MONASH University

HIGH-FUNCTIONING AUTISM SPECTRUM DISORDER:

PHENOTYPIC SUBGROUPS, DIAGNOSTIC INSTRUMENTS, AND PREDICTORS OF BEHAVIOURAL AND EMOTIONAL FUNCTIONING

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Abstract

Objectives

Autism spectrum disorder (ASD) is highly heterogeneous, with phenotypic variability and behavioural complexity greatest within higher-functioning individuals without intellectual disability (i.e., 'high-functioning ASD'). Historically, differentiating between high-functioning ASD subgroups, Asperger's disorder (AS) and autistic disorder without intellectual disability (i.e., high-functioning autism, HFA), has been extensively debated. While distinction between AS and HFA was found to be unreliable, the phenotypic variability in high-functioning ASD has questioned the utility of DSM-5's dimensional diagnostic approach for this subgroup of ASD. The phenotypic heterogeneity also impacts the reliability of standardised diagnostic tools, making the clinical diagnostic process difficult and challenging in high-functioning ASD. Further to this, the high prevalence of behavioural and emotional difficulties in childhood and early adolescent years adds to the variability and clinical complexity. The association between behavioural and emotional dysfunction in high-functioning ASD, and the core ASD diagnostic features and/or other aspects of neurocognitive functioning is unclear.

The current thesis comprised three main aims: (1) to investigate whether childhood high-functioning ASD subgroups could be identified based on profiles of core ASD symptomatology; (2) to evaluate the relationship between the 'gold standard' ASD diagnostic instruments (the Autism Diagnostic Observation Schedule-Second Edition, ADOS-2; and Autism Diagnostic Interview-Revised, ADI-R) throughout childhood in high-functioning ASD; and (3) to explore predictors of behavioural and emotional functioning within the school setting in childhood high-functioning ASD. These thesis aims were addressed in three separate studies; Aim (1) was the principle aim of this thesis, and Aims (2) and (3) were subsidiary aims.

Method

Sixty-one children (5-14 years; 51 male) without cognitive impairment and with parent reported clinical diagnosis of DSM-IV-TR autistic disorder (*n*=25) or AS (*n*=29), or DSM-5 ASD (*n*=7), participated in Study One. Data from the ADOS-2 and ADI-R were subject to exploratory cluster analysis in this study. Study Two (*n*=57) was limited to verbally fluent participants (i.e., evaluated with Module 3 ADOS-2) and examined the level of agreement between diagnostic classifications according to the ADI-R and ADOS-2 in two childhood age groups (5-8 and 9-13 years). The relationship between ratings of social interaction (SocInt), communication (Comm), and restricted, repetitive behaviours and

interests (RRBI) were also explored. Study Three (n=38) used stepwise linear regression to examine whether teacher ratings of behavioural and emotional functioning could be predicted by factors that represented ASD symptomatology and aspects of neurocognitive functioning.

Results

In Study One, two subgroups with unique profiles across core ASD symptom domains were identified: (i) a Severe Social Impairment subgroup with greater SocInt (ADI-R *Md*=18.5; ADOS-2 *Md*=8.5) and Comm (ADI-R *Md*=16.0; ADOS-2 *Md*=4.0) deficits, but lower lifetime severity of RRBI (ADI-R *Md*=3.5); and (ii) a Moderate Social Impairment subgroup with the reverse pattern of lower SocInt (ADI-R *Md*=14; ADOS-2 *Md*=5.0) and Comm deficits (ADI-R *Md*=12; ADOS-2 *Md*=2.0), but greater lifetime severity of RRBI (ADI-R *Md*=5).

In Study Two, poor to fair agreement (κ=-.21 to .24) was found between diagnostic classifications according to the ADI-R and ADOS-2 algorithms across the two age groups examined. The strength of the association between ratings of SocInt and Comm across the measures was weaker for older (9-13 years: r_s(SocInt)=.23, p>.05, r_s(Comm)=.24, p>.05) compared to younger children (5-8 years: r_s(SocInt)=.59, p<.01, r_s(Comm)=.60, p<.01). Ratings of RRBI were not significantly correlated for either age group (5-8 years: r_s=-.01, p>.05; 9-13 years: r_s=.24, p>.05).

In Study Three, teacher reported Externalising Problems (F=5.13, Adjusted R^2=.23, p<.05), School Problems (F=9.23, Adjusted R^2=.25, p<.01), and Adaptive Skills (F=10.40, Adjusted R^2=.32, p<.01) were significantly predicted by one factor representing working memory, perceptual reasoning, and expressive and receptive language. In contrast, the domains of neurocognitive functioning and ASD symptomatology assessed in this study did not significantly predict Internalising Problems.

Conclusion

This thesis found preliminary evidence supporting that phenotypic subgroups can be defined within high-functioning ASD based on unique profiles of impairment across the social communication and repetitive behaviour dimensions characteristic of the disorder. While similarities between the newly identified subgroups and previous conceptualisations of AS and HFA were evident, the clinical characteristics found to differentiate between the Moderate and Severe Social Impairment subgroups differed to

those previously thought to be important discriminators between AS and HFA. Findings suggest that a combination of dimensional and categorical approaches may be informative in the classification of ASD; subdividing high-functioning ASD into subgroups would reduce the variability represented within the single diagnostic group, thereby providing greater clarity in clinical and educational settings by conveying additional information beyond the diagnostic label.

Further, this thesis demonstrated that the ADI-R and ADOS-2 (Module 3) evaluate different phenotypic aspects in high-functioning ASD, particularly in older children. This variability between the 'gold-standard' diagnostic tests adds complexity to the diagnostic decision making process, demonstrating the need to develop assessment methods to evaluate diagnostic characteristics in this population. In particular, the ASD diagnostic algorithms require further development with high-functioning children before they can be relied upon for diagnosis.

Lastly, findings suggest that cognitive and language difficulties place individuals at greater risk for teacher reported behavioural difficulties and adaptive skill deficits than ASD specific symptomatology. Therefore, cognitive and communication strategies may be more beneficial in improving functioning within the school setting than interventions targeting ASD symptomatology. Further, evidence that neurocognitive functioning and ASD symptomatology were poor predictors of internalising problems in this population suggests that screening emotional wellbeing and targeting this domain in intervention is important to ensure support needs are identified and managed.

Thesis Including Published Works: General Declaration

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes three original papers submitted for publication in peer-reviewed journals. The core theme of the thesis is examination of childhood high-functioning autism spectrum disorder, including diagnostic classification, diagnostic instruments, and characterisation and prediction of functioning. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Psychological Sciences under the supervision of Dr Renee Testa, Professor Efstratios Skafidas, and Professor Christos Pantelis.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 2-4, my contribution to the work involved the following:

Thesis Chapter	Publication Title	Publication Status	Nature and extent of candidates contribution
2	A Cluster Analysis Exploration of Childhood High-functioning Autism Spectrum Disorder Subgroups	*Submitted*	Study design and management; participant recruitment; data collection; data analysis; manuscript synthesis and preparation. Approx. 70% of total contribution.
3	Characterising Current Behaviour and Diagnosing High-functioning Autism Spectrum Disorder using the ADI-R and ADOS-2	*Under Review*	Study design and management; participant recruitment; data collection; data analysis; manuscript synthesis and preparation. Approx 80% of total contribution.
4	Predicting Teacher Rated Behavioural and Emotional Functioning in Childhood High-Functioning Autism Spectrum Disorder based on ASD Symptomatology and Neurocognitive Functioning	*Under Review*	Study design and management; participant recruitment; data collection; data analysis; manuscript synthesis and preparation. Approx 80% of total contribution.

I have renumbered sections of submitted papers in order to generate a consistent presentation within the thesis.

Student Signature: [redacted] **Date:** 14/08/2015

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student and co-authors' contributions to this work.

Main Supervisor Signature: [redacted] **Date:** 14/08/2015

Publications and Conference Proceedings During Candidature

This thesis constitutes manuscripts published, accepted or submitted to academic journals:

Klopper, F., Testa, R., Pantelis, C., & Skafidas, E. (submitted). A cluster analysis exploration of childhood high-functioning autism spectrum disorder subgroups. *The British Journal of Psychiatry*.

Klopper, F., Skafidas, E., Pantelis, C., & Testa, R. (under review). Characterising current behaviour and diagnosing high-functioning autism spectrum disorder using the ADI-R and ADOS-2. *Journal of Autism and Developmental Disorders.*

Klopper, F., Skafidas, E., Pantelis, C., & Testa, R. (under review). Predicting teacher rated behavioural and emotional functioning in childhood high-functioning autism spectrum disorder based on ASD symptomatology and neurocognitive functioning. *Journal of Autism and Developmental Disorders.*

Parts of this thesis were presented or accepted for presentation at local and international conferences and symposiums:

Klopper, F., Testa, R., Pantelis, C. & Skafidas, E. (2014). Subtypes of high-functioning autism spectrum disorder in children. *Poster presented at the International Neuropsychological Society Mid-year Meeting, Jerusalem, Israel; and the Victorian Autism Conference, Melbourne, Australia.*

Klopper, F., Skafidas, E., Chana, G., Zantomio, D., Everall, I.P., Pantelis, C. & Testa, R.R. (2014). A cluster analysis exploration of the clinical phenotype of subgroups within autism spectrum disorder. *Mini-presentation at the Biological Psychiatry Australia (BPA) Conference, Melbourne, Australia.*

Klopper, F., Skafidas, E., Pantelis, C. & Testa, R. (2014). The ADI-R and ADOS-2 in high-functioning autism spectrum disorder: current behaviour and diagnostic algorithms. *Poster presented at the Australasian Society for Autism Research (ASfAR) Biennial Conference, Melbourne, Australia. Accepted for oral presentation at the Asia Pacific Autism Conference, Brisbane (September 2015).*

Klopper, F., Skafidas, E., Pantelis, C., & Testa, R. (2015). Predicting teacher rated behavioural and emotional functioning in childhood high-functioning autism spectrum disorder based on ASD symptomatology and neurocognitive functioning. *Accepted for poster presentation at the Asia Pacific Autism Conference, Brisbane (September, 2015).*

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List of Abbreviations

AD: Autistic disorder

ADHD: Attention deficit hyperactivity disorder

ADI-R: Autism Diagnostic Interview-Revised

ADOS-2: Autism Diagnostic Observation Schedule-Second Edition

ADOS-G: Autism Diagnostic Observation Schedule-Generic Version

AS: Asperger's disorder

ASD: Autism spectrum disorder

BASC-2: Behaviour Assessment System for Children-Second Edition

BASC-2 TRS: Behaviour Assessment System for Children-Second Edition, Teacher Rating Scales

BSI: Behavioural Symptoms Index

CCC-2: Children's Communication Checklist-Second Edition

CDD: Childhood disintegrative disorder

CELF-4: Clinical Evaluation of Language Fundamentals-Fourth Edition

CELF-Preschool 2: Clinical Evaluation of Language Fundamentals-Preschool, Second Edition

DSM-5: Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, Text Revision

ELI: Expressive Language Index

FSIQ: Full-scale intelligence quotient

fMRI: functional magnetic resonance imaging

GCC: General Communication Composite

HFA: High-functioning autism

PDD: Pervasive developmental disorder

PDD-NOS: Pervasive developmental disorder-not otherwise specified

PRI: Perceptual Reasoning Index

PSI: Processing Speed Index

mGluR5: metabotropic glutamate receptor 5

mTOR: mammalian target of rapamycin

RLI: Receptive Language Index

RRBI: Restricted, repetitive patterns of behaviour, interests, and activities

SIDI: Social Interaction Difference Index

SNPs: Single nucleotide polymorphisms

UOT: Unstuck and On Target

WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition

WMI: Working Memory Index

WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence-Third Edition

WRAML-2: Wide Range Assessment of Memory and Learning-Second Edition

VCI: Verbal Comprehension Index

Preface

This thesis comprises five chapters that explore issues associated with the diagnostic classification, diagnostic instruments, and characterisation and prediction of functioning in children and young adolescents with autism spectrum disorder (ASD) without intellectual disability (i.e., 'high-functioning ASD'). Chapter 1 provides a general introduction to this thesis. This includes review of the DSM-IV (American Psychiatric Association, 2000) and DSM-5 (American Psychiatric Association, 2013) approaches to classifying ASD, with a focus on implications of the change in classification system for high-functioning ASD. Aspects of heterogeneity that contribute to the complexity of diagnostic practices, clinical classification, and prediction of outcome in high-functioning ASD are also reviewed. This introduction leads to the three general aims of this thesis; Aim One formed the primary focus of this thesis and thus the literature review (Chapter 1) and thesis discussion (Chapter 5) examines issues associated with this aim in the greatest detail. Chapters 2, 3, and 4 are experimental chapters that present manuscripts examining the three thesis aims. Chapter 2 details an investigation of childhood subgroups within high-functioning ASD; Chapter 3 examines the level of agreement between the 'gold standard' ASD diagnostic tools in high-functioning children with clinically diagnosed ASD; and Chapter 4 explores predictors of behavioural and emotional functioning in childhood high-functioning ASD. Lastly, Chapter 5 presents a General Discussion, which integrates the main findings with previous research in high-functioning ASD and discusses broader implications of the research. The experimental chapters of this thesis (i.e., Chapters 2, 3, and 4) represent manuscripts that have been submitted for publication in peer-reviewed journals. Given this, a degree of repetition across the chapters was unavoidable; however, efforts have been made to limit this where possible. The experimental chapters include a preamble, which assists in linking the chapters to maintain cohesion throughout the thesis.

CHAPTER 1: BACKGROUND

1.1. Chapter Introduction

This chapter reviews literature relevant to the main aims of this thesis: (1) to investigate the presence of phenotypic subgroups in children with autism spectrum disorder (ASD) without cognitive impairment (i.e., 'high-functioning ASD'); (2) to examine the 'gold standard' diagnostic tools in high-functioning ASD throughout childhood years; and (3) to explore whether ASD symptomatology and aspects of neurocognitive functioning (general cognitive ability, new learning and memory, language, and pragmatic communication) can predict behavioural and emotional functioning within this population.

The most recent edition of the Diagnostic and Statistic Manual of Mental Disorders (i.e., DSM-5, American Psychiatric Association, 2013) has progressed from a categorical conceptualisation of pervasive developmental disorders (PDD) to a dimensional approach of ASD. This chapter firstly introduces the DSM-IV (American Psychiatric Association, 2000) defined subtypes of PDD and reviews previous concerns regarding the reliability and validity of the diagnostic categories that led to modification of the classification of PDD in DSM-5. Although not reflected in DSM-IV classifications, clinicians and researchers commonly differentiated AD into *low*- and *high*-functioning subgroups based on the presence or absence of intellectual disability, respectively; between 50-75% of individuals with PDD also met criteria for intellectual disability (i.e., full-scale intelligence quotient less than 70) (Matson & Shoemaker, 2009). The differentiation between high-functioning ASD subgroups, autistic disorder (AD) without cognitive impairment (i.e., 'high-functioning autism', HFA) and Asperger's disorder (AS), forms a particular focus of this review, given the relevance to the principle aim of this thesis. The concept of an *autism spectrum*, as represented in DSM-5, is introduced and key changes from DSM-IV to DSM-5 that are relevant to this thesis are summarised. Sources contributing to significant heterogeneity in ASD are subsequently reviewed and statistical approaches to identifying high-functioning ASD phenotypic subgroups to reduce the variability currently represented within the single ASD diagnostic group are discussed. Lastly, this chapter introduces current assessment guidelines for ASD diagnosis, with a focus on the utility of the 'gold standard' ASD diagnostic tools within high-functioning ASD.

1.2. DSM-IV Pervasive Developmental Disorders (PDD)

1.2.1. Section Introduction

The DSM-IV (American Psychiatric Association, 1994) and its revision (i.e., DSM-IV-TR, American Psychiatric Association, 2000) previously defined five categories of PDD, namely: AD, AS, pervasive developmental disorder–not otherwise specified (PDD-NOS), childhood disintegrative disorder (CDD), and Rett's Disorder. The core diagnostic features of the PDD subtypes were pervasive impairment in reciprocal social interaction; pervasive impairment in communication skills; and/or the presence of restricted, repetitive patterns of behaviour, interests and activities (RRBI). Diagnostic criteria differentiated between the DSM-IV categories by a number of clinical features, including whether an individual presented with impairment within two or three of the core symptom domains; the severity of impairment within each domain; early language development; cognitive ability; and developmental trajectories (e.g., period of language or skill regression) (American Psychiatric Association, 2000). While DSM-IV included CDD and Rett's Disorder within PDD, distinctions in developmental course, clinical characteristics, and aetiological mechanisms questioned their association with the other subtypes of PDD (see Gillberg, 1994; Malhotra & Gupta, 2002; Neul et al., 2010; Rutter, 1994). Given this, clinical and research settings commonly conceptualised only AD, AS, and PDD-NOS as representing the autism spectrum. The below sections briefly describe key clinical features associated with AD, AS, and PDD-NOS; CDD and Rett's disorder are excluded from this discussion due to their distinction from the other subtypes typically considered to represent the autism spectrum ('PDD' henceforth used to represent AD, AS, and PDD-NOS only). This section concludes with a review of the concerns that contributed to debate regarding the utility of differentiating between PDD subtypes. The validity of distinguishing between high-functioning ASD subgroups (i.e., AS and HFA) forms a focus of this discussion, given relevance to the principle aim of this thesis (Aim One).

1.2.2. Autistic Disorder (AD)

Autistic disorder was defined by impairment across domains of reciprocal social interaction, communication, and RRBI (American Psychiatric Association, 2000). A meta-analysis of studies from 2000-2008 estimated the prevalence of AD to range from 9.2 to 40.5/10,000, with an average prevalence of 20.6/10,000 (Fombonne, 2009).

As stated in the Chapter Introduction, despite not being included in DSM-IV the term HFA was often used across clinical and research settings to describe individuals with AD

without intellectual disability. Thus, HFA referred to individuals with symptomatology across the three core symptom domains characteristic of AD, but without a history of intellectual disability, typically operationalized as full-scale intelligence quotient (FSIQ) greater than 70 (Ghaziuddin & Mountain-Kimchi, 2004; Koyama, Tachimori, Osada, Takeda, & Kurita, 2007; Mukaddes, Herguner, & Tanidir, 2010). Following systematic review of the literature, Fombonne (2003, 2005) reported that approximately 30% of individuals with AD had intellectual functioning within normal limits (range of 0-60% across past studies). While there is a well-recognised over-representation of boys with AD, with an average population estimate of a 4.2:1 male to female ratio (Fombonne, 2009), the gender ratio varies with intellectual ability; a 1.9:1 male to female ratio was reported in individuals with intellectual disability, while a 5.75:1 male to female ratio was found in higher-functioning individuals with intellectual ability in the average range (Fombonne, 2003, 2005).

1.2.3. Asperger's Disorder (AS)

Asperger's disorder described individuals without intellectual disability but with pervasive impairment in reciprocal social interaction and the presence of RRBI (American Psychiatric Association, 2000). In contrast to AD, individuals with AS did not show clinically significant deficits in communication. This criterion was operationalized by the absence of delay or deviance in language acquisition, whereby individuals who used single communicative words by age two and spontaneous and meaningful phrases by age three were classified with AS (American Psychiatric Association, 2000). Fombonne (2009) estimated the average AS prevalence to be one third or one quarter of AD, affecting approximately 6/10,000 individuals. The authors acknowledged, however, that this estimate was based on a limited number of studies due to the recent introduction of AS as a separate diagnostic category in DSM-IV; thus, the prevalence estimate was considered conservative.

Similar to HFA, individuals with AS had no history of intellectual disability and were considered 'high-functioning'. The primary clinical features distinguishing HFA and AS were related to early language development, as described above; however, given the difficulties of relying on retrospective parent report to characterise early developmental milestones, in the clinical setting children diagnosed with a language disorder at a later age were not considered to have AS. An additional area of confusion in both clinical and research settings was application of the DSM-IV hierarchy rule, which stipulated that a diagnosis of AD was given precedence over AS (American Psychiatric Association, 2000).

Several researchers argued that although individuals with AS may not have significant delays in language acquisition, they commonly presented with other communication deficits that would satisfy this second criterion for AD, thereby making a diagnosis of AS virtually unattainable (Eisenmajer et al., 1996; Mayes, Calhoun, & Crites, 2001; Miller & Ozonoff, 1997; Szatmari, Archer, Fisman, Streiner, & Wilson, 1995). Debate regarding differentiation between AS and HFA is expanded further below in section 1.2.6.

1.2.4. Pervasive Developmental Disorder–Not Otherwise Specified (PDD-NOS)

Pervasive developmental disorder–not otherwise specified categorised individuals with characteristics of PDD who did not meet full criteria for AD or AS (American Psychiatric Association, 2000). All individuals with PDD-NOS displayed pervasive impairment in social interaction; however, they did not meet criteria for pervasive communication impairment or RRBI (American Psychiatric Association, 2000). Fombonne (2009) estimated the average prevalence of PDD-NOS to be 37.1/10,000, indicating that it represented a high proportion of individuals diagnosed with PDD.

1.2.5. Challenges Associated with DSM-IV Defined Subtypes of PDD

The reliability and validity of differentiating between AD, AS, and PDD-NOS according to the existing DSM-IV criteria was extensively debated. Variability in diagnostic practices in classifying individuals with each subtype was evident between clinicians (K. Williams et al., 2008) and across autism assessment service providers (Lord, Petkova, et al., 2012), and the distinction between subtypes was reportedly unstable longitudinally (Daniels et al., 2011; Woolfenden, Sarkozy, Ridley, & Williams, 2012). In Australia, clinicians acknowledged 'upgrading' a child's symptoms to meet criteria for a diagnosis of AD or other PDD subtype in cases where there was diagnostic uncertainty (Skellern, Schluter, & McDowell, 2005). Diagnostic confusion was greater for milder forms of PDD (i.e., AS and PDD-NOS) rather than classical AD. Skellern and colleagues reported that the uncertainty in diagnosis could have reflected complexity in determining the aetiology of symptomatology, such as whether the clinical features represented a transient stage of development, were related to environment or family stressors, or were associated with other conditions (e.g., language disorders, attention dysfunction, emotional regulation, or intellectual disability). While providing a clinical diagnosis in this situation served to increase access to services in a system that requires categorical classification for funding support, it further reduced the validity of the clinical label(s).

Together, the abovementioned concerns questioned the reliability and validity of the DSM-IV defined PDD subtypes and prompted debate regarding the most meaningful classification for this population (see Happe, 2011; Willemsen-Swinkels & Buitelaar, 2002). The controversy centered on whether the DSM-IV categories of PDD represented meaningful and qualitatively distinct disorders (i.e., different developmental trajectories, responsiveness to intervention, or aetiological mechanisms), or whether all individuals with PDD exhibited the same core deficits and were differentiated only by the severity of impairment, suggesting a dimensional conceptualisation of an *autism spectrum*. As noted in earlier sections, despite HFA not being included as an independent diagnostic category in DSM-IV, this term was commonly used clinically and in research settings to describe individuals with AD without intellectual disability. The validity of the distinction between HFA and AS was extensively debated (see Ghaziuddin, 2010; Tsai, 2013), with researchers questioning whether it was informative to differentiate individuals without intellectual disability into these subgroups based on differences in early language milestones (Bennett et al., 2008; Mayes et al., 2001). Research examining this issue is reviewed in the section below.

1.2.6. Debate Regarding the Differentiation between Asperger's Disorder and High-functioning Autism (HFA)

In the clinical setting, reliably diagnosing AS and HFA was hampered by difficulties establishing early language development retrospectively (American Psychiatric Association, 2010), whilst research studies were challenged by the use of different diagnostic criteria to define the subgroups across studies. For example, as described section 1.2.3, it was argued that applying the DSM-IV hierarchy rule significantly limited or precluded a diagnosis of AS (Eisenmajer et al., 1996; Mayes et al., 2001; Miller & Ozonoff, 1997; Szatmari et al., 1995), as individuals with PDD without intellectual disability who met age expected language developmental milestones still exhibited deficits in communication (Lewis, Murdoch, & Woodyatt, 2007; Volden, Coolican, Garon, White, & Bryson, 2009). To address this issue, a number of studies reversed the DSM-IV hierarchy rule to give a diagnosis of AS precedence over AD (Bennett et al., 2008; Starr, Szatmari, Bryson, & Zwaigenbaum, 2003; Szatmari et al., 2009; Szatmari et al., 2000). In doing so, the diagnostic classification of individuals differed across studies, limiting the ability to compare results in a reliable manner (Klin, Pauls, Schultz, & Volkmar, 2005).

Further to issues regarding consistently classifying individuals with HFA and AS, it proved difficult to establish reliable similarities and differences between the groups

when they were directly compared. Early language developmental milestones were not a consistent and reliable differentiator of profiles of neuropsychological functioning (Ghaziuddin & Mountain-Kimchi, 2004; Klin, Volkmar, Sparrow, Cicchetti, & Rourke, 1995; Koyama et al., 2007; Manjiviona & Prior, 1995; Mayes & Calhoun, 2001; Miller & Ozonoff, 2000), linguistic ability (Lewis et al., 2007; Mayes & Calhoun, 2001), or RRBI (South, Ozonoff, & McMahon, 2005). Mayes and Calhoun (2001) additionally reported that language-defined subgroups did not display significant differences in ASD characteristics (defined in this study as social interaction, perseveration, somatosensory disturbance, atypical developmental pattern, mood disturbance, and problems with attention and safety), motor functioning, or psychopathology (e.g., anxiety, depression, oppositional and aggressive behaviour). As early language developmental milestones were not consistently associated with other domains important for child development and functioning, results suggested that dividing high-functioning ASD into subgroups based on early language development may not be informative.

Consistent with this view, research did not support divergent developmental trajectories between HFA and AS. When symptom profiles were retrospectively examined, parent reported difficulties of individuals with HFA were more severe than those with AS during preschool years; however, the differences between groups diminished with age (Dissanayake, 2004; Gilchrist et al., 2001). When prospective longitudinal data was examined, both the prognosis (Szatmari et al., 2000) and predictors of outcome (Szatmari, Bryson, Boyle, Streiner, & Duku, 2003) differed between HFA and AS. Individuals with AS maintained advantage over HFA over time; however, similar rates of improvement across the subgroups suggested that they followed similar developmental trajectories (Starr et al., 2003; Szatmari et al., 2000). The authors suggested that rather than conceptualizing AS and HFA as categorically distinct disorders, it may be most informative to consider them as representative of different, but potentially overlapping, developmental trajectories of the *single* disorder of ASD (Starr et al., 2003; Szatmari, 2000; Szatmari et al., 2003).

Taken together, research findings questioned the clinical utility of defining HFA and AS as distinct subgroups based on the existing criteria, leading to alternative avenues of differentiating higher-functioning individuals into clinical groups being explored. The impact of language on functioning was of key interest given the historical importance of this variable in the classification of ASD. When high-functioning subgroups were instead defined based on structural language ability, ASD with structural language impairment

evidenced by deficits in grammar and syntax ('HFA'), was reportedly associated with greater ASD symptomatology and poorer adaptive functioning than ASD without structural language impairment ('AS') (Bennett et al., 2008; Szatmari et al., 2009). There was only limited agreement between the allocation of individuals to subgroups when children were classified according to early language milestones compared to structural language ability (Bennett et al., 2008), showing that overlap between the two indices of functioning was limited. The greater prognostic value of the latter approach suggested that structural language ability might provide a clinically useful distinction of high-functioning ASD subgroups by helping to inform developmental trajectories.

In contrast to Bennett et al. (2008), however, Szatmari et al. (2009) reported that subgroups defined by structural language impairment were differentiated primarily by symptom severity and followed similar trajectories over time. Such differences in the severity of impairment, as opposed to distinctions in the profile of phenotypic characteristics between subgroups, could be more supportive of a dimensional classification system rather than the categorical subtype approach. Language functioning and ASD symptoms could both be considered as dimensions of functioning, with impairment in both dimensions potentially associated with a different developmental trajectory in ASD compared to when ASD symptomatology occurs in isolation of structural language impairment.

Consistent with this conceptualisation, the DSM-5 classification of ASD has moved from subtypes to a dimensional notion of a spectrum disorder (American Psychiatric Association, 2013). In contrast to the DSM-IV categorical system (American Psychiatric Association, 1994, 2000), all individuals (i.e., AD, AS, and PDD-NOS) are classified within a single diagnostic group of ASD (all DSM-IV subgroups in combination henceforth referred to as ASD). A further change in DSM-5 is the classification of ASD according to a dyad of core diagnostic features that vary in the severity of impairment across individuals, rather than the triad of symptoms as represented in DSM-IV. The DSM-5 diagnosis of ASD is based on: 1) the degree of impairment in 'social communication and interaction' skills (henceforth referred to as 'social communication' deficits), and 2) the presence of RRBI. An individual is described with regard to the severity of impairment within each of these two core domains, demonstrating the potential dissociation between the levels of impairment across symptom areas (e.g., where an individual may require 'very substantial support' with regard to social communication deficits, but comparatively less support to manage aspects of RRBI). In recognition of the variability

in ASD, DSM-5 prescribes that individuals' level of cognitive and language ability be specified alongside core ASD symptom severity ratings. The implications of conceptualising ASD within a dimensional rather than categorical framework are discussed in the section below.

1.3. DSM-5 Autism Spectrum Disorder (ASD): Progression to a Dimensional Classification System

In contrast to the DSM-IV (American Psychiatric Association, 1994, 2000) focus on differences between individuals with ASD to define clinical subgroups, the DSM-5 (American Psychiatric Association, 2013) dimensional approach emphasises a dyad of impairments that are core to the disorder and similar across individuals; social communication deficits and RRBI. Social communication deficits are described across three symptom areas (i.e., impairments in social-emotional reciprocity, deficits in nonverbal communication, *and* difficulties in developing, maintaining, and understanding social relationships). While individuals must show deficits within each of the three subdomains of social communication to meet diagnostic criteria for ASD, each individual will vary with regard to the type and combination of deficits. DSM-5 also prescribes that individuals with ASD show evidence of at least two symptoms of RRBI (i.e., stereotyped/repetitive speech or movements; adherence to routines; restricted interests; *or*, hyper- or hypo-sensory responsiveness) across the lifetime, with significant variability in the manifestation of RRBI symptomatology observed. An individual may even meet criteria for ASD if there is no *current* evidence of impairment associated with RRBI.

While progression to the dimensional approach in DSM-5 eliminates the previous confusion in diagnosing subtypes, as per DSM-IV, the removal of defined subtypes and classification of all individuals within the single diagnostic category increases the phenotypic heterogeneity included under this diagnostic label. The variability in the expression and combination of social communication and RRBI symptomatology both between individuals with ASD, and within individuals over the lifetime, raises concerns that the new DSM-5 classification system minimizes potentially important differences between individuals. Debate remains regarding the possibility of categorically distinct subtypes, particularly with individuals without intellectual disability, where phenotypic variability and complexity is greatest. The potential reintroduction of high-functioning ASD subgroups in future revisions of the DSM continues to be discussed (Tsai, 2013). By creating the single diagnostic category in DSM-5, we can explore new ways of reducing

the phenotypic heterogeneity represented within the single diagnostic group. Using knowledge gained from the latest research demonstrating areas of heterogeneity in high-functioning ASD, there is the potential to redefine clinically meaningful subgroups in this population. The following section examines areas of heterogeneity in high-functioning ASD that contribute to the clinical complexity of the disorder.

1.4. DSM-5 Defined High-functioning ASD is a Heterogeneous Disorder

1.4.1. Section Introduction

ASD presents a diagnostic and clinical conundrum, as individuals can present with variability in the manifestation of the core ASD features as well as areas of cognitive, behavioral and emotional functioning not included in the diagnostic criteria. Complexity and variability in behaviour appears to be particularly apparent in high-functioning ASD; higher functioning individuals with ASD are more likely to experience psychiatric difficulties, such as depression and anxiety, than lower functioning individuals (Knoll, 2008; Witwer & Lecavalier, 2010). There is also greater variability in outcome, with some individuals gaining functional independence and employment in adulthood, while others require a greater degree of lifelong support (Hofvander et al., 2009; Whitehouse, Watt, Line, & Bishop, 2009). This variability in high-functioning ASD adds to the complexity of clinical diagnostic decision-making, prediction of outcome, and theoretical frameworks of diagnostic classification. The variability in clinical presentation likely reflects multiple, interacting aetiological mechanisms, including genetic and environmental influences. This section will review a number of the key constructs that vary between individuals with high-functioning ASD, including developmental trajectories, cognition, language functioning, and behavioural and emotional wellbeing. Variability in possible aetiological mechanisms in ASD that may contribute to the clinical variability in this disorder are also discussed.

1.4.2. Developmental Course

A recent meta-analysis of 85 studies reported that 32.1% of individuals with ASD show regression in skills or language during early development, with an average age of onset of 1.78 years (Barger, Campbell, & McDonough, 2013). There was variability with regard to the type of regression; 24.9% experienced language regression; 38.1% showed regression in language and/or social skills; 32.5% had mixed regression (e.g., adaptive functioning and language/social skills); and 39.1% were classified with unspecified regression. Prospective examination of skill development revealed that 86% of young children with ASD showed regression in social communication skills within the first

three years of life, whilst only 16% of parents reported observing a loss of skills during this period (Ozonoff et al., 2010). Regression may therefore occur at much higher rates than is noted by parents. While a number of factors have been hypothesised to be associated with regression in ASD, including epilepsy (Oslejskova et al., 2008), genetics (Molloy, Keddache, & Martin, 2005), and mitochondrial disease (Shoffner et al., 2010), the aetiology and the long-term impact of regression in ASD remains unclear (for review see K. Williams, Brignell, Prior, Bartak, & Roberts, 2015).

In contrast to retrospective parent reports suggesting that ASD symptom severity across core domains generally declines over time, particularly within social interaction and communication domains (Fecteau, Mottron, Berthiaume, & Burack, 2003), a number of recent prospective studies have demonstrated that trajectories can be more varied, with symptomatology that may worsen or improve throughout development (Gotham, Pickles, & Lord, 2012; Lord, Luyster, Guthrie, & Pickles, 2012; Szatmari et al., 2015; Venker, Ray-Subramanian, Bolt, & Weismer, 2014). While consistent ASD symptom severity for individuals with moderate-severe symptomatology has been reported for the vast majority of individuals (i.e., 78-88%) during preschool (Szatmari et al., 2015; Venker et al., 2014) and adolescent years (Gotham et al., 2012), a smaller proportion of individuals experience improving (7-14%; Gotham et al., 2012; Szatmari et al., 2015; Venker et al., 2014) or worsening (8-9%; Gotham et al., 2012; Venker et al., 2014) symptomatology over time.

Predictors of ASD symptom trajectories differ across past studies, with nonverbal cognitive ability (Venker et al., 2014), verbal cognitive ability (Gotham et al., 2012), language functioning (Venker et al., 2014), adaptive skills (Gotham et al., 2012; Venker et al., 2014), and gender (Szatmari et al., 2015) significantly associated with the identified trajectories across some but not all studies. Other factors that may be important in understanding ASD symptom trajectory include social and environmental influences, such as the strength of family, peer, and student-teacher relationships; exposure to stressful or challenging life events (e.g., parental divorce, bullying or peer rejection); and access to interventions. Personal variables, such as temperament, resilience, and emotional wellbeing may also contribute to ASD symptomatology by affecting the way in which a child interacts with their environment and other individuals.

When examining trajectories of adaptive skills, Szatmari et al. (2015) described three distinct developmental courses: 1) lower adaptive functioning at study outset, and

worsening functioning over time (29.2%); 2) moderate adaptive functioning at initial assessment and consistent skill level over time (49.9%); and 3) higher adaptive functioning at baseline and improving trajectory (20.9%). Interestingly, there was limited overlap between the trajectories of ASD symptomatology and adaptive functioning throughout development, indicating that improvement in one dimension did not necessarily convey improvement in the other. Moreover, it suggests that predictors for ASD symptomatology and adaptive skills may differ. As with ASD symptomatology, the aetiology of adaptive skill deficits is likely multifactorial, with aspects associated both with ASD symptomatology, neurocognitive functioning, and the abovementioned family, personal, and environmental variables potentially impacting adaptive functioning throughout development.

1.4.3. Cognitive Functioning

The level of intellectual functioning impacts the clinical phenotype of ASD. In comparison to low-functioning ASD, individuals with high-functioning ASD generally present with less severe ASD symptomatology (Mayes & Calhoun, 2004, 2011), better adaptive functioning (Liss et al., 2001), and more positive outcome (Harris & Handleman, 2000; Howlin, Goode, Hutton, & Rutter, 2004). Thus, inclusion of all individuals with ASD within a single diagnostic category, irrespective of cognitive ability, means that the diagnostic label represents individuals with significant differences in clinical features and support needs. For example, non-verbal individuals with severe cognitive and language impairment are now included within the same diagnostic category as individuals who are highly intelligent but show severe social-pragmatic impairments. Accordingly, DSM-5 has emphasised the importance of cognition in understanding the phenotype and developmental trajectory in ASD by including intellectual ability as a specifier alongside ASD diagnosis.

Beyond looking at the presence or absence of intellectual disability as an overall index of functioning in ASD, research has examined the patterns of strengths and weaknesses across domains of cognition in the search for potential characteristic or diagnostic cognitive profiles. When individuals with ASD were included within a single sample (i.e., not differentiated into AS, AD or PDD-NOS subgroups), participants were equally distributed between three subgroups based on performance across verbal and nonverbal domains: comparable verbal and nonverbal abilities, superior verbal to nonverbal ability, and superior nonverbal to verbal ability (Tager-Flusberg & Joseph, 2003). This demonstrated the variability in cognitive ability in ASD and showed that a

single profile was not representative of all individuals. In high-functioning ASD, profiles were examined as a means of potentially validating categorical differentiation between individuals. Previous research reported that individuals with HFA have superior nonverbal to verbal cognitive ability, while individuals with AS exhibit the reverse pattern, suggesting that different cognitive profiles might be important phenotypic markers of the two subgroups (Klin et al., 1995). This proposition, however, was challenged by evidence that the disparate cognitive profiles were not highly consistent within each diagnostic group, with both AS and HFA subgroups containing individuals who had profiles typical of the other subgroup (Ghaziuddin & Mountain-Kimchi, 2004). It has also been suggested that individuals with high-functioning ASD may show a characteristic profile on subtests of Wechsler Intelligence scales, with stronger performances on Block Design (i.e., evaluating visuoperceptual and visuoconstruction abilities) and weaker performances on Comprehension (i.e., assessing social knowledge and judgement) (Noterdaeme, Wriedt, & Hohne, 2010); however, this profile has not been consistently evident across all individuals (Siegel, Minshew, & Goldstein, 1996; D. L. Williams, Goldstein, Kojkowski, & Minshew, 2008). Overall, this variability suggests that intelligence is best conceptualised independently from diagnostic classification (Ankenman, Elgin, Sullivan, Vincent, & Bernier, 2014), as there is no profile of cognitive strengths and weaknesses that is consistently observed across individuals to support its use as a diagnostic marker in high-functioning ASD.

A number of theories attempting to account for the social communication deficits and RRBI diagnostic features of ASD from the perspective of neurocognitive functioning have been proposed; three of the most prominent theories focus on executive dysfunction, impaired theory of mind, and weak central coherence. Understanding the contribution of neurocognitive functioning to ASD symptomatology could assist in identifying targets for intervention with the aim of reducing core deficits of the disorder. While a detailed review of these competing theories is beyond the scope of this thesis, each theory will be introduced and discussed briefly below (for comprehensive review see Happe & Frith, 2006; Levy, 2007; Pisula, 2010; Vanegas & Davidson, 2015).

The executive functioning theory of ASD proposes that executive level deficits, such as difficulties with shifting attention, cognitive flexibility, planning, working memory, self-monitoring and inhibiting behaviour, form primary deficits in ASD (Pennington & Ozonoff, 1996; Russell, 1997). For example, it has been thought that difficulties shifting attention and the tendency to perseverate may be associated with aspects of RRBI.

Profiles of executive functioning in ASD have received extensive research attention; however, studies have not identified a consistent set of executive skills that are impaired in the disorder (Geurts, Corbett, & Solomon, 2009; Geurts, Sinzig, Booth, & Happe, 2014; Hill, 2004; Russo et al., 2007). This challenges the notion that executive deficits can underlie core aspects of the ASD phenotype. Geurts et al. (2014) re-examined data from three studies (Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004; Happe, Booth, Charlton, & Hughes, 2006; Sinzig, Morsch, Bruning, Schmidt, & Lehmkuhl, 2008) that found different patterns of executive functioning in ASD and reported that between 32-75% of individuals with ASD did not show impairment in the executive skills assessed (inhibition, working memory, cognitive flexibility, and planning). An important consideration is the method used to evaluate executive functioning skills; all executive skills were measured via standardised assessment, without inclusion of parent/teacher behavioural ratings. The structured testing environment can limit the ability to observe executive level difficulties, which may otherwise be evident across other environments where there is less structure and greater cognitive demands. Nonetheless, the research to date does not support consistent impairment in a specific component(s) of executive functioning in this disorder, suggesting that executive deficits cannot fully account for the varied profiles of social communication functioning and RRBI evident in this population.

The theory of mind account of ASD proposes that the social difficulties in ASD are underpinned by deficits in forming mental representations of the thoughts and feelings of others in social interaction (for review see Pisula, 2010). Deficits in inferring mental states based on facial expressions, for example, could contribute to the limited empathic responses often seen in people with ASD. Impaired joint attention, which is evident early in development in children with ASD, has been proposed as precursor to later deficits in theory of mind (Baron-Cohen & Ring, 1994), highlighting an important focus of intervention in attempt of ameliorate later impairment in social communication. While the theory of mind account provides a theoretical explanation for the social communicative and pragmatic deficits of ASD (see section 1.4.4: Language Functioning for discussion of pragmatic communication in ASD), it has been criticised for not adequately accounting for the non-social deficits in ASD, such as RRBI (Frith & Happe, 1994). This theory is also challenged by evidence that autism specific social communication deficits are evident prior to the typical age of theory of mind development (Levy, 2007), demonstrating that there must be other interacting mechanisms at least partly contributing to the profile of difficulties in ASD.

The weak central coherence theory (Frith, 1989; Frith & Happe, 1994) proposes that individuals with ASD have a cognitive bias towards finer details in the environment (i.e., local information processing), and difficulty integrating these local components to develop an overall gestalt (i.e., global information processing). It was thought that this deficit may underpin the superior visuospatial skills (e.g., Block Design subtest on Wechsler Intelligence scales) often thought to be associated with ASD. Further, this cognitive bias was proposed to be associated with difficulties recognising facial expressions and emotions, and weaknesses in language processing (e.g., by a tendency to focus on single words at the detriment of interpreting meaning provided by the broader context of a sentence) often observed in ASD. Weak central coherence has also been thought to be associated with aspects of RRBI (Chen, Rodgers, & McConachie, 2009), potentially contributing to the preference for sameness and narrow interests. Yet, not all individuals with ASD show weak central coherence and the expected profile of superior visual skills, and people with ASD can process information globally when instructed to do so (Happe & Frith, 2006; Pisula, 2010). Rather than weak central coherence representing a deficit that is causative in the development of core ASD impairments, it may represent one area of difficulty commonly occurring alongside ASD symptomatology, potentially within the broader domain of executive dysfunction (for review see Happe & Frith, 2006).

The aforementioned theories provide a framework to understand some clinical features associated with ASD, but no theories to date have adequately accounted for the presence of social communication deficits together with RRBI in this disorder, or for the range of deficits observed in this population. Given the diversity in this clinical population, it seems most reasonable that multiple and interacting deficits in cognition likely contribute to the phenotypic characteristics of this disorder. More recently, it has been proposed that ASD symptom domains may reflect distinct causal mechanisms at the levels of genetics, neurology cognition, and behaviour. The theory of the 'fractionable autism triad' (i.e., reflecting social interaction, communication and RRBI, as per DSM-IV) proposes that theory of mind, executive dysfunction, and weak central coherence may all be relevant to understanding the different areas of impairment in ASD (Brunsdon & Happe, 2014; Happe & Ronald, 2008; Happe, Ronald, & Plomin, 2006). Consistent with this notion, it may be possible to identify high-functioning ASD subgroups differentiated by their pattern of ASD specific symptomatology, reflecting underlying distinctions at the level of neurocognitive functioning. Differences of this kind may implicate different brain regions or networks in symptom development and disorder expression,

potentially representing different aetiological mechanisms on the pathway to disorder development. This, in turn, could raise considerations for intervention needs and clinical management. Further, the identification of distinct subgroups would argue against the DSM-5 dimensional approach.

1.4.4. Language Functioning

Language is multifaceted and complex, including domains of morphology, syntax, semantics, prosody, phonology and pragmatic communication. The variability and complexity of language functioning in ASD has made it a primary focus of research. While deficits in the social use of language (i.e., pragmatics) are common to all individuals with ASD (Volden et al., 2009), impairment across other domains of language is more variable. Structural language impairments, such as impaired use of grammar and syntax, are commonly observed (reported frequencies ranging from 57% (Loucas et al., 2008) to over 70% (Kjelgaard & Tager-Flusberg, 2001) in ASD research samples). The high prevalence of structural language impairment in ASD has raised questions about a potential shared aetiology between the two diagnoses, with the boundaries between the disorders the subject of ongoing debate (D.V.M Bishop, 2010; Taylor, Maybery, Grayndler, & Whitehouse, 2014). Individuals with ASD can also have unusual language functioning, including immediate and delayed echolalia, stereotyped or idiosyncratic phrasing, or unusual tone or intonation of speech. A review of functioning in ASD across all language domains is beyond the scope of the current thesis (for review see Eigsti, de Marchena, Schuh, & Kelley, 2011; Tager-Flusberg & Caronna, 2007; Tager-Flusberg, Paul, & Lord, 2005). Relevant to this study given the historical debate of using language functioning to differentiate high-functioning ASD subgroups, the variability and potential prognostic importance of early language development compared with structural language functioning in ASD is briefly reviewed below. Profiles of expressive and receptive language functioning, and also difficulties associated with higher-level, pragmatic communication in ASD are also considered.

Delays or difficulties in speech and language development are commonly amongst the first concerns reported by parents in children with ASD (De Giacomo & Fombonne, 1998). Language development in ASD is highly variable; while individuals often have delayed language development, with an estimated 25-50% of individuals remaining nonverbal, a proportion of children with ASD meet language milestones at age expected rates (for review see Eigsti et al., 2011; Tager-Flusberg & Caronna, 2007; Tager-Flusberg et al., 2005). As described in section 1.2, the age of language acquisition was previously

used by clinicians and researchers as a means of differentiating individuals with high-functioning ASD into AS and HFA subgroups; contrary to this notion, it has been suggested that the presence or absence of structural language impairment may be more strongly associated with adaptive skills and ASD symptom severity in later childhood, thereby potentially having greater prognostic value in differentiating high-functioning ASD subgroups (i.e., rather defining subgroups based on the presence or absence language delay) (Bennett et al., 2008; Szatmari et al., 2009). Bennett et al. reported that some children who met age expected language milestones had impaired structural language functioning according to standardised measures, suggesting that the agreement between these two indices of functioning may be limited. In a later study, it was supported that early language milestones were not associated with later ASD symptom severity or adaptive social skills; however, delayed language development predicted later structural language impairment and difficulties with adaptive communication, suggesting that this marker may still have prognostic value (Kenworthy et al., 2012). Taken together, these studies showed that understanding both the language developmental milestones and language functioning can be important in ASD, with both markers potentially predicting different areas of functioning in later childhood.

While expressive language skills (i.e., the use of language) have often been reported to be more advanced than receptive language ability (i.e., the understanding of language) in ASD (Ellis Weismer, Lord, & Esler, 2010; Hudry et al., 2010), this discrepancy has not been universally supported (Kjelgaard & Tager-Flusberg, 2001; Luyster, Kadlec, Carter, & Tager-Flusberg, 2008). Inconsistent findings across studies may relate to differences in the measures used to assess language functioning. Nonetheless, in a recent meta-analysis of language studies, Kwok et al. (2015) concluded that the past research does not support the notion of a typical profile of language functioning in ASD. Rather, patterns of strengths and weaknesses in language functioning in ASD appear to be highly variable, such that no single feature of language dysfunction is present in all individuals. In high-functioning ASD, language competence across expressive and receptive domains has been reported to range from severe deficits to above average ability during childhood and adolescent years (Lewis et al., 2007). Lewis, Murdoch, and Woodyatt described four subgroups of children and adolescents with high-functioning ASD with different language profiles: 1) mild-to-moderate receptive and moderate-to-severe expressive language difficulties; 2) mild receptive and mild-to-moderate expressive difficulties; 3) severe receptive and expressive difficulties; and 4) average or

above average receptive and expressive language difficulties. The variability in language functioning evident in this clinical population demonstrates the importance of evaluating language as part of ASD assessments, as has been specified in DSM-5. The different language profiles may each be associated with different patterns of strengths and weaknesses across other areas, such as social, behavioural, and academic functioning. Understanding each individual's language ability is therefore important to develop tailored intervention strategies; a child with the first language profile, for example, would require vastly different intervention and strategies compared to a child with the third profile.

Pragmatic communication describes the ability to use language and nonverbal behaviours (e.g., eye contact and gesture) appropriately in social interaction, requiring adaption of communication style to the changing social demands across different contexts. Even in the absence of structural language impairment, deficits in pragmatic communication are universal in ASD (Volden et al., 2009) and persist for life (Rapin & Dunn, 2003). Pragmatic deficits in ASD are evidenced by over-literal interpretation of language, difficulty understanding narrative humour and sarcasm, over-inclusive language, difficulty in turn-taking in conversation, disinhibited and socially inappropriate comments, overly formal and pedantic language style, impaired prosody, and difficulty interpreting facial expressions, amongst others (Martin & McDonald, 2003). These areas of difficulty common to ASD can make social interaction confusing and complex. Even in high-functioning children with average or advanced structural language development, pragmatic communication deficits can be severe. By impacting social interaction and communication proficiency, pragmatic communication deficits have the potential to impact upon social connectedness and hinder the development of friendships, which in turn, may have consequences for emotional wellbeing. Pragmatic deficits, such as difficulties turn-taking in conversation, and appropriately interpreting and using nonverbal cues, may reduce willingness to engage in social interaction, which could be associated with increased acting out and attention seeking behaviour. In support of this theory, pragmatic communication deficits were found to predict externalising behavioural problems in non-clinical preschool children, including hyperactivity and a lack of pro-social behaviours (Ketelaars, Cuperus, Jansonius, & Verhoeven, 2010); difficulties in pragmatic communication were more predictive of behaviour problems than structural language impairment. This suggests that pragmatic communication deficits may be more important for behavioural and emotional functioning in higher functioning individuals with ASD, given the greater potential for

disparity to exist between the level of language and cognitive ability, and pragmatic communication skills. Indeed, a recent study in high-functioning ASD supported the notion that pragmatic communication difficulties were associated with greater externalising and internalising symptomatology during childhood years (Boonen et al., 2014). Together, these studies suggest that pragmatic communication difficulties may provide important targets for intervention, with the potential to improve behavioural and emotional functioning in high-functioning ASD.

1.4.5. Behavioural and Emotional Functioning

Individuals with ASD experience higher rates of behavioural and emotional difficulties than typically developing peers (Goldin, Matson, Konst, & Adams, 2014; Hass, Brown, Brady, & Johnson, 2012; Knoll, 2008; Mahan & Matson, 2011; Volker et al., 2010). Within ASD, higher-functioning individuals are particularly at risk (Knoll, 2008; Witwer & Lecavalier, 2010). In high-functioning ASD, the estimated frequency of at least one comorbid psychiatric disorder ranges from 74% (Mattila et al., 2010) to over 90% (Kusaka et al., 2014; Mukaddes & Fateh, 2010), meaning that it is not unexpected for a child to experience psychiatric problems in addition to core ASD symptomatology. The most commonly occurring comorbid conditions include behavioural disorders (e.g., attention deficit hyperactivity disorder (ADHD), conduct disorder, and oppositional defiant disorder), anxiety disorders, mood disorders, and tic disorders (Kusaka et al., 2014; Mattila et al., 2010; Mukaddes & Fateh, 2010; Vasa & Mazurek, 2015). The high prevalence of these comorbid conditions with high-functioning ASD suggests that psychiatric symptomatology outside of core ASD symptoms, such as anxiety and depression, may form part of the broader phenotype in this population.

Comorbid mood, anxiety, and behavioural disorders are associated with poorer functioning in ASD (Mattila et al., 2010). Behavioural and emotional difficulties can impact upon social relationships (Stice, Ragan, & Randall, 2004), cognitive (Harrison & Owen, 2001) and daily functioning (Angkustsiri et al., 2012; Papazoglou, Jacobson, & Zabel, 2013). Behavioural and emotional difficulties can also make diagnosis more complex in ASD; it may be difficult to discern whether withdrawn behaviour and limited interest in, or initiation of, social interaction may be representative of core ASD symptomatology or otherwise may reflect low mood or anxiety symptoms. Moreover, behavioural and emotional difficulties can impact responsiveness to intervention and therapy (Rhyne, 2009). In this way, characterising these clinical features has important implications for diagnostic decision-making and clinical management.

Both genetic and environmental factors are likely important in the development of behavioural and emotional difficulties in high-functioning ASD. While aspects of behavioural and emotional dysfunction are positively correlated with general cognitive ability in ASD (e.g., features of ADHD, anxiety, and depression; Witwer & Lecavalier, 2010), the mechanisms and causal pathways underlying this association is unclear. Further to cognition, the level of language and communication functioning has also been associated with some aspects of behavioural and emotional dysfunction in high-functioning ASD (Witwer & Lecavalier, 2010) and may contribute to areas of difficulty. ASD specific symptomology may also play a role in the development of behavioural and emotional dysfunction by impacting the development of peer relationships. The relative importance of each of these factors in predicting behavioural and emotional dysfunction in high-functioning ASD remains unclear.

1.4.6. Aetiological Mechanisms

Increasingly the term "autisms" has been used in discussion regarding ASD, reflecting the idea that the diagnostic group encompasses multiple phenotypes, potentially representing different aetiological mechanisms. While sporadic cases of ASD occur in the absence of significant family history (W. F. Hu, Chahrour, & Walsh, 2014), evidence of high concordance rates in identical twins (Bailey et al., 1995; Frazier et al., 2014) and of the 'broader autism phenotype' in relatives of affected individuals (Bolton et al., 1994; Sasson, Lam, Parlier, Daniels, & Piven, 2013) supports the high heritability of ASD. It is likely that the differences in clinical features between individuals result from multiple and interacting aetiological mechanisms, including genetic (W. F. Hu et al., 2014), epigenetic (Loke, Hannan, & Craig, 2015; Shulha et al., 2012), and environmental factors (Juul-Dam, Townsend, & Courchesne, 2001).

A number of prenatal (e.g., advanced maternal and paternal age; bleeding, medication, and diabetes during pregnancy), perinatal (e.g., preterm birth, breech position, and planned caesarian birth), and neonatal (e.g., small for gestational age, low Apgar scores, neonatal encephalopathy, hyperbilirubinemia, and birth defects) risk factors have been associated with ASD; however, these risk factors have been found to be of low magnitude suggesting they may only have a small causative role, if any, in the development of ASD (Guinchat et al., 2012). Gardener, Spiegelman, and Buka (2011) additionally identified umbilical cord complications, fetal distress, birth injury or trauma, multiple birth, maternal haemorrhage, low birth weight, feeding difficulties, and

neonatal anemia with an increased risk of ASD. Both Guinchat et al. (2012) and Gardener et al. (2011) emphasised that although exposure to these factors during the peri- and neonatal periods may increase the risk for ASD, no single factor can be directly causally linked to the disorder. While the abovementioned risk factors may have a shared role in contributing to the clinical phenotype in individuals at greater genetic risk for ASD, it seems unlikely that they make independent and causative contributions to the development of the disorder.

While several genetic disorders are associated with ASD phenotypic characteristics, including Rett's Disorder (*MECP2*), Fragile X (*FMR1)*, tuberous sclerosis (*TSC1* or *TSC2*) and neurofibromatosis (*NF1*), no single gene has been identified as causative in ASD. Rare genetic mutations with large effect sizes have most commonly been associated with the ASD phenotype, with 10-20% of individuals with ASD having identifiable *de novo* mutations. However, each of the known mutations associated with ASD accounts for less than 1% of cases, demonstrating the genetic heterogeneity of the disorder (Jeste & Geschwind, 2014). A recent review reported that over 100 disease genes and 44 genomic loci may be associated with ASD diagnosis or ASD behaviours, suggesting that the ASD phenotype may be representative of hundreds of genetic and genomic disorders (Betancur, 2011). A number of genetic markers identified in the review by Betancur had previously been shown to be causative in intellectual disability. The large number of genes potentially involved was also shown in a study by Skafidas et al. (2014), which identified over 230 single nucleotide polymorphisms (SNPs) in 125 genes. In this study both risk and resilience SNPs were identified and combined into a polygenic risk score for the disorder. Overlap between genetic mutations associated with ASD and commonly occurring medical disorders, including epilepsy, and sleep and motor disorders, has also recently been described elsewhere (Jeste & Geschwind, 2014). These findings may suggest possible common underlying mechanisms for the disorders (Chana et al., 2015; Zantomio et al., 2015), or otherwise could indicate that the genetic markers identified may be associated with behaviours common across the different clinical groups, rather than core ASD clinical features.

Beyond genetics, recent research has begun investigating a possible role of epigenetic factors in ASD. Epigenetics refers to molecular factors that influence gene expression by forming complexes at regulatory DNA regions, without changing the DNA sequence. Both genetic and environmental (e.g., smoking, stress) factors can influence epigenetics (Loke et al., 2015). Epigenetic factors may mediate the relationship between the

abovementioned pre-, peri-, and neonatal risk factors and the development of ASD in individuals who are at genetic risk for the disorder. Loke, Hannah, and Craig proposed a model depicting how such interactions between genetic (e.g., family and de novo genetic variants) and epigenetic factors (e.g., from the prenatal environment) may contribute to disrupted neurodevelopmental pathways in ASD. To date, DNA CpG methylation is the most extensively examined epigenetic marker, although the effect sizes in ASD have been found to be of low magnitude (Loke et al., 2015). Nonetheless, examination of epigenetic factors is a promising area of research with the potential to improve our understanding of reported associations between genetics and environmental risk factors in the development of ASD.

The genetic heterogeneity evident in ASD highlights the complexity of genotype and phenotype interactions in individuals with the diagnosis. In view of the different clinical features evident between individuals with ASD, it is not surprising that multiple genes and environmental factors may be involved in disorder expression. The different clinical features of ASD are likely to be at least partly genetically independent (Geurts et al., 2014; Jeste & Geschwind, 2014). As such, large individual differences in the difficulties experienced by each individual with ASD may be expected; no one clinical feature, such as a specific cognitive deficit or area of strength is likely to be present in all individuals with the disorder. Promisingly, while there are multiple genes implicated in ASD, the different genes may converge on common biological pathways; for example, the mammalian target of rapamycin (mTOR) pathway has been associated with the abovementioned *TSC1*, *TSC2*, and *NF1* genes (Vorstman et al., 2014). Further, metabotropic glutamate receptor 5 (mGluR5) has been proposed as a potential convergent pathway contributing to the development of ASD symptomatology based on mouse models (Chana et al., 2015; Zantomio et al., 2015). This means that the biological heterogeneity of ASD may be less than the genetic heterogeneity of the disorder. From a medical intervention perspective, this would reduce the number of potential targets for pharmaceutical interventions to biological pathways found to be common to ASD, such as the mTOR and mGluR5 pathways, rather than focusing on the multiple and interacting genetic mechanisms.

Importantly, human studies exploring potential genetic, epigenetic, and biological pathways that may be implicated in ASD have often included phenotypically heterogeneous participants (i.e., representing the broad spectrum of ASD). Nonverbal individuals, for example, may have been included in the same study samples as higher-

functioning individuals with average or above average intelligence. It remains unclear whether the aetiological mechanisms underpinning ASD in individuals with intellectual disability are the same as those contributing to disorder development in individuals without intellectual disability. The cause of intellectual disability may be independent from ASD, or alternatively ASD characteristics may contribute to the development of intellectual impairment (Vivanti, Barbaro, Hudry, Dissanayake, & Prior, 2013). In view of the phenotypic distinctions between individuals with and without intellectual disability (e.g., in ASD symptom severity (Mayes & Calhoun, 2004, 2011), adaptive functioning (Liss et al., 2001), and developmental trajectories (Harris & Handleman, 2000; Howlin et al., 2004)), it seems plausible that neurobiological mechanisms potentially contributing to symptom expression or disorder development may differ between low- and high-functioning individuals. Beyond this broad distinction within ASD based on intellectual ability, the clinical variability evident in high-functioning ASD alone suggests that it may be possible to further differentiate high-functioning ASD into phenotypic subgroups. The identification of such subgroups would aid future exploration of neurobiological factors that may be uniquely associated with clinical characteristics or disorder development, taking our knowledge a step further to identifying therapeutic approaches that can be more closely tailored to the clinical phenotype.

1.4.7. Section Summary

The broad subgroup of high-functioning ASD includes individuals with different levels of neurocognitive functioning and variable psychiatric comorbidities. These factors can all impact daily functioning, developmental trajectories, and prognosis, increasing the diversity between individuals. While overlap between individuals with high-functioning ASD exists, the variability in these aforementioned domains makes it a highly heterogeneous clinical group. From the perspective of diagnostic classification systems, the multiple sources of variability make it challenging to identify a core set of features that couple individuals within a single diagnostic group. From a clinical and educational perspective, the label of ASD does not provide sufficient information to understand the individual's current level of functioning, plan interventions, and/or predict their outcomes.

While previous notions of high-functioning ASD subgroups were found to be unreliable and therefore lacked clinical utility, it seems plausible that the phenotypic heterogeneity represented within this population may reflect multiple subgroups with both overlapping and unique clinical features. Distinguishable high-functioning ASD

phenotypes may exist, but it is likely that the previous DSM-IV-TR diagnostic criteria did not adequately delineate the defined subtypes (Ghaziuddin, 2010; Miller & Ozonoff, 2000). Moving forward using a more dimensional approach, as per DSM-5, individual differences can be determined by characterizing symptom profiles. Data that examines such differences in an objective manner is a potential way forward to assess the utility of subtypes. Beyond informing debate regarding diagnostic classification systems, examining phenotypic characteristics in this way is important as differences in the clinical presentation of individuals with high-functioning ASD may represent underlying distinctions in neurocognitive and/or neurobiological functioning. As suggested above, these could reflect different aetiological mechanisms contributing to disorder development, which may indicate the need for different intervention and management approaches based on the distinguished clinical phenotypes. Cluster analysis is a statistical technique that can assist in identifying subgroups based on objective criteria; this approach is introduced in the following section and studies that have employed this analysis technique to explore possible high-functioning ASD subgroups are then reviewed.

1.5. Statistical Approaches to Identifying High-functioning ASD Phenotypic Subgroups

1.5.1. Cluster Analysis

Given the complexity and variability in the phenotype of ASD, exploratory statistical techniques are increasingly being employed in the search for more homogenous groups with similar disorder profiles. Cluster analysis provides an objective statistical method of exploring the way that phenotypic characteristics group together. Individuals are clustered together based on statistical criteria, so that the differences between individuals within a cluster are minimised, and the differences between individuals across clusters are maximised (Everitt, 2011)..

A number of studies that have utilised cluster analytic techniques to investigate the possibility of phenotypic subgroups within ASD have included participants with a broad range of cognitive ability. Two- (Eagle, Romanczyk, & Lenzenweger, 2010; Stevens et al., 2000), three- (Bitsika, Sharpley, & Orapeleng, 2008; Lane, Young, Baker, & Angley, 2010; Wiggins, Robins, Adamson, Bakeman, & Henrich, 2012), and four-cluster solutions (Eaves, Ho, & Eaves, 1994; V. W. Hu & Steinberg, 2009; Munson et al., 2008; Sevin et al., 1995; Shen, Lee, Holden, & Shatkay, 2007) have been described. Some authors have reported that the identified clusters displayed different profiles of symptomatology,

supporting the DSM-IV categorical view of ASD (Eagle et al., 2010; V. W. Hu & Steinberg, 2009; Lane et al., 2010; Sevin et al., 1995). In contrast, other authors have reported that the clusters differed primarily in the quantity or severity of symptoms, and were therefore more representative of a continuous phenotype, as represented in DSM-5 (Bitsika et al., 2008; Shen et al., 2007; Stevens et al., 2000; Wiggins et al., 2012).

Given that intellectual ability has previously been found to affect the phenotype of ASD (Mayes & Calhoun, 2004, 2011), the inclusion of individuals functioning at different levels of cognitive ability in these studies may have impacted the clustering solution (Ring, Woodbury-Smith, Watson, Wheelwright, & Baron-Cohen, 2008; Verte et al., 2006). Individuals with intellectual disability (i.e., an FSIQ less than 70) have been found to have a clinical presentation and developmental course significantly different to those that are placed within the Average or Above Average range (Harris & Handleman, 2000; Howlin et al., 2004; Liss et al., 2001; Mayes & Calhoun, 2011). As suggested above, given the marked differences of higher-functioning individuals with ASD, they may have different neurobiological underpinnings relative to their lower-functioning counterparts. It is therefore important that the potential confounding effect of intellectual capacity is accounted for when examining the presence of ASD subgroups. There have been few such cluster analytic studies to date; research investigating empirically defined childhood high-functioning ASD subgroups are reviewed in the following section.

1.5.2. Empirically Defined Phenotypic Subgroups within Childhood High-functioning ASD

In two high-functioning ASD cluster analytic studies, three-cluster solutions were identified that were considered to loosely align with DSM-IV classifications of 'autistic like', 'Asperger like', and 'PDD-NOS like' (Prior et al., 1998; Verte et al., 2006). On closer examination, the subgroups were primarily differentiated by the severity of impairment on core ASD symptoms (Verte et al., 2006), or by variability in the severity of cognitive, communicative, and behavioural difficulties (Prior et al., 1998). Given quality or type of ASD symptomology was not a significant factor, the findings were considered supportive of the DSM-5 spectrum of ASD. When employing a data driven approach to explore potential subgroups, however, the clusters identified will differ according to the variables analysed. Both Prior et al. (1998) and Verte et al. (2006) only sampled ASD symptomatology via parent report, which may have provided a biased perspective on child functioning due to reliance on the parents' recollection, interpretation, and reporting accuracy. The ability to capture the true heterogeneity of this population was also limited by only analyzing the presence or absence of symptoms (Prior et al., 1998),

or by solely examining symptom domain scores (Verte et al., 2006). The sample of clinical variables may therefore have been limited and impacted the ability to reveal clinically meaningful and different subgroups.

In a study investigating high-functioning ASD in both children and young adults, Kamp-Becker and colleagues (2010) utilized both parent report and clinician observation to characterise ASD symptomatology, as well as neuropsychological assessment to evaluate cognitive functioning (intelligence, emotion recognition, theory of mind, spatial perception, executive function, and attention). Results did not support the presence of empirically derived clusters when analysis was completed independently for current ASD symptoms (clinician observation), symptomatology during early development (retrospective parent report), and current neuropsychological functioning. Given the complex nature of the ASD phenotype and the significant variability between individuals, it may be overly simplistic to attempt to identify clusters on the basis of behavioural, developmental, or neuropsychological variables independently of each other.

Bitsika et al., (2008) did not limit their analysis to ASD symptoms; they adopted cluster analysis to examine ASD severity (Childhood Autism Rating Scale total score), together with other functional indices, including cognition and adaptive functioning. Three behaviorally based clusters that differed in reciprocal social interaction, communication, and adaptive functioning were described. The subgroups differed significantly in both the severity and profile of symptoms across core domains, supporting the potential to differentiate qualitatively distinct clusters within ASD. Characterization of core symptomatology together with associated clinical features may therefore help to capture the phenotypic heterogeneity in ASD. Whilst the sample was primarily high-functioning individuals (i.e., 75% AS), the intellectual ability of participants with AD (23% of sample) and PDD-NOS (2% of sample) was not restricted; the range of scores on cognitive assessment and the proportion of participants with intellectual disability was not reported. This variability in the level of intellectual ability of participants may have influenced the clustering solution.

More recently, latent profile analysis has been used to examine the dimensional profile of ASD features. In their study of childhood ASD (full range of cognitive ability), Greaves-Lord and colleagues (2013) identified six phenotypic classes when ASD symptomatology was examined using parent questionnaire. Three classes aligned with the DSM-5 conceptualisation of ASD, characterised by impairment within both social

communication (i.e., social interest and reciprocity; understanding social information and pragmatic communication) and RRBI domains (i.e., resistance to change; stereotyped behaviours and sensory interests). Within these classes, Class 1 had severe impairment across all subdomains. Classes 2 and 3 had moderate-high impairment across social communication subdomains; Class 2 had moderate-high stereotyped behaviours and comparatively low resistance to change, while class 3 showed the reverse pattern. In contrast to Classes 1-3, the authors indicated that Classes 4-6 were primarily represented by children without intellectual disability and were less consistent with the DSM-5 concept of ASD. Class 4 was characterised by severe resistance to change, with comparatively low levels of stereotyped behaviours and social communication deficits; in contrast, Class 5 displayed moderate difficulty understanding social information and communication but low impairment across both RRBI subdomains. Interestingly, Class 6 was subclinical on all ASD domains and was characterized by attention and disruptive problems. These findings suggest that the diagnostic complexity of high-functioning ASD may not be adequately captured by DSM-5. Moreover, results support the ability to differentiate the ASD phenotype into smaller subgroups when clinical features are more closely examined. Evidence for subgroups of individuals with different profiles of impairment and levels of support needs is a step forward in developing avenues of reducing the clinical variability and improving the clinical classification of this disorder.

1.5.3. Section Summary

Given the complexity and variability of the ASD phenotype, information regarding both early development and current ASD symptomatology is important to comprehensively understand the similarities and differences between individuals. It is surprising that high-functioning ASD cluster analytic studies to date have commonly relied on either parent or child assessment measures to characterise functioning independently of one another, without adopting both assessment techniques together in the single study. The Autism Diagnostic Interview-Revised (i.e., ADI-R; Lord, Rutter, & Le Couteur, 1994) caregiver interview, and the Autism Diagnostic Observation Schedule-Second Edition (i.e., ADOS-2; Lord, Rutter, et al., 2012) child assessment are the most widely used and validated measures for ASD diagnosis and symptom characterisation (see section 1.6.2 for elaboration on these tools). Administration of both tools together is considered the 'gold standard' assessment battery in diagnosing ASD. Exploration of potential childhood high-functioning ASD subgroups using these 'gold standard' assessments together may better evaluate phenotypic subgroups.

An additional factor potentially confounding previous studies of high-functioning ASD is the wide age range of the samples evaluated. While a number of studies have explored potential phenotypic subgroups within high-functioning ASD in combined samples of children and late adolescents or young adults (Greaves-Lord et al., 2013; Kamp-Becker et al., 2010; Lewis et al., 2007; Prior et al., 1998), few studies have focused on the childhood and young adolescent years (Bitsika et al., 2008; Verte et al., 2006). The phenotype of preschool children with high-functioning ASD may differ considerably from that of adolescents and adults; therefore, including wide age ranges may impact the clustering solution and interpretation of results. Restricting the age range of the sample may limit the impact of variability in clinical features throughout development and produce more reliable results.

Taken together, these earlier studies validate the use of cluster analytic techniques in the pursuit of understanding whether there are meaningful subgroups within high-functioning ASD. The identification of phenotypic groups in childhood years, when individuals are most likely to be referred for diagnostic clinical assessments, is particularly important. The identification of childhood subgroups that display unique phenotypic profiles will enable future examination of potentially divergent developmental trajectories. This would benefit clinicians and affected individuals and their families by helping inform expected outcomes. Further, with the identification of more homogeneous subgroups, we will be better able to explore potential neurocognitive and neurobiological mechanisms that may contribute to the different phenotypes.

1.6. Diagnosing and Characterising Functioning in High-functioning ASD

1.6.1. Section Introduction

In the absence of a biological marker and diagnostic test for ASD, clinicians are reliant on behavioural observation and informant report to formulate ASD diagnosis. Given the complexity of the ASD phenotype, practice guidelines recommend a multidisciplinary assessment to characterise the broad areas of functioning implicated in the disorder. Informant report regarding developmental history and current functioning, as well as direct behavioural observation, and administration of semi-structured assessment tools all form important components of the ASD diagnostic process (Falkmer, Anderson, Falkmer, & Horlin, 2013; Filipek et al., 2000; Filipek et al., 1999; Ozonoff, Goodlin-Jones, & Solomon, 2005; Wilkinson, 2014). This section firstly introduces the 'gold standard'

tools recommended for ASD diagnostic assessment and discusses factors that may impact the clinical utility of these tools with high-functioning children. Second, in view of the variability and complexity of the ASD clinical phenotype, other domains of development that are important to consider when evaluating functioning in childhood high-functioning ASD are discussed. Further to section 1.4.5 above, this section also briefly reviews factors that may contribute to behavioural and emotional functioning in ASD, which have important implications for predicting functioning and clinical management in this population. The information contained within the sections below is most pertinent to the subsidiary aims of this thesis (i.e., Aim Two and Aim Three).

1.6.2. ASD Diagnostic Assessments

There are a number of measures that purport to evaluate the ASD clinical phenotype, including screening questionnaires, caregiver interviews, and structured observation assessments completed by a trained clinician. As already emphasised, the most well validated ASD assessment tools are the ADI-R (Lord et al., 1994) and ADOS-2 (Lord, Rutter, et al., 2012). Administration of these measures together is considered the 'gold standard' assessment for ASD diagnosis (Filipek et al., 2000; Filipek et al., 1999; Ozonoff et al., 2005; Wilkinson, 2014). Prior to introduction of the ADOS-2, the ADOS-Generic (ADOS-G, Lord, Rutter, DiLavore, & Risi, 2002) was the 'gold standard' play based assessment. The ADOS (-G and -2) is a direct observational assessment, while the ADI-R is a caregiver interview regarding current behaviour and early development (see section 7.1, Appendix A: ASD Symptom Characterisation, for detailed description of the tools). Both tools purport to evaluate functioning within core ASD symptom domains and provide diagnostic algorithms to support clinical decision-making.

A key challenge in using standardised assessment tools for ASD diagnosis is ensuring that ASD symptomatology is reliably evaluated across the full range of the autism spectrum. With regard to the ADI-R and ADOS, the characterisation of symptomatology varies according to child age, cognition (significant for ADOS only), and language functioning (Gotham, Pickles, & Lord, 2009; Gotham, Risi, Pickles, & Lord, 2007; Hus & Lord, 2013). In particular, sensitivity and specificity of the ADOS (-G and -2) diagnostic algorithms is lowest for higher functioning, verbal children and adolescents (Gotham et al., 2008; Gotham et al., 2007). There are a number of factors that may contribute to the weaker psychometric properties of the ADOS within this population. Firstly, the average age of first parental concern is older for higher-functioning children (10.5 months for AD and 24.4 months for AS) and a formal diagnosis is received at a later age (mean of

38.3 months for AD and 87.8 months for AS) (Rosenberg, Landa, Law, Stuart, & Law, 2011). As such, individuals from a wider range of chronological age (e.g., from preschool to school aged years) and developmental levels (e.g., below average to superior intellectual ability) are being evaluated using the same diagnostic tools. In view of the phenotypic differences between low- and high-functioning ASD, different assessment methods may be required for the two subgroups of ASD to reliably characterise symptomatology. Behaviours may be more subtle and complex in high-functioning ASD, making it more difficult to detect impairment in these individuals in a small number of assessment sessions. Higher-functioning individuals may also benefit from the highly structured one-to-one assessment format (Ozonoff et al., 2005), making it more difficult to characterise areas of difficulty in the absence of functional observation across different environments (e.g., at school where social demands are greatly increased).

It is acknowledged that practice guidelines (Filipek et al., 1999) and the ADI-R and ADOS-2 test publishers (Lord, Rutter, et al., 2012; Lord et al., 1994) emphasise that standardised tools form only a component of the ASD diagnostic process. The principal concern is that by being classified as 'gold standard' diagnostic instruments, clinicians may place emphasis on ADI-R and ADOS-2 results during the ASD diagnostic process, particularly when the clinical presentation is complex and/or when a clinician has limited experience. Inconsistencies in diagnostic classifications according to the ADI-R and ADOS-G test algorithms have been reported in toddlers (Ventola et al., 2006), and individuals with intellectual disability during later childhood and adolescent years (de Bildt et al., 2004; Gray, Tonge, & Sweeney, 2008), demonstrating the potential for error if solely relying on the tools for diagnosis. To the authors' knowledge, the level of agreement between the 'gold standard' tools in higher-functioning children and young adolescents is yet to be characterised. Given the complexity of the diagnostic process in this population, examination of the relationship between the measures seems particularly important within this subgroup of ASD to better inform use of the instruments in practice. Directly comparing the instruments in high-functioning ASD throughout childhood years will enable examination of the potential impact of age on symptom characterisation and diagnostic classification by test algorithms.

1.6.3. Other Important Areas of Assessment: Cognition, Language, Adaptive Functioning, and Behavioural and Emotional Wellbeing

As reviewed in section 1.4, high-functioning ASD encompasses a broad group of individuals who can show large discrepancies in functioning across different domains

important for child development. Given the unique profiles of strengths and weaknesses displayed by each individual with ASD, comprehensive characterisation of functioning beyond the core ASD deficits central to the diagnosis is important to support the development of tailored management strategies. Language and cognitive ability have important clinical implications with regard to predicting everyday functioning (Kanne et al., 2011; Liss et al., 2001) and prognosis (for review see Magiati, Tay, & Howlin, 2013). The clinical importance of evaluating these constructs in addition to ASD specific symptomatology has long been recognized in practice guidelines (Filipek et al., 2000; Filipek et al., 1999). In a recent survey of Australian paediatricians, who are often one of the first points of contact when concerns regarding a child's behaviour and development are raised, 30.8% of clinicians reported consistently referring children for cognitive assessments when formulating ASD diagnoses; 29.1% consistently referred for psychological assessments; and 33.1% consistently referred for language assessments (Albein-Urios et al., 2013). Barriers to accessing services was highlighted as an important factor limiting referral rates. The proportion of children who did not receive referral for these assessments cannot be determined from these data; the findings suggest, however, that a large proportion of paediatricians do not consistently include psychological, cognitive, and language assessments when a diagnosis of ASD is queried, highlighting the variability in paediatric practice in Australia. DSM-5 has re-enforced the importance of considering the developmental profile of each individual by stipulating that the level of cognitive and language impairment must be specified alongside the severity of social communication and RRBI symptomology central to the disorder. For this to be achieved, findings by Albein-Urios et al. suggest that in addition to improved accessibility to assessment services, there may be a need for a cultural shift, whereby the minimum standard for ASD diagnostic assessments is more widely adopted as including evaluation of cognition and language.

Characterising the level of intellectual functioning and language can assist in predicting outcome and is required to access funding in Australia, but this construct alone does not provide information regarding daily living skills (i.e., adaptive functioning) across different environments. One example of this is evidence of significant discrepancies between actual and predicted academic functioning (based on general cognitive ability) in children with ASD (Estes, Rivera, Bryan, Cali, & Dawson, 2011); more information is required than intellectual ability to gain an accurate understanding of daily functioning. Research examining predictors of adaptive functioning in ASD have often included individuals with varied levels of intellectual ability; in such studies, stronger cognitive

and language functioning has been associated with more positive trajectories of adaptive functioning throughout childhood years (Baghdadli et al., 2012; Szatmari et al., 2015), suggesting these variables may also be important in high-functioning ASD.

The relationship between ASD symptomatology and adaptive functioning in ASD is unclear; in the broad spectrum of ASD, a negative association between ASD symptom severity and adaptive functioning has been supported in some (Baghdadli et al., 2012; Perry, Flanagan, Dunn Geier, & Freeman, 2009), but not all studies Liss, 2001 #677]. Inconsistent findings have also been reported across high-functioning ASD samples, where a number of studies have reported significant negative relationships between ASD severity and adaptive functioning (Kenworthy, Case, Harms, Martin, & Wallace, 2010; Liss et al., 2001) while others have found negligible associations (Klin et al., 2007; Saulnier & Klin, 2007). In a large childhood sample that included all levels of cognitive ability, Kanne et al. (2011) found adaptive functioning was significantly associated with ASD severity when measured via parent report but not child observation, suggesting that differences in methodology may have contributed to disparities across past studies. Inconsistencies may also be related to participant characteristics (e.g., variability in developmental level and chronological age between study samples), or differences in the index of ASD severity used (e.g., overall ASD severity score compared with domain or symptom scores). High-functioning ASD studies to date have not used the 'gold standard' parent and child assessment measures together to characterise ASD symptomatology. Using both measures in combination, together with comprehensive evaluation of cognitive and language functioning, could help clarify the relative importance of these constructs in predicting adaptive dysfunction in HF-ASD.

As reviewed in section 1.4.5, individuals with high-functioning ASD are at greater risk for behavioural and emotional dysfunction than those with low-functioning ASD and typically developing children (Knoll, 2008; Witwer & Lecavalier, 2010). The school environment can be particularly challenging for children with ASD, given the greater social pressures, cognitive load, and demands for attention, as well as the likelihood that more limits are placed on behaviour (e.g., repetitive behaviours that may serve to reduce anxiety). Screening of behavioural and emotional functioning in the school setting is therefore important in ASD diagnostic and functional assessments, in order to identify support needs and guide intervention planning. Understanding whether ASD specific symptomatology and neurocognitive functioning predict behavioural and emotional functioning in high-functioning ASD could improve our understanding of

factors contributing to clinical variability in this population, and could also lead to novel targets for intervention.

1.6.4. Section Summary

The varied phenotype of high-functioning ASD poses significant challenges to the characterisation of functioning and diagnostic process. Differences in the clinical phenotype of low- and high-functioning ASD may be sufficient to warrant different assessment methods for these two subgroups of ASD. Greater clarity in diagnostic practices with high-functioning children can be achieved through improved understanding of the relationship between the currently available 'gold standard' tools in evaluating ASD symptomatology in this subgroup of the autism spectrum. This is particularly relevant at the current time given the recent revision of the ADOS (i.e., from ADOS-G (Lord et al., 2002) to ADOS-2 (Lord, Rutter, et al., 2012)). Understanding similarities and differences in the characterisation of symptomatology by the tools most commonly used in both clinical and research settings will increase awareness of possible strengths and limitations of the different assessment methods (i.e., parent report compared with child observation) in this population, with the view of identifying potential ways to improve diagnostic tools moving forward.

There is also a need to better understand factors associated with the clinical phenotype of ASD that place higher-functioning individuals at greater risk for behavioural and emotional difficulties. Understanding the relationship between these factors and core ASD symptomatology, as well as other aspects of neurocognitive functioning implicated in ASD (e.g., cognitive ability, language function, and new learning and memory) will improve clinicians' ability to predict areas of difficulty and develop tailored management strategies.

1.7. Broad Thesis Aims

Based on the previous sections in this chapter, three broad thesis aims were developed:

1. To investigate whether phenotypic subgroups could be identified in childhood high-functioning ASD based on profiles of core ASD symptomatology;
2. To evaluate the relationship between the 'gold standard' ASD diagnostic instruments, the ADI-R and ADOS-2, throughout childhood years in high-functioning ASD; and
3. To explore potential predictors of behavioural and emotional functioning in childhood high-functioning ASD within the school setting.

These thesis aims were addressed in three separate studies. Aim (1) formed the principle focus of this thesis; this aim was addressed in the Study One, which is presented in experimental Chapter 2. Aims (2) and (3), which were subsidiary thesis aims, are subsequently detailed in experimental Chapter 3 and Chapter 4, respectively.

CHAPTER 2: A CLUSTER ANALYSIS EXPLORATION OF CHILDHOOD HIGH-FUNCTIONING ASD SUBGROUPS

2.1. Preamble to Chapter 2

As detailed in Chapter 1, there is concern that the DSM-5 (American Psychiatric Association, 2013) classification of ASD overlooks potentially meaningful differences between individuals with the disorder. Given the great heterogeneity represented within the single diagnostic category of ASD, researchers and clinicians continue to debate the presence of phenotypic subgroups in this population, particularly among high-functioning individuals. Examining the possibility of distinguishable phenotypic subgroups within childhood high-functioning ASD formed the primary aim of this thesis; the study addressing this aim is presented in this chapter. Surprisingly, investigations of possible high-functioning ASD subgroups to date have not used both of the 'gold standard' child assessment and parent report measures in combination (the ADI-R and ADOS-2) to examine ASD phenotypic characteristics; we addressed this limitation of past studies by comprehensively evaluating ASD symptomatology for all child participants using both of the 'gold standard' diagnostic measures. Beyond ASD symptom profiles, differences between the identified subgroups in aspects of neurocognitive functioning were also explored.

The manuscript presented in this chapter was submitted for publication in the '*The British Journal of Psychiatry'* in July 2015. The section numbering has been modified to maintain consistent presentation throughout the thesis. See thesis Chapter 7: Appendices for additional information regarding the tools used to evaluate ASD symptomatology (Appendix A), cognition (Appendix B), language and communication (Appendix C), and behavioural and emotional functioning (Appendix D) in this study. If abbreviations or citations used in this manuscript were not used in thesis Chapters 1 or 5, they are not included in the thesis abbreviations or thesis references lists.

2.2. Declaration for Chapter 2

Monash University

Declaration by candidate

In the case of Chapter 2 (Study One Manuscript), the nature and extent of my contribution to the work was the following:

Nature of Contribution	Extent of Contribution (%)
Conceptualisation and design of study; ethics approval; participant recruitment; data collection, management and analysis; and manuscript preparation and submission for publication.	70%

The following co-authors contributed to the work.

Name	Nature of Contribution
Efstratios Skafidas	Conceptualisation of study; data analysis; and revision of statistical analysis and results sections in manuscript.
Renee Testa	Conceptualisation of study; supervision; data analysis; and revision of drafts.
Christos Pantelis	Conceptualisation of study; supervision; and revision of drafts.

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

Candidates Signature: [redacted]	**Date:** 14/08/2015
Main Supervisor's Signature: [redacted]	**Date:** 14/08/2015

A Cluster Analysis Exploration of Childhood High-Functioning Autism Spectrum Disorder Subgroups

Running title: Childhood HF-ASD Subgroups

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Declaration of Interests
None.

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2.3. Abstract

Background: The heterogeneity in autism spectrum disorder (ASD) remains poorly understood, particularly in high-functioning ASD (HF-ASD) where phenotypic variability is most pronounced.

Aims: To investigate whether children with HF-ASD are differentiable into clinically meaningful subgroups.

Method: Data from commonly used ASD diagnostic instruments in 61 children (5-14 years) with HF-ASD were subject to exploratory cluster analysis. Cognition, language, pragmatic communication, and behaviour were used to explore subgroups.

Results: HF-ASD could be sub-divided into Moderate and Severe Social Impairment subgroups. The Severe Social Impairment subgroup displayed poorer social interaction and communication skills, but lower lifetime severity of restricted/repetitive behaviours. This subgroup also had greater cognitive and language difficulties, and poorer adaptive functioning.

Conclusions: Clinically meaningful HF-ASD subgroups can be identified based on the profile of impairment across core ASD features. Both categorical and dimensional approaches may be useful in classifying ASD, with neither alone being adequate.

Keywords: Autistic spectrum disorders, high-functioning autistic spectrum disorders, diagnostic classification.

Abbreviations:

ADI-R: Autism Diagnostic Interview-Revised

ADOS-2: Autism Diagnostic Observation Schedule-Second Edition

ASD: Autism spectrum disorder

BASC-2 TRS: Behaviour Assessment System for Children-Second Edition, Teacher Rating Scales

CCC-2: Children's Communication Checklist-Second Edition

CELF-4: Clinical Evaluation of Language Fundamentals-Fourth Edition

CELF-Preschool-2: Clinical Evaluation of Language Fundamentals-Preschool, Second Edition

ELI: Expressive Language Index

HF-ASD: High-functioning autism spectrum disorder

PRI: Perceptual Reasoning Index

PSI: Processing Speed Index

RLI: Receptive Language Index

RRBI: Restricted, repetitive patterns of behaviour, interests, and activities

VCI: Verbal Comprehension Index

WISC-IV: Wechsler Intelligence Scale for Children-Fourth Edition

WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence-Third Edition

WRAML-2: Wide Range Assessment of Memory and Learning-Second Edition

2.4. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterised by impaired social communication and restricted, repetitive behaviours, interests, and activities (RRBI) (American Psychiatric Association, 2013). DSM-5 (American Psychiatric Association, 2013) has classified ASD as a spectrum, eliminating the need to diagnose specific autistic subtypes as per DSM-IV-TR (American Psychiatric Association, 2000). Yet, given that there is significant phenotype variability in ASD within the domains of behaviour, development, and neurocognition, there are concerns that this approach minimises the identification of heterogeneity, particularly with individuals without intellectual disability (i.e., 'high-functioning ASD', HF-ASD). This is relevant given that previous studies have identified potential ASD subgroups based on clinical features using cluster analysis (Bitsika, Sharpley, & Orapeleng, 2008) and latent profile analysis (Greaves-Lord et al., 2013). Past studies, however, have not utilized the 'gold standard' parent report and child evaluation measures in combination to characterise the phenotype in HF-ASD, which may better evaluate phenotypic subgroups. This study used cluster analysis to explore symptom and functional (cognitive, language, behavioural and emotional) profiles within an Australian sample of children with HF-ASD. HF-ASD formed the focus of the study, due to the greater phenotypic variability and diagnostic uncertainty in this population. We utilised the 'gold standard' parent interview and child assessment measures to provide a comprehensive evaluation of ASD specific characteristics, which is unique relative to other HF-ASD cluster analytic investigations. Understanding phenotypic profiles within HF-ASD is important for diagnostic classification systems, as well as clinically and educationally, to inform management strategies.

2.5. Method

2.5.1. Participants

Sixty-one children without cognitive impairment and with parent reported clinical diagnosis of DSM-IV-TR autistic disorder, Asperger's disorder, or pervasive developmental disorder-not otherwise specified (American Psychiatric Association, 2000), or a diagnosis of DSM-5 ASD (American Psychiatric Association, 2013), participated with their primary caregivers (all diagnoses henceforth referred to as ASD). Twenty-two participants had previously been diagnosed by a multidisciplinary group involving author RT, a paediatrician, and a speech pathologist or occupational therapist, and were subsequently invited to participate in the months following diagnosis. Remaining participants were recruited through psychologists and psychiatrists known

to the research team (*n*=24), or via public advertisement on autism specific websites (*n*=15). Diagnosing clinicians for participants recruited through public advertisement were not contacted to verify diagnosis.

Child participants (51 males; 5.1:1 male to female ratio) were aged between five and 14 years (*M*=8.81, *SD*=2.36). All assessments were completed in English. All children had Verbal Comprehension Index (VCI; *M*=97.43, *SD*=16.02) or Perceptual Reasoning Index (PRI; *M*=105.98; *SD*=14.10) scores greater than 80 according to Wechsler scales of intelligence (Wechsler, 2002, 2004).

Children were excluded if they had a diagnosed neurological disorder (e.g., cerebral palsy), a history of traumatic brain injury, or if there was a known biological cause of ASD symptoms, such as perinatal exposure to rubella, thalidomide, valproate, and herpes encephalitis, or genetic disorders such as tuberous sclerosis, fragile-X, Angelman or Cornelia de Lange syndromes. Participants with a history of seizures or epilepsy were not excluded to enable exploration of whether they displayed different clinical features or clustered together in a unique clinical phenotype of ASD: one participant had diagnosed epilepsy, two experienced febrile convulsions as infants, and one participant had experienced two seizures across his lifetime (aetiology unknown).

2.5.2. Materials

2.5.2.1. ASD Symptomatology

The Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) caregiver interview and the Autism Diagnostic Observation Schedule-Second Edition (ADOS-2; Lord et al., 2012) child assessment characterised ASD specific symptomatology. The ADI-R evaluates early development, language, communication, play, interests and behaviours. Each item has two ratings: 1) current behaviour, and 2) level of functioning between the child's fourth and fifth birthdays, or an 'Ever' rating reflecting highest level of impairment across the lifetime. An examiner trained to research reliable standard administered the ADI-R (author FK).

The ADOS-2 (Lord et al., 2012) is a semi-structured, play based assessment that evaluates communication, social interaction, and RRBI. The measure contains five modules, administered according to expressive language level and chronological age. Either Module 2 (*n*=4) or 3 (*n*=57) was administered as appropriate. A subset of children (*n*=7) had been assessed using the previous version of the ADOS-2 (i.e., ADOS-

Generic; Lord, Rutter, DiLavore, & Risi, 2002) in the past 12-months. Of these participants, two were evaluated via other research projects where the examiner was trained to research reliable standards. A clinical psychologist specialising in ASD and regularly using the ADOS-G in diagnostic assessments had assessed five participants. The ADOS-2 was not re-administered to these participants to prevent potential practice effects; parents provided consent for past results to be accessed and items/diagnostic algorithms were re-coded to match ADOS-2 criteria. All remaining children completed the ADOS-2 with an examiner trained to research reliable standard (author FK). FK attended regular ADOS-2 supervision meetings to maintain reliability.

2.5.2.2. Cognition, Behaviour and Emotional Functioning

The Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler, 2004) or Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III; Wechsler, 2002) were used to assess general cognitive ability, as appropriate to developmental level. Significant variability between scores prevented calculation of reliable full-scale intelligent quotients for many participants. VCI (i.e., verbal cognitive ability) and PRI (i.e., nonverbal cognitive ability) scores were instead used to address exclusion criteria. In addition, VCI, PRI, and Processing Speed Index (PSI) scores were used to explore characteristics of the clusters.

Verbal Learning and Story Memory subtests from the Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2; Sheslow & Adams, 2003) were used to examine new learning and memory functioning. Immediate, delayed, and recognition memory standard scores were analysed.

The Behavior Assessment System for Children-Second Edition, Teacher Rating Scale (BASC-2 TRS; Reynolds & Kamphaus, 2004) was used to evaluate behavioural and emotional functioning in the school setting. Externalizing Problems, Internalising Problems, School Problems, Behavioural Symptoms Index, and Adaptive Skills Composite *T*-scores were compared across clusters. BASC-2 TRS were not returned for 11 participants.

2.5.2.3. Language and Pragmatic Communication

The Clinical Evaluation of Language Fundamentals-Fourth Edition (CELF-4; Semel, Wiig, & Secord, 2003a) or CELF-Preschool, Second Edition (CELF-Preschool-2; Semel, Wiig, & Secord, 2003b) were used to evaluate language functioning, as appropriate to

developmental level. Receptive Language Index (RLI) and Expressive Language Index (ELI) standard scores were compared across clusters. One participant did not complete the CELF-4.

Parents completed the Children's Communication Checklist-Second Edition (CCC-2; Bishop, 2003). The General Communication Composite and Social Interaction Difference Index scores, and formal language, pragmatic language, and non-language domain scores were compared across clusters. The CCC-2 was not returned for one participant; responses for five other participants were unreliable according to standard scoring criteria and excluded from analysis.

2.5.3. Procedure

Study approval was obtained from The Royal Children's Hospital (32023) and the Monash University (2012000837) Human Research and Ethics Committees. Written informed consent was obtained from all parents of child participants. Parents confirmed their child had a previous diagnosis of ASD prior to participating. As clinical diagnosis is formed based on all available information, including scores on standardised measures, it was considered the 'gold standard' for diagnosis in this study rather than classification based on ADI-R and ADOS-2 diagnostic algorithms. All assessment sessions were completed at Sunshine Hospital, Monash University, author RT's private practice, or at participants' homes. With caregiver consent, ADOS-2 assessments were video recorded and later coded from video. The order of test administration for child assessments varied to increase engagement. Breaks were given as required, with some assessments completed over two days. Cognitive and language assessments completed in the past two years, and ADOS (-G or -2) evaluations completed within the past year, were not re-administered to prevent practice effects; caregivers consented for past results to be used in this study.

2.5.4. Statistical Analysis

2.5.4.1. Cluster Analysis

Twenty-one ADOS-2 items consistent across Modules 2 and 3 were subject to cluster analysis. Two Module 3 items (*Overall Level of Non-echoed Spoken Language*; and *Language Production and Linked Nonverbal Communication*) were excluded as they were not applicable for the majority of participants, or there was limited variability in scores due to the high-functioning sample such that data were not appropriate for analysis. Six items only available in Module 3 judged to be highly clinically relevant were also

included. See Supplementary Material (Appendix A) for ADOS-2 variables selected and recoded for analysis.

Sixty-one ADI-R items considered most clinically relevant were selected for cluster analysis. In order to limit missing data owing to variability in coding procedures across items, the maximum value (i.e., greatest level of impairment) was determined for each variable, offering an indication of *lifetime* presence and severity of each symptom. It was considered that this value, in addition to current behaviour items as measured by the ADOS-2, would offer the most comprehensive perspective of ASD characteristics. See Supplementary Material (Appendix B) for ADI-R variables selected and recoded.

Participant ratings on the 88 ADOS-2 and ADI-R variables were explored statistically using complete linkage cluster analysis. This hierarchical agglomerative clustering technique seeks to find the most compact clusters while also maximising the distance between the clusters (Everitt, 2011). Complete linkage cluster analysis therefore attempts to maximise the degree of separation between clusters while also maintaining cohesion with the cluster. This technique was considered the most appropriate to address the aims of the current study, whereby greater differences between the clusters would represent greater separation between the groups based on the clinical features analysed. In doing so, strengthening the proposition that any identified clusters represent qualitatively distinct subgroups. Analysis was completed for ADOS-2 and ADI-R variables independently, and also in a combined solution of ADOS-2 and ADI-R data together. To determine the optimal number of clusters in each instance, the Calinksi Harabasz Criterion (Calinski & Harabasz, 1974) compared the solutions when 1, 2, 3, …10 clusters were produced. The similarity between clustering solutions when only ADOS-2 data, only ADI-R data, or combined ADOS-2 and ADI-R data were included was examined using the Rand Index (Rand, 1971). The stability of each solution was additionally evaluated using bootstrapping techniques, whereby a 60% concordance rate between solutions following removal of a random case and re-running of analysis was considered a stable solution. Through this examination process, all clustering solutions were judged to display adequate stability. Cluster analysis was completed using Matlab (version 2014).

2.5.4.2. Cluster Characterisation

ADI-R and ADOS-2 diagnostic algorithm Reciprocal Social Interaction, Communication, and RRBI domain scores were tallied as prescribed in the test protocols. The ADOS-2

also includes a Social Affect domain score, which represents the sum of Reciprocal Social Interaction and Communication domains. Due to non-normality of data, Mann-Whitney *U* tests evaluated which ADOS-2 and ADI-R domains significantly differed between clusters, and which variables maximally separated the groups; bonferroni correction adjusted for multiple comparisons. Spearman's rho examined the relationships between ADI-R and ADOS-2 domain scores; ADI-R and ADOS-2 variables that maximally separated the groups; and cognitive and language data. Variables describing general cognitive functioning and language ability were continuous and normally distributed, and there were greater than 20 participants in each group; as such, independent sample *t*-tests were permitted to determine if there were significant differences between mean scores for each cluster. Due to non-normality of the data, Mann-Whitney *U* tests examined differences between scores on the WRAML-2, CCC-2, and BASC-2 TRS. Chi-squared test for independence examined cluster differences on categorical variables where minimum expected cell count was greater than five (i.e., co-morbid Attention Deficit Hyperactivity Disorder, and family history of ASD); Fisher's Exact Test was employed when minimum expected cell frequency was less than five (i.e., gender, ASD diagnosis, frequency of co-morbid psychiatric disorders, and a history of pregnancy/birth complications, seizures/epilepsy, loss of language, or loss of skills), with Freeman-Halton extension for two-rows by three-columns contingency tables. Cluster characteristics were explored using Matlab (version 2014) and IBM SPSS Statistics 21 (Release 21.0.0.0).

2.6. Results

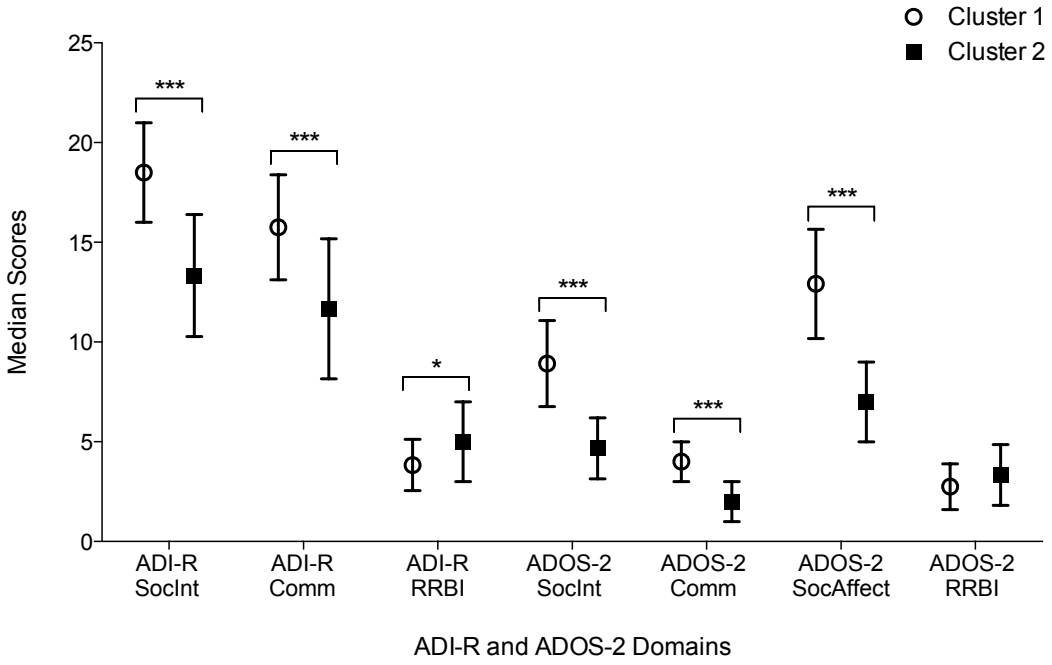
2.6.1. Cluster Analysis

According to Calinski Harabasz Criterion (Calinski & Harabasz, 1974), a two-cluster solution was optimal when current (ADOS-2) and lifetime (ADI-R) developmental and behavioural variables were subject to complete linkage cluster analysis. Consistent with this result, a two-cluster solution was also optimal when ADOS-2 and ADI-R data were examined independently. All three solutions were shown to be stable using bootstrapping techniques. The Rand Index examined concordance rates between the solutions. As expected, the clustering solution varied when different variables were included in the analysis: concordance between ADOS-2 and ADI-R solutions was 49.29%; between ADI-R and combined ADOS-2/ADI-R was 50.82%; and between ADOS-2 and combined ADOS-2/ADI-R was 59.13%. In further evaluation of stability of the solution, complete linkage cluster analysis was repeated with cases with VCI less than 75 (n=4) removed from analysis, and when variables were dichotomized prior to

clustering the data. In both instances, two-cluster solutions best described the data, with the clusters maximally separated by social communication variables (Supplementary Material, Appendix C). The initial solution with combined ADOS-2 and ADI-R data was considered the most informative when exploring cluster characteristics given it included the most clinical information for each participant, without reducing variability by dichotomizing items or limiting the sample size. Findings below describe characteristics of the clusters when both ADI-R and ADOS-2 variables for all 61 participants were analysed.

2.6.2. Cluster Characterisation: ASD Symptomatology

Median ADI-R and ADOS-2 Reciprocal Social Interaction, Communication, and RRBI domain scores are displayed in Figure 1. Mann-Whitney *U* tests (Supplementary Material, Appendix D) revealed that Cluster 1 had significantly greater impairment within Reciprocal Social Interaction and Communication domains on both the ADI-R and ADOS-2 (p<.001). In contrast, Cluster 2 had significantly greater lifetime severity of RRBI according to the ADI-R (p<.05). The difference in ADOS-2 RRBI domain scores did not reach significance (p>.05).



Error bars represent interquartile range (Quartile 1 - Quartile 3). ADI-R: Autism Diagnostic Interview-Revised. ADOS-2: Autism Diagnostic Observation Schedule-Second Edition. SocInt: Reciprocal Social Interaction impairment. Comm: Communication impairment. RRBI: Restricted, repetitive behaviours, interests, and activities. SocAffect: summed scores across ADOS-2 SocInt and Comm domains.
***P<.001, *P<.05.

Figure 1. Median ADI-R and ADOS-2 diagnostic algorithm domain scores for Clusters 1 and 2.

Mann-Whitney *U* tests with bonferroni correction revealed that ten ADI-R and ADOS-2 variables relating to social interaction and communication skills maximally separated the clusters (Table 1). Cluster 1 demonstrated greater impairment across all variables that maximally separated the groups. Differences in ADI-R and ADOS-2 RRBI ratings were not significant at an individual item level after bonferroni correction.

Table 1

Mann-Whitney U Results for ADI-R and ADOS-2 Variables that Maximally Separated the Clusters

	Cluster 1		Cluster 2		U^2	*z*	*r*
	Md	***IQR***	***Md***	***IQR***			
ADI-R Variables							
Social Smile	2.0	1.0-3.0	1.0	0.0-2.0	169.0***	-4.1	-0.5
Social Response	2.0	1.0-2.0	1.0	0.0-1.0	186.5***	-4.0	-0.5
Interest in Children	2.0	2.0-3.0	1.0	0.0-2.0	188.0***	-3.8	-0.5
ADOS-2 Variables							
Conversation	2.0	1.8-2.0	1.0	1.0-2.0	197.5***	-3.9	-0.5
Gesture	1.0	1.0-2.0	0.0	0.0-1.0	189.5***	-3.9	-0.5
Quality of Response	1.0	1.0-2.0	1.0	0.0-1.0	201.5***	-4.0	-0.5
Reciprocal Comm.	1.0	1.0-2.0	1.0	0.0-1.0	212.0***	-3.6	-0.5
Rapport	1.0	1.0-2.0	0.0	0.0-1.0	193.0***	-3.8	-0.5
Asks for Information	3.0	1.8-3.0	1.0	0.0-2.0	155.5***	-4.3	-0.6
Insight-Relationships	2.5	1.8-3.0	1.0	1.0-2.0	188.0***	-3.8	-0.5

ADI-R, Autism Diagnostic Interview-Revised; ADOS-2, Autism Diagnostic Observation Schedule-Second Edition; *Md*, Median; *IQR*, Interquartile Range (Quartile 1–Quartile 3); *r,* approximate value of *r* ($r=z/\sqrt{N}$) calculated as index of effect size.

***$P<.001$.

2.6.3. Cluster Characterisation: Development, Cognitive, and Language Functioning

There was no significant difference between clusters in the frequency of co-morbid Attention Deficit Hyperactivity Disorder (Cluster 1: 27.30%; Cluster 2: 23.10%; $\chi^2=0.1$, $p>.05$, phi=-.05) or parent reported family history of ASD (siblings and other relatives; Cluster 1: 59.10%; Cluster 2: 76.90%; $\chi^2=2.15$, $p>.05$, phi=0.19). The frequency of other clinical variables compared using Fisher's Exact Tests (i.e., gender; co-morbid psychiatric diagnosis; ASD classification (i.e., HFA, AS, or ASD); pregnancy/birth

complications; history of seizure or epilepsy; and loss of language or skills) did not differ significantly between the clusters (p>.05; Supplementary Material, Appendix E).

Independent samples t-tests compared the clusters with regard to developmental variables, and current cognitive and language functioning (Table 2). Figure 2 displays z-scores for each cluster on these variables.

Table 2

Independent Samples t-tests Comparing Developmental, Cognitive, and Language Variables

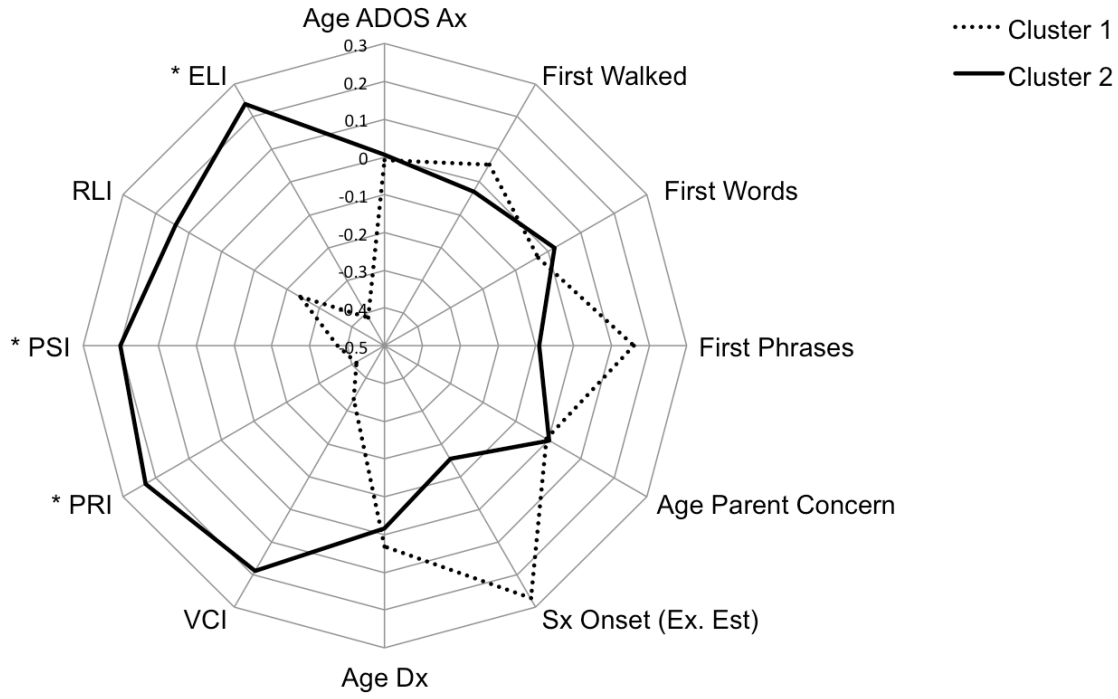
	Cluster 1 ***n*=22**		**Cluster 2** ***n*=39**		***t***	***p***
	M	***SD***	***M***	***SD***		
Development						
Age ADOS Ax (yrs)	8.79	2.17	8.83	2.49	-0.06	.96
First Walked (mths)	14.29	4.43	13.95	3.91	0.30	.76
First Words (mths)	16.77	7.51	17.19	8.61	-0.19	.85
First Phrases (mths)	27.27	9.44	25.05	8.50	0.94	.35
Age Parent Concern (mths)	38.77	19.18	38.97	28.51	-0.03	.98
Sx Onset (Ex Est; mths)	27.00	8.64	22.95	9.76	1.62	.11
Age Dx (yrs)	7.25	2.50	7.13	2.58	0.18	.86
Cognition						
Verbal Comp. Index	92.05	16.53	100.47	15.09	-2.02	.05
Perceptual Reason. Index	100.18	11.91	109.26	14.31	-2.52	.01*
Processing Speed Index	90.40	16.68[a]	98.90	12.90[b]	-2.14	.04*
Language						
Receptive Language Index	91.09	17.19	97.42	15.98	-1.44	.16
Expressive Language Index	86.59	19.92	99.42	18.12	-2.55	.01*

M, Mean; *SD*, Standard Deviation; Mths, age in months; Yrs, age in years; Ax, Assessment; Sx, Symptoms; Sx Onset (Ex. Est.), examiners estimate of age developmental abnormalities first evident; Dx, Diagnosis.

a. *n*=20.

b. *n*=37.

*P<.05 (two-tailed).



Age Parent Concern: child age at time of first parent concerns regarding language, relationships, or behaviour. Sx Onset (Ex. Est): Examiners estimate of the age developmental abnormalities were first evident. Age Dx: Parent reported age of diagnosis. VCI: Verbal Comprehension Index. PRI: Perceptual Reasoning Index. PSI: Processing Speed Index. RLI: Receptive Language Index. ELI: Expressive Language Index.
*P<.05.

Figure 2. Radar plot of *z*-scores for clusters 1 and 2 on developmental, cognitive, and language variables.

There were no significant differences between the clusters on the developmental variables measured (Table 2). Cluster 1 had greater impairment in nonverbal cognitive ability, processing speed, and expressive language skills relative to Cluster 2. With regard to WISC-IV/WPPSI-III subtests**,** Cluster 1 had significantly greater impairment in abstract reasoning across nonverbal (Cluster 1 M=10.33, SD=3.29; Cluster 2 M=12.22, SD=2.78; t=-2.31, p<.05, two-tailed) and verbal domains (Cluster 1 M=8.79, SD=3.60; Cluster 2 M=11.00, SD=3.60; t=-2.08, p<.05, two-tailed). Cluster 1 was also characterised by significantly slower performance on a task of information processing (Cluster 1 M=8.21, SD=3.46; Cluster 2 M=10.40, SD=2.25; t=-2.81, p=.01, two tailed). Differences across other WISC-IV/WPPSI-III subtests did not reach significance.

As ELI and PRI scores differed significantly across the clusters, Spearman's rho evaluated whether the scores correlated significantly with ADI-R and ADOS-2 domain scores, or with items that maximally separated the groups (Supplementary Material,

Appendix F). There were no significant correlations between PRI scores and the aforementioned variables. Regarding domain scores, ELI scores were significantly correlated with ADI-R Social Interaction (r_s=-.28, p<.05, r_s^2=.08, small effect); ADOS-2 Communication (r_s=-.29, p<.05, r_s^2=.08, small effect); and ADOS-2 Social Affect domain scores (r_s=-.29, p<.05, r_s^2=.08, small effect). With regard to ADI-R and ADOS-2 variables, ELI scores correlated significantly with ADI-R *Social Response* (r_s=-.30, p<.05, r_s^2=.09, medium effect); ADOS-2 *Asks for Information* (r_s=-.36, p<.01, r_s^2=.13, medium effect); and ADOS-2 *Insight into Relationships* (r_s=-.47, p<.01, r_s^2=.22, medium effect). As the correlations between ELI scores and ADI-R/ADOS-2 domain and item scores were relatively weak with small to medium effect sizes, ELI scores were not covaried when exploring cluster characteristics.

Mann-Whitney *U* tests compared median scores on indices of new learning and memory (WRAML-2), behaviour and emotional functioning (BASC-2 TRS), and communication (CCC-2) across the clusters (Supplementary Material, Appendix G). Standard scores regarding immediate and delayed recall, and recognition memory were within the average range for both clusters, with no significant differences between subgroups. The clusters did not differ significantly on CCC-2 index or domain scores. Relative to the normative population, ratings for both groups were reduced for all language, pragmatic, and non-language domains, with greater deficit particularly apparent for Social Relations. There were no significant differences between the clusters with regard to BASC-2 TRS Externalising, Internalising, or School Problems, or Behavioural Symptoms Index scores. Relative to the normative population, median Internalising Problems and Behavioural Symptoms Index *T*-scores for both Clusters were comparably high and within the *At-Risk* range. In contrast, Cluster 2 (*Average* range) had significantly better Adaptive functioning than Cluster 1 (*At Risk* range).

Mann-Whitney *U* tests compared the clusters on BASC-2 TRS Adaptive Skills subdomains. Compared with Cluster 1, Cluster 2 performed significantly better (i.e., higher scores) across domains of Study Skills (Cluster 1 *Md*=39.00, Cluster 2 *Md*=46.00; *U*=194.50, *z*=-2.10, *p*<.05, *r*= -.27), Social Skills (Cluster 1 *Md*=37.50, Cluster 2 *Md*=44.50; *U*=179.00, *z*=-2.40, *p*<.05, *r*=-.31), Leadership (Cluster 1 *Md*=40.00, Cluster 2 *Md*=45.00, *U*=180.00, *z*=-2.38, *p*<.05, *r*=-.34), and Functional Communication (Cluster 1 *Md*=40.00, Cluster 2 *Md*=45.00, *U*=180.00, *z*=-2.38, *p*<.05, *r*=-.34). There was no significant difference between median Adaptability *T*-scores (Cluster 1 *Md*=37.00, Cluster 2

Md=40.00; *U*=241.50, *z*=-1.16, *p*>.05), with both clusters scoring within the *At-Risk* range.

2.7. Discussion

This exploratory study described two childhood HF-ASD clusters based upon the pattern and severity of ASD symptomatology. Results indicate that HF-ASD can be differentiated into Severe (Cluster 1) and Moderate Social Impairment (Cluster 2) subgroups when social communication skills are more closely examined. The identified subgroups were differentiated by different variables to those previously conceptualized as distinguishing HF-ASD subgroups. The Severe Social Impairment subgroup was characterised by greater impairment in social interaction and communication skills, but lower lifetime severity of RRBI. In contrast, the Moderate Social Impairment subgroup was characterised by greater impairment in lifetime severity of RRBI. These profile differences support the notion of two phenotypic subgroups of HF-ASD.

Importantly, while the social interaction and communication skills of the Moderate Social Impairment subgroup were significantly stronger than the Severe Social Impairment subgroup, the degree of impairment within these domains was significant enough to warrant ASD clinical diagnoses. In addition to the disparate profiles of ASD specific symptomatology, the Severe Social Impairment subgroup manifests poorer nonverbal cognitive ability, processing speed, and expressive language. Importantly, the variability in ASD symptomatology was not accounted for by these differences in cognitive and language skills. The clusters did not differ with regard to new learning and memory skills, on which they performed in the average range. They also did not differ on parent reported language and pragmatic communication skills, with both groups showing difficulties in areas consistent with ASD diagnosis. Based on teacher report, the Moderate Social Impairment cluster had significantly stronger social and study skills, leadership, and functional communication. These skills, together with the stronger language and cognitive functioning, may mask areas of difficulty at first impression. It is notable, for example, that this subgroup had greater lifetime severity of RRBI, but did not differ from the Severe Social Impairment subgroup on ratings of current RRBI based on the ADOS-2 evaluation. Further, both clusters had comparably high risk of behavioural symptoms and internalizing problems relative to the normative population. Taken together, results reinforce that comprehensive assessment across multiple domains of functioning is important in order to understand the profile of strengths and weaknesses and inform management strategies in HF-ASD. In particular, evaluation of

emotional wellbeing should be included in diagnostic and functional assessments, given the increased risk of these difficulties in this clinical population.

Past cluster analytic studies exploring the presence of clinically meaningful subgroups within HF-ASD are conflicting. Several studies have described subgroups differing primarily in the *severity* of impairment across social and cognitive skills (Kamp-Becker et al., 2010; Prior et al., 1998; Verte et al., 2006), which support the DSM-5 dimensional view of ASD. Others, however, have identified clusters with *unique profiles* of social interaction and communication skills (Bitsika et al., 2008; Greaves-Lord et al., 2013), thereby providing evidence to support a categorical approach of ASD subgroups. Using comprehensive data regarding current and lifetime ASD symptomatology, the current study identified two clusters of HF-ASD, Severe and Moderate Social Impairment subgroups, with different severity profiles across core symptom domains. This supports the idea that it is possible to describe clinically meaningful subgroups within HF-ASD. It is notable that although analysis consistently revealed that two cluster solutions maximally separated the subgroups and best explained the data, the clusters were maximally separated by only ten social interaction and communication variables. Thus, considerable overlap remained regarding many of the core ASD features evaluated.

Our findings suggest that drawing on both dimensional and categorical frameworks of ASD is needed, whereby individuals vary along continuous core dimensions of ASD, but where subgroups with differing profiles along dimensions of social communication and RRBI can be described. The DSM-5 requirement for clinicians to specify the level of impairment within social communication and RRBI domains could provide an avenue of identifying the subgroups described in this study within the clinical setting. Relative to using only the DSM-5 dimensional approach, differentiating individuals into subgroups in this way would convey additional clinical information within the shorthand diagnostic label (i.e., providing an indication of the severity of social communication difficulties, RRBI, and level of neurocognitive functioning). In doing so, providing greater clarity in clinical and educational settings, with implications for tailoring management strategies.

2.7.1. Methodological Issues & Limitations

We restricted the age range to limit variability accounted for by different developmental levels. In doing so, it is acknowledged that results describe ASD phenotypic subgroups within this limited childhood age only, which may change over time with development.

Given the study focus on high-functioning children with ASD, the results and implications cannot be generalised to children with ASD and intellectual disability. Future replication with children of different ages and ability levels will therefore be important to examine the reliability and validity of defining subgroups within the broader spectrum at different stages of development. While all participants were evaluated with the ADI-R and ADOS (-G or -2), ASD classification according to the test diagnostic algorithms was not required for study inclusion. A subset of participants (n=16) did not meet cutoff scores on both measures; all participants, however, met diagnostic cutoff on one of the measures and were considered to meet diagnostic criteria based on all information available. Our sample size provided a stable clustering solution and thus was considered adequate to examine the primary aim. The small sample relative to the number of variables, however, limited the power of examination. With greater power, other variables may have differentiated the subgroups. For example, differences in ratings of ADOS-2 *Stereotyped Language* (p=.001); and ADI-R *Use of Other's Body to Communicate* (p=.004) and *Hand and Finger Mannerisms* (p=.01) did not meet the stringent criteria after bonferroni correction. Further, the Moderate Social Impairment subgroup had greater lifetime severity of RRBI (ADI-R), but differences between current RRBI (ADOS-2) were not significant (p=.08). Limited power may have influenced this finding. Alternatively, the non-significant difference may reflect changes in RRBI with development, such that differences between subgroups can be captured in ADI-R *lifetime* ratings, but not via the time limited observational assessment. In this regard, the single 45-minute ADOS-2 may have lacked sensitivity to capture RRBI symptomatology in this sample. Surprisingly, the clusters did not differ on CCC-2 pragmatic communication indices, despite the noted differences in social communication skills according to the ADI-R and ADOS-2. Multiple CCC-2 items were summed to calculate the pragmatic communication domain scores, thereby reducing variability to a single summary value that may not have adequately captured the variability to identify differences in pragmatic communication.

2.7.2. Future Directions

The clinical utility of defining childhood HF-ASD clusters based on differential profiles of impairment across core ASD domains requires examination with large samples and longitudinal study design. Comprehensive description of unique HF-ASD phenotypic subgroups supports future exploration of biological or genetic mechanisms potentially contributing to disorder profiles and may relate to different underlying aetiological mechanisms. Understanding these processes better may inform clinicians regarding

predicted developmental trajectories, functional outcomes, and responsiveness to intervention.

2.7.3. Conclusion

This exploratory study described two HF-ASD clusters differentiated by the severity of social communication difficulties and lifetime severity of RRBI. The Severe Social Impairment subgroup had greater impairment in social interaction and communication skills, but lower lifetime RRBI severity; in contrast the Moderate Social Impairment subgroup showed the reverse pattern. Despite the unique symptom profiles identified, significant overlap in aspects of core ASD symptomatology remained. Results suggest a combination of dimensional and categorical approaches may be informative in understanding HF-ASD phenotypic variability. Individuals may vary on dimensions of ASD, but can be differentiated into more homogenous subgroups based on profiles of symptoms across core domains. Defining behavioural phenotypes of ASD provides novel avenues to delineate genetic and other relevant biomarkers.

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2.9. Supplementary Material

2.9.1. Appendix A: ADOS-2 Variables Selected and Recoded Prior to Analysis

Table 1

ADOS-2 Variables Selected and Recoded Prior to Analysis

Variables Consistent Across Modules 2 and 3		**Sx Rating**
A2	Speech Abnormalities Associated with Autism (Intonation/Volume/Rhythm/Rate)	0, 1, 2
A3	Immediate Echolalia	0, 1, 2, 3
A4	Stereotyped/Idiosyncratic Use of Words or Phrases	0, 1, 2, 3
A8	Conversation	0, 1, 2, 3
A9	Descriptive/Conventional/Instrumental/Informat. Gestures	0, 1, 2, 3
B1	Unusual Eye Contact	0, 2
B2	Facial Expressions Directed to Others/Examiner	0, 1, 2
B4	Shared Enjoyment in Interaction	0, 1, 2, 3
B7	Quality of Social Overtures	0, 1, 2, 3
B8	Amount of Social Overtures	0, 1, 2, 3
B9	Quality of Social Response	0, 1, 2, 3
B10	Amount of Reciprocal Social Communication	0, 1, 2, 3
B11	Overall Quality of Rapport	0, 1, 2, 3
C1	Imagination/Creativity	0, 1, 2, 3
D1	Unusual Sensory Interest in Play Material/Person	0, 1, 2, 3
D2	Hand and Finger and Other Complex Mannerisms	0, 1, 2, 3
D3	Self Injurious Behaviour	0, 1, 2
D4	Excessive Interest in or References to Unusual or Highly Specific Topics or Objects or Repetitive Behaviours;	0, 1, 2, 3
E1	Overactivity/Agitation	0, 1, 2, 3
E2	Tantrums, Aggression, Negative or Disruptive Behaviour	0, 1, 2, 3
E3	Anxiety	0, 1, 2
Variables Unique to Module 3		
A5	Offers Information	0, 1, 2
A6	Asks for Information	0, 1, 2, 3
A7	Reporting of Events	0, 1, 2, 3
B5	Comments on Others' Emotions/Empathy	0, 1, 2
B6	Insight into Typical Social Situations and Relationships	0, 1, 2, 3
D5	Compulsions or Rituals	0, 1, 2

Sx: Symptom

ADOS-2 Variable Recoding

Ratings of 8 or 9 were recoded to 0 for the cluster analysis, as is convention for recoding items to be included in the ADOS-2 diagnostic algorithm. While some ADOS-2 items have a rating of 7, no participants in our sample achieved this rating and thus no recoding was necessary prior to analysis. Unusual Eye Contact is rated either 0 (appropriate gaze) or 2 (poorly modulated eye contact) according to the ADOS-2 protocol. To maintain consistency with dichotomous variables included in the ADI-R (see Appendix B), ratings of 2 were recoded to 3 for the cluster analysis. Four participants had missing data due to variability across ADOS-2 Modules (i.e., different variables included in Modules 2 and 3) and versions (i.e., ADOS-G versus ADOS-2). Using scores from participants with complete ADOS-2 ratings in combination with ADI-R scores, regression equations were generated using the partial least squares method in order to predict participant scores for the missing values.

2.9.2. Appendix B: ADI-R Variables Selected and Recoded Prior to Analysis

ADI-R Variable Selection

Sixty-one items considered most clinically relevant were selected for cluster analysis (Table 2). Three variables relating to age at symptom onset were excluded given the overlapping information sampled by the items; instead, an estimate of the age that developmental abnormality was first evident based on clinical judgement was included. One value regarding loss of language, and another regarding loss of skill was included in analysis. Detailed items pertaining to, for example, age and duration of loss, and association with physical illness, were excluded. 'Initiation of appropriate activities' was excluded from analysis as the hierarchy of difficulties used to code the item differed from the ordinal scale used for other variables. Isolated special skills were excluded, as they do not form a central diagnostic feature for ASD and were open to bias due to reliance on parent report.

ADI-R Variable Recoding

Continuous variables representing age of first walking, first words, first phrases, and age at symptom onset were recoded into categorical variables whereby 0: typical development; 1: mild delay/abnormality in specified area; 2: moderate delay/abnormality in specified area; and 3: severe delay/abnormality in specified area (Table 2). Classification boundaries were chosen based on the clinical experience of a senior clinical neuropsychologist (author RT). As ADI-R loss of language and loss of skills items are rated on different scales, variables were recoded to a 0-3 scale to improve consistency across items (0: no loss, 1: probable loss, and 3: definite loss). In order to limit missing data owing to variability in coding procedures across selected variables, a maximum value was generated for each variable, which reflected the most severe *lifetime* rating for each participant. It was considered that this value, in addition to current behaviour items as measured by the ADOS-2, would offer the most comprehensive perspective on ASD characteristics for each individual.

Table 2

ADI-R Variables Selected and Recoded Prior to Analysis

Variable Number and Description		Variable Included and/or Recoded for Analysis
5	Age First walked	Recoded into categorical variables: <18 months=0; 19-24 months=1; 25-30 months=2; ≥31=3; 996=0
9	Age First single words	Recoded into categorical variables: <18 months=0; 19-24=1; 25-35 months=2; ≥36=3; 996=0; 997=1
10	Age first phrases	Recoded into categorical variables: <30 months=0; 31-36 months=1; 37-42 months =2; >42=3; 997=1
11	Loss of language	Recoded 0-3 scale: 0=0; 1=3
20	Loss of skills	Recoded 0-3 scale: 0=0; 1=1; 2=3
29	Comprehension simple language	Max rating across current/most abnormal 4-5 rating
31	Use other's body to communicate	Max rating across current/ever ratings
32	Articulation/pronunciation	Max rating across current/age 5.0 years ratings
33	Stereotyped utterances and delayed echolalia	Max rating across current/ever ratings
34	Social verbalization/chat	Max rating across current/ever ratings
35	Reciprocal conversation	Max rating across current/ever ratings
36	Inappropriate questions or statements	Max rating across current/ever ratings
37	Pronominal reversal	Max rating across current/ever ratings
38	Neologisms/idiosyncractic language	Max rating across current/ever ratings
39	Verbal rituals	Max rating across current/ever ratings
40	Intonation/volume/rhythm/rate	Recoded 7=0; Max rating across current/ever ratings;
41	Current communicative speech	Max rating across current/age 5.0 years ratings

Table 2 Continued

Variable Number and Description		Variable Included and/or Recoded for Analysis
42	Pointing to express interest	Max rating across current/most abnormal 4-5 rating
43	Nodding	Max rating across current/most abnormal 4-5 rating
44	Head shaking	Max rating across current/most abnormal 4-5 rating
45	Conventional/instrumental gestures	Max rating across current/most abnormal 4-5 rating
46	Attention to voice	No recoding (*current* only rated if <5 years; most abnormal 4-5 rating used)
47	Spontaneous imitation of actions	Max rating across current/most abnormal 4-5 rating
48	Imaginative play	Max rating across current (under 10)/most abnormal 4-5
49	Imaginative play with peers	Max rating across current (over 4 and under 10)/most abnormal 4-5 rating
50	Direct gaze	Not edited (Most abnormal 4-5 rating used as current only for under 5, so all n/a for current sample)
51	Social smiling	Max rating across current/most abnormal 4-5 rating
52	Showing and directing attention	Max rating across current/most abnormal 4-5 rating
53	Offering to share	Max rating across current/most abnormal 4-5 rating
54	Seeking to share enjoyment with others	Max rating across current/most abnormal 4-5 rating
55	Offering comfort	Max rating across current/most abnormal 4-5 rating
56	Quality of social overtures	Max rating across current/most abnormal 4-5 rating
57	Range of facial expressions used to communicate	Max rating across current/most abnormal 4-5 rating
58	Inappropriate facial expressions	Max rating across current/ever ratings
59	Appropriateness of social responses	Max rating across current/most abnormal 4-5 rating
61	Imitative social play	Max rating across current (under 10)/most abnormal 4-5
62	Interest in children	Max rating across current (under 10)/most abnormal 4-5

Table 2 Continued

Variable Number and Description		Variable Included and/or Recoded for Analysis
63	Response to approaches of other children	Max rating across current (under 10)/most abnormal 4-5
64	Group play with peers	Max rating across current (over 4 and under 10)/most abnormal 4-5 rating
65	Friendships	Max rating across current (over 5)/most abnormal 10-15
66	Social Disinhibition	Max rating across current (over 5)/most abnormal 4-5
67	Unusual preoccupations	Max rating across current/ever ratings
68	Circumscribed interests	Max rating across current/ever ratings
69	Repetitive use of objects or interest in parts of objects	Max rating across current/ever ratings
70	Compulsions/rituals	Max rating across current/ever ratings
71	Unusual sensory interests	Max rating across current/ever ratings
72	Undue general sensitivity to noise	Max rating across current/ever ratings
73	Abnormal, idiosyncratic, negative response to specific sensory stimuli	Max rating across current/ever ratings
74	Difficulties with minor changes in own routines/personal environment	Max rating across current/ever ratings
75	Resistance to trivial changes in environment	Max rating across current/ever ratings
76	Unusual attachment to objects	Recoded 0=0; 1=1; 2,6=2; 3=3; 7=1; Max rating across current/ever ratings
77	Hand and fingers mannerisms	Max rating across current/ever ratings
78	Other complex mannerisms or stereotyped body movements	Max rating across current/ever ratings
79	Midline hand movements	Max rating across current/ever ratings
80	Gait	Max rating across current/ever ratings
81	Aggression toward caregivers or family members	Max rating across current/ever ratings

Table 2 Continued

Variable Number and Description		Variable Included and/or Recoded for Analysis
81	Aggression toward non-caregivers or nonfamily members	Max rating across current/ever ratings
83	Self-injury	Max rating across current/ever ratings
84	Hyperventilation	Max rating across current/ever ratings
85	Faints/fits/blackouts	Max rating across current/ever ratings
87	Interviewers judgement on age when developmental abnormalities first manifest	Recoded into categorical variables: ≥61=0; 37-60=1; 19-36=2; ≤18=3

2.9.3. Appendix C: Additional Analysis Exploring Stability of Clustering Solution

All participants in the current study were classified as high-functioning based on VCI and/or PRI scores; however, there was some variability between participants with regards to level of cognitive functioning, particularly for VCI scores. To explore stability of the clustering solution, the cluster analysis procedure was repeated after excluding participants with a VCI less than 75 (*n*=5). Consistent with the initial analysis, a two-cluster solution remained optimal according to Calinski Harabasz criterion. After adjusting for multiple comparisons with Bonferroni correction, five social interaction and communication variables maximally separated the clusters (ADI-R: *Social Smile*, *Social Response*; ADOS-2: *Conversation, Quality of Response*; *Rapport*, and *Asks for Information*). Given agreement in the variables that reached significance in comparison to the original solution, it was considered that inclusion of the cases with relatively lower VCI scores did not significantly alter cluster characteristics.

Variability across rating procedures for ADI-R and ADOS-2 items had the potential to influence the clustering, with some variables rated on a 0-2 scale, and others on a 0-3 scale. To address this issue and to further examine of stability of the clustering solution, ADI-R and ADOS-2 variables were dichotomized to represent 1) absence of behaviour/symptom (i.e., typical development); or 2) abnormality of type specified. While this procedure removes variability available for analysis, it could also have simplified interpretation of results by clarifying the presence/absence of each symptom across the lifetime. Consistent with the initial solution, a two-cluster solution was optimal according to the Calinksi Harabasz Criterion. Furthermore, the clusters were again maximally separated by social interaction and communication variables. Specifically, prior to bonferroni correction, ADI-R variables that significantly differentiated the clusters included *Inappropriate Questions*, *Offers Comfort*, *Interest in Children*, and *Response to Children*; and significant ADOS-2 variables included: *Gesture*, *Reciprocal Communication*, *Rapport*, *Asks for Information*, *Amount of Overtures*.

2.9.4. Appendix D: Mann-Whitney U tests Comparing ADI-R and ADOS-2 Diagnostic Algorithm Domain Scores

Table 3

Mann-Whitney U Tests Comparing ADI-R and ADOS-2 Domain Scores

	Cluster 1		Cluster 2		U^2	*z*	*r*
	Md	***IQR***	***Md***	***IQR***			
ADI-R							
Social Interaction	18.5	16.0 - 21.0	14.0	14.0 - 16.0	163.0***	-4.0	-0.5
Communication	16.0	13.0 - 18.3	12.0	12.0 - 15.0	196.0***	-3.5	-0.5
RRBI	3.5	2.8 - 5.3	5.0	5.0 - 7.0	272.0**	-2.4	-0.3
ADOS-2							
Social Interaction	8.5	7.0 - 11.3	5.0	5.0 - 6.0	147.5***	-4.3	-0.5
Communication	4.0	3.0 - 5.0	2.0	2.0 - 3.0	122.5***	-4.7	-0.6
Social Affect	12.0	10.8 - 16.0	7.0	7.0 - 9.0	106.0***	-4.9	-0.6
RRBI	2.5	1.8 - 4.0	3.0	3.0 - 5.0	313.0**	-1.8	-0.2

Md, Median; *IQR*, Interquartile Range (Quartile 1–Quartile 3); *r,* Approximate value of *r* ($r=z/\sqrt{(N)}$ calculated as index of effect size; ADI-R: Autism Diagnostic Interview-Revised; RRBI, Restricted, repetitive behaviours, interests and activities; ADOS-2, Autism Diagnostic Observation Schedule-Second; Social Affect, summed scores across ADOS-2 Social Interaction and Communication and domains.

***$P<.001$, *$P<.05$.

2.9.5. Appendix E: Results of Fisher's Exact Tests Comparing the Frequency of Clinical Variables across Clusters

Table 4

Results of Fisher's Exact Tests Comparing the Frequency of Clinical Variables across Clusters

	Cluster 1	**Cluster 2**	***p***
	% Yes	**% Yes**	**(two-tailed)**
Gender (% Male)	86.4	82.1	0.7
Female: Male Ratio	1:6.3	1:4.6	-
Co-morbid Psychiatric Diagnosis	22.7	20.5	1.0
ASD Diagnosis	-	-	0.2[a]
High-Functioning Autism	54.5	33.3	-
Asperger's Disorder	31.8	56.4	-
ASD	13.6	10.3	-
Pregnancy/Birth Complications	-	-	0.8[a]
Yes	50.0	59.0	
No	22.7	20.5	
Unknown	27.3	20.5	
History of Seizure or Epilepsy	9.1	5.1	0.6
Loss of Language	4.5	12.1	0.4
Loss of Skills	9.1	15.4	0.7

ASD, autism spectrum disorder; Pregnancy/birth complications, as reported by parents, including: prematurity, low birth weight, emergency caesarian, jaundice at birth, infection during pregnancy, gestational diabetes, loss of amniotic fluid during pregnancy, ventriculomegaly in utero. Loss of skills: probable and definite loss of skills combined to single variable.

a. Freeman-Halton extension employed.

2.9.6. Appendix F: Spearman's Coefficients between ELI and PRI Scores, and ADI-R and ADOS-2 Domain and Item Scores

Table 5

Spearman's Coefficients between ADI-R and ADOS-2 Domain Scores, and Perceptual Reasoning and Expressive Language Index Scores

	ELI	**PRI**
	r_s (r_s^2)	r_s (r_s^2)
ADI-R Domains		
Social Interaction	-.28* (.08)	-.13
Communication	-.17	-.11
RRBI	.04	-.01
ADOS-2 Domains		
Social Interaction	-.23	-.05
Communication	-.29* (.08)	-.08
Social Affect	-.29* (.08)	-.07
RRBI	.14	.04

r_s^2, reported as measure of effect size for significant relationships only. ELI, Expressive Language Index (CELF-4 or CELF-Preschool-2); PRI, Perceptual Reasoning Index (WISC-IV or WPPSI-III); ADI-R, Autism Diagnostic Interview-Revised; RRBI, Restricted, repetitive, and stereotyped patters of behaviour and activities; ADOS-2, Autism Diagnostic Observation Schedule-Second.

*P<.05.

Table 6

Spearman's Coefficients between ADI-R and ADOS-2 Variables that Maximally Separated the Clusters, and Perceptual Reasoning and Expressive Language Index Scores

	ELI	PRI
	r_s (r_s^2)	r_s (r_s^2)
ADI-R Items		
Social Smile	-.16	-.14
Social Response	-.30* (.09)	-.18
Interest in Children	-.12	-.01
ADOS-2 Items		
Conversation	-.20	-.10
Gesture	-.19	.01
Quality of Response	-.24	-.16
Reciprocal Communication	-.23	-.15
Rapport	-.24	-.04
Asks for Information	-.36** (.13)	-.16
Insight into Relationships	-.47** (.22)	-.09

r_s^2, reported as measure of effect size for significant relationships only. ADI-R, Autism Diagnostic Interview-Revised; ADOS-2, Autism Diagnostic Observation Schedule-Second.

**P<.01, *P<.05.

2.9.7. Appendix G: Mann-Whitney U tests Comparing Clusters on WRAML-2, BASC-2 TRS, and CCC-2 Scores

Table 7

Mann-Whitney U Tests Comparing Clusters on WRAML-2, BASC-2 TRS, and CCC-2 Scores

	Cluster 1		Cluster 2		U^2	*z*	*r*
	Md	***IQR***	***Md***	***IQR***			
WRAML-2							
VL – Immediate	11.0	9.0 - 13.3	11.0	8.0 - 12.0	388.5	-0.6	-0.1
VL – Delayed	10.0	6.8 - 12.0	9.0	8.0 - 13.0	405.5	-0.4	-0.1
VL – Recognition	10.0	8.0 - 12.3	11.0	9.0 -13.0	342.0	-1.2	-0.2
SM – Immediate	9.0	6.8 - 10.3	10.0	8.0 - 11.0	377.5	-0.8	-0.1
SM – Delayed	8.0	4.8 - 10.3	9.0	5.0 - 10.0	403.5	-0.4	-0.1
SM – Recognition	10.5	7.5 - 12.0	11.0	9.0 - 13.0	349.0	-1.1	-0.1
BASC-2 TRS							
Externalising	55.0	48.0 - 71.8	52.5	50.5 - 65.0	281.0	-0.4	-0.1
Internalising	65.0	51.0 - 72.3	62.5	54.0 - 76.0	281.0	-0.4	-0.1
School Problems	59.5	50.0 - 64.3	54.0	48.0 - 62.3	263.0	-0.7	-0.1
BSI	64.0	59.0 - 75.3	63.5	56.5 - 72.0	272.5	-0.6	-0.1
Adaptive Skills	37.0	33.3 - 40.5	43.0	37.5 - 47.5	152.0*	-2.8	-0.4

Table 7 Continued

	Cluster 1		Cluster 2		U^2	*z*	*r*
	Md	***IQR***	***Md***	***IQR***			
CCC-2							
GCC	35.0	25.0 - 46.0	40.0	27.3 - 51.3	313.0	-0.5	0.6
SIDI	-6.0	-14.0 - 2.0	-8.0	-14.8 - -1.5	267.0	-0.9	0.4
Speech Output	6.0	1.0 - 9.0	7.5	3.0 - 12.0	272.0	-1.2	-0.2
Syntax	4.0	1.0 - 6.0	5.0	3.0 - 8.0	265.0	-1.4	-0.2
Semantics	5.0	3.0 - 7.0	6.0	3.0 - 7.0	332.0	-0.2	-0.0
Coherence	5.0	3.0 - 6.0	4.0	3.0 - 6.8	336.0	-0.1	-0.0
Inapprop. Initiat.	5.0	5.0 - 6.0	5.0	3.0 - 6.0	258.5	-1.5	-0.2
Stereotyped Conv.	5.0	2.0 - 6.0	4.0	3.0 - 6.0	316.5	-0.5	-0.1
Conv. Context	4.0	2.0 - 5.0	3.0	1.3 - 5.8	334.0	-0.1	-0.0
Nonverbal Comm.	2.0	1.0 - 4.0	3.0	2.0 - 4.8	274.0	-1.2	-0.2
Social Relations	1.0	0.0 - 3.0	2.0	0.0 - 4.0	275.0	-1.2	-0.2
Interests	4.0	3.0 - 5.0	5.0	3.0 - 6.0	316.0	-0.5	-0.2

Md, Median; *IQR*, Interquartile Range (Quartile 1–Quartile 3); *r,* approximate value of *r* ($r=z/\sqrt{(N)}$ calculated as index of effect size; WRAML-2, Wide Range Assessment of Memory and Learning-Second; VL, Verbal Learning; SM, Story Memory; CCC-2, Children's Communication Checklist-Second; GCC, General Communication Composite; SIDI, Social Interaction Difference Index; Inapprop. Initiat, Inappropriate Initiation; Stereotyped Conv, Stereotyped Conversation. Conv. Context, Conversational Context; Nonverbal Comm, Nonverbal Communication; BASC-2 TRS, Behavioural Assessment System for Children-Second, Teacher Rated Scale; BSI, Behavioural Symptoms Index.

*$P<.05$.

CHAPTER 3: CHARACTERISING CURRENT BEHAVIOUR AND DIAGNOSING HIGH-FUNCTIONING ASD USING THE ADI-R AND ADOS-2

3.1. Preamble to Chapter 3

In Chapter 2, we found that the high-functioning ASD subgroups differed in their ratings of lifetime severity of RRBI as measured by ADI-R, but not according to ratings of current functioning on the ADOS-2. This suggests that the two measures may differ in their evaluation of RRBI in high-functioning ASD, potentially adding complexity to the diagnostic decision making process. In the absence of a genetic biomarker for ASD, clinicians rely on behavioural observations and informant reports to characterise functioning and diagnose the disorder. Understanding the relationships between these 'gold standard' measures in evaluating ASD symptom domains and diagnostically classifying high-functioning children is therefore important to inform clinical practice. To the author's knowledge, the level of agreement between the ADI-R and the recently revised ADOS-2 has not previously been examined in high-functioning children with ASD. To address this gap in the literature, the study detailed in this chapter aimed to examine the relationship between these 'gold standard' tools in children with clinically diagnosed high-functioning ASD throughout development by (1) comparing the level of agreement between diagnostic classifications according to the test algorithms, and (2) examining the relationship between ADI-R and ADOS-2 symptom ratings within core domains of impairment.

The manuscript presented in this chapter was submitted for publication in the '*Journal Autism and Developmental Disorders*' in July 2015. The section numbering has been modified to maintain consistent presentation throughout the thesis. See Chapter 7: Appendices for additional information regarding the tools used to evaluate ASD symptomatology in this study (Appendix A). If abbreviations or citations used in this manuscript were not used in thesis Chapters 1 or 5, they are not included in the thesis abbreviations or thesis references lists.

3.2. Declaration for Chapter 3

Monash University

Declaration by candidate

In the case of Chapter 3 (Study Two Manuscript), the nature and extent of my contribution to the work was the following:

Nature of Contribution	Extent of Contribution (%)
Conceptualisation and design of study; ethics approval; participant recruitment; data collection, management and analysis; and manuscript preparation and submission for publication.	80%

The following co-authors contributed to the work.

Name	Nature of Contribution
Renee Testa	Conceptualisation of study, supervision, data analysis and revision of drafts
Efstratios Skafidas	Conceptualisation of study; data analysis; revision of statistical analysis and results sections in manuscript.
Christos Pantelis	Conceptualisation of study, supervision and revision of drafts.

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

Candidates Signature: [redacted]	Date: 14/08/2015
Main Supervisor's Signature:	Date: 14/08/2015

Characterising Current Behaviour and Diagnosing High-functioning Autism Spectrum Disorder using the ADI-R and ADOS-2

Running title: Using the ADI-R and ADOS-2 in High-functioning ASD

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Declaration of Interests
The authors declare that there is no conflict of interest.

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3.3. Abstract

Understanding differences between the 'gold standard' autism spectrum disorder (ASD) diagnostic tools (Autism Diagnostic Interview-Revised, ADI-R; Autism Diagnostic Observation Schedule-Second, ADOS-2) in evaluating symptomology and diagnostically classifying children is important to inform diagnostic practices. We examined this in "high-functioning" children without intellectual disability, being more difficult to diagnose compared to low-functioning children due to phenotypic variability and behavioural complexity. Associations between ADI-R/ADOS-2 Social Interaction and Communication scores reduced as age increased, while ratings of restricted, repetitive behaviours and interests were not correlated. Results showed the measures evaluate different characteristics throughout childhood, particularly in later years. Agreement between ADI-R/ADOS-2 classifications ranged from poor to fair. These inconsistencies add to the complexity of diagnostic decision-making, emphasising the need for development of standardised assessment tools for older verbal, higher-functioning children.

Keywords: High-functioning autism spectrum disorder; autism spectrum disorder; assessment; diagnosis; ADOS-2; ADI-R.

Abbreviations:

AD: Autistic disorder
ADI-R: Autism Diagnostic Interview-Revised
ADOS-2: Autism Diagnostic Observation Schedule-Second Edition
ADOS-G: Autism Diagnostic Observation Schedule-Generic Version
AS: Autism spectrum
ASD: Autism spectrum disorder
HF-ASD: High-functioning autism spectrum disorder
RRBI: Restricted, repetitive behaviours, interests and activities

3.4. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterised by social communication deficits and restricted, repetitive behaviours, interests, and activities (RRBI) (American Psychiatric Association, 2013). Heterogeneity in clinical phenotypic characteristics, including core ASD symptomatology, cognition, and language, makes clinical diagnostic decision-making challenging. For this reason, there has been increasing reliance on standardised assessment tools to support diagnosis.

The Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994), and the Autism Diagnostic Observation Schedule-Second (ADOS-2; Lord, Rutter, et al., 2012) are the 'gold standard' tools for ASD diagnostic assessment. The measures purport to assess ASD symptomatology across Social Interaction, Communication, and RRBI domains, as per DSM-IV-TR (American Psychiatric Association, 2000), and include diagnostic algorithms. In contrast to the ADOS-2 direct observational approach, the ADI-R utilises parent report to characterise current ASD symptomatology and to retrospectively evaluate early development. The ADI-R offers a developmental perspective, drawing on parent observation across different environments over time. Thus, while both tools target the same core symptom domains, they provide different and complimentary perspectives on behaviour.

Revision of the original ADOS (i.e., ADOS-Generic, ADOS-G; Lord, Rutter, DiLavore, & Risi, 2002) to ADOS-2 (Lord, Rutter, et al., 2012) resulted in a new diagnostic algorithm. This revised algorithm includes Social Affect (Reciprocal Social Interaction and Communication difficulties combined) with the addition of the previously excluded RRBI. Based upon current ASD symptomatology, the ADOS-2 diagnostic algorithm provides cutoff scores for 'Autistic Disorder' ('AD'), 'Autism Spectrum' ('AS'), or non-spectrum ('Not ASD'). Sensitivity to ASD has been maintained across ADOS-G and ADOS-2 algorithms, whilst the level of specificity between 'AD', 'AS', and non-spectrum classifications has improved (Gotham, Risi, Pickles, & Lord, 2007). The ADOS-2 is divided into five modules as follows: Toddler Module for children aged 12-30 months; Module 1 for children aged over 31 months who do not consistently use phrase speech; Module 2 for children using phrase speech but who are not verbally fluent; Module 3 for fluent speaking children/young adolescents with expressive language level of at least four years of age; and Module 4 for verbally fluent older adolescents/adults. ADOS (-G and -2) sensitivity and specificity is lowest for Module 3 (Gotham et al., 2007). A

contributing factor to the poorer psychometric properties of this module may be its use with a wide range of ages and developmental levels, with individuals from early childhood to young adolescence being evaluated with the same tasks. Notably, the need to develop methods to evaluate higher-functioning, verbal individuals has been acknowledged by test developers (Gotham et al., 2007).

In contrast to the evaluation of current functioning in ADOS-2, the ADI-R diagnostic algorithm is based on retrospectively reported functioning between ages four to five years. Individuals are classified as 'AD' or 'Not AD' based on the algorithm; there is no cutoff score for 'AS'. ADOS-2 diagnostic algorithm classifications show greater consistency with consensus clinical diagnosis than the ADI-R (Gray, Tonge, & Sweeney, 2008; Zander, Sturm, & Bolte, 2015). When ADI-R and ADOS-G algorithm classifications are directly compared, concordance rates have varied widely from poor to moderate (e.g., κ=.28, de Bildt et al., 2004; κ=.35, Gray et al., 2008; κ=-.09 to -.07, Ventola et al., 2006). Discordance between these 'gold standard' measures is problematic in clinical and research settings where they are utilised for diagnosis. In children with intellectual disability, age appears to affect agreement between the measures, with concordance being substantial (κ=.61 to .67) in younger children, but only slight in older children and adolescents (κ=.15 to .20; de Bildt et al., 2004). Further, moderate consistency (κ=.54 to .62) between the measures was found when the ADI-R current behaviour algorithm was used, so that symptom ratings across the tools were based on the same developmental period (Le Couteur, Haden, Hammal, & McConachie, 2008). This suggests that agreement between the ADI-R and ADOS-2 may be improved when the measures assess the same age period.

With regard to characterising current symptomatology, ADI-R and ADOS-G ratings of Social Interaction and Communication difficulties show moderate (r=.46 and r=.49, respectively; Chawarska, Klin, Paul, & Volkmar, 2007) to large (r=0.71 and r=0.64, respectively; Le Couteur et al., 2008) correlations in toddlers. The strength of association between RRBI scores across the measures is more variable, with non-significant (Chawarska et al., 2007) to large (r=0.51; Le Couteur et al., 2008) correlations reported. Variability in ADOS-G (Gotham, Pickles, & Lord, 2009; Gotham et al., 2007) and ADI-R (Hus & Lord, 2013) symptom ratings according to age, expressive language, and IQ (significant for ADOS only) may contribute to the variability in research findings. Moreover, the lack of agreement/consistency across the measures adds to uncertainty with regard to establishing current symptomatology.

This study explored the relationship between the ADI-R and the recently revised ADOS-2 in a sample of verbal, higher functioning children with ASD, for whom standardised diagnostic tools are not as psychometrically sound. The potential impact of chronological age on agreement between the measures was examined. To the authors' knowledge, this is the first study to examine the level of agreement between the 'gold standard' diagnostic tools in high-functioning children. We aimed to evaluate whether (1) agreement in ADI-R and ADOS-2 (Module 3) diagnostic algorithm classifications in HF-ASD varied across two childhood age periods: 5-8 and 9-13 years; and (2) the strength of the association between ASD symptom domains as measured by the ADI-R and ADOS-2 varied across the younger and older childhood age groups.

3.5. Method

3.5.1. Participants

This study was completed within an overarching project investigating subtypes of children with HF-ASD. Sixty-one children with parent reported clinical diagnosis of DSM-IV-TR autistic disorder, Asperger's disorder, or pervasive developmental disorder-not otherwise specified (American Psychiatric Association, 2000) or a diagnosis of ASD according to DSM-5 criteria (American Psychiatric Association, 2013), were recruited to the project with their primary caregivers (all diagnoses henceforth referred to as ASD). Individuals were eligible to participate if they had Verbal Comprehension Index and/or Perceptual Reasoning Index scores greater than 80, as measured by Wechsler Intelligence Scales (Wechsler, 2002, 2004). Twenty-two children previously diagnosed by author RT in conjunction with a paediatrician, and either an occupational therapist or speech pathologist, voluntarily participated in the months following diagnosis. Remaining participants were recruited through psychologists or psychiatrists known to the research team and experienced in ASD diagnosis (n=24), or via advertisement on autism specific websites (n=15).

For the greater study, children were excluded if they had a diagnosis of intellectual disability; a neurological disorder (e.g., cerebral palsy); history of traumatic brain injury; or known biological cause of ASD symptoms (e.g., perinatal exposure to rubella, thalidomide, valproate, and herpes encephalitis, or genetic disorders such as tuberous sclerosis, fragile-X, Angelman or Cornelia de Lange syndromes). For this study, only participants assessed using ADOS-2: Module 3 (verbally fluent) were eligible; children from the overarching study assessed with Module 2 (phrase speech; n=4) were excluded.

The remaining 57 participants (47 males) were aged between five and 13 years (*M*=8.53, *SD*=2.32). All assessments were completed in English. All children had Verbal Comprehension Index (*M*=97.50, *SD*=16.24) or Perceptual Reasoning Index (*M*=105.84; *SD*=13.98) scores greater than 80 according to the Wechsler scales of intelligence (Wechsler, 2002, 2004).

3.5.2. Materials

3.5.2.1. ASD Symptomatology

The ADOS-2 (Lord, Rutter, et al., 2012) semi-structured, play based assessment involves one interactive session with a trained examiner (40 to 60 minutes). All participants were evaluated with Module 3, appropriate for verbally fluent children and adolescents.

The ADI-R (Lord et al., 1994) semi-structured caregiver interview (90-150 minutes) explores early development, communication skills, social development, interests and behaviours. The diagnostic algorithm is based on (1) retrospectively reported functioning between ages four to five years within Social Interaction and Communication domains; and (2) greatest lifetime symptom severity within the RBBI domain. A behaviour algorithm summarising current impairment within the same symptom domains is also available. ADI-R current behaviour scores are not equivalent to diagnosis due to omission of early developmental variables; however, direct comparison between ADI-R current behaviour and ADOS-G algorithms is supported in the test manual.

3.5.2.2. General Cognitive Ability

The Wechsler Intelligence Scale for Children-Fourth Edition (Wechsler, 2004) or Wechsler Preschool and Primary Scale of Intelligence-Third Edition (Wechsler, 2002) evaluated general cognitive ability.

3.5.3. Procedure

Study approval was obtained from The Royal Children's Hospital (Project 32023) and the Monash University (Project 2012000837) Human Research and Ethics Committees. Written informed consent was obtained from all parents of child participants. Assessment sessions were completed at Sunshine Hospital, Monash University, author RT's private practice, or the participants' home. All assessments were completed according to standardised procedures outlined in test manuals. Parents provided signed

informed consent for results from cognitive assessments completed outside the project within the previous two years to be included in the study.

The examiner who completed ADI-R and ADOS-2 assessments (author FK) met research reliability standards for both measures. FK also attended regular ADOS-2 supervision meetings to maintain research reliability. With parental consent, ADOS-2 assessments were video recorded and later coded from video (n=51). Five participants had been assessed using ADOS-G (Lord et al., 2002) external to the study within the preceding 12-months. Task administration is comparable across ADOS-G and ADOS-2 (Lord, Rutter, et al., 2012) and both versions evaluate functioning within the same symptom domains. ADOS-2, however, includes slight modification to the wording of several behavioural observation variables and a revised diagnostic algorithm. The ADOS-2 was not re-administered to these participants to prevent potential practice effects. Parents consented for previous results to be included and ratings/diagnostic algorithms were amended to match ADOS-2 coding. All analyses were repeated with these participants excluded to ensure external data did not significantly influence results.

3.5.4. Statistical Analysis

3.5.4.1. ADOS-2 and ADI-R Diagnostic Algorithm Classifications

Cohen's Kappa (κ) examined consistency between ADOS-2 and ADI-R diagnostic algorithm classifications. While the ADI-R classifies individuals as 'AD'/'Not AD', the ADOS-2 adopts the categories of 'AD'/'AS'/'Not ASD'. Kappa statistic requires variables to have an equal number of categories to examine classification agreement. To address this issue, individuals classified as 'AS' on the ADOS-2 (n=7) were either (1) excluded from analysis; (2) included within the ADOS-2 'Not ASD' subgroup; or (3) included within the ADOS-2 'AD' subgroup, thereby allowing comparison between dichotomous classifications across the measures. Approaches (2) and (3) are consistent with previous research (de Bildt et al., 2004; Ventola et al., 2006). To determine whether agreement between classifications varied according to participant age, analysis was completed with (1) all participants; (2) participants aged 5-8:11 ('Group 1'); and (3) participants aged 9 and older ('Group 2'). Age cutoffs were consistent with de Bildt et al. (2004), which investigated level of agreement between the measures in children with ASD and intellectual disability. Comparing the level of agreement between the tools across the same childhood age groups in a sample of children with high-functioning ASD assists in understanding whether measure concordance differs according to intellectual level.

3.5.4.2. ADOS-2 and ADI-R Diagnostic Algorithm and Current Behaviour Domains

ADOS-2 and ADI-R diagnostic algorithm domain scores were tallied according to the test manuals. Spearman's rho evaluated the strength of association between domain scores across the measures for all participants combined, and for Groups 1 and 2 separately.

For current behaviour algorithms, the individual behaviors assessed by each tool were examined to ensure consistency within the items measured by each of the instruments (as opposed to relying upon the summed behavioral domains described). For current Communication and RRBI domain scores, the ADOS-2 and ADI-R vary with regard to the variables included within each domain. For example, the ADOS-2 includes a single variable describing 'stereotyped/idiosyncratic use of words or phrases' within the RRBI domain; in contrast, the ADI-R includes four variables related to 'stereotyped repetitive, or idiosyncratic speech' within the Communication domain. Therefore, the four ADI-R items describing 'stereotyped, repetitive, or idiosyncratic speech' were excluded from the ADI-R Communication domain and included instead within the RRBI domain for analysis, making the items assessed by the ADI-R and ADOS-2 more consistent. Items included within the ADI-R and ADOS-2 Social Interaction domains were not modified and were tallied according to test protocols.

Consistent with DSM-5 (American Psychiatric Association, 2013), RRBI encompassed five subdomains in this study: (1) Stereotyped Language; (2) Unusual Sensory Interests; (3) Motor Mannerisms; (4) Interests, Preoccupations, & Repetitive Behaviours; and (5) Compulsions and Rituals. Variables from the two measures were matched at face value (Supplementary Material – Appendix A). For some subdomains, multiple ADI-R variables were summarised into a single item in order to sample characteristics encompassed by an associated ADOS-2 item. For example, the ADOS-2: Module 3 has a single item encompassing 'excessive interest in or references to unusual or highly specific topics or objects or repetitive behaviours'; in contrast, the ADI-R includes separate items for 'circumscribed interests', 'unusual preoccupations', and 'repetitive use of objects or interest in parts of objects'. As these three ADI-R items appear to target the same areas of functioning evaluated by the single ADOS-2 variable the rating of greatest severity across the ADI-R items was retained for further analysis, thereby providing a single summary score indexed on the same scale as the ADOS-2. The RRBI subdomain scores for both the ADI-R and ADOS-2 were summed to calculate a current RRBI domain score for each measure.

Spearman's rho evaluated relationships between ADI-R and ADOS-2 current Communication, Social Interaction, and RRBI domain scores. Results were interpreted against conservative alpha level (p<.01) to adjust for multiple comparisons.

3.5.4.3. ADOS-2 and ADI-R Ratings of Current RRBI Symptoms

Spearman's rho examined correlations between RRBI variables matched at face value across the ADI-R and ADOS-2. Contingency tables of concordance between severity ratings across the instruments were examined, and Cohen's Kappa evaluated the level of agreement. The proportion of children with concordant and discordant ratings across the measures was examined. ADI-R ratings were subtracted from those of the ADOS-2, such that the value of zero represented concordant ADOS-2 and ADI-R ratings; a negative value represented greater severity of ADI-R compared with ADOS-2; and a positive value indicated the reverse pattern. The sign test evaluated whether there were significant median differences (p<.01) between ratings when all participants were included, and when Groups 1 and 2 were compared.

There were no appreciable differences between results when participants evaluated with ADOS-G by external examiners were excluded. Findings reported relate to all 57 participants. IBM SPSS Statistics 21 (Release 21.0.0.0) was employed for statistical analyses.

3.6. Results

3.6.1. ADOS-2 and ADI-R Diagnostic Algorithm Classifications

According to the ADOS-2 diagnostic algorithm, 81% (n=46) of participants were classified 'AD', 12% (n=7) 'AS', and the remaining 7% (n=4) 'Not ASD'. For the ADI-R, 70% (n=40) met cutoff scores for 'AD'. Table 1 reports the agreement between ADI-R and ADOS-2 diagnostic algorithm classifications for all participants together, and for Groups 1 and 2. Regardless of age, agreement between ADI-R and ADOS-2 classifications was poor (i.e., κ<0.0; Landis & Koch, 1977) both when (1) ADOS-2 'AS' participants were excluded, and when (3) ADOS-2 'AS' participants were included with 'AD' participants. When (2) ADOS-2 'AS' participants were included with 'Not ASD' participants, agreement between classifications was slight (i.e., $\kappa \leq 0.2$; Landis & Koch, 1977) for the whole sample and poor for Group 2, but improved to fair (i.e., $0.2 < \kappa \leq 0.4$; Landis & Koch, 1977) for Group 1.

Table 1

Agreement between ADI-R and ADOS-2 Diagnostic Algorithm Classifications

		ADI-R Classifications				Agreement	
		'AD'		'Not AD'			
ADOS-2 Classifications		**n**	**%**	**n**	**%**	**%**	**κ**
1. 'AD' vs 'Not AS'							
All	'AD'	33	66.0	13	26.0	66.0	-.14
	'Not ASD'	4	8.0	0	0.0		
Group 1	'AD'	20	66.7	9	30.0	66.7	-.06
	'Not ASD'	1	3.3	0	0.0		
Group 2	'AD'	13	65.0	4	20.0	65.0	-.21
	'Not ASD'	3	15.0	0	00.0		
2. 'AD' vs 'AS'/'Not ASD'							
All	'AD'	33	57.9	13	22.8	64.9	.07
	'AS'/'Not ASD'	7	12.3	4	7.0		
Group 1	'AD'	20	60.6	9	27.3	69.7	.24
	'AS'/'Not ASD'	1	3.0	3	9.1		
Group 2	'AD'	13	54.2	4	16.7	58.4	-.10
	'AS'/'Not ASD'	6	25.0	1	4.2		
3. 'AD'/'AS' vs 'Not ASD'							
All	'AD'/'AS'	36	63.2	17	29.8	63.2	-.13
	'Not ASD'	4	7.0	0	0.0		
Group 1	'AD'/'AS'	20	60.6	12	36.4	60.6	-.06
	'Not ASD'	1	3.0	0	0.0		
Group 2	'AD'/'AS'	16	66.7	5	20.8	66.7	-.19
	'Not ASD'	3	12.5	0	0.0		

All: N=57; Group 1: 5-8:11 years (n=33); Group 2: 9-13 years (n=24). 1. ADOS-2 'AD' vs 'Not ASD': participants classified 'AS' on ADOS-2 (n=7) excluded. 2. ADOS-2 'AD' vs 'AS'/'Not ASD': participants classified 'AS' on ADOS-2 included within 'Not ASD' subgroup. 3. ADOS-2 'AD'/'AS' vs 'Not ASD': participants classified 'AS' on ADOS-2 included within 'AD' subgroup. Kappa (κ): measure of agreement; κ<0.0: poor; $\kappa \leq 0.2$: slight; $0.2<\kappa\leq0.4$: fair; $0.4<\kappa\leq0.6$: moderate; $0.6<\kappa\leq.8$: substantial; and $\kappa>0.8$: almost perfect agreement (Landis & Koch, 1977).

3.6.2. ADOS-2 and ADI-R Diagnostic Algorithm and Current Behaviour Domains

Table 2 displays Spearman's coefficients between ASD symptom domains as measured by the ADOS-2 and ADI-R. For the ADI-R diagnostic algorithm, ADOS-2 and ADI-R Communication scores correlated significantly for Group 1 (large effect) but not Group 2. While Social Interaction domain scores correlated at p<.05 for Group 1, and RRBI

domain scores correlated at $p<.05$ for Group 2, these relationships were not interpreted as significant once allowing for multiple comparisons.

For the ADI-R current behaviour algorithm, Communication and Social Interaction scores across the measures correlated significantly (medium effect) when all participants were evaluated together. The association between these domains was large when Group 1 was evaluated; correlations were not significant for Group 2. Current RRBI domain scores were not significantly correlated across the groups ($p>.05$).

Table 2

Spearman's Coefficients between ADI-R and ADOS-2 Diagnostic Algorithm and Current Behaviour Domains

	ADI-R Diagnostic Algorithm			ADI-R Current Behaviour		
ADOS-2 Domain	**All**	**Group 1**	**Group 2**	**All**	**Group 1**	**Group 2**
Social Interaction	.32*	.39*	.17	.45**	.59**	.23
Communication	.38**	.54**	-.05	.46**	.60**	.24
RRBI	.20	.07	.44*	.10	-.01	.24

*$p<.05$, **$p<.01$ (two-tailed). All: $N=57$; Group 1: 5-8:11 years ($n=33$); Group 2: 9-13 years ($n=24$). ADI-R: Autism Diagnostic Interview-Revised; ADI-R Current Behaviour: Current Behaviour Algorithm; ADOS-2: Autism Diagnostic Observation Schedule-Second; RRBI: Restricted, repetitive behaviours, interests and activities.

3.6.3. ADOS-2 and ADI-R Ratings of Current RRBI Symptoms

RRBI subdomain ratings were further examined to understand the weak association between RRBI domain scores across the ADI-R and ADOS-2. Ratings of Stereotyped Language correlated significantly across the measures when all participants were included ($r_s=.33$, $r_s^2=.11$, $p=.01$) and when Group 2 was evaluated ($r_s=.55$, $r_s^2=.30$, $p=.01$). When Group 1 was examined, Motor Mannerisms was the only subdomain to correlate significantly ($r_s=.44$, $r_s^2=.19$, $p=.01$). There was no significant relationship between ratings of Unusual Sensory Interests; Interests, Preoccupations, and Repetitive Behaviors; and Rituals or Compulsions for any groups (Supplementary Material – Appendix B).

Cohen's Kappa evaluated the consistency between RRBI subdomain ratings across the measures, where symptomatology was rated absent (0), mild (1), moderate (2), or severe (3) (Table 3). When all participants were evaluated together, consistency between ratings was slight across all RRBI subdomains. For Group 1, agreement

between Motor Mannerisms was fair, but concordance between all other subdomains remained slight or poor. Within Group 2, agreement between ratings of Stereotyped Language was fair; comparisons across all other subdomains were slight or poor.

Table 3

Agreement between ADOS-2 and ADI-R Ratings of Current RRBI

	All		Group 1		Group 2	
	%	*κ*	%	*κ*	%	*κ*
Stereotyped Language	40.4	.09	30.3	-.07	54.1	.31
Sensory Interests	43.9	.15	45.5	.15	41.7	.14
Motor Mannerisms	40.4	.13	45.4	.22	29.2	-.06
Int/Preoc/Rep.Beh	28.1	.05	30.3	.05	25.1	.03
Rituals/Compulsions	38.6	.11	42.4	.18	33.4	.01

All: N=57; Group 1: 5-8:11 years (n=33); Group 2: 9-13 years (n=24). %: Percentage agreement between ratings across measures. Int./Preoc/Rep.Beh: Circumscribed Interests, Unusual Preoccupations, Repetitive Behaviours. Kappa (κ): measure of agreement; $\kappa<0.0$: poor; $\kappa\leq0.2$: slight; $0.2<\kappa\leq0.4$: fair; $0.4<\kappa\leq0.6$: moderate; $0.6<\kappa\leq.8$: substantial; and $\kappa>0.8$: almost perfect agreement (Landis & Koch, 1977).

For RRBI subdomains, the number of children who received the same rating across the ADI-R and ADOS-2 was tabulated alongside the number of children who attracted a higher rating on the ADI-R compared with the ADOS-2, and those with the reverse pattern (Table 4). Both Groups 1 and 2 were significantly more likely to be rated with greater severity of circumscribed interests, unusual preoccupations, and repetitive behaviour on the ADI-R in comparison to the ADOS-2. In contrast, only Group 1 was significantly more likely to be rated as displaying more severe rituals or compulsions on the ADOS-2 relative to the ADI-R.

Table 4

Concordance and Discordance between ADOS-2 and ADI-R Ratings of Current RRBI

	All				Group 1				Group 2			
	ADOS-2 = ADI-R	**ADOS-2 > ADI-R**	**ADI-R > ADOS-2**	***p***	**ADOS-2 = ADI-R**	**ADOS-2 > ADI-R**	**ADI-R > ADOS-2**	***p***	**ADOS-2 = ADI-R**	**ADOS-2 > ADI-R**	**ADI-R > ADOS-2**	***p***
Stereotyped Language	40.4	21.1	38.6	.12	30.3	21.2	48.5	.09	54.2	20.8	25.0	1.0
Sensory Interests	43.9	21.1	35.1	.22	45.4	18.2	36.4	.24	41.7	25.0	33.3	.79
Motor Mannerisms	40.4	19.3	40.4	.06	45.5	21.2	33.3	.48	33.3	16.7	50.0	.08
Int/Preoc/ Rep.Beh	28.1	7.0	64.9	.00**	30.3	9.1	60.6	.00**	25.0	4.2	70.8	.00**
Rituals/ Compuls.	38.6	47.4	14.0	.00**	42.4	48.5	9.1	.00**	33.3	45.8	20.8	.21

p<.01 (two-tailed). All: N=57; Group 1: 5-8:11 years (n=33); Group 2: 9-13 years (n=24). Int/Preoc/Rep.Beh: Circumscribed Interests, Unusual Preoccupations, Repetitive Behaviours. Rituals/Compuls: Rituals or Compulsions. **ADOS-2=ADI-R: % participants rated with same symptom severity across measures; **ADOS-2>ADI-R:** % participants rated with greater severity on ADOS-2 compared to ADI-R; **ADI-R>ADOS-2:** % participants rated with greater severity on ADI-R compared to ADOS-2.

3.7. Discussion

In this study we examined the level of agreement between the 'gold standard' ASD assessment tools, the ADI-R and ADOS-2 (Module 3), across two childhood age groups in HF-ASD. In the first part of the study, participants who did not meet full criteria for Autism on the ADOS-2, but met cutoff scores for Autism Spectrum, were excluded; only children classified as Autism or Not Autism were compared across the measures. Measures of agreement between the ADI-R and ADOS-2 diagnostic algorithm classifications were close to zero both for younger (5-8 years) and older children (9-13 years). Similarly, the strength of agreement between the measures was close to zero across both age groups when participants classified as Autism Spectrum on the ADOS-2 were included within the Autism group. Agreement between classifications according to the measures was also examined when participants classified as Autism Spectrum on the ADOS-2 were included within the Not Autism group. When this occurred, concordance between the ADI-R and ADOS-2 remained poor for older children, but improved for younger children (fair range). Overall, results demonstrate significant discordance between ADI-R and ADOS-2 diagnostic algorithm classifications, highlighting the complexity in making a diagnosis in clinical and/or research settings where the diagnostic algorithms are utilised.

One possible cause for the disparate results between the tools is that the ADI-R diagnostic algorithm is based on retrospectively reported functioning between ages four to five (Social Interaction and Communication domains) and greatest lifetime symptom severity of RRBI. In contrast, the ADOS-2 diagnostic algorithm is based on current functioning only. Therefore, for a child aged over five years, the diagnostic algorithms for the measures are based on different developmental periods. ASD developmental trajectories vary (Szatmari et al., 2015), with improvement of some skills and worsening of others over time (Lord, Luyster, Guthrie, & Pickles, 2012). Clinical features retrospectively reported between ages four to five likely differ from symptomatology evident during an ADOS-2 evaluation completed at an older age. Reliance on retrospective report for the ADI-R diagnostic algorithm may further introduce bias, as the reliability of information is impacted by the length of time between the past event and the date of current assessment (Hus, Taylor, & Lord, 2011). Further, ADI-R ratings vary across repeated administrations (Hill et al., 2001; Jones et al., 2015). This, in addition to changing symptomatology throughout development, may partly explain the poor agreement between the measures.

Given this, we examined the correlations between symptom domains as measured by the ADI-R and ADOS-2 across childhood age groups to better understand whether symptom characterisation by the tools differs throughout development. For the diagnostic algorithms, Social Interaction and Communication domains correlated significantly across the measures for younger (p<.05 and p<.01, respectively) but not older participants. This supports the notion that differences in the developmental and chronological age assessed by the ADI-R and ADOS-2 diagnostic algorithms may contribute to poor agreement between the tools for these domains.

Interestingly, however, correlations of current Social Interaction and Communication impairment across the measures were also significant for younger (p<.01) but not older children. Taken together, evidence that ADI-R scores from both the diagnostic and current behaviour algorithms showed weak correlations with ADOS-2 scores in older children with HF-ASD demonstrates that the differences are not fully explained by confounds associated with reliance on retrospective reports. Rather, other differences between the ADI-R and ADOS-2, such as the method of symptom evaluation, are likely important, where results demonstrate that at later ages the two instruments are indexing ASD symptomatology differently. Differences between these measures may be magnified in the older, high-functioning children because of the greater complexity and variability of the behaviours at this older stage. If this is true, modifying the ADI-R diagnostic algorithm to include current behaviour ratings (which permits the ADI-R and ADOS-2 to evaluate the same age period) is unlikely to resolve the differences between symptom ratings across the measures in this population.

Results differed for RRBI domain scores. Current scores did not correlate significantly across the ADI-R and ADOS-2 for either age group, demonstrating that the tools evaluate different aspects of functioning with regard to current RRBI symptomatology. Interestingly, when examining the diagnostic algorithms, RRBI scores correlated at p<.05 across the measures for the older group only. For the ADI-R diagnostic algorithm, the RRBI domain score is based on greatest lifetime symptom severity rather retrospectively reported functioning between ages four to five years. Results suggest that when characterising RRBI in high-functioning children, the developmental perspective becomes particularly important, whereby parent reports regarding lifetime impairment is more closely associated with clinician observation of current functioning. This finding could also be related to the ADI-R and ADOS-2 criteria used to score RRBI characteristics. The ADOS-2 rating system for RRBI has a relatively low threshold, such

that a child who shows mild symptomatology across a number of areas can achieve a high overall score on this domain. This score may be more closely associated with the extent to which a child has *ever* displayed this symptomatology at home (i.e., as per the "ever" rating on the ADI-R), rather than with the parent reported severity of *current* symptomology.

Most notably, our results emphasise the importance of utilising both informant report and child observation to characterise RRBI in HF-ASD. Both age groups were significantly more likely to be rated with greater severity of circumscribed interests, unusual preoccupations, or repetitive behaviours based on the ADI-R compared to the ADOS-2. This suggests that the ADOS-2 did not provide sufficient opportunity to observe these aspects of RRBI, regardless of age. Conversely, parents of the younger group were significantly less likely to report rituals or compulsions relative to that observed during the ADOS-2, raising the possibility that (1) parents of younger children had greater difficulty identifying these clinical features, or did not see it as significantly impacting functioning relative to clinical judgment during the ADOS-2; (2) ADI-R questions may lack sensitivity in probing this symptom area in younger children; or (3) the ADOS-2 may be over-sensitive or may over-pathologise rituals or compulsions in younger children. From the current data it is not possible to determine which measure is over- or under- representing the true symptom severity. Results highlight, however, that utilising one information source independently from the other may inaccurately estimate symptom severity in HF-ASD.

Taken together, these findings demonstrate that the ADI-R and ADOS-2 evaluate different phenotypic characteristics in HF-ASD. The different information sources utilised by the measures has previously been emphasised as a key factor contributing to limited agreement between the tools (de Bildt et al., 2004). By utilizing parent report, the ADI-R assessment is based upon observations across multiple settings over the lifetime. As age increases and functioning changes over time, current behaviour may be referenced against past behaviour (Jones et al., 2015) or sibling functioning to inform parent reports of symptom severity. In contrast, the ADOS-2 direct observational approach provides an indication of functioning during one structured and standardised session, without consideration of historical information. Higher-functioning children may benefit from the ADOS-2 assessment format of one-to-one interaction with an adult, such that functioning observed during the assessment may differ considerably to that displayed in other environments where there are multiple stimuli and greater social

demands, such as when interacting with groups of people. As ADOS-2 scoring prescribes that only behaviour observed within the session can be coded, there is potential to underestimate the presence or severity of symptomatology when relying on the diagnostic algorithm. Further, as age increases, children with HF-ASD may learn skills to mask difficulties such that the clinical presentation within the ADOS-2 may differ to that observed by parents.

3.7.1. Limitations

The limited sample size impacted the power of analysis, particularly when comparisons were evaluated against a more conservative alpha value to allow for multiple comparisons. Further, in the absence of a control group it was not possible to examine the discriminant validity of the ADI-R and ADOS-2. Similarly, there was no independent and operationalised clinical characterization of severity of impairment within each domain. This would have offered insight as to whether the ADOS-2 or ADI-R was over- or under-representing certain symptom areas.

3.7.2. Conclusion

The importance of utilising child observation and parent report is well recognised in ASD diagnosis. In particular, administering the ADI-R and ADOS-2 in combination has been repeatedly emphasised (de Bildt et al., 2004; Gray et al., 2008; Le Couteur et al., 2008; Zander et al., 2015); however, disagreement between the diagnostic algorithm classifications with high-functioning children and young adolescents cautions against relying on the algorithms in practice. The ADI-R and ADOS-2 both provide important perspectives that are potentially non-overlapping and complimentary, with both being informative to aid diagnosis. Here we demonstrate that the tools evaluate different aspects of RRBI throughout childhood/early adolescence and that as age increases the relationship between the measures in evaluating social and communication deficits weakens. The significant limitations in currently available diagnostic tools necessitates that clinical opinion remains the 'gold standard' for ASD diagnosis. There is a need to develop methods of evaluating ASD symptomatology in older, high-functioning children, where behaviours are more complex and varied, and where there is greater disparity between the currently available measures. The goal should be to develop a standardised measure that combines information obtained from parent report and child observation within the single tool, so that results from each evaluation can easily be directly compared. Further, inclusion of teacher and other clinician reports within the same measure would allow a more comprehensive overview upon which to base diagnosis.

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3.9. Supplementary Material

3.9.1. Appendix A: ADI-R and ADOS-2 Variables Compared to Explore Current Restricted and Repetitive Behaviours and Interests (RRBI)

Table 1

Current RRBI Variables Compared across the ADI-R and ADOS-2

Stereotyped Language	
ADOS-2	Stereotyped/Idiosyncratic use of words or phrases (item A-4)
ADI-R	Stereotyped utterances and delayed echolalia (item 33)
Unusual Sensory Interests	
ADOS-2	Unusual sensory interest in play material/person (item D-1)
ADI-R	Unusual sensory interests (item 71)
Motor Mannerisms	
ADOS-2	Hand and finger and other complex mannerisms (item D-2)
ADI-R	Hand and finger mannerisms (item 77)
	Other complex mannerisms or stereotyped body movements (item78)
Interests, Preoccupations, & Repetitive Behaviours	
ADOS-2	Excessive interest in or references to unusual or highly specific topics or objects or repetitive behaviours (item D-4)
ADI-R	Circumscribed interests (item 68)
	Unusual preoccupations (item 67)
	Repetitive use of objects or interest in parts of objects (item 69)
Rituals or Compulsions	
ADOS-2	Compulsions or rituals (item D-5)
ADI-R	Verbal rituals (item 39)
	Compulsions/rituals (item 70)

ADOS-2: Autism Diagnostic Observation Schedule-Second Edition. ADI-R: Autism Diagnostic Interview-Revised. RRBI: Restricted, repetitive behaviours, interests and activities.

3.9.2. Appendix B: Spearman's Coefficients between ADOS-2 and ADI-R Ratings of Current RRBI

Table 2

Spearman's Coefficients between Current RRBI Subdomain Ratings on the ADI-R and ADOS-2

	All	Group 1	Group 2
Stereotyped Language	.33**	.18	.55**
Unusual Sensory Interests	.26	.29	.23
Motor Mannerisms	.31*	.44**	-.08
Int/Preoc/Rep.Beh	.21	.21	.23
Rituals or Compulsions	.02	.08	-.05

*p<.05, **p=.01 (two-tailed). All: N=57; Group 1: 5-8:11 years (n=33); Group 2: 9-13 years (n=24). RRBI: Restricted, repetitive behaviours, interests and activities. ADI-R: Autism Diagnostic Interview-Revised. ADOS-2: Autism Diagnostic Observation Schedule-Second. Int/Preoc/Rep.Beh: Circumscribed Interests, Unusual Preoccupations, and Repetitive Behaviours.

CHAPTER 4: PREDICTING TEACHER RATED BEHAVIOURAL AND EMOTIONAL FUNCTIONING IN CHILDHOOD HIGH-FUNCTIONING ASD BASED ON ASD SYMPTOMATOLOGY AND NEUROCOGNITIVE FUNCTIONING

4.1. Preamble to Chapter 4

Chapters 2 and 3 of this thesis demonstrated the complexity associated with phenotypic variability in high-functioning ASD, both with regards to diagnostic classification and diagnostic decision-making. While these early chapters focused on core ASD symptomatology, clinical features outside of the core diagnostic criteria can also significantly impact functioning in high-functioning ASD, with implications for clinical management and prognosis. It is therefore important that clinical evaluation goes beyond assessment of core ASD features to understand functioning in this population. One key area is behavioural and emotional functioning. While it is well recognised that higher-functioning individuals with ASD are at greater risk for behavioural and emotional difficulties than lower functioning individuals with ASD and typically developing peers, factors contributing to the elevated rates of these difficulties are unclear. The study reported in this chapter addressed aim (3) of this thesis, which was to examine whether ASD specific symptomatology and aspects of neurocognitive functioning can predict teacher reported behavioural and emotional functioning in high-functioning ASD. This study extends previous research by using the 'gold standard' parent report and child observation measures to evaluate ASD symptomatology. General cognitive ability, new learning and memory, language functioning, and pragmatic communication were also examined as potential predictors of behavioural and emotional functioning. The comprehensive evaluation of ASD symptoms and areas of neurocognitive functioning often implicated in ASD allowed investigation of which aspects of functioning were most predictive of behavioural and emotional difficulties in high-functioning ASD.

The manuscript presented in this chapter was submitted for publication in the '*Journal of Autism and Developmental Disorders*' in June 2015. The section numbering has been modified to maintain consistent presentation throughout the thesis. See Chapter 7: Appendices for additional information regarding the tools used to evaluate ASD symptomatology (Appendix A), cognition (Appendix B), language and communication (Appendix C), and behavioural and emotional functioning (Appendix D). If abbreviations or citations used in this manuscript were not used in thesis Chapters 1 or 5, they are not included in the thesis abbreviations or thesis references lists.

4.2. Declaration for Chapter 4

Monash University

Declaration by candidate

In the case of Chapter 4 (Study Three Manuscript), the nature and extent of my contribution to the work was the following:

Nature of Contribution	Extent of Contribution (%)
Conceptualisation and design of study; ethics approval; participant recruitment; data collection, management and analysis; and manuscript preparation and submission for publication.	80%

The following co-authors contributed to the work.

Name	Nature of Contribution
Renee Testa	Conceptualisation of study, supervision, data analysis and revision of drafts
Efstratios Skafidas	Conceptualisation of study; data analysis; revision of statistical analysis and results sections in manuscript.
Christos Pantelis	Conceptualisation of study, supervision and revision of drafts.

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

Candidates Signature: [redacted]	**Date:** 14/08/2015
Main Supervisor's Signature:	**Date:** 14/08/2015

Predicting Teacher rated Behavioural and Emotional Functioning in Childhood High-functioning Autism Spectrum Disorder based on ASD Symptomatology and Neurocognitive Functioning

Running title: Predicting Behavioural and Emotional Functioning in Childhood HF-ASD

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Declaration of Interests

The authors declare that there is no conflict of interest.

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4.3. Abstract

It is recognised that children with high-functioning autism spectrum disorder (HF-ASD) are at risk for behavioural and emotional dysfunction, including internalising and externalising symptomatology. Factors contributing to these difficulties are unclear; we investigated whether ASD symptomatology and/or neurocognitive functioning predicted teacher rated areas of difficulty. Stepwise linear regression showed that aspects of cognition and language ability predicted Externalising Problems, School Problems, and Adaptive Skills. New learning and memory, and repetitive, stereotyped behaviour and communication predicted Behavioural Symptoms Index scores. The model did not significantly predict Internalising Problems. Results suggest that cognition and language may be more important in understanding behavioural and emotional difficulties in HF-ASD than ASD symptomatology. These findings support interventions focusing on cognitive and communication strategies. **Keywords:** High-functioning autism spectrum disorder; high-functioning autism; Asperger's disorder; externalising problems; internalising problems; adaptive functioning.

Abbreviations

ADI-R: Autism Diagnostic Interview-Revised
ADOS-2: Autism Diagnostic Observation Schedule-Second
ADOS-Generic: Autism Diagnostic Observation Schedule-Generic Version
ASD: Autism Spectrum Disorder
BASC-2 TRS: Behaviour Assessment System for Children-Second, Teacher Rating Scales
BSI: Behavioural Symptoms Index
CELF-4: Clinical Evaluation of Language Fundamentals-Fourth
CELF-Preschool 2: Clinical Evaluation of Language Fundamentals- Preschool, Second
CCC-2: Children's Communication Checklist-Second
HF-ASD: High-functioning Autism Spectrum Disorder
PRI: Perceptual Reasoning Index
PSI: Processing Speed Index
RRBI: Restricted, repetitive behaviours, interests and activities
VCI: Verbal Comprehension Index
WISC-IV: Wechsler Intelligence Scale for Children-Fourth
WMI: Working Memory Index
WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence-Third
WRAML-2: Wide Range Assessment of Memory and Learning-Second

4.4. Introduction

Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental disorder characterised by impaired social communication, and restricted, repetitive behaviours and interests (RRBI) (American Psychiatric Association, 2013). Co-morbid behavioural and emotional difficulties are frequently observed (Goldin, Matson, Konst, & Adams, 2014; Hass, Brown, Brady, & Johnson, 2012; Knoll, 2008; Mahan & Matson, 2011; Volker et al., 2010), and are most prevalent in individuals without intellectual disability (i.e., 'high-functioning' ASD, HF-ASD). Psychiatric disorders (Brereton, Tonge, & Einfeld, 2006; Hofvander et al., 2009; Mukaddes & Fateh, 2010), including depression and anxiety, occur more frequently in children with HF-ASD relative to both low-functioning ASD and typically developing peers (Knoll, 2008). Behavioural and emotional dysfunction has the potential to reduce cognitive (Harrison & Owen, 2001) and daily functioning (Angkustsiri et al., 2012; Papazoglou, Jacobson, & Zabel, 2013), affect social relationships (Stice, Ragan, & Randall, 2004), increase teacher and caregiver stress (Lecavalier, Leone, & Wiltz, 2006), and impede intervention and therapy (Rhyne, 2009). Thus, understanding predictors of impairment has important clinical and educational implications to aid identification of individuals at risk, and assist the development of tailored management strategies.

Whilst it is acknowledged that social skill deficits (Macintosh & Dissanayake, 2006) and impaired pragmatic communication (Volden, Coolican, Garon, White, & Bryson, 2009) inherent in ASD can impact the development of peer relationships and isolate individuals (Volker et al., 2010), the effect of RRBI (i.e., circumscribed interests, unusual preoccupations, and repetitive motor mannerisms) can also play a significant role. Although special interests provide enjoyment and relaxation for an individual with ASD, and can support engagement in intervention and social interaction if the interest is shared with their peers (Boyd, Conroy, Mancil, Nakao, & Alter, 2007; Kryzak, Bauer, Jones, & Sturmey, 2013; Kryzak & Jones, 2015; Porter, 2012), they may serve as a way to avoid social interaction (Attwood, 2004). Further, they may socially isolate the child from peers when they are unusual in quality (Safran, Safran, & Ellis, 2003) or are not age appropriate.

Recent studies have investigated the impact of social isolation and RRBI on mood disturbance in ASD. A model describing a bidirectional relationship between ASD symptomatology, mood dysregulation and anxiety has been proposed (Wood & Gadow, 2010). In this model, stressors related to social communication deficits (e.g., confusion

in social situations, peer rejection) and RRBI (e.g., limitations placed on engaging in repetitive behaviours, hyper-responsiveness to sensory stimuli) are theorized to be associated with increased anxiety and negative affectivity. This is thought to increase personal distress, social avoidance, and repetitive and challenging behaviours. Attempts to validate the model have demonstrated a complex interplay between these factors. Green and colleagues (2012) found that hyper-sensory responsiveness preceded anxiety development and predicted later anxiety symptomatology, but not vice-versa. In contrast, Wigham et al. (2014) reported that the relationships between hyper-/hypo-sensory responsiveness, repetitive motor mannerisms, and insistence on sameness were mediated both by anxiety and intolerance of uncertainty. Thus, while the constructs may be highly correlated, the causal mechanisms remain unclear.

Clinical features that do not form part of the core ASD diagnostic features but are commonly observed in this population, such as cognitive and language difficulties, may also be associated with behavioural and emotional dysfunction. Given the high prevalence of language disorders in ASD, examining whether language difficulties predict behavioural and emotional problems is particularly relevant. With regard to internalising problems (e.g., depression, anxiety and withdrawal), impaired language functioning may negatively impact confidence in social interaction and reduce motivation for social contact with peers. This, in turn, has potential to impact self-confidence and contribute to social withdrawal. Consistent with this, expressive language difficulties significantly predicted internalising problems in children with ASD who had varied levels of cognitive ability (Hartley, Sikora, & McCoy, 2008), supporting the potential benefit of communication strategies in reducing the risk of internalising problems. Understanding whether this relationship is also evident in children with ASD without intellectual disability will help inform intervention approaches at the high-functioning end of the autism spectrum.

In children without ASD, language problems are also associated with higher rates of teacher reported externalising behaviours, including conduct problems and difficulties associated with hyperactivity and inattention (Lundervold, Heimann, & Manger, 2008). Early language impairment has also been associated with later behavioural problems (based on emotional, conduct, hyperactivity, and peer problems composite score) in a non-clinical population based sample (Clegg, Law, Rush, Peters, & Roulstone, 2015), supporting the notion that language functioning has important implications for behavioural and emotional wellbeing in individuals without ASD. Although Hartley et al.

(2008) found that expressive language was associated with attention problems and aggressive behaviour in ASD individuals, the most robust predictor of externalising problems was nonverbal cognitive ability. This factor accounted for 10% of the variance in externalising symptomatology, demonstrating that other variables also contribute to the development of behavioural problems in this population. Pragmatic communication deficits (i.e., impairment in the social use of language) may be important in this regard; in a non-clinical sample of preschool children, pragmatic communication skills were more predictive of behavioural problems than structural language ability (Ketelaars, Cuperus, Jansonius, & Verhoeven, 2010). General cognitive ability was not examined in this study, which precluded investigation of the relative importance of this construct in predicting externalising behaviours compared with language and communication skills. Examination of these multiple aspects of neurocognitive functioning in a single study will help clarify the contribution of each domain to behavioural and emotional functioning in HF-ASD.

Adaptive functioning describes learned skills required to complete age expected activities, including practical (e.g., self care, occupational and financial skills), conceptual (e.g., reading, and writing), and social (e.g., interpersonal skills and social responsibility) tasks (Tasse et al., 2012). Adaptive functioning was found to be predictive of long-term outcomes in HF-ASD (Farley et al., 2009), demonstrating the prognostic importance of maximising adaptive skills throughout development in children with ASD without intellectual disability.

Predictors of adaptive dysfunction in ASD have been examined in a number of studies. In a recent longitudinal examination of preschool children with ASD involving all levels of intellectual ability, adaptive functioning was significantly predicted by general cognitive ability, language functioning, and age at diagnosis (Szatmari et al., 2015). This suggested that cognitive and language functioning may form important targets for intervention; however, individuals with ASD display disproportionate impairment in adaptive skills relative to their level of intellectual functioning, with this disparity greatest in HF-ASD (Bolte & Poustka, 2002; Liss et al., 2001; Saulnier & Klin, 2007). Liss et al. (2001) suggested that the association between neurocognitive functioning and adaptive skills may differ according to the level of intellectual ability; cognitive ability predicted adaptive skills in low-functioning ASD, whereas language and verbal memory predicted adaptive functioning in high-functioning individuals. Thus, understanding predictors of impairment in HF-ASD may be more complex and multifactorial than low-functioning

ASD, with factors beyond general cognitive ability likely important. Further, this demonstrated the importance of controlling for the level of cognitive ability to allow examination of factors that may be uniquely associated with impairment at the high-functioning end of the autism spectrum.

The relationship between adaptive functioning and ASD severity in HF-ASD has also been examined, but is less clear. Moderate to strong correlations between parent-reported ASD symptomatology and adaptive skill deficits have been reported (Kenworthy, Case, Harms, Martin, & Wallace, 2010; Liss et al., 2001); however, other studies using play-based assessments to characterise ASD symptomatology have reported negligible associations between ASD severity and parent reported adaptive skills (Klin et al., 2007; Saulnier & Klin, 2007). These results suggest that the method of evaluation may contribute to variability across studies, where parent reported adaptive skills correlates significantly with parent reported ASD symptomatology but not clinician observations. Utilising both parent report and child observation to evaluate core ASD symptoms would help clarify the association between ASD symptomatology and adaptive functioning in HF-ASD.

We have chosen to focus on HF-ASD in this study, due to the increased prevalence of behavioural and emotional dysfunction in this subgroup of individuals with ASD. The primary aim of this exploratory study was to investigate whether ASD symptomatology, as measured by the 'gold standard' ASD diagnostic tools, and aspects of neurocognitive functioning could predict domains of behavioural and emotional functioning in this population. ASD symptomatology (parent report and child observation), cognition (general cognitive ability, and new learning and memory), language and pragmatic communication skills were evaluated for all participants, allowing simultaneous exploration of these variables as potential predictors of behavioural and emotional difficulties. Given the wide age range of the childhood sample (6-13 years), age was additionally included as a predictor to examine whether it contributed variability to behavioural and emotional functioning throughout this broad developmental period. These variables were chosen given past studies finding relationships between them and emotional/behavioural problems, as reviewed above. This study, however, extended prior research by considering relationships between these variables using underlying latent factors, and then exploring their ability to predict emotional/behavioural functioning. We utilised the Behavioural Assessment System for Children-Second, Teacher Rating Scale (BASC-2 TRS; Reynolds & Kamphaus, 2004) to evaluate

Externalising Problems, Internalising Problems, Behavioural Symptoms, School Problems and Adaptive Skills. Understanding predictors of impairment as measured by this tool will help with identification of individuals at risk of behavioural and emotional difficulties in the school setting, and will also help inform intervention targets based on identified areas of difficulty.

4.5. Method

4.5.1. Participants

This study was completed within an overarching project investigating subtypes of children with ASD without intellectual disability (i.e., HF-ASD). Sixty-one children with parent reported clinical diagnosis of DSM-IV-TR autistic disorder, Asperger's disorder, or Pervasive Developmental Disorder-Not Otherwise Specified (American Psychiatric Association, 2000) or a diagnosis of ASD according to DSM-5 criteria (American Psychiatric Association, 2013), were recruited to the project with their primary caregivers (all diagnoses henceforth referred to as ASD). Individuals were eligible to participate if they had Verbal Comprehension Index (VCI) and/or Perceptual Reasoning Index (PRI) scores greater than 80, as measured by Wechsler Intelligence Scales (Wechsler, 2002, 2004). Twenty-two participants had previously been diagnosed by author RT in association with a paediatrician, and either an occupational therapist or speech pathologist, and were subsequently invited to participate. Remaining participants were recruited through private clinical psychologists, neuropsychologists, or psychiatrists known to the research team and experienced in diagnosis and intervention with children with ASD (n=24); and via public advertisement on autism specific websites (Autism Victoria and Autism Spectrum Australia; n=15). Children were excluded if they had a diagnosis of intellectual disability (as per above stated criteria); a neurological disorder (e.g., cerebral palsy); history of traumatic brain injury; or known biological cause of ASD symptoms (e.g., perinatal exposure to rubella, thalidomide, valproate, and herpes encephalitis, or genetic disorders such as tuberous sclerosis, fragile-X, Angelman or Cornelia de Lange syndromes).

For the purposes of the current study, only participants with completed BASC-2 TRS questionnaires were eligible. Eleven participants from the overarching project did not return BASC-2 TRS and were consequently excluded from analysis. Of the remaining 50 participants with BASC-2 TRS questionnaires, an additional 12 participants were excluded from this study due to missing data on cognitive, language, or ASD specific variables; given that the data was missing completely at random (Little's Missing

Completely at Random Test $\chi^2(230)=229.78$, $p=.49$), listwise deletion was not considered to bias results (Schafer & Graham, 2002).

The 38 participants (34 males) included in this study were aged six to 13 years ($M=8.84$, $SD=2.05$). All children had VCI ($M=97.21$, $SD=17.61$) or PRI ($M=106.34$; $SD=13.96$) scores greater than 80. The majority of participants ($n=35$) were born in Australia and spoke only English ($n=31$), or a combination of English and another language ($n=4$) at home. Thirty-two participants were Caucasian and six were from ethnic minority groups (3 Asian, 1 Italian, and 2 unknown). Fifteen participants had a parent reported diagnosis of AS; 17 of HFA; and six of ASD. Eleven participants had a co-morbid diagnosis of Attention Deficit Disorder or Attention Deficit Hyperactivity Disorder. Of these, a subgroup of participants had clinically diagnosed anxiety ($n=3$), depression ($n=1$), and Oppositional Defiant Disorder ($n=1$). Excluding participants with Attention Deficit (Hyperactivity) Disorder, four participants had clinically significant anxiety, and one participant was diagnosed with both Obsessive Compulsive Disorder and depression. One participant had epilepsy; two experienced febrile convulsions as infants; and one participant had experienced two seizures across his lifetime (aetiology unknown). Twelve participants reported current psychotropic medication use: 3 methylphenidate alone; 3 methylphenidate and other (1 clonidine; 1 fluoxetine; 1 clonidine and fluoxetine); 3 selective serotonin reuptake inhibitors; and 1 anti-epileptic medication use. Four participants were taking melatonin.

4.5.2. Materials

4.5.2.1. Teacher Rated Behavioural and Emotional Functioning

The BASC-2 (Reynolds & Kamphaus, 2004) is one of the most widely used measures for the assessment of behavioural and emotional functioning by school psychologists (Volker et al., 2010) and has been validated for use in ASD (Goldin et al., 2014; Hass et al., 2012; Knoll, 2008; Mahan & Matson, 2011; Volker et al., 2010). BASC-2 TRS child (6-11 years; $n=33$) and adolescent forms (12-21 years; $n=5$) were used in this study. Both forms include Clinical Scales summarising Externalizing Problems (Hyperactivity, Aggression, Conduct Problems); Internalising Problems (Anxiety, Depression, Somatisation); School Problems (Attention, Learning Problems); and BSI (Hyperactivity, Aggression, Depression, Attention Problems, Atypicality, Withdrawal subscales). An Adaptive Skills composite summarises Adaptability, Social Skills, Leadership, Study Skills, and Functional Communication subscales. *T*-scores are determined based on age and gender. For the Clinical Profile, classifications for *Average* ($T=41$-59); *At Risk* ($T=60$-

69; i.e., severe enough to impair daily functioning, but not at severity for clinical diagnosis); and *Clinically Significant* impairment (*T*≥70) are specified. For Adaptive Skills, *Average* (*T*=41-59); *At-Risk* (*T*=31-40), and *Clinically Significant* (*T*≤30) classifications are indicated.

4.5.2.2. ASD Specific Characteristics

The Autism Diagnostic Observation Schedule-Second (ADOS-2; Lord et al., 2012) play based assessment, and the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) caregiver interview characterised ASD specific symptomatology. These tools are the 'gold standard' assessment measures for ASD. ADI-R and ADOS-2 ratings of current impairment within Social Interaction, Communication, and RRBI domains were examined.

4.5.2.3. General Cognitive Functioning

The Wechsler Intelligence Scale for Children-Fourth (WISC-IV; Wechsler, 2004) or Wechsler Preschool and Primary Scale of Intelligence-Third (WPPSI-III; Wechsler, 2002) evaluated general cognitive functioning, as appropriate for developmental level.

4.5.2.4. New Learning and Memory

Immediate, delayed, and recognition memory standard scores from the Verbal Learning and Story Memory subtests of the Wide Range Assessment of Memory and Learning-Second (WRAML-2; Sheslow & Adams, 2003) were examined.

4.5.2.5. Language and Communication

The Clinical Evaluation of Language Fundamentals-Fourth (CELF-4; Semel, Wiig, & Secord, 2003a) or Clinical Evaluation of Language Fundamentals-Preschool, Second (CELF-Preschool 2; Semel, Wiig, & Secord, 2003b) evaluated receptive and expressive language. In addition, parents completed the Children's Communication Checklist-Second (CCC-2; Bishop, 2003) to evaluate pragmatic communication. The CCC-2 General Communication Composite and Social Interaction Difference Index scores were included in analysis.

Table 1 summarises the assessment measures employed to evaluate ASD symptomatology and neurocognitive functioning, and the variables selected for analysis.

Table 1

Assessment of ASD Symptoms and Neurocognitive Functioning: Measures and Predictor Variables Included in Analysis

Measures	Variables
ADI-R[a]	Social Interaction
	Communication
	RRBI
ADOS-2[b]	Social Interaction
	Communication
	RRBI
WISC-IV or WPPSI-III	Verbal Comprehension Index (VCI)
	Perpetual Reasoning Index (PRI)
	Working Memory Index (WMI)
	Processing Speed Index (PSI)
CELF-4 or CELF-Preschool 2	Receptive Language Index (RLI)
	Expressive Language Index (ELI)
WRAML-2	Verbal Learning subtest – Immediate Recall
	Verbal Learning subtest – Delayed
	Verbal Learning subtest – Recognition
	Story Memory subtest – Immediate
	Story Memory subtest – Delayed
	Story Memory subtest – Recognition
CCC-2	General Communication Composite (GCC)
	Social Interaction Difference Index (SIDI)
Other	Age

ADI-R: Autism Diagnostic Interview-Revised; ADOS-2: Autism Diagnostic Observation Schedule-Second; WISC-IV: Wechsler Intelligence Scale for Children-Fourth; WPPSI-III: Wechsler Preschool and Primary Scales of Intelligence-Third, CELF-4: Clinical Evaluation of Language Fundamentals-Fourth; CELF-Preschool 2: Clinical Evaluation of Language Fundamentals-Preschool, Second; WRAML-2: Wide Range Assessment of Memory and Learning-Second; CCC-2: Clinical Evaluation of Language Fundamentals-Second. a. Current behaviour algorithm domain scores; b. Diagnostic algorithm domain scores.

4.5.3. Procedures

Study approval was obtained from The Royal Children's Hospital and the Monash University Human Research and Ethics Committees. Written informed consent was obtained from all parents or legal guardians of child participants. All assessment sessions were completed at Sunshine Hospital, Monash University, author RT's private practice, or at the participant's home. Parents or legal guardians did not observe child

assessment sessions, and children were not present during caregiver interviews. The order of test administration for child assessments varied on a case-by-case basis to increase participant engagement. Breaks were given as required, with some assessments completed over two days.

An examiner who met research reliability standards (author FK) on the ADI-R and ADOS-2 completed assessments for individuals evaluated via the project (*n*=34). Caregivers provided signed informed consent for ADOS-2 assessments to be video recorded; assessments were subsequently coded from video. A subgroup of participants (*n*=4) had completed the ADOS (i.e., ADOS-Generic, Lord, Rutter, DiLavore, & Risi, 2002; or ADOS-2, Lord et al., 2012) within the preceding year. The ADOS-2 was not re-administered to prevent potential practice effects. Caregivers consented for past results to be accessed and ADOS-Generic ratings were recoded to match ADOS-2 ratings where possible. Parents also consented for cognitive and language measures completed outside of the study in the past two years to be included.

4.5.4. Statistical Analysis

BASC-2 TRS *T*-scores were classified (e.g., *Average*, *At Risk*, *Clinically Significant*) according to standard procedure. The proportion of participants assigned each clinical rating, and the means and standard deviations for the overall sample on each composite and subscale were examined.

Given the small sample size relative to the number of predictor variables of interest, it was necessary to employ data reduction methods. Exploratory factor analysis was utilised to reduce 21 variables (Table 1) to a smaller number of factors sharing common variance. Maximum likelihood factor analysis with minimum mean squared error prediction was employed. This method of data reduction was selected over principal components analysis as it provides a more intuitive method of determining which of the original variables load significantly on the retained factors, thereby improving the ability to interpret each factor. Due to correlations between factors (Supplementary Material – Appendix A), promax rotation was utilised. Given the exploratory nature of this study, factors with an eigenvalue greater than one were retained for further analysis. The scree plot was also examined to support suitability of retaining factors according to this criterion. These two approaches were chosen to guide decision-making as including a smaller number of factors by using stricter inclusion criteria could have resulted in important relationships within this data being missed. Given the small

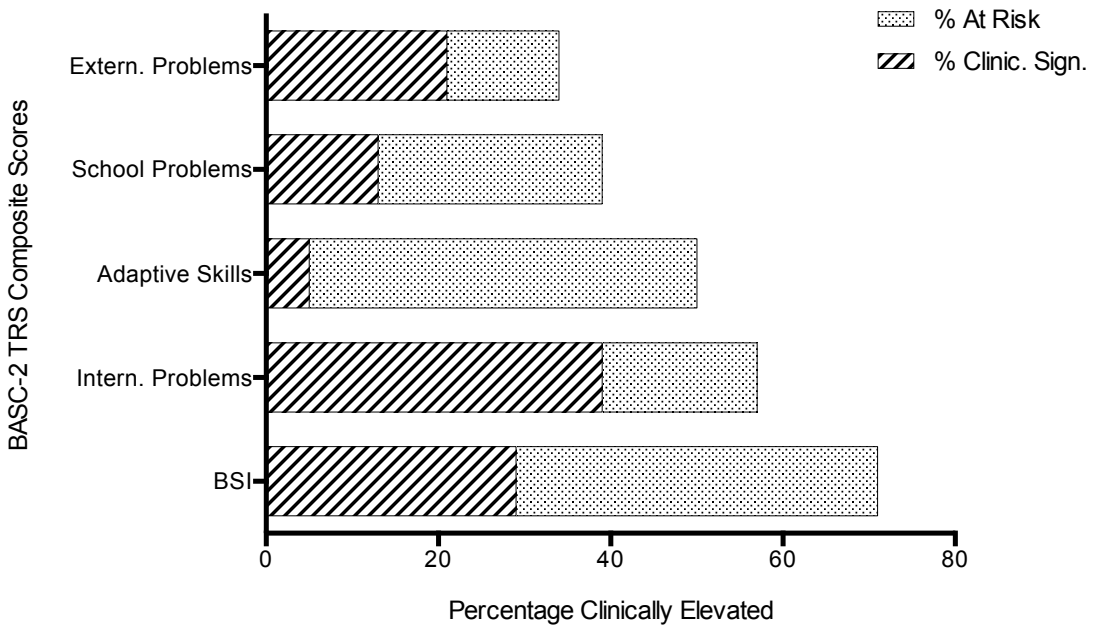
sample size, variables with strong relationships to the factors were used to interpret the meaning of each factor; this was defined in the current study as >.65 (i.e., within *very good* range according to Comrey and Lee (1992)).

Factor scores, which provide a measure of the shared variation between indicators of a factor, were retained as observed variables to use in subsequent regression modeling. Stepwise linear regression was employed to identify the combination of the observed variables that best predicted each of the BASC-2 TRS composite scores. This regression method was selected as the study was exploratory and there were no a priori hypotheses about the relative importance of each of the observed variables in predicting the BASC-2 TRS domains. Analysis was repeated with participants with high leverage based on Cook's distance (>.01) excluded from each model, thus finding the most compact model while remaining statistically significant. Group characteristics and suitability for data reduction techniques were examined using IBM SPSS Statistics 21 (Release 21.0.0.0). Matlab (version 2014b) was used for subsequent analyses.

4.6. Results

4.6.1. Descriptive Statistics

The number of children assigned each clinical descriptor on the BASC-2 TRS composite and subscale scores, and the group means and standard deviations for each scale, were examined. At a group level, none of the mean composite or subscale scores fell within the *Clinically Significant* range; however, mean Internalising Problems and BSI composite scores, and Anxiety, Depression, Atypicality, Withdrawal and Adaptability subscales were within the *At Risk* range (see Supplementary Material – Appendix B for frequencies and descriptive statistics). The percentage of participants who were rated within *Clinically Significant* or *At Risk* ranges on BASC-2 TRS composite and subscale scores are presented in Figures 1 and 2, respectively.



Extern. Problems: Externalising Problems Index; Intern. Problems: Internalising Problems Index; BSI: Behavioural Symptoms Index.

Figure 1. Percentage of participants rated within *Clinically Significant* or *At Risk* ranges on BASC-2 TRS composite scores

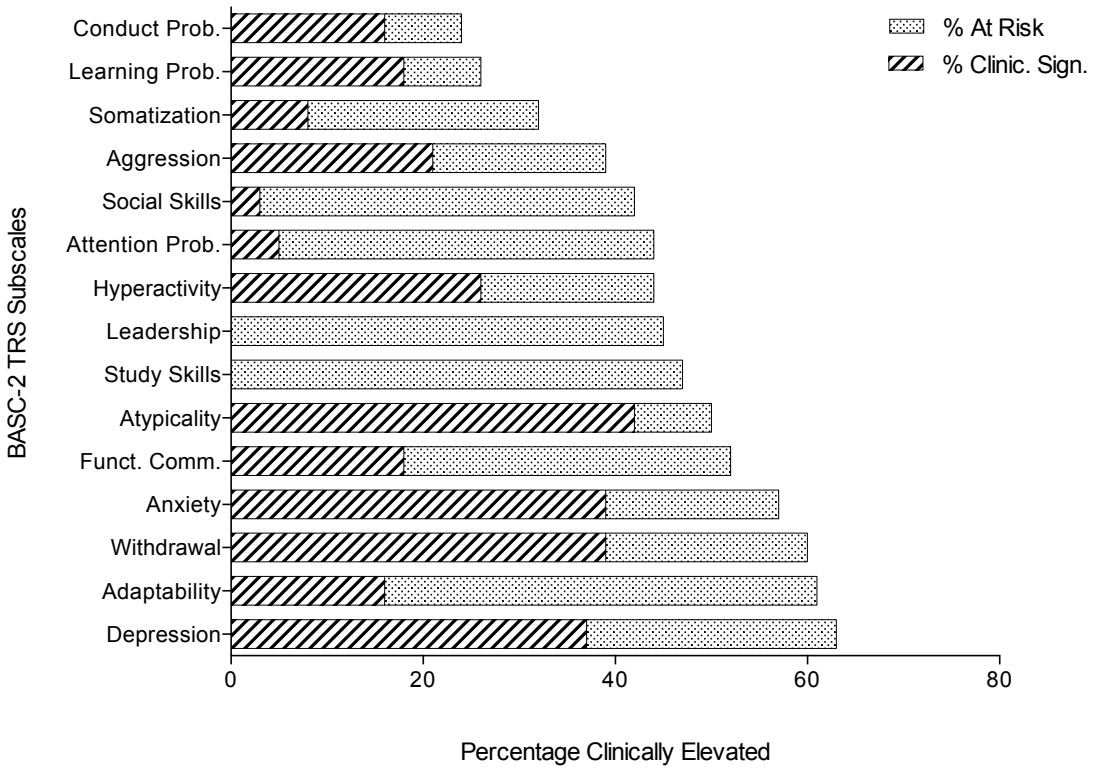


Figure 2. Percentage of participants rated within *Clinically Significant* or *At Risk* ranges on BASC-2 TRS subscale scores

Over 70% of participants were rated within *At Risk* (42%) or *Clinically Significant* (29%) ranges on the BSI composite score (Figure 1). Internalising Problems were the next most frequently endorsed area of difficulty, with 39% of participants rated within the *Clinically Significant* range, and 18% of participants *At Risk* for impairment. Half the sample was rated within the *At Risk/Clinically Significant* range for Adaptive Skills. With regard to BASC-2 TRS subscales (Figure 2), approximately 60% of participants were rated *At Risk* or within the *Clinically Significant* range for Depression, Adaptability, Withdrawal, and Anxiety, while half the sample achieved these classifications for the Functional Communication and Atypicality subscales.

4.6.2. Factor Analysis

Descriptive statistics for the predictor variables subjected to factor analysis are reported in Supplementary Material – Appendix C. Prior to factor analysis, the suitability for data reduction methods was assessed. Inspection of the covariance matrix revealed many coefficients of .3 and above. The Kaiser-Meyer-Oklin equaled .684, indicating there were sufficient items predicted by each factor. Further, Bartlett's Test of Sphericity was significant (p<.001), supporting factorability of the covariance matrix. When the 21 predictor variables were analysed, maximum likelihood analysis revealed six factors with eigenvalues exceeding 1 (see Supplementary Material – Appendix D for eigenvalues and variance explained). Together, these factors accounted for 77.5% of the variance. The first factor explained 33.2% of the variance; the second 14.6%; the third 9.8%; the fourth 7.9%; the fifth 6.9%; and the sixth factor accounted for 5.0% of the variance. The scree plot (Supplementary Material – Appendix E) was inconclusive, with points of inflexion at 4, 5, and 6 factors. The most conservative approach was selected, such that six factors were retained for further analysis. While factors 5 and 6 contained only one variable, these factors were retained for subsequent analysis given the exploratory nature of this study and the potential importance of these factors in predicting the domains of interest. Due to the small sample size, items with factor loadings >.65 were used to interpret the meaning of each factor. Variables with factor loadings surpassing this criterion are reported in Table 2 (see Supplementary Material – Appendix F for factor loadings for all 21 predictor variables included in factor analysis).

Table 2

Factor Loadings based on Exploratory Factor Analysis

	Factors					
	1	**2**	**3**	**4**	**5**	**6**
Perceptual Reasoning Index	0.67					
Receptive Language Index	1.14					
Expressive Language Index	0.88					
Working Memory Index	0.78					
Verbal Learning- Immediate Recall		0.92				
Verbal Learning- Delayed Recall		0.84				
Verbal Learning- Recognition		0.78				
Story Memory- Delayed Recall		0.75				
ADI-R Current RRBI			0.98			
General Communication Composite			-0.67			
ADOS-2 Reciprocal Social Interaction				0.86		
ADOS-2 Communication				0.73		
ADOS-2 RRBI					-0.99	
Age						-1.03

ADI-R: Autism Diagnostic Interview-Revised. ADOS-2: Autism diagnostic Observation Schedule-Second. RRBI: Restricted, repetitive behaviours, interests and activities.

Based on the factor loadings, the following factor descriptions were derived: Factor 1 – Language and General Cognitive Function; Factor 2 – New Learning and Memory; Factor 3 – Parent Reported RRBI and Communication Skills; Factor 4 – Examiner Rated Social Communication Skills; Factor 5 – Examiner Rated RRBI; and Factor 6 – Age.

4.6.3. Stepwise Linear Regression

Correlation statistics between the six retained factors (i.e., observed variables) and the five BASC-2 TRS composite scores (i.e., dependent variables) included in the regression analysis are reported in Table 3.

Table 3

Spearman's Coefficients between BASC-2 TRS Composite Scores and Retained Factors

	Factors					
	1	**2**	**3**	**4**	**5**	**6**
Extern. Problems	-.47**	-.46**	.16	.24	.06	.23
Intern. Problems	-.23	-.26	.20	.03	-.09	-.17
School Problems	-.59***	-.35*	.29	.30	.07	.23
BSI	-.51**	-.45**	.27	.32*	.06	.11
Adaptive Skills	.67***	.52**	-.30	.47**	-.16	-.15

*p<.05; **p<.01; ***p<.001. Extern Problems: Externalising Problems Index; Intern. Problems: Internalising Problems Index; BSI: Behavioural Symptoms Index. Factor 1 – Language and General Cognitive Function; Factor 2 – New Learning and Memory; Factor 3 – Parent Reported RRBI and Communication Skills; Factor 4 – Examiner Rated Social Communication Skills; Factor 5 – Examiner Rated RRBI; and Factor 6 – Age.

Stepwise linear regression determined which of the observed variables significantly predicted BASC-2 TRS composite scores. The six observed variables were regressed against BASC-2 Externalising, Internalising, and School Problems, BSI, and Adaptive Skills composite scores. For each analysis, the statistical criterion for entry was based on an F-test change in the Sum of Squared error (probability $p \leq .05$); the criterion for subsequent removal was the probability that the F-test change in the sum of squared error was $p \geq .1$. For each BASC-2 TRS composite score, analysis was first completed with all participants included. Analysis was repeated with participants with high leverage (Cook's distance >.01) removed. Interpretation of the findings according to the two solutions did not differ appreciably; thus, results below describe models determined when cases with high leverage were excluded. Using only the retained factor scores as variables in the regression analysis ensured that multicollinearity and singularity could not confound results.

The regression statistics and fit indices for the stepwise regression of predictors against BASC-2 TRS composite scores are reported in Tables 4 and 5, respectively.

Table 4

Regression Statistics for Stepwise Regression Predicting BASC-2 TRS Composite Scores

Variables	Predictors		Beta	SE	*t*
Extern. Problems	Step 1	Factor 1	-3.40	1.76	- 2.27*
		Constant	56.17	1.30	43.19***
School Problems	Step 1	Factor 1	-5.04	1.66	- 3.04**
		Constant	58.06	1.78	32.84***
BSI	Step 1	Factor 2	-8.05	2.12	- 3.79**
	Step 2	Factor 3	4.96	2.00	2.47*
		Constant	66.93	1.95	34.26***
Adaptive Skills	Step 1	Factor 1	4.71	1.31	3.60**
		Constant	40.55	1.39	29.13***

* $p<.05$; ** $p<.01$; *** $p<.001$. SE: Standard Error. Extern Problems: Externalising Problems Index; BSI: Behavioural Symptoms Index.

Table 5

Fit Indices for Regression Models Predicting BASC-2 TRS Composite Scores

	n	df	Adjusted R^2	RMSE	F
Extern. Problems	15	13	.23	4.40	5.13*
School Problems	26	24	.25	8.93	9.23**
BSI	26	23	.43	9.94	10.40***
Adaptive Skills	26	24	.32	7.03	12.99**

*$p<.05$; ** $p<.01$; *** $p<.001$. *df*: error degrees of freedom. RMSE: Root Mean Squared Error. *F:* F-statistic versus constant model. Extern. Problems: Externalising Problems Index; BSI: Behavioural Symptoms Index.

Prediction was best for BSI, with 43% of the variance in scores explained by Factors 2 and 3 (Table 5). Given the limited theoretical underpinning for ADI-R Current RRBI and CCC-2 General Communication Composite to load together on a single factor (i.e., Factor 3), and the observation that Factor 3 was not significantly correlated with BSI according to Spearman's rho analysis (Table 3), the stepwise regression predicting BSI scores was repeated with Factor 3 excluded. When Factor 3 was removed, Factor 2 was the only significant predictor of BSI scores, accounting for 33% of the variance (regression statistics and fit indices not shown). Factor 1 was the only significant predictor of

Adaptive Skills, with 32% of the variance in scores explained by this factor. The regression models predicted 25% of the variance in School Problems, and 23% of variance in Externalising Problems. For both of these models, Factor 1 was the only significant predictor. Internalising problems were not significantly predicted by any of the observed variables (not tabulated), and Factors 4 – 6 did not significantly predict any of the BASC-2 TRS composite scores.

4.7. Discussion

The results of this study support previous evidence of elevated behavioural and emotional difficulties in HF-ASD. Mean BASC-2 TRS scores were within the *At Risk* range across subscales of Depression, Anxiety, Withdrawal, Atypicality, and Adaptability. Results are consistent with previous research exploring teacher reported difficulties within HF-ASD (Barnhill et al., 2000; Foley Nicpon, Doobay, & Assouline, 2010; Hass et al., 2012). Attention difficulties (Barnhill et al., 2000), and additional deficits in adaptive functioning (i.e., Functional Communication, Study Skills, Leadership, and Social Skills; Hass et al., 2012) have also previously been reported. While mean scores within these subscales fell within the *Average* range in this study, inspection of individual classifications revealed that over 40% of participants had clinically elevated scores (i.e., *At Risk* or *Clinically Significant* ranges). The consistency across multiple studies emphasises that these aspects of behavioural and emotional functioning are common areas of difficulty for children with HF-ASD within the school setting.

At the level of BASC-2 TRS composite scores, BSI was the most highly endorsed area of difficulty, with over 70% of participants within the *Clinically Significant* or *At Risk* ranges. This broad composite score comprises Hyperactivity, Aggression, Depression, Attention Problems, Atypicality, and Withdrawal subscales. It encompasses multiple areas of impairment related to aspects of externalising, internalising, and school problems, as well as more ASD related difficulties of atypical and withdrawn behaviour. Against predictions, general cognitive functioning and language ability did not predict BSI. Rather, scores were predicted by two of the observed variables reflecting new learning and memory functioning (Factor 2), and parent reported current RRBI and general communication proficiency (Factor 3). The association between Factor 3 and BSI may be understood within the context of Atypicality and Withdrawal subscales of BSI. While Factor 3 was not significantly correlated with BSI, this factor contributed significantly to the prediction of BSI scores according to the regression analysis. The non-significant correlation between BSI and Factor 3, but subsequent significant *p*-value

of this factor in the regression analysis may be due to covarying for the other factors in the regression. Additionally, correlation tests the strength of the linear relationship between two variables, whereas regression seeks to minimise the prediction error (based on sum of squared error); therefore, it is possible that an independent variable can add to prediction of a dependent variable, despite a non-significant linear relationship. As this factor explained an additional 10% of the variance in BSI scores once new learning and memory functioning was included within the model, it was considered to significantly improve prediction accuracy.

The connection between verbal new learning and memory and BSI was somewhat unexpected. New learning and memory is multifaceted and reliant on multiple cognitive processes. Broadly speaking, it can be summarised as involving intake and registration of new information into short-term memory stores; consolidation into long-term storage; and subsequent retrieval of information from long-term storage. Deficits in language processing, attention, processing speed, and working memory impact the efficiency of all stages of this process. Further, aspects of executive functioning, including strategy development and organisation of information in memory stores, can impact encoding of information and thereby influence the efficiency of recall over time. Thus, the association between verbal new learning and memory functioning and BSI may be more reflective of higher order cognitive difficulties rather than a primary impairment in memory. An additional consideration is the potential domain-specific nature of the association between new learning and memory functioning and BSI scores. Inclusion of nonverbal new learning and memory functioning may have revealed a different factor structure and association with BSI. While examination of bilateral memory functioning was beyond the scope of thesis study, it provides an avenue for future research to examine stability across domains.

Internalising problems were also highly prevalent in this sample, with almost 60% of participants classified with clinically elevated levels of internalising symptomatology. Against expectation, language functioning, ASD symptomatology, and age did not significantly predict Internalising Problems. The level of cognitive ability was also not significantly associated with Internalising Problems. Results suggest that in children with ASD without intellectual disability, the level of cognitive and language functioning is not a primary factor contributing to internalising symptoms; other aspects of neurocognitive functioning that were not examined in this study, such as higher-level executive functioning (e.g., insight and self-awareness) may be more important in the

development of internalising problems in this population. In view of the prevalence of internalising problems in HF-ASD, in addition to the poor prediction of impairment based on other domains of functioning most commonly examined (i.e., intellectual ability and language functioning), our findings demonstrate that independent and targeted assessment of internalising symptomology is an important component of comprehensive diagnostic and functional assessments.

At closer inspection of the Internalising Problems composite scores, it was evident that the elevated ratings were primarily driven by Depression and Anxiety, with approximately 60% of participants rated within the *At Risk* or *Clinically Significant* range for these subscales. It is notable that despite these elevated scores, only a small proportion of participants had a previous clinical diagnosis of depression (2%) or anxiety (21%). There are several factors that may have contributed to this finding. Firstly, it may reflect symptomatology occurring at sub-clinical levels, potentially mediated by medication use or intervention for some individuals. Further, teacher ratings of anxiety and depressive symptomatology may reflect behaviours inherent in the ASD clinical phenotype (e.g., difficulty with, or limited interest in, social engagement) rather than reflecting a clinically relevant anxiety or depressive disorder. Alternatively, it may represent a subgroup of children who display clinically elevated symptomatology within these domains which has not been recognised and/or diagnosed, and who consequently may not be receiving appropriate support.

Teacher reported Externalising Problems (i.e., Hyperactivity, Aggression, Conduct Problems), School Problems (i.e., Attention and Learning Problems), and Adaptive Skills (i.e., Adaptability, Social Skills, Leadership, Study Skills, and Functional Communication) were significantly predicted by one factor that represented working memory, perceptual reasoning, and expressive and receptive language. In contrast, variables representing ASD specific social interaction and communication impairments, and RRBI, did not predict impairment within these BASC-2 TRS domains, regardless of whether parent report or child observation was utilised. Consistent with Klin et al. (2007), results suggest that variables influencing the development of adaptive skills may differ from those influencing the manifestation of core ASD symptomatology. This study additionally shows that variables outside of core ASD deficits are also more important in the development of externalising behaviour and school problems. Results emphasise that understanding and effectively using language, and taking in and processing both verbal and visual information, appear to be important factors. Proficiency in these areas

is important within the school setting to allow, for example, a student to follow instructions and engage with academic tasks, which in turn supports learning. Current evidence that these cognitive and language skills, rather than social pragmatics and RRBI specific to ASD, have greater influence on school functioning raises important considerations for intervention planning.

Education and intervention guidelines (National Research Council, 2001) recommend targeting ASD symptomatology in intervention programs, including social and communication difficulties, RRBI, and play skills; however, research demonstrating that reduced ASD severity is associated with improved adaptive functioning or reduced behavioural problems is needed to support focus on these clinical features in intervention. Improved adaptive functioning following intervention is particularly important, given the disproportionate impairment in this domain in HF-ASD (Bolte & Poustka, 2002; Liss et al., 2001; Saulnier & Klin, 2007) and the association between adaptive skills and long-term outcome (Farley et al., 2009). Contrary to this, our results add to a growing literature base showing that ASD symptomatology and adaptive skills are relatively independent constructs (Klin et al., 2007; Saulnier & Klin, 2007; Szatmari et al., 2015), thereby challenging the notion of targeting ASD specific deficits to improve functional outcome (Wood, Fujii, Renno, & Van Dyke, 2014). Our results suggest that daily living skills should be separately evaluated in HF-ASD and directly targeted in intervention, perhaps highlighting an important role for occupational therapists and behaviour analysis practitioners in the management of individuals with HF-ASD. Further, the current findings suggest that cognitive and communication strategies may have greater efficacy in improving these aspects of behaviour and school functioning through indirect effects, rather than targeting ASD specific deficits.

4.7.1. Limitations

The findings of this study should be considered preliminary and exploratory due to the small sample size, limiting the generalizability of results. The small sample prevented exploration of potential predictors of behavioural and emotional functioning at the level of individual BASC-2 TRS subscales, with analyses instead focused on predictors of the BASC-2 composite scores. In the absence of a typically developing control group, the study was limited to a descriptive analysis of the profile of behavioural and emotional functioning in HF-ASD. Approximately 30% of the sample was taking psychotropic medications, which may have impacted scores on cognitive and behavioural measures, (i.e., teacher ratings may have underestimated the degree of behavioural disturbance of

participants taking methylphenidate). The study was strengthened by the comprehensive evaluations of ASD symptomatology using the 'gold standard' diagnostic tools, as well as assessment of cognitive and language functioning; however, other variables potentially important in understanding current behavioural and emotional functioning, such as executive functioning (e.g., cognitive flexibility, initiation, self-regulation) (Pugliese et al., 2014; Visser, Berger, Van Schrojenstein Lantman-De Valk, Prins, & Teunisse, 2015), and past and current intervention, were not examined. Parental factors, including inter-parental conflict, aversiveness, parental over-involvement, and less warmth have also been found to be important in this regard (Hui Yap & Jorm, 2015) and provide a valuable avenue for future research. Children with high-functioning ASD may be able to suppress difficulties at school but then display greater impairment at home where they have the flexibility and support to do so. Parent report in addition to teacher evaluation of behavioural and emotional dysfunction may therefore have offered different insights into areas of difficulty (Barnhill et al., 2000; Foley Nicpon et al., 2010; Volker et al., 2010). Past research has also suggested that predictors of functioning may differ between males and females (Szatmari et al., 2015). Examination of gender differences was not possible due to the small number of female participants. While this is a common challenge in ASD research due to the over-representation of males with the disorder, investigation of potential differences in BASC-2 TRS profiles and predictors provides an important avenue for future research to support development of tailored management strategies for each gender. Lastly, while the BASC-2 is commonly used clinically and in research to evaluate behavioural and emotional wellbeing in children and adolescents, inclusion of a targeted measure of adaptive functioning (e.g., the Vineland Adaptive Behaviour Scales) could have provided a more detailed and robust indication of adaptive skills in this population.

4.7.2. Conclusion

This study re-enforced past evidence of frequent behavioural and emotional problems in HF-ASD within the school setting. Most notably, our results suggest that areas of behavioural and emotional dysfunction are largely independent from core ASD symptomatology. In particular, internalising problems were highly prevalent in this sample but were independent from ASD severity, as well as cognitive and language functioning. Given this, it is important that screening of emotional wellbeing forms part of ASD diagnostic and functional assessments to identify areas of difficulty and ensure individuals have access to appropriate supports. Further, results supported the notion that adaptive skill deficits need focused intervention, independent from approaches

targeting ASD symptomatology. In addition to directly targeting daily living skills in intervention approaches, cognitive and communication strategies may assist behavioural and emotional functioning in HF-ASD through indirect effects. The high prevalence of adaptive skill deficits within this population, and the independence of this construct from ASD specific impairments, is consistent with the recent proposal to include adaptive functioning as a separate specifier in DSM (Szatmari et al., 2015). This will emphasise to clinicians the importance of evaluating adaptive functioning, in addition to ASD severity, cognitive and language ability in ASD, ultimately permitting the development of tailored management strategies.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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4.9. Supplementary Material

4.9.1. Appendix A: Correlations between Retained Factors from Exploratory Factor Analysis

Table 1

Spearman's Coefficients between the Factors Retained from Exploratory Factor Analysis

	Factor 1	**Factor 2**	**Factor 3**	**Factor 4**	**Factor 5**
Factor 1	-				
Factor 2	.55**	-			
Factor 3	-.37*	-.02	-		
Factor 4	-.37*	-.15	.43**	-	
Factor 5	-.28	-.03	.11	-.25	-
Factor 6	-.05	.02	.06	-.08	.32

** p<.01, * p<.05 (two-tailed). Factor 1 – Language and General Cognitive Function; Factor 2 – New Learning and Memory; Factor 3 – Parent Reported RRBI and Communication Skills; Factor 4 – Examiner Rated Social Communication Skills; Factor 5 – Examiner Rated RRBI; and Factor 6 – Age.

4.9.2. Appendix B: BASC-2 TRS Classifications

Table 2

BASC-2 TRS Clinical and Adaptive Scales: Frequencies, Means, and Standard Deviations

CLINICAL SCALES	Clin. Sign.		At Risk		Average		Low		Total	
	n	%	*n*	%	*n*	%	*n*	%	*M*	*SD*
Externalising Problems	8	21.1	5	13.2	24	63.2	1	2.6	58.1*	11.5
Hyperactivity	10	26.3	7	18.4	20	52.6	1	2.6	59.5*	11.4
Aggression	8	21.1	7	18.4	23	60.5	0	0.0	58.6*	13.0
Conduct Problems	6	15.8	3	7.9	28	73.7	1	2.6	54.7*	11.5
Internalising Problems	15	39.5	7	18.4	15	39.5	0	0.0	65.5*	13.9
Anxiety	15	39.5	7	18.4	15	39.5	1	2.6	64.8*	15.7
Depression	14	36.8	10	26.3	14	36.8	0	0.0	66.3*	13.4
Somatization	3	7.9	9	23.7	26	68.4	0	0.0	55.4*	13.8
School Problems	5	13.2	10	26.3	23	60.5	0	0.0	56.8*	9.8
Attention Problems	2	5.3	15	39.5	20	52.6	1	2.6	56.8*	9.2
Learning Problems	7	18.4	3	7.9	28	73.7	0	0.0	55.7*	10.6
Behav. Symptoms Index ^	11	28.9	16	42.1	11	28.9	0	0.0	65.5*	11.5
Atypicality	16	42.1	3	7.9	19	50.0	0	0.0	66.1*	15.0
Withdrawal	15	39.5	8	21.1	14	36.8	1	2.6	66.4*	10.9

Table 2 Continued

ADAPTIVE SCALES	**Clin. Sign.**		**At Risk**		**Average**		**Low**		**Total**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	***M***	***SD***
Adaptive Skills Composite	2	5.3	17	44.7	18	47.4	1	2.6	41.3*	8.5
Adaptability	6	15.8	17	44.7	13	34.2	2	5.3	39.6*	8.9
Social Skills	1	2.6	15	39.5	18	47.4	4	10.5	44.1*	10.2
Leadership	0	0.0	17	44.7	20	52.6	1	2.6	43.2*	7.4
Study Skills	0	0.0	18	47.4	18	47.4	2	5.3	43.4*	8.9
Functional Comm.	7	18.4	13	34.2	15	39.5	3	7.9	41.1*	10.0

N=38. *: Mean *T* score within the *At Risk* range. Clin. Sig.: Clinically Significant. ^Λ: Behavioural Symptoms Index: composite score includes Hyperactivity, Aggression, Depression, Attention Problems, Atypicality and Withdrawal subscales. No participants scored within the *Very Low* range on any Clinical Scales, or in the *Very High* range on any Adaptive Scales; these classifications were omitted from the table for simplicity.

4.9.3. Appendix C: Descriptive Statistics for Predictor Variables Included in Analysis

Table 3

Descriptive Statistics for Predictor Variables Included in Factor Analysis

Measure	Variable	*Median*	*IQR*
ADOS-2	Reciprocal Social Interaction	6.0	4.0 – 9.0
	Communication	3.0	1.0 – 4.0
	RRBI	3.0	2.0 – 4.0
ADI-R	Reciprocal Social Interaction	10.5	5.8 – 2.0
	Communication	8.0	5.0 – 11.3
	RRBI	4.0	3.0 – 6.3
CCC-2	GCC	36.0	24.8 – 46.0
	SIDI	-7.0	-15.0 – 0.0
WRAML-2	VL – Immediate	11.0	8.0 – 13.0
	VL – Delayed	9.0	7.0 – 12.0
	VL – Recognition	11.0	8.0 – 12.3
	SM – Immediate	9.0	7.0 – 10.3
	SM – Delayed	8.0	4.0 – 10.0
	SM – Recognition	10.5	8.0 – 13.0
		Mean	***SD***
WISC-IV	Working Memory Index	92.4	16.5
	Processing Speed Index	94.8	16.0
CELF-4	Receptive Language Index	95.6	18.4
	Expressive Language Index	95.3	21.0

ADOS-2: Autism Diagnostic Observation Schedule-Second. ADI-R: Autism Diagnostic Interview-Revised (current behaviour algorithm). CCC-2: Children's Communication Checklist-Second. WRAML-2: Wide Range Assessment of Memory and Learning-Second. WISC-IV: Wechsler Intelligence Scale for Children-Fourth. CELF-4: Clinical Evaluation of Language Fundamentals-Fourth. RRBI: Restricted, repetitive behaviours, interests, and activities. GCC: General Communication Composite. SIDI: Social Interaction Difference Index. VL: Verbal Learning subtest. SM: Story Memory subtest. *IQR*: Interquartile Range (Quartile 1–Quartile 3). *SD*: Standard Deviation.

4.9.4. Appendix D: Table of Eigenvalues and Variance Explained

Table 4

Eigenvalues and Variance Explained

Factor	Eigenvalue	% Variance Explained
1	6.98	33.23
2	3.07	14.60
3	2.06	9.82
4	1.66	7.89
5	1.46	6.95
6	1.05	4.98
7	0.85	4.03
8	0.70	3.32
9	0.66	3.14
10	0.50	2.36
11	0.45	2.13
12	0.31	1.49
13	0.29	1.37
14	0.25	1.18
15	0.20	0.97
16	0.16	0.75
17	0.14	0.66
18	0.11	0.53
19	0.06	0.28
20	0.05	0.22
21	0.02	0.11

4.9.5. Appendix E: Exploratory Factor Analysis Scree Plot

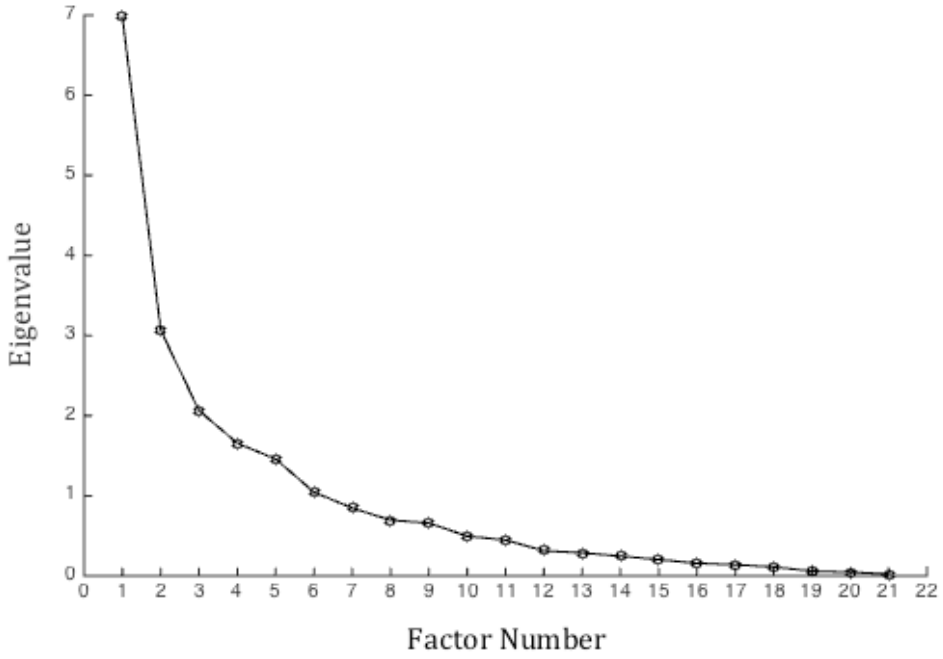

Figure 1. Scree plot

4.9.6. Appendix F: Factor Loadings for all Predictor Variables Included in Analysis

Table 5

Factor Loadings for all Predictor Variables Included in Exploratory Factor Analysis

		Factors					
Measure	**Variable**	**1**	**2**	**3**	**4**	**5**	**6**
ADI-R	Social Int.	- .09	.17	.48	.57	.20	.14
	Comm.	- .06	.21	.57	.28	- .10	- .07
	RRBI	.29	- .11	.98a	- .10	- .17	- .04
ADOS-2	Social Int.	.23	- .19	- .10	.86[a]	.17	.15
	Comm.	- .09	- .07	- .01	.73[a]	.07	.15
	RRBI	- .21	- .10	.06	- .24	- .99[a]	.21
WISC-IV or	VCI	.63	.38	.00	.03	- .03	- .16
WPPSI-III	PRI	.67[a]	- .16	.11	- .21	.01	.14
	WMI	.78[a]	.04	- .20	.15	.03	- .11
	PSI	.31	.23	- .20	- .20	.42	.19
CELF-4 or	RLI	1.14[a]	- .13	.21	.02	.25	- .02
CELF-P2	ELI	.88[a]	.11	.04	- .02	.03	.06
WRAML-2	VL – Immediate	.01	.92[a]	- .02	- .05	.09	- .01
	VL – Delayed	- .12	.84[a]	.07	- .06	.11	- .05
	VL – Recognition	- .03	.78[a]	- .04	- .10	.08	.11
	SM – Immediate	.33	.56	.04	.04	- .17	.21
	SM – Delayed	- .12	.75[a]	- .23	.01	.01	- .22
	SM – Recognition	.26	.47	.21	- .09	- .21	.17
CCC-2	GCC	.15	.05	- .67[a]	.07	- .23	.18
	SIDI	- .65	.02	.04	- .17	.29	.29
Other	Age	.09	.00	.09	- .26	.20	-1.03[a]

a: Factor loadings >.65. ADI-R: Autism Diagnostic Interview-Revised (current behaviour algorithm). ADOS-2: Autism Diagnostic Observation Schedule-Second. WISC-IV: Wechsler Intelligence Scale for Children-Fourth. WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence-Third. CELF-4: Clinical Evaluation of Language Fundamentals-Fourth. CELF-P2: Clinical Evaluation of Language Fundamentals-Preschool, Second. WRAML-2: Wide Range Assessment of Memory and Learning-Second. CCC-2: Children's Communication Checklist-Second. RRBI: Restricted, repetitive behaviours, interests, and activities. Social Int: Social Interaction domain score. Comm: Communication domain score. VCI: Verbal Comprehension Index. PRI: Perceptual Reasoning Index. WMI: Working Memory Index. PSI: Processing Speed Index. RLI: Receptive Language Index. ELI: Expressive Language Index. VL: Verbal Learning subtest. SM: Story Memory subtest. GCC: General Communication Composite. SIDI: Social Interaction Difference Index.

CHAPTER 5: GENERAL DISCUSSION

5.1. Chapter Introduction

Previous research has demonstrated the phenotypic heterogeneity in high-functioning ASD (previously defined in Chapter 1 as describing individuals with ASD without intellectual disability, including Asperger's disorder, AS, and High-functioning autism, HFA). As reviewed in Chapter 1, the operationalization of ASD, in addition to the diagnostic decision-making process, is greatly challenged by this clinical variability. It has also hindered the capacity to accurately assess functioning in individuals with ASD and the ability to predict their clinical and functional outcome. To investigate this further, the principle aim of this thesis was to (1) explore whether childhood high-functioning ASD subgroups could be identified based on profiles of core ASD symptomatology (Chapter 2). In addition, this thesis aimed to (2) examine the relationship between the 'gold standard' ASD diagnostic tools, the ADI-R (Lord et al., 1994) and ADOS-2 (Lord, Rutter, et al., 2012), in diagnosing and characterising functioning in high-functioning ASD throughout childhood years (Chapter 3), and (3) investigate whether ASD symptomology and aspects of neurocognitive functioning predict behavioural and emotional difficulties within the school setting in childhood high-functioning ASD (Chapter 4).

The General Discussion integrates the main findings of this thesis with previous research in high-functioning ASD. This chapter is differentiated into three main sections corresponding to each of the main thesis aims. At the start of each section, an introduction directs the reader to the main focus in the following passage, in order to maintain cohesion throughout the chapter. The key findings are then briefly reviewed, and broader implications of the results with regard to clinical practice and future research are discussed. Investigating the presence of high-functioning ASD phenotypic subgroups (i.e., Aim One) formed the primary focus of this thesis; as such, the discussion primarily explores the theoretical and clinical implications of identifying such subgroups. This includes (a) potential neurobiological differences between the Moderate and Severe Social Impairment subgroups; (b) implications of the study findings with regard to high-functioning ASD diagnostic classification systems (i.e., using a dimensional and/or categorical approach); (c) comparison of the newly identified subgroups with previous definitions of high-functioning ASD subgroups (i.e., AS and HFA); (d) using phenotypic markers to identify the high-functioning ASD subgroups in practice and planning interventions based on subgroup profiles; and (e) future validation of the high-functioning ASD subgroups identified in this thesis. The implications of Aims Two and Three with regard to both future research and clinical

practice are also discussed. This includes potential limitations of using the ADI-R and ADOS-2 in clinical and research settings (i.e., related to Aim Two), and considerations for planning interventions for children with high-functioning ASD based on predictors of behavioural and emotional functioning (i.e., related to Aim Three). Thesis limitations and their potential impact on the interpretation of results are then reviewed, and an overall thesis conclusion is provided.

5.2. Aim One: Exploring Phenotypic Subgroups in High-functioning ASD

5.2.1. Section Introduction

Chapter 2 examined whether clinically meaningful high-functioning ASD subgroups could be identified based on early development and current clinical features specific to the diagnosis. To our knowledge, this is the first study that seeks to identify potential childhood high-functioning ASD subgroups using both of the 'gold standard' ASD diagnostic instruments, the ADI-R (Lord et al., 1994) and ADOS-2 (Lord, Rutter, et al., 2012). Cognitive, language, pragmatic communication, and behavioural and emotional functioning were also examined to comprehensively characterise the identified subgroups.

5.2.2. Summary of Main Findings

As described in Chapter 2, exploratory cluster analysis revealed two phenotypic subgroups that were differentiated by a) the degree of reciprocal social interaction and communication impairment and b) the severity of RRBI exhibited. Ten social interaction and communication variables maximally separated the clusters, dividing the sample into Moderate and Severe Social Impairment subgroups. The key factors differentiating the identified subgroups are reported below (Figure 1).

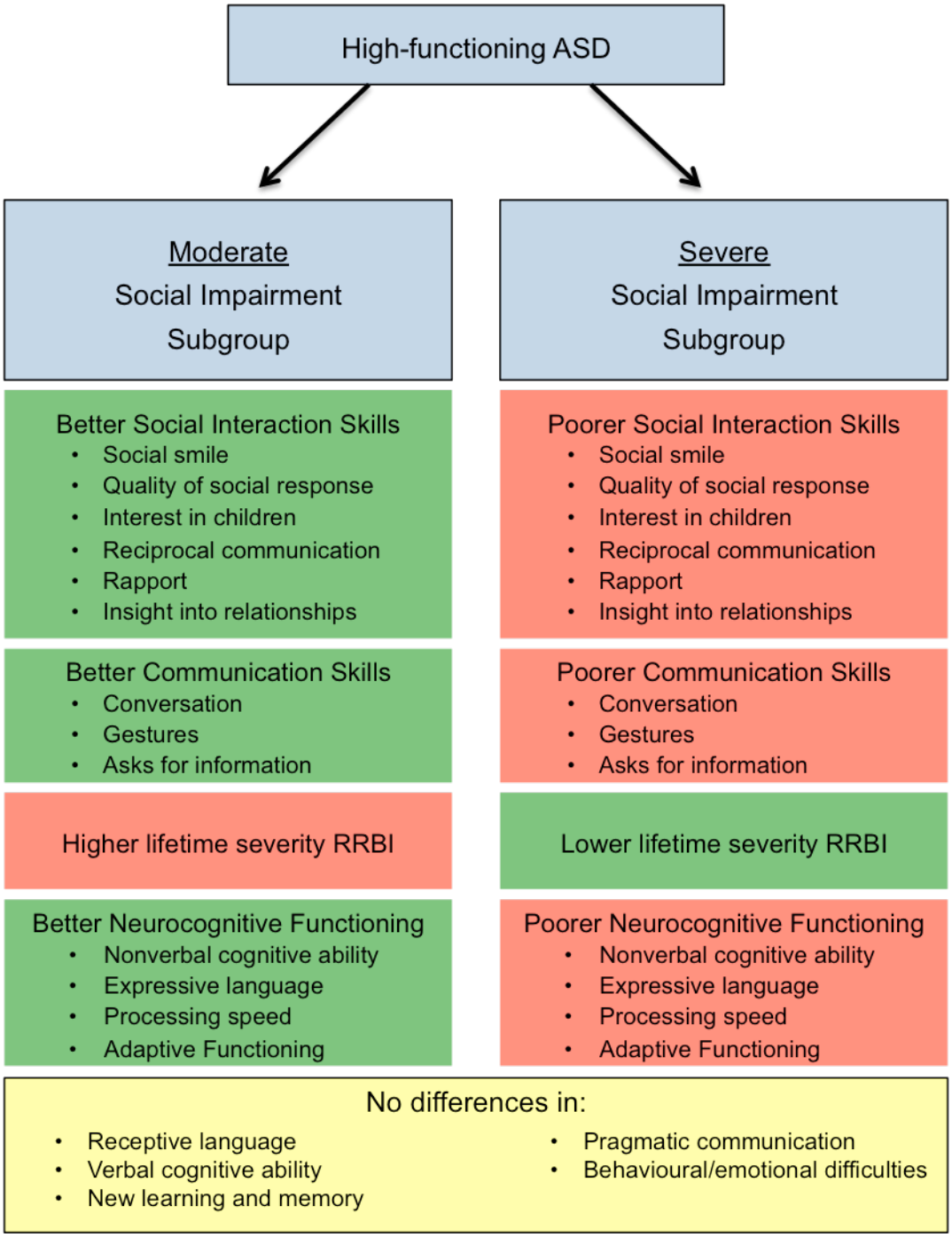

Figure 1. Clinical features differentiating the high-functioning ASD Moderate and Severe Social Impairment subgroups.

The two clusters showed unique disorder profiles at the level of core domains of impairment central to ASD. As depicted in Figure 1, the Severe Social Impairment subgroup was characterised by greater severity of social interaction and communication difficulties (ADI-R and ADOS-2), but lower lifetime severity of RRBI (ADI-R). In contrast, the Moderate Social Impairment subgroup showed the reverse profile of significantly

lower severity of social interaction and communication deficits (ADI-R and ADOS-2), but greater lifetime severity of RRBI (ADI-R). The identified clusters also differed in a number of domains of neurocognitive functioning evaluated in this study; specifically, the Severe Social Impairment subgroup had significantly poorer nonverbal cognitive ability, processing speed, expressive language, and adaptive functioning scores. Notably, general cognitive ability, language, and adaptive functioning scores demonstrated only weak to moderate associations with ASD symptom domains (derived from the ADOS-2 and ADI-R); thus, the unique ASD symptom profiles of the Moderate and Severe Social Impairment subgroups could not be fully accounted for by differences in functioning across these domains of neurocognitive functioning.

Differences between the subgroups in the degree of 'social interaction and communication deficits' (hereafter referred to as 'social communication deficits', as per DSM-5), and in the level of neurocognitive functioning primarily reflected differences in the severity of impairment, and therefore could provide support for the DSM-5 dimensional classification of ASD. Importantly, however, the subgroup with less severe social communication deficits (i.e., the Moderate Social Impairment subgroup) was found to have significantly greater severity of lifetime RRBI; by contrast, the Severe Social Impairment subgroup had lower severity of lifetime RRBI. This counterintuitive dissociation between the subgroups in the relative impairment in RRBI and social communication deficits supports the idea that high-functioning ASD subgroups with unique profiles across core ASD difficulties can be identified, which is contrary to the DSM-5 approach of using a purely dimensional classification system. More specifically, the current findings suggest that there is a group of children with high-functioning ASD who are characterised by rigid thinking, over-focused interests, and/or repetitive, stereotyped behaviours, within the context of less severe disability in aspects of social, cognitive, and language functioning. Such children might previously have been considered to have AS, although this diagnosis has been fraught and recently dropped from DSM-5. This issue is elaborated below. Evidence of dissociated profiles of impairment across the core ASD domains could suggest that the two high-functioning ASD phenotypic subgroups differ in their underlying neurobiological mechanisms. This may indicate the presence of unique causal mechanisms for the development of the disorder in each subgroup and support the need for different management and intervention approaches. Differentiating individuals into subgroups, as described in this study, could provide greater clarity in the clinical setting by increasing the level of detail conveyed by the diagnostic label. These key implications of identifying high-functioning

ASD subgroups will be discussed further below, starting firstly with consideration of neurobiological mechanisms that may be associated with the differentiated phenotypic profiles of the identified subgroups.

5.2.3. Potential Neurobiological Differences between the Moderate and Severe Social Impairment Subgroups

This section discusses brain networks, neurotransmitter systems, and aspects of neurocognition that may be associated with the different levels of severity of social communication deficits and RRBI in the high-functioning ASD subgroups described in this thesis.

A number of studies have investigated neurological correlates of core domains of impairment in ASD; while there are some inconsistencies evident with regard to the direction of effects (i.e., over and under activity) and the brain regions/networks reported to be associated with phenotypic characteristics, a recent systematic review concluded that there is evidence of dissociation between brain networks associated with core ASD symptoms (Pina-Camacho et al., 2012). This is important as it suggests that the neurological underpinning of the core domains of impairment in ASD may be at least partially distinct. Specifically, Pina-Camacho et al. (2012) reported that fronto-temporal and limbic networks were most consistently associated with social and pragmatic language deficits in ASD, whereas fronto-striato-cerebellar networks were most consistently related to RRBI symptomatology. Consistent with this, a different review published in the same year emphasised the role of the "social brain" in social deficits in ASD (e.g., prefrontal cortex, temporoparietal junction, posterior superior temporal sulcus, inferior frontal gyrus, amygdala, fusiform gyrus, and anterior insular cortex), and supported the involvement of frontostriatal networks in cognitive control tasks that correlate with RRBI symptomatology (Dichter, 2012). Therefore, dissociation of subgroups based on the severity of social communication and RRBI symptomatology (i.e., as per the current study, where the Severe Social Impairment subgroup showed greater social communication deficits but lower RRBI symptomatology, and the Moderate Social Impairment subgroup the reverse pattern), could suggest different brain networks may be preferentially impacted in each of the subgroups. More specifically, the Severe Social Impairment subgroup may show greater involvement of abovementioned "social brain" networks, while the Moderate Social Impairment subgroup could show greater differences in the fronto-striato-cerebellar networks associated with RRBI.

Evidence of such a distinction between the neural networks implicated in the Moderate and Severe Social Impairment subgroups is important as it may reflect distinct neurobiological trajectories for development of disorder characteristics (Johnson et al., 2005; Johnson, Grossmann, & Cohen Kadosh, 2009; Uhlhaas, Roux, Rodriguez, Rotarska-Jagiela, & Singer, 2010). Future neuroimaging studies examining the "social brain" and fronto-striatal-cerebellar pathways in high-functioning ASD throughout development will therefore be important to validate the current solution and improve our understanding of potential neurobiological differences between the subgroups. A recent study using resting-state functional magnetic resonance imaging (fMRI) to examine functional connectivity in corticostriatal circuitry in individuals at risk for psychosis has demonstrated that it is possible to identify and correlate disrupted connectivity with psychotic symptomatology (Dandash et al., 2014); such an approach may be useful in high-functioning ASD. Further to this, Just and colleagues (2014) demonstrated the potential of using associations between neural activity (as evident using fMRI) and social concepts related to self to accurately discriminate adults with high-functioning ASD from controls. Further research is needed to examine the utility of these approaches in children, as well as the sensitivity and specificity in distinguishing individuals from different clinical groups, particularly those with multiple comorbid diagnosis, as is often seen in ASD. Studies such as these, however, provide novel ways forward of extending the current findings. Most notably, if reliable neurobiological differences between the high-functioning ASD subgroups described in this thesis can be identified, there is potential for characteristics of the neural networks to act as neuroimaging biomarkers to aid subgroups classification. This could improve the capacity to predict clinical presentation and subgroup membership from early childhood years, which would enable targeted intervention that could potentially ameliorate or significantly reduce the impact of the said deficit. From an allied health perspective, this may include targeted social skills training and/or psychological and speech therapy. Potential intervention approaches for the Moderate and Severe Social Impairment subgroups are proposed below in section 5.2.6.

Differences in neurotransmitter systems, such as serotoninergic and dopaminergic systems, have also been implicated in the neurobiological underpinnings of ASD. There is both independent action and complex interaction between these neurotransmitter systems. While extensive research has investigated a possible role for these systems in ASD, the relationship between neurotransmitters and core domains of impairment remains unclear. Given previous reports of an association between serotonin and

repetitive, obsessional behaviours in other psychiatric disorders (Nakao, Okada, & Kanba, 2014), it could be hypothesised that this neurotransmitter system may be implicated in the greater severity of RRBI in Moderate Social Impairment subgroup described in this thesis. Importantly, however, while pharmacological studies have reported that selective serotonin reuptake inhibitors can reduce RRBI in adults with ASD, the positive effects generally have not been supported in children (for recent reviews see Baribeau & Anagnostou, 2014; LeClerc & Easley, 2015; Politte, Henry, & McDougle, 2014) and concerns regarding an increased risk of adverse events have been noted (K. Williams, Brignell, Randall, Silove, & Hazell, 2013). Thus, neurotransmitter systems may have different roles in ASD symptomatology throughout development, demonstrating that longitudinal examination of functioning is particularly important.

Further to this complexity, associations between neurotransmitters and ASD symptoms have been reported to vary across different brain regions. For example, reduced serotonin binding in anterior and posterior cingulate cortices has been reported to correlate with impaired social cognition in adults with high-functioning ASD, whereas reduced binding in the thalamus has been associated with repetitive and/or obsessive behaviour and interests (i.e., components of RRBI) (Nakamura et al., 2010). Dopamine has also been implicated in aspects of both of the core domains of impairment in ASD; for example, in males with ASD the dopamine-2-receptor gene has been found to be associated with both social communication impairment and RRBI symptomatology (as measured by the ADI-R) (Hettinger et al., 2012), while dopamine activity via the dopamine-3-receptor gene has been reported to have a specific association with insistence on sameness behaviour in both males and females (Staal, 2014; Staal, de Krom, & de Jonge, 2012). Evidently, much remains unclear regarding the involvement of these neurotransmitter systems in ASD, with both age and gender potentially important in understanding variability in neurotransmitter action in this disorder. It seems plausible, however, that the differentiated clinical profiles of the high-functioning ASD subgroups identified in this thesis may be associated with underlying differences at this level of neurobiological functioning. As suggested by the above discussion, this is important as involvement of different neurotransmitter systems in the high-functioning ASD subgroups could indicate differences in their responsiveness to pharmacological interventions. For example, it could be hypothesised that greater severity of RRBI within the Moderate Social Impairment subgroup may be associated with disrupted serotonin binding within the thalamic regions, as per Nakamura et al. (2010). Pharmacological interventions targeting serotonergic receptors within this region, therefore, may have

greater efficacy in reducing RRBI symptomatology in this subgroup. To understand this further, however, there is a need for carefully planned, randomized controlled trials of pharmacological interventions targeting specific neurotransmitter systems in paediatric populations, with clearly operationalised hypotheses regarding the expected impact on social communication and RRBI.

A final consideration regarding potential differences between the high-functioning ASD subgroups that could contribute to the differentiated ASD symptom profiles are potential distinctions in underlying neurocognitive functioning. As described in Chapter 1, the theory of the 'fractionable autism triad' (Brunsdon & Happe, 2014; Happe & Ronald, 2008; Happe, Ronald, et al., 2006) proposes that the core domains of impairment in ASD may be associated with different underlying neurocognitive mechanisms. Consistent with this approach, the differences in the profile of deficits of the high-functioning ASD subgroups described in Chapter 2 may be associated with distinct patterns of neuropsychological deficits. Importantly, while the subgroups described in this thesis showed differences in aspects of general cognitive ability, language, and adaptive functioning, only weak to moderate associations were found between these indices and ASD symptom domain scores. This suggests that social communication deficits and RRBI were largely independent of the neurocognitive domains measured in this study; however, other neurocognitive domains that were not examined in this thesis may be important in this regard. For example, it has been theorized that individuals who show over-focused interests, repetitive behaviour, and difficulty shifting, as characteristic of RRBI symptomatology in ASD, may have weak central coherence (Chen et al., 2009). Central coherence refers to the tendency to focus on specific details, rather than integrate information as a whole. Based on this theory, it may be hypothesised that the Moderate Social Impairment subgroup, with significantly greater RRBI symptomatology, may show weak central coherence relative to the Severe Social Impairment subgroup. Other aspects of executive functioning, such as cognitive flexibility and response inhibition, may also be particularly important in the Moderate Social Impairment subgroup, given previous evidence of an association between these cognitive characteristics and RRBI (Lopez, Lincoln, Ozonoff, & Lai, 2005). While examination of these broader aspects of neurocognitive functioning was beyond the scope of this thesis, investigating these domains forms an interesting avenue of future research.

Based on the notion that there are separable neurobiological mechanisms implicated in the Moderate and Severe Social Impairment subgroups, another way forward is to examine aspects of neurocognitive functioning that are associated with the "social brain" and fronto-striato-cerebellar circuits to examine whether there are different levels of disruption in the identified subgroups. For example, brain regions implicated in the "social brain" include the medial prefrontal cortex, which has been associated with the ability to make inferences about the intention of others (i.e., associated with theory of mind); the fusiform gyrus in processing faces; and the amygdala in identifying emotions in facial expressions (Dichter, 2012). Neuropsychological tasks that examine these skills, therefore, could assist in validating whether the Moderate and Severe Social Impairment subgroups differ with regard to the brain regions and networks implicated based on these study findings. Further, as suggested above based on Dichter (2012), tasks examining cognitive control (e.g., inhibition, motor control, visual search tasks), implicated in fronto-striatal networks could be informative in validating dissociated functioning with regard to RRBI symptomatology.

Given previous reports of an association between anxiety and RRBI symptomatology in ASD (Lidstone et al., 2014; Rodgers, Glod, Connolly, & McConachie, 2012; Wigham, Rodgers, South, McConachie, & Freeston, 2014), an additional consideration for the Moderate Social Impairment subgroup is psychological wellbeing. Interestingly, the subgroups described in this study did not differ in parent ratings of anxiety symptomatology. This suggests that anxiety was not a significant factor contributing to the greater RRBI symptomatology in the Moderate Social Impairment subgroup; rather, other neurobiological or neurocognitive factors, such as those discussed above, may be more important drivers of RRBI in this subgroup. Consistent with this proposition, Chapter 4 of this thesis reported that internalising problems were not significantly associated with RRBI symptomatology in this high-functioning ASD sample, supporting the notion that other aspects of functioning not evaluated in this study may contribute to this symptom domain.

In summary, future evidence of distinct neurobiological or neurocognitive mechanisms in the Moderate and Severe Social Impairment subgroups would support the clinical utility of differentiating children with high-functioning ASD based on the characteristics identified in this study. Such findings would challenge the notion of only using a dimensional diagnostic classification system for ASD, as dictated by DSM-5. While the current study requires future validation (see section 5.2.7), based on the results of this

thesis it is proposed that a combination of dimensional and categorical classification systems could be the most meaningful approach for the diagnostic classification of this disorder. The potential benefits of utilising a combined approach for ASD diagnostic classification are discussed in the following section.

5.2.4. Implications for the Diagnostic Classification of High-Functioning ASD: Combining Dimensional and Categorical Approaches

According to DSM-5 (American Psychiatric Association, 2013), all individuals with ASD display clinically significant impairment within the dimensions of social communication and RRBI. The manifestation of individual symptoms within these domains may differ greatly between individuals. In this way, the DSM-5 conceptualisation of ASD focuses on similarities between individuals, rather than differences. Consequently, DSM-5 ASD encompasses a phenotypically heterogeneous population, somewhat limiting the clinical utility of the diagnostic label. The 'ASD' label, for example, does not communicate potential differences in aetiology or prognosis. Further, it does not capture differences in associated clinical features, such as the levels of cognitive, language, and adaptive functioning. Supplementary information accompanying the diagnostic label is therefore required in order to understand the specific individual with ASD. Without this, clinicians are unable to inform management or intervention strategies, or predict clinical outcomes. While it is acknowledged that the DSM-IV categorical conceptualisation of ASD was found to be lacking (Lord, Petkova, et al., 2012; Woolfenden et al., 2012), there are important limitations of utilising a single, broad diagnostic category of ASD, as per DSM-5. As reviewed in Chapter 1, such limitations have led to approaches over recent years to reduce the variability in the broad spectrum of ASD by identifying more homogeneous subgroups (Ausderau et al., 2014; Greaves-Lord et al., 2013; Lane, Dennis, & Geraghty, 2011; Veatch, Veenstra-Vanderweele, Potter, Pericak-Vance, & Haines, 2014), with a smaller number of studies focusing on potential higher functioning ASD subgroups (Bitsika et al., 2008; Kamp-Becker et al., 2010; Prior et al., 1998; Verte et al., 2006), that have demonstrated the most clinical variability in the ASD spectrum.

Cluster analytic studies of high-functioning ASD to date generally have not found evidence for clinically meaningful, empirically derived subgroups within the high-functioning end of the autism spectrum; results have primarily supported the DSM-5 spectrum approach of ASD (Kamp-Becker et al., 2010; Prior et al., 1998; Verte et al., 2006). As detailed in Chapter 2, however, this thesis reported evidence against this notion and identified two childhood high-functioning ASD clusters defined based on the

profiles of ASD symptom severity. As discussed in the above sections of this Discussion, high-functioning ASD subgroups that show unique profiles of ASD symptomatology may reflect underlying distinctions between neurobiological, neurocognitive, and aetiological mechanisms between the subgroups. This, in turn, may be associated with differences between the subgroups with regard to developmental trajectories and intervention needs. From a clinical perspective, understanding these factors is important to inform management approaches and improve prediction of functioning, thereby maximising the clinician's capacity to educate families regarding the cause, clinical features, and prognosis of the disorder.

The DSM-5 has removed the definition of ASD subgroups and has instead adopted a continuous/dimensional framework where the severity of impairment within core domains is described. Specifying the severity of impairment within social communication and RRBI domains will support the identification of individuals with non-uniform symptom profiles in the clinical setting. The subgroups identified in this thesis could be described in this way. The Moderate Social Impairment subgroup, for example, could be described as having Level 2 severity of RRBI ("requiring substantial support"), but only Level 1 severity ("requiring support)" of social communication difficulties. A categorical approach, based on the identification of subgroups with similar profiles of impairment, may therefore complement the use of the dimensional classification system in describing this clinical population. Relative to using only the DSM-5 dimensional framework, using the more descriptive diagnostic label (i.e., High-functioning ASD with Moderate Social Impairment or Severe Social Impairment) would convey additional clinical information within the shorthand diagnostic label (i.e., providing an indication of the severity of social communication difficulties, RRBI, and level of neurocognitive functioning). This would offer greater clarity in the clinical and educational setting by improving the ability to predict the clinical presentation and level of functioning of a child when a comprehensive assessment report is unavailable. From a case management perspective, this would improve the clinical utility of the diagnostic label by communicating information about level of functioning that is important for understanding areas of strength and weakness in order to identify targets of intervention. Overall, differentiating individuals into subgroups in this way would reduce the phenotypic variability represented within the broader category of ASD, thereby increasing the clinical utility of the diagnostic label.

Current evidence supporting the notion of clinical high-functioning ASD subgroups that exhibit unique phenotypic profiles contrasts with a number of previous high-functioning ASD investigations reviewed in Chapter 1 (Kamp-Becker et al., 2010; Prior et al., 1998; Verte et al., 2006). Important differences between the current study and previous investigations of high-functioning ASD subgroups may have improved the validity and reliability of our findings. Firstly, participants with intellectual disability were excluded, allowing examination of high-functioning ASD subgroups without the confounding factor of cognitive impairment (as per, Bitsika et al., 2008). Further, in contrast to previous studies (Bitsika et al., 2008; Kamp-Becker et al., 2010; Prior et al., 1998; Verte et al., 2006), ASD specific characteristics were comprehensively examined using both of the 'gold standard' parent report and child observation ASD assessment measures. As supported by the findings of Chapter 3 of this thesis, the ADI-R and ADOS-2 provide different perspectives on functioning; thus, examining phenotypic characteristics using both forms of assessment was important to gain a comprehensive understanding of ASD symptomatology. Participant ratings (by parent report and clinician observation) on individual symptoms were the subject of cluster analysis, rather than overall domain or summed severity scores, supporting a more in depth analysis of phenotypic characteristics. As a result of the above, the detail of the data collected may have permitted a more thorough analysis of the high-functioning ASD phenotype, and enabled the current study to identify high-functioning ASD subgroups that was not possible when clinical and behavioural data was limited (as in previous investigations). Notably, our findings have been supported by a more recent study by Greaves-Lord and colleagues (2013) who identified six classes of participants based on profiles of ASD symptomology. Of these, two classes containing mainly high-functioning individuals were differentiated by the pattern of social communication and RRBI symptomatology; one of these classes showed severe resistance to change, with comparatively low levels of stereotyped behaviours and social communication deficits, while the other showed moderate difficulty understanding social information and social communication but low impairment across both RRBI subdomains. This supports our notion that profiles of impairment in social communication and RRBI deficits may be informative in describing high-functioning ASD subgroups.

In summary, the current findings challenge the notion of DSM-5 that conceptualises ASD as a continuum, without differentiated subgroups. As reviewed in Chapter 1, prior to the introduction of DSM-5 high-functioning ASD was differentiated into AS and autistic disorder. Although the classification of HFA was not recognised in DSM-IV, this term was

commonly used across clinical and research settings to describe individuals with autistic disorder without intellectual disability. Given this historical debate regarding the validity of high-functioning ASD subgroups, the next section considers overlap between the newly identified high-functioning ASD subgroups and previous notions of AS and HFA.

5.2.5. Overlap Between the Moderate and Severe Social Impairment Subgroups and Previous Conceptualisations of Asperger's Disorder and High-Functioning Autism

The previous distinction between AS and HFA based on language functioning was unreliable and thereby lacked clinical utility (reviewed in Chapter 1). Rather than focusing on language functioning, the present study investigated whether profiles of ASD specific social communication deficits and RRBI could differentiate high-functioning ASD subgroups. Given this contrast between the previous (i.e., AS/HFA) and current approach to subgrouping high-functioning ASD (i.e., Moderate/Severe Social Impairment), it is interesting that there is overlap between phenotypic characteristics of the newly identified subgroups and clinical features that were commonly associated with AS and HFA in the past. Relative to HFA, children with AS were often considered to show stronger social communication skills, potentially related to their superior language functioning. Despite strong expressive language ability on standardised assessment, language use in AS was often characterised by pedantic language and unusual, stereotyped phrasing (i.e., classified within the RRBI domain of ASD symptomatology, as per DSM-5). Further, AS was often thought to be associated with unusual and intense circumscribed interests. Based on these prominent clinical features commonly associated with AS, there are notable similarities between the Moderate Social Impairment subgroup and previous clinical conceptualisations of AS (i.e., stronger social communication skills and expressive language ability, but greater severity of lifetime RRBI). Conversely, the Severe Social Impairment subgroup fits more closely with the previously described HFA subgroup, with relatively greater severity of deficits in social communication, cognition, and language function.

Despite these similarities, the clinical features differentiating the Moderate/Severe Social Impairment subgroups differed to those that were previously considered to distinguish AS/HFA. Most notably, the newly identified subgroups were comparable in early language development, which was previously the primary clinical feature used to differentiate AS and HFA. Rather, it was ASD specific social communication characteristics that were the most important differentiating features between these

newly identified subgroups. Evidence that the Moderate and Severe Social Impairment subgroups contained similar proportions of individuals diagnosed with HFA and AS also supports the notion that the newly identified subgroups were distinguished by different clinical features to those which previously defined AS and HFA.

Despite this, it is notable that Moderate and Severe Social Impairment subgroups show similar core features to original notions of HFA and AS. This overlap could suggest that the abovementioned aspects of the clinical phenotype often thought to be more commonly associated with HFA and AS may have been meaningful, but that differentiating the subgroups based on language functioning was not the most informative means of discriminating subgroups in practice. Rather, the current results suggest that differentiating subgroups based on profiles of ASD specific impairment, as opposed to language development, could be informative. Future research will be important to examine whether dividing high-functioning ASD into subgroups in this way is meaningful with regard to predicting outcome and understanding neurobiological, neurocognitive, and aetiological mechanisms (see section 5.2.7). Nevertheless, the prospect of using such phenotypic characteristics to aid subgroup classification in clinical practice may be meaningful; this notion is discussed further in the section below.

5.2.6. Identifying Moderate and Severe Social Impairment Subgroups in Clinical Practice and Planning Interventions Based on Subgroup Profiles

As detailed in Chapter 2, analysis of differences in individual symptom ratings (according to the ADOS-2 and ADI-R) between the Moderate and Severe Social Impairment subgroups revealed that the severity of impairment in ten social communication variables maximally separated the subgroups. Compared with the Moderate Social Impairment subgroup, the Severe Social Impairment subgroup showed greater deficits in a number of aspects of social-emotional reciprocity (i.e., back and forth, reciprocal conversation and communication; expressing interest in others by asking for information; and responsiveness to social approaches by others), nonverbal communication (i.e., social smiles and gesture use), and in developing and understanding relationships (i.e., parent reported interest in other children and insight into relationships); differences between RRBI symptom ratings did not reach significance after bonferroni correction, suggesting that a lack of power may have limited the ability to detect differences in this domain. It is acknowledged that consideration of the differences between the subgroups based on these social communication variables alone would provide support for a purely dimensional

approach to ASD classification (i.e., where the subgroups were differentiated only by the severity of impairment); however, the observation that these ten social communication variables distinguished subgroups that differed in their lifetime severity of RRBI (i.e., in the opposite direction to the severity of social communication deficits), suggests that they could provide meaningful phenotypic markers to distinguish subgroups with different symptom profiles at the broader symptom level. Replication of the current study results with a larger sample is required; if the findings are validated in future research, however, these social communication skills could act as markers to provide a more efficient means of sub-classifying high-functioning ASD individuals to Moderate and Severe Social Impairment subgroups in clinical practice.

From a clinical perspective, identifying intervention approaches that are appropriate for each individual's needs forms an important focus following diagnostic characterisation. Differences in the severity of social communication impairment and RRBI symptomatology between the Moderate and Severe Social Impairment subgroups suggests that the groups may benefit from interventions that focus on different aspects of functioning. More specifically, the greater severity of social communication deficits in the Severe Social Impairment subgroup suggests that individuals within this subgroup may benefit from interventions targeting social-emotional functioning. The Secret Agent Society (Beaumont, Rotolone, & Sofronoff, 2015; Sofronoff, Silva, & Beaumont, 2015) is one such intervention that has been developed specifically for high-functioning children with ASD aged 8-12 years and has been shown to be efficacious in improving social functioning (discussed further below in section 5.4.3).

Conversely, given evidence of an association between RRBI symptomatology and aspects of executive functioning (as discussed above in section 5.2.3), the Moderate Social Impairment subgroup (i.e., with greater severity of RRBI) may receive greater benefit from intervention targeting executive functioning. A recently developed executive function intervention, Unstuck and On Target (UOT; Cannon, Kenworthy, Alexander, Werner, & Anthony, 2011), uses a cognitive behaviour approach to target insistence on sameness, flexibility, goal setting, and planning. In comparison to a standard social skills intervention, UOT with high-functioning children has been reported to be associated with greater gains in problem solving ability, flexibility, planning/organising, rule following, and transition between tasks. Importantly, UOT has been reported to be associated with comparable gains in social skills relative to standard social skills intervention (Kenworthy et al., 2014). In acknowledging that the

Moderate Social Impairment subgroup still experiences social communication deficits sufficient to meet criteria for ASD diagnosis, the UOT intervention could be a particularly valuable approach by improving functioning across both core domains of ASD impairment, while maintaining a focus on the cognitive domains potentially important in the development of RRBI that are most prominent in this subgroup.

The current evidence of high-functioning ASD subgroups leads to a number of potential future research initiatives to replicate, validate, and extend the current findings. The section below discusses directions for future research following this study.

5.2.7. Avenues for Future Research: Validating High-functioning ASD Subgroups

To achieve the most benefit and utility in the differentiation of children with high-functioning ASD into subgroups, a revised classification system needs to convey meaningful information to clinicians, affected individuals and their families. While understanding ASD specific symptomatology is important, differentiation of individuals into subgroups that conveys the level of functioning across other clinical domains that impact upon daily functioning, such as cognition, language, and adaptive skills, would also be beneficial. Differentiating individuals with high-functioning ASD into phenotypic subgroups will only add value to the current dimensional classification approach if it improves the clinical utility of the diagnostic label. This would be supported by greater capacity for the revised diagnostic categories to convey clinically relevant and reliable information regarding the clinical presentation and level of functioning of a child. A number of future research initiatives are required to extend the findings of this study and validate the subgroups identified in order to support the clinical utility of differentiating high-functioning ASD into subgroups, including:

1. Replication of the study with a larger sample to increase power of the analysis and examine the reliability of the findings across other high-functioning ASD populations;
2. Longitudinal investigation to examine the reliability and stability of cluster differentiation throughout development and, therefore, investigate whether the high-functioning ASD subgroups described in this thesis are informative in predicting longer-term outcome;
3. Investigation of broader domains of neurocognition that were beyond the scope of this thesis (e.g., central coherence, cognitive control, social cognition), which may contribute to the differentiated disorder profiles reported in this study; and
4. Neuroimaging studies exploring potential differences at the level of brain structure and function, which could suggest distinction in aetiological

mechanisms and a need for different intervention and management approaches for each subgroup. Importantly, the comprehensive characterisation of functioning beyond core ASD impairments (i.e., general cognitive ability, language, communication skills, and behavioural and emotional functioning) allows clinical features commonly associated with ASD to be accounted for in analysis, potentially improving the ability to determine which neurobiological factors are uniquely associated with ASD specific features.

5.2.8. Section Summary

The current findings have questioned using only a dimensional classification system for ASD, as per DSM-5, by demonstrating that it may be possible to identify subgroups of high-functioning children who show unique profiles of impairment across the core ASD symptom domains. It is proposed that adopting a combined dimensional and categorical approach could improve the capacity for the 'ASD' diagnostic label to communicate information about abilities outside of the core ASD impairments that are relevant to clinical management. This thesis forms the foundation for future research investigating potential differences in neurobiology, neurocognition, developmental trajectories, and responsiveness to intervention of the identified subgroups. Future evidence of cluster stability, with maintenance of meaningful differences between the clusters over time, would support the clinical utility of differentiating high-functioning ASD subgroups based on the phenotypic characteristics identified in this study, and argue against adopting only a dimensional approach to ASD classification.

5.3. Aim Two: Characterising Current Behaviour and Diagnosing High-functioning ASD using the ADI-R and ADOS-2

5.3.1. Section Introduction

The variability in the ASD clinical phenotype challenges the ability of standardised diagnostic tools to maintain a high level of reliability and validity of ASD symptom characterisation across the broad spectrum of ASD. Variability between diagnostic classifications according to the 'gold standard' measures have previously been reported in low-functioning children with ASD (de Bildt et al., 2004), and preschool samples representing children with a wide range of cognitive ability (Gray et al., 2008; Ventola et al., 2006); to the author's knowledge, however, the level of agreement in school-aged children with high-functioning ASD had not previously been examined. The second aim of this thesis addressed this gap in the literature. The section below first reviews the main findings of this study; the clinical and research implications of differences in

symptom characterisation and diagnostic classification according to the measures are then discussed.

5.3.2. Summary of Main Findings

In Chapter 3, the consistency between classifications according to the ADOS-2 and ADI-R diagnostic algorithms in high-functioning ASD across two childhood age groups: 5-8 years ('Young' group) and 9-13 years ('Old' group) was examined. The strength of the association between the measures in evaluating ASD symptom domains across the two childhood age groups was also explored. This study reported limited agreement (i.e., ranged from poor to fair) between the ADI-R and ADOS-2 diagnostic algorithm classifications in high-functioning ASD throughout childhood years. When the strength of the association between *current* ASD symptom domain scores was examined to better understand the discordance between the classification systems, ratings of Social Interaction and Communication difficulties correlated significantly between the measures for the 'Young' subgroup only (i.e. 5-8 years and not the 9-13 year old age group). Results therefore suggested that age was an important factor related to the correlation between the measures, and that greater difference between the assessment domain scores was seen as child age increased. In contrast to this, *current* RRBI domain scores did not correlate significantly for either age group, demonstrating that the ADI-R and ADOS-2 differ in their evaluation of RRBI in high-functioning ASD. When subdomains of RRBI were more closely examined, it was found that both the younger and older children were more likely to be rated with greater severity of circumscribed interests, unusual preoccupations, and repetitive behaviours on the ADI-R compared to the ADOS-2, whilst only the younger children were rated with significantly greater severity of rituals or compulsions on the ADOS-2 relative to the ADI-R.

A number of factors that potentially contributed to the differences between the measures were reviewed in Chapter 3, including differences between the assessment format (i.e., parent report compared with child assessment, and the questions and/or activities used to evaluate functioning), and issues that may relate more directly to the high-functioning population assessed (e.g., potentially greater capacity to mask areas of difficulty in isolated assessment sessions). Nonetheless, evidence of disagreement between the ADI-R and ADOS-2 in evaluating ASD characteristics in high-functioning children raises issues associated with the use of the measures across both clinical and research settings. These implications are discussed in the sections below.

5.3.3. Using the ADI-R and ADOS-2 in Clinical Settings

As described in Chapters 1 and 3, the ADI-R and ADOS-2 are the most extensively validated diagnostic tools, with practice guidelines recommending administration of both tools as the 'gold standard' battery for ASD diagnosis (Falkmer et al., 2013; Filipek et al., 2000; Filipek et al., 1999). The results from this thesis, however, highlight concerns with regard to the clinical utility of the tools in high-functioning ASD. It is acknowledged that the ADI-R and ADOS-2 provide different perspectives on functioning due to the varied assessment techniques employed by each measure (i.e., parent report compared with child observation). As 'gold standard' diagnostic instruments purporting to evaluate the ASD clinical phenotype, however, reliable characterisation of functioning across ability levels and throughout childhood years is required to support their use with the broad spectrum of ASD. Furthermore, agreement between diagnostic classifications based on the algorithms contained within the instruments is required to support their clinical utility. Against this notion, ADI-R and ADOS-2 diagnostic classifications according to the test algorithms were found to be inconsistent in high-functioning ASD throughout childhood years. While standardised measures form only one component of the diagnostic process, the limited agreement between the diagnostic classification systems has the potential to add confusion to the already complex diagnostic process in high-functioning ASD. Relying on classifications based on diagnostic algorithms may potentially lead to misdiagnosis. This is particularly relevant to clinicians with less experience, who may have greater potential to rely on the algorithm classification to guide diagnostic formulation. For this reason, clinical opinion based on information from multiple sources and diagnostic processes continues to form the true 'gold standard' for high-functioning ASD diagnosis.

The current findings of limited agreement between the tools is particularly important considering the issues associated with the feasibility of the measures in practice. In a recent Australian survey, paediatricians most commonly reported using information from informal observation (82.4% of the time) and parent report (73.3% of the time) when formulating ASD diagnoses (Albein-Urios et al., 2013). Significant barriers to accessing the currently available 'gold standard' tools in some diagnostic settings clearly exist, including the expense associated with the training and assessment materials required for the use of the ADI-R and ADOS-2. The time involved in administering the ADI-R and ADOS-2 also greatly impacts the feasibility of utilising both instruments together in practice. This may lead clinicians to administer one measure in isolation of the other, or to rely on informal practices. Alternatively, clinicians may modify the tool

to better fit their clinical setting by only selecting specific items to administer. For example, less than half of the ADI-R items administered in the full interview are included in the diagnostic algorithm. Selective administration may, however, impact the reliability of the assessment if clinicians solely focus on these diagnostic questions and rely on the 'score' to inform their clinical decision making process.

The current evidence of disagreement between the ADI-R and ADOS-2 in high-functioning ASD, together with abovementioned challenges associated with the feasibility of using these 'gold standard' tools in practice, demonstrates that there is a need for continued development of ASD assessment measures. Based on the current findings, tools that evaluate core symptoms required for ASD diagnosis in a high-functioning ASD population would appear to be particularly important. The high-functioning ASD group may differ significantly enough from lower functioning groups that different assessment tools, or versions of current measures, are required to better characterize these individuals and understand their symptom profiles. The findings described in Chapter 3 emphasised the importance of utilising both parent report and child observation to evaluate functioning in high-functioning ASD. Parent report, based on a lifetime of knowledge, provides a different viewpoint to clinician observation, with both perspectives being important. Using only one assessment type in isolation of the other may clearly bias the information gathered, and have significant implications for diagnosis and management strategies. Evidently, a measure that evaluates functioning based on both information sources within the single tool would be optimal. The development of standardised measures that consider early development as well as current functioning within the single instrument may also offer greater certainty in diagnostic classifications.

The findings reported in this thesis regarding the ADI-R and ADOS-2 also raise broader issues regarding the use of the tools in the research settings, where the tools are often reported to be used "to confirm diagnosis" in research samples (e.g., Cheung et al., 2009; McNally Keehn, Lincoln, Brown, & Chavira, 2013; Witwer & Lecavalier, 2010). Potential implications of using the ADI-R and ADOS-2 in this manner are discussed in the section below.

5.3.4. Using the ADI-R and ADOS-2 in Research Settings

Based on the current evidence of disagreement between the ADI-R and ADOS-2, studies that employ the ADI-R or ADOS-2 diagnostic algorithm cutoff scores in isolation from

clinical opinion as a means to evaluate whether an individual has ASD may erroneously include or exclude individuals from the study sample. As demonstrated in this thesis, relying solely on the diagnostic algorithms for classification may be particularly problematic with higher-functioning children and adolescents. While diagnostic algorithm classifications can be supportive of a clinical diagnosis, classification based on the algorithms should not be used in isolation for diagnostic decision-making. Clinical opinion remains the 'gold standard' for ASD diagnosis, which is proposed to be a more appropriate minimum requirement for ASD research studies.

5.3.5. Section Summary

This study has improved our understanding of the strengths and limitations of the currently available 'gold standard' assessment tools in high-functioning ASD. Potential factors affecting the reliability and validity of these tools were highlighted, and the importance of utilising both parent report and child assessment to evaluate functioning was demonstrated.

5.4. Aim Three: Predicting Behavioural and Emotional Functioning in High-functioning ASD

5.4.1. Section Introduction

Understanding the pattern of strengths and weaknesses across multiple domains, including cognition, language, and behavioural and emotional functioning, is necessary to evaluate support needs in ASD (Klin, Sparrow, Marans, Carter, & Volkmar, 2000), and predict developmental trajectories and prognosis. Behavioural and emotional difficulties comorbid with ASD can adversely impact daily living skills (e.g., functional independence) within the home and school environments, as well as social and academic functioning. Beyond this impact at the level of the individual and their family, health economics research has demonstrated the importance of treating psychiatric illness in individuals with ASD, revealing that the societal costs for comorbid anxiety disorders contributes to the overall costs associated with ASD (van Steensel, Dirksen, & Bogels, 2013). The financial burden may therefore be reduced if interventions can effectively improve behavioural and emotional wellbeing. For these reasons, maximising behavioural and emotional functioning in children with high-functioning ASD is an important component of clinical management. To better understand factors associated with behavioural and emotional functioning in high-functioning ASD, Chapter 4 of this thesis examined whether teacher ratings of behavioural and emotional functioning (as measured by the BASC-2 TRS, Reynolds & Kamphaus, 2004) could be predicted based on

ASD symptomatology (parent report and child observation), cognition, language ability, pragmatic communication skills, and age.

5.4.2. Summary of Main Findings

As detailed in Chapter 4, using stepwise linear regression this study found that a single factor representing language and cognitive functioning predicted Externalising Problems, School Problems, and Adaptive Skills; factors reflecting ASD specific symptomatology did not predict scores in these domains. The Behavioural Symptoms Index was significantly predicted by two factors reflecting (1) new learning and memory, and (2) parent reported RRBI and Communication Skills. In contrast, the Internalising Problems Index was not predicted by any of the latent variables, suggesting that impairment within this domain was largely independent from ASD symptomatology and the aspects of neurocognitive functioning evaluated in this study.

Chapter 4 of this thesis demonstrated that it is possible to improve our understanding of factors that predict behavioural and emotional difficulties in childhood high-functioning ASD, to inform decisions regarding skills to target in intervention. The implications of these findings with regard to both predicting areas of behavioural and emotional dysfunction in high-functioning ASD and in planning interventions were discussed in Chapter 4. The below section expands the discussion regarding implications for understanding externalising and internalising problems in high-functioning ASD, which are among the most commonly cited areas of concern with regard to behavioural and emotional functioning in this population.

5.4.3. Reducing Externalising Behaviors in High-functioning ASD

Externalising behaviours (e.g., hyperactivity, aggression, and conduct problems) create challenges within the school setting as a child displaying behaviours of this kind is unlikely to be taking in and learning information required to thrive in the academic setting. Further to the implications of externalising problems on academic achievement, such difficulties can greatly impact social relationships. Externalising behaviours have been shown to be some of the most stressful and challenging issues to manage within the school environment (National Research Council, 2001). Greater hyperactivity/impulsivity and opposition/defiance in children with ASD has been associated with conflictual and dependent student-teacher relationships (Hamre & Pianta, 2001; Robertson, Chamberlain, & Kasari, 2003). This student-teacher relationship is an important component of a child's success in school (Hamre & Pianta,

2001). The challenges faced by teachers in managing these behaviours can impact this student-teacher relationship, which could have flow on effects to the child's peer relationships and development (Robertson et al., 2003). Thus, identifying and understanding factors contributing to externalising problems has important implications with regard to social and educational functioning by improving the capacity to develop strategies that may be effective in ameliorating such difficulties.

As reported in Chapter 4, evidence that cognitive and language functioning can predict externalising problems suggests that the behaviours of concern may reflect underlying difficulties engaging, understanding, and communicating effectively in the school environment. Interventions should be focused on these deficits rather than relying on overt behavioural management techniques, which can prove to be ineffective within home and school environments. Targeting externalizing behaviours by helping a child to better communicate and understand their emotional and social functioning may have the best outcomes. More recent programs that have begun to target such skills have had positive results; the Secret Agent Society is one such program that was developed for high-functioning ASD children. Recent research has provided preliminary evidence supporting its efficacy in reducing behavioral problems at school and home, as well improving emotion regulation abilities and social skills (Beaumont et al., 2015; Sofronoff et al., 2015). In Beaumont et al., parents and teachers reported that the children appeared happier going to school, showed improved participation in classroom and play activities, and demonstrated improved emotional awareness and self-esteem following the intervention. Interestingly, in both of the studies, improvements in behaviour were evident despite the intervention not directly targeting behavioural issues; greater socio-emotional competence (e.g., improved understanding of social situations and social interaction skills), and knowledge of more adaptive self-calming strategies were thought to underpin the fewer behavioural concerns (Beaumont et al., 2015; Sofronoff et al., 2015). This supports findings of the current thesis suggesting targeting skills required for effective communication, and engaging and understanding the environment, provides a promising avenue for interventions to reduce behavioural and emotional concerns in high-functioning ASD.

5.4.4. Predictors of Internalising Problems in High-functioning ASD: Considerations for Future Research

While this thesis supported previous reports of the high prevalence of internalising symptomatology (e.g., depression, anxiety) in high-functioning ASD, the neurocognitive

variables evaluated in this study did not significantly predict this domain of functioning. Perhaps most notably given past reports of an association between anxiety and RRBI (Lidstone et al., 2014; Rodgers et al., 2012; Wigham et al., 2014), it was surprising that core ASD symptoms did not predict internalising symptomatology in our sample. Analysis of internalising symptom domain scores rather than anxiety and depression subscales, which was precluded due to the small sample of this study, may have contributed to the non-significant findings. Past research has also suggested that aspects of RRBI may be associated with different neurocognitive factors, where a positive association between anxiety and higher-level RRBI (i.e., insistence on sameness, restricted interests, routines and rituals), but not lower-level RRBI (i.e., repetitive motor and sensory behaviours), has been reported (Lidstone et al., 2014; Rodgers et al., 2012). Differentiating between lower- and higher-level aspects of RRBI was not possible in the current study given the small sample and numerous neurocognitive predictors being examined; future research may therefore benefit from differentiating between types of RRBI when examining predictors of internalising symptomatology in this population.

Broader areas of functioning may also need to be evaluated to understand the high prevalence of internalising symptomology in high-functioning ASD. It has been proposed that individuals with ASD become more aware of social difficulties (Attwood, 1998) and differences from their peers throughout adolescence (Carrington, Templeton, & Papinczak, 2003), which may contribute to elevated rates of depressive and anxiety symptomatology. The onset of puberty may further contribute to mood symptoms during this age period, particularly if an individual feels socially disconnected and has difficulty identifying emotions and communicating their concerns. Examination of a child's insight into their deficits and concept of self, and how it develops over time through childhood to adolescence may therefore further our understanding of factors contributing to the elevated levels of internalising problems in high-functioning ASD. Further to this, supports offered in the home and school, and the temperament of the child and family may also be informative in better understanding elevated internalising problems in high-functioning ASD.

5.4.5. Section Summary

This thesis has improved our understanding of factors associated with externalising problems within the school setting in children with high-functioning ASD. Results can aid the identification of individuals at risk by improving our understanding of the neurocognitive factors that may predispose an individual to greater behavioural and

emotional difficulties. The study findings could help inform intervention approaches by targeting areas of functioning shown to predict behavioural problems in high-functioning ASD. Further, by demonstrating that ASD symptomatology and neurocognitive functioning may not significantly predict internalising problems in high-functioning ASD, future research efforts can be directed to other aspects of functioning that may be more important in understanding internalising symptoms in this population.

5.5. Thesis Limitations

5.5.1. Section Introduction

This section briefly reviews the main limitations of this thesis and discusses their potential impact on the reported findings. Future directions to overcome these limitations in study design are also proposed.

5.5.2. Main Thesis Limitations and their Potential Impact on Results

Although considered relatively large for a study of children with high-functioning ASD, the sample sizes of the studies contained within this thesis were relatively small given the statistical analytic techniques adopted. This is considered to have had the most impact on the studies reported in Chapters 2 and 4. For Chapter 2 (i.e., regarding subgroups within high-functioning ASD), the limited sample size relative to the large number of variables examined significantly limited the power of investigation. A conservative alpha level was selected to reduce the risk of type 1 error, which consequently limited the ability to detect group differences. With a larger sample, other clinical variables may have significantly differed between groups.

The findings reported in Chapter 4 (i.e., regarding predictors of behavioural and emotional functioning in high-functioning ASD) should be considered experimental and preliminary due to the small sample size, which limits the generalizability of results. Given the small sample, it was necessary to employ exploratory factor analysis as a data reduction technique prior to examining predictors of behavioural and emotional functioning. Future replication with a larger sample would enable confirmatory factor analysis techniques to be employed in order to further examine the reliability of the solution found using exploratory methods in this study. Given the small sample, factor loadings for each predictor variable were evaluated against a conservative value (>.65) when interpreting the meaning of each factor; with a larger sample, this strict criterion could have been lowered such that other variables may have been interpreted as contributing meaningfully to the retained factors. Notably, inspection of the factor

loadings for variables that did not surpass this criterion (Chapter 4 – Appendix F) revealed that the initial interpretation of the factors was representative of the broader variables; for example, the Verbal Comprehension Index loaded primarily on the 'Language and General Cognitive Function' factor (Factor 1; factor loading .63); immediate and delayed recall loaded primarily on the 'New Learning and Memory' factor (Factor 2; factor loadings of .56 and .47, respectively); and parent reported ASD specific communication deficits loaded primarily on the 'Parent reported RRBI and Communication Skills' factor (Factor 3; factor loading .57). As the variables that approached the criterion for factor interpretation were consistent with other variables loading on each factor, the use of the stringent criteria to evaluate the factor loadings was not considered to appreciably impact study interpretation.

The limited sample size also raises the question of the management of missing data for the study described in Chapter 4. Of the participants with available BASC-2 TRS questionnaires (n=50), 12 participants had missing data on the neurocognitive measures that were examined as predictors. While the data was missing completely at random (p>.05 for Little's Missing Completely at Random test), such that using listwise deletion was not considered to significantly bias results (Schafer & Graham, 2002), this method reduced the power of investigation. Analysis was repeated using single imputation of the missing data to allow the larger sample of 50 participants to be included in analysis; there were no appreciable differences between interpretation of study findings based on the latter analysis. Further, despite listwise deletion and the noted limitations in the sample size of this study, study findings were statistically significant (aside from the non-significant prediction of Internalising problems) and a large amount of variance (i.e., 23-43%) in several domains of behavioural and emotional functioning could be explained by the predictor variables. Nonetheless, for the abovementioned reasons, the studies described in Chapters 2 and 4 and require replication with larger samples to examine the stability and generalizability of the findings.

An additional limitation with implications for the study described in Chapter 2 is the cross sectional study design, where analysis was based on symptomatology evaluated at one time point. The developmental trajectories of the high-functioning ASD subgroups described in the study are therefore undetermined, and the stability of the high-functioning ASD clusters needs to be examined longitudinally. This will permit a better understanding of the clinical utility of the subgroups reported in this study. As this

study examined symptomatology and functioning in high-functioning children only, findings cannot be generalised to children with intellectual disability. Given the phenotypic variability seen in ASD throughout development, including children at different developmental levels and chronological ages may alter the clustering solution. Future replication and expansion of current study with individuals representing the broader autism spectrum is needed to explore the presence of phenotypic subgroups within the wider ASD population.

A further limitation impacting the studies reported in Chapters 3 and 4 was the absence of a control group. For Chapter 3 (i.e., regarding the use of the ADI-R and ADOS-2 in high-functioning ASD), a control group (e.g., typically developing peers and/or a language disorder control group) would have enabled examination of the discriminant validity of the ADI-R and ADOS-2, which would have improved our understanding of the clinical utility of the measures in higher-functioning populations. In Chapter 4, inclusion of a control group (e.g., age matched peers without ASD, and/or children with low functioning ASD) would have permitted direct comparison of the frequency of behavioural and emotional difficulties across the different populations. Further, this would have enabled comparison of predictors of behavioural and emotional functioning across the groups, which could assist the development of tailored management strategies for the different clinical populations.

Lastly, the use of psychotropic medications by participants was not controlled for in analysis. Whilst only a small portion (n=12) of participants reported medication use at the time of data collection, there is the possibility that it impacted study findings. This limitation is most important for the study described in Chapter 4, where approximately 30% of the sample reported psychotropic medication use. Behavioral and emotional functioning may have been affected by the medications (e.g., methylphenidate for ADHD), which may have altered teacher's perception and ratings of functioning. Similarly, although the effects were considered to be relatively minimal, psychotropic medications could have impacted aspects of cognitive functioning (e.g., processing speed, attention function), with potential implications for the studies reported in Chapters 2 and 4. To overcome this in the future, researchers could exclude individuals using psychotropic medications; however, this may produce a biased sample with lower levels of symptom severity and functional impairment, further reducing generalizability of the findings. Alternatively, for the study described in Chapter 4, researchers could recruit a larger sample and complete additional analyses comparing predictors of behavioural

and emotional functioning for individuals both with and without psychotropic medication use.

5.6. Thesis Conclusion

This thesis examined issues associated with ASD classification systems, diagnostic tools, and predictors of behavioural and emotional functioning in childhood high-functioning ASD. In contrast to the historical differentiation between AS and HFA based on language development, the findings of this thesis suggest that profiles of ASD specific characteristics may provide meaningful differentiation between childhood high-functioning ASD phenotypic subgroups. The current evidence for high-functioning ASD phenotypic subgroups forms the foundation for future examination of potential differences in neurobiological and neurocognitive functioning of the clusters, as well as the investigation of the stability and outcome of the subgroups throughout development. If validated, this could have direct implications for the conceptualisation of ASD and clinical management of individuals with the disorder. Most notably, these results contribute to debate regarding the classification of ASD as a dimensional or categorical disorder, providing a novel perspective that utilising both approaches may be the most beneficial approach moving forward. Further, this thesis highlighted issues associated with the currently available ASD diagnostic tools for higher-functioning children and adolescents. Variability in symptom evaluation and diagnostic classifications by the 'gold standard' assessment tools reflects the difficulty faced by clinicians in accurately characterising symptomology and making diagnostic decisions relating to high-functioning ASD. Findings demonstrate the need for continued development of assessment measures for higher-functioning individuals. Finally, this thesis corroborated the high frequency of behavioural and emotional difficulties in children and adolescents with high-functioning ASD, emphasising that ASD diagnostic assessments that do not include independent evaluation of adaptive functioning and psychological wellbeing may fail to recognize important areas of difficulty that require tailored intervention approaches. Lastly, this thesis found that cognitive and language functioning is more predictive of school behaviour than ASD symptom severity, which has important implications clinically and educationally by providing areas to target in intervention.

CHAPTER 6: THESIS REFERENCES

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CHAPTER 7: THESIS APPENDICES

7.1. Appendix A: ASD Symptom Characterisation

7.1.1. The Autism Diagnostic Observation Schedule-Second Edition (ADOS-2)

The ADOS-2 (Lord, Rutter, et al., 2012) is standardized, semi-structured assessment protocol that purports to evaluate current communication and social interaction skills, play, and restricted and repetitive behaviours. It is considered to be one of the 'gold standard' assessment tools for the direct evaluation of ASD symptomatology. In addition to characterising symptomatology across domains of Social Interaction, Communication, and RRBI, the ADOS-2 includes a diagnostic algorithm to aid diagnostic classification. For the algorithm, scores across domains of Social Affect (Social Interaction and Communication domains combined) and RRBI are summed. Total scores are compared to cut-off values for *Autism* and *Autism Spectrum*.

ADOS-2 items are generally rated on either a 0-to-2, or 0-to-3 scale. The ratings are as follows: 0 – no abnormality or absence of the symptom/behaviour specified; 1 – mild abnormality of type specified; 2 – symptom/behaviour specified is definitely present; and 3 – symptom/behaviour is definitely present and causes clear-cut social impairment. A value of 8 is assigned when an item is not applicable (e.g., developmental stage has not yet been met); 9 represents administration error; and 7 is included for limited number of items where an alternative presentation is noteworthy in relation to a specific variable, but the deficit may not be specific to ASD (e.g., stuttering or stammer in regards to speech abnormalities). For the diagnostic algorithms, ratings on a number of variables considered central to ASD diagnosis are converted to a 0-to-2 scale (i.e., 3 is recoded to 2; 7, 8, 9 are recoded to 0), and summed.

The ADOS-2 includes five modules, administered according to the chronological age and expressive language level of the individual being assessed. For the purpose of the current thesis, either Module 2, appropriate for individuals with phrase speech (n=4), or Module 3 (n=57), appropriate for verbally fluent individuals with expressive language level of at least four years, was administered. All three studies contributing to this thesis used the ADOS-2 domain scores (i.e., Reciprocal Social Interaction, Communication, and Restricted Repetitive Behaviours domains) as indices of current ASD specific impairment. The second study (Chapter 3) additionally employed the ADOS-2 diagnostic algorithm classifications.

Given the recent introduction of the ADOS-2, a subgroup of participants (n=7) had previously been evaluated using the original ADOS (ADOS-G; Lord et al., 2002) in the

preceding 12-months. The rating of sensitivity to ASD has been maintained across ADOS-G and ADOS-2 algorithms, whilst the level of specificity between 'AD', 'AS', and non-spectrum classifications has improved (Gotham et al., 2007). The tasks employed to evaluate functioning are comparable across the ADOS-G and ADOS-2. To avoid potential practice effects for this subgroup of participants, the ADOS-2 was not re-administered. Instead, caregivers provided signed informed consent for the results of the ADOS-G assessment to be included in the current studies. The updated ADOS-2 protocol does include the addition of new behavioural rating items and contains slight modifications to a number of the existing variables. The ADOS-2 diagnostic algorithm has also been revised to include RRBI, which was previously excluded from ADOS-G algorithm. To address this, original notes for the ADOS-G assessments were accessed where possible, and items and diagnostic algorithms were re-coded to match ADOS-2 criteria. Where there was insufficient information or missing data, items were assigned a coding of 9.

7.1.2. The Autism Diagnostic Interview-Revised (ADI-R)

The ADI-R (Lord et al., 1994) is a standardized, semi-structured clinical diagnostic instrument for assessing autism in children and adults. It is a parent/caregiver interview which consists of 93 items assessing early development; acquisition and loss of language/other skills; language and communication functioning; social development and play; interests and behaviours; and general behaviours, including special isolated skills. The ADI-R is the 'gold standard' parent report ASD diagnostic measure; administration of both the ADI-R the ADOS-2 forms the 'gold standard' assessment battery for ASD diagnosis.

Each ADI-R item has two ratings: one representing current behaviour, and another reflecting either the level of functioning in the time period between the child's fourth and fifth birthday, or an 'Ever' rating reflecting highest level of impairment across the lifetime. There is variability in scoring convention across items, with some items rated on a continuous scale reflecting age of onset; others on an ordinal a 0-2 or 0-3 scale (with higher scores indicating poorer functioning); and some presentations incurring a rating of 4, 6, or 7 for specific ADI-R items. Consistent with the ADOS-2, a code of 8 represents when an item is not applicable (e.g., developmental stage has not yet been met), and a 9 represents not known/not asked.

The ADI-R includes a current behaviour algorithm that summarises current functioning according to a select number of items across domains of Social Interaction,

Communication, and RRBI. In addition, a diagnostic algorithm according to ICD-10 and DSM-IV criteria is available. For this algorithm, Social Interaction and Communication domain scores are based on functioning between ages 4-5 years across a number variables considered central to diagnosis. In contrast, the RRBI domain scores for the diagnostic algorithm include ratings summarizing the greatest lifetime severity across a selection of symptoms. For all domains, ratings of 3 are recoded to two for the algorithms and summed. A diagnosis of *Autistic Disorder* is supported when scores within each domain meet or exceed specified cutoffs, and onset of the disorder is evident by 36 months of age.

The ADI-R variables included in analysis varied across the studies contributing to this thesis. For the first study (Chapter 2), ratings of severity between ages 4-5 years and scores of greatest lifetime symptom severity were evaluated. Current domain scores were additionally compared across groups. Study Two (Chapter 3) used symptom domain scores according to the current behaviour and diagnostic algorithms and employed the diagnostic classifications according to the test algorithms. Lastly, Study Three (Chapter 4) examined the domain scores according to the current behaviour algorithm as published in the test protocol.

7.2. Appendix B: Cognitive Evaluation

7.2.1. General Cognitive Ability

The Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler, 2004) and the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III; Wechsler, 2002) are considered the 'gold standard' tools for the assessment of general cognitive ability in children. For the purposes of this thesis, the WISC-IV was administered to children aged between 6-14 years, while the WPPSI-III was employed for children less than 6 years of age. Variability between scores prevented the calculation of reliable Full Scale Intelligence Quotients for the majority of participants; instead, Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI; WISC-IV only) scores were examined. Refer to the test manuals for details regarding subtest administration and scoring (Wechsler, 2002, 2004).

7.2.2. New Learning and Memory

The Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2, Sheslow & Adams, 2003) is a standardised tool for the assessment of new learning and memory in individuals 5-90 years of age. Two verbal subtests from this measure were employed in this thesis: Verbal Learning and Story Memory. Both subtests evaluate immediate, delayed, and recognition memory. The Verbal Learning subtest is a list-learning task (13 words for children aged 5-8; and 16 words for individuals aged 9 and over), whilst the Story Memory task involves more complex verbal information with semantic structure. Both subtests were administered and scored according to instructions outlined in the test manual (Sheslow & Adams, 2003).

7.3. Appendix C: Assessment of Language and Communication Skills

7.3.1. Structural Language

The Clinical Evaluation of Language Fundamentals-Fourth Edition (CELF-4; Semel, Wiig, & Secord, 2003a) is a standardised measure to evaluate language and communication in individuals aged 5-21 years old. The instrument includes 16 subtests to evaluate Receptive Language, Expressive Language, Language Content, Language Structure, Language Memory, and Working Memory. The standardised Receptive Language Index (RLI) and Expressive Language Index (ELI) scores were evaluated in this thesis. All subtests were administered and scored according to the standardised procedures prescribed in the test manual (Semel et al., 2003a).

The Clinical Evaluation of Language Fundaments-Preschool, Second Edition (CELF-Preschool 2; Semel, Wiig, & Secord, 2003b) is the corresponding measure for evaluation of language and communication in children aged 3-6 years. Consistent with the CELF-4, the CELF-Preschool-2 examines Expressive Language, Receptive Language, Language Content, and Language Structure. A subgroup of participants had completed CELF-4 or CELF-Preschool-2 evaluations in the 12 months preceding study participation. Language measures were not re-administered with these participants to prevent potential practice effects; parents consented for CELF-4 or CELF-Preschool-2 scores to be accessed and RLI and ELI scores were included in analyses.

7.3.2. Parent Reported Language and Pragmatic Communication

The Children's Communication Checklist-Second Edition (CCC-2; D. V. M Bishop, 2003) is a 70-item questionnaire completed by parents or teachers. It contains ten scales to assess formal language (Speech Output, Syntax, Semantics, and Coherence), pragmatic language use (Inappropriate Initiation, Stereotyped Conversation, Use of Conversational Context, and Nonverbal Communication), and non-language domains (Social Relationships and Interests). Two standardised composite scores are derived based on subscale scores. The General Communication Composite (GCC) is based on the language and pragmatic communication scales; this index aids identification of children with significant communication problems (low scores indicate poorer functioning). Secondly, a Social Interaction Difference Index (SIDI) is derived by subtracting the sum of language scaled scores from the sum of the pragmatic scaled scores. A large negative SIDI value is supportive of significant pragmatic skill deficits relative to structural language skills, consistent with the communication profile common in ASD.

For the purposes of this thesis, parents or legal guardians of child participants completed the CCC-2. The first study investigated scaled score for all ten scales, as well as the GCC and SIDI index scores. In Study Three, only GCC and SIDI scores were evaluated. CCC-2 scores were not evaluated in Study Two.

7.4. Appendix D: Evaluating Behavioural and Emotional Functioning

7.4.1. Behavioural Assessment System for Children–Second Edition (BASC-2)

The BASC-2 (Reynolds & Kamphaus, 2004) is a standardised multiple-choice questionnaire (100-139 items) examining behaviour and emotional functioning. Informants rate the frequency of target behaviours on a four-point scale, ranging from "Never" observed to "Almost Always" occurs. The BASC-2 is one of the most widely used measures by school psychologists (Reynolds & Kamphaus, 2004; Volker et al., 2010) and has been validated for use in ASD (Goldin et al., 2014; Hass et al., 2012; Knoll, 2008; Mahan & Matson, 2011; Volker et al., 2010). Both Parent and Teacher completed forms are available; the Child (ages 6 to 11) and Adolescent (ages 12 to 21) forms take approximately 10–20 minutes to complete. For the purposes of this thesis, only the BASC-2 Teacher Rated Scale (BASC-2 TRS) was administered (Study One and Study Three only). For Study One, BACS-2 TRS forms were not returned for 11 participants. From the participants who returned BASC-2 TRS forms (n=50) for Study One, two participants were aged between 5 and 6 years when they participated; teachers completed the BASC-2 TRS when the child reached 6 years of age, allowing uniformity across the sample (time from study participation to BASC-2 TRS completion: 4.2 – 8.3 months). All participants in Study Three were aged over 6 years.

The BASC-2 Clinical Profile comprises Externalizing Problems (Hyperactivity, Aggression, and Conduct Problems subscales); Internalising Problems (Anxiety, Depression, and Somatisation subscales); School Problems (Attention Problems and Learning Problems subscales); and Behavioural Symptoms Index (BSI; Hyperactivity, Aggression, Depression, Attention Problems, Atypicality, Withdrawal subscales) composite scores. In addition, an Adaptive Skills Composite score is available, which consists of Adaptability, Social Skills, Leadership, Study Skills, and Functional Communication subscales. Questionnaires were scored as prescribed in the test manual (Reynolds & Kamphaus, 2004). Age and gender adjusted *T*-scores were calculated for all BASC-2 TRS subscales and composite scores. For the Clinical Profile, a *T*-score of 41-59 denotes *Average* functioning; 60-69 represents an *At-Risk* participant; and scores greater than or equal to 70 indicate *Clinically Significant* difficulties. For the Adaptive scales, a *T*-score of 41-59 is indicative of *Average* functioning; scores of 31-40 are *At-Risk*; and scores at or below 30 are considered *Clinically Significant*. BASC-2 TRS composite scores were evaluated in Study One and Study Three only.