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Exploring the Neurocognitive and Electrophysiological Correlates of Challenging Behaviours in Adolescents with Autism Spectrum Disorder

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**Exploring the Neurocognitive and
Electrophysiological Correlates of Challenging
Behaviours in Adolescents with Autism Spectrum
Disorder**

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Thesis submitted for the degree of Doctor of
Philosophy, 2017.

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Abstract

Young people with autism spectrum disorder (ASD) are characterised by high rates of co-occurring emotional and behavioural problems, one of the most concerning being challenging behaviours, which can include aggression to the self and others, and extreme non-compliance. However, the drivers of these behaviours are largely unknown. One approach to understanding psychopathology in individuals with ASD is to explore how individual variability in cognitive functioning relates to co-occurring difficulties. This thesis tested whether functioning in selected cognitive and electrophysiological domains was associated with challenging behaviours, using two independent, well-characterised samples of young people with ASD. Analyses showed that adolescents with ASD were characterised by impairments in executive functioning (EF) not only when compared against both typically developing individuals, but also against oppositional defiant/conduct disorder (ODD/CD) and attention deficit hyperactivity disorder (ADHD). However, within adolescents with ASD, behaviourally measured EF impairments were only associated with co-occurring ADHD symptoms, but not other emotional or behavioural problems. Electrophysiological indices of EF were not related to any co-occurring problems. Electrophysiological indices of perceptual processing (PP) were associated with both behaviour problems and anxiety symptoms. Finally, structural equation modelling (SEM) showed that different domains of challenging behaviours were associated with different cognitive impairments; poorer theory of mind (ToM) was associated with increased self-injurious behaviour (SIB), whereas poorer PP was associated with increased externalising behaviours. Results suggest certain cognitive domains may be important to consider when developing aetiological models of challenging behaviours in young people with ASD.

Statement of Work

The primary sample included in this thesis (Chapters 3, 4 & 5) came from the QUEST study, funded by the National Institute for Health Research (NIHR) and part of the larger IAmHealth study headed by Professor Emily Simonoff (Institute of Psychiatry, Psychology and Neuroscience, King's College London). I reviewed the relevant literature and proposed appropriate cognitive and electrophysiological tasks for use in Wave 2 of the QUEST study. After discussion within the team I then programmed said tasks and collected the majority of the resulting experimental data. As part of the QUEST testing team, I conducted a significant proportion of the ADOS assessments and standardised cognitive tests, and assisted with the preparation of the ethics submission and participant recruitment. I had sole responsibility for analysing and interpreting the experimental data, under the guidance of supervisors and collaborators. Three additional samples were contrasted against the QUEST sample in Chapter 3. The data from these three samples was previously collected by others but analysed by myself under supervision of Professor Simonoff and Professor Katya Rubia.

The other major sample used in the current thesis was selected from the Special Needs and Autism Project (SNAP) funded by the Medical Research Council. The data used in Chapter 6 was previously collected by others but analysed by myself under supervision of Professor Simonoff. Input into this analysis and the resulting chapter was received from Professor Tony Charman, Professor Andrew Pickles, Professor Francesca Happé, Dr Rachel Kent, Dr Susie Chandler, Dr Silia Vitoratou (Institute of Psychiatry, Psychology and Neuroscience, King's College London), Professor Gillian Baird (Guy's and St Thomas' NHS Foundation Trust) and Dr Catherine Jones (Cardiff University).

Acknowledgements

First and foremost I would like to thank the funding bodies that supported my PhD, the Medical Research Council and the Institute of Psychiatry, Psychology and Neuroscience, as without them this work would not have taken place. Next, I would like to thank the families that took part in the research projects, and kindly gave up their precious time to complete the assessments. Spending time with these families, and especially adolescents with ASD, has taught me so much in ways I could not have predicted.

I would also like to thank my two supervisors Professors Emily Simonoff and Francesca Happé. I have become a better researcher, and overall scientist, due to your feedback, suggestions and advice. In particular Emily, who has always been on-hand to offer support and guidance not only during my PhD, but since I came to work in the department as a fresh-faced UCL graduate. I am so glad I had the chance to work with someone so intelligent and committed to high quality research; it has been truly inspirational (and extremely enjoyable).

I would also like to thank Professors Tony Charman and Andrew Pickles, who although were not official supervisors, nonetheless offered me endless guidance and assistance throughout my PhD. I also want to thank all the other people who have helped me during my PhD, including most people in the Child and Adolescent Psychiatry department, but also specifically Charlotte Tye, Lizzie Shepherd, Rachel Kent (for talking science), Joanne Tarver, Steve Lukito, and especially Adam Naples, who always offered excellent advice on all things EEG from across the pond. Also a special thanks to the QUEST research team, it really was a joy to work with you all!

I need to thank all my friends for listening to me talk about one very specific topic for three years, and Martin, for being the best partner I could hope for (but also for being a Stata whizz). Finally, I need to thank my parents for supporting me through my academic career thus far, and never once questioning my continual studies. A special shout out goes to my mum for being the most talented, ambitious, accomplished, and fun-loving woman I have ever known. She has never let anything hold her back from achieving her goals, and I strive to do the same.

List of Abbreviations

ABAS-C Adaptive Behaviour Assessment System – Communication subscale

ADHD Attention deficit hyperactivity disorder

ADI-R Autism Diagnostic Interview – Revised

ADOS-2 Autism Diagnostic Observation Schedule – 2

ADOS-G Autism Diagnostic Observation Schedule – Generic

ANOVA Analysis of variance

ANCOVA Analysis of co-variance

ARI Affective Reactivity Index

ASD Autism spectrum disorder

CAPA Child and Adolescent Psychiatric Assessment

CD Conduct disorder

CFA Confirmatory factor analysis

CFI Comparative fit index

DBC Developmental Behaviour Checklist

DSM Diagnostic and Statistical Manual of Mental Disorders

EEG Electroencephalography

EF Executive functioning

EFA Exploratory factor analysis

ER Emotion recognition

ERP Event-related potential

fMRI Functional magnetic resonance imaging

ICD International Classification of Diseases

ICV Individual coefficient of variability

ID Intellectual disability

MARS Maudsley Attention and Response Suppression battery

MMN Mismatch negativity

MSEL Mullen Scales of Early Learning

ODD Oppositional defiant disorder

PDD Pervasive developmental disorder

PDD-NOS Pervasive developmental disorder – not otherwise specified

PONS Profile of Neuropsychiatric Symptoms

PP Perceptual processing

RBS-R Repetitive Behavior Scale-Revised

RDoC Research domain criteria

RT Reaction time

RMSEA Root mean square error of approximation

ROWPVT Receptive One Word Picture Vocabulary Test

SCAS Spence's Child Anxiety Scale

SCQ Social Communication Questionnaire

SD Standard deviation

SDQ Strengths and Difficulties Questionnaire

SEM Structural equation modelling

SIB Self-injurious behaviour

SNAP Special Needs and Autism Project

SRS Social Responsiveness Scale

ToM Theory of mind

TLI Tucker-Lewis fit index

TROG-E Test for Reception of Grammar – Electronic Version

WASI Wechsler Abbreviated Scale of Intelligence

WPPSI Wechsler Preschool and Primary Scale of Intelligence

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1 Introduction

This chapter will first provide an overview of the clinical presentation, epidemiology and the current literature regarding the aetiology of autism spectrum disorder (ASD). Then, this chapter will review previous work relating to the prevalence of challenging behaviours in individuals with ASD, and studies that have tested how individual characteristics, such as age, sex and IQ, are associated with challenging behaviours. Next, the thesis will outline the cognitive phenotype approach, and how this may be helpful in understanding the potential drivers of challenging behaviours in young people with ASD. Finally, key findings regarding domains of cognitive functioning, which are known to be impaired in ASD populations, will be critically discussed, and the limited research regarding how these are associated with challenging behaviours will be considered. The chapter will conclude with a summary of the key research questions to be answered by this thesis.

1.1 ASD

ASD is a neurodevelopmental disorder defined by the presence of symptoms in two domains. The first domain involves persistent impairment in social communication and social interaction, including atypical non-verbal communication such as poorly modulated eye contact, and impairments in social-emotional reciprocity and developing, maintaining, and understanding relationships. The second domain involves restricted and repetitive patterns of behaviour, for example stereotyped and repetitive patterns of movement, and restricted, fixated interests or adherence to strict routines (see Figure 1 for full diagnostic criteria; American Psychiatric Association, 2013). These symptoms must be present from an early age (e.g., before 3 years of age). The most recent edition of the Diagnostic and Statistical Manual of

Mental Disorders (DSM-5) classification system has also included sensory processing hypo- and hypersensitivities in the diagnostic criteria, which fall within the restrictive and repetitive patterns of behaviour domain. Previous editions of the DSM (DSM-IV) had separate diagnostic categories of autism, Asperger's disorder and pervasive developmental disorder – not otherwise specified (PDD-NOS), however, these have all been subsumed under the umbrella term ASD in DSM-5 (American Psychiatric Association, 2013). In the most recent edition of the International Classification of Diseases (ICD-10), ASD diagnoses are still separated into 'childhood autism', 'Asperger syndrome', 'atypical autism' and 'other pervasive developmental disorders' (World Health Organisation, 1992). For ease, this thesis will use ASD throughout, in keeping with the most recent edition of DSM.

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; see text):

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.

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):

4. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
5. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behaviour (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
6. 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 interests).
7. Hyper- or hyporeactivity to sensory input or unusual interest 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).

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 functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and ASD frequently co-occur; to make comorbid diagnoses of ASD and intellectual disability, social communication should be below that expected for general developmental level.

Figure 1. DSM-5 Diagnostic Criteria for ASD

1.2 Epidemiology of ASD

ASD is recognised as a heterogeneous disorder; individuals with a wide range of intellectual ability may present with a range of symptoms, which may vary in severity (Frith & Happé, 2005). Although symptoms may vary in presentation and severity over time, ASD is seen as a life-long disorder, and has been estimated to have a prevalence of around 1% in the general population (Baird et al., 2006; Baxter et al., 2015; Elsabbagh et al., 2012; Y. Kim et al., 2011). ASD presents more often in males, with a ratio of 4:1 (Fombonne, 2003), although more recent estimates have suggested a slightly lower ratio when more thorough ascertainment methods are used (Mattila et al., 2011). Research has found a considerable co-occurrence between ASD and intellectual disability (ID; defined as having an IQ<70). ASD has been found to be prevalent in individuals with ID (De Bildt, Sytema, Kraijer, & Minderaa, 2005; Emerson, 2003), and around 50% of individuals with ASD also have co-occurring ID (Charman, Pickles, et al., 2011).

1.3 Aetiology of ASD

Twin studies have demonstrated ASD is a highly heritable disorder, with identical twins showing 60–98% concordance, compared to 0–53% in fraternal twins (A. Bailey et al., 1995; Tick, Bolton, Happe, Rutter, & Rijsdijk, 2016). Family studies have found similar results, reporting a 20% prevalence rate of ASD in children who have an older sibling with ASD (Ozonoff et al., 2011), in comparison to around 1% in the general population. Taken together, research has suggested heritability for ASD is around 90% (Rutter, 2005), far higher than most childhood psychiatric disorders. The heritability of ASD is thought to be likely due to the interactive effects of alteration in both rare and common genes, along with de novo mutations

(Abrahams & Geschwind, 2008). In addition to the strong genetic component associated with ASD, research has also highlighted that severe environmental conditions may play a causal role, as case studies have reported ASD symptoms have developed after brain injury due to encephalitis (Ghaziuddin, Tsai, Eilers, & Ghaziuddin, 1992), valproate use in pregnancy (Christensen et al., 2013) and after experiencing prolonged and severe environmental deprivation (Rutter et al., 1999). However, these environmental risk factors only account for rare cases, and are not thought to be general risk factors for ASD (Rutter, 2005). The origins of ASD are thus thought to be largely genetic, but the precise neurobiological pathway is still largely unknown; it is thought to be due to atypical brain development early in the lifespan, yet the mechanisms of this are unclear. Currently, the most well-known theories implicate abnormal synaptic functioning (Geschwind & Levitt, 2007) and an inhibitory/exhibitory imbalance (Rubenstein & Merzenich, 2003) in the aetiology of ASD.

1.4 Co-occurring Mental Health Problems in ASD

A breadth of research has demonstrated that co-occurring psychiatric disorders are highly prevalent in children and adolescents with ASD (Gadow, DeVincent, & Drabick, 2008; Gjevik, Eldevik, Fjæran-Granum, & Sponheim, 2011; Leyfer et al., 2006; Lundström et al., 2014; Salazar et al., 2015; Simonoff et al., 2008). Studies have found around 70% of young people with ASD meet DSM-IV criteria for an additional psychiatric disorder (Gjevik et al., 2011; Leyfer et al., 2006; Simonoff et al., 2008), far higher than in typically developing individuals, where prevalence has been estimated at 10-13% (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; H. Green, McGinnity, Ford, & Goodman, 2004). It is important to note that studies

which have utilised population-based samples (e.g., Simonoff et al., 2008) and those which have recruited from specialist schools (e.g., Gjevik et al., 2011) have found comparable rates of psychopathology in ASD, suggesting that the high prevalence rates are not merely an artefact of sampling from populations that might be more likely to have a more severe presentation (e.g., Berkson's bias; Berkson, 1946). Rates of emotional and behavioural problems in ASD have been found to be higher than in those with ID (Brereton, Tonge, & Einfeld, 2006; Farmer & Aman, 2011), suggesting high prevalence rates are not simply due to the increased proportion of individuals with ASD also having ID.

There are still a number of outstanding questions for the field of psychopathology in individuals with ASD. First, how to accurately differentiate between symptoms of co-occurring mental health problems and the symptoms of ASD. This question is particularly pertinent for certain disorders, for example distinguishing between rituals and compulsions in obsessive compulsive disorder (OCD), and repetitive behaviour and interests in ASD, or between social avoidance due to anxiety in social phobia and avoidance of social interactions in ASD due to impairments in social cognition. Few specialised instruments to assess mental health difficulties have been developed for individuals with ASD (Hanratty et al., 2015; Leyfer et al., 2006). Difficulties assessing mental health symptoms in individuals with ASD are also complicated by the communication and language impairments found in this population, which may especially hinder the identification of internalising disorders such as anxiety and depression.

Second, it is not known whether the phenomenology, developmental trajectory and risk factors for mental health difficulties in ASD are the same as those in non-ASD populations. Research is needed to build ASD-specific models of mental health

difficulties, and compare these against those from non-ASD populations. This will in part inform clinical practice, specifically, which early warning signs and risk factors should be considered when trying to identify individuals with ASD at high risk of developing mental health difficulties, and whether using comparable interventions to those used in non-ASD populations is appropriate.

1.5 Challenging Behaviours

One of the most concerning domains of mental health problems found in individuals with ASD is that of challenging behaviours. The term challenging behaviours was originally used to describe certain types of behaviour problems in individuals with ID, and can cover a wide range of phenomena. Challenging behaviours have been defined as “behaviour of such intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy” (Emerson, 1995). These are found to occur in around 10-17% of individuals with ID, with the most prevalent being severe non-compliance, aggression and self-injurious behaviours (SIB) (Emerson et al., 2001b; Oliver & Richards, 2015). SIB has been defined as self-directed acts that cause tissue damage (Tate & Baroff, 1966), and can include a variety of behaviours including hitting self with objects, hitting self against objects, scratching and biting the self, head banging and inserting objects into the body.

Research has found that individuals with ASD exhibit higher levels of challenging behaviours (Brereton et al., 2006) and more severe SIB (Bodfish, Symons, Parker, & Lewis, 2000) than individuals with ID. Within ID populations having a concurrent ASD diagnosis has been found to increase the likelihood of challenging behaviours (Lundqvist, 2013; McClintock, Hall, & Oliver, 2003). It should be noted that

although challenging behaviours are prevalent in ID and ASD populations, challenging behaviours are found in a range of psychiatric diagnoses (e.g., self-harm within depression) and can occur across the intellectual spectrum (see Figure 2) (Xenitidis, Russell, & Murphy, 2001).

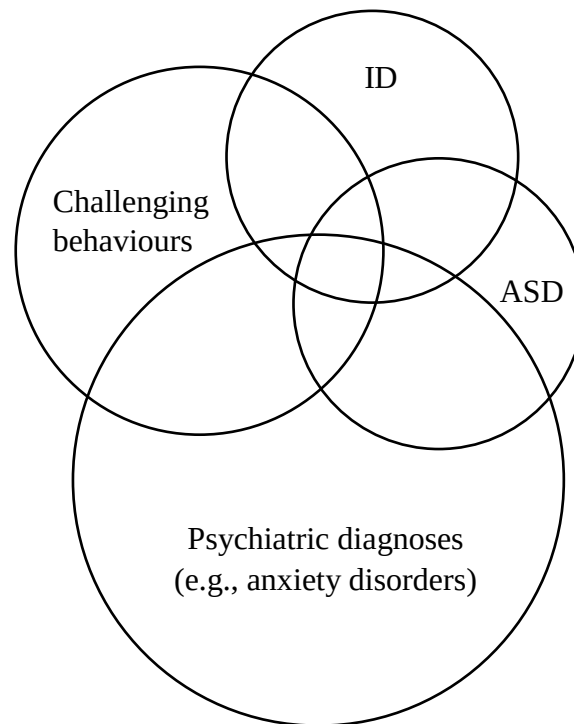


Figure 2. Relationship between Challenging Behaviours, ASD, ID and Mental Health Problems.

Adapted from Xenitidis, Russell and Murphy (2001).

1.5.1 Prevalence of Challenging Behaviours in ASD

Research into challenging behaviours in ASD can at times be inconsistent in its definition, in part due to the heterogeneous cluster of behaviours that fall under this umbrella term. In general, research has focused either on DSM-defined diagnoses which encapsulate some of the behaviours that fall under the term of challenging behaviours, namely oppositional defiant disorder (ODD) and conduct disorder (CD),

or on specific behaviours (e.g., aggression, SIB). Therefore, the following sections will focus first on prevalence rates of ODD and CD, then on specific behaviours such as aggression and SIB. The impact of these types of behaviours as a whole on individuals with ASD will be discussed.

1.5.2 ODD/CD

The DSM-5 diagnostic criteria for ODD and CD are outlined in Figure 3 and Figure 4. Estimates for the prevalence of ODD/CD in young people with ASD have varied between 7-37% (de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2007; Gadow, DeVincent, Pomeroy, & Azizian, 2004, 2005; Gjevik et al., 2011; Leyfer et al., 2006; Lundström et al., 2014; Mattila et al., 2010; Simonoff et al., 2008). The only study that utilised a population-based (as opposed to clinical) sample found 30% of adolescents with ASD also met criteria for ODD/CD (Simonoff et al., 2008). In general, rates of ODD/CD in ASD are much higher than those found in general population epidemiological samples, where the prevalence of ODD/CD in children and adolescents has been estimated at between 6-7% (Costello et al., 2003; H. Green et al., 2004), and direct comparisons have found that ASD populations have higher rates of ODD/CD than typically developing children (Gadow et al., 2005; Guttman-Steinmetz, Gadow, & DeVincent, 2009; Mayes et al., 2012).

A. A pattern of angry/irritable mood, argumentative/defiant behaviour, or vindictiveness lasting at least 6 months as evidenced by at least four symptoms from any of the following categories, and exhibited during interaction with at least one individual who is not a sibling.

Angry/Irritable Mood

1. Often loses temper.
2. Is often touchy or easily annoyed.
3. Is often angry and resentful.

Argumentative/Defiant Behaviour

4. Often argues with authority figures or, for children and adolescents, with adults.
5. Often actively defies or refuses to comply with requests from authority figures or with rules.
6. Often deliberately annoys others.
7. Often blames others for his or her mistakes or misbehaviour.

Vindictiveness

8. Has been spiteful or vindictive at least twice within the past 6 months.

Note: The persistence and frequency of these behaviours should be used to distinguish a behaviour that is within normal limits from a behaviour that is symptomatic. For children younger than 5 years, the behaviour should occur on most days for a period of at least 6 months unless otherwise noted. For individuals 5 years or older, the behaviour should occur at least once per week for at least 6 months, unless otherwise noted. While these frequency criteria provide guidance on a minimal level of frequency to define symptoms, other factors should also be considered, such as whether the frequency and intensity of the behaviours are outside a range that is normative for the individual's developmental level, gender, and culture.

B. The disturbance in behaviour is associated with distress in the individual or others in his or her immediate social context (e.g., family, peer group, work colleagues), or it impacts negatively on social, educational, occupational, or other important areas of functioning.

C. The behaviours do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder.

Figure 3. DSM-5 Diagnostic Criteria for ODD

A. A repetitive and persistent pattern of behaviour in which the basic rights of others or major age appropriate societal norms or rules are violated, as manifested by the presence of at least three of the following 15 criteria in the past 12 months from any of the categories below, with at least one criterion present in the past 6 months:

Aggression to People and Animals

1. Often bullies, threatens, or intimidates others.
2. Often initiates physical fights.
3. Has used a weapon that can cause serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun).
4. Has been physically cruel to people.
5. Has been physically cruel to animals.
6. Has stolen while confronting a victim (e.g., mugging, purse snatching, extortion, armed robbery).
7. Has forced someone into sexual activity.

Destruction of Property

8. Has deliberately engaged in fire setting with the intention of causing serious damage.
9. Has deliberately destroyed others' property (other than by fire setting).

Deceitfulness or Theft

10. Has broken into someone else's house, building, or car.
11. Often lies to obtain goods or favours or to avoid obligations (i.e., "cons" others).
12. Has stolen items of nontrivial value without confronting a victim (e.g., shoplifting, but without breaking and entering; forgery).

Serious Violations of Rules

13. Often stays out at night despite parental prohibitions, beginning before age 13 years.
14. Has run away from home overnight at least twice while living in the parental or parental surrogate home, or once without returning for a lengthy period.
15. Is often truant from school, beginning before age 13 years.

B. The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.

C. If the individual is age 18 years or older, criteria are not met for antisocial personality disorder.

Figure 4. DSM-5 Diagnostic Criteria for CD

When considering the studies that have reported lower prevalence rates of ODD/CD in youth with ASD (7% in both Gjevik et al., 2011; Leyfer et al., 2006), this may be in part due to the diagnostic criteria for ODD/CD not effectively capturing the phenomenology of behaviour problems in youth with ASD (Brereton et al., 2006; Gjevik et al., 2011), and may be in part influenced by the sensitivity of the instrument used (e.g., in-depth interview vs. questionnaires). Features of the diagnostic criteria for ODD such as ‘often blames others for his/her mistakes or misbehaviour’, ‘is spiteful and vindictive’, and features of CD such as ‘often lies to obtain good or favours or to avoid obligation’ (American Psychiatric Association, 2013) may require a more mature level of cognitive thinking and awareness, along with intact social knowledge – domains in which individuals with ASD are reported to have difficulties. Supportingly, although ODD is more common than CD in both ASD and non-ASD populations, comparison of age-matched samples have shown that the ODD/CD ratio is higher in ASD (Costello et al., 2003; Simonoff et al., 2008). When adolescents with ASD + attention deficit hyperactivity disorder (ADHD), characterised by persistent symptoms of age-inappropriate inattention, hyperactivity and impulsivity, were compared against those with ADHD alone, the ASD + ADHD group were only rated as more severe on aspects of ODD which did not rely on social understanding, namely ‘loses temper’ and ‘easily annoyed’, but not those which were more focused on social relationships (e.g., ‘tries to get even’ and ‘blames others’) (Guttmann-Steinmetz et al., 2009). Given the problems in applying ODD/CD criteria to youth with ASD, often specific types of externalising symptoms (e.g., aggression) are focused on, rather than diagnostic categories.

1.5.3 Aggression

In a large multi-site study (N=1584) of young people aged 2-17 with ASD (mean age 6 years), 54% of caregivers of children and adolescents reported their child as currently demonstrating physical aggression (Mazurek, Kanne, & Wodka, 2013). Similar figures have been reported elsewhere from other multi-site child outpatient samples (mean age 8 years) using parent-rated ASD-specific questionnaires to measure co-occurring behaviour problems (Matson, Wilkins, & Macken, 2008). A study that utilised the Simons Simplex Collection, a multi-site study that includes families with only one child with ASD, found 68% of young people aged 4-17 (mean age 9 years) with ASD had demonstrated aggression at some point in their lives towards caregivers, but also 49% had demonstrated more pervasive aggressive behaviour to both caregivers and non-caregivers (Kanne & Mazurek, 2011). The studies listed so far predominately used yes/no questions to determine the presence of aggressive behaviour, which could in part explain the high prevalence rates reported. Others have also found high rates of aggressive behaviour in samples of children with ASD using questionnaire measures, such as the Behavior Problems Inventory (54-56%) (McTiernan, Leader, Healy, & Mannion, 2011; Murphy, Healy, & Leader, 2009), and observational ratings of behaviour (34-58%) (Bronsard, Botbol, & Tordjman, 2010), however all of these studies utilised samples of individuals with ASD with high rates of ID.

Other studies have reported slightly lower rates of aggressive behaviour problems when validated measures were used, such as the Child Behavior Checklist (CBCL). Here, studies have found 19-25% of children and adolescents with ASD demonstrate clinically significant aggression (Farmer et al., 2014; Hartley, Sikora, & McCoy, 2008; A. Hill et al., 2014). Slightly higher rates are found using parental interview,

where 33% of high functioning children with ASD aged 4-14 years were found to demonstrate aggressive behaviour and 60% severe temper tantrums (e.g., occurring everyday) (Dominick, Davis, Lainhart, Tager-Flusberg, & Folstein, 2007). However, lower rates of aggression are also reported; one study found only 8% of newly-diagnosed preschool children (2-4 years) with ASD exhibited clinically significant aggression using the CBCL (Georgiades et al., 2011), and another large sample (n=1609) of both high and low functioning children with ASD (6-16 years) found 17% displayed problematic aggressive behaviour as rated by the Pediatric Behavior Scale (Mayes et al., 2012). Interestingly, this same study found that 67-78% showed problematic oppositional and explosive behaviour, suggesting there may be some aspects of challenging behaviours that are more common than others.

Additionally, this aggressive behaviour appears to present frequently in some children with ASD, as studies have found 20% demonstrated aggressive behaviour three times a week or more, using information gathered from parents shortly after diagnosis from a population-based database (n=863) (Maskey, Warnell, Parr, Le Couteur, & McConachie, 2013). It should be noted that the majority of the studies referenced above (Farmer et al., 2014; Hartley et al., 2008; A. Hill et al., 2014) utilised clinically referred samples, which may have influenced prevalence rates. However, studies using population-based samples of young people with ASD and standardized measures, found around 20% of caregivers reported conduct problems (including aggression) as being a problem (Lecavalier, 2006; Maskey et al., 2013). This suggests that the rates of aggression from clinical samples outlined above were not dramatically inflated. It should also be noted that many of these studies utilised samples with a wide age range (4-14 years in Dominick et al., 2007; 1-21 years in Farmer et al., 2014; 2-17 years in A. Hill et al., 2014; 3-21 years in Lecavalier.,

2006). In non-ASD populations, rates of aggression are found to decline with age (Tremblay et al., 2004), thus prevalence rates of aggression may differ between children and adolescents with ASD. Another factor to consider is the variability in cognitive ability within ASD samples, which, given the association between challenging behaviours and ID, could influence prevalence rates. However, even when individuals with ASD are compared against those with ID, research has found those with ASD have higher levels of disruptive behaviour (Brereton et al., 2006), and significantly higher scores on indices of bullying, hostility and physical aggression (Farmer et al., 2014).

1.5.4 SIB

Prevalence rates of SIB have been found to range from 33-50% in samples of individuals with ASD and ID (Baghdadli, Pascal, Grisi, & Aussilloux, 2003; Dominick et al., 2007; McTiernan et al., 2011; Richards, Oliver, Nelson, & Moss, 2012; Shattuck et al., 2007). The most prevalent behaviours in ASD are hitting self with one's own body, hitting oneself against objects, biting and scratching oneself (Richards et al., 2012). Differences in prevalence estimates could be due to the age and cognitive ability of the participants in the samples. Studies with the highest estimates have typically used younger samples, with those who reported prevalence rates of around 50%, using samples with a combined mean age of 9 years (Baghdadli et al., 2003; Richards et al., 2012), as compared to those who included adolescent samples, where a prevalence rate of 36% was found (Rattaz, Michelon, & Baghdadli, 2015). Similar to the critique of research studies which examined the prevalence of aggression in ASD, most of the samples looking at SIB in ASD have also included a significant proportion of participants with ID, which could have influenced prevalence rates. Few studies have directly compared SIB in ASD as compared to in

ID populations. One study found that the prevalence of SIB in individuals with ASD (50%) was significantly higher than those with Down's syndrome (18%), but comparable to those with Fragile X syndrome (55%) (Richards et al., 2012). A meta-analysis found within those with ID, an additional diagnosis of ASD led to a six-fold increase in risk for exhibiting SIB (McClintock et al., 2003).

1.6 Stability of Challenging Behaviours in ASD

In non-ASD populations aggressive behaviour has been found to decline over time (Tremblay et al., 2004). However, the trajectory of challenging behaviours in ASD appears more stable. One study looked at change in the level of co-occurring psychiatric symptoms in an ASD sample with a wide range of IQ (50-129) from 12 - 16 years old age (Simonoff et al., 2013). Results showed found no significant change in CD symptoms using ASD-specific cut offs from age 12 to age 16. From a wide range of potential predictors, improvement in CD symptoms was only predicted by greater neighbourhood deprivation and special school attendance. IQ and ASD severity did not predict change over time. Another study found no significant difference in the percentage of individuals who met diagnostic criteria for disruptive behaviours in childhood (61% at age 6-12 years) and adolescence (51% at age 12-20 years) in a sample of individuals with PDD-NOS (Verheij et al., 2015). Parent-reported stereotypy was the only significant predictive factor for persistence of externalising behaviours. Age, sex, gender and IQ were not significant predictors. The stability of challenging behaviours is similar to that reported in ID populations (Emerson et al., 2001a; Taylor, Oliver, & Murphy, 2011), although one systematic review found aggression and SIB increased with age from childhood into adulthood

in individuals with ID, yet noted the literature regarding aggression was inconsistent (Davies & Oliver, 2013).

Alternatively, some research has suggested that challenging behaviours may decline with age in ASD (Shattuck et al., 2007; Tonge & Einfeld, 2000). One study found as a group there was decline in challenging behaviours, although up to 50% of the sample did not show any improvement (Shattuck et al., 2007), and a significant proportion still showed concerning levels of challenging behaviours. Overall, it appears that challenging behaviours in individuals with ASD often continue past childhood, which is of concern as older individuals have the potential to cause more harm to themselves and others when exhibiting challenging behaviours.

1.7 Impact of Challenging Behaviours in ASD

Aside from the immediate physical impact of SIB and aggressive behaviours on the individual in question, challenging behaviours can have a negative impact on many spheres of an individual's life. Challenging behaviours have been associated with increased caregiver stress (Lecavalier, Leone, & Wiltz, 2006) and teacher burn out (Hastings & Brown, 2002), and the presence of SIB has been associated with poorer parent-rated quality of life (Rattaz et al., 2015). Individuals with ASD who exhibit challenging behaviours are found to have more functional impairment (Mattila et al., 2010; Witwer & Lecavalier, 2010), be more likely to be admitted to residential care (Emerson, 2001), and are five times more likely to be hospitalized (Mandell, 2008). Others have also suggested that challenging behaviours can also have a significant impact on learning achievement and the development of social relationships (Emerson, 2001).

1.8 Associations between Individual Characteristics and Challenging Behaviours in ASD

In general, research has found few individual characteristics are associated with mental health problems in ASD, and the literature regarding significant associations is highly variable. The main individual characteristics that have been studied are cognitive functioning, sex, age and ASD severity. A summary of the research regarding how each domain is related to challenging behaviours in ASD populations is outlined below.

1.8.1 Cognitive Functioning

Studies have found lower IQ to be associated with higher levels of aggressive and destructive behaviour in individuals with ASD (Dominick et al., 2007; A. Hill et al., 2014; McTiernan et al., 2011). However, those studies that measured ODD symptoms found that children with ASD and $IQ \geq 70$ had more severe ODD symptoms than those with $IQ < 70$ (Gadow et al., 2005). Finally, others have found no association between IQ and ODD/CD symptoms or aggression (Gadow, DeVinent, & Schneider, 2008; Gjevik et al., 2011; Mazurek et al., 2013; Simonoff et al., 2008).

Lower non-verbal cognitive functioning and language have also both been reported to be associated with aggressive behaviour in clinical samples (Dominick et al., 2007; Hartley et al., 2008), however, a large population-based sample ($n=863$) of children with ASD found no association between language level and aggressive behaviour (Maskey et al., 2013). Conversely, in a sample of children with ASD enriched for emotional and behavioural problems, verbal children were more likely to be diagnosed with ODD as compared to those who were non-verbal (Witwer & Lecavalier, 2010). The authors of the latter study suggested this may be due to the

nature of some ODD symptoms requiring a certain level of language (e.g., argues with others, blames others).

In terms of SIB, lower IQ, along with impaired language and communication, has consistently been found to be associated with increased likelihood, frequency and severity of SIB in ASD (Baghdadli et al., 2003; Carroll et al., 2014; McTiernan et al., 2011; Rattaz et al., 2015; Richards et al., 2012; Richman et al., 2013).

Additionally IQ has been found to be predictive of change in SIB between childhood and adolescence in ASD and ID samples (Rattaz et al., 2015).

1.8.2 Sex

Two studies have found an association between sex and ODD symptoms in children with ASD; one found symptoms were more severe in males as compared to females using teacher-reported ODD symptoms (aged 6-12 years) (Gadow, DeVincent, & Schneider, 2008), and another found the same pattern of results using parental psychiatric interview in slightly younger children (4-8 years) (Salazar et al., 2015). However, the majority of studies have found sex to be unrelated to the presence or severity of aggressive and non-compliant behaviours (Brereton et al., 2006; Farmer & Aman, 2011; Farmer et al., 2014; Gadow et al., 2004; Gjevik et al., 2011; Hartley et al., 2008; A. Hill et al., 2014; Kanne & Mazurek, 2011; Kozlowski, Matson, & Rieske, 2012; Maskey et al., 2013; Murphy et al., 2009). This is different to non-ASD populations, where male gender has been consistently found to be a risk factor for externalising disorders (Maughan, Rowe, Messer, Goodman, & Meltzer, 2004). However, the majority of studies of individuals with ASD listed above had limited numbers of female participants, which may have constrained their power to detect sex differences. Additionally, it is unclear whether males and females were matched

on other key characteristics (e.g., IQ, ASD severity). With regards to SIB, one study found no sex differences in a sample of adolescents with ASD (Rattaz et al., 2015).

1.8.3 Age

Whilst some studies have found younger individuals with ASD display more aggressive behaviour (Farmer et al., 2014; Kanne & Mazurek, 2011; Mazurek et al., 2013), others have found no association between age and challenging behaviours in ASD populations (Farmer & Aman, 2011; Gjevik et al., 2011; Hartley et al., 2008; A. Hill et al., 2014; Murphy et al., 2009).

1.8.4 ASD Severity

Two samples of children with ASD, one of children aged 6 years and under, and the other of children aged 6-12 years, both found that individuals with a diagnosis of Asperger's/PDD-NOS (which some have argued index a less severe ASD presentation than a diagnosis of autism) had more severe ODD symptoms than those with a diagnosis of autism (Gadow et al., 2004, 2005). A similar finding has been reported in older samples (age range 6-17 years), in that those with PDD-NOS were more likely to have ODD/CD than those with Asperger's or autistic disorder (Gjevik et al., 2011). In a large clinical sample, those with less severe ASD symptoms, as rated using observer measures, were more likely to have aggressive behaviour problems (A. Hill et al., 2014).

Conversely, others have found those with a diagnosis of autism had higher rates of aggressive behaviour than those with Asperger's/PDD-NOS (Farmer & Aman, 2011), and some have reported a positive association between ASD severity and challenging behaviours (Matson et al., 2008). Finally, others (including two population-based samples) have found no relationship with ASD severity (Hartley et

al., 2008; Kanne & Mazurek, 2011; Maskey et al., 2013; Simonoff et al., 2008).

Here, discrepancies might be due to how challenging behaviours were conceptualised. As mentioned previously, ODD/CD symptoms, especially those involving deception, lying or bullying, may be less common in individuals with ASD as they require more advanced cognitive and social understanding. Thus, these types of behaviour may be more likely to be present in individuals with less severe ASD symptoms (e.g., those with Asperger's/PDD-NOS), whereas less complex and more physical behaviours may be more likely to be present in those with more severe ASD symptoms. However, there is on-going debate about how to measure ASD severity, as studies have found wide variability in the use of diagnostic categories in individuals with ASD (Lord, Petkova, Hus, & et al., 2012), thus limiting the conclusions one can draw from studies that use type of diagnosis as a metric of ASD severity. Additionally, the effect of common method variance should be held in mind when considering studies that have reported a relationship between parent-rated ASD severity and parent-rated challenging behaviours (e.g., Matson et al., 2008), along with the inclusion of 'stereotypy' as a challenging behaviour (as there will undoubtedly be item overlap with questionnaires of ASD severity, specifically on items regarding repetitive behaviours).

In terms of SIB, the literature is limited. Higher levels of ASD severity have been reported to be contemporaneously associated with higher levels of SIB (Baghdadli et al., 2003), and to predict increase in SIB between childhood and adolescence, over and above the effects of age (Rattaz et al., 2015).

1.8.5 Other Characteristics

Finally, certain characteristics aside from those listed above have been found to be associated with challenging behaviours. One study found family psychiatric history

predicted the presence of ODD (Gadow, DeVincent, & Schneider, 2008), but this association was not specific to externalising behaviours as it predicted a range of parent-reported co-occurring difficulties. Others have found parent-rated impulsivity and stereotypy to be associated with SIB in individuals with ASD (Richards et al., 2012; Richman et al., 2013), and the association remained after controlling for IQ and severity of ASD symptoms (Richman et al., 2013).

1.9 The Functional Approach to Challenging Behaviours in ASD

There are many theoretical perspectives to consider when trying to understand potentially drivers of challenging behaviours in individuals with ASD. One well-known perspective is the functional, or applied behaviour analysis (ABA), perspective. This approach focuses on the function challenging behaviours may serve for a given individual, and proposes that challenging behaviours may begin as alternative methods of communication in individuals with compromised communicative ability. For example, challenging behaviours might be used to gain attention from a caregiver, or to escape unwanted demands. Through repeated interactions between the individual and their social and physical environment (also known as schedules of reinforcement), these behaviours become associated with value, or positive valence. Broadly speaking, challenging behaviours may be met with positive reinforcement (e.g., gaining attention from caregivers, obtaining desired item) or negative reinforcement (e.g., avoiding and escaping unwanted situations or stimuli).

Within ASD populations, functions of challenging behaviours have been found to be comparable to those in non-ASD populations (e.g., social functions such as gaining attention or wanting to escape demands), but also some have been found which are

more ASD-specific (e.g., retaining repetitive routines, avoiding specific sensory stimuli) (Chiang, 2008; O'Reilly et al., 2010; Reese, Richman, Belmont, & Morse, 2005). ABA interventions focus on identifying environmental contingencies through behavioural observation, then using hypothesis-testing and environmental manipulation to identify antecedents (and thus the function) of challenging behaviours. These types of assessments then inform interventions that serve to both lessen inadvertent reinforcement of certain behaviours, and also to replace challenging behaviours with more adaptive forms of communication (Carr & Durand, 1985). In ID populations, functional analysis is recommended by NICE guidelines (National Institute for Clinical Excellence, May 2015) and has been shown to effectively decrease SIB (Iwata et al., 1994). However, in ASD the evidence base for its efficacy in reducing challenging behaviours is more limited (Horner, Carr, Strain, Todd, & Reed, 2002; Machalicek, O'Reilly, Beretvas, Sigafoos, & Lancioni, 2007). Indeed, as challenging behaviours often serve non-social functions in individuals with ASD, for example, occurring only when specific routines and rituals are interrupted, it may be less clear how to intervene effectively. This is in comparison to non-ASD populations, where the focus of treatment is often on promoting more appropriate communication strategies and decreasing inadvertent positive reinforcement (e.g., attention) from caregivers, which appear more amenable to intervention.

Although the functional perspective is a useful and often used approach, it is limited in its ability to identify risk and protective factors of challenging behaviours in individuals with ASD, beyond that of limited communication. Additionally, the functional perspective cannot account why the profile and prevalence of challenging behaviours varies across different genetic syndromes (e.g., increased self-injury in

Cornelia de Lange and Prader-Willi, but not Angelman Syndrome) with comparable levels of ID (Oliver et al., 2013). This variation suggests that there are other factors, beyond impaired communication and inadvertent environmental reinforcement, to consider.

Taking a cognitive approach, as described below, can identify other important potential drivers. This is not to say the cognitive approach is better, but should be considered complementary. For example, if specific areas of cognition were found to be associated with challenging behaviours, it would suggest that ABA-minded interventions in ASD populations, whilst continuing to focus on communication and inadvertent reinforcement, could also consider other domains (e.g., non-verbal aspects of cognitive functioning). More detail about taking a cognitive approach to challenging behaviours in ASD is outlined below.

1.10 The Cognitive Phenotype Approach

An alternative approach to understanding challenging behaviours in ASD is to take the cognitive phenotype approach. This approach focuses upon the ‘intermediate’ phenotype between genes and behaviour, either taking a categorical approach and examining cognitive functioning in individuals with psychiatric disorders, or taking a dimensional approach and testing how cognitive functioning relates to specific domains of symptoms. The rationale behind this being that if impairments in cognition are associated with a given psychiatric diagnosis or group of symptoms, then this can offer clues as to potential mechanisms that may drive atypical behaviour, and signpost future research studies towards cognitive targets to test as predictors in longitudinal studies. If a predictive relationship between cognition and

behaviour is supported, this can inform the design of novel interventions, where causality can be tested.

Cognitive functioning can be examined using behavioural indices (typically performance on a given task), or combined with neuroimaging to give information about patterns of brain activation during a specific task. This can then uncover not only how people process certain types of information, but also the neural signal for a particular cognitive process. When used in clinical populations, this can highlight the particular areas of the brain or specific circuits that may be affected in a given disorder, which in turn can prompt research into the biological and genetic influences upon functioning in these neural systems. The neurocognitive approach can be applied to understanding the aetiology of challenging behaviours in individuals with ASD. Thus, the key first step is to test if certain cognitive domains are associated with the presence of challenging behaviours in individuals with ASD, which will in turn inform longitudinal and intervention studies of co-occurring emotional and behavioural problems in ASD. The most obvious domains of cognition to test first are those known to be impaired in individuals with ASD. An outline of these is given below.

1.11 Profile of Cognitive Impairments in ASD

1.11.1 Theory of Mind

Theory of mind (ToM) is the ability to appreciate that both oneself and other people have internal mental states, and to be able to accurately understand and predict other people's behaviour on the basis of these mental states (Frith, Morton, & Leslie, 1991; Premack & Woodruff, 1978). In classic tests of ToM (e.g., the Sally Ann task), which rely on accurate inference of mental states to pass successfully, studies

have found children with ASD failed more often than both typically developing individuals and individuals with ID (Baron-Cohen, Leslie, & Frith, 1985). Since this early study, a breadth of research has demonstrated that individuals with ASD show difficulty on a range of tasks that tap ToM abilities (Frith, 2012). In addition, research has found adults with ASD, who may pass verbal-response behavioural tests of ToM (Bowler, 1992), do not spontaneously infer mental states in studies that used eye-gaze to measure implicit anticipation of behaviour (Senju, Southgate, White, & Frith, 2009). Inherent difficulties in ToM are thought to underlie the social and communication symptoms of ASD, as ToM task performance has been found to correlate with measures of social symptom severity (Lerner, Hutchins, & Prelock, 2011; Shimon, Weizman, Yoran, & Raviv, 2012), however, a relationship between the two has not consistently been reported (Cantio, Jepsen, Madsen, Bilenberg, & White, 2016; Pellicano, Maybery, Durkin, & Maley, 2006).

1.11.2 Emotion Recognition

Similar to the ToM literature, research into the emotion recognition (ER) abilities of individuals with ASD has proposed that a domain-specific impairment in socio-cognitive abilities underpins the symptoms of ASD. Here, research has focused on the ability to accurately identify and label emotional expressions of others. Meta-analyses have found a general impairment in ER ability in individuals with ASD (Uljarevic & Hamilton, 2012), although others have reported opposing findings (C. Jones, Pickles, et al., 2011), and some suggest ER difficulties could be a function of co-morbid alexithymia rather than intrinsic to ASD (Cook, Brewer, Shah, & Bird, 2013). Difficulties in ER, specifically in the recognition of anger, have been found to be associated with communication impairment and increased overall symptom severity (Bal et al., 2010).

1.11.3 Executive Functioning

Executive functioning (EF) is an umbrella term referring to a set of higher order cognitive functions which serve to achieve future goals (Welsh & Pennington, 1988), including inhibition, planning/working memory, cognitive flexibility/set shifting. Individuals with ASD have been found to exhibit widespread impairments across a variety of different EF tasks (Brunsdon et al., 2015; E. Hill, 2004); the most documented being in cognitive flexibility (Landry & Al-Taie, 2016; Ozonoff et al., 2004), although more recent meta-analyses have also suggested additional impairments in inhibition (Geurts, Bergh, & Ruzzano, 2014). Difficulties in cognitive flexibility have been proposed to lead to real-life difficulties in adaptively switching one's behaviour in response to environmental demands, and may underpin the symptoms of restricted and repetitive patterns of behaviour in ASD (Turner, 1997). Associations have been found between restricted and repetitive behaviours and difficulties shifting to and maintaining a new response (Miller, Ragozzino, Cook, Sweeney, & Mosconi, 2015), as well as the number of task errors made when shifting between sets (Yerys et al., 2009). However, similar to the heterogeneity of ToM research, others have found no association between EF ability and restricted and repetitive behaviours (Cantio et al., 2016; Faja & Dawson, 2014; Pellicano et al., 2006), or ASD symptoms in general (Liss et al., 2001). Reduced inhibition may also play a role in the ability of individuals with ASD to inhibit repetitive patterns of behaviour, with one study having found a trend relationship between response inhibition ability and restricted and repetitive behaviours (Van Eylen, Boets, Steyaert, Wagemans, & Noens, 2015). Aggregate scores from EF tasks of planning ability, cognitive flexibility, and inhibitory control in children with ASD have been found to predict improvement in both social communication ability and restricted

and repetitive behaviours three years later (Pellicano, 2013), suggesting EF may play a role in both the social and non-social symptom domains in ASD.

One point to consider is the specificity of EF impairments to individuals with ASD, as EF impairments have also been reported in individuals with ODD/CD (Morgan & Lilienfeld, 2000), and in those with ADHD (Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008). As outlined above, although impairments in cognitive flexibility are thought to be characteristic of individuals with ASD, research has also found flexibility impairments in ADHD and ODD/CD (Toupin, Déry, Pauzé, Mercier, & Fortin, 2000; Willcutt et al., 2008). Similarly, although impairments in inhibition are found in individuals with ASD (as discussed above), these are thought to be especially characteristic of individuals with ADHD (Lipszyc & Schachar, 2010; Rubia, Smith, & Taylor, 2007), and have also been reported in those with ODD/CD (Hobson, Scott, & Rubia, 2011; Oosterlaan, Logan, & Sergeant, 1998; Van Goozen et al., 2004). Furthermore, ASD, ODD/CD and ADHD are all found to show a more inconsistent and variable response pattern, as evidenced by increased response time variability (Karalunas, Geurts, Konrad, Bender, & Nigg, 2014; Kofler et al., 2013; Willcutt et al., 2008).

Results from studies comparing groups of individuals with ASD against those with ADHD are mixed. Some have reported evidence of specificity, for instance, finding only individuals with ADHD, but not those with ASD, show impairments in inhibition (Happé, Booth, Charlton, & Hughes, 2006; Ozonoff & Jensen, 1999; Sinzig, Morsch, Bruning, Schmidt, & Lehmkuhl, 2008), and conversely only individuals with ASD, but not those with ASD, show impairments in cognitive flexibility (Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2004; Ozonoff & Jensen, 1999). However, others have failed to find group differences (Geurts et al., 2004; M.

C. Goldberg et al., 2005). A review of the literature could not find any direct comparisons of ASD and ODD/CD in terms of EF impairments. Thus, it remains unclear whether impairments in EF, specifically in inhibition and cognitive flexibility, are particularly specific to individuals with ASD, or are found trans-diagnostically in populations of individuals characterised by behaviour problems.

1.11.4 Perceptual Processing

The fourth cognitive domain that has been widely studied in ASD populations is that of perceptual processing (PP). There are many similar theories within this field focused on understanding how people with ASD process and experience perceptual input, for example, weak central coherence (Happé & Frith, 2006), empathizing vs. systemizing (Baron-Cohen, 2009), and enhanced perceptual functioning (Mottron, Dawson, Soulières, Hubert, & Burack, 2006). For simplicity this thesis will focus upon just one, the hypo-priors theory (Pellicano & Burr, 2012), as this framework is most pertinent to understanding additional emotional and behavioural problems in ASD (see also Gomot & Wicker, 2012; Sinha et al., 2014 for similar frameworks). Typical perception of the world is an active process that is continually formulating and updating hypotheses about our environment. Based on past experience we build ‘priors’ (similar to internal working models) based on prediction, which guide how we perceive on-going events and experiences. One example of how expectation can modulate how we perceive the world around is visual illusions. Here, typically developing individuals will see the most likely interpretation of an ambiguous image, rather than the most accurate.

Additionally, in this adaptive model of perception, attentional resources are diverted to important stimuli, whereas irrelevant stimuli are filtered out and ignored. One example of the adaptive nature of on-going perception is habituation. This is when,

in typically developing individuals, the brain's response to repeated events decreases exponentially over time, allowing the individual to filter out the seemingly irrelevant repetitive stimuli and conserve attentional resources (Rankin et al., 2009).

Pellicano and Burr suggest that individuals with ASD have broader priors, in that they have fewer internal constraints to guide incoming perceptual information (but see Brock, 2012; Teufel, Subramaniam & Fletcher, 2013; Van de Cruys, de-Wit, Evers, Boets, & Wagemans, 2013 for debate). This leads to more limited prediction of future events, meaning that on-going perceptual experiences are less adaptively guided by expectation and past experience. Experimental findings support this framework, which have shown that individuals with ASD are less fooled by visual illusions (Happé, 1999), less influenced by prior expectation in both linguistic and visuo-spatial tasks (Brunsdon et al., 2015; Ropar & Mitchell, 2002), and that prior experience impacts less on sensory discrimination in individuals with ASD (Tannan, Holden, Zhang, Baranek, & Tommerdahl, 2008). Neuroimaging studies have found lower levels of habituation in response to repeated presentations of visual stimuli in individuals with ASD, and one study found the degree of habituation was associated with symptom severity (Kleinhans et al., 2009; Swartz, Wiggins, Carrasco, Lord, & Monk, 2013). Another study found nine month old 'high risk' infants (who have an older sibling with ASD) did not show habituation to repeated auditory stimuli (Guiraud et al., 2011). Decreased influence of prior experience in ASD may underlie the well-documented atypical responses to sensory and perceptual inputs (e.g., hypo- and hyper-sensitivity, sensory seeking behaviours) (Baranek, David, Poe, Stone, & Watson, 2006; Crane, Goddard, & Pring, 2009; Leekam, Nieto, Libby, Wing, & Gould, 2007; Liss, Saulnier, Fein, & Kinsbourne, 2006), as the brain is unable to

adaptively attenuate its response to irrelevant events and focus its resources on important stimuli.

1.12 Electrophysiological Measurement of Brain Activity

As mentioned previously, cognitive tasks can be paired with assessment of brain functioning to uncover the neural basis of specific cognitive processes, and to compare patterns of brain functioning between groups of interest. Exploring the neural correlates of challenging behaviours in ASD will help to identify aspects of neural functioning associated with said behaviours, which may offer insights into potentially causal mechanisms. One method for measuring neural functioning during cognitive tasks is electroencephalography (EEG). EEG records on-going fluctuations in voltage using electrodes placed on the scalp surface. These fluctuations are caused by changing electrical activity within pyramidal cells near the skull surface (Luck, 2005), and are thought to measure changes in neural activity within the brain. By combining EEG recording with experimental paradigms, one can time-lock the EEG recording to the presentation of specific stimuli. The resulting EEG response to a given event is known as an event-related potential (ERP). By averaging ERPs over many trials, one can separate the ‘signal’ of the brain’s response to an event, from the ‘noise’ of on-going fluctuations in brain activity. This is thought to be an accurate reflection of an individual’s neural response to a given event. The brain’s response to an event typically consists of multiple peaks and troughs, known as components, which are characterised by their timing, polarity and topography (Luck, 2005). See Figure 5 for a schematic waveform to illustrate the timing of different ERP components.

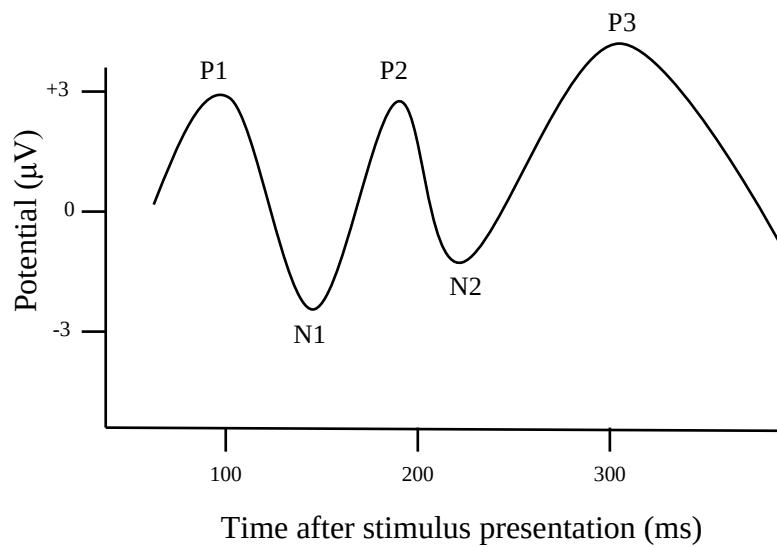


Figure 5. Schematic Representation of a Basic Event-Related Waveform

One can examine different components at different areas of the scalp to gain insights into the neural basis of specific cognitive processes. Early components such as the P1 are thought to represent more perceptual and automatic processing of stimuli (e.g. the physical properties of a stimulus), whereas later components such as the P300 represent more effortful and attentional cognitive processes (Banaschewski & Brandeis, 2007). The EEG/ERP method has proven useful in gaining insights into child psychopathology, especially in neurodevelopmental populations (Banaschewski & Brandeis, 2007; McPartland, Bernier, & South, 2015). This is due to the applicability of EEG to a wide range of subjects, including those who are minimally verbal or have ID. EEG is more applicable as it is relatively non-invasive. Collecting EEG data only requires the subject to tolerate a net of electrodes being placed on the scalp. Researchers can use simple tasks or paradigms to collect information about cognitive functioning, which do not necessarily require a verbal or behavioural response. Another advantage is that one can remove movement artefact

on a trial-by-trial basis, meaning that even if a participant moves during data collection (as is more likely in neurodevelopmental disorder populations), it does not render the whole data collection session invalid.

Aside from these practical advantages, EEG is an excellent method for studying cognitive processes due to its temporal sensitivity. EEG directly records fluctuations in neural activity at a millisecond level of precision; meaning one can examine both early (100-250ms post stimulus) and late (>250ms post stimulus) ERP components. This temporal sensitivity allows researchers to distinguish and study distinct stages within a complex cognitive pathway, allowing them to understand which aspects of processing may be atypical.

1.13 Domains of Atypical Brain Functioning in ASD

Complementing the research reviewed above, which details how certain cognitive processes are found to be impaired in individuals with ASD, researchers have used EEG recording to study how brain functioning may be altered in individuals with ASD during said cognitive processes. A brief review of key components indexing specific cognitive processes, and how they are altered in individuals with ASD, is given below. More information on specific components and the literature relating to them will be given in relevant chapters.

1.13.1 Electrophysiological Indices of Social Processing

The first area of findings relates to the processing of social information. In addition to the behavioural impairments (e.g., recognition accuracy) outlined above, EEG studies have found individuals with ASD show atypical brain response when processing social stimuli (Kröger et al., 2014; Lerner, McPartland, & Morris, 2013; McPartland, Dawson, Webb, Panagiotides, & Carver, 2004; Senju, Tojo, Yaguchi, &

Hasegawa, 2005; Webb, Dawson, Bernier, & Panagiotides, 2006). One of the most well studied ERP components in relation to social processing is the N170, so named as it represents a negative deflection found 170ms after stimuli presentation. The N170 is typically found in the posterior temporal lobe and is of greater amplitude in the right hemisphere. In typically developing individuals, the N170 has been found to have a greater amplitude for faces than for non-face stimuli, and therefore is thought to reflect some nature of face-specific processing (Eimer, 2011). N170 amplitude is also found to be associated with social skills in both typically developing children (Hileman, Henderson, Mundy, Newell, & Jaime, 2011) and adults (Meaux, Roux, & Batty, 2014). Although the exact meaning of the N170 still remains under debate, it has been widely used to study the development of face processing in typical and atypical populations. In addition to its sensitivity to face vs. non-face stimuli, the characteristics of the N170 are found to be modulated by different emotional expressions, with studies having found typically developing individuals show shorter latencies for positive faces and increased amplitude for fearful faces (Batty & Taylor, 2003).

Research has found both children and adults with ASD exhibit increased latency (Hileman et al., 2011; McPartland et al., 2004; O'Connor, Hamm, & Kirk, 2005) and decreased amplitude (A. J. Bailey, Braeutigam, Jousmäki, & Swithenby, 2005; O'Connor et al., 2005) of the N170 in response to viewing a face, which has been proposed to reflect slowed and less efficient processing (Dawson, Webb, & McPartland, 2005). Furthermore, unlike typically developing individuals who show right hemisphere lateralization, the topography of the N170 has been found to be altered in individuals with ASD, which has been interpreted as indexing reduced neural specialization for social stimuli (Dawson et al., 2005; McPartland et al.,

2004). In addition to these alterations in the brain's response to viewing a face, studies have found children with ASD do not show a differentiated neural response to direct vs. averted gaze in the same manner as typically developing children do (Senju et al., 2005). Research has also demonstrated that atypical ERP response in individuals with ASD is not limited to processing faces, as atypical responses have also been found in response to hearing vocal emotions (Fan & Cheng, 2014; Lerner et al., 2013), viewing human figures in motion (biological motion) (Kröger et al., 2014) and when completing ToM tasks (Happé et al., 1996; Kana, Keller, Cherkassky, Minshew, & Just, 2009). In summary, the literature suggests individuals with ASD exhibit atypical brain activity across a wide-range of social-cognitive tasks, which may potentially underpin both the behavioural impairments seen in neuropsychological tasks, and the symptoms of ASD.

1.13.2 Electrophysiological Indices of EF

Unlike the breadth of research focused on the neural correlates of social processing, few studies have focused on the neural correlates of EF in individuals with ASD (Jeste & Nelson, 2009). Said studies of EF have mostly utilised some variant of a visual oddball task, which features rare targets randomly presented in a stream of frequently presented standard stimuli. These types of paradigms are thought to tap into attentional orienting and switching abilities. When paired with different response requirements for the target and standard stimuli (similar to Go/NoGo or continuous performance task paradigms) this allows researchers to also measure response selection and inhibition. Most research using these paradigms focuses on two ERP components. The first is the N2, a negative component localized to the fronto-central regions, found around 250ms after stimuli presentation. In typically developing populations N2 amplitude has been found to be greater in response to

low frequency stimuli, and is therefore thought to reflect conflict monitoring (Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003). The other frequently studied ERP component is the P300, a positive deflection found 300-500ms after stimuli presentation and localized to the parietal areas (although some suggest increasing anteriorization with age; Jonkman, Lansbergen, & Stauder, 2003; Valko et al., 2009). P300 amplitude has been found to be greater for target as compared to standard stimuli, and additionally, as task difficulty increases, P300 amplitude for the target stimuli decreases (Isreal, Chesney, Wickens, & Donchin, 1980); thus it has been interpreted as indexing allocation of attentional resources (Polich, 2007). In terms of how these components are altered in ASD populations, research using variants of the visual oddball task has found both children (Kemner, van der Gaag, Verbaten, & van Engeland, 1999; Wang, Yang, Liu, Shao, & Jackson, 2017) and adults (Strandburg et al., 1993) with ASD exhibit larger P300 amplitudes. This increase in amplitude is thought to index the additional effort required to shift and allocate attention to the target stimulus in individuals with ASD. Conversely, others have found children with ASD show decreased N2 and P300 responses to target stimuli as compared to typically developing children (Verbaten, Roelofs, Van Engeland, Kenemans, & Slangen, 1991). In this study, a similar pattern was found between children with ASD and those with CD, who provided a psychiatric comparison group, thus it remains unclear how specific these alterations are to ASD. Finally, others have found no alterations in N2 or P300 amplitude in individuals with ASD (Courchesne, Lincoln, Yeung-Courchesne, Elmasian, & Grillon, 1989; Pritchard, Raz, & August, 1987; Sokhadze et al., 2009; Tsai, Pan, Wang, Tseng, & Hsieh, 2011). One potential explanation for the conflicting results is differences in the age of the samples, as one study found children with PDD-NOS showed

decreased P300 amplitude as compared to typically developing controls but no differences were found in adolescents with PDD-NOS (Hoeksma, Kemner, Kenemans, & van Engeland, 2006). One study measured response selection and inhibitory control (as opposed to the sustained attention/attentional switching as outlined above) using a continuous performance task. Here, results showed that children with ASD exhibited reduced N2 enhancement to NoGo relative to Go trials, relative to both children with ADHD and typically developing children (Tye et al., 2013). In addition to alterations in the amplitude of ERP response, research has also found increased latency of both the N2 and P300 in individuals with ASD (Sokhadze et al., 2009; Townsend, Harris, & Courchesne, 2009; Tsai et al., 2011), which is thought to index slowed conflict monitoring and attentional shifting to the target stimulus.

1.13.3 Electrophysiological Indices of PP

The breadth of studies documenting sensory processing atypicalities in individuals with ASD (Baranek et al., 2006; Leekam et al., 2007; Liss et al., 2006) has prompted researchers to explore whether the brain's response to incoming perceptual information might be altered in individuals with ASD. As many individuals report both hypo- and hyper-sensitivity to auditory information (Baranek et al., 2006), much research has focused on the integrity of auditory processing, using oddball paradigms. In these paradigms, a deviant stimulus that varies in duration, frequency or intensity, is randomly inserted into a run of repeated (standard) stimuli. In typically developing populations, the neural response to the deviant stimuli is more negative than that to the standard stimuli, and this deflection is typically most pronounced over the fronto-central area, 100-200ms after stimuli presentation

(Näätänen & Alho, 1995). This difference in neural response between the deviant and standard stimuli is known as the mismatch negativity (MMN).

Unlike the P300, the MMN is not attention-dependent and is elicited even when participants are not attending to sounds (e.g., when watching a movie). MMN amplitude and latency has been found to be related to how different the deviant is from the standard stimuli, and was associated with individual discrimination skills measured behaviourally (Amenedo & Escera, 2000; Kujala, Kallio, Tervaniemi, & Näätänen, 2001; Näätänen & Alho, 1995), suggesting it is an index of individual sound-discrimination sensitivity. The MMN has been found early in childhood, and the mechanisms are assumed to be comparable across the lifespan (Gomot, Giard, Roux, Barthélémy, & Bruneau, 2000). To link this with the hypo-priors framework (Pellicano & Burr, 2012), where it is proposed that typically developing individuals have priors, based on previous experiences, which guide on-going perception, the MMN is an example of how neural mechanisms prioritize the processing of novel stimuli (the deviant sound), whereas repeatedly experienced stimuli (the standard stimuli) are less deeply processed.

With regards to how the MMN is altered in individuals with ASD, findings are mixed (for a review see O'Connor, 2012). Some authors have found hyper-sensitivity to changes in auditory stimuli, as indexed by increased MMN amplitude, to changes in pitch and tone of speech stimuli in both ASD (Lepistö et al., 2008; Lepistö et al., 2005), and ASD and ID populations (Ferri et al., 2003). Others have not found differences in amplitude, instead finding decreased MMN latency in children with ASD to changes in the pitch of puretones (Gomot, Belmonte, Bullmore, Bernard, & Baron-Cohen, 2008; Gomot et al., 2011), although one study found increased latencies (Jansson-Verkasalo et al., 2003). As experimental research

in typically developing populations has found shorter MMN latencies when there is more difference between the deviant stimuli and the standard stimuli (e.g., greater difference in tone/pitch/volume), some suggest findings of decreased latency illustrate how children with ASD process slightly deviant events as if they were much more deviant, highlighting hyper-sensitivity to change (Gomot & Wicker, 2012).

Conversely, others have reported attenuated neural response to change in incoming stimuli in ASD populations. One study found young children (3-4.5 years) with ASD failed to show an MMN to changes in speech sounds (Kuhl, Coffey-Corina, Padden, & Dawson, 2005), and additionally, that failure to exhibit an MMN was associated with more severe observer-rated ASD symptoms. Others have reported attenuated amplitudes in high-functioning boys with ASD to both deviant words and pseudo-words (Ludlow et al., 2014) and pitch deviant puretones (Andersson, Posserud, & Lundervold, 2013). Furthermore, and one of these studies found smaller MMN amplitudes were associated with higher sensory sensitivity scores (Ludlow et al., 2014). Others have reported similar findings, in that children with ASD showed attenuated neural response to both duration deviants (Vlaskamp et al., 2017), and both standard and novel puretone sounds (Donkers et al., 2015). In the study by Donkers and colleagues, greater attenuation of the N2 component, following a more attenuated P1 component, to standard tones, was associated with more severe caregiver-rated sensory seeking behaviours.

Another study suggests differences in sensory processing in ASD are dependent upon attentional focus, as although attenuated MMN to pitch change in puretones was found in children with ASD during non-attended conditions, when participants were instructed to listen to the sounds, there was no difference between the ASD and

typically developing group (Dunn, Gomes, & Gravel, 2008). However, sample size differed between the non-attended ($n=68$) and attended conditions ($n=20$), which may have limited power to detect group differences in the attended condition. The authors also found a significant association between age and the likelihood of the presence of the MMN, with 29% of children aged 6-8 years with ASD showing an MMN, as compared to 57% of children aged 11-12 with ASD.

Research has also found the MMN in children with ASD is more laterally distributed, as compared to the expected MMN fronto-central topography in typically developing children (Gomot et al., 2008). Others have reported similar atypical localization of the MMN in children with ASD (Jansson-Verkasalo et al., 2003).

Together, research suggests that the neural processing of perceptual information, specifically in the auditory domain, is altered in individuals with ASD. However, the directionality of the effect (e.g., hyper-responsivity or hypo-responsivity to changes in incoming stimuli) remains unclear, although more studies appear to be published supporting the idea of hypo-sensitivity. One possible explanation for the equivocal results is the heterogeneity within ASD. Both hypo- and hyper-responsiveness to sensory stimuli are found in ASD, sometimes within the same individual (Leekam et al., 2007). This is especially important to consider in electrophysiological studies as most of the studies discussed above used small samples, meaning individual differences may be more likely to influence results. Following on from this, another potential explanation is differences in the cognitive ability of samples (high functioning in Ludlow et al., 2013 and Andersson et al., 2013 vs. with concurrent ID in Gomot et al., 2011 and Ferri et al., 2003), along with age (as in Dunn et al., 2008).

Finally, differences could be due to the type of stimuli used (speech vs. puretones) and how the standard and deviant stimuli differed (e.g., in pitch, tone or duration).

The three available research studies examining neural indices of habituation in individuals with ASD have already been mentioned in Section 1.11.4. However, to review the limited research on habituation in individuals with ASD in more detail, one study found that unlike low risk infants, high risk infants (who had an older sibling with ASD) did not show a decrease in ERP response over repeated presentations of the standard stimulus, using an auditory oddball paradigm similar to those described above (Guiraud et al., 2011). Decreased activation of the amygdala over repeated presentations of faces has also been found in children (Swartz et al., 2013) and adults (Kleinhans et al., 2009) with ASD. However, the conclusions one can draw about habituation in ASD from studies that find decreased habituation to faces are limited by both the samples and stimuli used, and the type of data collected. In terms of the data collected, these two studies utilised functional magnetic resonance imaging (fMRI). This is a method for measuring neural activity, using the haemodynamic response within areas of the brain as a proxy for brain activity. Therefore, the end result is a summation of all activity (excitatory and inhibitory) in a given brain region. Thus, although studies did not find reduced amygdala activation in response to later-presented as compared to earlier-presented faces in individuals with ASD (as was found in the typically developing group), it is unclear whether this truly demonstrates that individuals with ASD were not habituating. Second, as face stimuli were used, it is hard to know if this really represents decreased habituation for all perceptual (including low-level) information, or just specifically to social stimuli, which individuals with ASD are known to have difficulty processing.

In summary, the ERP method has revealed significant differences in a variety of cognitive processes in individuals with ASD. The most consistent findings relate to the processing of social stimuli, with more mixed findings reported for EF and PP. Differences in paradigms and samples utilised are likely to contribute to the heterogeneity within the literature.

1.14 Potential Overlap between Cognitive Impairments in ASD and Cognitive Impairments Associated with Behaviour Problems in Non-ASD Populations

As outlined in Section 1.11, individuals with ASD are characterised by impairments in both social and non-social cognitive processes, and alterations in their related neural signatures. How impairment in these domains relates to co-occurring mental health and behavioural problems remains unknown. However, research in ODD/CD populations, characterised by behavioural problems, suggests that there may be some overlap in cognitive impairments in individuals with ASD, and individuals with ODD/CD. This could, in part, explain the increased rates of behaviour problems in individuals with ASD. Literature relating to impairments in social processing, EF and PP in ODD/CD populations is briefly outlined below.

In terms of impairments in social cognition, ER impairments have been found in adolescents with both child-onset and adolescent-onset CD, although they appear to be more marked in the child-onset group (Fairchild, Van Goozen, Calder, Stollery, & Goodyer, 2009). Meta-analyses have found an aggregate impairment in the recognition of fear in individuals with antisocial behaviour (Marsh & Blair, 2008). The results of these behavioural studies are complemented by neuroimaging paradigms, which have found dampened neural response to fearful faces in children

with CD and high levels of callous-unemotional traits (A. Jones, Laurens, Herba, Barker, & Viding, 2009).

Children with ODD/CD are also characterised by impairments in EF, as demonstrated by neuropsychological studies, which have found impairments in response inhibition (Hobson et al., 2011; Oosterlaan et al., 1998), and EEG studies which have found reduced N2 amplitudes (Albrecht, Banaschewski, Brandeis, Heinrich, & Rothenberger, 2005). Additionally, a consistent association has been reported between aggressive behaviour and reduced P300 amplitude in oddball tasks (Gao & Raine, 2009; Harmon-Jones, Barratt, & Wigg, 1997; Patrick, 2008) and reduced P300 amplitudes have been found in children and adolescents with ODD/CD (Banaschewski et al., 2003; Iacono, Carlson, Malone, & McGue, 2002). This suggests potentially similar impairments in stimulus categorisation and attentional allocation to those found in youth with ASD. Similar to children with ASD (Landry & Al-Taie, 2016), children with ODD/CD have also been found to exhibit decreased performance in set shifting tasks, suggesting impairment in cognitive flexibility (M.-S. Kim, Kim, & Kwon, 2001; Toupin et al., 2000; Willcutt et al., 2008).

One point to bear in mind when reviewing the literature on EF impairments in ODD/CD populations is the well-documented co-occurrence of ODD/CD and ADHD (Ford, Goodman, & Meltzer, 2003; Steinhausen et al., 2006). Given that youth with ADHD are also characterised by difficulties in EF (Willcutt et al., 2008) and show similar attenuations in P300 amplitude (Brandeis et al., 2002; Strandburg et al., 1993; Tye et al., 2013) as to those with ODD/CD, it is unclear whether unrecognised ADHD could be driving the EF impairments reported in ODD/CD populations. If this were the case, EF impairments in individuals with ASD may not

be related to challenging behaviours, but instead be associated with ADHD symptoms.

From the literature reviewed above, it appears there may be some overlap in cognitive impairments between individuals with ASD and those with ODD/CD, although few have specifically compared the two groups (although see A. Jones, Happé, Gilbert, Burnett, & Viding, 2010; Schwenck et al., 2012). This overlap suggests that these domains of cognition could potentially be related to challenging behaviours in ASD. The overlap between ODD/CD and ADHD in non-ASD populations, suggests that any research investigating the association between EF impairments and challenging behaviours in individuals with ASD should also consider the role of ADHD symptoms.

1.15 Focusing on Cognitive Phenotypes to Understand Challenging Behaviours in ASD

There are very few studies that have tested whether functioning in different cognitive domains is associated with challenging behaviours in ASD. One study found that difficulties in recognising surprise was associated with severe mood problems in adolescents with ASD (Simonoff et al., 2012). Although a range of EF domains were tested, no significant associations were found. Another study found poorer ToM task performance was associated with self-rated aggression in children with ASD (Pouw, Rieffe, Oosterveld, Huskens, & Stockmann, 2013). Others have found an association between parent-reported inflexibility and aggressive behaviour in individuals with ASD (Lawson et al., 2015; Visser, Berger, Prins, Van Schrojenstein Lantman-De Valk, & Teunisse, 2014). Finally some have found parent-reported sensory sensitivities to be related to externalising behaviours (Ashburner, Ziviani, &

Rodger, 2008; A. Baker, Lane, Angley, & Young, 2008; Tseng, Fu, Cermak, Lu, & Shieh, 2011). Further details of these studies will be given in the relevant experimental chapters.

To our knowledge, only one study thus far has studied the relationship between neural functioning and challenging behaviours within ASD. Yang and colleagues found that less default mode network activation in the prefrontal cortex and lateral parietal cortex during a social processing task was associated with higher levels of disruptive behaviour (Yang et al., 2017). The brain regions associated with disruptive behaviour were distinct from those associated with ASD symptom severity, and the association between default mode network and disruptive behaviour remained when ASD severity was accounted for. This suggests the association between the default mode network in these areas and disruptive behaviour was not merely due to those participants with disruptive behaviour also having increased ASD severity. Although this study is an encouraging first step into this area of research, the sample size was limited (e.g., 7 participants in the ASD + disruptive behaviour group). It is also unclear what decreased default model activity means in terms of the neural mechanisms that may lead to higher levels of disruptive behaviour.

1.16 Summary and General Aims

It is clear that the rates of challenging behaviours are high in individuals with ASD, and they have a negative impact upon a young person's life. However, the literature regarding individual characteristics associated with challenging behaviours in ASD is limited. Currently, it remains unclear which factors may underpin challenging behaviours in ASD, and therefore the best way to intervene.

There is a considerable breadth of literature demonstrating that individuals with ASD are characterised by a range of cognitive impairments, namely in social cognition, EF and PP (although the specificity of EF impairments remains unclear). Although studies have looked at how these relate to the core symptoms of ASD, very few have looked at how they relate to co-occurring emotional and behavioural problems. Limited research from both ASD and non-ASD samples suggests impairment in certain cognitive domains may be associated with challenging behaviours. However, previous research in ASD samples looking at how individual characteristics relate to challenging behaviours has utilised small samples, consisting of predominately male subjects and often use $IQ \geq 70$ as an inclusion criteria. Furthermore, many previous studies have relied on parent report to measure both child characteristics and challenging behaviours, which could have influenced results. Thus, this thesis will explore the neurocognitive and electrophysiological correlates of challenging behaviours using two well-characterised samples of young people with ASD with a wide range of ability. The current thesis will use task performance to measure cognitive functioning, giving an objective measure of ability in different domains, along with EEG recording to examine how differences in neural functioning are related to challenging behaviours. Identifying associations between cognition and behaviour is a key first step in generating hypotheses of the underpinning of challenging behaviours, and for informing future longitudinal studies. These can then test the predictive value of said cognitive impairments, which can facilitate greater understanding of the mechanisms that may contribute to challenging behaviours in individuals with ASD. The thesis consists of four experimental chapters, as outlined below.

- Chapter 3 tests EF ability in individuals with ASD against not only typically developing individuals, but also two other populations characterised by EF impairments and behaviour problems; individuals with ADHD and individuals with ODD/CD.
- Following on from this, Chapter 4 tests the associations between EF performance, along with ERP indices of EF integrity (N2, P300), and challenging behaviours within individuals with ASD.
- Chapter 5 tests the association between electrophysiological indices of PP (MMN and habituation) and challenging behaviours in individuals with ASD.
- Chapter 6 uses structural equation modelling (SEM) to test whether ToM, ER, EF and PP abilities are associated with specific aspects of challenging behaviours in ASD.

The thesis will conclude with a summary of all findings, a discussion of the strengths and limitations of the work, and the clinical implications of the results.

2 Methods

This chapter provides information on the study methodology, including an overview of sample selection, the assessments, questionnaires and neurocognitive tasks administered, EEG data acquisition, data cleaning and the statistical analysis. Further details specific to individual studies are given within individual chapters. All chapters used data from the QUEST sample, outlined below, except for Chapter 6, which used a different sample (the Special Needs and Autism Project (SNAP); Baird et al., 2006), and Chapter 3, which used, in addition to the QUEST sample, three other samples as comparison groups. A summary of the additional samples used is given within the relevant chapters.

2.1 QUEST study overview

2.1.1 Funding and Ethical Approval

The QUEST follow-up study was conducted at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN), supported by a National Institute for Health Research grant to Professor Emily Simonoff. Participating families gave their written informed consent and the study was approved by Camden and King's Cross Ethics Sub-Committee (14/LO/2098).

2.1.2 Sample Selection and Recruitment

Participants were part of a longitudinal sample recruited at age 4-8 years (Salazar et al., 2015). See Figure 6 for a breakdown of the sampling strategy. The target population for the study was all children born between 01/09/2000 and 31/08/2004, living in two London boroughs (one inner and one outer London), who had all received a clinical diagnosis of ASD by the age of 5 years. Secondary care services

and local autism support groups identified 447 children as being eligible for the study. Clinical diagnoses of ASD were established by local multidisciplinary teams, led by a community paediatrician, using structured assessments such as the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003), the Developmental, Dimensional and Diagnostic Interview (3DI; Skuse et al., 2004), the Diagnostic Interview for Social and Communication Disorders (DISCO; Wing, Leekam, Libby, Gould, & Larcombe, 2002) and the Autism Diagnostic Observation Schedule – Generic (ADOS-G; Lord et al., 2000). A total of 277 children were successfully recruited into the study at age 4-8 years. At Wave 1, the sample had a wide range of cognitive ability, with IQs ranging from 19-120. ASD symptomatology was assessed with the Social Communication Questionnaire - Lifetime Version (SCQ; Rutter, Bailey, & Lord, 2003); all cases with a low SCQ score (total <10; n=28) were reviewed with clinicians and their ASD diagnoses confirmed. At this point, the sample was split into an ‘Extensive’ subsample (n=176) that received the core assessments, and an ‘Intensive’ subsample (n=101) that received a more detailed assessment. All participating girls were invited into the Intensive subsample in order to make sex comparisons possible, as well as a random selection of boys, stratified to provide equal numbers on IQ (≥ 70), borough (inner/outer London), age (≥ 6.8 years) and SCQ score (≥ 22).

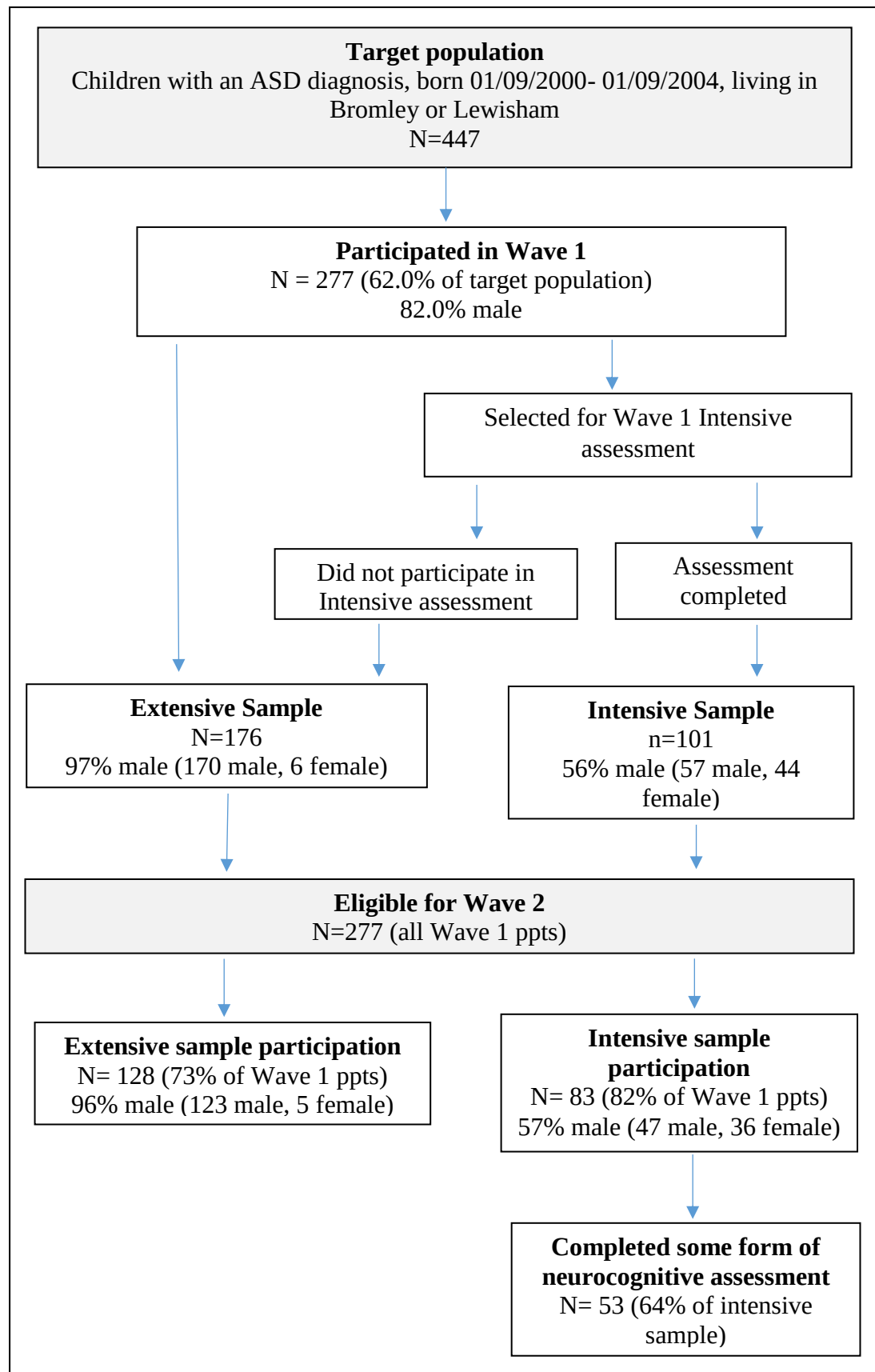


Figure 6. Summary of QUEST Sample Recruitment and Selection

The sample was followed-up at age 11-15 years, and the Extensive/Intensive sampling design employed at age 4-8 was retained. 76% (n=211) of the original sample (n=277) participated in the follow-up: 128 participants formed the Wave 2 Extensive subsample and 83 participants formed the Wave 2 Intensive subsample. See Table 1 for comparison of demographic information for those that took part at Waves 1 and 2 vs. those who took part in Wave 1 only. Although both parental and child characteristics were included in this attrition analysis, it would be expected that parental characteristics would be more likely to influence whether families agreed to part at Wave 2, whereas child characteristics would be more predictive of whether they were able to access the assessments once they had agreed to taking part in the research. However, neither parental education nor child characteristics influenced whether or not families took part again at Wave 2 (see Table 1).

Table 1. Attrition Analysis of Intensive Sample at Wave 1 vs. Wave 2

Mean (SD)	Wave 1 and Wave 2 participation (n=83)	Wave 1 participation only (n=18)	Test of group means
IQ at T1	65.03 (29.12; 19-120)	70.81 (21.70; 25-110)	ns
Male : Female Ratio	47:36	10:8	ns
SCQ total at T1	19.69 (6.99; 3-34)	21.33 (7.62; 6-31)	ns
DBC total behaviour problem score at T1	71.33 (28.76; 13-139)	79.00 (25.08; 41-127)	ns
Parental Education (less than A-level vs. A-level or greater)	36:44	7:11	ns

DBC indicates Developmental Behaviour Checklist; SCQ Social Communication Questionnaire.

Within the Intensive subsample ASD diagnosis was confirmed using the ADOS-2 (Lord, Rutter, et al., 2012). Based on information from previous data sets of young people with ASD, rules were set by the research project's lead statistician regarding when the ADI-R should also be administered. The ADI-R was administered if a) twice the ADOS-2 score plus the SCQ score lay between 12 and 46 inclusive or, b) if twice the ADOS-2 algorithm score minus the SCQ score was less than or equal to -5, or was greater than or equal to 17. This was to capture participants who were not being rated highly by the combined SCQ and ADOS-2 scores, or those in which there was a large discrepancy between the SCQ and the ADOS-2 scores. The ADI-R was required in 66/83 cases. Both the autism cut-offs recommended by Rutter et al. (2003) and the ASD cut-offs recommended by Risi et al. (2006) were applied to the ADI-R data. All participants were above the diagnostic cut-offs for autism or autism spectrum disorder on either or both the ADOS-2 and the ADI-R.

Intensive participants were invited to take part in the neurocognitive assessment. Given the wide range of cognitive ability at Wave 1 and the nature of the neurocognitive assessments, it was not expected that all those within the Intensive sample would be to access this section of the assessment day. Of the 83 participants within the Intensive subsample, 53 completed some combination of the neurocognitive tasks outlined below. This thesis presents briefly data from the total Intensive sample in this Chapter, but is mainly focused upon the subsample of participants who completed the neurocognitive tasks. More detailed demographic information about the Intensive total and subsamples is given in Section 2.7.

2.2 Measures

2.2.1 Diagnostic Instruments

2.2.1.1 *Autism Diagnostic Observation Schedule – 2 (ADOS-2)*

The ADOS-2 (Lord et al., 2000) is considered a gold-standard instrument for assessing current ASD symptoms, and consists of a semi-structured play and conversation-based assessment that lasts between 45-60 minutes. Behaviour observed during the assessment is then coded and scored 0-2 and 0-3 (dependent upon the item) in multiple domains indexing aspects of social reciprocity, communication, and restricted and repetitive behaviours, with a higher total score reflecting greater difficulties. Based on the total score, a calibrated severity score is calculated, scored 0-10, which takes into account age and language level, and has proposed as a more valid index of ASD severity than the total score (Shumway et al., 2012). Participants were assessed with either the Module 1, 2, or 3 ADOS-2 dependent upon their verbal abilities. All ADOS-2 assessments were administered by a trained researcher and co-scored by a second trained researcher, and final scores reflected consensus scores between the two coders.

2.2.1.2 *Autism Diagnostic Interview – Revised (ADI-R)*

The ADI-R (Rutter, Le Couteur, et al., 2003) is also considered a gold-standard diagnostic tool for ASD. The ADI-R is a semi-structured caregiver interview that focuses on caregiver report of an individual's developmental history. Behaviours described are coded and scored 0-3, with a higher score indicating greater difficulties. Scores are summed to provide a total score in three domains (social interaction difficulties, communication problems and restrictive and repetitive behaviours and interests), each of which has its own cut-off. In the interest of

minimizing participant burden, only the items that load onto the ADI-R diagnostic algorithm were asked. A trained researcher completed all ADI-Rs, and any coding queries were discussed within the team or with a post-doctoral researcher who was highly experienced in ADI-R administration.

2.2.2 Parent-Rated Questionnaires

Hard copies of all questionnaires can be found in Appendix 1.

2.2.2.1 Adaptive Behaviour Assessment System (ABAS) – Communication

Subscale

The ABAS (Harrison & Oakland, 2003) uses a behaviour-rating format to assess adaptive behaviour and related skills for individuals 5-89 years of age. ABAS scores describe a person's general adaptive behaviour as well as their functioning in ten related adaptive skill areas: communication, community use, functional academics, school/home living, health and safety, leisure, self-care, self-direction, social, and work (for older adolescents and adults). Statements are scored from 0-3 (is not able, never when needed, sometimes when needed, always when needed), indexing whether or not the person is able to complete a given behaviour. Current analyses utilised the communication subscale (ABAS-C). A higher score reflects greater communication skills.

2.2.2.2 Affective Reactivity Index (ARI)

The ARI (Stringaris et al., 2012) was used to assess participants' level of irritability and includes six items relating to feelings/behaviours specific for irritability and one question assessing impairment due to irritability. Statements are scored from 0-2 (not true, somewhat true or certainly true), and the total is the sum of the six items relating to feelings/behaviours specific to irritability. A higher score is indicative of a higher level of irritability. Excellent internal consistency has been reported from

mixed clinical and control samples ($\alpha = 0.92$), and scores are found to be significantly higher in those with bipolar disorder and severe mood dysregulation, as compared to those without a psychiatric diagnosis (Stringaris et al., 2012). As the ARI has limited use in ASD samples, before beginning analyses the internal reliability of the total ARI score was assessed in the total pooled QUEST Intensive ($n=83$) and Extensive sample ($n=128$). The internal consistency was good ($\alpha=0.90$), and comparable that found in other samples of young people with ASD ($\alpha = 0.82$) (Mikita et al., 2015).

2.2.2.3 Developmental Behaviour Checklist (DBC)

The DBC (Einfield & Tonge, 1992, 2002) is a 96-item questionnaire designed to assess emotional and behavioural problems in young people with developmental disabilities and ID. The DBC consists of five subscales of antisocial/disruptive, self-absorbed, communication, anxiety and social relating. Each description is scored from 0-2 (not true as far as you know, somewhat or sometimes true, very true or often true) and summed to give a total behaviour problem score. A higher score is indicative of greater emotional and behavioural problems. Excellent internal consistency ($\alpha = 0.94$) has been reported from large epidemiological samples ($N=1093$), along with high correlations ($r=0.70-0.86$) with other measures of emotional and behavioural disturbance (Einfield & Tonge, 1992, 2002). Scores from the DBC have also been found to correlate highly ($r=0.81$) with clinicians' ratings of psychopathology. The DBC also has been found to have good sensitivity and specificity in relation to discriminating between clinical vs. nonclinical cases, as indicated by the area under the ROC curve of 0.92 (Einfield & Tonge, 1992, 2002).

2.2.2.4 *Spence's Child Anxiety Scale (SCAS)*

The SCAS (Nauta et al., 2004) is a 38-item questionnaire used to assess current symptoms of anxiety in 6-18 year olds. Items are scored from 0-3 (never, sometimes, often, always) with higher scores indicating greater anxiety symptoms. The SCAS consists of six subscales indexing generalized anxiety, separation anxiety, social phobia, obsessive-compulsive disorder, fears of physical injury, and panic attacks and agoraphobia. Excellent internal consistency ($\alpha = .92-.93$) (Russell & Sofronoff, 2005; Sofronoff, Attwood, & Hinton, 2005), and convergent validity with DSM-IV defined anxiety disorders (Zainal et al., 2014) has been reported from samples of young people with ASD.

2.2.2.5 *Social Communication Questionnaire (SCQ) – Current Version*

The SCQ (Rutter, Bailey, et al., 2003) is a 40-item questionnaire used to assess current ASD symptom severity. Items on the SCQ are based on key domains on the ADI-R. Statements are scored according to whether certain difficulties have been observed in the last three months (0 = present, 1 = absent), with a higher score indicating greater difficulties. Good internal consistency has been reported in samples of individuals with ASD ($\alpha = 0.90$) (Berument, Rutter, Lord, Pickles, & Bailey, 1999), and it has been shown to effectively identify ASD case-ness with a sensitivity of 94.6% and specificity of 63.3% (Charman et al., 2007).

2.2.2.6 *Strengths and Difficulties Questionnaire (SDQ)*

The SDQ (Goodman, Ford, Simmons, Gatward, & Meltzer, 2000) is a 25-item questionnaire used to measure psychiatric symptoms. The SDQ comprises three psychiatric subscales of hyperactivity/inattention (ADHD symptoms), conduct problems and emotional problems, along with further subscales of peer-relationship

problems and prosocial behaviour. Statements are scored from 0-2 (not true, somewhat true or definitely true). A higher score is indicative of greater difficulties, except for in the prosocial behaviour subscale where a lower score indicates more difficulties in this domain. Large epidemiological samples of typically developing youth ($N=9998$) find good internal consistency for the total difficulties score ($\alpha = 0.82$) and satisfactory consistency overall (mean $\alpha = 0.73$) (Goodman, 2001). The SDQ has been shown to identify clinically assessed psychiatric diagnoses with a sensitivity of 94.6% and a specificity of 63.3% (Goodman et al., 2000). Individuals scoring in the top 10% of the population have been found to have a substantial increase in psychiatric risk, with an odds ratio of 15 of having a DSM-IV diagnosis (Goodman, 2001). The SDQ has been shown to maintain good psychometric properties when used with individuals with an ID (Emerson, 2005), and to successfully detect change in additional mental health problems following intervention in populations of young people with ASD (Chalfant, Rapee, & Carroll, 2007). The majority of the current analyses focused upon the three psychiatric subscales of ADHD symptoms, conduct problems and emotional problems. Similar to the ARI, before beginning analyses, the internal reliability of the three subscales was assessed in a pooled ASD sample. This sample consisted of the all QUEST Intensive and Extensive participants combined with SNAP participants used in Chapter 6 ($n=100$), giving an adequate sample size ($n=311$) to assess how the instrument performs in populations of adolescents with ASD. Internal reliability was generally acceptable, and comparable to those reported in community samples (ADHD symptoms subscale $\alpha=0.79$ in ASD sample vs. $\alpha=0.77$ in community sample; conduct problems subscale $\alpha=0.65$ in ASD sample vs. $\alpha=0.63$ in community

sample; emotional problems subscale $\alpha=0.74$ in ASD sample vs. $\alpha=0.67$ in community sample) (community sample estimates taken from Goodman, 2001).

2.2.3 Direct Assessments

2.2.3.1 Cognitive Ability

IQ was estimated using one or more of the following tests, depending on the child's age and developmental level: the Wechsler Abbreviated Scale of Intelligence (n=50, WASI; Wechsler, 1999), the Wechsler Preschool and Primary Scale of Intelligence (n=11, WPPSI; Wechsler, 2012) and the Mullen Scales of Early Learning (n=16, MSEL; Mullen, 1997). IQ data was missing from six participants, three due to the young person opting out of any direct assessments, and three due the young person being so low functioning they were unable to access any cognitive assessments. For the WASI and the WPPSI, two tests of perceptual ability (Block Design, Matrix Reasoning), and two tests of verbal ability were administered (Vocabulary, Similarities). Scores from these sub-tests were combined and compared against the age of the participant to provide a full scale IQ. For the MSEL all tests of were administered, consisting of sub-tests of gross motor, visual reception, fine motor, expressive language and receptive language. As the WPPSI and MSEL were used out of age range, age-equivalents were calculated and a ratio IQ derived [ratio IQ = (age-equivalent/chronological age) x 100] (Terman & Maude, 1960). Those with an MSEL ratio IQ <20 were assigned an IQ of 19 to reflect their very low ability.

2.2.3.2 Receptive Language

The Receptive One Word Picture Vocabulary Test was used to estimate receptive language ability (ROWPVT; Brownell & Martin, 2010). This required participants to select pictures of named objects, actions and concepts. Data was collected from 58

participants, the remainder missing due to the young person opting out of any direct assessments (n=3), or due the young person being so low functioning they were unable to access the assessment (n=22). The standard score (mean of 100, SD of 15) was used in current analyses. Scores of 85-115 are considered to be within the average range of functioning.

2.3 Assessment Procedure

Families were invited for a research day at the IoPPN, which typically began at 10am and lasted until 4.30pm. Families were sent a link to a video beforehand, outlining what the day would involve, and a ‘social story’ of the EEG recording procedure to encourage participation and minimise anxiety. For a subset of families where the participant was especially anxious or hesitant to travel, researchers completed the majority of assessments at their home first, and then invited them to visit the IoPPN and complete the EEG assessments at a later date. In general, the project aimed to be as inclusive as possible, therefore although the order of the assessments was largely kept constant; flexibility was introduced when necessary, and some assessments were completed at different locations (e.g., some at home, some at the IoPPN). In the morning participants completed the ADOS-2 (around one hour) and a cognitive and language assessment (around 45 minutes), followed by two short (around 5 minutes each; Go/NoGo and Switch tasks) neurocognitive tasks on a portable laptop. They were then offered a lunch break. After this, following EEG preparation (approximately 15 minutes), participants completed a visual oddball task (Chapter 4), a PP task (Chapter 5), and two other EEG tasks that are not reported on in this thesis, with a total duration of approximately 60 minutes. Participants were given short breaks in between tasks as often as required. All

neurocognitive (Chapters 3 and 4) and EEG tasks (Chapters 4 and 5) are described in the relevant chapters. Whilst the participants completed the neurocognitive task battery, parents completed questionnaires assessing their child's ASD severity and additional mental health problems, and completed the ADI-R if necessary. The day ended with a parent-child interaction task (around 20 minutes). All families were compensated for their time and travel costs.

2.4 EEG Acquisition Procedure

The general EEG data acquisition method is detailed below, with individual analyses described in the respective chapters. Participants were seated facing a screen in a custom-built, dimly-lit psychophysiology laboratory cubicle, which was shielded from electrical noise using a Faraday cage. A research assistant kept the participant company whilst the EEG cap was being administered and remained in the testing room whilst EEG tasks were completed, and when necessary encouraged participants to remain as still as possible during task completion.

Participant's head circumference was measured and an appropriate sized cap chosen. Chinstraps were used to keep the cap in place. A decision was made not to use the face straps that hold the electrodes that record eye movements (ocular channels) in place, as early in the data collection it was noticed that some participants could not tolerate the feeling, leading to task refusal. Measurement was taken between each participants' nasion and inion, and between the preauricular points, to ensure cap was positioned with the vertex electrode (Cz) in the center. Participants were asked to remain as still as possible during the recording, and were given regular breaks to move around in between tasks. High-density scalp EEG was recorded continuously using a 128-channel HydroCel Geodesic Sensor Net system (Electrical Geodesics,

Eugene, OR) with 500 Hz sampling rate. Voltages were referenced online to the vertex electrode (Cz). Impedances were checked to be below 40 k Ω before recording began. EEG data collection was continually monitored during recording and when necessary electrodes were adjusted for improved recording. All electrophysiological data was recorded with NetStation 5.1 software (Electrical Geodesics, Eugene, OR) and all tasks were delivered through E-Prime 2.0 experimental design software (Psychology Software Tools, Pittsburg, PA). Data were stored and analyzed offline.

2.5 EEG Preprocessing Procedure

EEG data was processed offline using BrainVision Analyzer 2.0 software (Brain Products, Munich, Germany). Data was down sampled to 256Hz, and the two channels positioned to record electro-ocular activity (126, 127) were discarded as these were not used during EEG acquisition. Data was then re-referenced to the average reference, by subtracting the mean of all electrodes from each electrode, and noise below 0.1Hz and above 30Hz was removed using Infinite Impulse Response (IIR) phase-shift free Butterworth filters. The data was manually inspected to identify and remove bad channels caused by fluctuating impedance or poor contact with the scalp. Those which were surrounded by four or more functioning channels were replaced using topographic interpolation using spherical splines. This method utilises the similar voltage from neighbouring channels to estimate the signal from the removed channel. Channels on the outer rim of the cap were not interpolated (see Figure 7 for a schematic representation of the EEG sensor net, electrodes in dark blue were those not interpolated).

Noisy segments of data (e.g., those which contained gross muscle artefacts) were removed prior to running independent component analysis (ICA; Jung et al., 2000)

to ensure extraneous noise was not included in ICA calculations. Infomax ICA was used to decompose each data set into maximally statistically independent components, and the components representing eye movements and other biological artefacts (e.g., pulse) were rejected based on the visual inspection of the component map. Artefact-free EEG data was obtained by back-projecting the remaining ICA components after they were multiplied using the reduced component-mixing matrix.

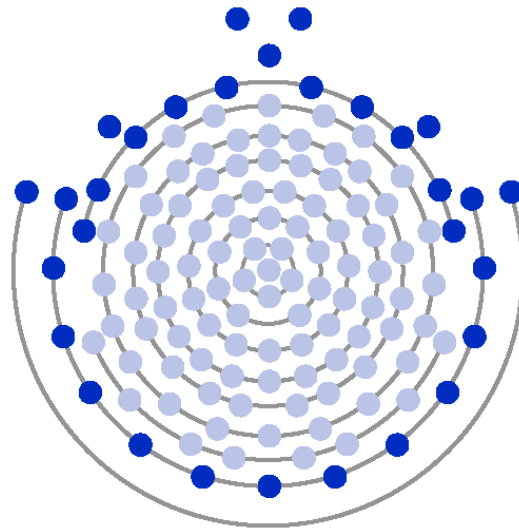


Figure 7. Schematic of EGI 128-Channel Geodesic Sensor Cap.

Semi-automatic artefact detection was subsequently performed to remove any segments with any additional artefacts greater than maximum-minimum values of $200\mu\text{V}$. Following these steps, continuous data was segmented in time based on when stimuli had been presented, and averaged across trials to create ERPs. Data was baseline corrected using the 100ms prior to stimuli presentation, to subtract ongoing brain activity from that specifically elicited by stimuli presentation. For each task, electrodes of interest were selected based on prior literature and maximal and minimal observed component amplitudes. The selected temporal window for component analysis was based on both prior literature, and consequent visual

inspection of the grand average of all participants' data. Consequently, each participant's individual waveform data was inspected to confirm that components of interest fell within the allotted temporal window. Semi-automatic peak detection was used to mark specific components, and the amplitude and latency of components were extracted for statistical analysis. Further details are noted in the individual chapters

2.6 Statistical Analysis

All analyses were completed in Stata 14 (StataCorp, 2015), apart from SEM analyses in Chapter 6 which used Mplus 7 (Muthén & Muthén, 2012). In Chapter 3 where EF in participants with ASD from the QUEST sample was compared against groups of adolescents with ADHD, ODD/CD and typically developing controls, analysis of variance (ANOVA) and analysis of co-variance (ANCOVA) were used to test group differences on neurocognitive task performance.

In Chapters 4 and 5 the association between electrophysiological response and emotional and behavioural problems was estimated using multivariate regression, with the primary outcome measures being the three psychiatric SDQ subscales (ADHD symptoms, conduct problems, emotional problems) and the ARI total score (measuring irritability). This multivariate approach was selected as it is statistically parsimonious and takes account of multiple testing amongst correlated outcomes. As discussed in Chapter 1, there are multiple conceptual frameworks around challenging behaviours, and the term can encompass a variety of concerning behaviours. Thus, it was decided that in addition to looking at the more overt manifestations of challenging behaviours, analyses would also test associations with other difficulties which frequently co-occur (e.g., emotional problems). This approach was selected as

it may help to disentangle the different components of challenging behaviours, and allow for identification of domain-specific relationships, which could have direct therapeutic implications.

The DBC total behaviour problem score total was used as a secondary outcome measure, as this is less specific than the SDQ subscales and the ARI, however is often used to capture challenging behaviours in ASD populations, and is well-suited for use in populations of individuals with lower cognitive ability (Brereton et al., 2006; Einfield & Tonge, 1992, 2002).

In Chapters 3, 4 and 5, when testing associations between cognition and behaviour, where significant or trend associations were found, results were first adjusted for age, sex and full-scale IQ. Age and IQ were included as covariates to account for underlying cognitive levels that might be influencing results. Sex was also included as a covariate as although there are no strong theoretical models regarding sex-differences in neurocognitive functioning, most studies of individuals with ASD have been underpowered to test for sex differences. As the current sample had a more even sex ratio, it was decided to include it as a covariate. Analyses did not adjust for communication ability as IQ and communication ability were highly correlated ($r=0.75$), and so it was not feasible to include communication as a covariate.

The second covariation analysis adjusted for age, sex, IQ and ASD severity, as measured by the ADOS calibrated severity score. This was to gain an understanding of how ASD severity related to any associations between cognition and behaviour and thus aid in the interpretation of results.

In Chapter 6 SEM was used to estimate the associations between domains of neurocognition, as measured by task performance, and two specific types of challenging behaviours; externalising behaviours and SIB. More details about this statistical method are given in the Chapter.

Where necessary, variables were assessed for normality by inspection of histogram plots, and transformed where required. All transformations were successful in achieving relative normality. Specific details of variable transformation are given in individual chapters. In Chapters 4 and 5 outliers in EEG data were identified using box and whisker plots (Stata command `graph box`). This identifies outliers as values outside 1.5 x the interquartile range +/- the value of the upper/lower quartile (Tukey, 1977). However, given that ASD is known to be a heterogeneous disorder, variation in neural functioning was expected and so it was unclear if ‘outliers’ represented true variation or statistical noise. Thus, given the lack of strong conceptual framework behind the exclusion of outliers in brain data in neurodevelopmental populations, analyses were conducted including, and then excluding outliers. Details of how many outliers were identified for each variable are given in individual chapters.

In Chapters 3 and 4 participants were excluded from analyses if they failed to respond correctly on at least 30 % of the baseline trials in the neurocognitive tasks (go trials in the Go/NoGo task, repeat trials in the Switch task), as advised by the task developer. This approach was taken to ensure that only participants who were attending to the task were included in the analyses, rather than exclude on the basis of statistical distribution (as was done with EEG data).

2.7 Sample Characteristics

Table 2 presents the demographic information for the total Intensive sample (n=83), and two corresponding sub-samples; those who completed neurocognitive assessments (n=53) and those who did not (n=30). Similar to Wave 1, the total sample was characterised by a wide range of IQ (19-129). The sample had a mean age of 13 years, and slightly more males than females. 41% (n=34) of the total sample were attending a mainstream school or a special unit within a mainstream school (2/34), and 52% (n=43) were attending a special school. The remainder were missing data regarding school type (n=6).

With regards to other demographic characteristics of the total Intensive sample, the ethnicity of the participants was as follows; 48% White, 31% Black/African/Caribbean/Black British, 8% Mixed, 2% Asian/Asian British and 2% Other. Forty-seven percent of parents were currently working, and 53% had parental education of A-levels or greater.

Attrition analyses showed that those who completed the neurocognitive assessments had higher IQ, higher receptive language and communication skills, lower ASD severity (as indexed by both the ADOS-2 and the parent-rated SCQ) and were more likely to be attending a mainstream school than those who did not complete the assessments (see Table 2). There was also a trend for those who completed the neurocognitive assessments to have a lower DBC total behaviour problem score. The total number of participants varied between neurocognitive tasks, as some participants were able to complete the full battery of neurocognitive tasks, whereas others were only able to complete a selection of tasks (see Figure 8 for a breakdown of individual task completion rates, and Appendix 2 for a list of all Intensive

participants and which tasks they completed, along with their sex, age, IQ, and language ability).

Table 2. Sample Characteristics and Attrition Analysis of Intensive Sample at Wave 2

Mean (SD; range)	Wave 2 Whole sample (n=83)	Wave 2 completed any neurocognitive assessment (n=53)	Wave 2 did not complete neurocognitive assessment (n=30)	Test of group differences
Age	13.45 (1.13; 11.4-15.7)	13.52 (1.08; 11.4-15.7)	13.33 (1.21; 11.4-15.6)	ns
Male : Female Ratio	47:36	33:20	14:16	ns
IQ	67.40 (32.40; 19-129)	83.25 (23.73; 27-129)	32.38 (18.34; 19-87)	$p<0.01$
ROWPVT	88.53 (24.93; 55-145)	90.98 (24.61; 55-145)	70.71 (20.92; 55-110)	$p<0.05$
ABAS-C	43.22 (19.19; 2-72)	50.00 (13.92; 5-71)	27.82 (20.86; 2-72)	$p<0.01$
School Type (mainstream/special school)	34/43	31/20	3/23	$p<0.01$
ADOS-2 severity	6.57 (2.61; 1-10)	6.23 (2.78; 1-10)	7.27 (2.07; 1-10)	$p<0.05$
SCQ	17.26 (6.68; 4-31)	16.16 (5.99; 4-27)	19.65 (7.57; 6-31)	$p<0.05$
DBC total behaviour problem score	56.52 (25.83; 3-127)	53.30 (26.12; 3-127)	62.96 (24.49; 23-110)	$p=0.06$
SDQ Emotional Problems	3.92 (2.48; 0-10)	4.14 (2.66; 0-10)	3.48 (2.06; 0-8)	ns
SDQ ADHD Symptoms	5.36 (2.42; 0-10)	5.08 (2.47; 0-10)	5.92 (2.25; 2-10)	ns
SDQ Conduct Problems	2.12 (1.67; 0-8)	2.14 (1.81; 0-8)	2.08 (1.38; 0-5)	ns
ARI	4.53 (3.40; 0-12)	4.34 (3.35; 0-12)	4.96 (3.522; 0-11)	ns

ABAS-C indicates Adaptive Behaviour Assessment Schedule - Communication Subscale; ADOS-2 Autism Diagnostic Observation Schedule; ARI Affective Reactivity Index; DBC Developmental Behaviour Checklist; SCQ Social Communication Questionnaire; SDQ Strengths and Difficulties Questionnaire; ROWPVT Receptive One Word Picture Vocabulary Test.

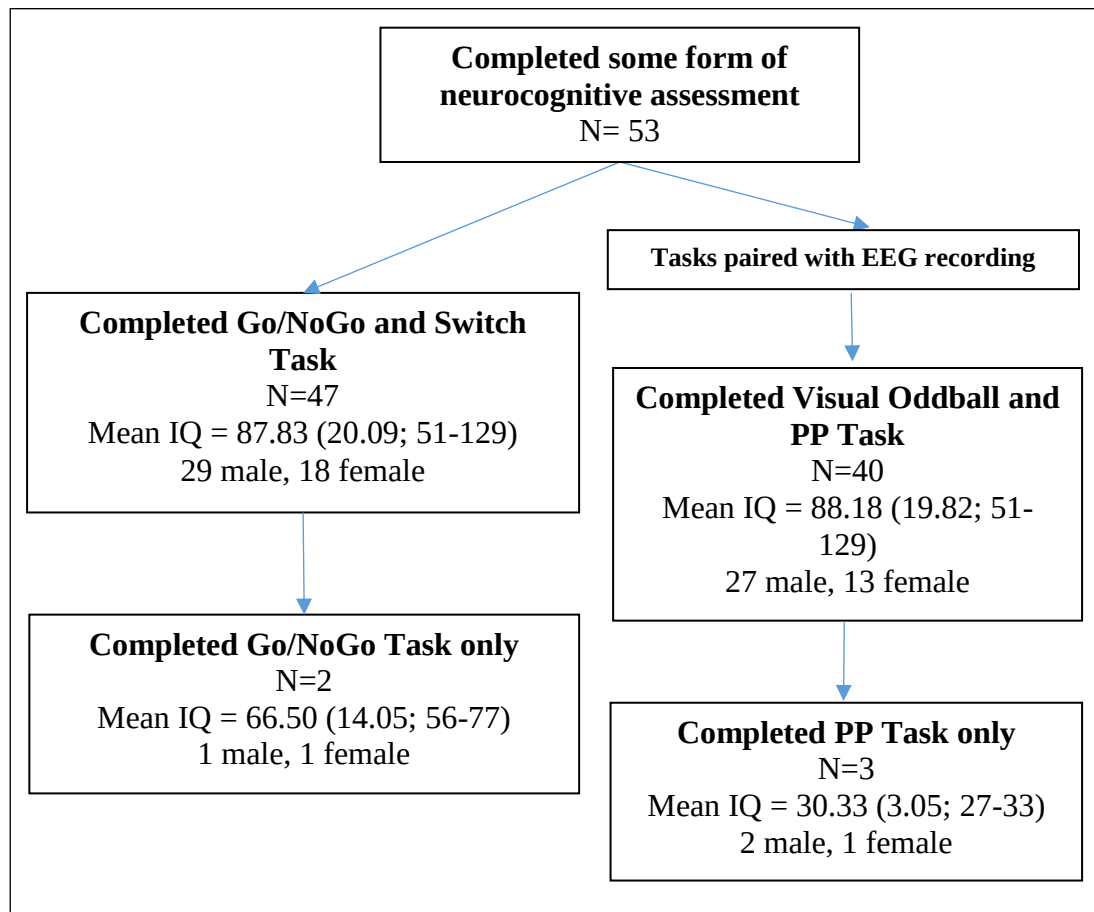


Figure 8. Completion Rates, Mean IQ (SD; range) for Individual Neurocognitive and EEG Tasks

In terms of associations between individual characteristics and emotional and behaviour problems, correlational analyses indicated several significant correlations between emotional and behaviour problems, but few between individual characteristics and co-occurring problems (see Table 3). Regression analyses found no significant associations between additional emotional and behaviour problems and age, sex, receptive language or ADOS-2 severity score. Significant associations were largely in keeping with expectations. IQ was positively related to SDQ emotional problems ($\beta = .02, p < 0.05$), and negatively related to SDQ ADHD symptoms ($\beta = -.02, p < 0.05$) and DBC total behaviour problem score ($\beta = -.29, p < 0.05$). Communication ability, as measured by the ABAS-C, was positively associated with SDQ emotional problems ($\beta = .03, p < 0.05$), but negatively related to SDQ ADHD symptoms ($\beta = -.05, p < 0.01$) and DBC total behaviour problem score ($\beta = -.30, p < 0.01$). School type was also associated with SDQ conduct problems ($\beta = 1.21, p < 0.01$), SDQ ADHD symptoms ($\beta = 1.12, p < 0.01$) and DBC total behaviour problem score ($\beta = .01, p < 0.05$), in that participants with higher levels of symptoms were more likely to be in a special school. Given that attendance in a special school could be due to either lower IQ or behavioural problems, the analysis was re-run, adjusting for IQ. Here, the association between SDQ conduct problems remained significant ($\beta = 1.51, p < 0.01$), and the association with DBC total behaviour problem score dropped to a trend ($\beta = .01, p = 0.09$).

Table 3. Bi-variate Correlations between Measures of Key Sample Characteristics

	Demographics				Language/ Communication		ASD severity		Co-occurring emotional and behavioural difficulties			
	1	2	3	4	5	6	7	8	9	10	11	12
Age (1)	-											
Sex (2)	.01	-										
IQ (3)	.04	-.02	-									
School Type (4)	-.02	-.05	-.67**	-								
ROWPVT (5)	.05	.13	.81**	-.54**	-							
ABAS-C (6)	.06	.03	.75**	-.65**	.39**	-						
ADOS-2 severity (7)	-.12	-.19	-.27*	.31**	-.22	-.30*	-					
SCQ (8)	-.08	-.07	-.44**	.25*	-.10	-.56**	.39**	-				
DBC-TBPS (9)	-.09	-.12	-.24*	.30**	-.10	-.39**	.13	.66**	-			
SDQ Emotion (10)	-.05	.00	.25*	-.12	.06	.27*	-.13	.08	.38**	-		
SDQ ADHD (11)	-.17	-.10	-.26*	.23*	-.10	-.37**	.18	.55**	.62**	.23	-	
SDQ Conduct (12)	.06	-.06	-.09	.31**	-.09	-.15	.05	.30**	.56**	.29*	.26*	-
ARI (13)	-.11	-.17	.03	.11	-.06	.01	-.01	.25*	.63**	.43**	.22	.53**

ABAS-C indicates Adaptive Behaviour Assessment Schedule Communication Subscale; ADOS-2 Autism Diagnostic Observation Schedule; ARI Affective Reactivity Index; DBC-TBPS Developmental Behaviour Checklist – total behaviour problem score; SCQ Social Communication Questionnaire; SDQ Strengths and Difficulties Questionnaire; ROWPVT Receptive One Word Picture Vocabulary Test. For binary variables; School Type 1=main stream school, 2=special school; Sex 1=Male, 2=Female. ** $p < 0.01$, * $p < 0.05$.

3 Testing the Specificity of Executive Functioning Impairments in Adolescents with ADHD, ODD/CD and ASD

3.1 Summary

One approach to understanding the behavioural presentation of individuals with ASD is to consider the role of underlying impairments in domains of cognitive functioning. Many have suggested EF is a key cognitive domain in which individuals with ASD have difficulties, and could potentially underpin both the core symptoms of ASD, but also co-occurring emotional and behavioural problems. However, ADHD and ODD/CD are also characterised by similar EF impairments, and therefore whether EF impairments are trans-diagnostic or disorder-specific remains relatively unknown. Adolescents with ASD (n=41) were compared against three other groups of 10-16 year olds; typically developing (TD; N=43), individuals clinically diagnosed with ADHD (N=21), and ODD/CD (N=26) on performance on a Go/NoGo and a Switch task. Only the ASD group demonstrated decreased probability of inhibition in the Go/NoGo task compared to all other groups. All three diagnostic groups demonstrated increased reaction time variability (RTV) compared to the TD group, and both the ODD/CD and the ASD group demonstrated increased premature responses. When controlling for ADHD symptoms and conduct problems, group differences in RTV were no longer significant, however the ASD group continued to demonstrate increased premature responses. No group differences were found in cognitive flexibility in the Switch task. The findings suggest that some EF impairments typically associated with ADHD may also be found in individuals with ASD.

3.2 Introduction

As outlined in Chapter 1, one approach to understanding psychopathology is the cognitive phenotype approach. This posits that psychiatric symptoms are underpinned by impairments in specific domains of brain/cognitive functioning, known as intermediate phenotypes (in the sense of between genes and behaviour), and said phenotypes should discriminate between diagnostic categories. These phenotypes may represent potential risk factors and targets for intervention. This approach has been applied to understanding how specific cognitive impairments may underpin the development of, and heterogeneity within, ASD (Viding & Blakemore, 2007). Along with difficulties in social cognition (e.g., impaired ToM and ER), individuals with ASD have also been found to have impairments in EF (Brunsdon et al., 2015; E. Hill, 2004). Studies have suggested the most notable difficulty is in cognitive flexibility, with a recent meta-analysis reporting an overall aggregate impairment as compared to typically developing populations (Landry & Al-Taie, 2016). However, impairments in flexibility have also been reported in individuals with ADHD and those with ODD/CD (Toupin et al., 2000; Willcutt et al., 2008). Similarly, although impairments in response inhibition and a premature response style are thought to be characteristic of individuals with ADHD (Lipszyc & Schachar, 2010; Rubia et al., 2007), impairments have also been found in youth with ODD/CD (Hobson et al., 2011; Van Goozen et al., 2004) and more recently in individuals with ASD (Geurts et al., 2014). Additionally, all three disorders have been found to demonstrate increased intra-subject response time variability (Kofler et al., 2013; Willcutt et al., 2008). Aetiologically, it is crucial to understand whether EF impairments are indicative of psychopathology in general or differentiate between diagnostic categories. Additionally, although this thesis is focused upon

understanding the correlates of challenging behaviours within individuals with ASD, and thus mainly uses within-ASD analyses, ADHD and ODD/CD are other psychiatric disorders that are characterised by behaviour problems and often co-occur with ASD. If comparable EF impairments are found between ASD, ADHD and ODD/CD this could shed light the elevated rates of challenging behaviours in individuals with ASD. Therefore, the specificity of EF impairments will be tested in the current chapter, and then how these EF impairments relate to challenging behaviours *within* the ASD group is tested in the next chapter (Chapter 4).

3.2.1 Flexibility

Despite the apparent overlap in EF impairments, as mentioned above, comparisons between disorders are limited and inconsistent. A handful of studies that have compared ADHD and ASD groups on cognitive flexibility have suggested specificity, in that results showed that only the ASD group exhibited impairment (Geurts et al., 2004; Ozonoff & Jensen, 1999). However, others have failed to find group differences (M. C. Goldberg et al., 2005; Happé et al., 2006). In terms of ADHD and ODD/CD, studies have found either both (Antonini, Becker, Tamm, & Epstein, 2015) or neither (Hobson et al., 2011) group show impairment in tasks of cognitive flexibility.

3.2.2 Inhibition

Similarly, some comparative studies of ADHD and ASD groups have also suggested specificity in the inhibition, as only those with ADHD were found to exhibit impairments (Happé et al., 2006; Ozonoff & Jensen, 1999; Sinzig et al., 2008), yet others have failed to find group differences (Geurts et al., 2004; M. C. Goldberg et al., 2005), and one study found that the ASD group showed the greatest impairment (Corbett, Constantine, Hendren, Rocke, & Ozonoff, 2009). A meta-analysis of six

studies found that both ADHD and ODD/CD were independently characterised by inhibition impairment (Oosterlaan et al., 1998), and comparison of individuals with ODD/CD with or without ADHD has found that both groups showed slower reaction time (RT) on the Stop task; however only the ODD/CD+ADHD group was impaired in motor inhibition in the Go/NoGo task (Hobson et al., 2011).

3.2.3 Intra-Individual Response Variability

In the third area of potential overlap, intra-individual response variability, studies have found increased intra-individual response variability in ADHD and ASD+ADHD groups but not in ASD alone (Tye et al., 2016), whereas some have reported increased intra-individual response variability in ASD but not ADHD (Geurts et al., 2008). Both continuous analyses of symptoms and group based comparisons found that both ADHD and ODD/CD were characterised by both intra-individual response variability and increased premature responses (Hobson et al., 2011; Scheres, Oosterlaan, & Sergeant, 2001).

As mentioned above, there appears to be overlap in the nature of EF impairments between ASD, ADHD and ODD/CD. These overlapping EF profiles support theoretical critiques of the current diagnostic system, which have highlighted that the search for discriminative phenotypes has not been as successful as hoped (Insel et al., 2010). This has led to suggestions of an alternative research framework that disregards diagnostic categories and focuses instead upon continuous associations between brain functioning and symptomatology (Insel et al., 2010). However, studies that have reported comparable impairments between the diagnostic groups have not consistently accounted for high rates of co-occurrence between these disorders. As discussed in Chapter 1, heightened rates of ODD/CD have been found in individuals with ASD (Gadow et al., 2005; Guttman-Steinmetz et al., 2009;

Mayes et al., 2012; Simonoff et al., 2008), but the reverse has not been found in terms of likelihood of ASD in ODD/CD samples. Additionally, studies find around 30% of young people with ASD meet diagnostic criteria for ADHD (Gjevik et al., 2011; Simonoff et al., 2008), and higher rates of autistic symptoms in young people with ADHD (Reiersen, Constantino, Volk, & Todd, 2007). Numerous studies have reported a significant overlap between ODD/CD and ADHD (Yoshimasu et al., 2012), with clinical and epidemiological studies having suggested a co-occurrence between 30-60% (Kadesjö & Gillberg, 2001; Steinhausen et al., 2006). Therefore, prior findings may in part reflect unacknowledged co-morbidity.

3.2.4 Aims

No study has directly compared EF in adolescents with ASD against not only typically developing (TD) individuals, but also against adolescents with ADHD, and ODD/CD. Furthermore, many prior comparative studies have not controlled for co-occurring symptoms. The current study compared three disorders, ADHD, ODD/CD and ASD, along with a TD group, whilst controlling for conduct problems and ADHD symptoms. Informed by the prior literature described above, group differences in response inhibition (Go/NoGo task) and cognitive flexibility (Switch task) were tested. Premature responses and intra-individual response variability were also tested across both tasks. It was hypothesised that all clinical groups would be characterised by impairments in response inhibition, with most severe impairments in the ADHD group, while the ASD group only would show impairments in cognitive flexibility. Additionally, it was hypothesised that increased premature responses would be more typical of ADHD, while increased intra-individual response variability would be observed in all groups.

3.3 Method

3.3.1 Sample

Across the ODD/CD, ADHD and TD groups only those aged 10-16 years were selected from original samples, which had a wider age range. This was to encompass a similar range to the ASD group. All participants had information on ADHD and ODD/CD symptoms, as rated by the SDQ, along with measures of neurocognitive task performance. Due to the post-hoc nature of the current study, information was not available on ASD symptoms in the ADHD, ODD/CD and TD groups. The ODD/CD group, along with part of the TD and ADHD groups included participants from a larger study contrasting ODD/CD and ADHD (see Hobson et al. (2011) for full details). The remainder of the TD and ADHD participants were taken from a different study exploring EF impairments in ADHD (see Rubia et al (2007) for full details). The ODD/CD and ADHD groups were both recruited through clinics. Informed consent was obtained for all participants.

ASD Group (n=41)

See Section 2.1 for a full description of participant recruitment and assessment and Section 2.7, Chapter 2 for a break-down of sample demographics by task completion. In the current chapter, participants were excluded if they scored above the population-defined cut-off of ≥ 4 on the conduct problems sub-scale on the SDQ (n=4). Those who were above threshold on the SDQ ADHD symptoms sub-scale cut-off of ≥ 7 (n=9) were retained in sensitivity analyses.

ODD/CD Group (n=26)

Adolescents were recruited from two existing longitudinal samples in which participants had been clinically referred for oppositional problems in childhood

(Scott et al., 2010; Scott et al., 2001). To confirm ODD/CD, parents were interviewed using the ODD/CD sections of the Child and Adolescent Psychiatric Assessment (CAPA; Angold & Costello, 2000). Participants were not included in the ODD/CD group if they met criteria for ADHD, or if they had ever received a clinical diagnosis of ADHD or ASD.

ADHD Group (n=21)

Participants from Hobson sample (Hobson et al., 2011) who met the criteria for ADHD but not ODD/CD formed part of the ADHD group (n=9). Participants had to have symptoms meeting ADHD criteria in at least one domain (i.e. home or school), and demonstrate ‘some impairment’ (defined here as above a 20% cut-off based on age-related published norms) in the other domain on the Conners’ ADHD Parent and Teacher Scales (Conners, 1997). Individuals were classified as meeting criteria if respondents endorsed at least six of the inattentive or hyperactive/impulsive items. Participants were also included in the ADHD group if they had a current clinical diagnosis of ADHD. In the same manner as the ODD/CD group, ADHD participants from the Hobson et al sample were not included if they had a clinical diagnosis of ASD. The remainder (n=12) of participants from the Rubia sample (Rubia et al., 2007) had a clinical diagnosis of hyperkinetic disorder (using ICD-10) and met DSM-IV criteria for ADHD-combined type as assessed by an experienced child psychiatrist using a standardized diagnostic interview (D. Goldberg & Murray, 2002). The assessment process also included information other sources (e.g., parents and teachers), developmental history, and behavioural observation of the child. Participants were excluded if they had another psychiatric disorder (including ODD/CD or ASD), neurological abnormalities or epilepsy. Participants taking stimulants were medication-free for at least 18 hours prior to testing. Participants

with ADHD taken from the Hobson sample vs. the Rubia sample did not differ in age, IQ or severity of ADHD symptoms (all $ps > 0.05$).

TD Group (n=43)

The TD group was a combination of participants from Hobson (n=32) and Rubia samples (n=11). This consisted of healthy adolescents with no history of, or current psychiatric disorder or ID, and who fell below cut-off on the SDQ hyperactivity and conduct sub-scales in the Rubia sample, and did not meet diagnostic thresholds on the Conners' or CAPA in the Hobson sample.

3.3.2 Neurocognitive Assessment

All participants completed two tasks selected from the computerised Maudsley Attention and Response Suppression task battery (MARS; Rubia et al., 2007), which has been used extensively to test EF in child and adolescent populations (e.g., Hobson et al., 2011; Rubia et al., 2006; Rubia et al., 2009). All researchers administering the tasks were trained by the battery developer.

3.3.2.1 Go/NoGo Task

This task measured selective motor response inhibition. A motor response has to be executed when green space ships appear (go trials; 74%) and inhibited when enemy planets appear (no-go trials; 26%). Stimuli were presented for 300ms, with an inter-trial interval of 1300ms. The task consisted of two blocks, one requiring right-handed and the other left-handed button-press responses. Each block had a duration of 2.5 minutes. The dependent variable was the percentage of successfully inhibited no-go trials (probability of inhibition).

3.3.2.2 Switch Task

This task measured visual-spatial attention shifting between two spatial dimensions, and was designed to keep other confounding cognitive abilities (e.g., working memory) to a minimum. Participants observed a grid divided into four squares, in the centre of which is a double-headed arrow, which switched between horizontal and vertical dimensions. The grid was displayed for 1600ms, and after 200ms a red dot appeared in any of the four corners of the grid. This dot was displayed for 1400ms. When the arrow was horizontal, participants were asked to press the left or right button according to the location of the dot; when the arrow was vertical, participants pressed either the top or bottom button. The inter-trial interval was 800ms. The switch from the vertical to the horizontal dimensions appeared in 29% of trials. The main dependent variables were the switch error and RT costs (mean errors/RT to switch trials - mean errors/RT to repeat trials).

3.3.2.3 Premature Responses and Intra-Individual Response Variability

For both tasks, percentage of premature responses, thought to measure an impulsive response style, as responses were made before stimuli have been processed (i.e., responses made 200 ms before and 100 ms after stimulus onset) and the intra-individual coefficient of variability (ICV) ($SD / \text{mean RT of responses} \times 100$) were calculated (Rubia et al., 2007). The distribution of premature responses was severely positively skewed, due to very few participants demonstrating a high percentage of premature responses. As data was so skewed that transformation would not reflect the underlying distribution and an ordinal approach was not appropriate, the variable was transformed into a binary variable for both tasks (no premature responses=0, any premature responses=1).

3.3.3 Cognitive Ability

Cognitive ability was largely estimated using the WASI, although two participants from the ASD sample were assessed using the WPPSI. See Section 2.2.3.1, Chapter 2 for more details on assessment of cognitive ability in the ASD sample. A sub-set of ADHD participants (n=7) were assessed using Raven's Standard Progressive Matrices (Raven, 1960), and scores were converted to estimated IQs on the basis of a series of Ravens-IQ extrapolations performed on larger datasets, by Lord, 1988 (unpublished). Mental age was also calculated, using the formula of $\text{IQ/chronological age} \times 100$ (Terman & Maude, 1960).

3.3.4 Statistical Analyses

Variables were transformed where necessary (probability of inhibition using square root, ICV for the Go/NoGo task using Box-Cox). Univariate ANOVAs first tested unadjusted group differences. Next, ANCOVA tested group differences adjusted for age, IQ and sex. This ANCOVA was our *primary* contrast. For the binary premature response variables, logistic regression followed by the Wald test was used.

Following this, SDQ conduct problems and ADHD symptoms were separately controlled for, in addition to age, IQ and sex, to explore the influences of sub-threshold traits upon any significant group differences in the adjusted ANCOVA. Two separate sensitivity analyses were conducted 1) excluding participants with $\text{IQ} < 70$ (N=9) and 2) excluding ASD participants scoring above the SDQ ADHD symptom subscale (N=9). Where group differences were found in our primary contrast, subsequent unadjusted and adjusted *post-hoc* group contrasts were also performed (adjusting for age, IQ, sex). Exploratory adjusted *post-hoc* contrasts were also conducted, separately adjusting for ADHD symptoms and conduct problems, in addition to age, IQ and sex. The details of all *post-hoc* contrasts are presented in the

Supplementary Appendix. The effect sizes of diagnostic group status were calculated using partial η^2 for continuous variables, and w for binary variables (Cohen, 1988).

3.4 Results

Table 4 shows group demographics. The ASD group was older than all other groups ($ps < 0.05$), and had lower IQ than the TD and ODD/CD groups ($ps < 0.01$). All three clinical groups had a lower mental age than the TD group ($ps < 0.05$), but were not significantly different from each other. The ADHD and TD groups had a higher percentage of male participants than the ODD/CD and ASD groups ($ps < 0.05$).

Table 4. Sample Demographics

Mean (SD; range)	TD (n=43)	ADHD (n=21)	ODD/CD (n=26)	ASD (n=41)	Group Differences
Age	12.79 (1.61; 10.17-16)	12.98 (1.47; 10.50-15.75)	12.31 (1.62; 10.20-15.51)	13.77 (1.08; 11.33-15.67)	ASD>TD*, ODD/CD**
IQ	104.95 (11.67; 75-130)	95.29 (13.26; 69-120)	101.42 (14.68; 72-130)	88.49 (19.71; 54-129)	TD>ASD**, ADHD** ODD/CD>ASD**
Mental Age	13.38 (1.90; 8.76-17.58)	12.34 (2.12; 9.14-16.78)	12.43 (2.15; 8.61-17.68)	11.87 (2.95; 6.35-18.02)	TD>ASD*, ADHD*, CD/ODD*
% male	83.72%	95.24%	65.38%	58.54%	ADHD>ASD**, ODD/CD* TD>ASD*
SDQ ADHD symptoms	2.53 (1.61; 0-6)	7.95 (2.04; 3-10)	6.58 (2.23; 1-10)	4.62 (2.49; 0-9)	ADHD, ODD/CD, ASD>TD** ADHD>ODD/CD*, ASD** ODD/CD>ASD**
SDQ conduct problems	1.16 (1.04; 0-3)	3.58 (1.54; 1-7)	5 (1.83; 1-8)	1.41 (1.12; 0-3)	ADHD, ODD/CD>TD** ODD/CD>ADHD**, ASD** ADHD>ASD**

SDQ indicates Strengths and Difficulties Questionnaire. ** $p<0.01$, * $p<0.05$.

3.4.1 Inhibition

Table 5 details task performance by group and Table 6 details the effect size of diagnostic group comparisons in each analysis. Group differences were found in probability of inhibition ($F(3,126) = 12.84, p < 0.01$). These remained when controlling for age, IQ and sex ($F(3, 123) = 10.76, p < 0.01$), ADHD symptoms, age, IQ and sex ($F(3, 118) = 10.33, p < 0.01$), and conduct problems, age, IQ and sex ($F(3, 116) = 10.29, p < 0.01$). Results remained significant in sensitivity analyses excluding those with $IQ < 70$ ($F(3, 117) = 9.40, p < 0.01$), and excluding those who scored above ADHD threshold in the ASD group ($F(3, 117) = 8.06, p < 0.01$). Unadjusted *post-hoc* contrasts found that the ASD group had a lower probability of inhibition than the TD group ($p < 0.01$), with the ADHD vs. TD group contrast near trend-level ($p = 0.11$). In addition, the ASD group had a lower probability of inhibition than the ADHD and ODD/CD groups ($p < 0.01$; Figure 9). Adjusted *post-hoc* contrasts found a comparable pattern of results when all covariates were controlled for (all $ps < 0.05$), however the ADHD vs. TD group contrast became fully non-significant when adjusted for age, IQ and sex.

3.4.2 Cognitive Flexibility

No group differences were found in the Switch task, for either RT ($p = 0.25$), or error ($p = 0.72$) costs. This remained when controlling for possible confounders and in sensitivity analyses.

Table 5. Group Performance on Go/NoGo and Switch task

Mean (SD; range)	TD (n=42)	ADHD (n=21)	ODD/CD (n=26)	ASD (n=41, n=37 for Switch task)
Go/NoGo: Probability of inhibition	84.33 (13.18; 28-100)	78.67 (15.86; 38-96)	81.62 (12.39; 50-100)	65.27 (18.76; 20-92)
Switch: RT Cost	42.61 (43.87; -29.86-160.40)	40.78 (53.37; -34.27-199.98)	66.80 (66.10; -114.44-230.65)	42.23 (56.82; -74.01-199.99)
Switch: Error Cost	4.56 (7.44; -8.29-29.14)	4.65 (8.28; -5.08-18.56)	5.76 (9.22; -9.47-27.53)	3.44 (7.01; -3.39-28.78)
Go/NoGo: Premature responses	23.81%	47.62%	50%	70.73%
Switch: Premature responses	4.88%	28.57%	34.62%	21.62%
Go/NoGo: ICV	22.94 (6.48; 13.93-42.10)	28.75 (7.89; 16.54-48.37)	26.70 (4.21; 17.31-32.93)	31.51 (12.54; 16.58-60.90)
Switch: ICV	24.68 (5.63; 16.98-36.48)	28.61 (6.49; 18.13-40.57)	30.18 (5.04; 19.99-42.57)	27.74 (5.51; 15.93-39.54)

ICV indicates intra-individual coefficient of variation; RT reaction time.

3.4.3 Premature Responses

Differences were found in the proportion of participants in each group who demonstrated premature responses on the Go/NoGo task ($X^2(3)=16.84, p<0.01$). These remained when controlling for age, IQ and sex ($X^2(3)=12.45, p<0.01$), ADHD symptoms, age, IQ and sex ($X^2(3)=9.54, p<0.05$), and conduct problems, age, IQ and sex ($X^2(3)=11.58, p<0.01$). Results remained significant in sensitivity analyses excluding those with IQ<70 ($X^2(3)=13.17, p<0.01$), and excluding those who scored above ADHD threshold in the ASD group ($X^2(3)=12.54, p<0.01$). Unadjusted *post-hoc* contrasts found that the ASD ($p<0.01$) and ODD/CD ($p<0.05$) groups had a higher proportion of individuals showing premature responses than the TD group.

The ADHD vs. TD contrast was significant at trend-level ($p=0.06$). The clinical groups were not significantly different from each other (Figure 9). *Post-hoc* contrasts adjusted for age, sex and IQ found the ASD group had a higher proportion of individuals showing premature responses than the TD group ($p<0.01$). The ODD/CD vs. TD contrast was at a trend-level ($p=0.06$). The ADHD vs. TD contrast became non-significant. Only the ASD vs. TD contrast remained significant when controlling for ADHD symptoms, age, IQ and sex ($p<0.05$) and when controlling for conduct problems, age, IQ and sex ($p<0.01$).

Differences were also found in the proportion of participants in each group who demonstrated premature responses on the Switch task ($X^2(3)=8.21, p<0.05$) but dropped to a trend level when controlling for age, IQ and sex ($X^2(3)=6.75, p=0.08$), but became non-significant when controlling for ADHD symptoms, age, IQ and sex ($p=0.32$), and conduct problems, age, IQ and sex ($p=0.14$). Group differences were significant in sensitivity analyses excluding those with $IQ<70$ ($X^2(3)=8.02, p<0.05$) and excluding those who scored above ADHD threshold in the ASD group ($X^2(3)=8.61, p<0.05$).

Table 6. Effect of Diagnostic Group in Un/Adjusted Tests of Group Means

		Co-variation Analyses			Sensitivity Analyses		
	Unadjusted group differences	Adjusted for IQ, age, sex	Adjusted for ADHD, IQ, age, sex	Adjusted for conduct problems, IQ, age, sex	Exclude IQ<70	Exclude those in ASD over ADHD cut off	Post-hoc contrasts of unadjusted group means
Effect size as indicated by partial η^2							
Go/NoGo: Probability of inhibition	0.23**	0.21**	0.21**	0.21**	0.19**	0.17**	ASD<CD/ODD**, ADHD**, TD**
Switch: RT Cost	0.03	0.04	0.04	0.02	0.04	0.04	-
Switch: Error Cost	0.01	0.02	0.02	0.02	0.01	0.02	-
Go/NoGo: ICV	0.15**	0.10**	0.05	0.08*	0.13**	0.13**	TD<ADHD**, ODD/CD**, ASD**
Switch: ICV	0.12**	0.09**	0.04	0.02	0.13**	0.13**	TD<ADHD**, ODD/CD**, ASD** ASD<ODD/CD*
Effect size as indicated by w							
Go/NoGo: Premature responses	0.36**	0.31**	0.27*	0.30**	0.33**	0.32**	TD<ADHD^ TD<ODD/CD* TD<ASD**
Switch: Premature responses	0.26*	0.23	0.17	0.21	0.26*	0.27*	-

ICV indicates intra-individual coefficient of variability; RT reaction time. ** p <0.01, * p <0.05 ^ p =0.06; for partial η^2 , 0.1= small, 0.6 = medium, 0.14 = large effect; for w , 0.1 = small, 0.3 = medium, 0.5 = large effect.

3.4.4 Intra-Individual Response Variability

Group differences in ICV were found on the Go/NoGo task ($F(3, 126)=6.84$, $p<0.01$). These remained when controlling for age, IQ and sex ($F(3, 123)=4.47$, $p<0.01$), and conduct problems, age, IQ and sex ($F(3, 116)=3.34$, $p<0.05$).

Controlling for ADHD symptoms, age, IQ and sex resulted in findings losing significance ($p=0.14$). Differences remained significant in sensitivity analyses excluding those with $IQ<70$ ($F(3, 117)=5.58$, $p<0.01$), and excluding those who scored above ADHD threshold in the ASD group ($F(3, 117) = 5.75$, $p<0.01$).

Group differences in ICV were also found on the Switch task ($F(3, 121)=5.67$, $p<0.01$), and remained when controlling for age, IQ and sex ($F(3, 118)=3.99$, $p<0.01$). Group differences became non-significant when controlling for ADHD symptoms, age, IQ and sex ($p=0.24$), and conduct problems, age, IQ, and sex ($p=0.61$). Sensitivity analyses showed that differences remained significant when excluding those with $IQ<70$ ($F(3, 113)=5.53$, $p<0.01$) and excluding those who scored above ADHD threshold in the ASD group ($F(3, 112)=5.57$, $p<0.01$).

In both tasks unadjusted *post-hoc* contrasts found that all clinical groups had higher ICV than the TD group (all $ps<0.01$). In the Go/NoGo task the clinical groups were not significantly different from each other (Figure 9), whereas in the Switch task the ODD/CD group had higher ICV than the ASD group ($p<0.05$). In the Go/NoGo task adjusted *post-hoc* contrasts showed that all three clinical groups had significantly higher ICV when controlling for age, IQ and sex (all $ps<0.05$). When controlling for ADHD symptoms, age, IQ and sex, and then conduct problems, age, IQ and sex, only the ASD group had higher ICV than the TD group ($p<0.05$ and $p<0.01$ respectively). In the Switch task adjusted *post-hoc* contrasts found that only the ADHD group ($p<0.05$) and the ODD/CD group ($p<0.01$) had significantly higher

ICV than the TD group when controlling for age, IQ and sex. The *post-hoc* contrast between the ODD/CD and TD group remained at trend level when controlling for ADHD symptoms, age, IQ and sex ($p=0.05$). The *post-hoc* contrast between the ADHD group and the TD group was not significant when controlling for conduct problems, age, IQ and sex.

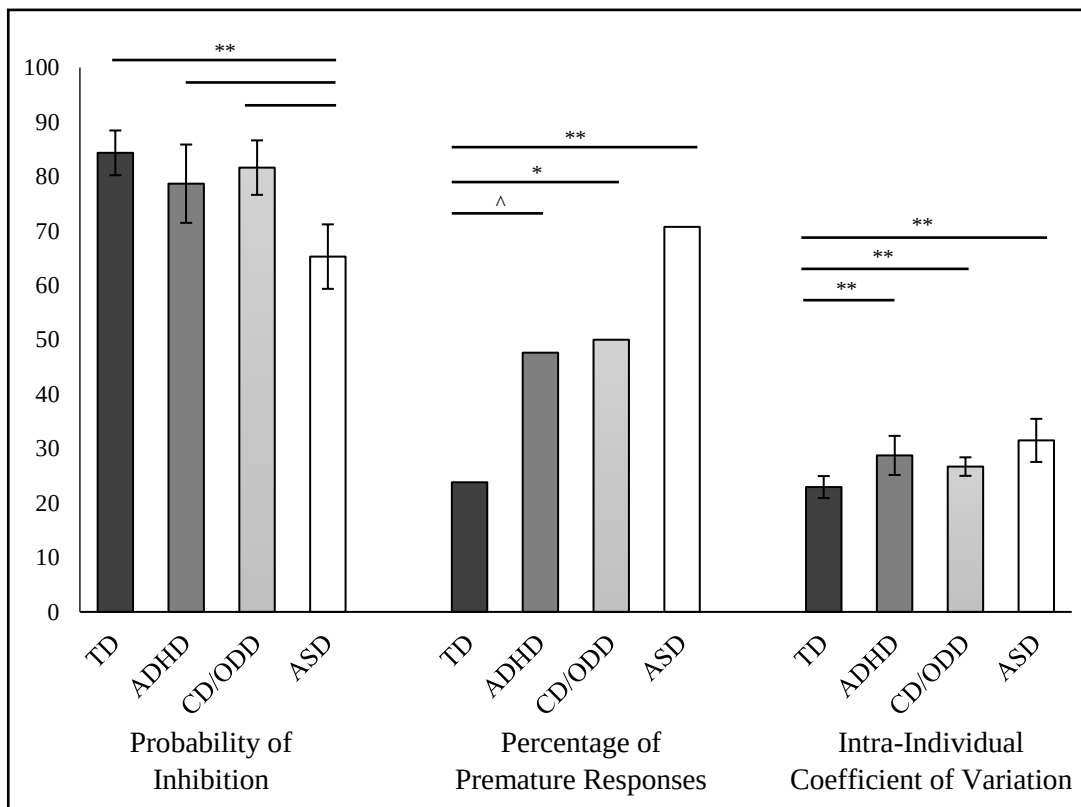


Figure 9. Group Performance on Go/NoGo task

** $p<0.01$, * $p<0.05$, ^ $p=0.06$

3.5 Discussion

One approach to understanding the mechanisms of psychopathology is to identify impairments in cognitive functioning associated with different psychiatric disorders. However, there is on-going debate as to whether diagnostic categories are associated with specific or shared cognitive phenotypes. Results indicate shared impairments in some performance measures; all three clinical groups demonstrated increased RTV; although co-variation analyses suggested that this might in part be due to co-occurring ADHD and ODD/CD symptoms. Additionally, both the ASD and the ODD/CD group showed increased premature responses, although only the ASD continued to show impairment when co-occurring ADHD symptoms were controlled for. Results also found disorder-specific impairments, in that only the ASD group showed impairment in inhibition in the Go/NoGo task, relative to the TD group. Contrary to our hypothesis, the ASD group did not show specific impairments in cognitive flexibility. Results suggest that some EF impairments previously thought to be more characteristic of ADHD, such as increased premature responding and RTV, and impaired response inhibition, may also be present in other disorders, such as ASD.

A more premature-impulsive and variable response style is typically attributed to ADHD (Rubia et al., 2007). Our findings, however, suggest that this may also be found in ODD/CD and ASD, although it is possible that co-occurring ADHD symptoms influenced impairments in the ODD/CD group. Although all three clinical groups demonstrated increased premature responses on the Go/NoGo task, only the ASD-TD and ODD/CD-TD contrasts remained significant, or at trend, when co-varying for IQ, age and sex. Further exploratory adjusted *post-hoc* contrasts suggested that ADHD symptoms may be in part driving the increased level of

premature responses in the ODD/CD group, as when ADHD symptoms, IQ, age and sex were controlled for, the ODD/CD vs. TD group contrast became non-significant. This was not the case for the ASD group, who had significantly higher levels of premature response than the TD group, even when ADHD symptoms and conduct problems were controlled for. In terms of the ADHD group, although the unadjusted *post-hoc* contrast between the ADHD and TD group was at a trend level, the contrast adjusted for age, IQ and sex was non-significant. Thus, differences between the ADHD and the TD group in age, IQ and gender may have contributed to significant results in the unadjusted contrast. However, given that in the original sample, those with ADHD had increased premature responses (Hobson et al., 2011), it is possible that by selecting a smaller sub-sample of ADHD cases (n=21) within a specific age range, the current study had limited our statistical power to detect significant effects.

All three clinical groups also demonstrated increased intra-individual response variability in both tasks, in agreement with prior literature (Geurts et al., 2008; Hobson et al., 2011; Kofler et al., 2013). However, when ADHD and ODD/CD symptoms were controlled for, the effect of group mostly lost significance. This suggests that increased RTV may have been in part accounted for by sub-threshold ADHD and ODD/CD symptoms, but was not related to ASD status. This is in line with findings that within those with ASD, only those with co-occurring ADHD show increased RTV (Tye et al., 2016). Interestingly, on the Switch task only the ADHD and ODD/CD groups demonstrated increased RTV, whereas the ASD group did not demonstrate any differences in RTV as compared to the TD group. As the Switch task could be seen as a slower task, in that it has longer stimuli presentation times than the Go/NoGo task, and speed of response was not stressed in this task, this could explain differences in RTV between the two tasks in the ASD group. Overall,

results regarding RTV suggest that although increased RTV is found across diagnostic categories (Willcutt et al., 2008), it may be a marker of co-occurring ADHD or ODD/CD symptoms, rather than a shared cognitive phenotype.

Contrary to our predictions, only the ASD group showed impairment in motor inhibition on the Go/NoGo task. This is in contrast to other studies that found inhibitory impairment was present in ADHD but not ASD (Corbett et al., 2009; Happé et al., 2006; Ozonoff & Jensen, 1999; Sinzig et al., 2008), but in line with recent meta-analyses that found an overall impairment in inhibition in individuals with ASD (Geurts et al., 2014). Differences in samples may partly explain disparities; prior work has only included individuals with ASD with IQ>70, and has used different tasks (e.g., Stroop task). The next step is to test whether this increased impulsivity (as indexed by increased likelihood of premature responses and decreased inhibition) within the ASD group is also associated with co-occurring emotional and behavioural problems (as is done in the next chapter).

Given prior literature (Willcutt et al., 2008), similar to our interpretation of the trend-level increase in premature responses in the ADHD group, it is suggested that the limited sample size impacted on the ability to detect significant differences.

Although the ADHD vs. TD contrast was not significant, the directionality of effect was in line with expectations (i.e. that ADHD were more impaired than TD; $p=0.11$), and is comparable to other studies that report inhibition impairments in ADHD (Lipszyc & Schachar, 2010; Rubia et al., 2007). No impairment in motor inhibition was found in the ODD/CD group. It may be that ODD/CD can be differentiated from ADHD and ASD by the nature of inhibition difficulties. Inhibition impairments in ODD/CD are found in more challenging inhibition tasks requiring withholding of an already triggered motor response such as the Stop task (Oosterlaan et al., 1998), but

not on tasks of relatively simpler, selective motor response inhibition such as the Go/NoGo task (Hobson et al., 2011).

It was unexpected that the ASD group did not show impairments in cognitive flexibility given prior research (Landry & Al-Taie, 2016). The use of a relatively simple *perceptual* switching task may be related to this spared performance, as compared to well-replicated impairments in ASD groups on the more difficult Wisconsin Card Sorting Task that requires *content* switching and also taps into working memory (Landry & Al-Taie, 2016). The lack of group differences in cognitive flexibility is in line with studies that found neither ADHD (M. C. Goldberg et al., 2005; Happé et al., 2006; Rubia et al., 2007), nor ODD/CD (Hobson et al., 2011) were characterised by such impairments, in particular in easy perceptual switch tasks like the one used in this study (although see Toupin et al., 2000 for opposing findings in ODD/CD).

Overall, the ASD group showed the most robust EF impairments, specifically in aspects of inhibition. This differs to previous work (Happé et al., 2006; Ozonoff & Jensen, 1999; Sinzig et al., 2008), and is most likely due to selection of a more representative group of individuals with ASD (e.g., not limited to IQ>70, potentially with other co-occurring diagnoses). However, results may not solely be due to these factors, as the findings remained when controlling for IQ and additional ADHD and ODD/CD symptoms, and in sensitivity analyses excluding those with ASD and IQ<70, and those above a clinically meaningful threshold for ADHD symptoms. Findings suggest ASD is characterised by not only impairments in social, but also in aspects of non-social, cognition.

One interpretation of results overall is that ASD is associated with disorder-specific impairments in EF (in premature responding and pre-potent response inhibition), however caution should be applied before making this claim as although current analyses did not find impairment in the ADHD group, a wealth of literature has demonstrated similar inhibition impairments in ADHD (e.g., Lipszyc & Schachar, 2010; Willcutt et al., 2008). Therefore it is suggested that the current null results are most likely due to power issues associated with small sample sizes, combined with the heterogeneity of EF impairments in ADHD. Further research is required, with larger samples of individuals with ADHD, to clarify the nature of shared impairments between ASD and ADHD. These findings would contribute to the wider debate regarding the validity of our current diagnostic systems, and support the idea that using measurable endophenotypes as indices of cognitive/brain functioning may yield fruitful insights into the aetiology of psychopathology (Gottesman & Gould, 2003).

3.5.1 Specific Strengths

To my knowledge this is the first study to directly compare EF among ADHD, ODD/CD and ASD groups. Strengths include accounting for co-occurring ADHD and ODD/CD symptoms, which prior studies (e.g., Happé et al., 2006; Ozonoff & Jensen, 1999) have not consistently done, attempting to screen for co-occurring disorders in the ADHD and ODD/CD groups, and using a more representative sample of individuals with ASD.

3.5.2 Specific Limitations

Due to the post-hoc nature of data analysis, we did not have information on ASD symptoms in the ADHD and ODD/CD groups. Although there is little evidence to suggest increased likelihood of ASD in those with ODD/CD, studies have found

ASD traits are elevated in those with ADHD (Reiersen et al., 2007). Thus, although the ADHD and ODD/CD group were screened for ASD diagnoses, it is possible that unacknowledged, sub-threshold ASD traits could have impacted upon our findings.

Additionally, unlike for the ODD/CD and ADHD groups, we did not have any formal diagnostic information on co-occurring psychopathology in the ASD group and instead used parent-rated symptoms to identify individuals with high levels of ADHD symptoms and conduct problems. Whether diagnostic assessments would identify the same individuals as parent-rated questionnaires is an open question. Another potential limitation is that samples were ascertained separately and at different times, and thus were mismatched on demographics. However, these demographic differences were controlled for in the analyses. Finally, a small sample size in the ADHD group (n=21) may have led to limited ability to detect significant impairments in this group.

3.5.3 Implications

Results suggest adolescents with ASD are characterised by EF impairments when compared to TD groups, but also may exhibit similar EF impairments to individuals with ADHD and ODD/CD, which are at times associated with behaviour problems. Therefore, the next chapter will test whether these EF impairments in individuals with ASD are associated with co-occurring emotional and behavioural problems. In terms of wider implications, current findings of shared difficulties in premature responding and response inhibition are in line with suggestions that specific, discriminative alterations in brain functioning are not consistently associated with diagnostic categories (Insel et al., 2010). Findings contribute to the wider debate regarding the biological validity of our current diagnostic systems, and support the idea that using measurable endophenotypes as indices of brain functioning may yield

more fruitful insights into the neurobiology of psychopathology, rather than relying on classification systems derived from observable behaviours (Gottesman & Gould, 2003). Whether the shared cognitive phenotypes found in the current study represent shared risk factors requires investigation in longitudinal samples.

4 Testing the Association between Measures of Executive Functioning and Emotional and Behaviour Problems in Adolescents with ASD

4.1 Summary

In Chapter 3, analyses showed that adolescents with ASD are characterised by impairments in EF, as evidenced by decreased inhibition, a higher likelihood of premature responding and a more variable response style, in comparison to typically developing individuals. This chapter tests how EF impairments in individuals with ASD relate to co-occurring emotional and behavioural problems. Adolescents with ASD completed a Go/NoGo task (n=49) indexing inhibition, and a Switch task (n=47), indexing cognitive flexibility, where behavioural parameters were collected. Participants also completed a visual oddball task (n=40), where behavioural parameters and ERPs were recorded. Neural indices of conflict monitoring (N2) and attentional orienting (P300) were examined. Results showed that participants with more ADHD symptoms exhibited greater EF impairments, as shown by a higher likelihood of premature responding, greater Switch RT cost and a more variable response style. This pattern of results remained when controlling for age, sex, IQ and ASD severity. No significant associations were found between N2 latency and N2 and P300 amplitude, and co-occurring emotional and behavioural problems. Results suggest specificity of associations between cognitive functioning and co-occurring difficulties in ASD, as EF impairments were selectively associated with ADHD. In addition, in contrast to non-ASD populations, findings suggest that certain EF impairments are not associated with behaviour problems in adolescents with ASD.

4.2 Introduction

Individuals with ASD have been found to exhibit impairment across a variety of EF tasks (Brunsdon et al., 2015; E. Hill, 2004), and show alterations in ERP components that index key EF abilities (Kemner et al., 1999; Strandburg et al., 1993; Tye et al., 2013; Verbaten et al., 1991; Wang et al., 2017). Given that EF impairments are implicated in models of behavioural problems in non-ASD populations, this chapter set out to test whether EF impairments are associated with challenging behaviours in individuals with ASD.

4.2.1 EF Impairments in ASD

Section 3.2, Chapter 3 covers the literature regarding relevant EF impairments in individuals with ASD as compared to typically developing individuals. In addition to neuropsychological EF tasks, which typically measure accuracy and RT, the neural indices of EF in ASD populations have also been investigated using oddball paradigms. These paradigms randomly present target stimuli in a stream of standard stimuli, and require participants to respond differently for the target vs. standard. They are thought to measure attentional orienting, along with response selection and inhibition. Two ERP components are typically studied; the N2, a negative component localized to the fronto-central regions, found around 250ms after stimulus presentation and thought to reflect conflict monitoring (Nieuwenhuis et al., 2003), and the P300, a positive deflection found 300-500ms after target stimuli presentation and localized to the parietal areas, which is thought to index flexible orienting of attention (Polich, 2007). For more information about these ERP components see Section 1.13.1, Chapter 1.

Studies using variants of visual oddball tasks have found individuals with ASD exhibit larger P300 amplitudes to target stimuli (Kemner et al., 1999; Strandburg et al., 1993; Wang et al., 2017), and increased N2 and P300 latency (Sokhadze et al., 2009; Townsend et al., 2009; Tsai et al., 2011). However, some have reported attenuated N2 (Tye et al., 2013) and P300 amplitudes (Verbaten et al., 1991), and others null findings (Courchesne et al., 1989; Hoeksma et al., 2006; Pritchard et al., 1987; Sokhadze et al., 2009; Tsai et al., 2011). Those who have found increased amplitude and latency propose this represents the additional effort required to flexibly shift and allocate attention to the novel information in individuals with ASD. Conversely, those who have found attenuated amplitudes and latencies suggest this represents delayed conflict monitoring and attentional shifting. Differences in samples and paradigms used have likely contributed to heterogeneity of findings.

4.2.2 EF Impairments in ODD/CD

Meta-analyses have found an overall EF impairment in individuals with antisocial behaviour (effect size=0.62), which remained when only studies with individuals with a diagnosis of CD were included (effect size=0.36) (Morgan & Lilienfeld, 2000). Impairments were found across a range of tasks, including those indexing planning, inhibition and flexibility. However, it should be held in mind that many neuropsychological studies of ODD/CD populations, including the aforementioned meta-analysis, have failed to take account of the high prevalence of ADHD in individuals with ODD/CD (Ford et al., 2003; Steinhausen et al., 2006), thus reports of EF impairments in individuals of ODD/CD could in part reflect co-occurring ADHD symptoms. In saying this, there appears to be some support for EF impairments that are specific to ODD/CD. A meta-analysis of eight studies concluded that impairments in response inhibition were characteristic of both ADHD

and ODD/CD populations, although the evidence for impairment in individuals with ODD/CD was less consistent (Oosterlaan et al., 1998). Impairments in response inhibition in adolescents with ‘pure’ ODD/CD have also been found using the Stop task (Hobson et al., 2011), and impairment on tasks of sustained attention, inhibition and cognitive flexibility have also been found in ODD/CD whilst accounting for ADHD symptoms (Toupin et al., 2000). One study found disruptive behaviours (including CD) and ADHD in a sample of adolescents were both separately associated with cognitive flexibility impairment (Aronowitz et al., 1994), and children with ODD/CD and co-occurring psychopathic traits have been found to show atypical brain activation in the prefrontal cortex, in comparison to both typically developing individuals and those with ADHD, during rule-change trials in reversal learning tasks (Finger et al., 2008).

In addition to the research detailed above which used neuropsychological tasks to measure EF, alterations have been found in those ERP components thought to measure attentional orienting. Adults with aggressive behaviour have been found to show reduced P300 amplitude in oddball tasks (Gao & Raine, 2009; Harmon-Jones et al., 1997; Patrick, 2008), and similar attenuation has been reported in children and adolescents with ODD/CD (Banaschewski et al., 2003; Iacono et al., 2002).

4.2.3 Association between EF and Challenging Behaviours within ASD and ID Populations

One study, using a large clinical sample of children with ASD (n=400), found parent-rated attention problems, which included features of inattention and hyperactivity, were associated with higher levels of aggressive behaviour problems (A. Hill et al., 2014). In terms of specific domains of EF, one study used path analysis to estimate associations between parent-rated EF and behaviour problems in

a sample of children with ASD and ADHD, and found the best fitting model showed that having a diagnosis of ASD predicted higher levels of inflexibility, and in turn greater inflexibility predicted higher levels of aggressive and oppositional behaviour (Lawson et al., 2015). In individuals with ASD, ID and ASD+ID, greater difficulty in cognitive shifting, when measured by caregivers, but not when measured by neuropsychological test performance, was associated with the presence of care-giver rated aggression in all groups (Visser et al., 2014). Shared method variance may have contributed to this differential finding. From a case-series of four individuals with Prader-Willi syndrome, which is characterised by mild-moderate ID, analyses found that participants exhibited more challenging behaviours during computerized switching tasks, as compared to non-switching tasks, and more challenging behaviours were exhibited in more difficult switching tasks as compared to easier switching tasks (Woodcock, Oliver, & Humphreys, 2011).

4.2.4 Aims

Research exploring the association between EF impairments and challenging behaviours in individuals with ASD is limited. However, past literature suggests a potential association between impairments in cognitive flexibility and challenging behaviours. Prior research also suggests that alterations in specific ERP components, namely the N2 and P300, are altered in both ASD populations, and in non-ASD populations with behaviour problems (e.g., those with ODD/CD). Thus, the current study aimed to test whether inhibition and cognitive flexibility, as measured by neuropsychological task performance, along with ERP parameters of conflict monitoring (N2) and attentional orienting (P300), were associated with co-occurring emotional and behavioural problems in adolescents with ASD. It was hypothesised that greater difficulties in EF, as indexed by both poorer performance in two

behavioural tasks, and reduced N2 and P300 amplitudes in an ERP paradigm, would be associated with higher rates of behaviour problems.

4.3 Method

4.3.1 Participants

Forty-seven participants completed the full EF task battery (Go/NoGo and Switch tasks). An additional two participants only completed the Go/NoGo task. In Chapter 3 participants with ASD who scored over the SDQ conduct problems subscale were excluded, however they were retained in current analyses. Forty participants completed the visual oddball task paired with EEG recording. See Section 2.1 for a full description of participant recruitment and assessment, and Figure 8, Section 2.7, Chapter 2 for a break-down of sample demographics by task completed.

4.3.2 Stimuli

4.3.2.1 *Go/NoGo and Switch Task*

The details of the Go/NoGo and Switch tasks are presented in Section 3.3.2, Chapter 3. As a brief reminder, the key outcome variable for the Go/NoGo task was the percentage of successfully inhibited no-go trials (probability of inhibition), and the key outcome variables for the Switch task were the Switch error cost and RT cost (mean errors/RT to switch trials – mean errors/RT to repeat trials). For both tasks percentage of premature responses (responses made 200ms before and 100ms after stimulus onset) and ICV ($SD/mean\ RT\ of\ responses \times 100$) were calculated.

4.3.2.2 *Oddball Task*

Visual stimuli were presented in an oddball paradigm. Stimuli were two randomly presented pictures, each centrally presented for 2000ms with a jittered inter-stimulus

interval of 800-1200ms (see Figure 10 for a pictorial representation of the task). The infrequently presented target (20% probability, 72 trials in total) and frequently presented standard (80% probability, 288 trials in total) consisted of four different cartoon characters from Mario Kart. These stimuli were selected to encourage participant interest and involvement. Participants were instructed to respond as quickly as possible and to press '1' for the target stimulus and '2' for the standard stimulus. Participants completed 8 practice trials before beginning the task. The paradigm was split into two blocks of 180 trials. In addition to EEG recording, data was collected on accuracy and RT for target and standard stimuli. The task lasted around 8 minutes.

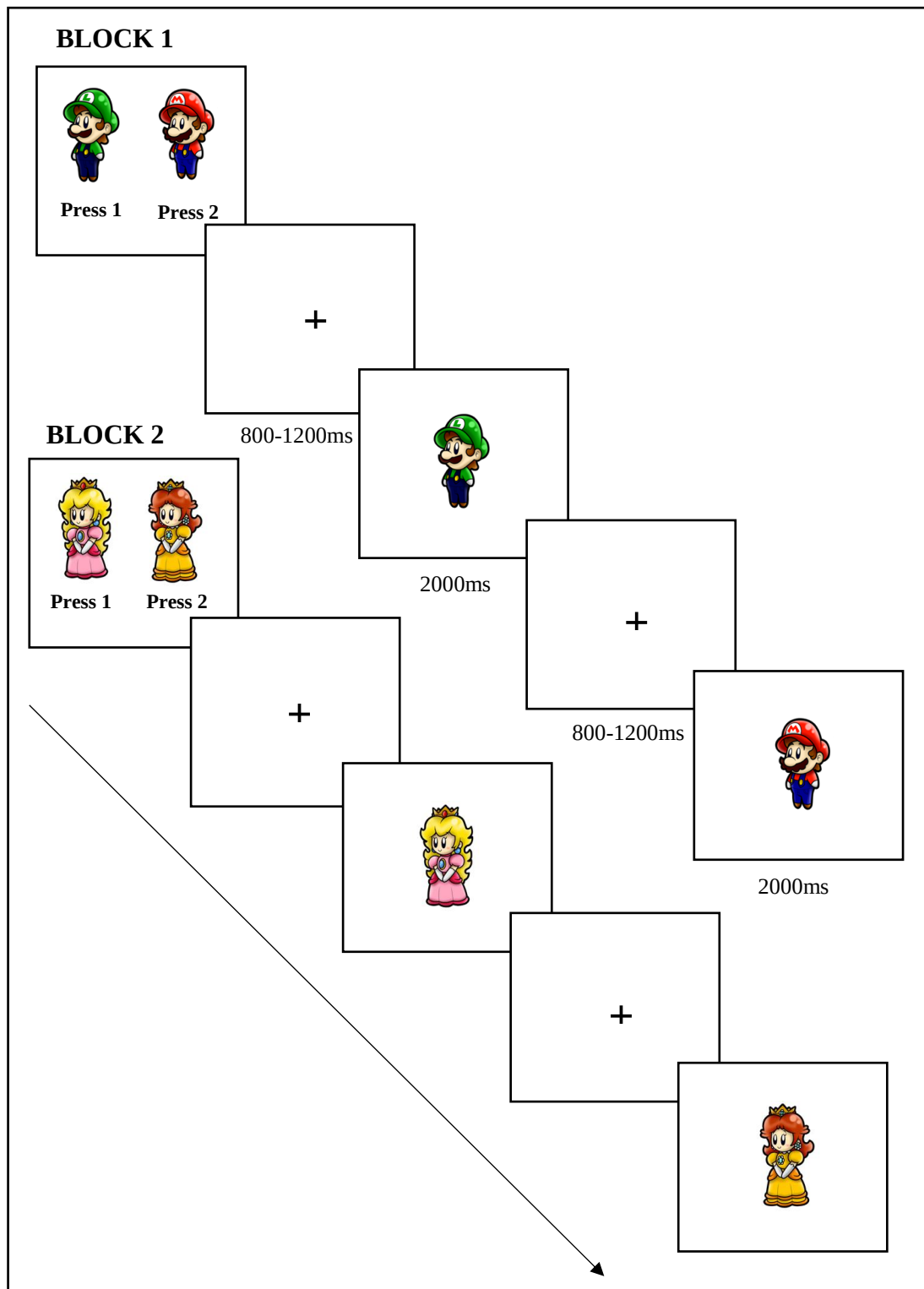


Figure 10. Schematic of Trial Structure in Visual Oddball Task

4.3.3 Procedure

Participants completed the Go/NoGo and Switch tasks on a portable laptop. They were given a short practice with encouragement from the examiner before beginning the main experiment. Participants completed the visual oddball task within the EEG suite, see Section 2.4 for further details. A researcher sat with the participant for all tasks to ensure they were still, relaxed and attending to the task. Participants were encouraged to stretch and move around in the break in between blocks in the oddball task.

4.3.4 EEG Recording and Pre-processing

See Sections 2.4 and 2.5, Chapter 2, for details of EEG data acquisition and general pre-processing.

4.3.5 ERP Analysis

Epochs of 700ms, including a -100ms prestimulus period, were extracted for the target and standard stimuli separately. The average amount of trials per condition was 47.76 (SD=10.53) for target stimuli and 71.97 (SD=0.16) for standard stimuli. Given the difference in probabilities there were substantially more standard than target trials. Therefore, the first valid 72 standard trials were selected for analysis, to give comparable trial numbers to the target trials. Two participants who had less than 20 valid trials were excluded. Epochs were separately averaged for standard and target stimuli. Baseline correction was performed using a 100ms prestimulus reference period. Electrodes of interest were selected based on prior literature (Brandeis et al., 2002; Nieuwenhuis et al., 2003; Tye et al., 2013) and confirmed with visual inspection. The N2 was extracted from a cluster of five electrodes (4, 5, 11, 12, 19) corresponding to the Fz area, and the peak amplitude of the most prominent negative deflection was measured in the 180-320ms latency range,

consistent with previous literature (Nieuwenhuis et al., 2003). The average latency to the peak was also measured. See Figure 11 for grand averages of N2 response to target and standards.

The P300 was extracted from two clusters, corresponding to the Cz (7, Cz, 31, 80, 106) and Pz (61, 62, 72, 78) areas. The P300 was also measured at Cz as literature suggests increased anteriorisation of the P300 with age (Jonkman et al., 2003; Valko et al., 2009). This was supported by our topographical maps (see Figure 12 for isocontour maps of grand average response to target stimuli). The mean amplitude in the 300-550ms window was calculated, as the activity within this time occurred over an extended period making it difficult to identify a clear peak (as in Tye et al., 2013). See Figure 13 for grand averages of P300 response to target and standards at Cz and Pz.

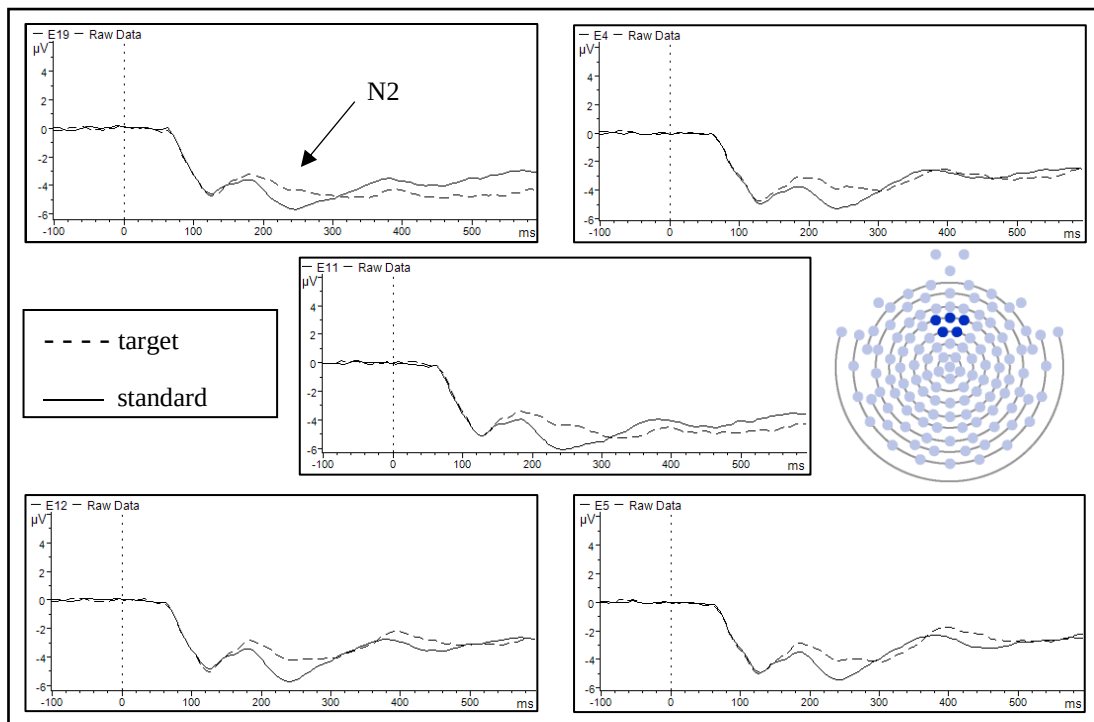


Figure 11. Grand Average of Waveforms to Standard and Target Stimuli at Fz

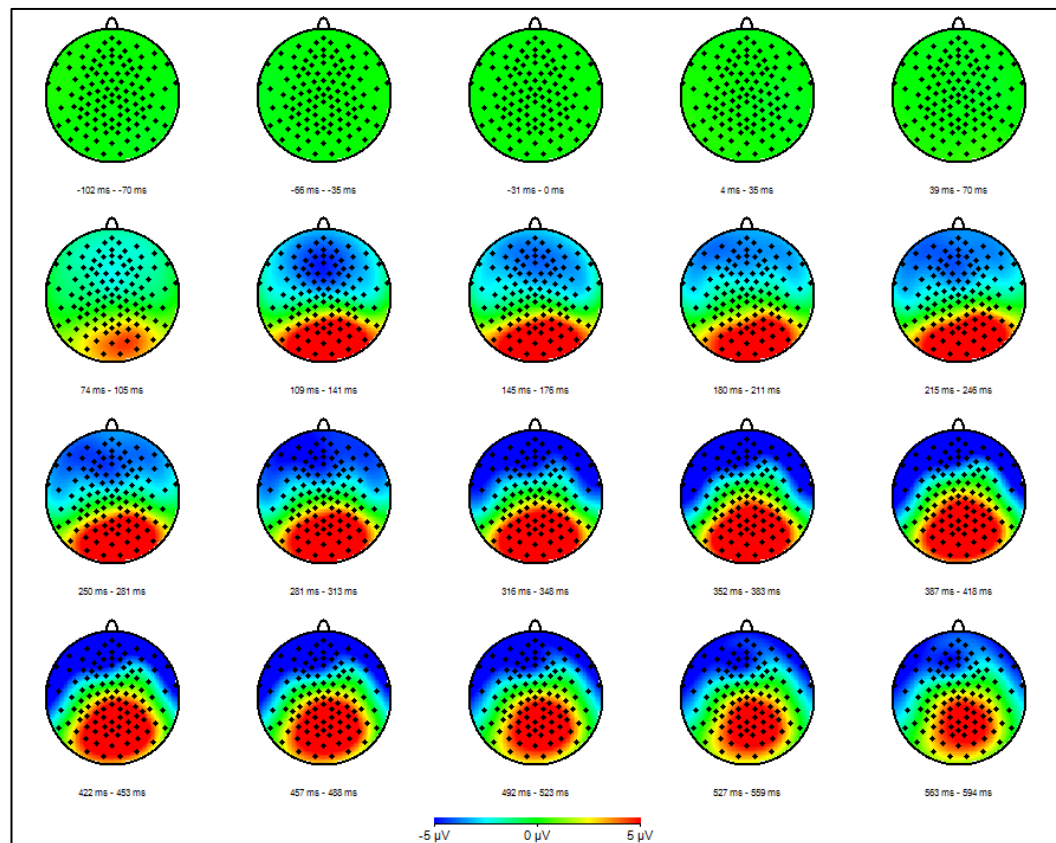


Figure 12. Isocontour Maps Based on Grand Average Response to Targets

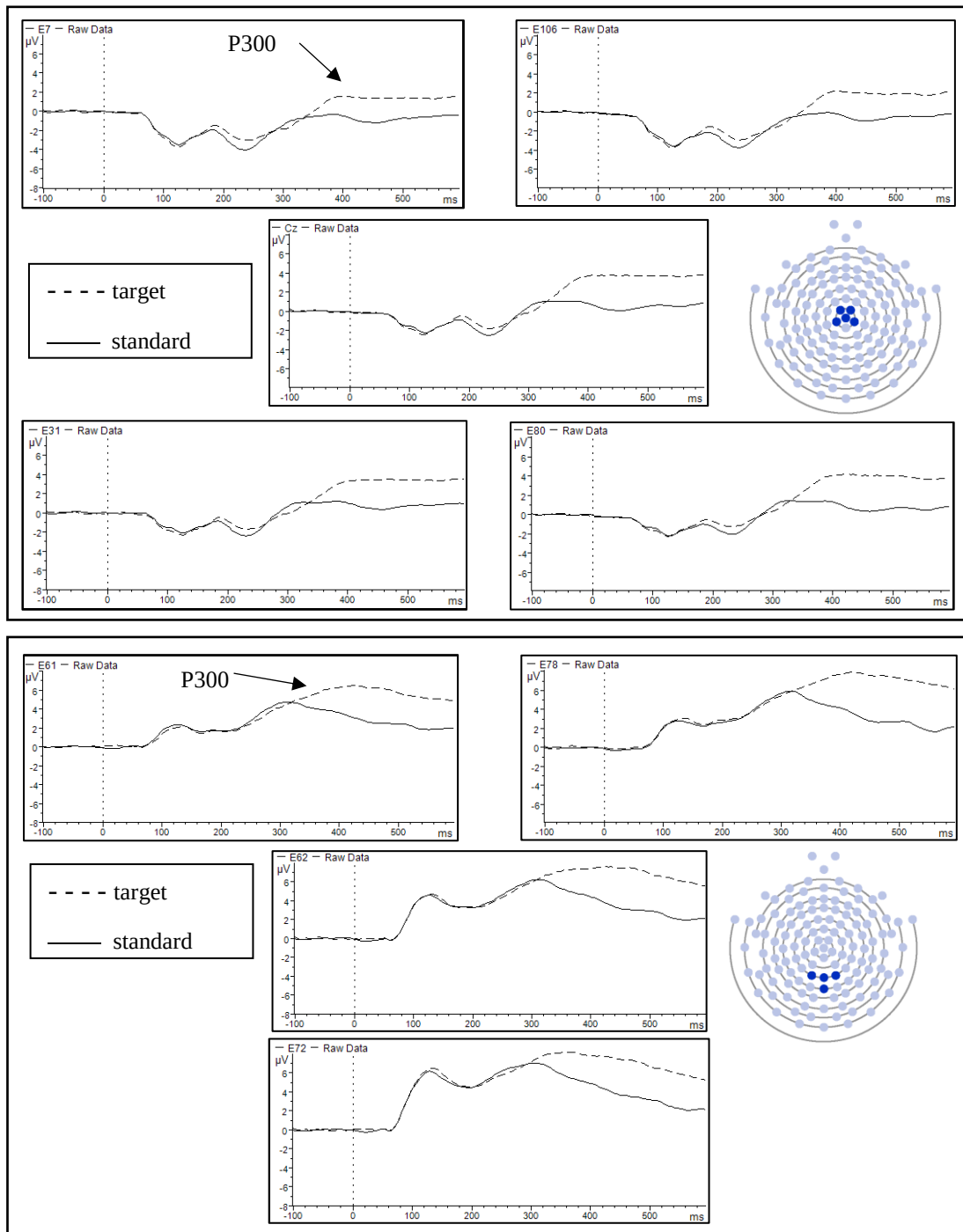


Figure 13. Grand Average of Waveforms to Standard and Target Stimuli at Cz (top) and Pz (bottom)

4.3.6 Analytic Strategy

4.3.6.1 *Go/NoGo and Switch Tasks*

Two participants were excluded from the Go/NoGo task and three participants excluded from Switch for failing to respond correctly on at least 30 % of the baseline trials (see Section 2.6, Chapter 2 for details). As the ICV in the Go/NoGo and the CV in the Switch task were significantly correlated in the current sample ($r=0.41$, $p<0.01$), the two were collapsed into one variable. The number of premature responses in the Go/NoGo and Switch tasks were not significantly correlated ($r=-0.14$, $p=0.37$) so were analysed separately. As in Chapter 3, the probability of inhibition variable was square root transformed, and the premature response variable was transformed to a binary variable (0=did not show any premature responses, 1=showed premature responses) across both tasks.

4.3.6.2 *Oddball Task*

Peak N2 latency and amplitude, and average P300 amplitude to target and standard stimuli were compared using planned pairwise comparisons. Key outcome measures were target RT and accuracy, along with N2 latency and peak amplitude, and mean P300 amplitude, to target stimuli. The N2 peak amplitude variable was negatively skewed and so square root transformed. Difference scores were also calculated for N2 peak amplitude and P300 average amplitude by subtracting the response to the target from the response to the standard. One outlier was identified in the N2 difference wave data, and two outliers in the mean P300 amplitude data at Pz. Analyses were conducted including and then excluding outliers (see Section 2.6, Chapter 2 for details).

The general analytic strategy is outlined in Section 2.6, Chapter 2. Primary analyses used multivariate regression to test for an association between behavioural/ERP parameters and SDQ subscales of emotional problems, ADHD symptoms and conduct problems, along with the ARI irritability scale. Secondary analyses used regression to test for an association between behavioural/ERP parameters and DBC total behaviour problem score. Results were first adjusted for age, sex and full scale IQ, and then for age, sex, IQ and ASD severity, as measured by the ADOS calibrated severity score. Two separate sensitivity analyses were also conducted, first excluding those taking medication known to affect brain functioning (n=5) and second excluding those with epilepsy (n=2).

4.4 Results

4.4.1 Go/NoGo Task

Average performance on key parameters from the Go/NoGo and Switch tasks are presented in Table 7. No significant associations were found with probability of inhibition ($ps=0.10-0.97$); however the association between ADHD symptoms and probability of inhibition was the closest to significance ($\beta=0.38, p=0.10$).

A significant association was found between the likelihood of premature response and SDQ ADHD symptoms ($\beta=1.61, p<0.05$). This association remained at a trend-level of significance when controlling for age, sex and IQ ($\beta=1.71, p=0.06$), age, sex, IQ and ASD severity ($\beta=1.73, p=0.07$). The association became non-significant when excluding participants taking medication ($\beta=1.22, p=0.13$), and but remained at a trend-level when excluding those with epilepsy ($\beta=1.54, p=0.05$). No associations were found with the other outcome measures ($ps=0.21-0.77$).

4.4.2 Switch Task

A significant association was found between Switch RT cost and SDQ ADHD symptoms ($\beta=0.02, p<0.05$; see Figure 14), and this remained significant when controlling for age, sex and IQ ($\beta=0.02, p<0.05$), and age, sex, IQ and ASD severity ($\beta=0.02, p<0.05$), and both when excluding participants taking medication ($\beta=0.02, p<0.05$), and those with epilepsy ($\beta=0.02, p<0.05$). No associations were found with the other outcome measures ($ps=0.14-0.69$). No significant associations were found with Switch error cost ($ps=0.42-0.99$). A trend association was found between likelihood of premature responses and ARI total score ($\beta=2.51, p=0.07$), and this remained at a trend when controlling for age, sex and IQ ($\beta=2.62, p=0.08$), although became non-significant when controlling for age, sex, IQ and ASD severity ($\beta=2.51,$

$p=0.10$). The association was significant when excluding participants taking medication ($\beta=2.67, p<0.05$), and at a trend when excluding those with epilepsy ($\beta=2.60, p=0.06$). No associations were found with the other outcome measures ($ps=0.23-0.92$).

4.4.3 Intra-Individual Response Variability

The ICV was significantly associated with SDQ ADHD symptoms ($\beta=0.15, p<0.01$; see Figure 14), and this association remained significant when controlling for age, sex and IQ ($\beta=0.15, p<0.05$), age, sex, IQ and ASD severity ($\beta=0.16, p<0.05$), and both when excluding participants taking medication ($\beta=0.14, p<0.05$), and those with epilepsy ($\beta=0.14, p<0.05$). No associations were found with the other outcome measures ($ps=0.12-0.88$).

Table 7. Average Performance of QUEST Sample on Key Variables from the Go/NoGo and Switch Tasks

Task	Variable	Mean	SD	Range
Go/NoGo (n=47)	Probability of inhibition	66.81	18.73	20 - 92
	Premature responses (present/absent)	33/14	-	-
Switch Task (n=44)	RT cost	45.82	54.95	-74.01 - 199.99
	Error cost	2.81	6.89	-9.56 - 28.78
	Premature responses (present/absent)	7/37	-	-
Across Tasks	ICV	29.27	7.62	16.55 - 46.63

ICV indicates intra-individual coefficient of variability; RT reaction time

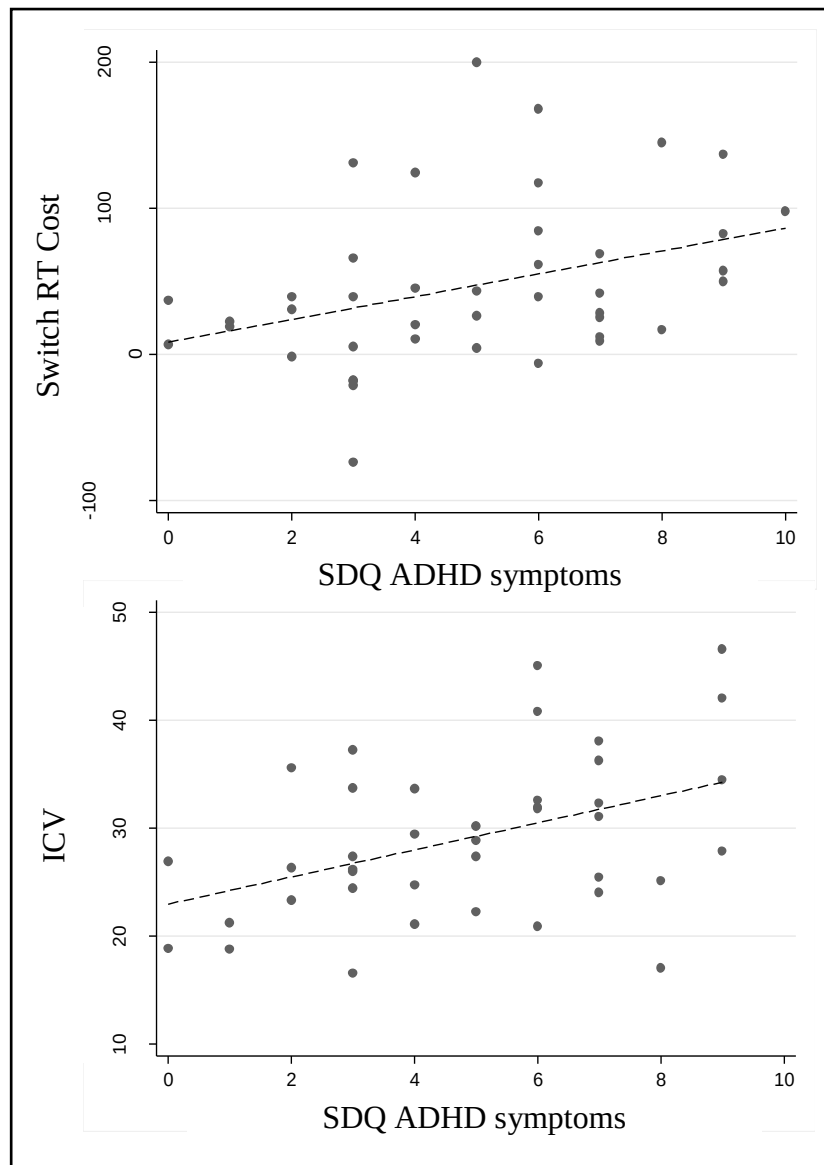


Figure 14. Association between ADHD symptoms and Switch RT Cost (top) and Intra-Individual Response Variability (as measured by the ICV) (bottom)

4.4.4 Oddball Task

Due to technological issues, behavioural data was only available for a subset of participants ($n=20$). Average RT was significantly higher for the target as compared to the standard trials (mean target RT = 557.37, SD=146.54, range 367.63-995.79; mean standard RT = 522.25, SD=150.64, range 326.46-959.87; $t(19)=-4.40$, $p<0.01$) and accuracy was significantly lower for the target as compared to the standard trials (mean target accuracy = 0.89, SD=0.09, range 0.68-1; mean standard accuracy = 0.96, SD=0.08, range 0.63-1; $t(19)=4.36$, $p<0.01$).

No significant associations were found between target RT ($ps=0.36-0.98$) or accuracy ($ps=0.30-0.56$) and emotional and behavioural problems, aside from an association between target accuracy and the DBC total behaviour problem score ($\beta=-157.66$, $p<0.05$), however this became non-significant when age, sex and IQ were controlled for ($\beta=-107.03$, $p=0.12$).

There was a trend correlation between target RT and relative difference in P300 amplitude to targets vs. standards at Pz ($r=-0.42$, $p=0.07$). No other significant correlations between behavioural performance and ERP parameters were found ($ps=0.13-0.93$).

N2

N2 amplitude was significantly smaller to targets than amplitude to standards (mean target amplitude = -5.49, SD=3.26, range -14.99- -1.08; mean standard amplitude = -6.96, SD=3.76, range -16.98- -1.54; $t(37)=4.42$, $p<0.01$). No differences were found in N2 target latency as compared to standard latency (mean standard latency = 246.34, SD=29.88, range 194.53-310.16; mean standard latency = 242.37, SD=31.19, range 179.69-309.38; $t(37)=0.58$, $p=0.28$).

No significant associations were found between N2 amplitude ($ps=0.43-0.91$) or latency ($ps=0.13-0.64$) and emotional and behavioural problems. Similarly, no associations were found with the N2 difference wave ($ps=0.20-0.98$), and a similar pattern was observed when outliers were excluded ($ps=0.67-0.98$), aside from a trend association with SDQ conduct problems ($\beta=0.27$, $p=0.09$), but this became fully non-significant when controlling for age, sex and IQ ($\beta=0.25$, $p=0.14$).

P300

Mean P300 amplitude was significantly greater to targets than mean amplitude to standards at both Cz (mean target amplitude = 2.25, SD=3.60, range -5.43-10.33; mean standard amplitude = 0.22, SD=1.96, range -5.28-4.11; $t(37)=4.95$, $p<0.01$) and Pz (mean target amplitude = 7.18, SD=4.11, range -0.67-18.48; mean standard amplitude = 4.32, SD=3.39, range -0.84-16.64; $t(37)=6.96$, $p<0.01$).

At Cz, no associations between mean target P300 amplitude and behaviour were found ($ps=0.20-0.60$). Similarly, at Pz no significant associations were found ($ps=0.34-0.98$), and a similar pattern was observed when outliers were excluded ($ps=0.45-0.98$).

At Cz, a trend association was found between relative difference in P300 amplitude to targets vs. standards at Cz and SDQ ADHD symptoms ($\beta=-0.30$, $p=0.09$), but this became fully non-significant when controlling for age, sex and IQ ($\beta=-0.27$, $p=0.19$). No associations were found with the other outcome measures ($ps=0.38-0.98$). At Pz, no significant associations were found between relative difference in P300 amplitude to targets vs. standards and emotional and behavioural problems ($ps=0.41-0.83$).

4.5 Discussion

This study investigated whether behavioural and neural indices of EF were associated with co-occurring emotional and behavioural problems in adolescents with ASD. Results showed significant associations between ADHD symptoms and behavioural indices of EF, in that those with more ADHD symptoms exhibited increased intra-individual response variability, higher likelihood of premature responses and increased RT cost on cognitive flexibility tasks. A trend association was also found between ARI total, indexing irritability, and higher likelihood of premature responses on the cognitive flexibility task. Analyses did not find any significant associations between emotional and behavioural problems and ERP parameters of conflict monitoring (N2) or orienting and allocation of attention (P300) in a visual oddball task. A trend was found between ADHD symptoms and the difference in mean P300 amplitude to targets as compared to standards, but this did not remain when age, sex and IQ were entered as covariates.

In keeping with prior literature (Bühler, Bachmann, Goyert, Heinzel-Gutenbrunner, & Kamp-Becker, 2011; Corbett et al., 2009; Sinzig et al., 2008; Tye et al., 2016), analyses showed a specific association between EF impairments and ADHD symptoms in individuals with ASD, which was not accounted for by age, IQ, sex or ASD severity. Results also largely remained significant in sensitivity analyses, however the association between premature responses on the Go/NoGo task and ADHD symptoms became non-significant when participants taking medication known to affect neural functioning were excluded (e.g., sertraline, methylphenidate, anti-epileptics). This may have been due to decreased power, as only 38 participants remained in the sample in these analyses, and supportingly the co-efficients were not drastically different in the main analyses using the whole sample ($\beta = 1.61$) as

compared to the sensitivity analyses using a sub-sample ($\beta=1.22$). This also may have been due to sensitivity analyses removing those participants with the highest ADHD symptoms, i.e., those taking methylphenidate. Results also found a trend association between the ARI irritability scale and premature responses on the Switch task. However, only seven participants demonstrated premature responses on this task, and so results should be replicated with larger sample sizes before any strong conclusions are drawn.

In terms of the current association between intra-individual response variability and ADHD symptoms, this concurs with previous work which found that when children with ASD, ADHD and ASD+ADHD were compared on intra-individual response variability using a four choice 'Fast' task, only the ADHD and ASD+ADHD group showed increased variability (Tye et al., 2016). Current analyses did not find a significant association between ADHD symptoms and probability of inhibition, but did find an association between premature responses, which is thought to tap into a similar construct (impulsivity) as the probability of inhibition variable. Supportingly, others have found children with ASD+ADHD showed worse inhibitory performance than children with ASD only (Bühler et al., 2011; Sinzig et al., 2008). The study by Sinzig and colleagues also found a similar pattern of results to current findings with regard to cognitive flexibility, in that the ASD+ADHD group required more time to shift between sets than the ASD group. Thus, the present results suggest, along with previous work (Tye et al., 2013; Tye et al., 2016), that individuals with ASD plus ADHD may present with an additive co-occurrence of the two disorders, especially in terms of EF impairments.

Although an association was found between cognitive flexibility and ADHD symptoms, no association was found with challenging behaviours, as measured by

either the SDQ conduct problems subscale or the DBC total behaviour problems score. This was unexpected, given that prior literature has reported an association between cognitive flexibility and challenging behaviours in ASD (Lawson et al., 2015; Visser et al., 2014) and ID populations (Woodcock et al., 2011), and impairments in cognitive flexibility in individuals with ODD/CD (Aronowitz et al., 1994; Morgan & Lilienfeld, 2000; Toupin et al., 2000). There are many potential explanations for the discrepancy between the current results and prior literature. First, how cognitive flexibility was measured could be important. In both studies mentioned above that used ASD populations, parent and carer ratings of both challenging behaviours and cognitive flexibility were used, whereas in the current study cognitive flexibility was measured using task performance. In the study by Visser and colleagues (2014), a significant association between cognitive flexibility and aggression was found only when carer-report was used to measure cognitive flexibility, whereas no association was found when performance measures of flexibility were used. Thus, prior associations may have, in part, been driven by rater effects inflating associations between cognition and behaviour through shared method variance. Another potential explanation is that although prior literature has reported EF impairments in individuals with ODD/CD (Aronowitz et al., 1994; Morgan & Lilienfeld, 2000; Toupin et al., 2000), many of these studies used samples predominantly composed of individuals with CD. As discussed in Section 1.5.2, Chapter 1, CD symptoms that require a more mature level of thinking and social cognition, such as ‘often lies to obtain goods or favours or to avoid obligation’ (American Psychiatric Association, 2013), are rarely found in individuals with ASD (Simonoff et al., 2008). Instead, ASD populations appear to present more often with behavioural symptoms which do not rely so much on social understanding and may

reflect emotional over-arousal, such as temper tantrums (Guttmann-Steinmetz et al., 2009). Thus, these differences in phenomenology may mean that research exploring the cognitive correlates of CD in ASD populations is only relevant to a small subgroup of individuals with ASD and challenging behaviours. A similar comment can be made as to the lack of association with ERP parameters collected during the visual oddball task, which were selected primarily due to their association with CD (Banaschewski et al., 2003; Gao & Raine, 2009; Harmon-Jones et al., 1997; Iacono et al., 2002; Patrick, 2008). Analysis of oppositional behaviours in non-ASD populations found that a cluster of symptoms encapsulating predominantly CD symptoms and aggressive behaviours, could be differentiated from another cluster encapsulating more irritability-type behaviours such as temper tantrums and anger (Stringaris & Goodman, 2009). Only the irritability cluster was associated with emotional disorders at three year follow up, suggesting these types of oppositional behaviour may be a mixture of emotional and behavioural difficulties. Given that individuals with ASD appear to present more with these types of ODD behaviours than archetypal CD symptoms such as stealing and lying (Guttmann-Steinmetz et al., 2009; Simonoff et al., 2008), affective-laden domains such as emotional dysregulation may be more relevant to understanding the types of challenging behaviours exhibited by individuals with ASD (Mazefsky et al., 2013), than non-emotional domains of cognition, such as EF.

An alternative explanation for the lack of association between EF and challenging behaviours in the current study, and perhaps a broader comment on research into ODD/CD populations, is that prior reports of EF impairments in ODD/CD may have been driven by unacknowledged ADHD symptoms. It has been suggested that support for the idea that EF impairments are an integral part of 'pure' ODD/CD is

limited, unlike the wealth of evidence highlighting the causal role of environmental factors such as parenting (Burke, Loeber, & Birmaher, 2002). If this proposal was accepted, then it is not surprising that the current study did not find an association between EF and conduct problems. Indeed, prior research has found no clear differences in EF profiles between children with ADHD as compared to those with ADHD+ODD/CD (Geurts et al., 2004; Nigg, Hinshaw, Carte, & Treuting, 1998). One study that specifically compared those with ‘pure’ ODD/CD against those with ADHD and ADHD+ODD/CD, found no main effect of ODD/CD diagnosis, and no significant associations between ratings of aggressive behaviour and EF ability (Clark, Prior, & Kinsella, 2000). A more recent study used a similar design, but split EF into ‘hot’ (reward-related decision making tasks) and ‘cool’ (sustained attention and cognitive flexibility tasks) domains. ODD/CD was associated with impairments in ‘hot’ but not ‘cool’ domains of EF (Hobson et al., 2011). Thus, it may be that either there are not consistent EF impairments in ODD/CD, or that only certain types of EF impairments, specifically ‘hot’ EF, traditionally thought to be more involved in motivational circuits (Zelazo & Muller, 2002), are impaired in ODD/CD, whereas impairments in ‘cool’ EF, indexing more abstract-cognitive abilities, and similar to those measured in the current study, are predominantly driven by co-occurring ADHD. This distinction may also be present in ASD populations, thus future work should collect data on both ‘hot’ and ‘cool’ EF in individuals with ASD, to test if there is a differential association between the two types of EF and challenging behaviours.

4.5.1 Specific Strengths

Current analyses used a comprehensive measurement of EF, including performance on two behavioural tasks and two ERP components thought to index key EF

processes. Thus, any patterns of results and subsequent conclusions drawn are not based on one task in isolation, and are thus less likely to be spurious.

4.5.2 Specific Limitations

It is possible, as discussed in Chapter 3, that the task selected to measure cognitive flexibility in the current study did not effectively detect the inflexibility often reported in individuals with ASD (Landry & Al-Taie, 2016). The same criticism could be made of the visual oddball task, in that it may have been too simple. Given it was known beforehand the sample had a wide range of cognitive ability, the ERP task presented in the current thesis was designed to have relatively simple instructions to encourage greater accessibility and participation. In the oddball task participants were required to make two different responses for two different pictures. These simple demands could have meant the paradigm did not elicit enough variation in conflict monitoring, inhibition and attention allocation to detect associations with challenging behaviours. However, the expected N2 and P300 response to targets was found, suggesting the tasks did elicit the neural components they were designed to provoke. Whether associations between N2 and P300 amplitude and challenging behaviours would be found in more demanding tasks, for example a continuous performance task, remains an unanswered question.

4.5.3 Implications

Although more research is required before any strong conclusions are drawn, findings tentatively suggest that impairments in EF domains, namely ‘cool’ EF abilities such as inhibition and cognitive flexibility, may not be relevant for models of challenging behaviours in adolescents with ASD. Although a trend association between irritability (as indexed by the ARI scale) and premature responses was found, this was based on a small number of participants. Future research could

explore this potential association using larger samples or different indices of premature responsiveness. As functioning in ‘hot’ EF domains, for example reinforcement learning and decision making (Matthys, Van Goozen, Snoek, & Van Engeland, 2004; Matthys, Vanderschuren, & Schutter, 2012), is found to be impaired in individuals with ODD/CD, the association between these domains and challenging behaviours should also be tested before any strong conclusions regarding the role of EF are drawn.

Results also suggest that EF impairments are selectively associated with ADHD symptoms in individuals with ASD, and thus that the neurocognitive correlates of ADHD in ASD are comparable to those in non-ASD populations. In terms of clinical implications, given the high prevalence of ADHD in youth with ASD (Simonoff et al., 2008), current results suggest that individuals with ASD should be given a full diagnostic and cognitive assessment, to determine where strengths and weaknesses may lie. In terms of research implications, results suggest that studies exploring the cognitive profile of individuals with ASD should measure and account for co-occurring ADHD symptoms, as these may contribute to heterogeneity in cognitive functioning. Understanding distinct and shared cognitive impairments is key to building aetiological models of co-occurring disorders, but also will provide potential cognitive and electrophysiological endophenotypes for genetic research.

5 Testing the Association between Electrophysiological Indices of Perceptual Processing and Emotional and Behavioural Problems in Adolescents with ASD

5.1 Summary

PP atypicalities are often reported in individuals with ASD, but how these relate to co-occurring emotional and behavioural problems has not been well explored. ERPs were recorded in response to both deviant and standard stimuli in an auditory oddball paradigm in adolescents with ASD (n=43). Response to deviant as compared to standard stimuli (MMN) and response to repeated presentations of standard stimuli (habituation) were measured. Results showed that greater sensitivity to changes in incoming auditory information, as indexed by increased MMN amplitude, was associated with higher levels of parent-rated behaviour problems. Conversely, greater habituation at both the early N1 component and the later N2 component was associated with higher levels of emotional problems. Upon more detailed analyses, this appeared to be driven by a selectively greater amplitude to the first standard stimuli that followed deviant stimuli. No significant associations were found to response for the second or third standard stimuli. A similar pattern of association was found with other measures of anxiety. Findings suggest that certain aspects of the cognitive profile (e.g., PP atypicalities) thought to underpin the core symptoms of ASD are also associated with co-occurring emotional and behavioural problems.

5.2 Introduction

A breadth of research has highlighted that individuals with ASD experience both hypo- and hyper-sensitivity to perceptual inputs from auditory, tactile and visual

sources (Baranek et al., 2006; Crane et al., 2009; D. Green, Chandler, Charman, Simonoff, & Baird, 2016; Leekam et al., 2007; Liss et al., 2006). The importance of atypical sensory experiences to people with ASD has been acknowledged in the most recent edition of the DSM, where these have now been included as part of the diagnostic criteria (see Figure 1, Chapter 1). This has led to suggestions that individuals with ASD process incoming perceptual inputs in an atypical manner. This hypothesis has been tested by comparing individuals with ASD against typically developing individuals in terms of the brain's response to changes in incoming perceptual information.

5.2.1 EEG Indices of PP

One of the most well studied neural indices of PP is the MMN component (Näätänen & Alho, 1995). This is a fronto-central negative component found around 100-200ms after stimuli presentation. In typically developing individuals, ERP amplitudes are found to be greater in response to deviant, as compared to standard stimuli, and this difference is known as the MMN (Näätänen & Alho, 1995). As MMN amplitude is found to be associated with individual discrimination skills (Amenedo & Escera, 2000; Kujala et al., 2001; Näätänen & Alho, 1995), some have suggested it is an index of individual sensitivity to changes in incoming information. In the oddball paradigms typically used to study perceptual discrimination between deviant and standard stimuli, one can also study habituation to the standard stimuli, which is where the neural response exponentially decreases over repeated presentations of the same stimulus. This is thought to allow the brain to filter out irrelevant repetitive stimuli and conserve attentional resources (Rankin et al., 2009), and highlights how, in typically developing populations, prior experience modulates processing of on-going perceptual information.

5.2.2 MMN Alterations in ASD

In terms of alterations in perceptual discrimination individuals with ASD, findings are mixed (for a review see O'Connor, 2012). Some have found increased MMN amplitude in individuals with ASD (Ferri et al., 2003; Lepistö et al., 2008; Lepistö et al., 2005), and decreased latency (Gomot et al., 2008; Gomot et al., 2011), which have been interpreted as indexing hyper-sensitivity to unpredictable changes (Gomot & Wicker, 2012). However, others have found decreased MMN amplitude (Andersson et al., 2013; Donkers et al., 2015; Kuhl et al., 2005; Ludlow et al., 2014; Vlaskamp et al., 2017) and increased MMN latency (Jansson-Verkasalo et al., 2003). Furthermore, some have reported an association between MMN attenuation and higher sensory sensitivity scores (Donkers et al., 2015; Ludlow et al., 2014). Differences in findings may be due to variation in the samples and experimental paradigms used. One study found attenuated MMN in children with ASD during non-attended conditions, but when participants were instructed to listen to the sounds, there was no difference between the ASD and typically developing group (Dunn et al., 2008). Additionally, in the same study, MMN was found to be associated with age, in that children with ASD were less likely to show an MMN response as compared to adolescents with ASD (Dunn et al., 2008).

5.2.3 Habituation in ASD

In terms of habituation, the literature in individuals with ASD is more limited. Reduced habituation has been found in response to repeated presentations of faces in individuals with ASD, and the degree of habituation was associated with ASD symptom severity (Kleinhans et al., 2009; Swartz et al., 2013). One study found infants at higher genetic risk of developing ASD, unlike low risk infants, did not show a decrease in ERP response over repeated presentations of a standard auditory

stimulus (Guiraud et al., 2011). Others, using a neural computational framework, have theoretically proposed that individuals with ASD rely less on previous experience to guide their on-going perception (Gomot & Wicker, 2012; Pellicano & Burr, 2012; Sinha et al., 2014). Thus, attenuated habituation is just one example of the brain being unable to learn from prior experiences to adaptively prioritize which perceptual inputs to disregard, and which to attend to.

5.2.4 Association between PP and Challenging Behaviours in ASD

Although no study has looked at neural indices of PP and emotional and behavioural problems in ASD, there is some extant literature primarily focused on questionnaire measures of sensory processing. A small sample pilot study (n=22) found that caregiver-rated sensory processing atypicalities were significantly correlated ($r=0.49$) with DBC-rated behavioural problems in children with ASD (A. Baker et al., 2008). Another study of young children (4-7 years) with ASD found parent-rated sensory avoidance was significantly associated with internalising problems, whereas sensory sensitivity was significantly associated with externalising problems (Tseng et al., 2011). Similar associations were found in a study that used teacher-rated questionnaires, where a significant correlation was found between tactile and movement sensitivity, and oppositional behaviour in children with ASD (Ashburner, Ziviani, & Rodger, 2008). However, the specificity of this association was unclear, as tactile sensitivity was also correlated with ADHD-type symptoms. In the same study, the authors also found an association between difficulties with auditory filtering and internalising problems. A number of studies have reported an association between parent-rated sensory hyper-sensitivity and anxiety symptoms in individuals with ASD (Lane, Reynolds, & Dumenci, 2012; Lidstone et al., 2014; Mazurek et al., 2013; Pfeiffer, Kinnealey, Reed, & Herzberg, 2005), including one

that used physiological reactivity to a sensory challenge as an index of sensitivity (Lane et al., 2012). One longitudinal study of toddlers with ASD found sensory over-sensitivity predicted increases in anxiety over and above child age, ASD symptom severity, cognitive ability, and maternal anxiety, but anxiety did not predict changes in sensory over-sensitivity (S. Green, Ben-Sasson, Soto, & Carter, 2012), suggesting there could be potential causal pathway between sensory processing atypicalities and anxiety in ASD.

No study has specifically explored the association between habituation and co-occurring emotional and behavioural problems in individuals with ASD. However, in typically developing adolescents decreased neural habituation in the amygdala in an emotional Go/NoGo task was found to be associated with higher levels of trait anxiety (Hare et al., 2008). In terms of how habituation could theoretically relate to anxiety, impaired habituation may lead to repeated and predictable perceptual inputs being experienced as novel and unpredictable, and neuroimaging research has found temporally unpredictable stimuli provoke anxiety behaviours in mice and humans (Herry et al., 2007).

5.2.5 Aims

In summary, it appears that individuals with ASD are characterised by impairments in response to deviant perceptual input, but also by decreased habituation to repeated presentation of the same stimuli. Questionnaire studies from individuals with ASD, and neuroimaging studies from typically developing individuals suggest that both of these impairments may be linked to emotional and behavioural problems. However, no study has specifically tested how neural indices of PP relate to emotional and behavioural problems in individuals with ASD. The aim of this study was to investigate whether neural responses to both deviant and standard stimuli in an

auditory paradigm were associated with co-occurring emotional and behavioural problems in adolescents with ASD. Based on prior literature, it was hypothesised that greater sensitivity to changes in perceptual information, as indexed by increased MMN amplitude, would be associated with higher levels of emotional and behaviour problems. Analyses also tested whether habituation was associated with emotional and behavioural symptoms, where it was hypothesised that decreased habituation would be associated with increased emotional difficulties.

5.3 Method

5.3.1 Participants

Forty-three participants with ASD completed a PP paradigm paired with EEG recording. See Sections 2.1 and 2.7, Chapter 2 for a full description of participant recruitment and assessment, and a breakdown of sample demographics by task completion.

5.3.2 Stimuli

Auditory stimuli were presented in an oddball paradigm (adapted from Guiraud et al., 2011). Stimuli were two tones, each of 100ms in duration with a rise of fall time of 5ms, and an inter-stimulus interval of 700ms. The infrequently presented deviant tone (8% probability) consisted of a 1200Hz tone. The frequently presented standard tone (92% probability) consisted of a 1000Hz tone. All tones were presented at 70dB SPL. Stimuli were presented randomly, with the restriction that at least three standard tones followed each deviant tone.

5.3.3 Procedure

Participants were seated within a sound attenuated EEG suite (see Section 2.4, Chapter 2 for details), where sounds were presented through two speakers, located

approximately 1m in front of the participant. Participants watched two soundless movies whilst the auditory stimuli were presented, and were given a short break between the two. To reduce movement artefact, a researcher sat with the participant for the duration of the paradigm to ensure they were still, relaxed and attending to the videos.

5.3.4 EEG Recording and Pre-processing

See Sections 2.4 and 2.5, Chapter 2, for details of EEG data acquisition and general pre-processing.

5.3.5 ERP Analysis

Epochs of 600ms, including a -100ms prestimulus period, were extracted for each stimulus. The average amount of trials per condition was 68 (SD=12.85) for standard stimuli and 69 (SD=12.64) for deviant stimuli. Epochs were separately averaged for standard and deviant stimuli. Baseline correction was performed using a 100ms prestimulus reference period. Electrodes of interest were selected based on prior literature (Banaschewski & Brandeis, 2007; Dunn et al., 2008; Gomot et al., 2000) and confirmed with visual inspection (see Figure 15). Amplitudes were extracted from a cluster of five electrodes (4, 5, 11, 12, 19) corresponding to the Fz area, and a cluster of five electrodes (7, Cz, 31, 80, 106) corresponding to the Cz area (see Figure 16) to be directly comparable with previous literature. However, the isocontour map (Figure 15) also highlighted that the negative deflection in response to deviant stimuli appeared most prominent over the left hemisphere in the current sample. Thus, amplitudes were also extracted from a cluster corresponding to F3 (20, 24, 28, 29). Additional analysis for this cluster is presented in Appendix 3, but in short, no significant associations were found. Peak amplitude of the most prominent negative deflection was measured in each participant in a 80–200ms latency range,

consistent with previous literature (Näätänen & Alho, 1995). Amplitudes for all electrodes in a cluster were averaged. See Figure 16 for grand averages of response to deviant and standard tones.

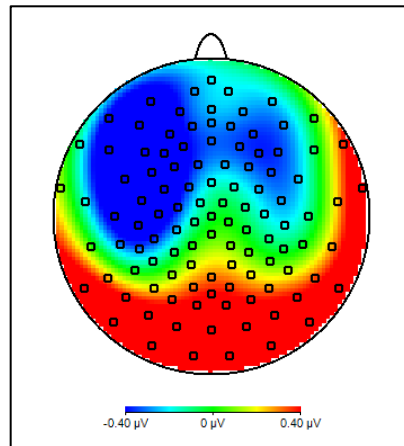


Figure 15. Isocontour Maps Derived from the Grand Average Response to Deviant Stimuli at 80-200ms

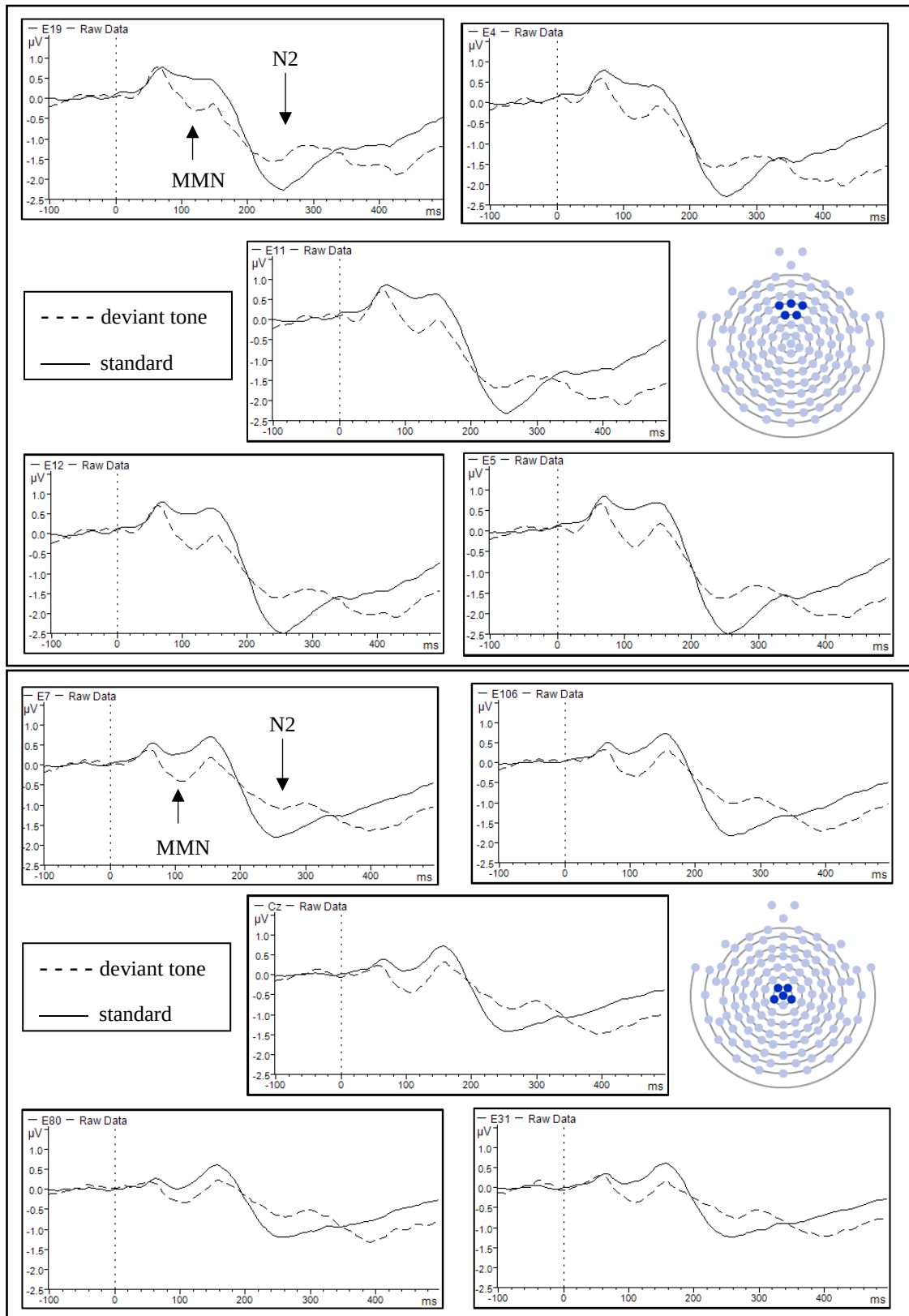


Figure 16. Grand Average of Waveforms to Standard and Deviant Stimuli at Fz (top) and Cz (bottom)

For MMN analysis, responses to all standards was averaged. For analysis of habituation, responses to the first (S1), second (S2) and third (S3) standard tone after a deviant tone were averaged separately. From inspection of the grand averages (Figure 16) it was clear that the ERP response to stimuli was characterised by two negative deflections, one early and one late. This second negative deflection was confirmed by inspection of the isocontour map derived from the grand average at 200-300ms (Figure 17). Thus, habituation analyses were conducted at the early N1 component (using the same latency window as was used in the MMN analysis; 80-200ms), but also the later negative-going component (N2; 210-300ms). Peak amplitude of the most prominent negative deflection in these latency ranges for S1, S2 and S3 was measured in each participant.

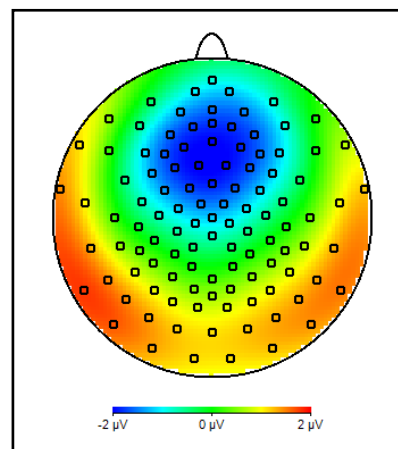


Figure 17. Isocontour Maps Derived from the Grand Average Response to Standard Stimuli at 200-300ms

5.3.6 Analytic Strategy

The general analytic strategy is outlined in Section 2.6, Chapter 2. To ensure that the paradigm had reliably elicited the MMN component, amplitudes to deviant and standard tones at Fz and Cz were compared using planned pairwise comparisons. MMN amplitude was measured as the difference waveform obtained by subtracting response to the deviant tones from response to the standard tones. Higher MMN amplitude indicated a greater response to the deviant, as compared to the standard, stimuli. A habituation index was measured as the difference waveform obtained by subtracting response to S1 from response to S3. A higher value indicates a greater decrease in ERP response between S1 and S3 (i.e. greater habituation). Where significant associations were found with the habituation index, planned follow up analyses looked at responses to each standard tone (S1, S2, S3) separately to clarify whether response to a specific standard tone was driving effects. As the S1 and S3 variables were negatively skewed, they were square root transformed. One outlier was identified in the MMN difference wave data, and two outliers in the habituation index data. Analyses were conducted including and then excluding outliers (see Section 2.6, Chapter 2 for details).

Primary analyses used multivariate regression to test for an association between ERP response and SDQ subscales of emotional problems, ADHD symptoms and conduct problems, along with the ARI irritability scale. Secondary analyses using regression to test for an association between ERP response and DBC total behaviour problem score. Where trend or significant associations were found, results were first adjusted for age, sex and full scale IQ, and then for age, sex, IQ and ASD severity, as measured by the ADOS calibrated severity score. Two separate sensitivity analyses

were conducted, first excluding those using medication known to affect brain functioning ($n=5$) and second excluding those with epilepsy ($n=2$).

5.4 Results

5.4.1 MMN

As highlighted by the grand average (Figure 16), the ERP response to deviant tones was significantly greater than the response to the standard tones at both Fz (mean standard amplitude = -0.21 , $SD=1.03$, range -2.63 - 1.97 ; mean deviant amplitude = -1.00 , $SD=-1.28$, range -3.67 - 1.53 ; $t(42)=4.67$, $p<0.01$) and Cz (mean standard amplitude = -0.39 , $SD=0.78$, range -3.40 - 1.27 ; mean deviant amplitude = -0.93 , $SD=-1.07$, range -3.71 - 1.11 ; $t(42)=3.90$, $p<0.01$), confirming the presence of the MMN.

At Fz, no association was found between MMN amplitude and behaviour ($ps=0.24$ - 0.59) and this pattern remained when outliers were excluded ($ps=0.25$ - 0.66). At Cz, no associations were found ($ps=0.41$ - 0.97), however when outliers were excluded a significant association was found between MMN amplitude and DBC total behaviour problem score ($\beta=9.51$, $p<0.05$), and this association remained at a trend level when controlling for age, sex and IQ ($\beta=9.40$, $p=0.07$), but became nonsignificant when controlling for age, sex, IQ and ASD severity ($\beta=8.77$, $p=0.11$). The association remained significant in sensitivity analyses, first excluding those using medication ($\beta=10.10$, $p<0.05$), and then excluding participants with epilepsy ($\beta=10.39$, $p<0.05$). Figure 18 depicts the association between MMN amplitude and DBC total behaviour problem scores, in that those with greater MMN amplitude had higher DBC total behaviour problem scores. This association was not specifically driven by response to either standard or deviant ones as neither was significantly

associated with DBC total behaviour problem score ($p=0.18$ and $p=0.78$ respectively).

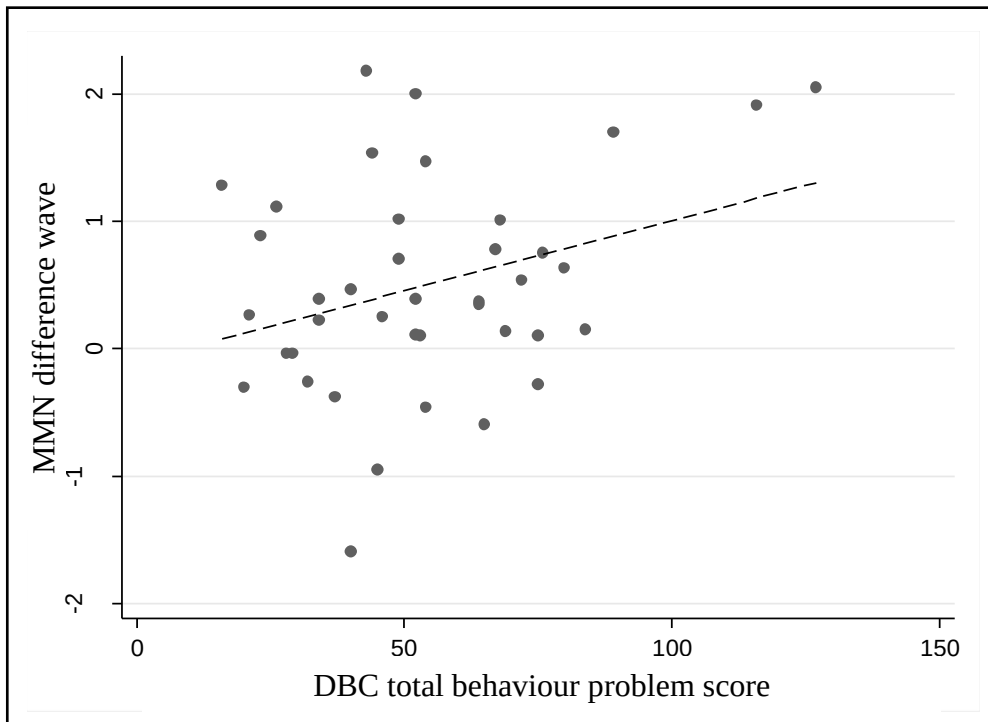


Figure 18. Association between Behaviour Problems and MMN Difference Wave

5.4.2 Habituation

At Fz, no associations were found between the habituation index, when measured at either the early or the late component, and behaviour ($ps=0.20-0.85$), and this pattern remained when outliers were excluded ($ps=0.19-0.99$).

At Cz, a higher score on the SDQ emotional problems subscale was associated with a greater habituation index at the early N1 component ($\beta=0.86$, $p<0.05$) and this remained at a trend with outliers excluded ($\beta=0.70$, $p=0.09$). The association remained when controlling for age, sex and IQ ($\beta=0.96$, $p<0.05$) and controlling for age, sex, IQ and ASD severity ($\beta=0.96$, $p<0.05$), and in sensitivity analyses excluding participants using medication ($\beta=0.88$, $p<0.05$), and excluding participants

with epilepsy ($\beta=0.84$, $p<0.05$). No associations were found with the other outcome measures ($ps=0.69-0.79$), and this pattern remained when outliers were excluded ($ps=0.33-0.99$).

At the later N2 component, the SDQ emotional problems subscale was also associated with the habituation index at Cz ($\beta=0.69$, $p=0.05$), and this became fully significant when outliers were excluded ($\beta=1.47$, $p<0.01$), and this association remained when controlling for age, sex and IQ ($\beta=1.77$, $p<0.01$) and controlling for age, sex, IQ and ASD severity ($\beta=1.80$, $p<0.01$), and in sensitivity analyses excluding participants using medication ($\beta=1.53$, $p<0.01$), and excluding participants with epilepsy ($\beta=1.49$, $p<0.01$). No associations were found with the other outcome measures ($ps=0.28-0.88$) and this pattern remained when outliers were excluded ($ps=0.16-0.55$).

Given that the directionality of association between habituation and anxiety was not what was expected (hypotheses predicted *decreased* habituation would be associated with greater anxiety), exploratory analyses were conducted with other measures of anxiety that were available to clarify the nature of the association. These were conducted at the N2 component, as this was where the effect appeared to be strongest. The first was the DBC anxiety subscale, where a significant association was found ($\beta=1.04$, $p<0.05$), and remained at a trend when adjusting for age, sex and IQ ($\beta=0.89$, $p=0.08$), and age, sex, IQ and ASD severity ($\beta=0.95$, $p=0.07$), and was significant excluding participants using medication ($\beta=1.03$, $p<0.05$), and excluding participants with epilepsy ($\beta=1.04$, $p<0.05$). The next was the SCAS total, where again a significant association was found ($\beta=9.01$, $p<0.01$), remained when adjusting for age, sex and IQ ($\beta=10.64$, $p<0.01$), and age, sex, IQ and ASD severity ($\beta=10.71$,

$p<0.01$), and when excluding participants using medication ($\beta=9.36$, $p<0.01$), and excluding participants with epilepsy ($\beta=9.12$, $p<0.01$).

5.4.3 Response to S1, S2, S3

To aid in the interpretation of finding of more emotional problems with greater habituation, analyses next tested how SDQ emotional problems were associated with N2 response to S1, S2 and S3. There was a selective association with S1, in that higher levels of SDQ emotional problems were associated with greater S1 amplitude ($\beta=2.09$, $p<0.05$), were not associated with the S2 ($p=0.78$) or S3 ($p=0.32$) (see Figure 19). This selective association remained significant when controlling for age, sex and IQ ($\beta=2.60$, $p<0.05$), controlling for age, sex, IQ and ASD severity ($\beta=2.65$, $p<0.05$), and when excluding those using medication ($\beta=2.06$, $p<0.05$), and participants with epilepsy ($\beta=1.88$, $p<0.05$). The same selective association with S1 was found using the SCAS ($\beta=17.53$, $p<0.01$). No association was found with the DBC anxiety subscale ($p=0.79$). Thus, although analyses began with a focus on habituation, results suggest that the habituation-anxiety association was likely driven by a selective association between anxiety symptoms and the first standard stimulus presented after the deviant stimulus.

Finally, to better understand the association between N2 response to S1 and anxiety, exploratory *post-hoc* analyses selected one item from the SCQ which related to repetitive behaviours. The item was ‘Does she/he ever say the same thing over and over again in exactly the same way or insist that you say the same thing over and over again?’ Those who endorsed this item had significantly higher N2 amplitude to S1 than those who did not endorse the item (mean amplitude of those who endorsed = -1.96, SD=1.29, range -4.41- -0.03; mean amplitude of those who did not endorse = -1.19, SD=1.04, range -3.18- -0.03; $t(39)=2.11$, $p<0.05$). To check this result was not

due to a general association with ASD severity, a similar analysis was performed using the total score of 17 items that load onto the 'social impairment' factor on the SCQ (based on factor analysis in Berument et al., 1999). No association between N2 response to S1 and severity of social impairment was found ($p=0.16$).

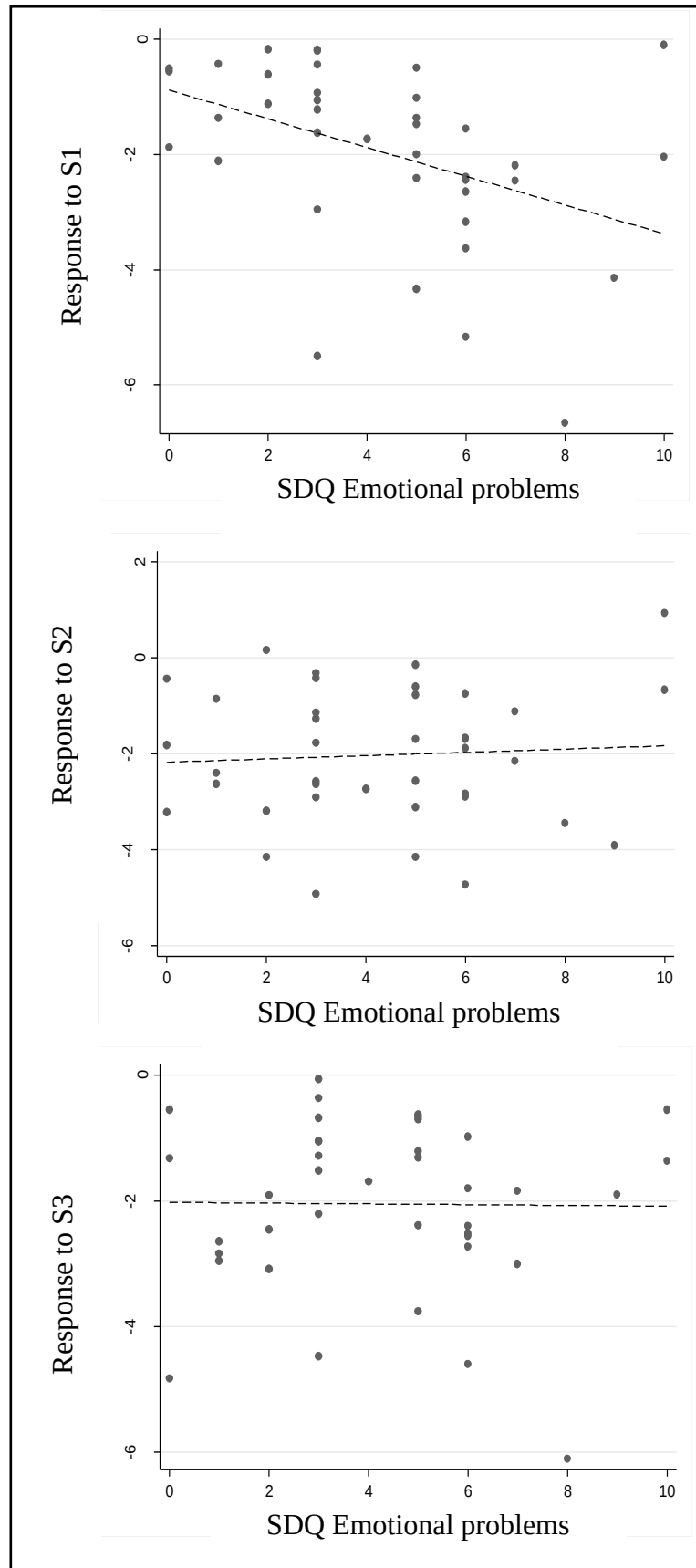


Figure 19. Association between Emotional Problems and N2 Amplitude to the First, Second and Third Standard Stimuli after a Deviant Stimuli.

5.5 Discussion

This study investigated whether neural indices of PP were associated with emotional and behavioural problems in young people with ASD. Results showed that increased sensitivity to deviant stimuli was associated with increased behaviour problems, whereas heightened response to standard stimuli following a deviant stimuli was associated with increased emotional problems, and this appeared to be mainly driven by anxiety symptoms.

The current finding of increased sensitivity to deviant stimuli, as measured by MMN amplitude, being associated with higher levels of challenging behaviours, as rated by the DBC total behaviour problem score, builds on prior work that found comparable relationships in ASD populations using care-giver ratings of perceptual sensitivity (Ashburner et al., 2008; A. Baker et al., 2008; Tseng et al., 2011). In the current study, the association remained at a trend when adjusting for age, sex and IQ, and in sensitivity analyses excluding those taking psychotropic medication and those with a diagnosis of epilepsy. However, the association became non-significant when ASD severity was also accounted for, in addition to age, sex and IQ. This is most likely to be due to ASD severity and PP atypicalities, as indexed by a greater MMN, being in some way related (and indeed they were found to be significantly correlated; $r=0.30$). This is unsurprising given that PP atypicalities are part of the diagnostic criteria for ASD. It is not possible to know from cross-sectional data, as is used in the current study, whether higher ASD severity leads to more atypical PP, or vice versa, and how these relate to challenging behaviours. This is a question that should be answered using longitudinal samples to track development and change over time.

Additionally, results showed that the association with MMN amplitude was not driven by response to either the standard or the deviant in isolation, but the relative

difference in neural response between the two. Given that the MMN has been shown to correlate with individual discrimination ability (Amenedo & Escera, 2000; Kujala et al., 2001; Näätänen & Alho, 1995), these results suggest that sensitivity to changes in perceptual input may be an important factor to consider in the aetiology of challenging behaviours in individuals with ASD. Additionally, given the paradigm was designed so participants were not necessarily attending to the auditory stimuli, this suggests that this hyper-sensitivity to perceptual changes may be present even if the stimuli are outside conscious awareness. This is in line with published clinical guidelines, that recommend taking into account individual sensory sensitivities when designing interventions for use with young people with ASD (National Institute for Clinical Excellence, August 2013). However, it should be held in mind that the DBC is a broad-brushstroke measure, and indexes a variety of types of challenging behaviours. From the association with the DBC total behaviour problem score it cannot be determined exactly what type of challenging behaviours hyper-sensitivity to perceptual input relates to, as prior literature has found associations to both a variety of difficulties (Ashburner et al., 2008; Lane et al., 2012; Mazurek et al., 2013; Pfeiffer et al., 2005; Tseng et al., 2011). This is addressed further in Chapter 6, where analyses consider different aspects of challenging behaviours separately.

Although analyses began with showing that increased habituation was associated with increased emotional problems, more in-depth analyses showed that this was likely to be driven by a selectively greater neural response to the first standard stimulus (S1) following a deviant stimulus. It should be stressed that these analyses were very exploratory and require replication, as the results were not hypothesised *a priori*. However, a comparable association was found using multiple measures of anxiety, suggesting this was unlikely to be due to a Type 1 error, and that the

association with the SDQ emotional problems subscale was likely to be driven by items indexing anxiety. Current findings build on prior work, which has mainly used questionnaire ratings to find associations between sensory over-responsivity and anxiety in individuals with ASD (D. Green et al., 2016; Lane et al., 2012; Lidstone et al., 2014; Mazurek et al., 2013; Pfeiffer et al., 2005), by using objective measures of perceptual sensitivity. Follow-up analyses indicated there also appeared to be an association between neural response to S1 and need for sameness, as rated by the SCQ item, ‘Does she/he ever say the same thing over and over again in exactly the same way or insist that you say the same thing over and over again?’. Thus, results are interpreted using the ‘intolerance of uncertainty’ framework (Boulter, Freeston, South, & Rodgers, 2014), which has been conceptualized as a tendency to react negatively to uncertain situations and events (Buhr & Dugas, 2002). Higher levels of parent and self-rated intolerance of uncertainty have been found in children and adolescents with ASD as compared to typically developing youth (Boulter et al., 2014; Chamberlain et al., 2013; Neil, Olsson, & Pellicano, 2016), and in both ASD and typically developing youth greater intolerance of uncertainty predicted higher levels of parent-rated anxiety, as measured by the SCAS (Boulter et al., 2014). In addition to the link between intolerance to uncertainty and anxiety, research has found that sensory sensitivity is related to both of these concepts. Wigham and colleagues used path modelling to demonstrate that intolerance of uncertainty and anxiety were mediating factors between sensory over-responsiveness and sameness behaviours in youth with ASD (Wigham, Rodgers, South, McConachie, & Freeston, 2015). Conversely, a recent study found that hypersensitivity mediated the association between anxiety and intolerance of uncertainty in children with ASD, whereas no such association was found in typically developing children (Black et al.,

2017). Others have found, when controlling for anxiety, intolerance of uncertainty was a significant predictor of sensory sensitivity in children with ASD (Neil et al., 2016). Thus, in the current study when uncertainty was introduced (by the deviant stimuli), this may have led to a heightened state of arousal in participants who were rated as being more anxious. This interpretation fits with existing literature, where temporally unpredictable auditory stimuli have been found to induce anxiety in mice and humans (Herry et al., 2007). The hyper-arousal induced by uncertainty was captured by the increased neural response to stimuli presented directly after the deviant (S1), but once it was recognised as one of the standard repeated stimuli, arousal decreased, thus explaining the lack of effect for S2 or S3. Given that increased N2 amplitude was also associated with a need for sameness, this suggests that those who showed a heightened neural response after an unpredictable perceptual input had a greater parent-rated need for sameness, again fitting within the intolerance of uncertainty framework.

There are currently two competing hypotheses regarding the mechanisms of sensory sensitivities, intolerance of uncertainty and anxiety. One proposes that sensory over-responsiveness leads to increased intolerance of uncertainty, and this in turn leads to increased anxiety and attempts to decrease uncertainty (Wigham et al., 2015). In support of this hypothesis, longitudinal studies find that sensory over-responsivity predicts the emergence of later anxiety symptoms in toddlers with ASD (S. Green et al., 2012). The alternative hypothesis proposes that difficulties dealing with uncertainty at a neural level may give rise to beliefs that uncertainty is intolerable and should be avoided. Desire to avoid this uncertainty thus leads to an increase in rumination and hyper-vigilance to sensory inputs, culminating in sensory sensitivities and high levels of anxiety (Neil et al., 2016). The current data cannot

make claims about the directionality of effects, or indeed if a different, unacknowledged factor was driving the association between these concepts, but instead complements results from questionnaire-based studies that find associations between sensory sensitivities, intolerance of uncertainty, anxiety and need for sameness by using more objective measures of PP. Furthermore, it should be noted that the current study did not measure intolerance of uncertainty, thus future work should specifically measure this construct, but also use longitudinal designs, to better disentangle causal pathways between sensory sensitivity, intolerance of uncertainty and anxiety, in individuals with ASD.

In terms how this fits with the hypo-priors theory discussed in the introductory section (Pellicano & Burr, 2012; Sinha et al., 2014), originally it was predicted the proposed decreased influence of previous experience in individuals with ASD would lead to less habituation in the current sample, and thus would be associated with greater emotional problems. Conversely, results actually found increased habituation was associated with emotional problems. However, this appeared to be driven by a selective association between anxiety and neural response to S1 (directly after the deviant stimuli) discussed above. This finding is interpreted with reference to the intolerance of uncertainty framework, suggesting the deviant stimuli induced a greater neural response to the following stimuli in those with a greater need for sameness (and higher intolerance for uncertainty). One could also interpret the results as highlighting that those who had a greater neural response to S1 had broader priors, as they could not use their prior experience to predict what was going to happen next, thus experienced every standard stimuli presented after the deviant stimuli as unpredictable, and therefore it elicited a heightened neural response each

time (despite the paradigm being designed so that after every deviant stimuli a standard stimuli would be presented, so was fully predictable in that respect).

5.5.1 Specific Strengths

The main strength of this chapter is the approach used. The PP paradigm did not require an overt response and thus allowed collection of EEG data from a larger sample of participants (IQ range of 29-129), including those with lower IQ who were unable to complete other tasks within the thesis. This allows one to draw stronger conclusions about ASD as a whole, rather than only individuals with ASD and higher IQ or those who are able to complete cognitive tasks, as is found in most studies of individuals with ASD.

5.5.2 Specific Limitations

The current study only measured one type of PP, and future research is needed to investigate if hyper-sensitivities in other modalities (e.g., visual, tactile) are also associated with emotional and behaviour problems in individuals with ASD.

5.5.3 Implications

Current results suggest that specific aspects of the neurocognitive profile associated with ASD should also be considered as potential drivers of co-occurring emotional and behaviour problems (although this requires empirical testing). Thus, a comprehensive sensory assessment could be helpful when planning interventions with individuals with ASD and challenging behaviours and anxiety symptoms. Although surveys have found sensory-based interventions are commonly used in individuals with ASD (V. Green et al., 2006), the specific targets of sensory interventions often differ, along with the methodologies used. Better characterization of PP atypicalities in individuals with ASD would guide the development of more

targeted interventions. The present results also suggest that a focus on intolerance of uncertainty may be helpful, especially as there is some preliminary evidence to suggest interventions targeting this concept may be efficacious in typically developing adolescents with anxiety disorders (Léger, Ladouceur, Dugas, & Freeston, 2003; Payne, Bolton, & Perrin, 2011).

6 Exploring the Neurocognitive Correlates of Externalising and Self-Injurious Behaviours in Young People with ASD

6.1 Summary

In Chapters 4 and 5, analyses tested whether impairments in specific cognitive domains were associated with challenging behaviours in young people with ASD. However, thus far in this thesis the different types of behaviour that fall under the heterogeneous category of challenging behaviours have not been considered separately. In the current study, the two domains of externalising behaviours and SIB were treated as two distinct, but correlated, outcome variables. Using a population-derived sample of 100 adolescents with ASD, parent-rated SIB and externalising behaviours were assessed alongside performance from a battery of neurocognitive tasks. Associations between the domains of ToM, ER, EF and PP, and SIB and externalising behaviours were estimated using data-driven SEM. Poorer ToM was associated with increased SIB, whereas poorer PP was associated with increased externalising behaviours. These associations remained when controlling for language ability. Results suggest that there may be specificity in the nature of cognition-behaviour associations within different types of challenging behaviours often exhibited by adolescents with ASD.

6.2 Introduction

As discussed in Chapter 1, Section 1.5, the umbrella term of challenging behaviours encompasses a wide range of phenomena (Emerson, 2001). Analyses thus far have used measures such as the DBC to capture challenging behaviours, and have found an association with sensitivity to changes in perceptual information, in that greater sensitivity was associated with higher DBC total behaviour problem score (Chapter 5). However, the DBC captures a range of emotional and behaviour problems, and so it is not possible to determine what types of challenging behaviours might be driving the aforementioned association with neurocognitive functioning. Thus, this chapter considers two types of challenging behaviours, which are often seen in individuals with ASD, separately. These are externalising behaviours, including conduct problems such as aggression and temper tantrums, along with severe non-compliance and refusal to meet demands (e.g. oppositionality), and SIB, which encapsulates a continuum of severity and topography. The two domains have been found to have differential correlates, in that SIB, but not externalising behaviours, has been reported to be associated with having lower verbal ability (Maskey et al., 2013), as well as having an IQ<70 (Carroll et al., 2014), supporting the importance of considering these two domains separately.

As discussed in Chapter 1, Section 1.11, a breadth of research has suggested that individuals with ASD are characterised by multiple difficulties in different cognitive domains (Brunsdon et al., 2015), the most notable being in ToM (Frith, 2012), ER (Uljarevic & Hamilton, 2012), EF (E. Hill, 2004) and PP (Pellicano & Burr, 2012). Research exploring how functioning in these domains relates to variability in challenging behaviours in ASD is sparse, and even more so when broken down into specific types of challenging behaviours.

6.2.1 Neurocognitive Correlates of Specific Domains of Challenging Behaviours

Analyses from a nationwide twin study found that the strongest predictor of child conduct problems was ASD symptoms, specifically in the domain of social interaction problems (Kerekes et al., 2014). Performance on computerised ToM tasks has been found to predict self-reported aggression in children with ASD (Pouw et al., 2013), and individuals with ASD and co-occurring aggressive behaviour have been found to exhibit greater parent-rated social and communication problems than those without aggressive behaviour (Kanne & Mazurek, 2011; Mazurek et al., 2013). Studies have found SIB in individuals with ASD and ID is also associated with poorer parent-rated social communication (Duerden et al., 2012), and socialization (Baghdadli et al., 2003).

Two studies have examined the link between ER and co-occurring behaviour problems in ASD, and used the same sample to find that difficulty identifying surprise was associated with the presence of additional severe mood problems (Simonoff et al., 2012), whereas that difficulty identifying fear was associated with co-occurring callous-unemotional traits (Carter Leno et al., 2015).

In terms of the association with EF, some studies have found aggressive behaviour in children with ASD to be associated with parent-rated inattention and hyperactivity (A. Hill et al., 2014) and inflexibility (Lawson et al., 2015; Visser et al., 2014). Similarly, SIB has been reported to be associated with significantly higher levels of impulsivity in individuals with ASD and ID (Richards et al., 2012).

In terms of PP, studies have found auditory hyper-sensitivity to be associated with externalising behaviours in individuals with ID (Lundqvist, 2013), and atypical

sensory processing was found to be the strongest single predictor of SIB in children with ASD (Duerden et al., 2012). Within a sample of individuals with fragile X syndrome, the presence of SIB was higher in individuals with a diagnosis of ASD, and also in those with sensory processing difficulties (Symons, Byiers, Raspa, Bishop, & Bailey, 2010).

6.2.2 SEM as a Method for Estimating Multiple Associations between Cognition and Behaviour

Prior literature, and results from Chapter 5, suggest that specific elements of cognition, which are thought to be impaired in individuals with ASD, may also be related to co-occurring challenging behaviours. Previous work has tested the role of a singular neurocognitive domain, whereas in the current chapter a comprehensive, data-driven approach was taken to exploring associations between four neurocognitive domains and two domains of behavioural outcomes. Current analyses use SEM, as it is an ideal statistical method for simultaneously estimating associations between multiple domains. One can build a measurement model, and a structural model using SEM. In the measurement model, SEM estimates the relationships between latent factors and observed variables. Latent factors are non-measured theoretical domains, where multiple measurable or observed indicators (e.g., test performance, questionnaire measures) are used to index the underlying latent domain. Here, latent factors were estimated for the neurocognitive domains of ToM, ER, EF, and PP, each underpinned by measured performance on relevant neurocognitive tasks. Exploratory and confirmation factor analyses are then used to test the validity of these measurement models. Once one is satisfied with the specified measurement model (the structure of observed variables that underpin one latent factor), one can also build a structural model, where associations between

multiple latent variables are estimated using independent regressions, allowing for exploration of how different latent domains relate to each other. Both measurement and structural models are assessed using indices of model fit, which are indicators of how well the model specified fits the actual data.

6.2.3 Aims

The current chapter tests how latent variables tapping specific neurocognitive domains (ToM, ER, EF, PP) relates to two domains of challenging behaviours (externalising behaviours and SIB) within a population-derived sample of adolescents with ASD. Current analyses use a different sample of adolescents with ASD to the one used in Chapters 3, 4 and 5, allowing for cross-sample comparisons. Where comparable associations between cognition and challenging behaviours are found using different samples and measures, this allows for stronger conclusions to be drawn regarding the generalisability of findings. Where discrepancies are found, this can highlight measure or sample-specific effects, and prompt further questions about unaccounted influences on results. In general, it was predicted that worse performance in neurocognitive functioning would be associated with higher levels of both externalising behaviour and SIB, however analyses were largely exploratory and data-driven, rather than relying on specific hypotheses.

6.3 Methods

6.3.1 Sample

A total of 100 adolescents with ASD, who had an $IQ \geq 50$, were assessed on the relevant measures as part of the Special Needs and Autism Project (SNAP) cohort (Baird et al., 2006). Of the participants, 54 met consensus criteria for childhood autism and 46 for other pervasive developmental disorders (ICD-10). The sample

consisted of 91 males and 9 females, with a mean age of 15.48 years ($SD = 0.46$; range 14.7–16.8), and a mean full scale IQ of 84.31 ($SD = 18.03$; range 50–119). This cohort, initially assessed as part of an autism prevalence study, was drawn from 56 946 children living in the South Thames area of the UK and born between July 1990 and December 1991. The cohort was assessed at mean ages of 12 and 16 years. Assessment at 16 years focused on the cognitive phenotype of ASD and only those who had estimated $IQ \geq 50$ at 12 years were included (Charman, Jones, et al., 2011). All received a consensus clinical ICD-10 ASD diagnosis, made using the ADI-R (Lord, Rutter, & Couteur, 1994) and ADOS-G (Lord et al., 2000), which also give an index of ASD severity, at age 12 years. Further details of these diagnostic instruments is available in Section 2.2.1, Chapter 2. Written informed consent was obtained from all parents and at age 16 years by the participant if their level of understanding was sufficient. The study was approved by the South East Multicentre Research Ethics Committee (REC) (05/MRE01/67).

6.3.2 Questionnaires

All of questionnaires and assessments listed below were administered to parents when participants were aged 16 years, unless stated otherwise. Testing took place in a quiet testing area and tasks were presented in one of four carefully selected orders. The battery was completed over two days of testing, with a median gap of 21 days (range 1-259 days) between sessions. Seventeen participants required a final day of testing to complete the battery.

The Profile of Neuropsychiatric Symptoms (PONS; Santosh, Gringras, Baird, Fiori, & Sala, 2015) is a 62-item questionnaire that assesses the severity and impact of 31 symptoms commonly reported in children and young people with

neurodevelopmental disorders. For each symptom, a brief definition is given, and the respondent is asked to report the overall frequency of that symptom (0–5) and its impact on everyday life (0–5). The two ratings are combined and averaged to provide an overall score for each symptom (0–5). Current analyses include items related to: oppositionality, aggression, explosive rage, antisocial behaviour, labile mood and self-injury.

The Repetitive Behavior Scale-Revised (RBS-R; Bodfish et al., 2000) is a 43-item questionnaire that assesses repetitive behaviours, and consists of six subscales (stereotyped behaviour, SIB, compulsive behaviour, routine behaviour, sameness behaviour and restricted behaviour). Respondents rate each behaviour from not occurring, to occurring and being a severe problem (0–3). Current analyses focused on items from the SIB subscale: hits body, hits self on surface, hits self with object, bites self, pulls at skin, scratches self, inserts items into body and picks skin.

Copies of the key outcome measures (PONS and RBS-R) can be found in Appendix 4.

The Social Responsiveness Scale (SRS; Constantino & Gruber, 2005) is a 65-item questionnaire that assesses social abilities in a six-month time frame. Respondents rate each behaviour from not true, sometimes true, often true to almost always true (0–4). Prior work has found the total score to be moderately correlated with the ADI-R and ADOS-G total scores ($r=0.48-0.59$), and has high sensitivity (0.78) and moderate specificity (0.67) (Charman et al., 2007). Current analyses used the total score. The SRS was administered, along with the other assessments of ASD severity outlined above in Section 6.3.1, when participants were aged 12 years.

6.3.3 Assessments

6.3.3.1 Receptive Language Ability

The Test for Reception of Grammar – Electronic Version (TROG-E; Bishop, 2005) was used to estimate standard scores for receptive grammar. The TROG-E requires participants to select pictures that correspond to sentences of increasing grammatical complexity. The TROG-E provides norms for individuals aged four years to adult.

6.3.4 Neurocognitive Measures

6.3.4.1 ToM

The Strange Stories task (Happé, 1994) was used as a general measure of mental state understanding. Participants were read a series of stories, which were also available in front of them and accompanied by an appropriate illustration. At the end of each story, participants were asked a question about the text. Correct answers demonstrated an understanding of the characters thoughts, feelings and intentions. The outcome variable was the average score across the four ToM stories.

The Frith–Happé animations (Abell, Happé, & Frith, 2000) consist of a series of silent videos of two-dimensional animations, requiring the participant to understand intentionality behind the moving shapes. Four animations depicted ToM interactions and two goal-directed interactions. The outcome variable was the average intentionality score, based on degree of mental state attribution for the four ToM trials. Data from this task have previously been reported by SNAP (C. Jones, Swettenham, et al., 2011).

False Belief Composite Score. A composite score was generated based on performance on two false belief tasks (Hughes et al., 2000; Sullivan, Zaitchik, & Tager-Flusberg, 1994). The first was the ‘combined false belief task’, which is a

combination of first- and second-order false belief tasks based on previous tasks measuring false belief understanding. The second task was the ‘second order false belief task’, which had greater verbal demands than the combined task. A total score of performance on the combined and second order false belief tasks was used, with points awarded for correctly passing and justifying each false belief question.

The Reading the Mind in the Eyes task (Baron-Cohen, Wheelwright, Spong, Scahill, & Lawson, 2001). The eyes test requires the participants to understand mental/emotional state “concepts” and match them to expression of eyes from black and white photos. Participants were shown black and white photographs of just the eye region of the face of 28 people. Participants were asked to pick which of four inner state words best described what the person in the photo is thinking or feeling. A point was awarded for each correct trial.

The Penny-Hiding task (Baron-Cohen, 1992) was used as a naturalistic and non-verbal measure of ToM, specifically indexing the participant’s ability to deceive the experimenter. The participant was given six trials of hiding the penny. Responses are coded for the type of deception errors made, with a total score calculated. It was possible to display more than one error on a trial. Given the distribution of the scores this variable was re-coded as ordinal (score range 0/1= ‘1’, 2/3= ‘2’, 4/5= ‘3’, ≥6= ‘4’).

6.3.4.2 ER

The verbal vocal expressions of emotion task (Sauter, 2006; Sauter, Eisner, Calder, & Scott, 2010), played recordings of actors expressing each of the emotions verbally whilst reading out neutral content (three-digit numbers). The total number of correct responses for each of the six emotions (happy, sad, fear, surprise, anger, disgust)

served as a measure of ER ability. Data from this task have previously been reported in the SNAP cohort (C. Jones, Pickles, et al., 2011).

6.3.4.3 EF

The Card Sort task was used as a measure of cognitive flexibility and response reversal adapted from a child-friendly version of the Wisconsin Card Sorting Task (Tregay, Gilmour, & Charman, 2009). Participants had to correctly sort cards to one of three alternative sets across three trials, with the correct set varying in each trial. The key variable was the number of incorrect responses made across all three trials.

The adapted Trail Making task was included as a measure of attentional switching and response reversal (Reitan & Wolfson, 1985). Participants were asked to ‘join the dots’ in numerical order, then, in a second trial, in alphabetical order, followed by a third trial switching between numbers and letters. The difference between the time taken on the first trial and the third trial comprised a measure of switching ability.

The Opposite Worlds task was taken from the Test of Everyday Attention for Children (Manly et al., 2001) and was included as a measure of interference inhibition. The task included a “same world” trial, where participants read out a series of the numbers 1 and 2; and the “opposite world” trial, where participants had to say the opposite to the number they were reading. Two same world trials and two opposite world trials were presented. The time taken to complete each world was recorded in seconds. The outcome variable was the subtraction of the mean same worlds completion time from the mean opposite worlds completion time.

The Score! Task was also taken from the Test of Everyday Attention for Children (Manly et al., 2001) and was included as a measure of sustained attention.

Participants have to keep a count of the number of ‘scoring’ sounds they hear on a tape across 10 trials. A trial was coded as correct if the correct amount of sounds was identified at the end of the trial. Given ceiling effects in the scores, the variable was re-coded as ordinal (0 incorrect trials = ‘1’, 1/4 incorrect trials= ‘2’, 5/10 incorrect trials= ‘3’). Data from the majority of the EF tasks, along with ToM tasks, have previously been reported in the SNAP cohort (Carter Leno et al., 2015; Hollocks et al., 2014).

6.3.4.4 PP

Auditory Processing

Auditory processing was assessed using the “Dinosaur” software programme created by Dorothy Bishop (Oxford University). In each dinosaur pairing, the participant was presented with one ‘standard’ stimulus, which did not change across the particular task, and a probe stimulus that varied. Participants had to decide which dinosaur made a 1) louder (intensity discrimination) or 2) longer (duration discrimination) sound, respectively. A detection threshold was established using a two-down/one-up (after two correct trials the perceptible difference between the two stimuli reduces; after one incorrect trial the perceptible difference between the two stimuli is increased) adaptive staircase procedure, where the task was made easier/harder dependent on on-going participant performance. This was used to determine the threshold at which the participant was correct on 75% of trials. The task was terminated after 6 reversals (changes in direction in the two-down/one-up procedure) or after 40 trials, and the final threshold score was the mean threshold value from the fourth reversal.

Visual Processing

Three tasks were presented (motion coherence, form-from-motion, and biological motion), and each task was preceded by a five trial practice, where feedback and discussion of their decision ensured that all participants understood the task. Similar to auditory tasks, a detection threshold was established using a two-down/one-up adaptive staircase procedure, where the task was made easier/harder depending on on-going performance. The tasks were terminated after seven reversals of the staircase. The threshold score was calculated as the average signal-to-noise ratio ($\text{signal}/(\text{signal} + \text{noise})$) of the seven reversals.

Motion coherence task: This task established a threshold for the ability to detect coherent motion. Both panels contained randomly positioned white dots. Dots moved with translational motion and were either signal elements that moved coherently (in the same direction) or random noise. The participant had to select the panel that contained the dots that “moved the same way”.

Form-from-motion task: This task establishes a threshold for the ability to use motion cues to detect form. In one panel a rectangle was positioned vertically and in the other it was positioned horizontally; the location of the rectangles within the panels was assigned randomly. The participant was shown an example of the target shape and asked “Where is the shape?”.

Biological motion task: This task establishes a threshold for the ability to detect biological motion. One display panel depicted a centrally positioned walker. The other panel presented a spatially identical but temporally scrambled version of the walker point light display, with the trajectories of the dots played temporally out of phase with each other (e.g. instead of the dots representing a foot and knee moving

forward together, they now might move in the opposite direction). The participant had to point to the panel that contained the “man walking”. In both the auditory and visual perception tasks, a higher final threshold indicated a greater amount of information required to detect the target stimuli, and thus worse performance. Data from these tasks have previously been reported in the SNAP cohort (C. Jones et al., 2009; C. Jones, Swettenham, et al., 2011).

6.3.5 Statistical Analyses

All variables were assessed for normality, and where necessary transformed using Box-Cox transformation (see Table 8). Eight neurocognitive variables were treated as ordinal variables due to extreme skew (Score!, Penny Hiding task, all ER variables) and all SIB items were treated as binary (present/absent) due to low incidence of individual SIBs. For all neurocognitive variables, a higher score was indicative of worse performance.

Table 8. Mean Raw Scores on Neurocognitive Measures

Latent Variable	Task (n of observations)	Mean (SD; range)
ToM	Strange Stories (n=88)*	0.85 (0.53; 0-2)
	Frith–Happé animations (n=87)*	2.87 (0.94; 0-4.75)
	Combined False Belief Task (n=99)*	4.75 (2.42; 0-8)
	Reading the Mind in the Eyes (n=94)*	17.02 (4.44; 6-25)
	Penny Hiding (n=100)^ ordinal categories are as follows 0/1=1, 2/3=2, 4/5=3, ≥6=4	2.32 (2.75; 0-14)
ER	Happiness (n=96)*	3.56 (1.42; 0-5)
	Sadness (n=96)*	4.23 (1.17; 0-5)
	Fear (n=96)*	2.73 (1.69; 0-5)
	Surprise (n=96)*	3.96 (1.23; 0-5)
	Anger (n=96)*	3.38 (1.72; 0-5)
	Disgust (n=96)*	2.46 (1.55; 0-5)
EF	Card Sort (n=98) +	7.24 (6.62; 1-36)
	Trail Making (n=88) +	63.39 (44.00; 13.37-257.09)
	Opposite Worlds (n=98) +	8.37 (7.49; -3.71-47.42)
	Score!(n=96)* ^ ordinal categories are as follows 0/5=3, 6/9=2, 10=1	7.68 (2.51; 0-10)
PP	Auditory Intensity Threshold (n=92) +	9.40 (6.56; 1-27.75)
	Auditory Duration Threshold (n=93) +	7.67 (6.70; 1-28.75)
	Visual Form Threshold (n=91) +	0.29 (0.17; 0.07-0.88)
	Visual Motion Threshold (n=89) +	0.19 (0.14; 0.30-.74)
	Visual Biological Motion Threshold (n=90) +	0.39 (0.14; 0.14-.83)

EF indicates executive functioning; ER emotion recognition; PP perceptual processing; ToM theory of mind *indicates reverse score used in SEM analysis; + transformed using Box-Cox; ^ transformed to ordinal data

6.3.5.1 SEM Analysis

Following the generation of outcome variables, SEM was used to estimate the association between performance on the four neurocognitive latent variables (ToM, ER, EF, and PP) and the scores on observed variables (SIB and externalising behaviours). Latent variable models for mixed data SEM were conducted in Mplus 7 (Muthén & Muthén, 2012). Given many of our variables were categorical the weighted least squares mean and variance adjusted (WLSMV) estimator was used. Model fit was examined using the relative χ^2 , the root mean square error of approximation (RMSEA), the comparative fit index (CFI), and the Tucker-Lewis fit index (TLI). A satisfactorily fitting model should have $RMSEA \leq 0.05$, CFI and TLI > 0.90 (Bentler, 1990; Tucker & Lewis, 1973).

6.3.5.2 Creation of Neurocognitive Variables

For all four neurocognitive latent variables (ToM, ER, EF, PP), EFA was also undertaken not to identify a new structure, for which a large sample would be required to be convincing, but to ensure that our data were not inconsistent with received wisdom, before assuming that structure held for the CFA. All individual neurocognitive latent variables had satisfactory fit.

6.3.5.3 Creation of Outcome Variables

Outcome variables of ‘externalising behaviours’ and ‘SIB’ were generated from parent-reported PONS and RBS items. From these measures relevant items were chosen that indexed either domain of behaviour. These were entered into an exploratory factor analysis (EFA) for mixed data, using maximum likelihood and promax rotation. The factor analysis was constrained to two factors. Both factors had

eigenvalues greater than 1 (externalising behaviours factor = 4.08, SIB factor = 1.89). All factor loadings were greater than 0.3, and all items loaded on the predicted factor (see Table 9) except the 'picks skin' item from the RBS-R. This item was therefore excluded from the outcome variable formation. A confirmatory factor analysis (CFA) indicated a two-factor solution in which latent variables were correlated ($r=0.48$), had good fit (relative $\chi^2=1.09$, RMSEA=0.03, CFA=0.98, TLI=0.97), and was better suited than a one-factor solution (relative $\chi^2=1.89$, RMSEA=0.10, CFA=0.74, TLI=0.69).

Table 9. Rotated Factor Loadings of Items from PONS and RBS-R onto Factors of Externalising and SIB

Item	Factor 1. Externalising Behaviours	Factor 2. SIB
PONS Oppositionality	0.77	-0.22
PONS Aggression	0.90	0.01
PONS Explosive Rage	0.88	0.01
PONS Antisocial Behaviour	0.42	-0.22
PONS Labile Mood	0.61	0.23
PONS Self Injury	0.37	0.40
RBS Hits Body	0.05	0.73
RBS Hits Self on Surface	0.02	0.75
RBS Hits Self with Object	-0.14	0.85
RBS Bites Self	0.04	0.47
RBS Pulls at Skin	0.07	0.47
RBS Scratches Self	0.16	0.41
RBS Inserts Items into Body	0.02	0.46

PONS indicates Profile of Neuropsychiatric Symptoms; RBS-R Repetitive Behavior Scale-Revised; SIB self-injurious behaviour.

Outcome variables were the sum of all items for each factor respectively. This approach was preferred to the EFA factor extracted scores to allow our results to be directly comparable with future samples. Observed sum-scores were used in the SEM model as measurements of the latent variables, as opposed to a full item to latent variable structure, to reduce the number of parameters the model had to estimate, given the modest sample size. The externalising behaviours variable was transformed to a normal distribution using Box-Cox transformation, and the SIB variable was treated as ordinal (scores ranged from 0-8).

6.3.5.4 Estimation of associations between neurocognitive latent variables and outcome variables

Step 1. Testing which neurocognitive latent variables were significantly associated with outcome variables. Missing data were imputed in Mplus, and results of SEM analyses were aggregated across 20 imputed data sets. All latent neurocognitive variables, SIB and externalising behaviours, were placed into a correlational model. Over a sequence of models the largest significant correlational pathway between the latent neurocognitive variables and the observed behavioural variables was set to a directional path and the least significant correlation/partial correlation was removed, until no further significant partial correlations remained. Correlations among latent neurocognitive variables and between externalising behaviour and SIB were retained in all models. To control for underlying ability that could impact on cognitive performance, in a similar manner to the rest of the work contained in this thesis, the effect of controlling for language on the final model was then examined.

Step 2. Testing the role of ASD severity in neurocognition-behaviour

associations. In order to explore the pathways between neurocognitive functioning, challenging behaviours and ASD severity, additional models were specified, where neurocognitive functioning predicted both challenging behaviours (direct path) and ASD severity, and ASD severity predicted challenging behaviours (indirect path). The neurocognitive domains entered into these models were those that remained significant from analyses in Step 1. An ASD severity latent factor was generated by the ADOS-G, ADI-R and SRS total scores.

Step 3. Testing the validity of significant associations using a binary variable of

SIB. Since the distribution of the SIB variable was highly skewed, the final model from Step 1 was re-created, treating SIB as a binary variable. This was performed only as a *post-hoc* analysis as treating the SIB variable as binary decreased power to detect significant associations with neurocognitive latent variables.

Step 4. Testing for mediation effects between highly correlated neurocognitive

domains. Follow up *post-hoc* mediation analyses were run using the *sem* and *estat effects* commands in Stata 14 to check the robustness of the final model, given the high correlation between latent neurocognitive variables meaning that performance in one neurocognitive domain could mediate performance in another domain. A mediation model proposes that one independent variable (here one neurocognitive variable) has an indirect effect on a dependent variable, by influencing another independent variable (the mediator variable, here a different neurocognitive variable), which in turn influences the dependent variable (here our observed outcomes of externalising behaviours and SIB). To test whether the indirect effect of latent variables was significant, factor scores for neurocognitive variables in the final

model were extracted using Mplus, and the coefficients of the indirect pathways were tested for significance.

The aim of these analyses was to identify which neurocognitive domains were associated with different symptoms of challenging behaviours. The data were modelled with paths in the direction from neurocognitive to symptom domains. Because the data are cross-sectional, results are unable to discriminate direction of effect, including reciprocal effects, between neurocognitive and symptom factors, and the direction of these paths should not be used to infer a causal association.

6.4 Results

For sample raw scores on neurocognitive tasks that made up the latent variables see Table 8. For sample raw scores from the PONS and RBS-R that made up the outcome variables of externalising behaviours and SIB, see Table 10.

Step 1. When all neurocognitive variables were placed in one model, correlations among latent neurocognitive variables were very strong (see Figure 20). The correlation between SIB and externalising behaviours was moderate ($r=0.38$). The strongest correlation between neurocognitive variables and behavioural outcomes was between ToM and SIB ($r=0.40$, $p<0.01$; Figure 20), whereas the correlation between ToM and externalising behaviours was the smallest and non-significant ($r=0.17$, $p=0.12$). The model was re-run, specifying the pathway from ToM to SIB as a predictive pathway, and removing the pathway from ToM to externalising behaviours, and allowing all remaining neurocognitive variables to correlate with behavioural outcomes.

Table 10. Sample Raw Scores of Items from the PONS and RBS-R Summed used to Form Outcome Variables

Item (n completed)	Mean Score (SD; Range)
PONS Oppositionality (n=94)	1.86 (1.40; 0-5)
PONS Aggression (n=92)	1.33 (1.33; 0-5)
PONS Explosive Rage (n=94)	1.10 (1.19; 0-5)
PONS Antisocial Behaviour (n=94)	0.22 (0.64; 0-5)
PONS Labile Mood (n=94)	0.91 (1.29; 0-5)
PONS Self Injury (n=94)	0.56 (1.12; 0-5)
RBS Hits Body (n=91)	0.41 (0.71; 0-3)
RBS Hits Self on Surface (n=89)	0.16 (0.50; 0-3)
RBS Hits Self with Object (n=91)	0.15 (0.47; 0-3)
RBS Bites Self (n=90)	0.11 (0.38; 0-3)
RBS Pulls at Skin (n=91)	0.14 (0.44; 0-3)
RBS Scratches Self (n=91)	0.18 (0.44; 0-3)
RBS Inserts Items into Body (n=92)	0.09 (0.41; 0-3)

PONS indicates Profile of Neuropsychiatric Symptoms; RBS-R Repetitive Behavior Scale-Revised. These data represent raw scores. All RBS items and the PONS self-injury item were treated as binary (present/absent) in analyses due to low incidence of SIB.

This model had acceptable fit (relative $\chi^2=1.22$, RMSEA=0.05, CFI=0.94, TLI=0.93). See Table 11 for a summary of all fit indices for the models outlined in Step 1. In this model, the next strongest correlation was between PP and externalising behaviours ($r=0.33$, $p<0.01$), whereas the correlation between PP and SIB was non-significant ($r=-0.05$, $p=.63$). Both the correlation between ER and SIB, and the correlation between EF and SIB, were non-significant ($r=-0.02$, $p=0.84$; $r=0.05$, $p=0.67$). The model was re-run, specifying in addition to the pathway from ToM to SIB, the pathway from PP to externalising behaviour as a predictive pathway, and removing the pathway from PP to SIB. The only correlations now

estimated were between ER and externalising behaviours, and between EF and externalising behaviours. This model showed acceptable fit (relative $\chi^2=1.19$, RMSEA=0.04, CFI=0.95, TLI=0.94). Both the correlation between ER and externalising behaviours ($r=0.03$), and the correlation between EF and externalising behaviours ($r=0.10$), were non-significant, therefore ER and EF were removed, giving the final model.

Table 11. Summary of Fit Indices for Models Outlined in Steps 1 and 3

	Summary	Relative χ^2	RMSEA	CFI	TLI
Model 1	Correlational model of all neurocognitive and behavioural outcomes.	1.20	0.05	0.95	0.94
Model 2	ToM set as predictor of SIB.	1.22	0.05	0.94	0.93
Model 3	In addition to ToM→SIB pathway, PP set as predictor of externalising behaviours.	1.19	0.04	0.95	0.94
Model 4	Final model with ToM→SIB and PP→externalising behaviours as predictive pathways. ER and EF variables removed.	1.35	0.06	0.92	0.90
Model 5	Adjust for language in Model 4.	1.64	0.08	0.87	0.84
Model 6	Adjust for IQ in Model 4.	2.08	0.10	0.81	0.75
Model 7	Treat SIB as binary variable in Model 4 (Step 3).	1.28	0.05	0.93	0.92

CFI indicates comparative fit index; EF executive functioning; ER emotion recognition; PP perceptual processing; RMSEA the root mean square error of approximation; SIB self-injurious behaviour; TLI Tucker-Lewis fit index; ToM theory of mind. A satisfactorily fitting model should have RMSEA $\leq$ 0.05, CFI and TLI >0.90.

The final model (Figure 21) continued to demonstrate acceptable model fit (relative $\chi^2=1.35$, RMSEA=0.06, CFI=0.92, TLI=0.90), and indicated a significant association between ToM and SIB ($\beta=0.37$, $p<0.01$) and between PP and externalising behaviours ($\beta=0.29$, $p<0.01$). Significant correlations were found between SIB and externalising behaviours ($r=0.33$, $p<0.01$), and between ToM and PP ($r=0.74$, $p<0.01$). Next, a model with directional paths from language ability to both neurocognitive domains and behavioural outcomes was investigated as an additional step, to explore effect of controlling for language on associations between neurocognitive domains and behaviour (Figure 22). Language was used a covariate here, as very strong correlations between IQ and neurocognitive variables ($r=-0.76$ - 0.81) meant that it was impossible to detect associations between neurocognitive variables and outcome measures. Including IQ in the model did not lead to an effective model, as indicated by poor model fit (see Table 11). With language included in the model the associations between neurocognitive domains and behaviour remained significant, along with the correlations between ToM and PP, and SIB and externalising behaviours (all $ps<0.05$). This model had poorer fit (relative $\chi^2=1.64$, RMSEA=0.08, CFI=0.87, TLI=0.84).

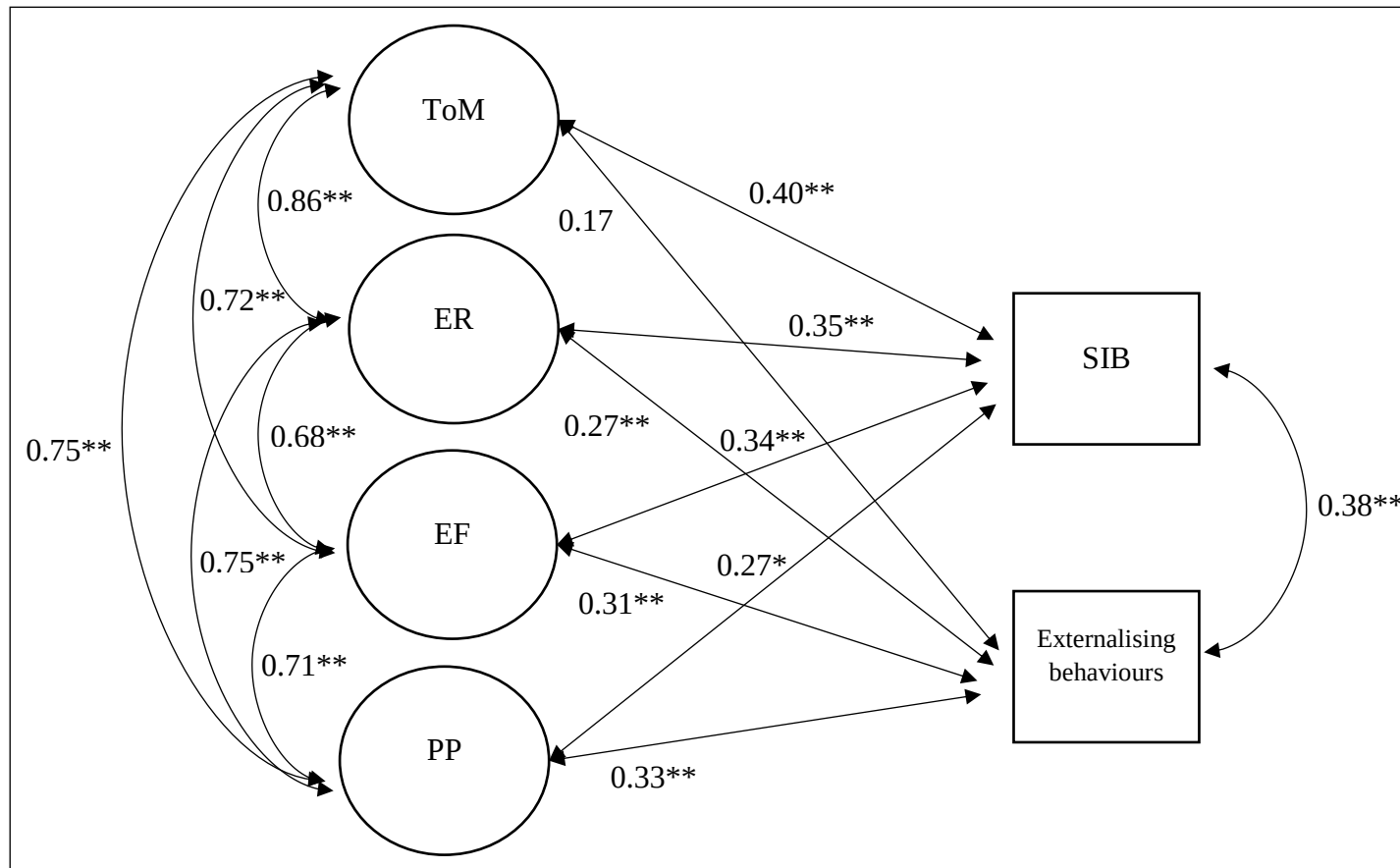


Figure 20. Initial Correlational Model of Associations between Neurocognitive Domains and Challenging Behaviours

EF indicates executive functioning; ER emotion recognition; PP perceptual processing; SIB self-injurious behaviour; ToM theory of mind. * $p < 0.05$, ** $p < 0.01$.

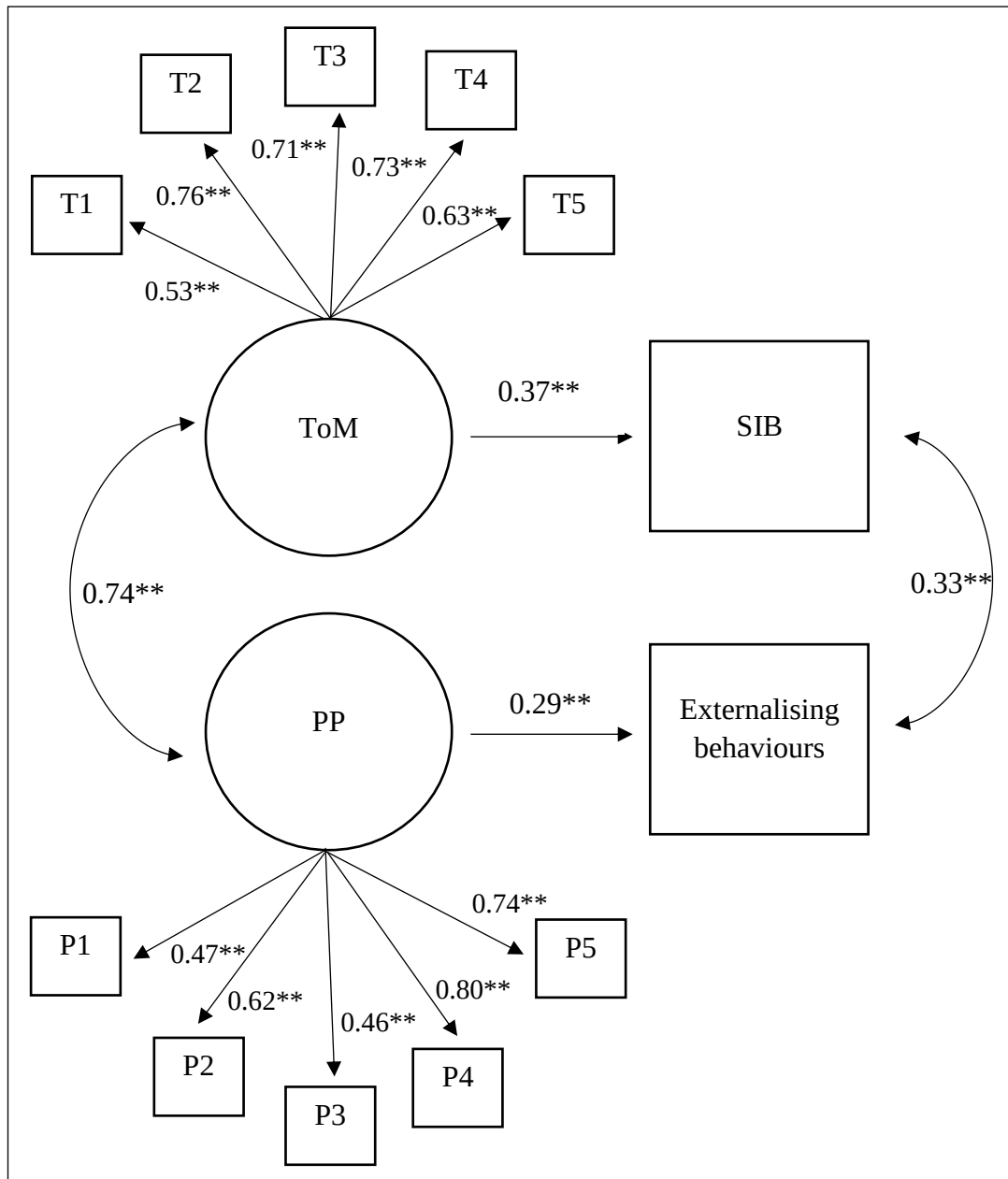


Figure 21. Final Model Depicting Relationship between Neurocognitive Domains and Aspects of Challenging Behaviours.

PP indicates perceptual processing; SIB self-injurious behaviour; ToM theory of mind. * $p < 0.05$, ** $p < 0.01$.

T1: Strange Stories task, T2: Frith–Happé animations task, T3: combined False Belief task, T4: Reading the Mind in the Eyes task, T5: Penny Hiding task, P1: Audio intensity discrimination, P2: Audio duration discrimination, P3: Visual form discrimination, P4: Visual motion discrimination, P5: Visual biological motion discrimination.

Step 2. Two separate models were specified to explore how ASD severity might account for the associations between neurocognitive domains of interest and behaviour identified in Step 1. In the first model, ToM was set to predict both ASD severity and SIB, and ASD severity set to predict SIB (structurally similar to the mediation models described in Step 4). Here, ToM significantly predicted ASD severity ($\beta=0.78, p<0.01$), however ASD severity did not predict SIB ($p=0.22$). The previously significant direct pathway from ToM to SIB was no longer significant in this model ($p=0.94$). This model was poorly fitting (relative $\chi^2=2.22$, RMSEA=0.11, CFI=0.82, TLI=0.75). In simple correlational analyses ToM and ASD severity were highly correlated ($r=0.78, p<0.01$). In the second model, PP was set to predict both ASD severity and externalising behaviours, and ASD severity set to predict externalising behaviours. Here, PP did not predict ASD severity ($p=0.67$), however ASD severity did predict externalising behaviours ($p<0.05$). The previously significant direct pathway from PP to externalising behaviours remained significant ($\beta=0.36, p<0.01$). Again, this model was poorly fitting (relative $\chi^2=2.07$, RMSEA=0.10, CFI=0.80, TLI=0.72). PP and ASD severity were not significantly correlated ($r=0.12, p=0.43$).

Step 3. Next analyses in Step 1 were re-run using the binary SIB variable. 48% of the sample (48/100) did not report any SIB, leaving 46% reporting some form of SIB, and six participants having missing data for all the SIB items that made up the summed score. A comparable pattern of model fit to that obtained in Step 1 was found (relative $\chi^2=1.28$, RMSEA=0.05, CFI=0.93, TLI=0.92; see Table 11) and the final pathways matched the final model obtained in Step 1, with a significant association between ToM and SIB ($\beta=0.35, p<0.05$) and between PP and externalising behaviours ($\beta=0.29, p<0.01$), and significant correlations between SIB

and externalising behaviours ($r=0.33, p<0.01$), and between ToM and PP ($r=0.74, p<0.01$).

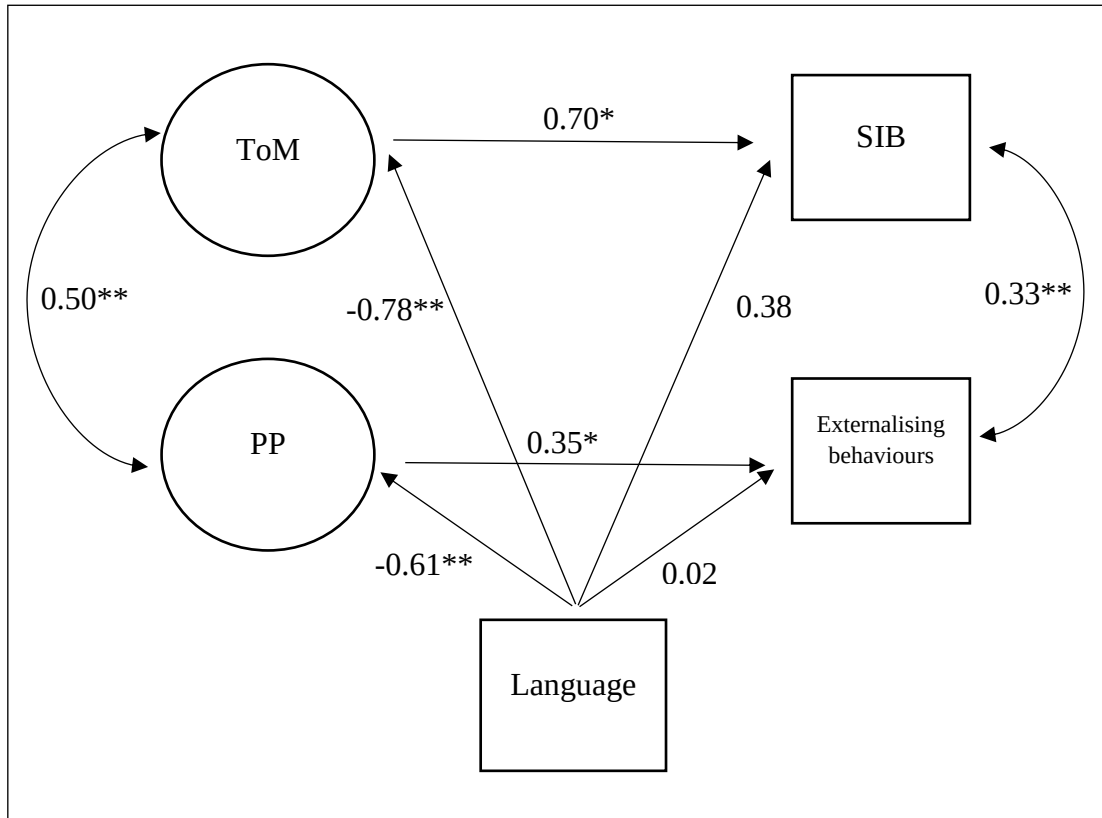


Figure 22. Model Depicting Associations between Neurocognitive Domains and Aspects of Challenging Behaviours Whilst Adjusting for Language

PP indicates perceptual processing; SIB self-injurious behaviour; ToM theory of mind. * $p<0.05$, ** $p<0.01$

Step 4. Given the high correlation between the ToM and PP latent variables, follow up *post-hoc* mediation analyses were conducted. Model 1 tested PP as a mediator of the association between ToM and SIB ($\text{ToM} \rightarrow \text{PP} \rightarrow \text{SIB}$). Model 2 tested ToM as a mediator of the association between PP and externalising behaviours ($\text{PP} \rightarrow \text{ToM} \rightarrow \text{externalising behaviours}$). In both models the indirect pathway coefficient was non-significant ($\beta=-0.14, p=0.68$ and $\beta=0.02, p=0.31$ for Model 1 and 2, respectively), indicating that mediation was an unlikely explanation of the observed associations.

6.5 Discussion

The current paper tested whether ability in specific neurocognitive domains was associated with externalising behaviours and SIB in a population-based sample of adolescents with ASD. Data-driven SEM, which allows for simultaneous estimation of the association between different domains of cognition and behaviour, indicated poorer PP was associated with increased externalising behaviours, whereas poorer ToM was associated with increased SIB. These associations between cognition and behaviour remained when language ability was controlled for. The association between ToM and SIB did not remain significant once ASD severity was included in the model as a predictor of SIB, unlike the association between PP and externalising behaviours, which remained significant. Non-significant mediation analyses suggested that, despite the high correlation between neurocognitive domains, there was some specificity within the reported associations between neurocognitive domains and aspects of challenging behaviours.

Caution should be taken in interpreting the current results due to a moderate sample size, and strong correlations between neurocognitive domains. However, results suggest there is some specificity in the associations found, as follow-up *post-hoc* mediation analyses found no indirect effect of PP upon SIB through mediation on ToM, or vice versa for ToM upon the association between externalising behaviours and PP. Additionally, within initial correlational analyses, the association between ToM and externalising behaviours was not significant. This is in contrast to prior research that reports an association between parent-reported social functioning and parent-reported aggressive behaviour (Kanne & Mazurek, 2011; Kerekes et al., 2014; Mazurek et al., 2013; Pouw et al., 2013). However, the majority of these studies, with the exception of Pouw and colleagues, did not specifically measure

ToM, instead measuring social functioning or communication, and relied on parent report. Therefore, it may be that some aspects of social functioning (e.g., communication) are related to externalising behaviours in ASD, whereas others, such as ToM, are not. Additionally, respondent differences could have contributed to conflicting results. A further point to consider is that previous studies have only measured aggressive behaviour, and did not specifically test the association between ToM and SIB. However, it should be held in mind that in the current study, reduced power in the context of highly correlated factors could lead to difficulties detecting pathways between cognition and behaviour.

The literature on neurocognitive correlates of SIB in ASD populations is limited; current analyses are the first to comprehensively test how ability in specific neurocognitive domains relates to SIB. Prior studies have found more general associations between parent-reported increased SIB and greater social difficulties and communication skills (Baghdadli et al., 2003; Duerden et al., 2012); our finding of poorer ToM performance being associated with increased SIB builds upon these and clarifies that challenging behaviours may not be solely due to difficulties in communication. Two interpretations of results are considered – that SIB may be a ‘distress signal’ in part due to negative emotions caused by lack of social understanding and difficulty communicating. An alternative interpretation is that reduced understanding of other’s thoughts and feelings may mean atypical behaviour is not moderated by social signals to the same degree, and thus SIB is not inhibited.

Analyses found that once ASD severity was entered into the model, the direct pathway from ToM to SIB became non-significant. In general, it is unsurprising that the selected areas of cognition and ASD severity were related in the current results,

as the cognition domains were originally selected due to their relevance to ASD. However, the nature of how these domains inter-relate has theoretical implications. If specific cognitive domains are thought of as causal factors, interventions for challenging behaviours should be targeted towards those domains. On the other hand, if these cognition-behaviour associations are merely indexing associations between overall ASD severity and behaviour, then interventions should focus on the ASD phenotype in general, rather than just specific domains of cognition such as ToM. The nature of the association between cognition, ASD severity and co-occurring emotional and behavioural problems can only be clarified with studies that use multiple measurements, at multiple time points. Finally, it also should be noted that ToM is a multi-faced construct, and effective ToM may rely on many abilities (e.g., language skills, abstract/conceptual thinking, and distinguishing self vs. other), thus, in addition to the questions raised in the preceding paragraph, future research should also attempt to disentangle what aspects of ToM might be driving the association with SIB.

The finding of poorer PP being associated with increased externalising behaviours is in line with prior research reporting associations between sensory processing and aggressive behaviour in young children with ASD (Hartley et al., 2008), and one study which specifically separated challenging behaviours in individuals with ID into SIB, stereotyped behaviour and aggressive behaviour, and found auditory hypersensitivity was predictive of aggressive behaviour, but not SIB (Lundqvist, 2013). In contrast to prior literature (Duerden et al., 2012; Symons et al., 2010), and although initial correlational analyses indicated poorer PP was significantly related to increased SIB, this association did not remain once the relationship between ToM and SIB was taken into account. Unlike in the case of the ToM-SIB association,

even when ASD severity was entered into the model, the direct pathway from PP to externalising behaviours still remained. This suggests that interventions specifically targeting PP (rather than ASD in general) may be helpful in decreasing externalising behaviours. However, confirmation of the causality of this pathway using longitudinal and intervention studies is required. An additional question for future research, and also pertinent to results from Chapter 5, is whether performance in the kinds of PP tasks used in the current analyses translate to ‘real-life’ sensory sensitivities.

Current analyses found a strong overlap between the neurocognitive domains of ToM, ER, EF and PP. Although some of these were to be expected (e.g., the overlap between ToM and ER), the association between others is less clear. Prior work using the current sample also found strong correlations between different tasks, which were not found in a non-ASD comparison group (C. Jones, Swettenham, et al., 2011). Earlier work also reports strong correlations between similar cognitive domains in individuals with ASD, but not in typically developing controls (Ozonoff et al., 2004). Widespread impairments in multiple areas of cognition could be characteristic of ASD (Brunsdon et al., 2015), and perhaps in part help to understand the widespread co-occurring psychopathology reported in young people with ASD (Simonoff et al., 2008).

Alternatively, the overlap could be due, in part, to other unmeasured factors which could influence performance across all tasks, such as inattention, motivation or general task understanding. In terms inattention, this is likely to be prevalent in individuals with ASD, as studies have found around 30% of this sample also met diagnostic criteria for ADHD (Simonoff et al., 2008), and elsewhere up to 55% of

young people with ASD have been found to have sub-threshold ADHD traits (Leyfer et al., 2006). In addition to general attentional difficulties, the high correlation among neurocognitive tasks may have been influenced by IQ. Current analyses are unable to shed light on this possibly. Additional analyses not reported here found controlling for IQ did not produce an effective model, as indicated by poor model fit, most likely in part due to high correlations between IQ and neurocognitive variables. Although this is a different approach to that taken in prior Chapters, where sex, age and IQ were controlled for, these used multivariate regression and ANOVAs, whereas current analyses used SEM. In SEM, analyses inform the user how well the proposed model fits to the data, whereas parametric analyses test how variability in one variable relates to variability in another. These parametric types of analyses cannot tell you, when you include covariates, if this is a better or worse way to describe the data, they merely partial out their effects. Thus, covariates are based on theoretical reasoning, rather than statistical evidence. In current analyses, when IQ was included in the model, it produced a model which did not accurately fit the data. The validity of controlling for IQ when studying cognitive domains is still a controversial topic, especially in populations with neurodevelopmental disorders. Critics of the co-variation approach argue that results of an IQ tests can be influenced by many developmental (e.g., the nature and onset of psychiatric symptoms, the type of education one has received) and contemporaneous (e.g., one's ability to complete the tasks effectively on the day) factors. Therefore, they argue it is inaccurate to see IQ as a latent, unchanging measure of an individual's ability. Instead scores from IQ tests may represent a measure of global function, which is the product of many bidirectional influences over a lifetime of development (Karmiloff-Smith, 2009). Thus, attempting to pull apart IQ and cognitive performance is

artificial and will produce overcorrected results that are hard to interpret (see Dennis et al., 2009 for a more detailed discussion).

6.5.1 Specific Strengths

The strengths of the current work include the wide range of cognitive tasks, tapping different domains, and a population-based sample of well-characterised individuals with ASD, who have a wide range of IQ (50-119). Use of a different sample and a different measurement of the challenging behaviour phenotype allows cross-sample comparison with results from Chapter 5, which also found an association between PP atypicalities and behaviour problems. A further strength of the current study is the use of SEM, which allows simultaneous estimation of the association between different domains of cognition and two aspects of challenging behaviours, whilst also controlling for the effect of language ability on these associations.

6.5.2 Specific Limitations

Overall, the final model found poorer ToM and PP ability were significant predictors of SIB and externalising behaviours respectively. However, remaining domains of EF and ER were still significantly correlated with externalising behaviours and SIB in initial analyses, but were not included in the final model based on the method of model selection. The method of selection based on entering first neurocognitive domains with the strongest association as predictors of behavioural outcomes may lead to inflated specificity in the resulting neurocognition – behaviour associations. It may be the case that if all domains were tested in a full model, using a larger sample, associations between EF and ER and domains of challenging behaviours would remain significant. In saying this, results from Chapter 4 appear to suggest that certain domains of EF may not be key correlates of challenging behaviours in

adolescents with ASD, although this requires future testing before any strong conclusions are drawn.

6.5.3 Implications

Results have two main implications. First, findings extend findings from Chapter 5 that suggest it may be important to consider PP atypicalities when testing hypotheses regarding potential drivers of challenging behaviours in individuals with ASD, but go one step further to suggest there may be specificity in associations between domains of cognitive functioning and types of challenging behaviours. Although the umbrella term of challenging behaviours is a useful clinical label, results suggest that different types of challenging behaviours are associated with different types of cognitive impairments, and so should be considered and potentially treated separately. Second, although much of the literature in the field aims to draw specific associations between different cognitive domains and behavioural characteristics, our results suggest these cognitive domains are so strongly correlated that the specificity of associations may be over-exaggerated unless studies attempt to use ‘purer’ measures of cognition, and account more widely for overlapping domains.

7 Discussion

This thesis sought to explore the neurocognitive and electrophysiological correlates of challenging behaviours in adolescents with ASD. The following sections will outline key findings from each chapter, discuss how these fit with existing literature, and consider the clinical implications of said findings. The strengths and limitations of the work as a whole will be discussed, followed by suggestions of future directions for this line of research.

7.1 Summary of Findings

The majority of analyses used the QUEST cohort, a clinically derived longitudinal sample consisting of 227 children with ASD who entered the study when they were 4-8 years old (Wave 1). Current analyses used data from Wave 2 of the study, where participants were between 11-15 years old, consisting of 76% of the original sample from Wave 1. The sample included individuals with a wide-range of IQ (19-129), and deliberately over-sampled females to obtain a near-equal sex ratio. Eighty-three adolescents made up the Intensively studied sample at Wave 2, where information on cognitive, language and communication ability, ASD severity and co-occurring emotional and behavioural problems was collected. Analyses focused upon this Intensive sample (n=83), specifically on the subgroup (n=53) that completed some combination of four neurocognitive tasks, two of which were paired with EEG recording. Analyses tested associations between neurocognitive and electrophysiological functioning, and parent-reported emotional and behavioural symptoms.

7.1.1 Demographic Correlates of Challenging Behaviours

In Chapter 2, analysis of sample characteristics found no significant associations between emotional and behavioural problems and age, sex, examiner-assessed receptive language or ASD severity. IQ and parent-reported communication ability were positively associated with emotional problems, but negatively associated with ADHD symptoms and behavioural problems. Participants with higher levels of behavioural problems were more likely to be in a special school, and this pattern remained when adjusting for IQ. Analyses also highlighted strong correlations between different domains of emotional and behavioural problems.

7.1.2 Specificity of EF Impairments to Individuals with ASD

In Chapter 3, analyses used data from three other samples (in addition to the QUEST sample) to compare performance on two EF tasks, indexing inhibition and cognitive flexibility, among adolescents with ASD, ADHD, ODD/CD, and TD controls. The ASD group demonstrated more severe impairments in inhibition compared to all other groups. All three diagnostic groups demonstrated increased premature responses and increased intra-individual response variability compared to the TD group, although increased intra-individual response variability appeared to be accounted for by sub-threshold ODD/CD and ADHD symptoms. None of the groups showed impairments in cognitive flexibility.

7.1.3 Neurocognitive and Electrophysiological Correlates of Challenging Behaviours

Analyses in Chapter 4, which used the same two EF tasks as Chapter 3, along with an additional ERP task tapping EF abilities, showed that behavioural EF impairments *within* the group of individuals with ASD were not associated with emotional or conduct problems, but were associated with ADHD symptoms.

Participants with higher rates of ADHD symptoms exhibited greater likelihood of premature responding, greater inflexibility and a more variable response style. This pattern of results remained when controlling for age, sex, IQ and ASD severity. In the ERP task, brain indices of conflict monitoring (N2 component) and attentional orienting (P300 component) were examined. No significant associations were found between ERP response and ADHD symptoms, or any other co-occurring emotional and behavioural problems.

Analyses in Chapter 5 focused on neural indices of PP collected during an auditory oddball paradigm, where participants passively attended to deviant and standard stimuli. Results showed that greater sensitivity to changes in incoming auditory information, as indexed by greater MMN amplitude (calculated as amplitude to deviant relative to standard stimuli), was associated with higher levels of parent-rated behaviour problems. Conversely, a greater neural response to the standard stimulus presented directly after a deviant stimulus was associated with higher levels of anxiety.

The final chapter (Chapter 6) used data from a different sample of adolescents with ASD, the SNAP cohort (Baird et al., 2006), to parse challenging behaviours into two distinct, but correlated types of behaviour, that are often exhibited by individuals with ASD; externalising behaviours and SIB. Here, data-driven SEM was used to estimate associations between four domains of cognition; ToM, ER, EF and PP, and externalising behaviours and SIB. Analyses showed that poorer ToM was associated with increased SIB, whereas poorer PP was associated with increased externalising behaviours, and associations remained when controlling for language ability. Non-significant mediation analyses suggested some degree of specificity in these associations.

7.2 Integration with Previous Literature

7.2.1 Sex Differences in Challenging Behaviours

In terms of how findings compare with previous literature, the current finding of a lack of association between sex and challenging behaviours concurs with previous studies (Brereton et al., 2006; Farmer & Aman, 2011; Farmer et al., 2014; Gadow et al., 2004; Gjevik et al., 2011; Hartley et al., 2008; A. Hill et al., 2014; Kanne & Mazurek, 2011; Kozlowski et al., 2012; Maskey et al., 2013; Murphy et al., 2009; Rattaz et al., 2015). The lack of consistent association between sex and behaviour problems in ASD populations differs to non-ASD populations, where males have been consistently found to have higher rates of CD/ODD (Costello et al., 2003). There is also some evidence to suggest there may be sex differences in challenging behaviours in ID populations, as one meta-analysis found that aggression, but not SIB, was higher in males (however the association between sex and aggression was only based on two studies) (McClintock et al., 2003). Some have suggested that one explanation for the lack of sex differences is that ASD is a neurobiological impairment which overrides or ‘trumps’ other risk factors, such as sex (Brereton et al., 2006; Simonoff et al., 2008),

However, a limited number of previous studies have found sex differences in challenging behaviours in ASD. One study found ODD symptoms were more severe in males, in a sample of children aged 6-12 years with ASD, but only using teacher-reported symptoms (Gadow, DeVincent, & Schneider, 2008). Analyses using parent-reported symptoms did not find sex differences. Previous analyses on the currently-used QUEST cohort at Wave 1, when participants were aged 4-8 years, also found a significantly increased likelihood of ODD diagnosis in males, when a semi-

structured parent-report interview (Preschool Age Psychiatric Assessment; Egger & Angold, 2004) was used to measure co-occurring psychiatric difficulties (Salazar et al., 2015). However, other analyses on Wave 1 data did not find sex differences when co-occurring difficulties were measured by the parent-reported DBC (Chandler et al., 2016). Thus, there could be certain challenging behaviours that are picked up by in-depth interviewing, but are missed by questionnaires such as the DBC, which are more prevalent in males with ASD. Future studies, using in-depth assessment of psychiatric symptoms, are required to better understand the association between sex and co-occurring emotional and behavioural problems in ASD.

7.2.2 ASD Severity and Challenging Behaviours

Current analyses also found no association between ASD severity and emotional or behavioural problems. Findings are in line with other studies which have not found an association between the two (Hartley et al., 2008; Kanne & Mazurek, 2011; Maskey et al., 2013; Simonoff et al., 2008). However, some have reported that both more (Baghdadli et al., 2003; Farmer & Aman, 2011; Matson et al., 2008) and less (Gadow et al., 2004, 2005; Gjevik et al., 2011; A. Hill et al., 2014) severe ASD is associated with higher levels of challenging behaviours. One potential explanation for these discrepancies is variation in the way in which ASD severity has been measured. Some work has relied on diagnostic categories as an index of severity (Gadow et al., 2004, 2005) (where a diagnosis of PDD-NOS and Asperger's is thought to encapsulate a less severe presentation than autism), and others have used parent-report (Baghdadli et al., 2003; Matson et al., 2008). Both methods have their limitations, as studies have found wide variability in how diagnostic categories are applied to individuals with ASD (Lord, Petkova, et al., 2012), and in terms of studies that have used all parent-reported data, having the same rater for two variables has

been found to increase the correlation between the two purely due to common method variance (Podsakoff, MacKenzie, & Podsakoff, 2012). The current study used the ADOS-2 to measure ASD severity, which is a semi-structured observational assessment, and all observational codes were co-rated between two ADOS-trained members of the research team. The calibrated severity score was used, as opposed to the total score, because it has been proposed as a more valid index of ASD severity (Shumway et al., 2012), due to it taking age and language level into account. Other studies which have used the ADOS to measure ASD severity have also not found an association between ASD severity and co-occurring emotional and behavioural problems (Hartley et al., 2008; Kanne & Mazurek, 2011; Simonoff et al., 2008). This suggests two things. First, that challenging behaviours in ASD should be viewed and treated as a separate entity, not merely a ‘side-effect’ of severe ASD, and second, that interventions for ASD in general may not be beneficial in reducing challenging behaviours in individuals with ASD (as the two are not associated). Instead, more targeted (e.g., specific areas of difficulty) interventions may be required.

7.2.3 IQ and Challenging Behaviours

Current analyses found participants with higher IQ and greater communication ability had higher levels of emotional problems, whereas those with lower IQ and communication ability had higher ADHD symptoms and behavioural problems.

In terms of anxiety, the association with higher IQ concurs with prior work in ASD populations (Gadow, DeVincent, & Schneider, 2008; Gotham, Brunwasser, & Lord, 2015; Hallett et al., 2013; Mazurek & Kanne, 2010; Sukhodolsky et al., 2008), although some have not found any association between the two (Simonoff et al., 2008; Strang et al., 2012). Some have suggested this association is due to a higher IQ leading to increased awareness of one’s social difficulties (Mazurek & Kanne, 2010),

or greater ability to be aware of, and anticipate aversive future events (S. Green et al., 2012). However, it is also possible the association also reflects both the difficulties individuals with low IQ have in communicating internalising symptoms, and the difficulties caregivers have in identifying these symptoms.

In terms of the finding of a negative association between IQ and communication ability and challenging behaviours, previous work is mixed, especially in regard to externalising behaviours. Some have not found evidence of an association between IQ and challenging behaviours in individuals with ASD when measured by the DBC total problem behaviour score (Brereton et al., 2006), severity of CD/ODD symptoms (Gadow, DeVinent, & Schneider, 2008), likelihood of CD/ODD diagnosis (Simonoff et al., 2008) or two aggression items on the ADI-R (Kanne & Mazurek, 2011). However, others have found lower cognitive ability to be associated with the presence of aggression (A. Hill et al., 2014; McTiernan et al., 2011), and poorer non-verbal cognitive functioning and expressive language to be correlated with aggressive behaviour (Hartley et al., 2008) in children with ASD. The literature appears less equivocal with regard to SIB, where lower IQ and poorer communication are found to be consistently associated with the presence and severity of SIB (Baghdadli et al., 2003; Carroll et al., 2014; McTiernan et al., 2011; Rattaz et al., 2015; Richards et al., 2012; Richman et al., 2013). Additionally, one meta-analysis found that SIB (but not aggression), was more likely in individuals with severe/profound ID, as compared to those with mild/moderate ID (McClintock et al., 2003), and others have found children with ASD who exhibited aggression and SIB were more likely to have an IQ<70 when compared against those who exhibited aggression alone, and those without aggressive behaviour (Carroll et al., 2014). One should also bear in mind when interpreting the current association between IQ and

communication ability, and the DBC total problem behaviour score, that the DBC is a broad-brush measure. Therefore, it is unknown if SIB, externalising behaviours, or other types of challenging behaviours were driving this association. Additionally, as the DBC was originally developed for use in ID populations, it asks about certain behaviours (e.g., bites others, smears or plays with faeces), that are unlikely to be seen in individuals with ASD and higher levels of IQ, but does not ask about other behaviours (e.g., more deliberate forms of self-harm, bullying) that may be more prevalent in individuals with ASD without ID. Therefore the current finding of an association between IQ and DBC may not necessarily mean that individuals with ASD and higher IQ are less likely to display challenging behaviours, but perhaps less likely to display certain types of challenging behaviours. A discussion of the complexities in best capturing challenging behaviours in individuals with ASD is presented in Section 7.5. It is also of note that the association between IQ and both challenging behaviours and ADHD symptoms in the current sample is similar to those reported in non-ASD samples, where lower IQ is associated with both aggression (Tremblay, 2000) and a diagnosis of ADHD (Kuntsi et al., 2004). This suggests that lower IQ may represent a global risk factor for behaviour problems, regardless of the presence of ASD.

Although the association between communication and behaviour problems lends support to the functional perspective, where impairments in communication are thought to be a major driver of challenging behaviours (Carr & Durand, 1985), it is unclear from the current results the independent contribution of communication, over and above that of IQ, as the two were strongly correlated.

Finally, strong correlations were found between emotional and behavioural problems, similar to in previous literature, where 40% of 10-14 year olds with ASD

had two or more psychiatric disorders in population-representative sample (Simonoff et al., 2008) and a nation-wide Swedish study that found multiple (four or more) co-occurring difficulties were present in 50% of 9 year old children with ASD (Lundström et al., 2014). Current results suggest a full assessment of co-occurring mental health difficulties in young people with ASD is crucial, in line with clinical guidelines (National Institute for Clinical Excellence, August 2013).

7.2.4 Association between ADHD Symptoms and EF in ASD

Results from Chapters 3 and 4 suggest two things. First, that ASD is isolation is characterised by difficulties in EF, especially in response inhibition. Second, that ADHD symptoms in ASD are associated with additional EF impairments, most notably a more premature and varied response style, and difficulties in cognitive flexibility. The first finding concurs with previous meta-analyses which have found an overall impairment in inhibition in individuals with ASD (Geurts et al., 2014), and suggests that individuals with ASD are not only characterised by impairment in domains of social cognition, but also in areas of non-social cognition. Previous research has found that EF abilities predict improvement in both social communication ability and restricted and repetitive behaviours three years later in children with ASD, over and above the influence of IQ (Pellicano, 2013). How EF abilities relate to domains of ASD symptoms in the current sample remains a question for future research. It was unexpected that no impairment in cognitive flexibility was found, given prior literature (Landry & Al-Taie, 2016; Ozonoff et al., 2004). This could have been because the task selected to measure cognitive flexibility in current analyses did not effectively detect the inflexibility often reported in individuals with ASD (as discussed in Section 3.5, Chapter 3). It also raises the question as to whether flexibility impairments are only seen in more

complex tasks (e.g., the Wisconsin Card Sorting Task), and if so whether the impairment lies in difficulties recruiting related executive abilities, rather than in pure flexibility per se.

The finding of an association between ADHD symptoms and EF impairments is in line with prior studies which suggest individuals with ASD + ADHD may present with an additive co-occurrence of the cognitive impairments associated with both disorders, and thus have a more severe profile of EF impairments (Bühler et al., 2011; Sinzig et al., 2008; Tye et al., 2013; van der Meer et al., 2012). Testing disorder-specific and shared cognitive impairments between ASD and ADHD will aid in the identification of candidate endophenotypes. Given the high co-occurrence between the two disorders (Simonoff et al., 2008; Steinhausen et al., 2006), and shared heritability (Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010), these endophenotypes could inform genetic studies that aim to better characterise the shared and non-shared neurobiological pathways from genes to behaviour between the two disorders (Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011).

Current analyses did not find an association between EF, as rated by both behavioural and neural indices, and emotional or behaviour problems (aside from the association with ADHD symptoms). Given prior research has reported an association between cognitive flexibility and challenging behaviours in ASD (Lawson et al., 2015; Visser et al., 2014) and ID populations (Woodcock et al., 2011), and cognitive flexibility impairments in individuals with ODD/CD (Aronowitz et al., 1994; Morgan & Lilienfeld, 2000; Toupin et al., 2000), it was hypothesised analyses would find an association between EF and challenging behaviours. Current null findings could be due to many different factors, as outlined in Section 4.5, Chapter 4. To briefly recap, this could be due to methodological reasons (e.g., the tasks used), or

reflect a true lack of association between EF and challenging behaviours in individuals with ASD. Given that prior work relied on parent-report, it is possible that shared measurement variance in part drove the previously reported significant associations between EF and challenging behaviours referenced above. Given that EF is an umbrella term for a variety of different abilities and domains, future research is needed to comprehensively test a variety of different EF domains before any strong conclusions are drawn regarding the relevance of EF to challenging behaviours in ASD. If it were the case that EF was comprehensively not found to be associated with challenging behaviours in ASD, this would suggest that more ASD-specific factors (e.g., PP, ToM) may be more important to consider than the domain-general factors often implicated in the aetiology of behaviour problems in non-ASD populations. One possibility to also consider, which could explain the current lack of direct association between EF and challenging behaviours, is that ADHD symptoms may be part of an indirect pathway from EF to challenging behaviours in individuals with ASD.

7.2.5 Association between Challenging Behaviours and PP in ASD

The current finding of an association between hypersensitivity to deviant perceptual input, as indexed by increased MMN amplitude, and challenging behaviours builds on previous work which has found similar associations with externalising behaviours using parent-report of perceptual and sensory sensitivity (Ashburner et al., 2008; A. Baker et al., 2008; Tseng et al., 2011). Given that the MMN was found relatively early in the processing pathway (80-120ms after stimuli were presented), and was elicited even though participants were not paying attention to the stimuli, this suggests that potentially pre-attentive neurobiological sensitivity to perceptual input could be an important causal mechanism of challenging behaviours in ASD to

consider. Analyses in Chapter 6 also found an association between PP and behaviour problems, although here the PP tasks were tapping ability to discriminate signal from noise in incoming perceptual information. A linking step would be to test how neural indices of early perceptual sensitivity relate to observed task performance on tests of perceptual discrimination. This would help to understand the pathways between PP and challenging behaviours in individuals with ASD. One (untested) hypothesis is that pre-attentive hyper-sensitivity to changes in perceptual information in the brain, paired with difficulty making sense of incoming perceptual input, may lead to over-arousal, distress or frustration, and consequently challenging behaviours. However, the reverse could also be true, in that generalised over-arousal leads to sensitivity to unpredictable events, even those outside of cognitive awareness (similar to as is suggested in models of post-traumatic stress disorder; PTSD).

Interestingly, previous repeated-measurement twin studies have found MMN amplitude to be highly reliable and heritable (Hall et al., 2006), thus potentially meeting criteria for an acceptable endophenotype (Gottesman & Gould, 2003). Future genetic studies could use MMN amplitude as endophenotype to better understand the neurobiological pathways from genetic risk to challenging behaviours in individuals with ASD. In addition to its reliability, the fact that information about MMN characteristics can be collected without behavioural responses (e.g., in very young infants), suggests that it might also be a worthwhile index of perceptual sensitivity to consider when designing longitudinal studies of co-occurring emotional and behavioural problems in individuals with ASD.

Analyses in Chapter 5 also found that a greater neural response to *standard* stimuli, presented directly after a deviant stimulus, was associated with higher levels of anxiety. This is different to the association between challenging behaviours and

MMN amplitude, as this indexed relative sensitivity to the *deviant* stimuli. Again, this finding builds on prior work that has found an association between parent-rated sensory over-responsivity and anxiety in individuals with ASD (Lane et al., 2012; Lidstone et al., 2014; Mazurek et al., 2013; Pfeiffer et al., 2005). As this selective neural response to the standard stimuli was higher in those who demonstrated more repetitive behaviours/need for sameness, results are interpreted within the intolerance of uncertainty framework (Boulter et al., 2014). Although tentative, an initial explanation of the results is that in participants who had greater intolerance of uncertainty (as indexed by higher levels of repetitive behaviour), the deviant stimuli induced a state of arousal, leading to a greater neural response to the first standard stimuli presented after the deviant stimuli. Repeated experiences of unpredictable events and over-arousal could in turn lead to heightened anxiety. However, as with the interpretation of the MMN results, the directionality of associations is unclear, as it is possible that participants who were more anxious exhibited a heightened neural response to unpredictable change in incoming stimuli, and exhibited more repetitive behaviours in an attempt to control anxiety levels. Thus, although it is unclear exactly how need for sameness, sensory over-responsivity, intolerance of uncertainty and anxiety relate to each other, with different research groups proposing different models of directionality (Neil et al., 2016; Wigham et al., 2015), results suggest that response to unpredictability could be an important factor to consider in models co-occurring emotional difficulties in adolescents with ASD (as has also been posited by Pellicano & Burr, 2012). This is in line with one longitudinal study that found that sensory over-responsivity predicted anxiety over a one year period, but anxiety did not predict sensory over-responsivity, in young children with ASD (S. Green et al., 2012). Thus, sensory over-responsivity could

potentially be a ‘red flag’ for the development of later emotional and behavioural problems in individuals with ASD, and thus assist in the identification of those most at risk, and allow interventions to be put in place before behaviours become severely entrenched. Finally, it should be noted that findings support clinical guidelines that emphasise the importance of considering individual sensory sensitivities when assessing individuals with ASD (National Institute for Clinical Excellence, August 2013).

7.2.6 Specificity of Associations within Domains of Challenging Behaviours

As in previous work (Carroll et al., 2014; McClintock et al., 2003), Chapter 6 found that two aspects of challenging behaviours often displayed by individuals with ASD, were independently associated with functioning in different cognitive domains.

Increased externalising behaviours were associated with poorer PP, whereas increased SIB was associated with poorer ToM. The literature on neurocognitive correlates of SIB in ASD populations is sparse and thus the current thesis is, to my knowledge, the first to comprehensively test how specific domains of neurocognitive functioning relate to SIB individuals with ASD. Results suggest that impairments in ToM, in addition to communication and more general social impairments (Baghdadli et al., 2003; Duerden et al., 2012), may be important to consider with regards to SIB. Analyses also suggested that these cognition-behaviour associations were somewhat specific, and that the pathway from PP to externalising behaviours was not simply indexing ASD severity. This was unlike the pathway from ToM to SIB, where ToM appeared to exert an effect on SIB through increased ASD severity. Using cross-sectional data means one cannot disentangle the directionality of effects, however, this will be important for future intervention studies, in terms of whether interventions for challenging behaviours target specific domains of cognitive

functioning (e.g., ToM) or the ASD phenotype more broadly. Results also suggest that research should consider different types of challenging behaviour separately, rather than using the umbrella term of challenging behaviours, as this may index a heterogeneous group of behaviours with different causal aetiologies.

7.3 Implications of the Present Work

Overall, the present findings suggest that specific aspects of neurocognitive functioning are associated with challenging behaviours in adolescents with ASD. This differs from the functional perspective, which proposes that challenging behaviours represent alternative methods of communication in individuals with compromised communicative ability, which are inadvertently reinforced by the external environment (e.g., by gaining caregivers attention). However, considering cognitive domains that may be important in the aetiology of challenging behaviours does not mean one should disregard the functional perspective, and indeed current analyses found communicative ability was associated with challenging behaviours. The two can potentially be reconciled using the Research Domain Criteria framework (RDoC; Cuthbert & Insel, 2013; Insel et al., 2010). RDoC stems from the recognition of the wide heterogeneity within diagnostic categories and extensive co-occurrence between diagnoses (Regier, Narrow, Kuhl, & Kupfer, 2009). These instances have led to a questioning of the underlying validity of diagnostic categories and reconsideration of current diagnostic systems. The RDoC approach proposes that the observable behaviours that current diagnostic systems are based on can be driven by multiple causes and reached by multiple routes. Thus, individuals with the same diagnosis may have dysfunction in different neurobiological systems, but superficially look similar (e.g., equifinality). Effective intervention should therefore

be based on the nature of neurobiological/cognitive dysfunction in a given individual, rather than a ‘one size fits all’ approach based on diagnostic categories. To fully understand the drivers of behaviour, RDoC calls for a united effort to integrate all levels of functioning, from genetic research, molecular biology, to neural and cognitive functioning. This is not to disregard the importance of the environment, and this can influence brain structure and function both developmentally and dynamically. One can apply RDoC’s call for integration across levels of understanding in psychiatric research to understanding challenging behaviours in individuals with ASD. Currently, although the functional approach has traditionally been used to ameliorate challenging behaviours in individuals with ASD, this broad-class approach is purely based on observable behaviours. Results from this thesis suggest that variation in underlying neurobiological systems may also be important to consider in the aetiology of challenging behaviours in individuals with ASD. Thus, it may be more fruitful to consider challenging behaviours as a heterogeneous group, and use these cognition-behaviour associations, which are likely to interact with other individual (e.g., communication ability) and environmental (e.g., inadvertent reinforcement) factors, to help to define different types, or clusters, of challenging behaviours, which have different aetiological pathways. This approach could refine diagnostic practice and knowledge of the potential neurobiological underpinnings, and could also inform clinical recommendations. Therefore, a full assessment of not only communicative ability, and potential inadvertent environmental reinforcement, but also functioning in relevant cognitive domains, could be used to inform the choice of intervention an individual with ASD may be best suited to receive.

7.4 Strengths of the Present Work

The first strength is the novelty of the approach taken. There is a limited body of research focused on understanding how variation in neurocognitive functioning may underpin variation in the behavioural phenotype of ASD, and despite the high prevalence of emotional and behavioural problems in individuals with ASD (de Bruin et al., 2007; Gadow et al., 2004, 2005; Gjevik et al., 2011; Leyfer et al., 2006; Lundström et al., 2014; Mattila et al., 2010; Simonoff et al., 2008), there is a paucity of ASD-specific models of psychopathology. Given the persistence of this psychopathology in youth with ASD (Simonoff et al., 2013), research is required to understand how to best predict and treat these co-occurring problems. A key first step is to explore the individual characteristics that are associated with challenging behaviours in individuals with ASD, as has been done in this thesis. Although previous work has looked at characteristics such as IQ, age, sex and ASD severity, few studies have looked specifically at domains of cognitive functioning. Focusing on carefully-selected cognitive domains such as PP or EF gives a deeper understanding of potential drivers of challenging behaviours beyond that of characteristics such as IQ and age, and may offer clues as to the specific neurocognitive mechanisms at play.

Additionally, the current study builds on prior work that has used parent-report of both cognitive functioning and behaviour (e.g., Lawson et al., 2015; Visser et al., 2014). Using the same rater means that results could be in part due to common method variance, rather than true cognition-behaviour associations. The current work used objective measures, such as performance on computer tasks, or neural response to stimuli, to index cognitive functioning, meaning that rater effects are less likely to influence results. However, it is still possible that parental characteristics influenced

ratings of child emotional and behavioural problems in the current thesis, as has been found in non-ASD populations (Briggs-Gowan, Carter, & Schwab-Stone, 1996). Other potential methods to capture emotional and behavioural problems include direct observation, however this is limited to a short ‘snapshot’ of behaviour, usually in an unrepresentative environment, or using multiple independent raters (e.g., parents and teachers), but there is uncertainty about how best to combine these different sources of information. Thus, it remains unclear the best way to accurately measure emotional and behavioural problems in youth with ASD, as each method has its limitations.

Another strength of the current work is the use of the EEG technique. Data such as RT or accuracy can give little information as to the covert processes that underpin performance, unlike neuroimaging techniques, which can give information about the neural underpinnings of cognitive processes. A search of the literature identified only one other study that has used neuroimaging (fMRI) to test whether differences in neural functioning are associated with behaviour problems in ASD (Yang et al., 2017). Unlike fMRI paradigms, where measurement of blood flow in the brain is taken as an indirect index of neural functioning (Logothetis & Pfeuffer, 2004), EEG recording allows for direct measurement of neural activation in real-time, allowing conclusions to be drawn about differences in processing efficiency during specific cognitive functions (e.g., early automatic vs. later and more effortful cognitive processes; Banaschewski & Brandeis, 2007; McPartland et al., 2015). Furthermore, using brain functioning as an index of variability in cognitive functioning allows one to collect data without requiring participants to make a response, as in Chapter 5. This permits a more inclusive approach to sampling, as reflected in the wide IQ range (27-129) of participants who took part in the PP task in Chapter 5. This

approach is in line with recent commentaries calling for the inclusion of historically understudied populations within ASD, namely those with ID or who are minimally verbal (Jack & Pelphrey, 2017).

A further strength is the use of two well-characterised samples of adolescents with ASD, where all participants had their diagnoses confirmed using ‘gold standard’ ASD diagnostic instruments. The QUEST sample was drawn from community-based clinics in regional boroughs, within a specific four-year time frame. The original sample aimed to include all children with an ASD diagnosis within the sampling frame and therefore minimise selection bias (e.g., as compared against studies which only include those who respond to adverts for study participation, or those who present to clinical services with co-occurring mental health difficulties). The QUEST sample also deliberately over-sampled females. Thus, although no sex differences were found in current analyses, one can be surer that the current results are not due to a lack of power to detect sex differences, unlike in many other studies.

The SNAP sample was population-derived, and thus thought to be representative of the general population of adolescents with ASD and $IQ > 50$. Both samples (QUEST and SNAP) included individuals with ASD with a wide range of IQ (27-129 in QUEST, 50-119 in SNAP). This is more representative of ASD as a whole, as although many studies of cognitive functioning in ASD will set $IQ \geq 70$ as an inclusion criteria, around 50% of individuals with ASD have $IQ < 70$ (Charman, Pickles, et al., 2011). Conclusions are then drawn from these types of studies about cognitive functioning in ASD in general. This is problematic as it relies on the assumption that the same processes are present in individuals with ASD without ID as compared to those with ASD and ID, which may not be true (Jack & Pelphrey, 2017). For example, epilepsy and syndromic forms of ASD are more prevalent in

individuals with ASD and ID as compared to those with ASD alone (Moss & Howlin, 2009; Woolfenden, Sarkozy, Ridley, Coory, & Williams, 2012), which suggests there could be differences in neural functioning between those with ASD and those with ASD + ID. Current findings are thus more applicable to ASD as a whole, rather than a subset of individuals with $IQ \geq 70$, although it should be acknowledged that those with the lowest cognitive ability were unable to access the cognitive tasks.

Finally, using these two separate samples of youth with ASD with different measures allowed for contrasting measurements of the challenging behaviour phenotype.

Given that associations between PP and challenging behaviours were found in both Chapter 5, where PP was measured using ERPs in the QUEST sample, and Chapter 6, where PP was measured using neurocognitive task performance in the SNAP sample, this suggests findings were not driven by methodological factors and may reflect true cognition-behaviour associations. Future work is needed to test whether the ToM-SIB association found in Chapter 6 replicates in different samples.

7.5 Limitations of the Present Work

In addition to the strengths outlined above, there are also a number of limitations specific to the current research. The first is the lack of control groups. Although the primary research aim was to test which neurocognitive domains are associated with challenging behaviours *within* individuals with ASD, the lack of control groups limits the interpretation of some of the results. For example, in Chapter 4, where no association was found between N2 or P300 amplitude and emotional or behavioural problems, without a control group it is impossible to know if this is because the task used was unable to pick up any associations between neural functioning and

behaviour problems (due to task specific factors), or if the lack of association is specific to ASD populations. The latter explanation would suggest that the correlates of behaviour problems in ASD differ to those in non-ASD populations, which in turn may suggest that behaviour problems in ASD, as compared to non-ASD populations, should be understood and treated differently. This type of information would have direct clinical implications.

However, recruiting an appropriate control group is a complex issue. Given that the current sample had a wide range of IQ (as is representative of ASD in general), any control group would ideally have a similarly wide IQ range, and include individuals with ID. Thus in a strict sense, this would not represent a ‘pure’ control group. It should also be considered which types of behaviours to compare between non-ASD and ASD groups. Given that types of behaviour problems commonly exhibited by individuals with ASD (e.g., tantrums and meltdowns, motoric SIB such as head banging and skin picking) may not be the same as the types of behaviour problems commonly found in populations without neurodevelopmental difficulties (e.g., ODD/CD symptoms such as lying and stealing), it is hard to know exactly which challenging behaviours would be appropriate to use as a outcome variable in such a study. One possible strategy is to compare individuals with ASD against a range of other disorders with known aetiologies (e.g., certain genetic syndromes), which have a different profile of cognitive impairments. This can highlight differences in types and rates of challenging behaviours between the groups, and in turn offer clues to how differences in neurobiological/cognitive functioning may underpin differences in the behavioural phenotype (including challenging behaviours) (see Dykens, 2000; Oliver et al., 2013; Paterson, Girelli, Butterworth, & Karmiloff-Smith, 2006 for more details and examples of this methodology).

Relatedly, another limitation, which is especially pertinent to Chapters 4 and 5, concerns the measures used. No associations were found between neurocognitive functioning and behaviour problems, as rated by the SDQ conduct problems subscale. The SDQ was originally chosen for use in the study as it is a widely-used and well-validated measure (Goodman, 2001; Goodman et al., 2000) and is relatively quick and easy to complete. However, the conduct problems subscale may not accurately capture the types of challenging behaviours exhibited by individuals with ASD. The scale consists of five items; often has temper tantrums or hot tempers, generally obedient, usually does what adults request, often fights with other children or bullies them, often lies or cheats and steals from home, school or elsewhere. Certain behaviours, for example, lying and cheating, are less likely to be exhibited by individuals with ASD as they rely on intact social cognition (Brereton et al., 2006; Guttman-Steinmetz et al., 2009). Lying and cheating effectively requires one to know that you should try to ‘fool’ another person, which is dependent on ToM abilities, which are known to be impaired in individuals with ASD (Frith, 2012). However, given that no associations were found between other measures of behaviour problems (ARI, DBC) and EF in Chapter 4, this suggests that the lack of association with the SDQ conduct problems subscale may not be solely due to use of an inappropriate measure.

There is still on-going debate as to how to best capture the type of behaviour problems exhibited by individuals with ASD, with some groups using measures specifically designed for use in populations with developmental disabilities, such as the DBC and the Aberrant Behaviour Checklist (Aman & Singh, 1986), but others using measures developed in typically developing populations to allow comparison with normed cut-offs, such as the Child Behavior Checklist (Achenbach & Rescorla,

2000). A recent systematic review suggested the Child Behavior Checklist and the Home Situations Questionnaire—PDD version (Chowdhury et al., 2010) had the most robust psychometric support, but concluded that the evidence for the reliability and validity of measures for obtaining information about challenging behaviours in children with ASD was extremely limited (Hanratty et al., 2015). Thus, further work is needed not only to validate existing measures for use in ASD populations, but also to consult with parents and caregivers to understand which types of challenging behaviours are most commonly exhibited by young people with ASD, and which they find most concerning. Special consideration should also be given as to the best way to identify and capture less behaviourally obvious symptoms (e.g., anxiety) in individuals with ASD who have limited language and lower cognitive ability (Sukhodolsky et al., 2008).

A further limitation of the current work is the use of moderately sized samples, which could have led to limited power to detect associations of smaller effect, especially among correlated cognitive variables (for example, in Chapter 6). Thus, additional work is required using larger sample sizes, to allow for more rigorous statistical testing.

Finally, one should also consider the validity and reliability of the measures used to index cognitive performance (Dubois & Adolphs, 2016 discuss these issues in relation to fMRI, but the same critiques can be applied to cognitive tests in general). Unlike questionnaires, where researchers are typically required to report on the psychometric indicators of a given measure, the same parameters are not often questioned in relation to neurocognitive tasks. If other factors, aside from the cognitive domain under question (e.g., mood on the assessment day, motivation, general task involvement), largely influence performance, this would suggest the

task itself is not particularly reliable. Efforts have been made to establish the reliability of certain cognitive tasks, with some reporting strong test re-test correlations for both ToM (Devine & Hughes, 2016; Hughes et al., 2000) and EF tasks (Wöstmann et al., 2013) in typically developing individuals, however, whether similar figures would be found in atypical populations remains unknown. In the current thesis, some of the tasks used (e.g., the Strange Stories task in Chapter 6, the Go/NoGo task in Chapters 3 and 4), and ERP components selected to index certain cognitive processes (e.g, P300 in Chapter 4, MMN in Chapter 5), are found to have moderate-strong reliability (Devine & Hughes, 2016; Hall et al., 2006; Hughes et al., 2000; Wöstmann et al., 2013), however the actual EEG tasks that were used were bespoke, as they were designed specifically with the wide-range of IQ of the QUEST sample in mind.

7.6 Reflections on the Cognitive Phenotype Approach

This thesis sought to test whether functioning in specific domains of cognition was associated with challenging behaviours in individuals with ASD. There are more general strengths and limitations to this approach that should be considered when interpreting the results as a whole. The cognitive phenotype approach to psychopathology posits that cognitive functioning represents a ‘midway’ between genes and behaviour, and thus that variation in cognition underpins variation in behaviour (as is depicted in Model 1 in Figure 23). To this end, mental health research has focused on searching for associations between cognition and psychiatric diagnoses or symptoms, under the assumption that atypical cognitive functioning drives atypical behaviour. It follows that if one can identify the underlying causes of behaviour, one can then attempt to decrease symptom severity by targeting

functioning in these specific cognitive domains (with either psychological or pharmacological interventions). However, it should be acknowledged that the evidence for causal pathways between cognition/brain functioning and behaviour is limited. If one considers how this approach has been applied to ASD, one recognisable example of a proposed cognitive phenotype would be impaired ToM. Although some have found ToM difficulties to be associated with social impairment in individuals with ASD (Lerner et al., 2011; Shimon et al., 2012), others have not found a relationship between the two (Cantio et al., 2016; Pellicano et al., 2006). Additionally, a significant association between cognitive functioning or activity in an area of the brain and behaviour is not evidence of causality. Atypical neurocognitive functioning could be associated with behaviour, but not part of the trajectory between genes and behaviour (Model 2 in Figure 23), be associated with behaviour due to both cognition and behaviour being associated with some unmeasured additional factor (Model 3) or even due to early atypical behavioural functioning causing alterations in cognition (Model 4). To bring this back to the example of ToM, although many assume that poor ToM causes social impairments, it is also possible that the original ‘insult’ (e.g., atypical brain development) could lead to simultaneously poor ToM and the ASD phenotype (Model 2), without ToM being a causal mechanism, or that ToM and ASD are both associated with some unknown, unmeasured additional factor (e.g., low-level difficulties in processing perceptual information; Model 3). Finally it is possible that an infant with genetic risk for ASD may be impaired in low-level attentional orientating to complex stimuli, leading to less learning about social stimuli in key developmental periods, and consequent impairments in ToM (Model 4). It should be stressed these are just simplistic

examples for illustrative purposes, as it is unlikely that one direct pathway characterises the emergence of ASD symptoms.

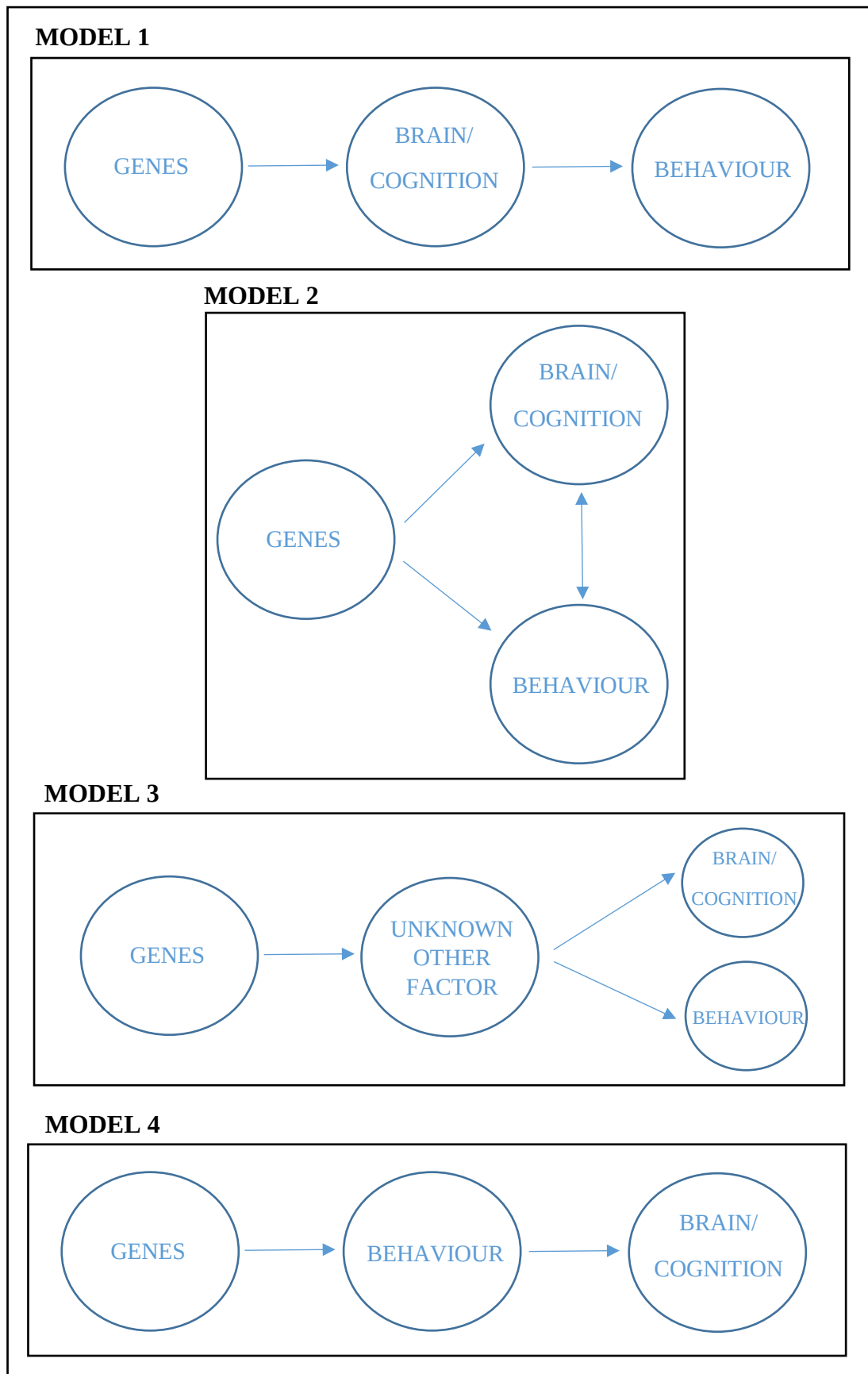


Figure 23. Simplified Models of Potential Pathways between Genes, Brain/Cognition and Behaviour

One approach, which allows stronger conclusions to be drawn regarding the primacy of brain/cognitive impairments, is to use longitudinal studies to look for neural/cognitive ‘risk factors’ which are present before a disorder is diagnosed. Interestingly, these types of studies have found both early social and non-social impairments predict later diagnosis of ASD (for a review see E. Jones, Gliga, Bedford, Charman, & Johnson, 2014). Longitudinal prediction does not equal causality, however, characterising the developmental pathways from birth to ASD can give clues as to the types of neurocognitive mechanisms that might be involved in the emergence of ASD symptoms. To rigorously test the causal role of cognitive domains one requires intervention studies, either targeting specific domains of cognition, or examining how cognition varies as a function of treatment response. As these are somewhat lacking in ASD (although see Dawson et al., 2012) a clearer illustrative example of how this design has been used is in the ADHD field, where pharmacological treatment studies have found limited associations between improvement in domains of EF, that thought to be impaired in individuals with ADHD, and reduction in ADHD symptoms (Coghill, Hayward, Rhodes, Grimmer, & Matthews, 2013; Coghill et al., 2014).

Finally, it should be noted that although this thesis has primarily focused on the role of cognition, a comprehensive model of psychopathology also acknowledges the role of environmental influences, which can have bi-directional effects with genes, cognition and behaviour (as has been briefly discussed in reference to the functional perspective). In the case of ASD, certain environmental factors, in addition to the proposed functional models of inadvertent reinforcement, have been found to longitudinally predict challenging behaviours (e.g., maternal criticism; J. Baker, Smith, Greenberg, Seltzer, & Taylor, 2011; Woodman, Smith, Greenberg, &

Mailick, 2015), and these influences and challenging behaviours exhibited by the young person are found to act in a bi-directional manner over time (Greenberg, Seltzer, Hong, & Orsmond, 2006). Thus, impairments in cognition should be considered as just one risk factor, which are likely to interact dynamically with other individual and environmental factors across the lifespan in individuals with ASD.

To conclude, the point of this section is not to completely disregard the utility of the cognitive phenotype approach, and cross-sectional research into cognition-behaviour associations, but merely to recognise what one can and cannot infer from this approach. Cross-sectional studies are crucial in informing longitudinal research studies as to which neurocognitive domains should be tested as predictors of psychopathology, and intervention studies as to which domains to target. Thus, the current thesis seeks to inform causal models of challenging behaviours in ASD, and inform future longitudinal studies testing predictors of challenging behaviours in (e.g., to consider the role of ToM, PP/sensory atypicalities). This in turn could lead to identification of ‘high risk’ individuals and allocation of resources to those most in need. Establishing an evidence-base for challenging behaviours will inform the design of tailored interventions for individuals with ASD.

7.7 Future Directions

The current thesis represents a first step into understanding the individual factors that may underpin challenging behaviours in young people with ASD. These findings require replication, especially the unexpected association between neural response to standard stimuli and anxiety found in Chapter 5. As outlined in Section 7.5, longitudinal studies are required to test the predictive role of the cognition-behaviour associations. Specifically, studies with multiple measures, over multiple time points,

are needed to test whether atypical ToM and PP predict change in challenging behaviours over time. As discussed in Section 4.5, future work could also test further whether other aspects of EF (e.g., reinforcement learning, decision making), aside from those tested in the current thesis, are associated with challenging behaviours.

As alluded to earlier in the previous section, although this thesis focused on individual variation in cognitive functioning, a comprehensive model should include other individual characteristics, and environmental influences (e.g., maternal criticism, inadvertent reinforcement) known to be associated with challenging behaviours, and consider how these may interact together over time, to fully understand the pathways to challenging behaviours in individuals with ASD.

7.8 Conclusions

The identification of correlates of challenging behaviours in ASD is a crucial first step in building aetiological models, and can inform future longitudinal and intervention studies. The current thesis used multiple methods to explore the cognitive and electrophysiological correlates of challenging behaviours in two well-characterised samples of adolescents with ASD. Results suggest certain neurocognitive domains are worthy of further investigation (PP, ToM), whereas other, namely certain aspects of EF, may not be as relevant. Clarifying the potential neurocognitive mechanisms that drive challenging behaviours in young people with ASD will allow the development of more comprehensive aetiological models, the identification of high risk individuals, and the development of targeted interventions.

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9 Appendices

Appendix 1: Parent Questionnaires Used in QUEST Study

Adaptive Behaviour Assessment System (ABAS) – Communication Subscale

Communication	Is Not Able	BEHAVIOR FREQUENCY			Check If You Guessed
		Never When Needed	Sometimes When Needed	Always When Needed	
1. Says the names of other people, for example, "Mama," "Daddy," or friends' names.	0	1	2	3	☐
2. Shakes head or says "yes" or "no" in response to a simple question, for example, "Do you want something to drink?"	0	1	2	3	☐
3. Says "Hello" and "Good-bye" to others.	0	1	2	3	☐
4. Names 20 or more familiar objects.	0	1	2	3	☐
5. Tells parents, friends, or others about his/her favorite activities.	0	1	2	3	☐
6. Uses sentences with a noun and a verb.	0	1	2	3	☐
7. Speaks clearly and distinctly.	0	1	2	3	☐
8. Looks at others' faces when they are talking.	0	1	2	3	☐
9. Pays attention during family discussions for as long as needed.	0	1	2	3	☐
10. Answers the telephone appropriately.	0	1	2	3	☐
11. Listens closely for at least five minutes when people talk.	0	1	2	3	☐
12. Nods or smiles to encourage others when they are talking.	0	1	2	3	☐
13. Repeats stories or jokes after hearing them from others.	0	1	2	3	☐
14. Says irregular plural nouns, for example, <i>knives</i> or <i>mice</i> .	0	1	2	3	☐
15. Ends conversations appropriately.	0	1	2	3	☐
16. Takes turns talking during conversations with people—is not too talkative or too quiet.	0	1	2	3	☐
17. Gives verbal instructions that involve two or more steps or activities.	0	1	2	3	☐
18. States his/her own telephone number.	0	1	2	3	☐
19. Starts conversations on topics of interest to others.	0	1	2	3	☐
20. Talks about realistic future educational or career goals.	0	1	2	3	☐
21. Places local telephone calls.	0	1	2	3	☐
22. States home address, including zip code.	0	1	2	3	☐
23. Answers complex questions that require careful thoughts and opinions, for example, questions about politics or current events.	0	1	2	3	☐
24. Uses up-to-date information to discuss current events.	0	1	2	3	☐
Total				72	Total Guessed

Affective Reactivity Index (ARI)

For each item, please mark the box for Not True, Somewhat True or Certainly True.

In the *last six months* and compared to others of the same age, how well does each of the following statements describe the behavior/feelings of your child? Please try to answer all questions.

	NOT TRUE	SOMEWHAT TRUE	CERTAINLY TRUE
Is easily annoyed by others	☐	☐	☐
Often loses his/her temper	☐	☐	☐
Stays angry for a long time	☐	☐	☐
Is angry most of the time	☐	☐	☐
Gets angry frequently	☐	☐	☐
Loses temper easily	☐	☐	☐
Overall, <i>irritability</i> causes him/her problems.	☐	☐	☐

Developmental Behavior Checklist (DBC)

-2-

Many of the following behaviours may not apply to the child or teenager in your care. For each item that does describe the person in your care, now or within the past six months, please circle the 2 if the item is very true or often true. Circle 1 if the item is somewhat or sometimes true of your child. If the item is not true of your child circle the 0.

0 = not true as far as you know 1 = somewhat or sometimes true 2 = very true or often true

If your child is unable to perform an item, circle the 0. For example, if your child has no speech, then for the item "Talks too much or too fast" circle the 0

Underline any you are particularly concerned about

Office Use Only	Please Circle	
1. ③	0 1 2	Appears depressed, downcast or unhappy
2. ③	0 1 2	Avoids eye contact. Won't look you straight in the eye.
3. ③ ③	0 1 2	Aloof, in his/her own world.
4. ③	0 1 2	Abusive. Swears at others.
5. ③	0 1 2	Arranges objects or routine in a strict order. Please describe: _____
6. ③	0 1 2	Bangs head.
7. ③	0 1 2	Becomes over-excited.
8. ③	0 1 2	Bites others.
9. ③	0 1 2	Cannot attend to one activity for any length of time, poor attention span.
10. ③	0 1 2	Chews or mouths objects, or body parts.
11. ④	0 1 2	Cries easily for no reason, or over small upsets.
12.	0 1 2	Covers ears or is distressed when hears particular sounds. Please describe: _____
13. ③	0 1 2	Confuses the use of pronouns e.g. uses "you" instead of "I".
14. ③ ③	0 1 2	Deliberately runs away.
15.	0 1 2	Delusions: has a firmly held belief or idea that can't possibly be true. Please describe: _____
16. ④	0 1 2	Distressed about being alone.
17. ③	0 1 2	Doesn't show affection.
18. ③	0 1 2	Doesn't respond to others' feelings, e.g. shows no response if a family member is crying.
19.	0 1 2	Easily distracted from his/her task, e.g. by noises.
20. ③	0 1 2	Easily led by others.
21. ③	0 1 2	Eats non-food items e.g. dirt, grass, soap.
22. ④	0 1 2	Excessively distressed if separated from familiar person.
23. ④	0 1 2	Fears particular things or situations, e.g. the dark or insects. Please describe: _____
24. ③	0 1 2	Facial twitches or grimaces.
25. ③	0 1 2	Flicks, taps, twirls objects repeatedly.
26. ④	0 1 2	Fussy eater or has food fads.
27. ③	0 1 2	Gorges food. Will do anything to get food e.g. takes food out of garbage bins or steals food.
28. ③	0 1 2	Gets obsessed with an idea or activity. Please describe: _____
29. ③	0 1 2	Grinds teeth.
30. ④	0 1 2	Has nightmares, night terrors or walks in sleep.

Office Use Only	Please Circle			
31. ①	0	1	2	Has temper tantrums, e.g. stamps feet, slams doors.
32. ①	0	1	2	Hides things.
33. ②	0	1	2	Hits self or bites self.
34. ②	0	1	2	Hums, whines, grunts, squeals or makes other non-speech noises.
35. ①	0	1	2	Impatient.
36.	0	1	2	Inappropriate sexual activity with another.
37. ①	0	1	2	Impulsive, acts before thinking.
38. ①	0	1	2	Irritable.
39. ①	0	1	2	Jealous.
40. ①	0	1	2	Kicks, hits others.
41. ①	0	1	2	Lacks self-confidence, poor self-esteem.
42. ②	0	1	2	Laughs or giggles for no obvious reason.
43. ①	0	1	2	Lights fires.
44. ②	0	1	2	Likes to hold or play with an unusual object, e.g. string, twigs; overly fascinated with something, e.g. water. Please describe: _____
45. ④	0	1	2	Loss of appetite.
46. ②	0	1	2	Masturbates or exposes self in public.
47. ①	0	1	2	Mood changes rapidly for no apparent reason.
48. ②	0	1	2	Moves slowly, underactive, does little, e.g. only sits and watches others.
49. ①	0	1	2	Noisy or boisterous.
50. ① ②	0	1	2	Overactive, restless, unable to sit still.
51. ③	0	1	2	Overaffectionate.
52. ②	0	1	2	Overbreathes, vomits, has headaches or complains of being sick for no physical reason.
53. ①	0	1	2	Overly attention-seeking.
54. ③	0	1	2	Overly interested in looking at, listening to or dismantling mechanical things e.g. lawnmower, vacuum cleaner.
55. ②	0	1	2	Poor sense of danger.
56. ③	0	1	2	Prefers the company of adults or younger children. Doesn't mix with his/her own age group.
57. ③	0	1	2	Prefers to do things on his/her own. Tends to be a loner.
58. ③	0	1	2	Preoccupied with only one or two particular interests. Please describe: _____
59. ①	0	1	2	Refuses to go to school, activity centre or workplace.
60. ②	0	1	2	Repeated movements of hands, body, head or face e.g. handflapping or rocking.
61. ③	0	1	2	Resists being cuddled, touched or held.
62. ③	0	1	2	Repeats back what others say like an echo.
63. ③	0	1	2	Repeats the same word or phrase over and over.
64. ③	0	1	2	Smells, tastes, or licks objects.
65.	0	1	2	Scratches or picks his/her skin.
66. ②	0	1	2	Screams a lot.

67.	0	1	2	Sleeps too little. Disrupted sleep.
68. ②	0	1	2	Stares at lights or spinning objects.
69. ③	0	1	2	Sleeps too much.
70. ③	0	1	2	Soils outside toilet though toilet trained. Smears or plays with faeces.
71. ③	0	1	2	Speaks in whispers, high pitched voice, or other unusual tone or rhythm.
72. ③	0	1	2	Switches lights on and off, pours water over and over; or similar repetitive activity. Please describe: _____
73. ①	0	1	2	Steals.
74. ①	0	1	2	Stubborn, disobedient or unco-operative.
75. ④	0	1	2	Shy.
76. ③	0	1	2	Strips off clothes or throws away clothes.
77. ①	0	1	2	Says he/she can do things that he/she is not capable of.
78. ③	0	1	2	Stands too close to others.
79.	0	1	2	Sees, hears, something which isn't there. Hallucinations. Please describe: _____
80.	0	1	2	Talks about suicide.
81. ①	0	1	2	Talks too much or too fast.
82. ③	0	1	2	Talks to self or imaginary people or objects
83. ①	0	1	2	Tells lies.
84.	0	1	2	Thoughts are unconnected. Different ideas are jumbled together with meaning difficult to follow.
85. ①	0	1	2	Tense, anxious, worried.
86. ①②	0	1	2	Throws or breaks objects.
87. ①	0	1	2	Tries to manipulate or provoke others.
88. ③	0	1	2	Underreacts to pain.
89. ③	0	1	2	Unrealistically happy or elated.
90. ③	0	1	2	Unusual body movements, posture, or way of walking. Please describe: _____
91. ④	0	1	2	Upset and distressed over small changes in routine or environment. Please describe: _____
92. ③	0	1	2	Urminates outside toilet, although toilet trained.
93. ①	0	1	2	Very bossy.
94. ③	0	1	2	Wanders aimlessly.
95. ①	0	1	2	Whines or complains a lot.
	0	1	2	Please write in any problems your child has that were not listed above
	0	1	2	_____
	0	1	2	_____
96.	0	1	2	Overall, do you feel your child has problems with feelings or behaviour, in addition to problems with development? If not, please circle the 0. If so, but they're minor, please circle the 1. If they're major problems, please circle the 2.

Please be sure you have answered all items

Are there any other comments you would like to make?

Spence's Child Anxiety Scale (SCAS)

BELOW IS A LIST OF ITEMS THAT DESCRIBE CHILDREN. FOR EACH ITEM PLEASE CIRCLE THE RESPONSE THAT BEST DESCRIBES YOUR CHILD. PLEASE ANSWER ALL THE ITEMS.

1.	My child worries about things.....	Never	Sometimes	Often	Always
2.	My child is scared of the dark.....	Never	Sometimes	Often	Always
3.	When my child has a problem, s(he) complains of having a funny feeling in his / her stomach	Never	Sometimes	Often	Always
4.	My child complains of feeling afraid.....	Never	Sometimes	Often	Always
5.	My child would feel afraid of being on his/her own at home.....	Never	Sometimes	Often	Always
6.	My child is scared when s(he) has to take a test.....	Never	Sometimes	Often	Always
7.	My child is afraid when (s)he has to use public toilets or bathrooms.....	Never	Sometimes	Often	Always
8.	My child worries about being away from us / me.....	Never	Sometimes	Often	Always
9.	My child feels afraid that (s)he will make a fool of him/herself in front of people.....	Never	Sometimes	Often	Always
10.	My child worries that (s)he will do badly at school.....	Never	Sometimes	Often	Always
11.	My child worries that something awful will happen to someone in our family.....	Never	Sometimes	Often	Always
12.	My child complains of suddenly feeling as if (s)he can't breathe when there is no reason for this.....	Never	Sometimes	Often	Always
13.	My child has to keep checking that (s)he has done things right (like the switch is off, or the door is locked).....	Never	Sometimes	Often	Always
14.	My child is scared if (s)he has to sleep on his/her own.....	Never	Sometimes	Often	Always
15.	My child has trouble going to school in the mornings because (s)he feels nervous or afraid.....	Never	Sometimes	Often	Always
16.	My child is scared of dogs	Never	Sometimes	Often	Always
17.	My child can't seem to get bad or silly thoughts out of his / her head.....	Never	Sometimes	Often	Always
18.	When my child has a problem, s(he) complains of his/her heart beating really fast.....	Never	Sometimes	Often	Always

19.	My child suddenly starts to tremble or shake when there is no reason for this.....	Never	Sometimes	Often	Always
20.	My child worries that something bad will happen to him/her.....	Never	Sometimes	Often	Always
21.	My child is scared of going to the doctor or dentist	Never	Sometimes	Often	Always
22.	When my child has a problem, (s)he feels shaky.....	Never	Sometimes	Often	Always
23.	My child is scared of heights (eg. being at the top of a cliff).....	Never	Sometimes	Often	Always
24.	My child has to think special thoughts (like numbers or words) to stop bad things from happening.....	Never	Sometimes	Often	Always
25.	My child feels scared if (s)he has to travel in the car, or on a bus or train	Never	Sometimes	Often	Always
26.	My child worries what other people think of him/her.....	Never	Sometimes	Often	Always
27.	My child is afraid of being in crowded places (like shopping centres, the movies, buses, busy playgrounds).....	Never	Sometimes	Often	Always
28.	All of a sudden my child feels really scared for no reason at all.....	Never	Sometimes	Often	Always
29.	My child is scared of insects or spiders.....	Never	Sometimes	Often	Always
30.	My child complains of suddenly becoming dizzy or faint when there is no reason for this.....	Never	Sometimes	Often	Always
31.	My child feels afraid when (s)he has to talk in front of the class.....	Never	Sometimes	Often	Always
32.	My child's complains of his / her heart suddenly starting to beat too quickly for no reason	Never	Sometimes	Often	Always
33.	My child worries that (s)he will suddenly get a scared feeling when there is nothing to be afraid of.....	Never	Sometimes	Often	Always
34.	My child is afraid of being in small closed places, like tunnels or small rooms.....	Never	Sometimes	Often	Always
35.	My child has to do some things over and over again (like washing his / her hands, cleaning or putting things in a certain order).....	Never	Sometimes	Often	Always
36.	My child gets bothered by bad or silly thoughts or pictures in his/her head	Never	Sometimes	Often	Always
37.	My child has to do certain things in just the right way to stop bad things from happening	Never	Sometimes	Often	Always
38.	My child would feel scared if (s)he had to stay away from home overnight.....	Never	Sometimes	Often	Always
39.	Is there anything else that your child is really afraid of?	YES	NO		
	Please write down what it is, and fill out how often (s)he is afraid of this thing:	Never	Sometimes	Often	Always
		Never	Sometimes	Often	Always
		Never	Sometimes	Often	Always

Social Communication Questionnaire (SCQ) – Current Version

Directions: Thank you for taking the time to complete this questionnaire. Please answer each question by circling *yes* or *no*. A few questions ask about several related types of behavior; please circle *yes* if *any* of these behaviors were present during the past 3 months. Although you may be uncertain about whether some behaviors were present or not, please answer *yes* or *no* to every question on the basis of what you think.

- | | | |
|--|-----|----|
| 1. Is she/he now able to talk using short phrases or sentences? If <i>no</i> , skip to question 8. | yes | no |
| 2. Do you have a to and fro “conversation” with her/him that involves taking turns or building on what you have said? | yes | no |
| 3. Does she/he ever use odd phrases or say the same thing over and over in almost exactly the same way (either phrases that she/he hears other people use or ones that she/he makes up)? | yes | no |
| 4. Does she/he ever use socially inappropriate questions or statements? For example, does she/he ever regularly ask personal questions or make personal comments at awkward times? | yes | no |
| 5. Does she/he ever get her/his pronouns mixed up (e.g., saying <i>you</i> or <i>she/he</i> for <i>I</i>)? | yes | no |
| 6. Does she/he ever use words that she/he seems to have invented or made up her/himself; put things in odd, indirect ways; or use metaphorical ways of saying things (e.g., saying <i>hot rain</i> for <i>steam</i>)? | yes | no |
| 7. Does she/he ever say the same thing over and over in exactly the same way or insist that you say the same thing over and over again? | yes | no |
| 8. Does she/he ever have things that she/he seems to have to do in a very particular way or order or rituals that she/he insists that you go through? | yes | no |
| 9. Does her/his facial expression usually seem appropriate to the particular situation, as far as you can tell? | yes | no |
| 10. Does she/he ever use your hand like a tool or as if it were part of her/his own body (e.g., pointing with your finger or putting your hand on a doorknob to get you to open the door)? | yes | no |
| 11. Does she/he ever have any interests that preoccupy her/him and might seem odd to other people (e.g., traffic lights, drainpipes, or timetables)? | yes | no |
| 12. Does she/he ever seem to be more interested in parts of a toy or an object (e.g., spinning the wheels of a car), rather than in using the object as it was intended? | yes | no |
| 13. Does she/he ever have any special interests that are <i>unusual</i> in their intensity but otherwise appropriate for her/his age and peer group (e.g., trains or dinosaurs)? | yes | no |
| 14. Does she/he ever seem to be <i>unusually</i> interested in the sight, feel, sound, taste, or smell of things or people? | yes | no |
| 15. Does she/he ever have any mannerisms or odd ways of moving her/his hands or fingers, such as flapping or moving her/his fingers in front of her/his eyes? | yes | no |
| 16. Does she/he ever have any complicated movements of her/his whole body, such as spinning or repeatedly bouncing up and down? | yes | no |
| 17. Does she/he ever injure her/himself deliberately, such as by biting her/his arm or banging her/his head? | yes | no |

18.	Does she/he ever have any objects (<i>other</i> than a soft toy or comfort blanket) that she/he <i>has</i> to carry around?	yes	no
19.	Does she/he have any particular friends or a best friend?	yes	no
20.	Does she/he ever talk with you just to be friendly (rather than to get something)?	yes	no
21.	Does she/he ever <i>spontaneously</i> copy you (or other people) or what you are doing (such as vacuuming, gardening, or mending things)?	yes	no
22.	Does she/he ever spontaneously point at things around her/him just to show you things (not because she/he wants them)?	yes	no
23.	Does she/he ever use gestures, other than pointing or pulling your hand, to let you know what she/he wants?	yes	no
24.	Does she/he nod her/his head to indicate <i>yes</i> ?	yes	no
25.	Does she/he shake her/his head to indicate <i>no</i> ?	yes	no
26.	Does she/he usually look at you directly in the face when doing things with you or talking with you?	yes	no
27.	Does she/he smile back if someone smiles at her/him?	yes	no
28.	Does she/he ever show you things that interest her/him to engage your attention?	yes	no
29.	Does she/he ever offer to share things other than food with you?	yes	no
30.	Does she/he ever seem to want you to join in her/his enjoyment of something?	yes	no
31.	Does she/he ever try to comfort you if you are sad or hurt?	yes	no
32.	If she/he wants something or wants help, does she/he look at you and use gestures with sounds or words to get your attention?	yes	no
33.	Does she/he show a normal range of facial expressions?	yes	no
34.	Does she/he ever spontaneously join in and try to copy the actions in social games, such as <i>The Mulberry Bush</i> or <i>London Bridge Is Falling Down</i> ?	yes	no
35.	Does she/he play any pretend or make-believe games?	yes	no
36.	Does she/he seem interested in other children of approximately the same age whom she/he does not know?	yes	no
37.	Does she/he respond positively when another child approaches her/him?	yes	no
38.	If you come into a room and start talking to her/him without calling her/his name, does she/he usually look up and pay attention to you?	yes	no
39.	Does she/he ever play imaginative games with another child in such a way that you can tell that each child understands what the other is pretending?	yes	no
40.	Does she/he play cooperatively in games that need some form of joining in with a group of other children, such as hide-and-seek or ball games?	yes	no

Strengths and Difficulties Questionnaire (SDQ)

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months or this school year.

Child's Name

Male/Female

Date of Birth.....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Appendix 2: List of all Intensive Participants to Highlight Which Assessments Were Completed

	EEG Tasks		Neurocognitive Tasks		Demographic Information			
ID	Perceptual Processing	Visual Oddball	Go/NoGo	Switch	Sex	IQ	Age	ROW PVT
519	x	x	x	x	M	129	13.7	115
502	x	x	x	x	F	125	12.9	124
441	x	x	x	x	M	123	13	123
126	x	x	x	x	F	118	12.1	114
458	x	x	x	x	M	115	15.7	120
165	.	.	x	x	F	112	13.9	105
733	x	x	x	x	F	110	14.7	145
326	x	x	x	x	F	108	15.2	137
118	.	.	x	x	F	107	13.4	127
17	.	.	x	x	M	106	14.7	107
48	x	x	x	x	M	105	14	95
496	x	x	x	x	M	105	13.3	116
516	x	x	x	x	M	104	13.5	109
39	x	x	x	x	F	101	15	80
197	x	x	x	x	F	101	11.9	145
715	x	x	x	x	M	100	11.4	93
182	x	x	x	x	M	97	13.5	98
273	x	x	x	x	M	93	14.2	87
131	x	x	x	x	M	91	13.2	85
69	x	x	x	x	F	90	13.6	83
86	x	x	x	x	F	89	14	105
748	x	x	x	x	F	88	11.9	112
185	.	.	x	x	M	88	13.2	.
96	x	x	x	x	F	87	12.7	76
186	x	x	x	x	M	87	13.7	110
745	.	.	.	.	M	87	11.7	87
290	x	x	x	x	M	86	14.3	116
714	x	x	x	x	M	86	13.5	104
322	x	x	x	x	M	84	12.4	112
503	x	x	x	x	M	80	13.6	86
116	x	x	x	x	M	79	14.4	81
130	x	x	x	x	M	79	14.6	91
703	x	x	x	x	M	79	12.8	90
162	x	x	x	.	F	77	11.8	79
37	x	x	x	x	M	76	14.4	75
235	x	x	x	x	F	76	14.4	75
74	.	.	x	x	M	73	12.9	65
269	x	x	x	x	M	71	13	66
108	.	.	x	x	F	70	12.5	72
332	x	x	x	x	M	68	12.6	61
25	x	x	x	x	M	67	14.5	55
106	.	.	x	x	F	66	14.1	78

230	x	x	x	x	M	64	11.8	63
426	.	.	x	x	F	64	14.4	70
243	x	x	x	x	F	63	13.7	72
22	.	.	.	.	F	62	14.7	71
293	.	.	.	.	F	61	11.7	110
449	x	x	.	.	M	60	13.7	66
198	x	x	x	x	M	59	13.7	62
145	x	x	x	.	M	56	15.4	59
57	.	.	x	x	F	54	13.1	72
240	.	.	x	x	M	54	11.4	60
155	.	.	.	.	M	54	11.8	62
320	x	x	x	x	M	51	11.4	89
44	.	.	.	.	M	50	13.4	.
313	.	.	.	.	F	48	12.1	55
311	.	.	.	.	F	35	12.5	.
179	x	.	.	.	F	33	14.2	.
274	x	.	.	.	M	31	15.6	55
492	.	.	.	.	F	30	12.2	55
30	.	.	.	.	F	29	13	55
473	.	.	.	.	M	29	13.1	.
32	.	.	.	.	M	28	14	.
227	x	.	.	.	M	27	13.9	55
253	.	.	.	.	F	27	15.6	.
63	.	.	.	.	M	24	12	.
158	.	.	.	.	F	23	14.5	.
46	.	.	.	.	F	19	11.4	.
54	.	.	.	.	M	19	14.7	.
148	.	.	.	.	M	19	13.7	.
236	.	.	.	.	F	19	13.4	.
238	.	.	.	.	M	19	14.3	.
252	.	.	.	.	M	19	12	.
432	.	.	.	.	F	19	13.2	.
436	.	.	.	.	F	19	15.4	.
462	.	.	.	.	M	19	12.3	.
479	.	.	.	.	M	19	13.8	.
114	.	.	.	.	F	.	14.5	.
196	.	.	.	.	F	.	12.8	.
283	.	.	.	.	M	.	12.8	.
297	.	.	.	.	M	.	14.9	.
334	.	.	.	.	F	.	13.8	.
454	.	.	.	.	F	.	14.6	.

ROWPVT indicates Receptive One Word Picture Vocabulary Test; x = task was completed, . = task was not completed.

Appendix 3: Additional Analysis of MMN Amplitude at F3

MMN amplitude to deviant tones was significantly greater than the response to the standard tones at F3 (mean standard amplitude = -0.34, SD=0.99, range -4.41-1.05; mean deviant amplitude = -1.33, SD=1.38, range -5.49-0.16; $t(42)=5.06$, $p<0.01$), confirming the presence of the MMN.

At F3, no association was found between MMN amplitude and behaviour ($ps=0.36-0.67$) and this pattern remained when outliers were excluded ($ps=0.18-0.99$).

Appendix 4: Key Outcome Parent Questionnaires Used in SNAP Study

Profile of Neuropsychiatric Symptoms (PONS) (key items)

The following questions are about **OPPOSITIONALITY** – child is oppositional, defiant, refuses reasonable requests by adults, deliberately annoys others, argues, blames others for his/her mistakes, refuses chores.

7. How often have you noticed these symptoms of OPPOSITIONALITY in the past month?
☐ All the time ☐ Very often ☐ Quite often ☐ Sometimes ☐ Rarely ☐ Never
8. How much do these symptoms of OPPOSITIONALITY interfere with everyday life?
☐ Extremely ☐ A great deal ☐ Quite a lot ☐ Moderately ☐ A little ☐ Not at all

The following questions are about **AGGRESSION** – child is aggressive, uses abusive language, throws things in anger, makes threatening gestures, or attacks others.

9. How often have you noticed these symptoms of AGGRESSION in the past month?
☐ All the time ☐ Very often ☐ Quite often ☐ Sometimes ☐ Rarely ☐ Never
10. How much do these symptoms of AGGRESSION interfere with everyday life?
☐ Extremely ☐ A great deal ☐ Quite a lot ☐ Moderately ☐ A little ☐ Not at all

The next few questions are about **EXPLOSIVE RAGE** – child suddenly loses temper, has temper outbursts that are 'over the top' or has episodes of temper that rapidly escalates and is explosive.

11. How often have you noticed these symptoms of EXPLOSIVE RAGE in the past month?
☐ All the time ☐ Very often ☐ Quite often ☐ Sometimes ☐ Rarely ☐ Never
12. How much do these symptoms of EXPLOSIVE RAGE interfere with everyday life?
☐ Extremely ☐ A great deal ☐ Quite a lot ☐ Moderately ☐ A little ☐ Not at all

The next few questions are about **ANTISOCIAL BEHAVIOUR** – child steals, starts fires, truants from school, is cruel to animals, gets into trouble with the law, or runs away from home.

13. How often have you noticed these symptoms of ANTISOCIAL BEHAVIOUR in the past month?
☐ All the time ☐ Very often ☐ Quite often ☐ Sometimes ☐ Rarely ☐ Never
14. How much do these symptoms of ANTISOCIAL BEHAVIOUR interfere with everyday life?
☐ Extremely ☐ A great deal ☐ Quite a lot ☐ Moderately ☐ A little ☐ Not at all

The following questions are about **SELF-INJURY** – child bites self, bangs head, picks, scratches, punches, slaps self.

27. How often have you noticed these symptoms of SELF-INJURY in the past month?
☐ All the time ☐ Very often ☐ Quite often ☐ Sometimes ☐ Rarely ☐ Never
28. How much do these symptoms of SELF-INJURY interfere with everyday life?
☐ Extremely ☐ A great deal ☐ Quite a lot ☐ Moderately ☐ A little ☐ Not at all

quickly, feels low and high almost at the same time. It is difficult to predict his/her mood.

45. How often have you noticed these symptoms of LABILE MOOD in the past month?
☐ All the time ☐ Very often ☐ Quite often ☐ Sometimes ☐ Rarely ☐ Never
46. How much do these symptoms of LABILE MOOD interfere with everyday life?
☐ Extremely ☐ A great deal ☐ Quite a lot ☐ Moderately ☐ A little ☐ Not at all

Repetitive Behavior Scale-Revised (RBS-R) – Self-Injurious Subscale

II. Self-Injurious Behavior Subscale

(DEFINITION: movement or actions that have the potential to cause redness, bruising, or other injury to the body, and that are repeated in a similar manner)

7	HITS SELF WITH BODY PART (Hits or slaps head, face, or other body area)	0
1	2	3
8	HITS SELF AGAINST SURFACE OR OBJECT (Hits or bangs head or other body part on table, floor or other surface)	0
1	2	3
9	HITS SELF WITH OBJECT (Hits or bangs head or other body area with objects)	0
1	2	3
10	BITES SELF (Bites hand, wrist, arm, lips or tongue)	0
1	2	3
11	PULLS (Pulls hair or skin)	0
1	2	3
12	RUBS OR SCRATCHES SELF (Rubs or scratches marks on arms, leg, face or torso)	0
1	2	3
13	INSERTS FINGER OR OBJECT (Eye-poking, Ear poking)	0
1	2	3
14	SKIN PICKING (Picks at skin on face, hands, arms, legs or torso)	0
1	2	3