADHD, only one activation cluster in the right IPL (BA40) was found.

Figure 5-3: Within-group brain activations during error monitoring



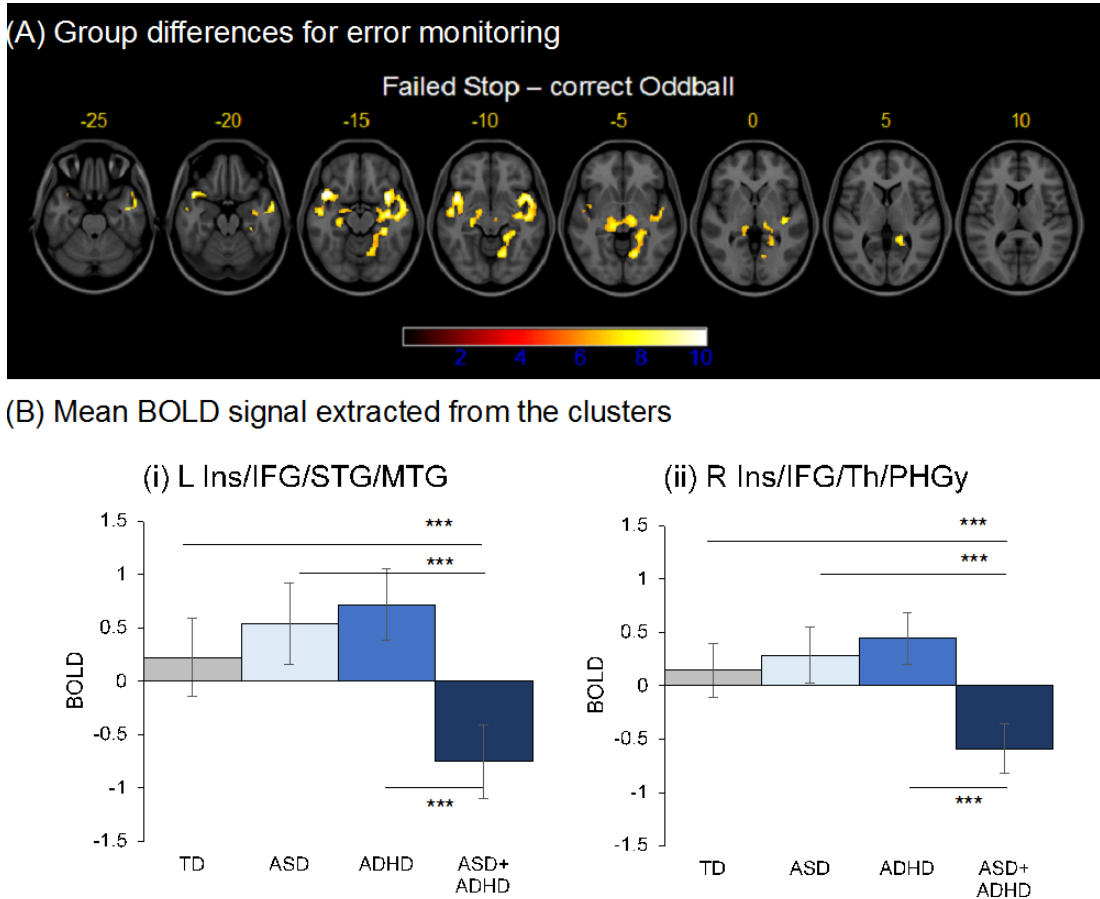
Note. Within-group brain activation clusters revealed during failed Stop-correct Oddball contrast corresponding to error monitoring in the TD group (A), ADHD group (B), and ASD+ADHD group (C). The clusters were obtained at a threshold cluster extent $k \geq 396$ voxels, corresponding to $p < .05$ FWE. No within-group brain activation clusters were observed at this threshold in the ASD group. Only increased activations are presented in the figure and images' left are the participants' left side.

Between-group Brain Activations

Differences between the groups were observed in two clusters (see Figure 5-4) comprising the left insula/IFG/STG/MTG (BA 13, 21, 22, 38, 47) and the right insula/IFG/thalamus(Th)/parahippocampal gyrus (PHGy). Univariate ANOVA analyses on the BOLD activation data extracted from these clusters were significant in the left insula/IFG/STG/MTG $F(3, 87) = 14.6$, $p < .001$ and right insula/IFG/Th/PHGy $F(3, 87) = 15.0$, $p < .001$. Post-hoc analyses, Dunn-Sidak corrected for independent groups, revealed that the ASD+ADHD group had smaller activation than the ASD

($ps < .001$), ADHD ($ps < .001$), and TD groups ($ps \leq .001$), which did not differ from each other, in both clusters (for peak coordinates and cluster sizes see Table 5-3).

Figure 5-4: Differences across groups in error-monitoring activations



Note. Covarying total movement, two clusters were revealed in the failed Stop-correct Oddball contrast corresponding to error monitoring processes, shown in (A). The clusters were obtained at a threshold cluster extent $k \geq 396$ voxels, corresponding to $p < .05$ FWE. Mean BOLD signal from the clusters and 95% confident intervals are plotted in (B). The ASD+ADHD group displayed reduced activation compared to the TD, ASD, and ADHD groups during error monitoring. Abbreviations: L/R = left/right, Ins=insula, IFG = inferior frontal gyrus, STG = superior temporal gyrus, MTG = middle temporal gyrus, Th = thalamus, PHGy = parahippocampal gyrus.

No significant influences of IQ across groups were found in both clusters, all $F_s(1, 86) \leq .20$, $ps \geq .65$, having covaried for IQ. The ANCOVA showed that the main effect of group remained significant for both the left insula/IFG/STG/MTG, $F(3, 86) = 14.3$, $p < .001$, and the right insula/IFG/Th/PHGy clusters, $F(3, 86) = 14.7$, $p < .001$, after covarying for IQ. Excluding individuals with stable SSRI, and covarying for IQ did not change the group effect in both clusters, $F_s(3, 73) = 15.1$, $ps < .001$. Furthermore, the group effects remained even after excluding individuals who were on any current medication from the analysis and simultaneously covarying for IQ, $F_s(3, 73) = 10.2$, $ps < .001$. Every post-hoc pairwise comparison on these additional

analyses in both clusters indicated that the ASD+ADHD group consistently showed an opposite pattern of activation compared to the ASD ($ps \leq .001$), ADHD ($ps \leq .001$), and TD group ($ps \leq .013$), which did not differ from each other.

Table 5-3: Peak coordinates, cluster sizes, and post-hoc analyses of error-monitoring contrast

Brain regions	BA	MNI coordinates			Z	k	Post-hoc
		x	Y	Z			
L ins/IFG/STG/MTG	13, 21,22, 38, 47	-46	14	-16	5.2	590	ASD***, ADHD***, TD*** > ASD+ADHD
		-52	-8	-10	4.0		
		-30	14	-18	3.7		
R ins/IFG/Th/PHGy	35, 36	36	10	-14	4.4	2652	ASD***, ADHD***, TD*** > ASD+ADHD
		50	8	-12	4.3		
		36	-12	-14	4.2		

Note. Two clusters revealed by the whole-brain ANOVA, covarying total head movement. Post-hoc comparison indicated significantly reduced activation in these clusters in the ASD+ADHD group relative to the ASD, ADHD, and TD groups, which did not differ to one another. The effect was robust to covarying for IQ and sensitivity analyses excluding individuals on medications.

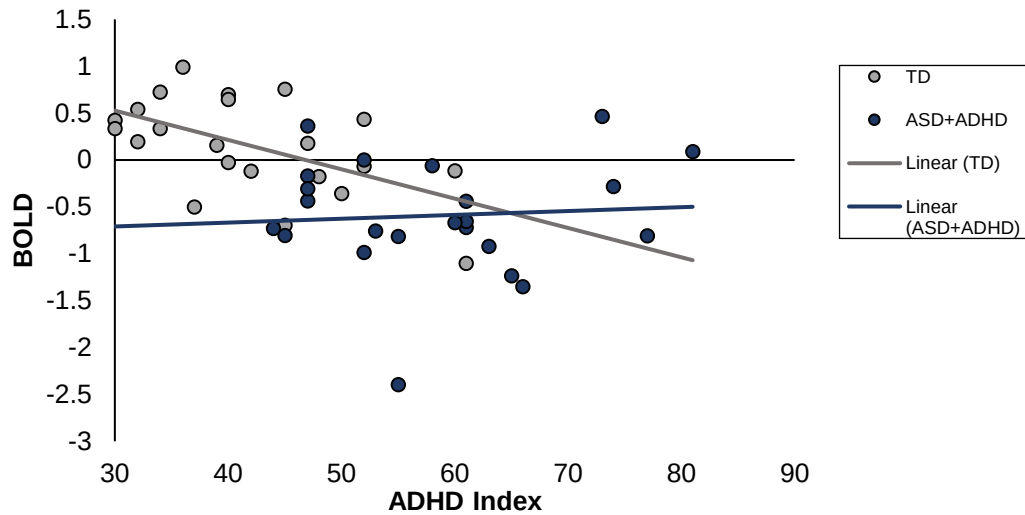
Correlational Analyses

Exploratory correlational analyses were conducted in the ASD+ADHD group and compared against the TD group. Self-rated ADHD difficulties correlated negatively with the error-monitoring cluster in the right ins/IFG/Th/PHGy, $r_{TD}(20) = -.55$, $p = .008$, in the TD group, but no equivalent correlation was found in the ASD+ADHD group, $r_{ASD+ADHD}(21) = .07$, $p = .75$. In both the TD and ASD+ADHD groups, the activations of the error-monitoring cluster on the right ins/IFG/Th/PHGy correlated with the SSRT, $r_{TD}(20) = -.50$, $p = .019$ and $r_{ASD+ADHD}(21) = -.45$, $p = .033$ (See Figure 5-5). The left ins/IFG/MTG/STG cluster did not correlate with the SSRT in the TD group, $r_{TD}(20) = -.24$, $p = .27$, but it did in the ASD+ADHD group, $r_{ASD+ADHD}(21) = -.46$, $p = .029$. No correlations were observed between the PES and activation in the left, $r_{TD}(20) = .29$, $p = .20$; $r_{ASD+ADHD}(21) = -.11$, $p = .62$, or the right clusters, $r_{TD}(20) = .31$, $p = .17$; $r_{ASD+ADHD}(21) = -.02$, $p = .93$. Self-rated autistic traits also did not correlate with activation in neither the left, $r_{TD}(20) = -.13$, $p = .55$ and

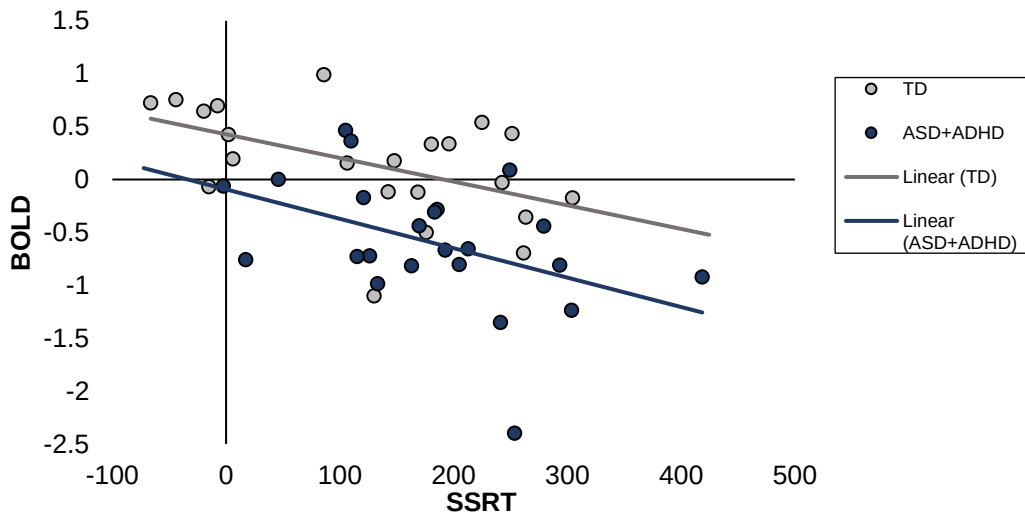
$r_{\text{ASD+ADHD}}(21) = -.036, p = .87$, nor the right clusters, $r_{\text{TD}}(20) = -.051, p = .82$ and $r_{\text{ASD+ADHD}}(21) = -.001, p > .99$.

Figure 5-5: Correlations between brain activations and ADHD symptoms and behavioural performance in the TD and ASD+ADHD groups

(A) Plot of mean BOLD signal from the right ins/IFG/Th/PHGy cluster against the ADHD index



(B) Plot of mean BOLD signal from the right ins/IFG/Th/PHGy cluster against the SSRT



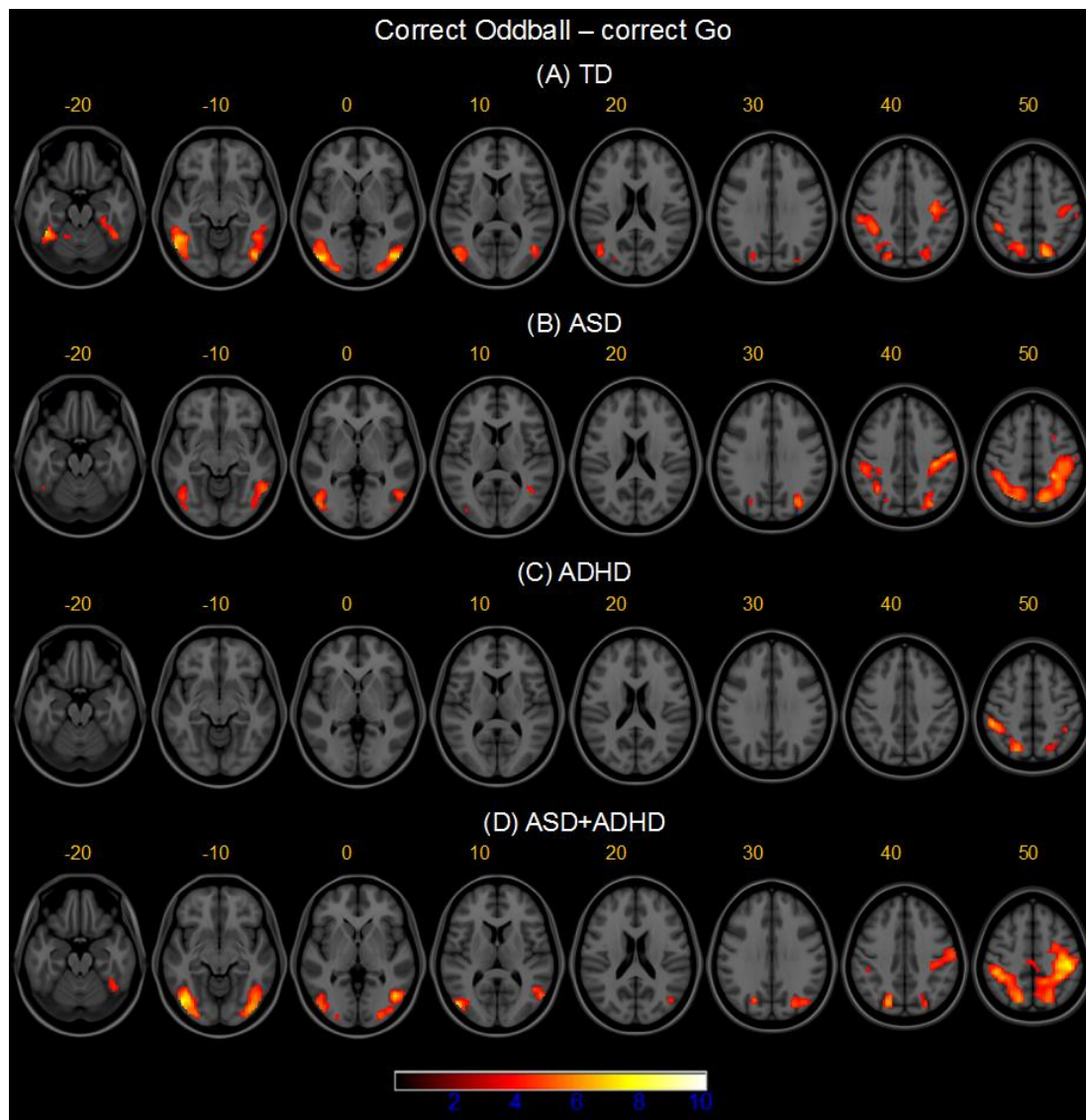
Note. Plots and trend lines between extracted mean BOLD signal from the right cluster against ADHD index (A) and against SSRT (B). Reduced activation was significantly associated with higher ADHD index, i.e., more ADHD related difficulties in the TD group, but not the ASD+ADHD group. Reduced BOLD activation was associated with longer SSRT, i.e., increased difficulties in response inhibition in both groups.

5.3.3.4 Attentional Contrast Oddball – Go

Within-group Brain Activations

As an additional analysis, Figure 5-6 displays within-group brain activations during the oddball trials, i.e. in relation to selective attention/target detection. The control group is associated with BOLD activation in bilateral ITG/MTG (BA37, 39), reaching

Figure 5-6: Within-group brain activations during selective attention



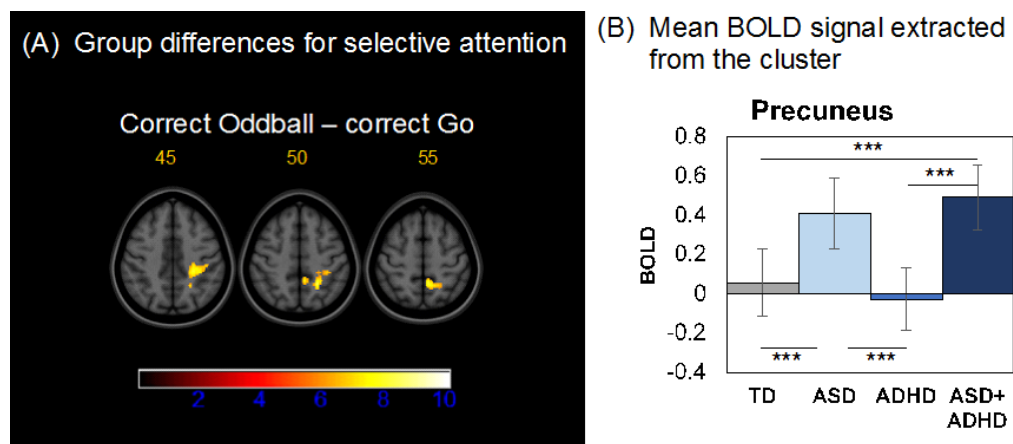
Note. Within-group brain activation clusters revealed during correct Oddball-correct Go contrast corresponding to selective attention in the TD (A), ASD (B), ADHD (C), and ASD+ADHD group (D). The clusters were obtained at a threshold cluster extent $k \geq 396$ voxels, corresponding to $p < .05$ FWE. Only increased activations are presented in the figure and images' left are the participants' left side.

into the middle/inferior occipital gyri (BA19, 18) and, on the left hemisphere, reached into the cerebellum. Activations were also observed in the bilateral SPL/precuneus

(BA7), reaching deep into IPS, right PMC (BA6), and left pre- and post-CG (BA4, 3). The ASD group showed extensive activation in several clusters in the bilateral SPL/IPL/precuneus/cuneus/superior occipital gyrus (BA7,19, 40), extending frontally to the pre- and post-CG (BA4, 3, 2, 1) on the right hemisphere, bilaterally in inferior occipital gyrus/FFG (BA19, 18), and in right PMC (BA6). The ASD+ADHD group was associated with similarly extensive brain activation as the ASD group, with activations observed in right precuneus/ SPL/IPL/IPS (BA7, 40), reaching frontally into right sensorimotor cortex and PMC (BA6), and ventrally into posterior MTG (BA39). Another cluster was observed in left SPL and IPS (BA40), and bilaterally, in ITG/MTG (BA37, 39), and middle and inferior occipital gyri (BA19, 18). Using the same threshold, the ADHD group showed the least activation bilaterally in SPL/IPS (BA7).

Between-group Activations

Figure 5-7: Differences across groups in selective-attention activations



Note. The right precuneus region differed across groups as shown in (A). The clusters were obtained at a threshold cluster extent $k \geq 396$ voxels, corresponding to $p < .05$ FWE. The ASD and the ASD+ADHD groups showed BOLD over-activation during selective attention compared to the TD and the ADHD group as shown on plot (B) Mean BOLD signal from the cluster are presented with 95 % confident intervals.

Group effect in the selective attention contrast was observed in a cluster in the right precuneus (BA7), $F(3, 87) = 10.6$, $p < .001$, as shown on Figure 5-7 (A). Pairwise comparison of the brain activation extracted from the cluster suggested

that the difference was driven by increased activation in the ASD and the ASD+ADHD groups, relative to the TD ($p = .012$ and $p = .001$, respectively) and the ADHD groups ($p = .001$ and $p < .001$, respectively) as shown on Figure 5-7 (B). The overall group effect remained, $F(3, 86) = 8.60$, $p < .001$, and so was the pattern of pairwise group differences ($ps < .05$) even after covarying for IQ. The latter exerted no influence on the between-group effect, $F(1, 86) = .50$, $p = .48$. As found in the error-monitoring contrast, the group effect stayed significant after the exclusion of individuals on SSRIs, while still covarying for IQ, $F(3, 82) = 7.97$, $p < .001$. The effect was still significant when all individuals on current medication were excluded, $F(3, 74) = 7.36$, $p < .001$. Pairwise comparisons in each additional analysis continued to show increased activations in the precuneus among individuals with ASD+ADHD relative to the controls ($ps \leq .004$) and the ADHD group ($ps < .002$). The activation in the precuneus in the ASD group remained increased compared to the ADHD group ($ps \leq .021$) and compared to the TD. The difference fell just below significance when the individuals with SSRI or any medications were excluded ($ps = .056$ and $.051$, respectively). The cluster and its peak coordinates are presented on Table 5-4.

Table 5-4: Peak coordinates, cluster size, and post-hoc analyses of the selective attention contrast

Brain regions	BA	MNI coordinates			Z	k	Post-hoc
		x	y	z			
R precuneus	7	10	-52	58	4.0	494	ASD, ASD+ADHD > ADHD***, TD***
		22	-50	50	3.8		
		24	-34	46	3.7		

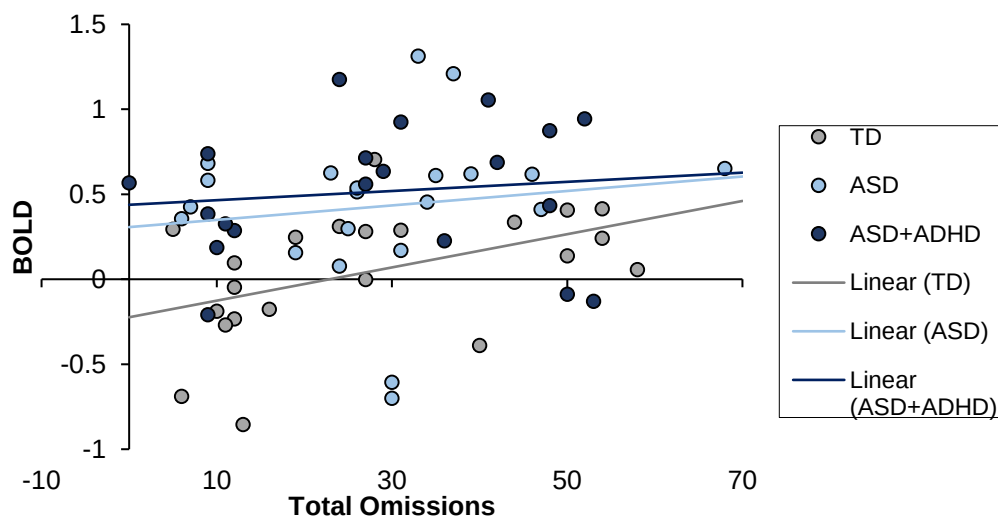
Note. A cluster in the right precuneus was revealed by the whole-brain ANOVA, covarying total head movement. Post-hoc comparison indicated significantly increased activation in this in the ASD+ADHD and the ASD groups relative to the, ADHD and TD groups, which did not differ to one another. The effect was robust to covarying for IQ and sensitivity analyses excluding individuals on medications.

Correlational analyses

A positive correlation was found between the brain activation in the right precuneus cluster and number of missed responses among the TD participants, $r_{TD}(20) = .46$,

$p = .032$. This was consistent with the view that reduced deactivation of the precuneus is associated with impaired selective attention. Neither the ASD, $r_{\text{ASD}}(19) = .14$, $p = .56$, nor the ASD+ADHD group, $r_{\text{ASD+ADHD}}(21) = .18$, $p = .41$, displayed significant correlations. No correlations were observed between the activation in the precuneus and ASD or ADHD behavioural traits.

Figure 5-8: Correlations between precuneus activation and the omissions rates



Note. Scatterplot and trend lines for the relationships between mean BOLD signal extracted from the precuneus cluster against missed responses, an index of attention difficulties. Increased activation was correlated with increased number of missed responses in the TD group but not in the ASD or ASD+ADHD groups which showed neural impairments.

5.4 Discussion

This study was the first investigation into the neural correlates of response inhibition and error-monitoring in groups of adults with ASD, ASD+ADHD and ADHD relative to controls. The study showed that the pure clinical groups did not differ from healthy controls or each other in their brain activation during motor response inhibition, regardless of whether the attentional oddball effect was controlled for. However, the ASD+ADHD group showed significantly reduced activation during error monitoring in two clusters encompassing left insula/IFG/ MTG/STG and in the right insula/IFG/Th/PHGy relative to TD and the pure groups. The activation in the

right hemisphere could be related to inhibition attempts that were too late to be successful as it was correlated with the SSRT in TD and ASD+ADHD groups, and the ADHD index in the control group only. Finally, both ASD and ASD+ADHD groups showed reduced deactivation relative to TD and ADHD groups in the right precuneus. This reduced deactivation was positively correlated with the number of missed responses in the TD group. The group effects in brain activation were found despite only weak evidence of task performance differences across groups, where SSRT was shown to be increased in the ADHD compared with the TD groups.

5.4.1 Reduced Activation in the Insula and Thalamus in the ASD+ADHD Group during Error Monitoring

Reduced activations in the ASD+ADHD group in the left insula/IFG/ MTG/STG and in the right insula/IFG/Th/PHGy during failed Stop-Oddball, relative to the TD, ASD, and ADHD groups could indicate neurofunctional abnormalities during error monitoring in the comorbid group. The reduced activation was maintained after covarying for IQ and excluding medicated participants, suggesting that this effect was a robust characteristic of individuals with dual diagnosis in the study. Activations in the bilateral insula, IFG, mPFC/dACC and bilateral IPL are typical during error detection (Hester et al., 2005; Klein et al., 2007; Rubia, Halari, Mohammad, et al., 2011). The insula, mPFC/dACC and IFG are key regions of the salience network (Klein et al., 2013; Menon, 2015; Menon & Uddin, 2010; Seeley et al., 2007). The overlapping activation during error monitoring and salience detection in these regions presumably reflects the salient experience of committing errors (Harsay et al., 2012; Klein et al., 2013).

Committing errors is an affectively aversive experience (Spunt, Lieberman, Cohen, & Eisenberger, 2012). It engages the autonomic nervous system and affects heart rates, skin conductance responses, and startle reflex (Hajcak, 2012).

Impairment in error monitoring as indexed by the electrophysiological signal ERN and abnormal ACC activation are thought to characterize anxiety, OCD, ASD and schizophrenia; and has thus been proposed as candidate transdiagnostic endophenotype across these disorders (Manoach & Agam, 2013; Proudfit, Inzlicht, & Mennin, 2013). The present findings suggest that IFG/AI and thalamic, and not ACC impairment, are the specific neural correlates of error monitoring in adults with ASD+ADHD.

The above interpretation of the findings could be challenged, however. The arrival of a stop signal after failed inhibition serves as a feedback for the mistake, thus eliciting a “whoops” effect that triggers implicit learning (Rieger & Gauggel, 1999). Under such conditions post-error response slowing is expected in the trial immediately after the failed stop is committed (Rubia et al., 2005; Schachar et al., 2004; Verbruggen & Logan, 2008). In this study, however, there was no evidence for a relation between these cluster activation and post-error behavioural adjustment. The lack of behavioural finding should be taken cautiously as it is likely that this study was not well-powered for behavioural analyses despite meeting sufficient sample size for a well-powered fMRI analysis (Thirion et al., 2007). There are also caveats for using the PES as an index of post-behavioural adjustment in this study. First, participants were aware that errors would occur half the time due to the task design. Second, they were instructed to be calm when they made a mistake to avoid involuntary motor movements in the MRI scanner. These instructions may have interfered with their post-error behavioural adjustment, which could possibly also explain the small magnitude of PES across groups. Nevertheless, the absence of relations between PES and brain activation could suggest that there was an alternative explanation for the neurofunctional impairment in the ASD+ADHD group.

An alternative explanation could be that the reduced frontostriatal activations was instead related to inhibitory actions that were too late to be successful.

According to the horse-race model of the stop-signal task performance, initiated Go processes are overtaken by the Stop processes during successful stopping (Logan et al., 1997; Verbruggen & Logan, 2009a), and conversely the already initiated Stop processes are falling behind the Go processes during unsuccessful stopping. Consequently, both failed and successful Stop processes elicit near-identical activations, encompassing regions such as the right hemispheric IFG, AI, dmPFC (pre-SMA), the globus pallidus and the STN (Aron & Poldrack, 2006; Boehler et al., 2010; Garavan, 2002). The association between the frontostriatal cluster and reduced SSRT in the right hemisphere for the ASD+ADHD and control groups did indeed reinforce this interpretation. Note, however, that interpretation was somewhat constrained by the fact that there was no significant difference of SSRT between the ASD+ADHD and the control groups, possibly due to the large variation of SSRT in the former. However, the absence of behavioural impairment in the presence of neural impairments during fMRI in the ASD or ADHD population is not uncommon (e.g., Chantiluke, Barrett, Giampietro, Santosh, Brammer, Simmons, et al., 2015; Cubillo et al., 2010, 2014; Kana et al., 2007; Ma et al., 2012; Shafritz et al., 2015), possibly since the arrivals of stop signals are more predictable in the online fMRI task than its offline version, which in turn was caused by the need to separate stop signals by at least 3-4 trials to account for hemodynamic delay in online task. In contrast, the signals in the offline task can be presented in more randomized and less predictable manner. The increased predictability of stop signals in the fMRI task leads to a loss of sensitivity towards behavioural performance. Finally, the task might have been more sensitive to tap behavioural performance in children than in adults with ADHD as findings have shown that children are more severely impaired than adults, in behaviour e.g., Alderson et al., 2007; Lipszyc & Schachar, 2010), brain structure and activations (Hoogman, ENIGMA group, Rubia, & Franke, 2017; Lei et al., 2015; Norman et al., 2016).

5.4.2 Increased Activations in the DMN in the ASD and ASD+ADHD Groups during Selective Attention

The contrast Oddball against Go trials revealed activations predominantly in the superior and inferior parietal regions. These regions are part of the dorsal attention network, which is activated during phasic alerting that triggers readiness for detecting environmental changes, presumably reflecting endogenous or top-down maintenance of attention (Corbetta & Shulman, 2002; Singh-Curry & Husain, 2009). In this study, the Oddball trials did not appear to evoke activations from the inferior prefrontal cortices (e.g., vIPFC or IFG) unlike during simple oddball detection or the CPT-AX task (Singh-Curry & Husain, 2009). This could be associated with the task-design, as the conventional oddball task typically prompt a behaviourally relevant and salient response when the rare Oddball but not when the Standard frequent stimuli appear (Vossel, Geng, & Fink, 2014). In the present task, both the Oddball and the standard Go trials required the same response. Therefore, the salience of the Oddball might have been reduced in comparison to that in the conventional task. Thus, it is possible that the Oddball trials evoked more top-down attention than bottom-up capture of attention in the present task.

In the ASD+ADHD and the ASD groups, enhanced precuneus activation (presumably reflecting reduced precuneus deactivation) was found during selective attention in this study. Reduced deactivation in precuneus regions during EF task have been found among children and adults with ASD (Chantiluke, Barrett, Giampietro, Brammer, Simmons, Murphy, et al., 2015; Christakou et al., 2013; Di Martino et al., 2013; Kennedy et al., 2006; Schmitz et al., 2006) and were typically attributed to the DMN abnormalities, reflecting lapses of attention and increased internal cognitive activities such as mind-wandering (Bonnelle et al., 2011; Christoff et al., 2009; Weissman et al., 2006). It is thus interesting that the activation in the right precuneus found in this study was positively correlated with omission errors in

the TD group, and while not significant, in the ASD and ASD+ADHD groups, supporting this interpretation of the role of this region as a DMN region in the context of selective attention.

Again, there was a lack group differences in omission errors to Go trials in the behavioural data that has constrained the interpretation for the findings. Furthermore, attentional difficulties are typical among children and adults with ADHD alone or ASD+ADHD (Adamo et al., 2014; Corbett, Carmean, et al., 2009; Sinzig, Morsch, Bruning, et al., 2008; Tye, Asherson, et al., 2014). Subtle task differences across studies could be the reason for these discrepancies but it is also possible that the neurofunctional impairment suggested by the present task is specific to ASD. In ASD, functional abnormalities in the precuneus and generally the DMN regions including the mPFC, PCC, and lateral parietal cortices, have been found not only during EF but also during social cognition tasks (Castelli et al., 2002; Kana et al., 2009; Lombardo et al., 2011; Murdaugh et al., 2012; Pantelis, Byrge, Tyszka, Adolphs, & Kennedy, 2015). The present study provided further support for the general presence of DMN deficits in adults with ASD, including those with co-occurring symptoms of ADHD during selective attention.

Despite previous findings of shared functional abnormalities between ASD and ADHD (Chantiluke, Barrett, Giampietro, Brammer, Simmons, Murphy, et al., 2015; Christakou et al., 2013; Di Martino et al., 2013), no indication of abnormal precuneus function was found in the ADHD group. The present finding was unexpected since evidence for task-related suppression of precuneus in ADHD has been presented previously (Dibbets et al., 2010; Liddle et al., 2011; Schulz et al., 2004). In the previous chapter I have highlighted the possibility that the individuals with ADHD might have reduced DMN deactivation during the entire task regardless of trial types as shown by Liddle et al. (2011). Although this interpretation is inconsistent with findings from Dibbets et al. (2010) and Schulz et al. (2004) that

found DMN deactivation in ADHD during inhibition trials, recent literature in adults with ADHD in fact suggested that they were unimpaired at down-regulating the DMN when switching from rest to task (Sidlauskaite, Sonuga-Barke, Roeyers, & Wiersema, 2016). Another finding has suggested that the true DMN abnormalities in adults with ADHD were not in the absolute failure to suppress the DMN at any tasks, but rather in the inability to adapt to “suboptimal, energetically challenging task conditions” (Metin et al., 2015, p. 212), i.e., during task with extreme event-rate presentations. These findings might explain why no task-related suppression in the DMN was observed in the ADHD group in this study.

5.4.3 The Absence of a Group Effect during Response Inhibition

The absence of a group effect in brain activation from the conventional response inhibition contrast of successful Stop against Go or Oddball trials was unexpected. In addition to the ANOVA, pairwise T-tests were carried out between the TD against each disorder group, which likewise revealed no activation differences, even when individuals with medication were excluded from the comparison. Group comparison in performance, i.e. of SSRTs also did not yield significant effects although pairwise comparison has shown that people in the ADHD group had shorter SSRT, and thus more inhibitory problem than the TD group. The absence of effect in performance particularly conflicts with previous findings of behavioural response inhibition deficits in children and adults with ADHD (Alderson et al., 2007; Lipszyc & Schachar, 2010). The lack of group differences also conflicts with well-established findings of under-activation in the right IFG/insula and the striatum, that is typically shown during motor inhibition in both children and adults with ADHD (Hart, Chantiluke, et al., 2014; Norman et al., 2016, Cubillo et al., 2010). Most importantly, the findings diverged from the behavioural findings using the GNG task (see Chapter 3), which suggested deficits in inhibition in both the ASD+ADHD and ADHD groups. However, as previously mentioned the study was not powered to detect neuropsychological

deficits and adults with ADHD have been less consistently shown to be impaired in inhibition measures (Lei et al., 2015; Norman et al., 2016).

Studies of response inhibition in adults with ADHD have shown less consistent findings than those in children. Some studies have shown no impairment during response inhibition (Carmona et al., 2012; C.-Y. Chen et al., 2015; Congdon et al., 2014) and a large study has even shown atypical laterality in ventrolateral impairments (van Rooij et al., 2015). Heterogeneous findings in fMRI studies of adults with ADHD have been attributed to, among others, mixed medication history and increased heterogeneity of adult, compared to the child samples (Cubillo & Rubia, 2010). Indeed, meta-analyses have shown that the proportion of participants exposed to stimulant in fMRI inhibition studies was associated with increased activations in bilateral IFG/AI, STL/MTL, and reduced activation in the SMA (Norman et al., 2016). These results appeared robust against current medication use, i.e., no impairments were evident among individuals with ADHD when individuals with medications (both SSRT and psychostimulant) were excluded from the analysis. However, it is unknown whether effect of past medication intake might have impacted upon these findings, as medication history was not collected during the study.

Findings in adults with ADHD would be influenced by increased heterogeneity in the population due to additional problems such as conduct problems and antisocial personality, anxiety, and substance abuse disorders (Biederman et al., 1993; Kessler et al., 2006; Molina & Pelham, 2014). Some of these problems were exclusion criteria for the study. Phone screening was conducted prior to inviting individuals into the study to rule out those with significant additional problems. However in-depth assessments using standardised instrument such as structured interviews were not conducted to completely rule out individual with additional psychiatric problems in the study.

Another likely explanation is age, which, as previous meta-analyses have shown, is associated with reduced abnormalities in the subcortical striatal structure and functions (Hart et al., 2013; Norman et al., 2016). Decline of hyperactive/impulsivity symptoms among adults with ADHD, have been widely documented in previous studies (Biederman et al., 2000; Faraone et al., 2005; J. Hill & Schoener, 1996), suggesting that the disorder is remitting with age. Likewise, (~40%) individuals who receiving their first-time ADHD diagnosis in adulthood, may have less symptom severity (Antshel et al., 2010; Barkley et al., 2008; Kolar et al., 2008). However, as shown in Chapter 3, individuals in the ADHD and the ASD+ADHD were impaired in response inhibition task and displayed more commission errors on the GNG task than the TD and ASD groups. Therefore, the proposed explanations for the lack of impairment in the ADHD group so far could only partial account for the current finding.

Against the backdrop of reduced consistency of neural impairment findings in adults with ADHD, possible increase of heterogeneity in the samples due to co-occurring problems, long-term therapeutic impact and age-dependent decrease of symptoms, and the detection of increased SSRT in the ADHD group when compared to the TD group, but apparent impairment on the GNG task, one may ask if the present stop-signal task has sufficient sensitivity for detecting response inhibition-related functional abnormalities among adults. At the stimulus presentation rate between 1700 – 2000 ms, the present stop-signal task is approximately twice as slow as the GNG task employed in Chapter 3. Studies in adults have shown that individuals can adopt different strategy beyond overriding planned action (see Verbruggen & Logan, 2009b). This could be a reason why no group effects were apparent across the behavioural outcomes of the present study, which also explained the apparent inconsistencies in the neuroimaging findings with the results of the neurocognitive study.

5.4.4 Findings in the Context of Comorbidity Debate

Chantiluke et al. (2014) concluded in their study that the ASD+ADHD group had the most pronounced neural impairments relative to pure ASD and ADHD groups, due to their weakest brain and temporal-discounting association in the frontal and striatal regions. Consistent with their interpretation, individuals with ASD+ADHD in this study also demonstrated the least neural activation during error monitoring when compared to the pure groups, which were undifferentiated from controls. I however refrained from concluding that the ASD+ADHD group had the most impairment overall as their task performance did not differ from young adults in the other clinical groups, even though the absence of group differences could have been related to the fMRI task's lack of power for detecting group differences.

It should be noted that neural impairments in the IFG/AI and thalamus observed in the ASD+ADHD group have been previously reported in children with ADHD, in some cases accompanied by post-error response slowing (Cubillo et al., 2010; Plessen et al., 2016; Rubia, Halari, Mohammad, et al., 2011; Vasic et al., 2014). In adults with ADHD, however, a recent study reported only a small cluster of reduced activations in the right IFG (C.-Y. Chen et al., 2015), with no behavioural performance impairment in the ADHD group, which was interpreted as improvement of neurofunctional impairment with age. Neural impairments in structure and function in ADHD have been found to be associated with a delayed brain maturation in ADHD (Hoogman et al., 2016; Rubia, 2007; P. Shaw et al., 2007, Sripada et al., 2014). Speculatively, it is thus possible that the observed error-monitoring related frontostriatal impairment found in the ASD+ADHD group reflected an ADHD-like neural phenotype with an extended maturational delay that may have grown out in the pure groups. This tentative explanation, however, needs to be further explored either in a longitudinal study or in a case-control design involving both adult and paediatric populations.

The ASD and the ASD+ADHD groups showed similar DMN over-activation during selective attention, which provides the first evidence, from the newly collected data for this thesis, for a possible shared neural impairment between the two disorder groups, distinct from the ADHD group. If indeed reduced DMN suppression in the ASD is disorder-specific relative to ADHD in adulthood, the precuneus abnormality in the ASD+ADHD group would constitute an additive pattern of the pure groups in adulthood. Note, however, that the present result differs from previous findings in children with ASD and with ADHD, which have shown shared reduced DMN suppression during sustained attention (Christakou et al., 2013) and reduced shared functional connectivity in the DMN in pure and comorbid ASD+ADHD groups (Di Martino et al., 2013). It is possible that the differing findings were influenced by age, as the present investigation was conducted in young adults. Further studies in samples with wider age range might help to elucidate the variation of findings.

5.4.5 Strengths and Limitations

A strength of this study was the inclusion of solely male participants. Although the female-to-male ratio of ADHD in adulthood is approximately equal (Fayyad et al., 2007; Simon et al., 2009), there are substantially more males than females with ASD according to epidemiology studies (Elsabbagh et al., 2012; Idring et al., 2012; Mattila et al., 2011). Studies in children and adults with ADHD suggested sex differences in neurocognitive performance, brain structures, and functions, with males showing higher levels of neurocognitive impairment (Bálint et al., 2009; Kasper et al., 2012; Park & Park, 2016; van Ewijk et al., 2015; Villemonteix, De Brito, Slama, et al., 2015). Evidence of sex differences among children and adults with ASD have also been reported (Frank, Baron-Cohen, & Ganel, 2015; Jung et al., 2015). Therefore, the recruitment of all male subjects has enhanced the homogeneity of participant characteristics across groups. Another strength of the

study was that a large proportion of the participants, including *all* participants in the pure ASD group, were non-medicated at the time of the study. These enabled a sensitivity analysis excluding individuals on any current psychotropic medication including, the SSRIs and psychostimulants.

Several weaknesses of this study included the non-homogeneous IQ distribution across groups. Despite my best efforts in participant recruitment, the group of controls and ADHD participants had significantly higher IQ than, particularly, the participants in the ASD group, who scored in the average range for their age group. Nevertheless, analyses have shown that the difference of IQ across groups did not influence the findings. The recruitment of uniformly right-handed participants across these samples was not feasible as there were frequent incidences of left-handedness among the participant pools with ASD (reviewed by Lindell & Hudry, 2013). No differences were found in the handedness across groups and there were approximately equal proportions of left-handed participants in each group. Another limitation is the number of participants per group, which, although exceeding 20 participants recommended for neuroimaging investigation (Desmond & Glover, 2002; Thirion et al., 2007), were still relatively quite small and could be underpowered to detect small effects. Finally, there was insufficient exploration of any other co-occurring psychiatric difficulties among the participants. Increased emotional, conducts, and peer relationships problems were observed among the clinical groups relative to controls on the SDQ17+, but the extent of their clinical significance was unknown as no in-depth assessments using more robust instruments such as structured clinical interview were carried out.

5.4.6 Implications and Future Directions

This study explored the neural correlates of inhibitory function, error monitoring, and selective attention in young adults with ASD, ASD+ADHD, and ADHD. The results

suggested that neural impairments in bilateral frontostriatal regions was most detectable in the ASD+ADHD group during error-monitoring, whereas reduced precuneus suppression was found in the ASD+ADHD and the ASD groups during selective-attention. Given that the neural impairments found in the adult ASD+ADHD group were similar to those typically found in younger populations with pure ADHD, it was possible that such phenotype represent a more persistent impairment for the comorbid group. Limiting the interpretation to this finding was the fact that the behavioural performance did not differ across groups. Also, there was no direct comparison between adult and children samples in the study to confirm the hypothesised persistent impairment in the comorbid group. Furthermore, there was a distinctive absence of group difference in inhibitory-related neural impairments. Although this was not entirely unexpected based on previous studies in adults with ADHD, the discrepant findings between the neurocognitive deficits in the earlier chapter and the performance results in the fMRI studies pointed towards a problem with task sensitivity. Future studies in this topic may thus consider exploring response inhibition using a range of approaches, including methods with higher sensitivity. Investigation into wider age ranges of participants would also be useful to increase our understanding of the stability of these neural phenotypes in the three disorder groups, throughout the developmental span.

6 Study V: An fMRI Study of Duration Discrimination in Adults with ASD, ADHD, and ASD+ADHD

6.1 Introduction

The sense of timing is an integral part of everyday functioning. Getting ready, turning up on time, or being able to wait for one's turn, could all be related to the ability to perceive time. Within the time perception literature, the term "interval timing" refers to the "perception, estimation and discrimination of durations" (Buhusi & Meck, 2005, p. 757) and is contrasted to "event timing", which reflects the order of events (Falter & Noreika, 2014). There is substantial evidence for deficits of interval timing among children and adults with ADHD (Barkley, Murphy, et al., 2001; Meaux & Chelonis, 2003; Plummer & Humphrey, 2009; Smith, Taylor, Rogers, Newman, & Rubia, 2002; Suarez, Lopera, Pineda, & Casini, 2013; Toplak, Rucklidge, Hetherington, John, & Tannock, 2003), and findings of impaired neural correlates for timing in that population (Hart et al., 2012; Rubia, Halari, Christakou, & Taylor, 2009; Smith et al., 2013; Vloet, Gilsbach, et al., 2010). Emerging evidence also suggests disturbances of timing among children with ASD (Allman et al., 2011; Bhatara et al., 2013; Falter et al., 2012; Maister & Plaisted-Grant, 2011; J. S. Martin et al., 2010); although no fMRI studies of interval timing have been conducted in this population to date. An fMRI study comparing individuals with ASD, ADHD, and ASD+ADHD would simultaneously reveal the neural correlates of timing function among individuals with ASD and be useful for exploring the neuropathology of ASD+ADHD group.

6.1.1 The Neuropsychological Model and Methods for Investigating Interval Timing

A classical neuropsychological model of interval timing is described within the framework of “scalar expectancy theory” (Gibbon, 1977; Gibbon, Church, & Meck, 1984), based on the observation that human and non-human species can be trained to anticipate a reward after a fixed time interval. After receiving such training, the subjects show anticipatory responses to the reward with high probability after the fixed interval, regardless of whether the reward was present or not. To explain this behaviour, Gibbon (1984) proposed an intrinsic timing function in the form of a pulse-generating “internal clock” or a “pacemaker”. This internal clock sends regular “pulses” to an “accumulator” throughout the duration. Under operant training condition, the pulse information is stored permanently in a “reference memory” (see Matell & Meck, 2000, p. 97), whereas under testing conditions, such as interval estimation, newly accumulating pulses in the working memory are compared to permanently stored information in the reference memory to decide on responses. Importantly, the interval timing has a scalar property akin to Weber’s law for sensory perception (Buhusi & Meck, 2005; Gibbon, 1977; Gibbon et al., 1984), that is, an individual’s performance or estimation on timing increased in variability as the length of training interval is increased.

Within the interval timing literature, distinctions have been made between subsecond and suprasecond timing, and between motor and perceptual timing (reviewed by Noreika et al., 2013). Subsecond timing is thought to be “automatic”, that is, it relies on brain circuitries associated with learned motor movement, instead of deliberate cognitive control (Lewis & Miall, 2003). In contrast, suprasecond timing relies on higher executive mechanisms such as working memory and sustained attention (Barkley, Murphy, et al., 2001). Human experimentation, and certainly those involving the clinical population, mostly require explicit responses, although

some tasks require primarily perceptual functions (see, e.g., Gooch, Snowling, & Hulme, 2011; Huang et al., 2012; Sonuga-Barke et al., 2010), while others require more motor actions (see e.g. Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Bauermeister et al., 2005; Brenner et al., 2015; J. S. Martin et al., 2010; McGee, Brodeur, Symons, Andrade, & Fahie, 2004; and other studies below).

Primarily perceptual timing methods, such as the duration discrimination (Smith et al., 2011, 2002) and temporal bisection tasks (Droit-Volet & Wearden, 2001; Kopec & Brody, 2010) were typically used for investigating subsecond timing. In both tasks, participants are typically asked to identify, between two stimuli, one which lasts slightly longer than the other (Smith et al., 2011). The time function ability could be judged from the number of correct identification or from the duration discrimination threshold (DDT), that is, the duration limen where discrimination is just feasible (Smith et al., 2002). Time estimation, production and reproduction are typically used for assessing suprasecond timing (Barkley, Murphy, et al., 2001; Bauermeister et al., 2005). The time reproduction task is an often-used paradigm, especially in ADHD and ASD studies (e.g., Bauermeister et al., 2005; Brenner et al., 2015; Maister & Plaisted-Grant, 2011; J. S. Martin et al., 2010; Pironti et al., 2016). In this task, participants are typically given sample durations by means of sound or light stimuli over a brief interval, and then they are required to replicate the intervals with motor actions, for example, by pressing a light or sound switch, and reproducing the timespan. Since time reproduction requires the individuals to memorise the sample durations and to replicate these after a delay, it is considered to involve the highest working memory load among timing tasks (Barkley, Murphy, et al., 2001).

6.1.2 The Neural Correlates of Interval Timing

Comprehensive reviews show that interval timing relies on the activation of the fronto-striato-thalamo-cerebellar circuitries, encompassing the premotor, prefrontal cortices, including the mPFC, dlPFC, IFG, subcortical structures such as the BG and thalamus, and the cerebellum (Buhusi & Meck, 2005; Droit-Volet, 2013; Noreika et al., 2013). These were supported by several meta-analyses of fMRI studies of timing among typically developing individuals (Lewis & Miall, 2003; Radua, Del Pozo, Gómez, Guillen-Grima, & Ortuño, 2014; Wiener, Turkeltaub, & Coslett, 2010). An early meta-analysis focused on the sub- or suprasecond timing distinction, whereby the findings suggested that the former timing function was associated with motor cortex activations, while the latter was associated with activations in the dorsal attentional network regions, including the right dlPFC and the parietal cortices (Lewis & Miall, 2003). However, the meta-analysis used over-inclusive selection criteria for the studies, some of which included inappropriate contrasts against a task-negative baseline, e.g., of resting or passive viewing.

Building from this early study, recent meta-analyses findings suggest that timing functions rely on a complex system distributed over a wide network of regions (Radua et al., 2014; Wiener et al., 2010). Across all task types, common activations were found in the bilateral SMA, and right IFG, and specific activations were associated with motor timing in the left insula, MFG, and right IPL. Furthermore, perceptual timing activated the left putamen and right insula (Wiener et al., 2010). Subsecond timing, which activated the bilateral MFG, IPL, right caudate/putamen/insula *and* the posterior cerebellum, was distinctive from suprasecond timing that activated the pre-CG, and bilateral insula over the common SMA and IFG activation. The simple dichotomisation of sub- and suprasecond timing and the findings of cerebellar activation in subsecond timing is consistent with a previous proposal (Penney & Vaitilingam, 2008). However, this was likely oversimplified as studies

have shown that subsecond time discrimination carried out by contrasting suprasecond intervals (e.g., 1300 ms against 1000 ms) elicit frontal activations in the ACC/SMA, bilateral dlPFC, right pre-/post-CG, and right IPL, among typically developing individuals (Gutyrchik et al., 2010; Smith et al., 2013; Smith, Taylor, Brammer, Halari, & Rubia, 2008). In contrast, the cerebellar activations were elicited when subsecond intervals were discriminated against another subsecond duration (Neufang, Fink, Herpertz-Dahlmann, Willmes, & Konrad, 2008; Shih, Kuo, Yeh, Tzeng, & Hsieh, 2009; Vloet, Marx, et al., 2010). This might indicate the influence of the scalar property of interval timing upon these findings. Finally, the meta-analysis by Radua et al. (2014) show that regions activated during timing tasks, such as the SMA, insula/operculum, dlPFC, thalamus and striatum, largely overlap with regions activated during cognitive control tasks, suggesting that individuals with neural impairments associated with cognitive control tasks will also show impairments during a timing task.

6.1.3 Interval Timing in ADHD and in ASD and Their Neural Correlates

For approximately two decades studies have amassed evidence for timing difficulties among children and adults with ADHD (Barkley, Edwards, et al., 2001; Barkley, Murphy, et al., 2001; Bauermeister et al., 2005; McGee et al., 2004; Pironti et al., 2016). These studies, primarily based on motor timing reproduction, typically showed that individuals with ADHD over- or underestimated time intervals when asked to reproduce them. Interval timing deficits extended into the subsecond perceptual domain in ADHD (Gooch et al., 2011; Huang et al., 2012; Smith et al., 2002; Sonuga-Barke et al., 2010; Toplak & Tannock, 2005). Using a duration discrimination approach, Smith (2002) found that on average 22 ADHD children had 50 ms longer DDT compared to age-matched controls. Other studies with larger samples of children with ADHD (> 40 children per group) using the same task, but different sensory modalities conducted by Toplak and Tannock (2005) and Huang et

al. (2012) also showed that children with ADHD had longer DDT than typically developing children. This indicated reduced sensitivity towards short time intervals. The study by Huang (2012) was especially interesting, as it showed that children with ADHD, both with and without hyperactive presentation, had equally impaired timing relative to controls. Timing deficits appeared to be specific to ADHD relative to dyslexia or specific reading disorders (Gooch et al., 2011; McGee et al., 2004). In addition, using several approaches for investigating timing, response inhibition, and delayed reward among 71 children with ADHD, Sonuga-Barke et al. (2010) concluded that timing deficits formed an independent domain of difficulties, over and above the two other cognitive functions and considered the difficulties as one of multiple pathways towards ADHD.

A meta-analysis of neuroimaging studies of timing in ADHD, which included studies of motor timing tasks, temporal discounting, and duration discrimination tasks, showed converging findings towards reduced activation in the right cerebellum, left IFC/insula, and left supramarginal gyrus, and increased activation in the precuneus and PCC regions, in the ADHD group relative to controls (Hart et al., 2012). An fMRI study in boys with ADHD showed reduced activation in the ACC and posterior cerebellum using a whole-brain analysis (Vloet, Gilsbach, et al., 2010); and using the whole-brain approach, one study found reduced activation in the ADHD boys relative to controls in the bilateral IFC, left insula/putamen, SMA/ACC, and right dlPFC (Rubia et al., 2014). On the other hand, an analysis using the ROI approach showed that single doses of MPH or atomoxetine resulted in upregulation of the right vlPFC/insula (Smith et al., 2013). No fMRI studies of timing functions in adults with ADHD have been performed to date, although an exploratory study has revealed a relationship between GM abnormalities and time reproduction impairment (Pironti et al., 2016). In this study, timing discrepancy scores, which are under- or overestimation during time reproduction task outside the scanner,

correlated with increased GMV in the right cerebellum lobule V among adults with ADHD. Taken together, timing deficits in ADHD are underpinned by abnormalities in several regions in the lateral and medial prefrontal cortices, including the IFG/insula, dlPFC and ACC/SMA, BG, parietal regions including PCC, IPC, precuneus, supramarginal gyrus, and cerebellum.

In ASD, evidence for time deficits is accumulating (Brenner et al., 2015; Maister & Plaisted-Grant, 2011; J. S. Martin et al., 2010; Szelag, Kowalska, Galkowski, & Pöppel, 2004). Maister and Plaisted-Grant (2011) showed, using the time reproduction task and standard durations between .5 and 45 s, that children with ASD made more reproduction errors relative to age- and IQ-matched controls for the shortest duration, possibly due to attentional deficits, and longest duration, possibly related to memory difficulties. Using standard durations between 4 and 20 s, Brenner et al. (2015) found that 27 children with HFA were significantly less accurate and less consistent in their time reproduction than typically developing controls. Younger children and those with poorer working memory appeared to have increased timing difficulties, and, interestingly, inattention and hyperactivity symptoms were neither related to accuracy nor consistency. Although no studies have investigated subsecond timing in individuals with ASD, some studies have used short intervals that would limit the confounding influence of working memory. Szelag et al. (2004) showed that children with autism with normal IQ reproduced their target durations off by 2 s on average, although the study relied on a small sample of seven autistic children only. Martin et al. (2010) found that among adults with HFA, interval reproduction for short durations between .5 to 4.1 s deviated significantly while longer durations were underestimated more compared to those reproduced by age- and IQ-matched controls.

No fMRI studies have investigated time interval perception in ASD. However, structural MRI studies in individuals with ASD have shown structural and functional

abnormalities in key regions of timing function. For instance, GM abnormalities in the cerebellum were common, especially in the left hemisphere (D'Mello & Stoodley, 2015; Ecker et al., 2012; Foster et al., 2015; Retico et al., 2016; Toal et al., 2010). Other brain regions implicated in timing functions where individuals with ASD have displayed GM abnormalities include: the BG (Bonilha et al., 2008; Foster et al., 2015; Toal et al., 2010), fronto-lateral regions such as the left and right dlPFC (Ecker et al., 2012; McAlonan et al., 2008), and the IFG (Abell et al., 1999; Cheng et al., 2011; Kosaka et al., 2010; Mengotti et al., 2011). The recent study by Chantiluke et al. (2015) showed reduced activations in the right dlPFC among children with ASD, shared with age-matched children with ADHD, during an n-back working memory task (a region and a cognitive function also implicated during timing tasks). Finally, in the only fMRI study of timing functions in individuals with ASD+ADHD to date, Chantiluke et al. (2014) showed that during the temporal discounting task, which involves both temporal foresight and reward choice (Cooper et al., 2013; Luhmann, 2009; Noreika et al., 2013; Rubia, Halari, Christakou, et al., 2009), boys with ASD+ADHD demonstrated the most pronounced neural impairments. These boys showed the weakest association with reward discounting, not only in reward and motivation- regions such as the vmPFC/OFC and ventral striatum, but also in regions such as the IFG that is implicated in timing functions. Given that these brain regions have been implicated in previous studies of timing perception and the evidence of impaired time reproductions in people with ASD, it is reasonable to expect that individuals with ASD, similarly to individuals with ADHD, would demonstrate neural impairments during the duration discrimination task.

6.1.4 The Aims of This Study

This study was aimed at investigating timing task performance among young adults with ASD, ADHD, and ASD+ADHD. Previous studies suggest that the difficulties in interval timing are characteristic of individuals with ADHD, supported by fMRI

studies in the population (e.g., Hart et al., 2012; Rubia et al., 2014; Smith et al., 2013). Based on several previous neurobehavioural studies, interval timing difficulties are also expected to be present among individuals with ASD (Brenner et al., 2015; Maister & Plaisted-Grant, 2011; J. S. Martin et al., 2010; Szelag et al., 2004). Although no fMRI studies have been conducted in this population, neural impairments and structural deficits have been reported in several key regions involved in timing functions, including the BG, dlPFC, IFG and cerebellum (e.g., Chantiluke, Barrett, Giampietro, Brammer, Simmons, & Rubia, 2015; D'Mello et al., 2015; Ecker et al., 2012; Foster et al., 2015; Toal et al., 2010). For these reasons, individuals with ASD or ADHD were expected to have equivalent behavioural and neural impairments during interval timings, as judged from their performance on the duration discrimination task. Based on findings from the previous chapter showing that individuals with ASD+ADHD were most impaired during a response inhibition task, and Chantiluke's (2014) study that has shown increased temporal reward discounting and weaker brain-behaviour correlations during duration discrimination among individuals with ASD+ADHD relative to ASD and ADHD groups. Individuals with ASD+ADHD were expected to show the most pronounced neural impairments relative to those with ASD or ADHD alone.

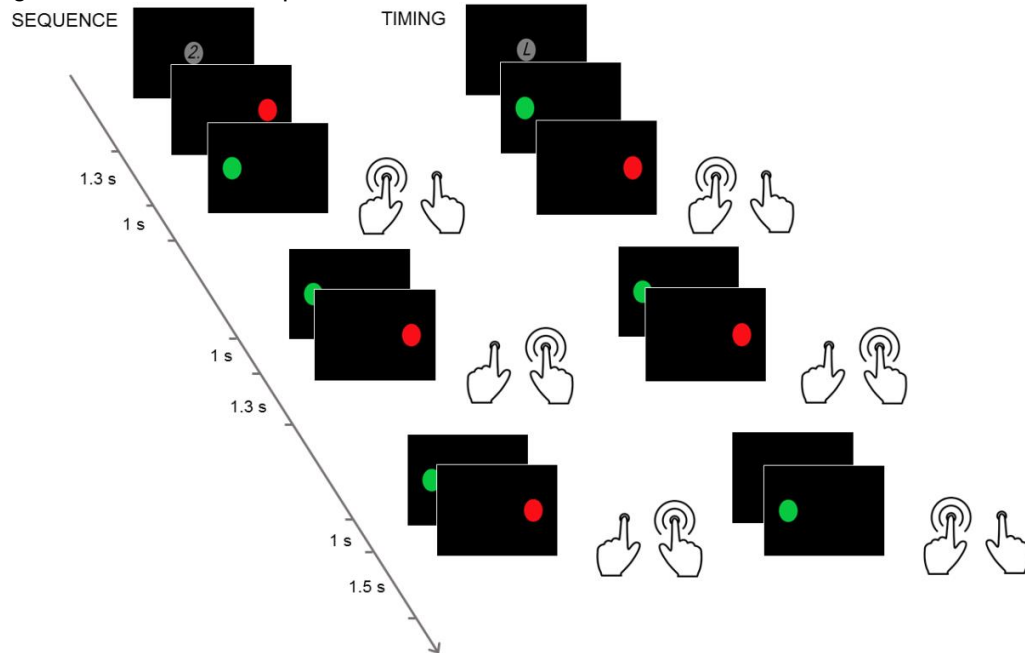
6.2 Methods

6.2.1 Participants

This study involved 107 young-adult males, aged 20-27 years with diagnoses of ASD, ADHD, ASD+ADHD, and a TD group with neither ASD nor ADHD (see Chapter 4 for full recruitment details and participant characteristics). Data from two participants with ASD, three participants with ADHD, and two participants with ASD+ADHD were rejected from the final analysis due to excessive head movement

beyond 3mm. One further participant was excluded from the ASD group as his behavioural data was lost due to technical error. Another participant's data from the ASD+ADHD group was also unused due to an incidental finding. The final sample comprised 26 TD controls, 23 individuals with ASD, 24 with ASD+ADHD, and 25 with ADHD.

Figure 6-1: Schematic representation of the duration discrimination task



Note. Blocks of Sequence (left) and Timing (right) for the duration discrimination task. Pairs of circles were presented one after another. One of the circles was red, always appearing on the right-hand side of the screen, and the other was green, always on the left-hand side. In the Sequence block, which was commenced by a grey circle labelled "2", participants were required to identify the circles that appeared later between the pairs. In the timing condition, which was commenced by a grey circle labelled "L" the participants were required to identify the circles that lasted longer.

6.2.2 The Duration Discrimination Task

This duration discrimination task probed the neural correlates of timing function in subsecond threshold, thus put minimal load on the working memory. The task consisted of two conditions: the (1) time discrimination and the (2) temporal order conditions, arranged in alternating-block design that offered good power of detection for timing perception in typically developing populations (Smith et al., 2011) and adolescents with ADHD (Hart, Marquand, et al., 2014; Rubia et al., 2014; Smith et al., 2013). The task consisted of 10 blocks alternating between the two conditions, starting with the temporal order condition. Each block began with a 3s cue

consisting of a grey circle depicting the number “2” or the letter “L” that indicated the upcoming condition to the participants, i.e., the number 2 indicated the beginning of the temporal order condition, while the letter L indicated the time discrimination condition. Each block lasted for 30 s and consisted of six trials lasting for 4.4 – 4.6 s. In each trial, a pair of circles (coloured green and red) was shown sequentially on the left- and the right-hand side of the screen. The green circle was always presented on the left, while the red was always on the right. There were equal numbers of trials where the left and the right circle appeared first. One circle, which could be the first or the second to appear, was shown for 1000 ms while the other for 1300, 1400, or 1500 ms. One block consisted of two trials each of the combinations: 1000 versus 1300 ms, 1000 versus 1400 ms, and 1000 versus 1500 ms; and each trial was followed by a 2100 ms response period. The participants responded to the task by pressing a left or right button. During the time discrimination condition, the participant had to indicate which circle, between the pairs, stayed longer on the screen, whereas in the temporal order condition, the participant had to indicate which circle was shown second. To align the participants’ response onsets temporally, they were asked to respond as soon as the second circle disappeared from the screen. The key behavioural variable of interest in this task was the number of errors, MRT and SDRT, where higher values indicated more difficulties.

6.2.3 Acquisition of fMRI Data

Imaging data were acquired on a General Electric (GE) MR750 3.0T MR scanner (General Electric, Milwaukee, WI, USA) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology, and Neuroscience, King’s College London, UK. An 8-channel head coil was used for RF transmission and reception. The echo planar image (EPI) gradient-echo pulse sequence (TR/TE = 2000/30ms, flip angle=75°, FOV = 21cm x 21cm, 64 x 64 matrix, in-plane resolution=3mm, slice

thickness=3 mm with gap of 0.3 mm) was used to acquire 41 slices of T2*-weighted MR images parallel to the inter-commissural plane, depicting BOLD contrast and covering the entire brain. The 5-minute scan resulted in 153 volumes in time series. A whole-brain high resolution structural T1 scan (Enhanced Fast *Gradient Echo* 3-Dimensional/EF-GRE3D), co-registered with individual activation maps during pre-processing, was also acquired in the inter-commissural plane with TE=3.016 ms, TR=7.312s, flip angle = 11°, 196 slices, FOV = 27cm x 27cm, 256 x 256 matrix, and slice thickness and gap of 1.2mm and 1.2mm.

6.2.4 Analysis of fMRI Data

All fMRI data went through standard pre-processing steps including slice-time correction, realignment, co-registration to the individual structural T1 scan, segmentation, normalisation and smoothing. Each participant's EPI data were normalised to the Montreal Neurological Institute (MNI) EPI template and smoothed using the 8-mm Gaussian kernel. Statistical analyses were conducted using the Statistical Parametric Mapping version 8 (SPM8). The analyses were done in two steps to ease the computational load. At the subject-level analyses, BOLD response to the experimental blocks was predicted using a vector of onsets and durations convolved with the canonical HRF. The contrast Timing versus Sequence were used to probe time processing. Seven nuisance regressors were included to control the effects of volume-to-volume head motion and abrupt movement above 1 mm. A high-pass filter was applied at the cut-off (128s) and a first-order autoregressive model was used to correct for time series correlation.

Within-group activations were reported using a stringent cluster extent threshold at $p < .05$ with family-wise error (FWE) correction and a voxel threshold of $p < .001$. At the group level, the two contrasts were submitted into a univariate ANCOVA, with group as independent factor and total movement, which was

computed in framewise displacement to capture the head movement from one volume to the next (Power et al., 2014), was included as a regressor in the group level analyses. Between-group activations were reported at corrected cluster size ≥ 396 voxels, corresponding to a cluster defining threshold of .001 and FWE-corrected alpha level of .05 (http://blogs.warwick.ac.uk/nichols/entry/spm5_gem_6/). As studies typically compare one disorder group against controls, pairwise *t*-tests between each clinical group and controls were conducted to allow comparison with the literature, even if the traditional ANOVA returned no significant findings. When significant clusters were found the BOLD activations for each individual subject were extracted from significant clusters using the MarsBaR toolbox (Brett et al., 2002), and subsequently analysed in the IBM SPSS Statistics for Windows version 22 (IBM Corp., 2013). Post-hoc analyses were conducted pairwise with Dunn-Sidak correction, and further comparisons were conducted on SPSS covarying for IQ, and excluding individuals on medications. In addition, correlations between brain activity and relevant behavioural and trait measures in the groups showing impairments were contrasted against the findings in the control group.

6.2.5 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows version 22 (IBM Corp., 2013). Group differences in continuous demographic data, such as age and IQ, and behavioural reports of hyperactivity symptoms and autistic traits, were assessed using the univariate ANOVAs. Performance data on the timing task was investigated using 4×2 (group × condition) mixed-design ANOVAs, exploring between-subject effect of group (TD, ASD, ADHD, ASD+ADHD) and comparing within-subject factor of condition (time discrimination, temporal order). Pairwise *t*-tests of behavioural performance between each clinical group and the typically developing controls were also carried out to mirror the analyses conducted on the brain data. Where a group effect was observed, post-hoc analyses, employing the

Dunn-Sidak correction for multiple comparisons of independent groups, were conducted to investigate the pairwise differences across groups and to explore the main influences for the differences.

6.3 Results

6.3.1 Group Characteristics

The group characteristics of this sample are presented in Table 6-1. The sample did not differ in age and handedness. However, FSIQ differed significantly and was higher in the ADHD and the TD groups compared to the ASD group, $F(3, 87) = 5.2$, $p < .002$. As found in the full sample (see Chapter 4), individuals in the ASD+ADHD or ADHD rated themselves as having higher inattention, hyperactivity and impulsivity, and overall ADHD index on CAARS than controls or the ASD group, all $F_s(3, 86) \geq 17.7$, all $ps < .001$. Multiple comparisons also suggested that individuals with ADHD rated themselves to have higher hyperactivity than those with ASD+ADHD ($p < .001$). Informant scores of DSM-IV inattention, hyperactivity/impulsivity, symptom numbers and ADHD index, obtained from among the clinical groups, were likewise significantly higher in the ADHD and the ASD+ADHD groups than the ASD group, all $F_s(3, 86) \geq 9.5$, all $ps < .001$. All individuals in the clinical groups reported higher difficulties in social reciprocity as measured on the SRS, $F(3, 86) = 18.4$, $p < .001$, than controls (all $ps < .001$); although ratings of informants suggested that the ADHD group had the lowest difficulty, with rating against the ASD+ADHD group reaching significance level. The SDQ hyperactivity ratings were consistent with the CAARS, with the ASD+ADHD and the ADHD groups rated themselves with higher ADHD symptoms than the controls and the ASD group (all $ps < .001$).

Table 6-1: Characteristics of participants in the study

	TD (n=26)	ASD (n=23)	ADHD (n=25)	ASD+ ADHD (n=24)	Group comparison		
					<i>F</i> (3,94)	<i>p</i>	Post-hoc
Age (SD)	23.4 (1.5)	23.0 (.7)	23.1 (1.9)	22.9 (1.3)	.46	.71	--
FSIQ (SD)	118.5 (12.1)	102.0 (19.8)	116.0 (13.2)	109.2 (14.8)	4.9	.003	ADHD, TD > ASD
Handedness (Range)	66.2 (-100-100)	68.3 (-100-100)	65.2 (-95-100)	51.9 (-100-100)	.29	.83	--
Left-handed	4	3	4	6	--	.71	--
Current stimulant	--	--	5	7	--	--	--
Current SSRI	--	--	3	2	--	--	--
CAARS self (t-scores)^a							
Inattention	44.2 (7.1)	45.4 (11.6)	66.1 (7.9)	62.3 (10.5)	36.0	<.001	ASD+ADHD, ADHD > ASD, TD
Hyperactive	44.9 (8.6)	46.2 (6.9)	65.1 (10.1)	57.6 (11.1)	26.1	<.001	ADHD > ASD+ADHD > ASD, TD
Impulsive	41.1 (5.8)	43.5 (11.5)	57.2 (9.5)	54.5 (11.1)	16.9	<.001	ASD+ADHD, ADHD > ASD, TD
ADHD index	41.8 (8.5)	44.6 (11.7)	65.2 (7.7)	59.1 (11.8)	31.3	<.001	ASD+ADHD, ADHD > ASD, TD
CAARS informant (t-scores)^b							
DSM-IV inattention	--	56.7 (12.7)	76.2 (20.7)	76.2 (20.3)	11.3	<.001	ASD+ADHD, ADHD > ASD
DSM-IV hyperactive	--	48.4 (11.0)	66.1 (17.8)	65.7 (18.5)	9.1	<.001	ASD+ADHD, ADHD > ASD
DSM-IV symptom no	--	52.4 (13.7)	73.3 (22.1)	76.0 (19.7)	10.9	<.001	ASD+ADHD, ADHD > ASD
ADHD index	--	48.8 (7.2)	60.4 (16.5)	64.5 (17.4)	7.3	<.001	ASD+ADHD, ADHD > ASD
SRS self (t-scores)							
Total SRS score	48.5 (6.1)	61.3 (8.9)	62.7 (6.9)	66.7 (12.2)	20.6	<.001	ASD+ADHD, ADHD, ASD > TD
SRS informant (t-scores)							
Total SRS score	--	63.8 (8.6)	56.9 (10.5)	69.9 (11.6)	9.4	<.001	ASD+ADHD > ADHD
SDQ17+ self							
Hyperactivity	2.4 (1.8)	3.4 (2.0)	7.4 (1.5)	6.9 (2.1)	42.8	<.001	ASD+ADHD, ADHD > ASD, TD
Emotion	1.1 (1.4)	3.8 (2.7)	4.2 (2.4)	4.3 (2.6)	11.7	<.001	ASD+ADHD, ADHD, ASD > TD
Conduct	1.2 (1.2)	1.5 (.9)	2.8 (1.9)	2.9 (1.8)	7.9	<.001	ASD+ADHD, ADHD > TD
Peer relations	2.5 (2.0)	3.5 (1.6)	2.1 (1.5)	3.4 (2.1)	3.2	.026	ASD > ADHD
SDQ17+ informant							
Hyperactivity	--	3.1 (1.9)	7.4 (2.0)	7.1 (1.7)	38.1	<.001	ASD+ADHD, ADHD > ASD
Emotion	--	3.4 (2.1)	4.0 (2.4)	4.7 (2.7)	1.7	.196	--
Conduct	--	1.3 (.9)	3.2 (2.1)	3.6 (2.5)	9.7	<.001	ASD+ADHD, ADHD > ASD
Peer relations	--	3.5 (1.3)	2.4 (1.8)	4.3 (2.1)	7.0	.002	ASD+ADHD > ADHD

Note. Abbreviations M = mean, SD = standard deviation, FSIQ = full-scale IQ, DX = diagnosis, CAARS = Conners Adult ADHD Rating Scale, SRS = Social Responsiveness Scale version 2, SDQ17+ = Strengths and Difficulties Questionnaires for age 17 years and above. Self-rated symptoms were indicated by 'self', while informant-rated symptoms (filled in by parents, partner, relatives or childhood friend) were indicated by 'informant'. ^{a,b}CAARS-self questionnaires were rated on the short form, whilst CAARS-informants were rated on the long versions thus generating different domain scores.

6.3.2 Behavioural Data

Table 6-2: Behavioural measures of the duration discrimination task across groups

	TD (n=26)	ASD (n=23)	ADHD (n=25)	ASD+ADHD (n=24)
% Error time discrimination (SD)	21.7 (10.6)	23.3 (15.7)	23.0 (14.2)	28.0 (13.4)
% Error temporal order (SD)	15.3 (12.7)	18.7 (6.0)	19.0 (13.3)	17.3 (14.3)
MRT time discrimination (SD)	591.3 (115.3)	560.1 (175.3)	618.1 (159.3)	572.3 (135.5)
MRT temporal order (SD)	426.4 (91.4)	402.4 (118.5)	437.5 (146.4)	427.4 (106.9)
SDRT time discrimination (SD)	203.9 (72.7)	192.3 (90.0)	220.6 (86.7)	224.9 (101.9)
SDRT temporal order (SD)	141.3 (74.2)	122.4 (63.2)	158.5 (80.2)	183.2 (91.2)

Note. Comparison of measures during the duration discrimination task indicated no difference across groups in performance in accuracy, MRT, and SDRT. The MRT and SDRT are in seconds, whereas accuracy is presented as raw number where the maximum was 30. MRT= Mean response time, SDRT = standard deviation of response time, a measure of response time variability, and SD = standard deviation.

Behavioural measures of the duration discrimination task are presented on Table 6-2. A 4×2 (group $\times$ condition) mixed-design ANOVA showed more errors in all groups during the time discrimination than the temporal order condition, $F(1,94) = 26.1$, $p < .001$. However, there was no significant effect of group, $F(3,94) = .81$, $p = .49$, or interaction group $\times$ condition, $F(3,94) = .44$, $p = .73$. The MRT was also longer during the time discrimination than the temporal order condition in all subjects, $F(1,94) = 149.5$, $p < .001$, but there was no significant group effect, $F(3,94) = .67$, $p = .57$, or group $\times$ condition effect, $F(3,94) = .32$, $p = .81$, during the task. Similarly, the analysis of the SDRT indicated an effect of condition, with longer SDRT in the time rather than temporal order condition $F(1,94) = 48.0$, $p < .001$, but not group, $F(3,94) = 1.90$, $p = .14$, or interaction effect between group $\times$ condition, $F(3,94) = .49$, $p = .67$. Overall these results suggested that the participants found the time discrimination condition more difficult than the temporal order condition, although these difficulties affected all groups equally. Pairwise independent t -tests between each clinical group against individuals in the TD group returned no difference between each clinical group and the TD in time discrimination error, MRT

time discrimination, and SDRT time discrimination, with the exception of a trend wise greater time discrimination errors in the ASD+ADHD group relative to controls, $t(48) = 1.91, p = .062$.

6.3.3 Neuroimaging Data of the Duration Discrimination

6.3.3.1 Motion

Group difference in the total volume-to-volume head movement in the x, y and z rotation and x, y and z translation was approaching significance, $F(3,94) = 2.65, p = .053$, primarily driven by the ASD group that has significantly more movement in the scanner than controls ($p = .037$). Total movement is covaried in the analysis of the brain activation data.

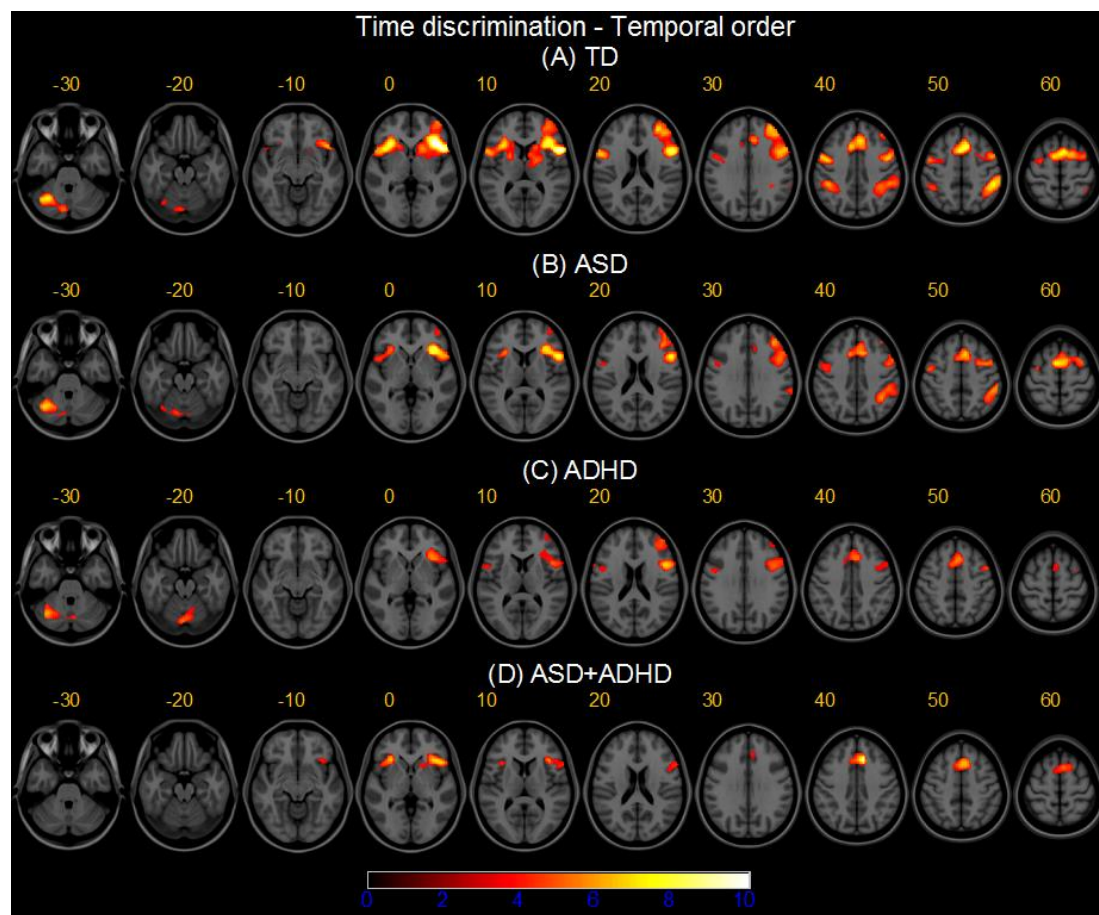
6.3.3.2 Brain Activations during Duration Discrimination

Within-group Activations

Regions of within-group activations for the contrast of time discrimination against temporal order are presented in Figure 6-2. The control group showed extensive clusters of frontal activation in right IFG and AI (BA47, 13, 44, 45, 46), reaching deep into the striatal and thalamic area, and frontally to the MFG, dlPFC (BA10, 9) and pre-CG (BA6), and medially to the mid-cingulate gyrus/medial PFC and the SMA (BA 32). Activations were also observed in the left IFG and AI (BA47, 13), reaching into the striatal/pallidum and in the bilateral IPL/supramarginal and angular gyri (BA40) and left posterior cerebellum. In the ASD group, clusters of activations were mostly overlapping with, but less extensive than in the control groups, and included the right IFG/AI (BA44, 45, 46, 13), reaching frontally to the MFG/dlPFC (BA6), and medially to the mid-cingulate gyrus/SMA (BA32) and at the premotor and SFG (BA10). Other clusters included the left IFG and AI (BA45, 13), right IPL/supramarginal/angular gyri (BA40), and left cerebellum, and left pre-CG (BA6).

Participants with ADHD showed smaller clusters than the controls and ASD groups in the right IFG/dIPFC (BA44, 45, 46, 9, 8) reaching into the pre-CG (BA6), left posterior cerebellum extending slightly to the right cerebellar lobe, cingulate gyrus reaching bilaterally to the mPFC and SMA areas (BA24, 32, 6), and in the left IFG/pre-CG (BA44, 45, 6). The clusters of activations in the ASD+ADHD group were the least extensive compared to the other groups. They were primarily found in the medial PFC and SMA (BA24, 32, 6), and bilateral AI and IFG (BA13, 47, 45), reaching into the caudate/putamen on the right hemisphere.

Figure 6-2: Within-group brain activations during duration discrimination

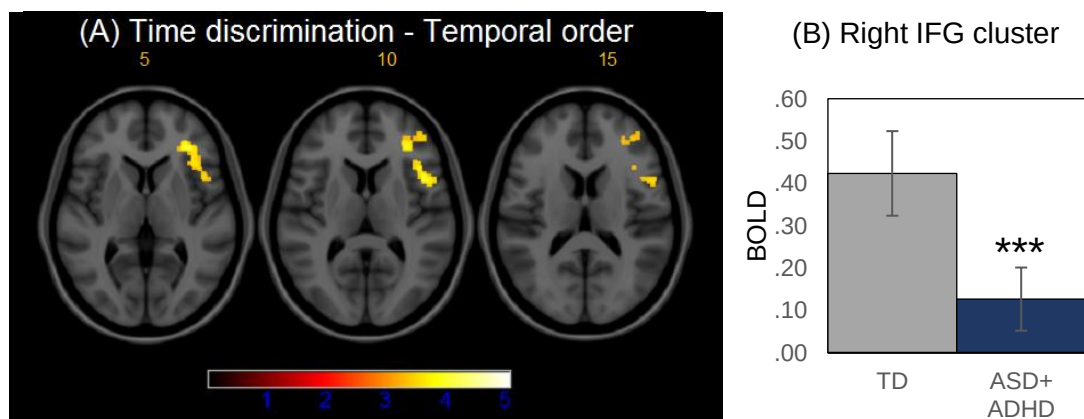


Note. Within-group brain activation clusters contrasting the block time discrimination against temporal order corresponding to duration discrimination in the TD (A), ASD (B), ADHD (C), and ASD+ADHD group (D). The clusters were obtained at a threshold cluster extent $k \geq 396$ voxels, corresponding to $p < .05$ FWE. Only increased activations are presented in the figure and images' left is the participants' left side.

Between-group Activations

Univariate ANOVA revealed no group effect in the brain activation for the time discrimination vs. temporal order contrast. Pairwise *t*-tests between each disorder groups relative to controls revealed reduced brain activation in the ASD+ADHD group in a cluster encompassing the right IFG/dIPFC and the ventral part of the pre-CG (BA47, 46, 45, 44, 6), $t(48) = 4.6$, $p < .001$. This remained significant when IQ was covaried, $t(47) = 3.8$, $p < .001$, likewise when all participants with SSRI, $t(45) = 3.8$, $p < .001$, and all on current medication were excluded from the ASD+ADHD group, $t(40) = 3.8$, $p = .001$ (Figure 6-3 and Table 6-3). No difference in brain activations were observed between the pure clinical groups and the TD controls even individuals with medication were excluded from the analyses.

Figure 6-3: Reduced BOLD activation in the ASD+ADHD group versus controls during duration discrimination



Note. Individuals with ASD+ADHD demonstrated reduced brain activation relative to controls during duration discrimination in a single cluster in the IFG/frontal operculum/dIPFC/pre-CG (A). The cluster was obtained at a threshold cluster extent $k \geq 396$ voxels, corresponding to $p < .05$ FWE. BOLD activation during duration discrimination were compared between the TD and the ASD+ADHD group in plot (B) Mean BOLD signal from the cluster are presented with 95 % confident intervals.

Table 6-3: Reduced activation cluster in the ASD+ADHD group versus controls

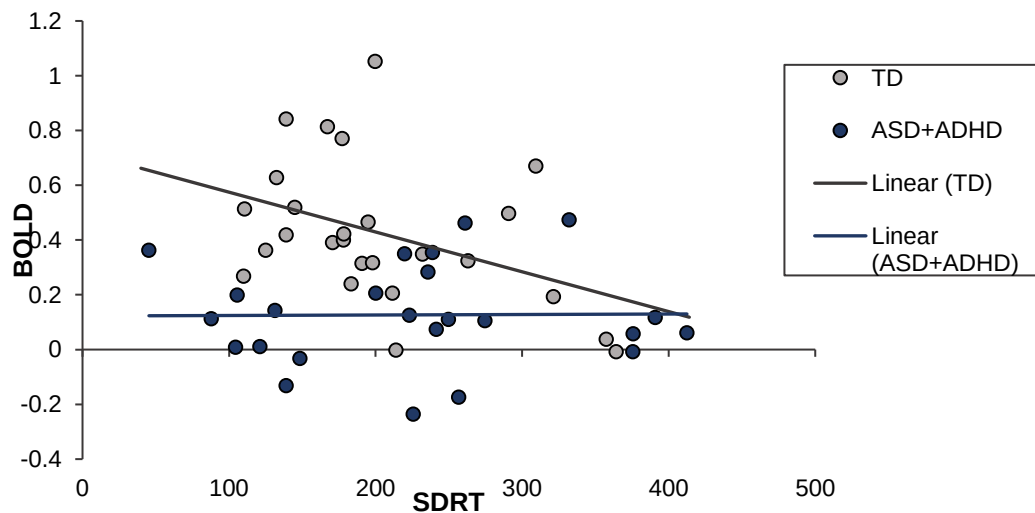
Brain regions	BA	MNI coordinates			<i>T</i>	<i>k</i>
		x	y	z		
R IFG/dIPFC/pre-CG	47, 46, 45, 44, 6	32	36	8	4.19	440
		46	12	10	3.98	
		42	20	10	3.70	

Note. A cluster in the right IFG/dIPFC/pre-CG was found to be reduced in the ASD+ADHD compared to the TD during the duration discrimination, covarying total head movement. The effect was robust to covarying for IQ and sensitivity analyses excluding individuals on medications.

Correlational Analyses

A significant negative correlation was found between the mean BOLD activation in the IFG cluster and the SDRT of the time discrimination in the TD group, $r_{TD}(25) = -.41$, $p = .039$, suggesting that reduced IFG activation was associated with increased response variability. No such relationship was apparent in the ASD+ADHD group, however, $r_{ASD+ADHD}(23) = .01$, $p = .97$. No significant correlation was found between brain activation and the MRT of the TD, $r_{TD}(25) = -.09$, $p = .67$, or ASD+ADHD group, $r_{ASD+ADHD}(23) = .26$, $p = .21$, and the task response accuracy of the TD, $r_{TD}(25) = .17$, $p = .41$, or ASD+ADHD group, $r_{ASD+ADHD}(23) = .21$, $p = .33$. No correlations between the BOLD activations and ADHD traits were found in the TD, $r_{TD}(25) = -.03$, $p = .89$ or ASD+ADHD group, $r_{ASD+ADHD}(23) = -.13$, $p = .54$. Furthermore, BOLD activations did not correlate with ASD traits, $r_{TD}(25) = -.09$, $p = .67$ and $r_{ASD+ADHD}(23) = .11$, $p = .62$.

Figure 6-4: Correlations between brain activations and SDRT in the TD and ASD+ADHD groups



Note. Scatterplot and trend lines for the relationships between mean BOLD signals extracted from the IFG/dlPFC/pre-CG cluster against SDRT, an index of difficulties performing the task. Reduced activation was correlated with increased SDRT in the TD group but not in the ASD+ADHD groups where neural impairments were observed.

6.4 Discussion

This study explored the similarities and differences of the neural underpinnings of duration discrimination performance across groups of typically developing young adults and those with ASD, ADHD, and ASD+ADHD. Findings of this study showed that individuals with ASD+ADHD had reduced activation in a cluster in the right IFG/dIPFC/pre-CG when the group was compared pairwise with the TD control group. Reduced activation of the cluster was associated with increased intra-subject SDRT in the TD group, but not in the ASD+ADHD group.

6.4.1 Reduced IFG/dIPFC Activations in the ASD+ADHD Group Relative to Controls

One possible interpretation for this finding was that the ASD+ADHD group was the most neurally impaired group. This interpretation is in line with that from a previous study (Chantiluke et al., 2014) and the previous chapter of this thesis. Chantiluke's (2014) study used a temporal reward discounting task that predominantly tested choice impulsivity in the context of rewards, although regions such as dIPFC, IFC, and insula, which mediated performance in this study are typically activated during cool EF thus could also be related to the temporal processing aspect of the task (Bickel, Pitcock, Yi, & Angtuaco, 2009; Christakou, Brammer, & Rubia, 2011; McClure, Laibson, Loewenstein, & Cohen, 2004). Supporting this interpretation was the finding from a meta-analysis by Radua et al. (2014) that showed that cognitive control tasks significantly overlapped with time estimation in their activation of left and right IFG and dIPFC. At the performance level, however, the ASD+ADHD participant group appeared to demonstrate, on average, only trend-level higher errors during the time discrimination condition compared to typically developing controls. However, as mentioned before, many previous fMRI studies in ADHD have also found neural abnormalities in similar regions despite no behavioural

impairments (Rubia, Halari, Christakou, et al., 2009; Vloet, Gilsbach, et al., 2010), which, as discussed previously, may be due to low power for performance data or loss of sensitivity in fMRI tasks over behavioural tasks.

Studies in typically developing adults have shown that the activations in the right frontal opercular/dIPFC are central to timing function, together with other areas such as bilateral SMA, AI, BG and IPL (Wiener et al., 2010). During duration discrimination, IFG and dIPFC activations have shown the most between-subject variability dependent on the duration discrimination difficulty (Tregellas, Davalos, & Rojas, 2006). The right IFG have also been found as one of the subset of regions including pre-SMA, ACC, and right caudate that increased in activation with increasing duration (Pouthas et al., 2005). Importantly, manipulating the difficulties of the control task appeared to vary the activation effect in many regions of the brain including dIPFC but not IFG/AI, supramarginal gyrus, and BG. This suggests the IFG is foremost related to timing rather than general task load (Livesey, Wall, & Smith, 2007). Overall the findings suggest that the IFG is a key region for duration discrimination and timing in typically developing adults. Its reduced activation the ASD+ADHD group in this study thus signified impairment of functions.

A significant negative correlation was found between the activation in the right IFG/dIPFC clusters and intrasubject SDRT in the TD group, suggesting that increased activation in this region reflected improved performance in the control group, but not in the ASD+ADHD group. In studies of individuals with ADHD, intrasubject SDRT has typically been found higher relative to typically developing controls in tasks such as sensorimotor timing (e.g. Rubia, 1999; Shiels Rosch, Dirlikov, & Mostofsky, 2013) and time estimation and reproduction tasks (e.g. Barkley, Edwards, et al., 2001; Barkley, Murphy, et al., 2001), which has been implicated in abnormal timing and attention functions. Intrasubject SDRTs during sensorimotor and time estimation tasks increase with interval lengths to be

estimated (Barkley, Edwards, et al., 2001; Barkley, Murphy, et al., 2001; Bauermeister et al., 2005; McGee et al., 2004; Pironti et al., 2016; Rubia, 1999), showing strong adherence to the scalar property of interval timing, which is consistent with the interpretation that the variable reflects timing function deficits.

Increased variability of SDRT could also reflect the difficulties in sustaining attention, in this case, to “the passage of time” (Zakay, 1993, p. 657). Intrasubject SDRT in tasks involving low presentation of stimuli such as the CPT (and not the GNG) has been thought to represent lapses in vigilance, and was typically increased in people with ADHD (Huang-Pollock et al., 2012). In fMRI studies, negative correlation has been reported between intrasubject response variability and BOLD activation in the insula, right inferior prefrontal, and STL among typically developing boys (Rubia, Smith, Brammer, & Taylor, 2007) evaluated on a low-frequency target detection task. Relatedly, by varying the likelihood of response according to duration or colour, and thus manipulating the attentional allocation to either condition, Coull et al. (2004) showed that up-modulated attention to time was associated with increased activation in right IFG and pre-SMA among others. Taken altogether, the under-activated right IFG/dIPFC cluster and its lack of association with the intrasubject SDRT in the ASD+ADHD group reinforces the interpretation of abnormal IFG/dIPFC functioning during time discrimination in this population.

6.4.2 The Lack of Impairments in the Pure Groups Relative to Controls

The absence of impairments during interval timing in the pure ASD and ADHD groups were unexpected. The hypotheses for the ASD group was based on behavioural studies mostly in children and one study in adults (Brenner et al., 2015; Maister & Plaisted-Grant, 2011; J. S. Martin et al., 2010; Szelag et al., 2004) supported by indirect evidence of structural abnormalities in brain regions such as cerebellum, BG, and bilateral dIPFC reported in past MRI studies (e.g., Bonilha et

al., 2008; D'Mello & Stoodley, 2015; Ecker et al., 2012; McAlonan et al., 2008). The hypothesis of neural impairments in the ADHD group was also directed by the available research in children (Smith et al., 2013, 2008; Vloet, Gilsbach, et al., 2010). Therefore, age could be a primary factor that set these findings apart.

Evidence of atypical neural development has been found among individuals with ASD. From age 11-35 years, vigilance-related brain activations in males with ASD in the IFC/insula/STL, mPFC, striato-thalamic, and lateral cerebellar regions either diminished or showing opposite relationship with age compared to the TD group (C. M. Murphy et al., 2014). Age-related structural changes have also been documented among individuals with ASD, mostly inferred from cross-sectional observations. For instance, in males with ASD from age approximately 10-30 years, GMV at the medial, superior and middle frontal gyri and cuneus increased with age while the opposite were observed in TD males (H. Y. Lin et al., 2015), perhaps reflecting lagging maturation. Adults with ASD might also develop compensatory mechanism during task as has been detected among children with ASD in the cerebellum during a sensorimotor task (Christakou et al., 2013). Note that while individuals with ASD in the study by Murphy et al. (2014) had greater intrasubject SDRT and MRT than controls, they demonstrated no more omission errors despite the observed neural impairments. Such findings may suggest compensatory mechanisms which was heterogeneous inter-individually and undetectable through fMRI studies.

None of the individuals with ASD was on medication at the time of the study, and the findings in the pure clinical groups remained even after excluding individuals with current medications. However, past medication intake could still influence the findings in this study, and medication history was not collected from the participants in this study, which was a limitation. Medication history might be more heterogeneous among individual with ASD than in their typically developing

peers and their ADHD counterpart. Among most frequently prescribed psychotropic medications in children with ASD were antidepressants, psychostimulants, antipsychotic and anxiolytics prescribed in a large proportion of children (Esbensen, Greenberg, Seltzer, & Aman, 2009; Oswald & Sonenklar, 2007). Over 50% of children were prescribed in the first year of a longitudinal study in adolescents and adults with ASD, with a significant increase of psychotropic medication up to 64% was recorded 4.5 years after the first survey that took place (Esbensen et al., 2009) in the U.S. Similar rates have also been reported in Canada among adults with ASD (J. K. Lake, Balogh, & Lunsy, 2012). Pharmacotherapy is prescribed at lower rate (i.e., 30%) in individuals with ASD in the U.K since no psychotropic medications are formally approved for the condition (M. L. Murray et al., 2014). Nevertheless, some individuals in this study may have taken psychotropic medication in the past which have a sustained long-term therapeutic impact or obscure the true difference between individuals in the pure groups from the TD controls.

The absence of IFG, BG and SMA impairments in the ADHD group the present study is inconsistent with previous reports of neural under-activation in these regions, mostly in children with ADHD during sensorimotor timing and duration discrimination (Christakou et al., 2013; Rubia et al., 2014; Rubia, Halari, Christakou, et al., 2009; Valera et al., 2010). As in the ASD group, the absence of neural impairments in these regions in the ADHD group might reflect age-dependent effect. The effect of age in the neural correlate of duration discrimination among individuals with ADHD has not been thoroughly investigated, although several meta-analyses of response inhibition studies have shown age-dependent reduction of abnormalities in the BG, specifically in the right caudate, which no longer appear to be impaired functionally in adults with ADHD during response inhibition (Hart et al., 2013; Lei et al., 2015; Norman et al., 2016), also shown using a meta-regression

analysis in Chapter 4. This was supported by findings of converging volume of caudate nucleus in late adolescents and early adulthood in people with ADHD and typically developing controls (Castellanos et al., 2002; Greven et al., 2015; Nakao et al., 2011). Hart et al. (2013) also pointed out that SMA under-activation was more prominently associated with children and not adults with ADHD while the opposite true for IFG impairments. These exploratory analyses have to be taken with cautions, however, meta-regression analyses conducted in the same study showed no age effect in these regions.

In adults with ADHD, factors such as medication history and the development of compensatory mechanism could also be related to the null findings in the current study (Cubillo & Rubia, 2010). Both single dose of atomoxetine and MPH have shown to normalise the functional impairments in the IFG/insula among children with ADHD during the duration discrimination tasks (Rubia et al., 2014; Smith et al., 2013). Further, psychostimulant exposures have been associated with normalised dlPFC functioning elicited by a collection of diverse tasks associated with timing functions (Hart et al., 2012). Medication effects have also been observed in relation to the IFG activations during response inhibition (Rubia et al., 2014, Norman et al., 2016, see also Chapter 4). Therefore, null findings in adult participants shown in the present study could be attributed to long-term therapeutic effect of ADHD medication.

Two other factors could have explained the lack of findings in the ADHD groups relative to controls and generally the small effect size of the findings. As pointed out in the previous chapter, in the interest of including as many participants possible who were not on current medication or who were medication-naïve, a significant proportion of individuals with ADHD have received their first-time diagnoses in adulthood. Although the diagnoses were given to the individuals who demonstrated difficulties childhood only, these participants might represent a subset

of individuals whose ADHD symptoms were less severe (Antshel et al., 2010; Barkley et al., 2008; Kolar et al., 2008). Finally, as the duration discrimination task has not been tested among adults with ASD or ADHD in the fMRI setting, it is pertinent to question its sensitivity in the adult population. Future studies in this population may consider using several measures of timing to increase the sensitivity of the study and the range of timing function in the adult population.

6.4.3 Findings in Relation to the Pure Groups and the Comorbidity Debate

There was an absence of group effects in the four-way ANOVA comparison across groups. However, the significant under-activation in the IFG/dIPFC cluster demonstrated by adults with ASD+ADHD compared to controls, as well as the lack of pairwise difference between the pure ASD or ADHD group relative to controls, could signify a specific impairment in the neural correlates of duration discrimination in the comorbid group. As also argued in the previous chapter, the resemblance of the present findings to those findings in children with ADHD (Smith et al., 2013, 2008; Vloet, Gilsbach, et al., 2010) might suggest that the reduced activation in the right IFG/dIPFC in the ASD+ADHD group represents an ADHD-like neural impairments that is more persistent in adulthood. However, this interpretation was constrained by the fact that only trend-level behavioural impairment was found in this group during time discrimination and the narrow age range of individuals involved in the study. Replication of the findings using a task that is sensitive to both neural and behavioural performance would be useful to confirm their links.

6.4.4 Strengths and Limitations

The strengths and limitations outlined in the previous chapter also apply to this study. Briefly, the inclusion of only male participants enhanced the homogeneity of participant across groups, and the large proportion of non-medicated participants at the time of the study allowed a sensitivity analysis excluding individuals on any

current psychotropic medication. The limitations included the non-homogeneous IQ distribution across groups, although covarying for IQ did not change the findings the two groups. Not all participants were right handed, although there were approximately an equal proportion of left-handed participants across groups. Furthermore, the number of participants in this study, while exceeding 20 participants recommended for neuroimaging studies (Desmond & Glover, 2002; Thirion et al., 2007) may be underpowered for investigating small effects and the behavioural responses towards fMRI tasks as the latter is typically less sensitive to behavioural changes than out-of-scanner tasks. Lastly, the study would benefit from in-depth assessment of psychiatric difficulties among participants to confirm that the findings were not influenced by undetected additional psychiatric problems in the samples.

6.4.5 Implications and Future Directions

Similar to findings in the previous chapter, the ASD+ADHD group appeared to have the most detectable neural impairments in the right IFG/dIPFC, a region that has been shown to serve both cognitive control and duration discrimination (Radua et al., 2014). Similar impairments have been observed in children with ADHD, which could suggest a persistence ADHD-like deficit among the ASD+ADHD group, although this should be further investigated in samples with wider age range to test for developmental effects. The pure group did not appear to have neural impairments, which could be due to age-related development, long-term medication effects and increased heterogeneity in the samples. It is possible that the duration discrimination task was not sufficiently sensitive for detecting timing difficulties among adults. Therefore, a multimeasure approach in samples of individuals with wider age range could be recommended for investigating time discrimination difficulties in these clinical groups.

7 General Discussion

The overarching aim of this thesis was to explore the neurocognitive and neural correlates for ADHD symptoms among individuals with a diagnosis of ASD. To this end, I examined the similarities and differences of the neurocognitive and neural underpinnings of ADHD and ASD diagnoses and symptoms using several approaches including statistical modelling, multimodal neuroimaging meta-analyses, and group comparison studies of newly collected data from convenience samples of young adults with ASD, ADHD, ASD+ADHD and typically developing controls in a series of neurocognitive and neuroimaging investigations. The thesis examines several research questions: (1) Are ADHD symptoms in ASD associated with the heterogeneous EF impairments, if so how? (2) How do groups of individuals with ASD, ADHD and ASD+ADHD compare in separate neurocognitive subdomains of EF and SC? (3) How do people with “pure” ASD and ADHD compare in their brain structures and functions? (4) How do the neural correlates of response inhibition in people with ASD, ADHD, and ASD+ADHD compare? (5) How do the neural correlates of timing in people with ASD, ADHD, and ASD+ADHD compare? And finally, (6) what comorbidity models fit the findings of these studies? I first will summarise the approaches that were taken and describe the major findings from the studies completed throughout the PhD, then discuss briefly the findings of this study, and pose some questions that can be addressed in future studies. The strength and limitations of the thesis are reviewed in the wider context of the comorbidity between ASD and ADHD. Finally, I will discuss the implications of the research included in this thesis and outline the future research direction.

7.1 Summary of Studies and Major Findings

Table 7-1 summarises all studies included in this thesis, their samples, and primary and secondary findings. The first study, reported in Chapter 2, was a statistical modelling of the relationships among EF deficits, ToM deficits, and ASD and ADHD symptoms among 100 predominantly male adolescents with $IQ \geq 50$ from the SNAP cohort, a population-based group of people with research diagnosis of ASD seen in the first time at the age of 10-12 years and now young adults (Baird et al., 2006). The study employed a multi-informant and multi-measure approach. Latent factors were modelled to capture the underlying constructs of EF deficits, ToM deficits, and ASD and ADHD symptoms from these measures, and SEM was used to model the relationships of these factors with one another. The main finding of the study was that the deficits of EF were specifically associated with ADHD symptoms, while deficits of ToM were specifically associated with ASD symptoms. Other findings can be found on Table 7-1.

The second study in Chapter 3 contrasted the performance of an array of cognitive functions broadly defined as part of the EF and SC among young adult males with diagnoses of ASD, ADHD, and ASD+ADHD against a TD control group. The study again employed a multi-measure approach. It used a range of computerised neurocognitive tasks assessing the EF subdomains of response inhibition, sustained attention, visuospatial working memory, temporal discounting, and cognitive flexibility, and the SC subdomains of ToM and emotion recognition. Information about the participants' ASD and ADHD traits were collected from the participants and for the participants in the clinical groups, ratings of those traits were also obtained from an informant, such as parent, sibling, or partner, who knew the

Table 7-1: Summary of studies and major findings

Study / Sample	Approaches	Primary findings	Secondary findings
Study I			
ASD (n = 100) Community sample	Modelling the relationships among latent factors EF, ToM, and symptoms of ASD and ADHD using multi-measure and multi-informant approach and structural equation model.	EF deficits were specifically associated with ADHD symptoms while ToM deficits were specifically associated with ASD symptoms.	- Symptoms of ADHD and ASD were correlated with each other but this was due to shared source of information from parents. - EF and ToM were correlated with one another but not when the variation related to IQ was controlled. - Controlling variation of EF and ToM which were related to IQ and controlling for source of information from parents did not change the specificity of relationships between EF and ADHD symptoms, and between ToM and ASD symptoms.
Study II			
TD (n = 26) ASD (n = 26) ADHD (n = 28) ASD+ADHD (n = 27) Convenience sample	Group comparison of the neurocognitive performance in response inhibition, sustained attention, visuospatial working memory, temporal reward discounting, cognitive flexibility, ToM, and FER across groups of young adult males with ASD, ADHD, ASD+ADH group and a TD group of matched age.	- Individuals with ADHD and with ASD+ADHD were impaired in measures of inhibition, sustained attention, and working memory, and the differences were robust to covarying IQ differences across groups. - Individuals with ASD alone were impaired on ToM and FER tasks but this was associated with the IQ differences across group.	- No association was found between ADHD traits and EF deficits and between ASD traits and SC deficits - Performance of temporal discounting task did not differ across groups but pairwise comparison suggested that individuals with ADHD alone were impaired relative to TD controls. - Cognitive flexibility performance did not differ across groups and was not impaired in the ASD group compared to the TD controls.
Study III			
fMRI studies ASD (n = 208) ASD _{CON} (n = 215) ADHD (n = 623) ADHD _{CON} (n = 607) VBM studies ASD (n = 1059) ASD _{CON} (n = 1077) ADHD (n = 1283) ADHD _{CON} (n = 1054)	Meta-analysis of inhibitory-related fMRI and VBM abnormalities in ASD and in ADHD relative to controls.	- ASD and ADHD were mostly separate disorders with relatively few shared abnormalities. - People with ASD displayed reduced activation in the ACC/dmPFC, dlPFC, IPL, precuneus during inhibition and the GMV deficits in the thalamus and enhanced PCC, - People with ADHD displayed specific decrease in the right IFG during inhibition and striatal GMV deficit. - Both conditions were associated shared impairment in the right IFG orbital part, extending to the right AI and shared reduced GMV in the rdACC/dmPFC and enhanced left precuneus GMV.	Psychostimulant exposures were associated with enhanced GMV in the vmOFC, and reduced GMV in the left IFG and right olfactory cortex; and functionally with increased activation right IFG and MTG among individuals with ADHD.
Study IV			

TD (n = 22) ASD (n = 21) ADHD (n = 25) ASD+ADHD (n = 23) Convenience sample	- Functional MRI study comparing the neural correlates of response inhibition, error monitoring across groups of young adult males with ASD, ADHD, ASD+ADHD and a TD group of matched age. - The investigation used the modified stop-signal task in an exploratory whole-brain approach.	- The ASD+ADHD group demonstrated reduced brain activations in the left insula/IFG/STG/MTG and the right insula/IFG/thalamus/PHGy during error monitoring. - Individuals in the ASD and the ASD+ADHD groups demonstrated reduced deactivations in the right precuneus during selective attention. - No group differences were found in the brain functions associated with successful response inhibition.	- The findings were robust to co-varying for IQ and when people with medications were excluded. - The error-monitoring activation in the right insula/IFG/thalamus/PHGy was negatively correlated with the SSRT and ADHD index in the TD but only with the SSRT in the ASD+ADHD group. - The precuneus activation was positively correlated with the error of omissions in the TD group but not in the ASD and the ASD+ADHD groups.
Study V			
TD (n = 26) ASD (n = 23) ADHD (n = 25) ASD+ADHD (n = 24) Convenience sample	- Functional MRI study comparing the neural correlates the neural activation related to interval timing function across groups of age-matched young adult males with ASD, ADHD, ASD+ADHD and a TD group. - The investigation used the duration discrimination task and a whole-brain exploratory approach.	- Pairwise comparisons of each clinical group against control revealed significantly reduced activations in the right IFG/dlPFC/pre-CG in the ASD+ADHD group compared to controls - No group effect was observed across the four groups.	- The findings were robust to co-varying for IQ and when people with medications were excluded. - Reduced BOLD activation in the right IFG/dlPFC/pre-CG was associated with increased SDRT in the TD but not the ASD+ADHD group.

Note. Abbreviations: TD = typically developing, ASD =autism spectrum disorder, ADHD = attention-deficit/hyperactivity disorder, EF = executive function, ToM = theory of mind, FER = facial emotion recognition, fMRI = functional magnetic resonance imaging, VBM = voxel-based morphometry, ACC = anterior cingulate cortex, dmPFC,= dorsomedial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex, IPL = inferior parietal lobule, IFG = inferior frontal gyrus, AI = anterior insula, rdACC = rostradorsal anterior cingulate cortex , dmPFC =dorsomedial prefrontal cortex, vmOFC = ventromedial orbital frontal cortex, STG = superior temporal gyrus, MTG = middle temporal gyrus, PHGy = parahippocampal gyrus and pre-CG = precentral gyrus.

participants well. The main findings from the study were that EF deficits, primarily response inhibition, sustained attention (in the context of a response inhibition task), and visuospatial working memory were found in the ADHD and the ASD+ADHD groups. ToM and FER deficits were found among individuals with ASD but this finding was IQ-dependent. Finally, no group effect was found in temporal reward discounting and cognitive flexibility.

The third study in Chapter 4 used published neuroimaging data on fMRI studies of inhibition and structural VBM studies in ASD and ADHD. The study contrasted the inhibitory-related impairments and structural deficits among individuals with ASD or ADHD, each relative to typically developing controls, using a meta-analytic approach. A general linear model was employed to explore specific and shared neural underpinnings of the two conditions, controlling for IQ and sex differences across groups. Conjunctive analyses were carried out to find shared and specific abnormalities between the disorder groups, and multimodal analyses were carried out to find co-existing inhibitory impairments and structural deficits within groups. Confirmatory meta-analyses were conducted with subsets of samples matched in IQ, sex, and age. The major finding is that in terms of brain structure and function deficits, ASD and ADHD are mostly different disorders with relatively few shared brain structure and function abnormalities. The ASD group demonstrated specific neural impairments in wide-ranging regions implicated in salience monitoring, set-maintenance, attention, and reduced deactivation in the DMN region, i.e. ACC/dmPFC, dlPFC, IPL, and precuneus. The ADHD group displayed consistent impairments in the regions implicated in action stopping, i.e., right-hemispheric IFG. Structurally, the ASD group demonstrated GMV deficits in thalamus and enhanced GMV in PCC. People with ADHD display specific GMV decrease in right caudate and putamen. Shared neural impairment was found in a

small cluster in right IFG orbital part and AI during response inhibition. Shared reduced GMV was found in the rdACC/dmPFC and left precuneus.

Study four in Chapter 5 was conducted on a subset of the young adults with ASD, ADHD, and ASD+ADHD, and controls whose neurocognitive data were reported in Chapter 3. Only data meeting the quality controls for MRI investigations were included in the study. The neural correlates of response inhibition, error monitoring, and sustained attention derived from several contrasting conditions during the performance of a modified stop-signal task performance were compared across groups using an exploratory whole-brain approach. The first main finding of this study was that individuals with ASD+ADHD had reduced activation in the left insula/IFG/STG/MTG and the right insula/IFG/thalamus/PHGy during error monitoring relative to the pure clinical and TD groups. The second finding was that both individuals in the ASD and the ASD+ADHD groups demonstrate reduced deactivation in the right precuneus during selective attention. The groups did not differ in the neural correlates of response inhibition. The group effects were robust after co-varying for IQ and when individuals with current medications were excluded from the analyses. The differences in neural activation from typical development were interpreted as neural impairments taking into accounts previous findings in individuals with ADHD, although the lack of behavioural impairments across groups somewhat constrained further interpretation.

In the fifth study in Chapter 6, a comparison was conducted across groups of young adults with ASD, ADHD, and ASD+ADHD, and controls, in the neurofunctional activation related to duration discrimination using an exploratory whole-brain analysis approach. No group effects were observed across the four groups. Thus, pairwise comparisons were conducted between each disorder group against the typically developing controls. With the latter approach, reduced BOLD activations were observed only in the ASD+ADHD group compared to controls in

the right IFG/dlPFC/pre-CG. The pure groups did not differ from controls when compared pairwise. The difference was robust to covarying for IQ and it remained when individuals with medications were excluded from the analyses. The findings suggested that the ASD+ADHD group was neurally impaired in right IFG/dlPFC/pre-CG. Again, the interpretation of these findings is constrained by the fact that no significant behavioural impairment was observed across the four groups of participants, although pairwise comparison between the ASD+ADHD and the TD group suggested trend-level increased error during time discrimination condition.

7.2 Discussion of Primary Findings

7.2.1 Increased EF but Not SC Deficits Is Associated with ADHD Symptoms in ASD

Greater EF deficits were found to be associated with increased ADHD symptoms in the ASD population. These findings were consistent with the results of previous group comparison studies in EF involving individuals with ASD, ADHD and ASD+ADHD (e.g. Adamo et al., 2014; Andersen et al., 2013; Buehler et al., 2011; Corbett, Constantine, et al., 2009; Sinzig, Morsch, Bruning, et al., 2008; Yerys et al., 2009). The causal nature of the relationship, that is, whether the increase of EF deficits leads to increased ADHD symptoms or the other way around, cannot be determined from the available data and study design. However, I have shown in this thesis that increased EF deficits was associated with ADHD symptoms, and conversely increased ADHD symptoms was associated with poorer EF. That is, in Chapter 2, following the model of neurocognitive function as an intermediate phenotype for behavioural symptoms, an increase of EF impairment and not SC deficits predicted the increase of ADHD symptoms among adolescents with ASD. Conversely, by grouping participants by their diagnoses, I have shown in Chapter 3 that young adult males with ASD+ADHD demonstrate more EF deficits than those

with pure ASD. The ASD+ADHD group had equivalent deficits as those with ADHD in response inhibition, sustained attention (with concurrent inhibitory load), and working memory but were better at FER and ToM than those with ASD alone. The latter finding reinforces the idea that the addition of ADHD symptoms in ASD is specifically associated with EF but not SC deficits in the ASD population.

7.2.2 Neurocognitive Phenocopy: Individuals with ASD Had Largely Different Neural Correlates from ADHD in a Meta-analysis of Inhibitory Control Functions

The brain abnormalities underlying ASD and ADHD largely differed with few shared impairments. In the context of inhibition functions alone, the findings suggest that unlike in ADHD, the inhibitory performance in individuals with ASD is underpinned by an array of neural functions largely unrelated to action stopping. This finding has an important implication in the model of comorbidity between ASD and ADHD. It suggests that the apparent inhibitory difficulties in ASD are partly attributable to neurocognitive phenocopy. This interpretation fits the previous meta-analytic findings showing that response inhibition difficulties among individuals with ASD are more heterogeneous than those in ADHD (e.g. Geurts, van den Bergh, et al., 2014; Kuiper et al., 2016; Lijffijt et al., 2005; Lipszyc & Schachar, 2010). Some studies report increased ADHD symptoms among groups of individuals with pure ASD on questionnaire measures compared to controls although they did not receive ADHD diagnoses (e.g. Happé, Booth, et al., 2006; Sinzig, Morsch, Bruning, et al., 2008; Tye, Asherson, et al., 2014). It is thus reasonable to assume that some individuals with ASD also demonstrate symptoms of ADHD to the degree that they are meeting the diagnostic criteria for the latter. A phenocopy at symptom levels may be one explanation as to why psychostimulant use among children with ASD is not as effective or received with as high response rates as those observed in children with

ADHD (Harfterkamp et al., 2012; Pearson et al., 2013; Posey et al., 2007; RUPP Autism Network, 2005).

7.2.3 The Right IFG During Error-monitoring and Duration Discrimination in ASD+ADHD

The neurocognitive studies in Chapters 2 and 3 have shown similar profile of EF impairments in those with ASD+ADHD and those with ADHD alone. These findings suggest that the two conditions might share a common neural underpinning. Among the findings presented in the meta-analysis Chapter 4 is the shared under-activation in the right insula/IFG between groups of individuals with ASD and with ADHD during response inhibition. One interpretation of this finding is that a small part of the neuropathology is shared between two otherwise very different conditions. However, cross-disorder traits among the ADHD and the ASD samples in most neuroimaging studies were inadequately controlled. Thus, it is also plausible that the shared neuropathology in the right IFG found in the meta-analysis in Chapter 4 reflects a proportion of individuals meeting the criteria for both ASD and ADHD in the samples. Interestingly reduced activations in the bilateral IFG/insula and the thalamus during error monitoring, and in the right IFG/dlPFC during duration discrimination were found among young adults with ASD+ADHD in Chapters 5 and 6. Both findings point towards the right IFG as a possible underpinning for executive function deficits among individuals with ASD+ADHD. This supports the conjecture that the overlapping ASD and ADHD neuropathology in the right IFG in the meta-analysis could indeed reflect a subpopulation of individuals meeting the criteria for both conditions.

The right IFG is a predominant region for cognitive control (Aron et al., 2014; Cai et al., 2014; Criaud & Boulinguez, 2013; B. J. Levy & Wagner, 2011) and salience detection (Menon & Uddin, 2010; Seeley et al., 2007; Taylor et al., 2009).

The region, as well as its homologue on the left hemisphere, is mostly consistently under-activated among children with ADHD during stopping, error monitoring, target detection and timing (e.g. Cubillo et al., 2012; Hart et al., 2012, 2013; Plessen et al., 2016; Rubia, Halari, Mohammad, et al., 2011; Rubia et al., 2005; Smith et al., 2013). Its reduced activation among adults with ASD+ADHD is thus an interesting finding in this thesis. The right IFG is one of the primary target regions for MPH among boys with ADHD (Rubia et al., 2014). Upon administration of MPH, clusters of the right IFG/insula/striatum are typically up-modulated in boys with ADHD (Rubia et al., 2014). Given the similar pattern of neural impairment in adults with ASD+ADHD in the present thesis and children with ADHD as found in the previous literature, one pertinent question is whether the impairments in the right IFG/insula in adults with ASD+ADHD constitute a more persistent pattern of the same impairment of younger ADHD population. It would be interesting to know if the impairment is reversible with psychostimulant use and if IFG under-activation can distinguish treatment responders from non-responders among individuals with the dual diagnoses of ASD+ADHD.

7.2.4 Shared DMN impairments in the ASD and ASD+ADHD

As found in Chapter 4, reduced precuneus suppression was found specific to ASD relative to the ADHD during inhibition. In line with this finding, young adults with ASD and ASD+ADHD were found to share increased activation in the precuneus, i.e., the DMN, during selective attention in Chapter 5. This is an interesting finding as enhanced activation in the precuneus have been thought to be reflect attentional lapses or internally directed cognitive activities (Christakou et al., 2013; Cubillo et al., 2012; Hart et al., 2012; Kennedy et al., 2006; Rubia, Smith, Halari, et al., 2009). The absence of impairments in the ADHD group and the shared impairments in the precuneus in the ASD and ASD+ADHD groups point towards a possible additive pattern of neural impairments in the comorbid relative to the pure groups. Note,

however, that the absence of precuneus over-activation in the ADHD group was unexpected given the previous findings of shared task-related reduced DMN suppression in children with ASD and ADHD (Chantiluke, Barrett, Giampietro, Brammer, Simmons, Murphy, et al., 2015; Christakou et al., 2013) and the reduced precuneus functional connectivity in children with ASD, ADHD and ASD+ADHD (Di Martino et al., 2013). As I have pointed out in Chapter 5, recent literature has shown that under specific conditions such as rest-to-task switching and optimum task challenge adults with ADHD do not display reduced precuneus deactivation (Metin et al., 2015; Sidlauskaite et al., 2016). Therefore, both age and task condition could be confounding factors for the present results that should be further explored.

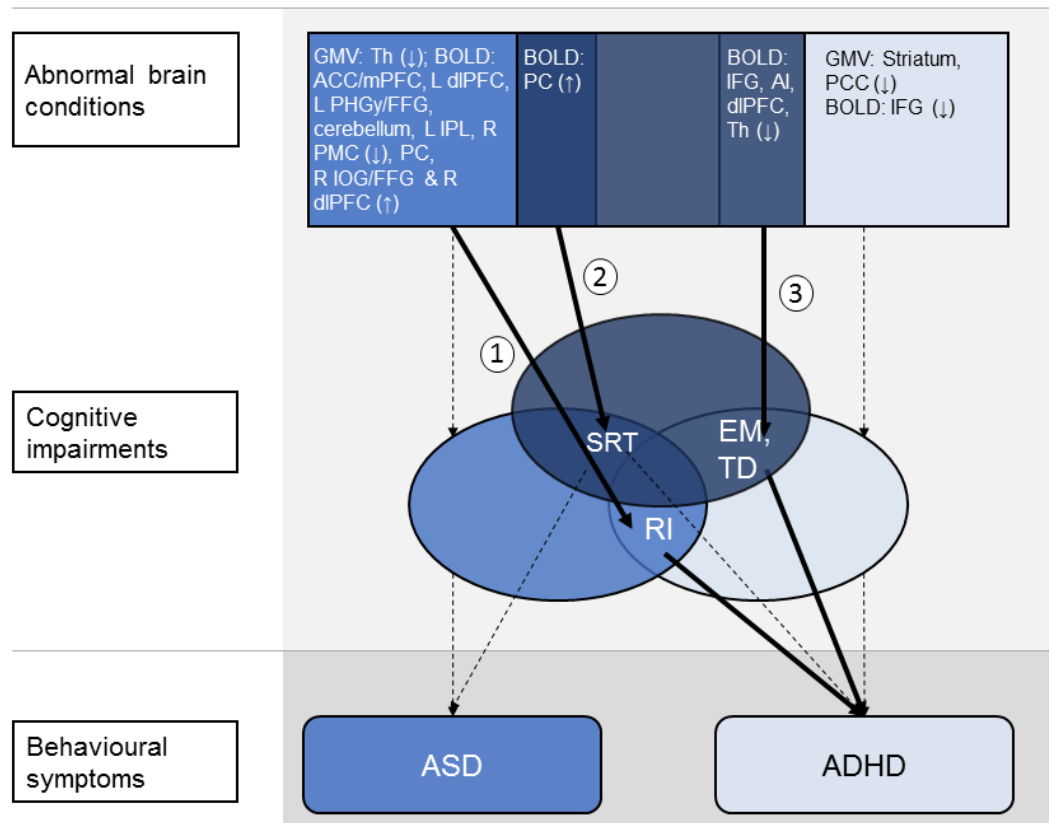
7.3 Further Questions Based on the Present Findings

7.3.1 Adults with ASD+ADHD: More Severe Persistent Impairments or Delayed Maturation?

Individuals with ASD+ADHD in this study exhibited the most detectable frontostriatal impairments during time estimation and error monitoring compared to the pure groups. Whether this finding also suggested that individuals with ASD+ADHD were more impaired than the other clinical groups during error monitoring, inhibition, selective attention and timing discrimination was still an open question as the behavioural data showed little evidence for impaired performance during each task. However, this interpretation is consistent with a previous finding on the comorbid group in children (Chantiluke et al., 2014). Furthermore, the neural impairments bore a close resemblance to those found during EF studies in children with ADHD and they were consistent with neuropsychological findings that have shown that individuals with ASD+ADHD have the most impairments during cool EF tasks such as working memory and the GNG tasks shown in Chapter 3. Finally, the interpretation is also in line with the suggested decline in the co-occurrence of ASD

and ADHD among adults (Hartman et al., 2016), which in turn suggests that those retaining dual diagnoses of ASD+ADHD in adulthood might represent individuals with a more persistent impairment.

Figure 7-1: Possible mechanisms for the co-occurrence of ADHD symptoms in ASD



Note. Several pathways to co-occurring ADHD symptoms in ASD are shown in thick lines: (1) phenocopy, applicable to response inhibition deficits across ages in some individuals with ASD (2) additive, appear to be shared in ASD and ASD+ADHD in adulthood this manifests as reduced deactivation of the DMN; (3) persistence of ADHD-related difficulties which is apparent in error monitoring and time discrimination among adults with ASD+ADHD. Blue symbols represent ASD-related abnormal brain conditions, cognitive impairments, and behavioural symptoms, navy blue symbols represent ASD+ADHD, and light blue symbols represent ADHD. Overlapping areas indicate co-existing impairments. Thick lines indicate the possible pathways towards disorder that has been explored in this study. Dotted lines indicate possible pathways that have not been explored in this thesis. Abbreviations: GMV = grey matter volume, Th = thalamus, BOLD = blood-oxygen level dependent, ACC/mPFC = anterior cingulate cortex/medial prefrontal cortex, L/R= left/right, dlPFC = dorsolateral prefrontal cortex, PHGy = parahippocampal gyrus, FFG = fusiform gyrus, IPL = inferior parietal lobe, PMC = premotor cortex, PC = precuneus, IOG = inferior occipital gyrus, IFG = inferior frontal gyrus, AI = anterior insula, PCC = posterior cingulate gyrus, SRT = self-referential thoughts, EM = error monitoring, TD = time discrimination, RI = response inhibition.

Given the close resemblance of the neural impairments found in the ASD+ADHD group to those in children with ADHD, I have posed a speculative interpretation in Chapter 5-6 that the neurofunctional impairment findings in the ASD+ADHD group relative to the pure groups may be an expression of an extended maturational delay in the former. Age-related functional activation changes have

been shown during duration discrimination, temporal discounting and error monitoring (Christakou et al., 2011; Rubia, 2007; Smith et al., 2011). Given that frontal regions such as the IFG, dlPFC structurally and functionally develop until mid-adulthood (Sowell, Peterson, et al., 2003, Rubia et al., 2013), these regions are probably more vulnerable to developmental delay (C. M. Murphy et al., 2014). Clinical evidence has also shown that people with ASD+ADHD has more severe difficulties in reigning externalising behaviours such as tantrum, delinquency and aggressiveness compared to an age-matched ADHD group (Goldin et al., 2013; Jang et al., 2013) or with ASD alone (F. Craig et al., 2015; Holtmann et al., 2007; Jang et al., 2013; Yerys et al., 2009). Further, individuals with ASD+ADHD also demonstrated poorer adaptive daily living skills than the pure groups (Rao & Landa, 2014; Sikora et al., 2012; Yerys et al., 2009), in some cases less than expected from the level of their cognitive ability (Ashwood et al., 2015). The speculative interpretation of delayed maturation could be further investigated in a wider age-range samples.

7.3.2 Moderated Neurocognitive Difficulties in the ASD+ADHD group: Variation of the Pure Groups or Cross-Disorder Interaction?

This question was based on several neurocognitive observations. First, individuals with ASD+ADHD appeared as impaired as individuals in the ADHD group on the sustained attention index of the GNG task but demonstrated performance in the same level as the ASD group on the sustained attention index of the CPT-AX task. Second, individuals with ASD+ADHD appear to consistently show a level of SC performance in between the TD group and the ASD group. As we have discussed in Chapter 3, one explanation for these findings might be that certain autistic or ADHD traits may down-moderate the neurocognitive phenotype of the counterpart group. Past studies have shown that children with ASD showed few difficulties in sustaining attention when compared to typically developing controls either on the GNG or the

CPT-AX task (e.g., Bogte et al., 2009; G. Goldstein et al., 2001; Pascualvaca et al., 1998), and both fMRI and behavioural studies have suggested a degree of sensory hypersensitivity in a substantial proportion of individuals with ASD (e.g., Cléry et al., 2013; Gomot et al., 2008; Jones et al., 2009; Karhson & Golob, 2016), which may support them in rare target detection tasks such as the CPT-AX. Interestingly, a recent clinical study suggests that individuals with HFA with ADHD demonstrate significantly less symptom of “careless mistakes”, which is typically related to working with details compared to individuals with ADHD alone (Joshi et al., 2014).

Similarly, the FER and ToM task performance among individuals with ASD+ADHD might also be a result of down-moderated autistic deficit by the ADHD traits. The reduced FER and ToM difficulties seen in the ASD+ADHD group relative to the ASD group cannot be explained by IQ, which did not differ between the two groups. Evidence suggests that individuals with ADHD have greater receptiveness to social influences than those with ASD alone. Among school-age children those with ADHD use more social context, nonverbal communication, and had better social relationship quality than those with ASD (Geurts & Embrechts, 2008). In addition, increased social motivation was associated with significantly improved performance of cognitive interference task among school-age children with ADHD but not those with ASD (Geurts, Luman, & van Meel, 2008). Supporting these behavioural findings, imaging studies have shown that boys with ADHD alone demonstrated specific increase of ventral striatum activation to both monetary and social rewards relative to an apparently blunted response in the region in age- and IQ-matched boys with ASD (Kohls et al., 2014). Complementing this finding, increased severity of combined autistic-like symptoms of reduced social interest, social understanding, stereotypy and resistance to change among approximately 240 children, adolescents, and adults with ADHD was negatively correlated with left caudate volume (O'Dwyer et al., 2016).

School-aged children with a diagnosis of ADHD, who were also referred to the ASD clinic due to presenting ASD traits, were found difficult to differentiate from verbally fluent age-matched children ASD. However, these children displayed a greater amount of social overtures, reciprocal social communication, socially directed facial expressions, and reduced unusual eye gaze (Grzadzinski et al., 2016). In addition, an unpublished study based on the Dutch Sample of Children and Adolescents (Scheres et al., 2001) with ASD, HKD, and ASD+HKD and controls showed that co-occurring HKD in the ASD population was associated with increased verbal fluency (Santosh, 2009). A previous study by Salley et al. (2015) indicated that individuals with ASD+ADHD and ASD are differentiated from those with ADHD alone and TD controls in the global score of social interaction and communication, although examining the domain scores, it appears that individuals with pure ASD consistently demonstrate higher average scores of difficulties than those with ASD+ADHD, in the domain social interaction, communication, stereotyped behaviour and creativity/play.

Whether children with ASD+ADHD might have similar social leanings to those of children with pure ADHD, which can help them develop social relationships and social cognition in adulthood is an interesting question to be researched further. To answer this question, we may start by comparing the social difficulties of these groups at symptoms levels to see if there are social abilities that are spared among individuals with ASD+ADHD. Only longitudinal studies however would be equipped to assessing the progression of these symptoms over time.

7.4 Strengths and Limitations of the Thesis

7.4.1 Strengths

A strength of the thesis is the use of several data sources for investigating the research topic, which allows it to be examined from different perspectives. The perspective of neurocognitive phenotypes and their relationships with behavioural symptoms such as those explored in Chapter 2 allow modelling of specific associations among EF and ToM with ASD and ADHD symptoms exclusively among individuals with ASD. The group comparison study widens the modelling approach by investigating a variety of cognitive functions, and not just the underlying EF, among diagnostically classified young adults with ASD, ADHD and ASD+ADHD. Meta-analysis studies have generated meaningful results for finding the similarities or differences in the neural underpinnings of several psychiatric disorders, including ASD, ADHD, developmental dyslexia, and schizophrenia (e.g. Norman et al., 2016; Stoodley, 2014; Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011). Its use in this thesis certainly gives additional insights into the phenocopy mechanism that might underlie the response inhibition difficulties among individuals with ASD. The fMRI methodology was particularly useful for assessing the differences between groups as has been demonstrated in several studies of children with neurodevelopmental conditions (e.g. Chantiluke et al., 2014; Christakou et al., 2013; Kohls et al., 2014) and combining this approach with neurocognitive approaches as has been done in this study facilitate a more critical appraisal of the fMRI findings.

Several other strengths of the study have been discussed in the previous chapters and will be reviewed here briefly. The inclusion of all male participants enhanced the homogeneity of subjects across groups, as well as the inclusion non-medicated participants in majority, which allowed a sensitivity analysis excluding

those individuals on current medication. Handedness was balanced across groups, although the inclusion of only right-handed subjects was not possible in the study. The fMRI investigations carried out for this thesis were among the few fMRI studies that investigate the co-occurrence of ASD and ADHD symptoms (e.g., Chantiluke et al., 2014; Di Martino et al., 2013) by contrasting individuals with ASD+ADHD against multiple comparators including the pure groups, who were well-defined diagnostically. The study is useful for disentangling the specific neural impairments related each disorder category, as well as neural impairments shared between the dual-diagnostic category and each pure condition, which can elucidate the mechanism underlying the co-occurrence of these disorders (Banaschewski et al., 2007).

7.4.2 Limitations

Several limitations in the studies reported in this thesis were a direct consequence of investigating the adult population. Both fMRI studies conducted in the present thesis detected little or no differences between the pure ASD and ADHD group relative to the healthy controls, which led to difficulties in interpreting the mechanism underpinning the comorbidity of ASD and ADHD. FMRI studies in adults with ADHD have yielded findings that are lower in effect size and more heterogeneous across studies (Cubillo & Rubia, 2010). Studies in adults will be affected by age-dependent changes in the disorder's form, for instance, reduced symptoms of hyperactivity and impulsivity in adults ADHD (Biederman et al., 2000; Faraone et al., 2005; J. Hill & Schoener, 1996). Age-dependent changes of brain structure and function in people with ASD (e.g. H. Y. Lin et al., 2015; C. M. Murphy et al., 2014) also reduce the comparability of brain findings in children and adults.

Mixed medication history among individuals with ASD (e.g. Esbensen et al., 2009; Oswald & Sonenklar, 2007) and long-term therapeutic effect of

psychostimulant medication in ADHD (e.g. Hart et al., 2013; Konrad, Neufang, Fink, & Herpetz-Dahlmann, 2007; Sheridan, Hinshaw, & D'Esposito, 2010) could be another source of heterogeneity in the samples and the lack of information about past treatment history was a limitation to the study. Increased variety of additional problems in adulthood such as conduct problems, antisocial personality, anxiety, and substance abuse disorders such as those found among individuals with ADHD (Biederman et al., 1993; Kessler et al., 2006; Molina & Pelham, 2014). People with additional problems would not be present in the clinical groups in substantial numbers due the imposed exclusionary criteria for the study and the phone screening that took place prior to inviting people to the study. However, increased difficulties in affect and behaviour observed among the clinical groups relative to controls on the SDQ17+, whether they indicate additional psychiatric difficulties or related to the typical ASD and ADHD presentation and to what extent they were clinically significant were unknown in this study. Future studies in adults should collect information about treatment history and should carry out in-depth assessment of psychiatric assessments to control any additional co-occurring problems in the clinical groups.

Improvement can be made with respect to measures, especially in those studies that generated novel data. The selection of measures was directed by the literature in ASD and ADHD, which is predominantly in childhood. The few available studies comparing individuals with ASD with ADHD, especially in adulthood, did limit the scope of measures to select from. Concerning trait measures, the SRS appears limited in its capacity to differentiate adults with ASD from those with ADHD. Previous studies suggest that the SRS had good specificity and sensitivity for differentiating children and adults with ASD from other clinical groups and typically developing controls (Bölte, 2012; Bölte, Poustka, & Constantino, 2008). However more recent studies have shown that the SRS ratings have reduced sensitivity

among children with non-ASD behaviour problems, including those with ADHD (e.g. Hus et al., 2013; Moul et al., 2015; Unterrainer et al., 2015). Even gold-standard measure such as ADOS and ADI-R do not always differentiate verbally fluent children with ASD from those with ADHD on every item levels (Grzadzinski et al., 2016). In this thesis, autistic trait measures have been used in secondary analyses to assess the relationships between neurocognitive performance and neuroimaging clusters were correlated with autism severity. The lack of significant findings may indicate true absence of relationship. However, the findings can also reflect the measure's lack of validity to index autistic severity among the clinical groups investigated. The use of additional measures such as the SCQ for indexing autism trait severity should be considered in future studies.

The selection of neurocognitive measures especially those applied in the MRI scanner is crucial for differentiating the three clinical groups. The stop-signal and duration discrimination task has been used consistently in previous clinical studies, particularly in the paediatric ADHD population (e.g. Chantiluke, Barrett, Giampietro, Santosh, Brammer, Simmons, et al., 2015; Cubillo et al., 2014; Rubia, Halari, Cubillo, et al., 2011). The stop-signal task is particularly elegant in its design, given its capacity to adjust its level of difficulties by tracking the participants' performance and keeping it at a specific level (e.g., Cubillo et al., 2014; Ray Li, 2006; Rubia et al., 2003). In contrast, the duration discrimination task was set at a fixed difficulty level, which may not be suitable for different age groups. In this regard, the stop-signal task is thus a more sensitive tool for investigating neural impairments than the duration discrimination task. Nevertheless, the differing conclusion regarding which clinical group demonstrate response inhibition difficulties based on the neurocognitive study in Chapter 3, i.e. both the ASD+ADHD and the ADHD groups, and the neuroimaging studies in Chapter 5, i.e., the ASD+ADHD group only, suggest that the stop-signal task may lack sensitivity for

detecting group differences in these samples, despite some findings of neural impairments in adults with ADHD using this task (Cubillo et al., 2010). The stop-signal task employed in Chapter 5 was approximately twice slower than the GNG task. It is possible that the relatively slower rate of stimulus presentation in the stop-signal renders it to be less effective at prepotentiating responses in the participants with adult ADHD or it may allow the participants to adopt a variation of strategies during the task beyond simply overriding planned action (see Verbruggen & Logan, 2009b). Conducting pre-scanning behavioural studies of a range of tasks, including those developed for scanning purposes out-of-scanner environment may be advisable in future fMRI studies in this topic.

7.5 Implications and Future Directions

Increased ADHD symptoms among individuals with ASD have been observed for nearly two decades, and only relatively recently researchers have attempted to investigate the biological underpinning of the co-occurrence of these conditions. Through this thesis, I have found that the co-occurrence of ADHD in the ASD population can be explained by several pathways that could result in several subpopulations of individuals with ASD+ADHD diagnosis with different characteristics. One of these pathways might be neurocognitive phenocopy, where individuals with ASD might have additional ADHD symptomatology due to a wide range of neurofunctional abnormalities unrelated to action stopping which however impair their performance on a response inhibition task. The second pathway is where adults with ASD+ADHD may have persisting impairments in the right IFG, a key region of action stopping consistently implicated in children and adolescents with ADHD. Also interesting are shared neural impairments in the ASD+ADHD and

the ASD groups which could indicate that impairments in the ASD+ADHD group in adulthood could be additive abnormalities of the pure groups.

Undoubtedly more studies in this topic are necessary to support the current conclusions. Replications of the present studies with carefully selected tasks and measures known to be sensitive to the adult populations would be recommended. Furthermore, fMRI studies can be completed in younger age groups, particularly in children and adolescents where cases of co-occurring symptoms appear to peak across the lifespan (Hartman et al., 2016). As advocated in Chapter 2, the use of multi-measure and multi-informant approach is advisable in this population group. Increasing the variety of cognitive domains to include working memory and sustained attention will give a fuller picture of the neural underpinning of ADHD symptoms in the ASD population. Therefore, expanding the scope of the study to include tasks in these domains would be a good strategy to further clarify the neurocognitive characteristics of ADHD symptoms in ASD and their neural correlates. Finally, given that the co-occurring symptoms of ASD and ADHD appear to change across the life span, future studies may attempt to investigate this topic in wider age ranges of participants with ASD, ADHD, and their co-occurring form. Such study will allow age-dependent changes to be investigated in all three clinical groups and may reveal the underlying reasons for the changing landscape of their comorbidity.

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