Visuo-perceptual correlates of autistic trait expression in children with Fragile X syndrome and Down Syndrome

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Abstract

Autism Spectrum Disorder (ASD) is a clinical umbrella term used to reference a neurodevelopmental profile of socio-communicative impairment and restricted, repetitive patterns of behaviour (RRB). In most cases, ASD is 'idiopathic' meaning that genetic aetiology is poorly defined. In other cases, ASD may present in genetic syndrome groups of known aetiology, like Fragile X syndrome (FXS) and Down syndrome (DS). There is research to suggest that these 'syndromic' forms of ASD manifest distinctly in terms of behavioural symptomatology; however, beyond this level of description, we know little of the nature of these comorbidities. Visuo-perceptual irregularities are well documented in idiopathic ASD populations; in particular, spatial orienting and visual search abilities are known to be affected. Prior to this doctorate research, it remained to be seen whether behavioural manifestations of autistic-like impairment in FXS and DS were characterised by similar visuo-perceptual abnormalities. This thesis presents a series of eye-tracking studies designed to characterise syndromic forms of ASD according to associated visuo-perceptual mechanism. The work that is presented here examines the visuo-perceptual correlates of autistic trait expression in neuro-typical (NT) children (n=56) and in three clinical paediatric cohorts: idiopathic ASD (n=16), FXS (n=7) and DS (n=15), focusing specifically on attentional disengagement and visual search performance. The results are consistent with the notion of syndrome-specific profiles of autistic-like impairment, extending the literature and elucidating the complex heterogeneity that is associated with ASD. Moreover, they illustrate the value of progressing beyond superficial behavioural indices of autistic-like impairment to examine, in a more fine-grained way, the neurocognitive features underpinning comorbid expressions of autistic-like deficit.

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Abbreviations

ADOS-2	Autism Diagnostic Observation Schedule, Second Edition
ANCOVA	Analysis of Covariance
APA	American Psychological Association
ASD	Autism Spectrum Disorder
BASIS	British Autism Study of Infant Siblings
BOLD	Blood-oxygen-level dependent
BPVS-3	British Picture Vocabulary Scale, Third Edition
DIS	Disengagement
DS	Down syndrome
DSM-5	Diagnostic and Statistical Manual, Fifth Edition
E-I	Excitatory-inhibitory
EEG	Electroencephalogram
ERP	Event related potential
FAC	Facilitation
Fmr1	Fragile X Mental Retardation 1
FMRP	Fragile X Mental Retardation Protein
FXS	Fragile X syndrome
GABA	Gamma-Aminobutyric Acid
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
IQ	Intelligence quotient
Leiter-3	Leiter International Performance Scales, Third Edition
MS	Milliseconds
NT	Neuro-typical
RBQ-2	Repetitive Behaviour Questionnaire, Second Edition
RRB	Restricted repetitive behaviour
SCQ	Social Communication Questionnaire
SRS-2	Social Responsiveness Scale, Second Edition
SRT	Serial reaction time
WHO	World Health Organisation

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Chapter 1. Introduction

1.1 Overview

This introductory chapter presents ASD in clinical terms preceding a description of its genetic landscape and an introduction to syndromic ASD with a primary focus on two high-risk genetic syndrome groups: FXS and DS. The current literature is reviewed in reference to theoretical perspectives on the emergence and expression of these syndromic forms of ASD. It is evident from this review that while there have been empirical insights into the nature of these comorbidities in terms of behavioural symptomatic expression and pathogenetic mechanism, the cognitive correlates were largely unknown.

Eye-tracking technologies offer a useful means of assessing visuo-perceptual function in reference to cognitive process. While ASD is defined on the basis of behaviour, a number of visuo-perceptual processes have been implicated in the development and expression of the idiopathic phenotype, offering useful mechanistic and theoretical insights. This literature is presented here with a primary focus on attentional disengagement and visual search efficiency in children and adults with idiopathic ASD, DS and FXS. The review illustrates that syndromic forms of ASD are poorly understood in terms of visuo-perceptual mechanism.

The chapter ends with a description of the current doctorate research: a cross-syndrome empirical study of visuo-perceptual performance in children with idiopathic ASD, FXS and DS. The layout of the thesis is presented, in addition to my original aims, objectives and research questions.

1.2. Autism Spectrum Disorder (ASD): A Clinical Classification

Originally conceptualised by Leo Kanner in 1943, ASD is a clinical umbrella term used to describe a behavioural phenotype characterised by a broad range of socio-communicative impairments and RRB. This dyadic definition is derived from the formal classification provided in the fifth edition of the 'Diagnostic and Statistical Manual of Mental Disorders' (DSM-5; American Psychiatric Association [APA], 2013). Prevalence estimates for ASD have been increasing steadily in recent decades (e.g., Pinborough-Zimmerman et al., 2012; Rutter, 2007).[1] Currently, it is diagnosed in approximately 1% of the general population (Baio et al., 2018; McManus et al., 2011) and more often in men than in women at a ratio of 3:1 (Loomes, Hull, & Mandy, 2017).[2]

As a behaviourally defined disorder, ASD is diagnosed by clinical assessment in line with the international standards set out in the DSM-5 (APA, 2013) and/or the tenth edition of the 'International Classification of Diseases' (ICD-10, World Health Organization [WHO], 1992). Median diagnostic age in the United Kingdom is 4 years (Brett, Warnell, McConachie, & Parr, 2016), with similar figures documented in the United States (Oswald, Haworth, Mackenzie, & Willis, 2017). Diagnoses of ASD tend to be stable - they persist throughout the life-span – and are related to poor inter-

[1] Increasing diagnostic rates may reflect shifts towards more lenient clinical criteria, greater awareness of ASD, and contemporary social factors including older reproductive ages in Western cultures (e.g., King & Bearman; King, Fountain, Dakhlallah, & Bearman, 2009; Maenner et al., 2014).

[2] In high-functioning ASD populations, this sex ratio supersedes 5:1. In cases of intellectual disability, the ratio drops to 2:1 (Newschaffer et al., 2007). Heightened prevalence estimates in males may reflect a gender-biased conceptualisation of the ASD phenotype and, by extension, the persistent use of insensitive diagnostic measures that fail to capture phenotypic traits in females (Lai, Lombardo, Pasco, Ruigrok, & Wheelwright, 2011; Mandy et al., 2012). Moreover, it has been proposed that females require greater aetiological load to manifest ASD and are, subsequently, less likely to do so (Robinson, Lichtenstein, Anckarsäter, Happé, & Ronald, 2013; Werling & Geschwind, 2013).

personal outcomes, academic attainment, psychological wellbeing and quality of life, particularly in cases of low intellectual ability (Moss, Mandy, & Howlin, 2017).

Clinical profiles are varied, with phenotypic traits including eye gaze aversion, diminished social reciprocity and a preference for engaging with non-social environmental elements (Leekam & Ramsden, 2006). Verbal signatures include irregular speech intonation, rhythm and pitch. Repetitive speech patterns and mimicry (i.e., echolalia) are equally characteristic of ASD, as are grammatical errors like pronoun reversals (Kanner, 1943). Other defining features of ASD include reduced communicative gesture production relative to NT norms, and a relative decrease in the quality and quantity of social referencing behaviours (e.g., index pointing; Johnson & Myers, 2007; Volkmar, Chawarska, & Klin, 2005).

Sensory atypicalities have most recently been incorporated into clinical classifications of ASD, despite low syndrome specificity (APA, 2013). Problem behaviours in relation to temperament, such as self-directed aggression, are also considered of phenotypic relevance (Dominick, Davis, Lainhart, Tager-Flusberg, & Folstein, 2007). In addition to these core symptomatic domains, motor deficits such as poor muscle tone, coordination and planning are well documented in ASD populations (Esposito, Venuti, Apicella, & Muratori, 2011; Hilton, Zhang, Whilte, Klohr, & Constantino, 2012; Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998).

Clinical heterogeneity is a key feature of ASD. Indeed, formal diagnostic systems are designed to allow for this variability in that only a proportion of the behaviours implicated in the phenotype are necessary for a diagnosis to be given (APA, 2013; WHO, 1994). This heterogeneity illustrates that ASD is not a distinct neurodevelopmental condition, but a collection of complex disorders unified broadly according to the dyadic of impairment that defines the phenotype. Indeed, we are

beginning to appreciate that there are multiple developmental routes to ASD diagnoses and that, by extension, each behavioural phenotypic manifestation emerges from a complex collage of environmental and genetic risk factors (Herbert, 2010; Ramaswami, 2018; Szatmari et al., 2015).

1.3. ASD: A Complex Aetiology

Phenotypic heterogeneity in ASD is reflected in the complexity of its aetiology. Broadly, we understand that behavioural manifestations of ASD can be traced back to basic-level deficits underpinned by genetically correlated neural irregularities in relevant brain circuits (Abrahams & Geschwind, 2008; Belmonte & Bourgeron, 2006; Persico & Bourgeron, 2006). More specifically, ASD risk may be linked to genetic and/or environmentally induced disturbances in cellular and molecular processes implicated in the encoding of proteins necessary for synaptic formation and stabilisation (i.e., synaptogenesis).

There is a strong genetic component to ASD, with heritability estimated at about 90% in monozygotic twin studies (Bailey et al., 1995; Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010; Sandin et al., 2014; Steffenburg et al., 1989). Yet the precise genetic architecture is diverse and complex (for reviews, see De Rubeis & Buxbaum, 2015; Ramaswami, 2018). Hundreds of risk alleles for ASD have been identified, each of small effect. Indeed, most cases of ASD are considered multi-genic (i.e., idiopathic) in reference to the fact that they arise from the cumulative impact of many of these common risk variants (Baird et al., 2006; Gaugler et al., 2014). A small percentage of ASD risk (5-10%) is associated with rare inherited mutations and de novo variants (Cook & Scherer, 2008; Gai et al., 2012). Included within this risk bracket are certain genetic syndrome groups of known aetiology. These include FXS, tuberous sclerosis complex (Gillberg, Gillberg, & Ahlsén, 2008; Webb, Fryer, & Osborne, 1996),

neurofibromatosis type 1 (Garg et al., 2013; Walsh et al., 2013), Angelman syndrome (Peters, Beaudet, Madduri, & Bacino, 2004) and Rett syndrome (Caglayan, 2010; for reviews, see Cass et al., 2003; Richards, Jones, Groves, Moss, & Oliver, 2015). Additionally, disorders characterised by the deletion of genetic material specific to a variety of autosomal chromosomes often feature high rates of ASD. Examples of these include Prader-Willi syndrome (Dimitropoulos & Schultz, 2007), Smith-Magenis syndrome (Dykens, Finucane, & Gayley, 1997) and William syndrome (Gillberg & Rasmussen, 1994; Klein-Tasman, Phillips, Lord, Mervis, & Gallo, 2009).

1.4. ASD in Syndromic Forms

High-risk genetic syndrome groups provide a unique opportunity to study ASD emergence and expression in the context of well-defined genetic aetiologies, offering insight into shared and/or differential neurodevelopmental pathways to ASD diagnoses (Karmiloff-Smith, 1998; Levitt & Campbell, 2009). The most frequently occurring of these clinical disorders – FXS and DS – are particularly attractive to researchers as they offer a relatively large empirical database in terms of neurocognitive profile and associations with ASD (Moss & Howlin, 2009). The following section provides an overview of each of these genetic syndromes according to genetic aetiology, neuropathology and general cognitive profile, before contextualising each in a discussion of syndromic ASD expression and risk.

1.4.1. Fragile X Syndrome (FXS)

FXS is the leading known genetic cause of ASD, with comorbidity documented in 20-50% of cases (Harris et al., 2008; Hatton et al., 2009; Philofsky, Hepburn, Hayes, Hagerman, & Rogers, 2004). Estimates vary widely, but FXS affects about 1 in 5,000 males and 1 in 4,000 - 8,000 females (e.g., Coffee et al., 2009; Youings et al., 2000). The monogenic disorder, first described by James Purdon Martin and Julia Bell in 1943,

is the result of excessive CGG trinucleotide repeats in the 5' untranslated region of the Fragile X mental retardation 1 (Fmr1) gene located on the X chromosome (Santoro, Bray, & Warren, 2012). Over 200 CGG repetitions yield a full Fmr1 mutation as the gene is then silenced and unable to express its product: the Fragile X Mental Retardation Protein (FMRP). This is a messenger RNA-binding protein required for typical neurodevelopment (Brown et al., 2001; Zalfa et al., 2003). In its absence, atypically high rates of protein synthesis cause morphological irregularities (e.g., increased dendritic spine length) in neuronal dendrites, with negative implications for synaptic function (Hilton, Martin, Heffron, Hall, & Johnson, 1991; Irwin et al., 2001; Jacquemont et al., 2018). Moreover, FMRP plays a role in the regulation of neuronal inhibition and excitation. Imbalances in excitatory glutamatergic and inhibitory GABAergic (pertaining to gamma-aminobutyric acid) neurotransmission are well documented in Fmr1 knockout mouse models (for review, see Paluszkiewicz, Martin, & Huntsman, 2011). Studies have shown that FMRP loss reduces GABA expression in the cortex, hippocampus and brain stem of these mice relative to wild-type controls (D'Hulst et al., 2006; El Idrissi et al., 2005). This defective GABAergic signalling creates an imbalanced excitatory-inhibitory (E-I) system characterised by neural circuitry hyperexcitability; this, in turn, is proposed to give way to the cognitive characteristics frequently observed in cases of FXS, such as inattention, executive dysfunction and sensory dysregulation (e.g., Ethridge et al., 2016; Wang et al., 2017).

Structural and functional neuroimaging studies have highlighted specific brain regions that are particularly vulnerable to Fmr1 mutation. Mostofsky and colleagues (1998), for instance, documented a significant reduction in the size of the cerebellar posterior vermis in individuals with FXS relative to adults with intellectual disability and NT controls. Other brain regions whose function is affected by Fmr1 status include the

caudate nucleus (Eliez, Blasey, Freund, Hastie, & Reiss, 2001) and the hippocampus (Kates, Abrams, Kaufmann, Breiter, & Reiss, 1997; Reiss, Lee, & Freund, 1994). Moreover, structural abnormalities have been linked to cognitive outcomes in cases of FXS. In adults, for instance, posterior vermis volumes have been found to correlate positively with intellectual ability, visuo-spatial performance and executive function (Mostofsky et al., 1998).

Similarly, studies employing functional magnetic resonance imaging (fMRI) have been useful in defining the neural aetiology underpinning the cognitive phenotype associated with FXS. Fronto-striatal regions, known to be involved in response inhibition, have been found to be especially affected in FXS. Hoeft and colleagues (2007) examined performance on a traditional Go-No Go paradigm in adolescents with FXS relative to NT controls matched on chronological age and a second control cohort characterised by developmental delay and subsequently matched in terms of IQ.[3] Unlike controls, successful performance in males with FXS was found to be associated with increased activation in left, rather than right, fronto-striatal regions. The authors interpreted this result as an indication that response inhibition in FXS occurs via compensatory processes brought about by the effects of the Fmr1 mutation on early brain maturation, to which the fronto-striatal network is especially vulnerable (Hoeft et al., 2007). This mirrored earlier reports of prefrontal dysfunction in females with FXS according to performance on a similar Go-No Go paradigm (Menon, Leroux, White, & Reiss, 2004).

The associated cognitive profile typically observed in cases of FXS is that of inattention, impulsivity, poor working memory function, language delays and motor deficits (Hagerman & Hagerman, 2002; Hall, DeBernardis, & Reiss, 2006; Kau et al.,

[3] Go-No Go paradigms typically require participants to view a series of letters and response with a key press to every letter except the letter X for which they are required to withhold this response.

2004; Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2007). It is the most common single-gene cause of intellectual disability with average IQ estimates of about 40 (Garber, Visootsak, & Warren, 2008). Autistic-like traits are extremely common in individuals with FXS; 90% of males display some form of behavioural atypicality that is phenotypically characteristic of ASD (Hernandez et al., 2009). Social deficits, like eye gaze aversion, sensory hypersensitivities and motor stereotypies such as hand flapping are well documented in FXS populations (Garber et al., 2008). A meta-analysis examining ASD prevalence across a range of high-risk genetic syndrome groups has estimated that approximately 22% of all individuals, and 30% of males, with FXS reach screening thresholds for ASD (Richards et al., 2015).

On account of this considerable phenotypic overlap, FXS has been proposed as a useful model to study ASD pathogenesis where genetic aetiology is well-defined (Hagerman, Hoem, & Hagerman, 2010; Soorya et al., 2013; Van Herwegen, Riby, & Farran, 2015). In terms of a potential common underlying mechanism, there is increasing evidence to suggest that expressions of idiopathic ASD are similarly characterised by irregularities in GABAergic synaptic systems (e.g., Gaetz et al., 2014; Zieminska et al., 2018). In one study, Puts and colleagues (2017) used magnetic resonance spectroscopy to examine in-vivo GABA levels in 10-year-olds with idiopathic ASD relative to NT controls matched for chronological age and perceptual reasoning ability. Their results revealed a reduced GABA concentration in the sensory cortices of children with ASD. Moreover, these GABAergic reductions were associated with increased tactile detection thresholds.

In terms of clinical profile, FXS and ASD share many common behavioural features. Still, there is growing evidence to suggest that similar-looking behavioural deficits in FXS and ASD reflect different underlying neuro-cognitive mechanisms (Gallagher & Hallahan, 2012; McDuffie, Thurman, Hagerman, & Abbeduto, 2015; Wolff et al.,

2012). Eye gaze avoidance in children with FXS, for instance, has been hypothesised to occur on account of generalised anxiety, as opposed diminished social motivation or interest (Cornish, Turk, & Levitas, 2007; Hall, DeBernardis, & Reiss, 2006). Similarly, symptomatic profiling of individuals with FXS who reach screening thresholds for ASD have provided evidence in support of a distinct phenotype. A cross-syndrome investigation of RRB prevalence and phenomenology by Moss and colleagues (2009) suggested that individuals with FXS are uniquely characterised by increased rates of motor stereotypy and echolalia, an increased preference for routine and a greater tendency to engage in restricted conversation. Furthermore, McDuffie and colleagues (2015) investigated socio-communicative abilities in 4- to 10-year-old boys with FXS relative to children with idiopathic ASD matched on chronological age and autistic trait severity. According to their results, trait expression in FXS was characterised by greater social reciprocity, increased use of gesture, and fewer compulsive and ritualistic behaviours, replicating the results of an earlier study by Wolff and colleagues (2012).

Intellectual disability has been proposed to play a greater role in the manifestation of syndromic forms of ASD (Skuse, 2007). In FXS, males with a dual diagnosis of ASD have been found more likely to score poorly on measures non-verbal intellectual ability relative to their peers with FXS and no ASD (e.g., Lewis et al., 2006). Lee and colleagues (2016) conducted a longitudinal study examining developmental indices of autistic trait expression in young children with FXS at two different time points (an average of 2.5 years apart) between 1 and 4 years of age. They documented a significant negative association between RRB severity and non-verbal intellectual ability but noted no such association in relation to severity of socio-communicative impairment. Consequently, the authors proposed that intellectual disability is only partly implicated in the emergence and expression of ASD in FXS. This suggests that associations

between general cognitive functioning and autistic trait expression in FXS may not be as robust as previously theorised.

While there have been considerable theoretical and empirical advances in our understanding of the pathogenetic and behavioural symptomatic profiles associated with ASD comorbidity in FXS, there is a gap in knowledge at the level of cognition. Studying the visuo-perceptual mechanisms underpinning ASD trait expression in FXS is one means of bridging this gap, offering novel insights into the precise nature of this comorbidity and elucidating the neuro-cognitive processes implicated in the phenotype. This is discussed in more detail following an introduction to DS in reference to aetiology, neuropathology, cognitive profile and behavioural phenotype.

1.4.2. Down Syndrome (DS)

DS is the most common chromosomal cause of intellectual disability, occurring in one in every 700 live births (Parker et al., 2010). It is diagnosed prenatally by amniocentesis or chorionic villus sampling, or postnatally by clinical assessment (Hindley & Medakkar, 2002). In most cases (≈ 95%), DS is caused by a full trisomy of chromosome 21 and, in a small minority of cases, a partial trisomy or translocation (Antonarakis, Lyle, Dermitzakis, Reymond, & Deutsch, 2004; Aula, Leisti, & Koskull, 2008; Lejeune, Gautier, & Turpin, 1959). In 1% of individuals, DS presents as a chromosomal mosaicism where some cells carry a third copy of chromosome 21 while others retain the normative two (Devlin & Morrison, 2004).

Contemporary insights into the genetic mechanisms underpinning DS expression reveal a complex and varied aetiological terrain (Roper & Reeves, 2006). Genetic overexpression as a consequence of the additional chromosome 21 is hypothesised to account for the emergence of the DS phenotype (Aït Yahya-Graison et al., 2007; Antonarakis et al., 2004). There are over 300 genes located on chromosome 21 (Hattori

et al., 2000). Increased gene dosage in DS has been proposed to exert its effects on cognition via changes to synaptic structure and function, most notably in the temporal lobes, hippocampi and cerebellum (Belichenko et al., 2009; Belichenko, Kleschevnikov, Salehi, Epstein, & Mobley, 2007; Pennington, Moon, Edgin, Stedron, & Nadel, 2003). Indeed, empirical enquiry into the neuropathology of DS has revealed structural and functional anomalies, most often in brain regions implicated in language and memory function (for review, see Edgin, 2013). For example, Losin and colleagues (2009) collected fMRI data from young adults with DS and chronological age-matched NT controls during a passive story listening task. This task featured two conditions; in one, the story words were presented in the correct order; in the other, they were inversely presented. While NT controls showed significantly increased activation in classic receptive language areas (e.g., superior and middle temporal gyri) in the normal story telling condition compared to the inverse condition, the DS cohort exhibited similar patterns of activation in both conditions. These findings point to functional irregularities in DS; however, without a control group matched according to cognitive ability, the authors were unable to determine whether the observed activation patterns were demonstrative of specific language impairment or global cognitive deficit in DS.

In another study, Pujol and colleagues (2015) collected resting-state fMRI data from adults with DS (n=20; age range: 18-32 years) and chronological age-matched NT controls with the aim to map regions of neuronal synchronicity. According to their results, resting-state activation patterns differed significantly in adults with DS relative to NT controls. Firstly, the authors noted increased connectivity in ventral brain systems involved in affective and semantic processes (for review, see Barrett, Mesquita, Ochsner, & Gross, 2007). These were the ventral frontal and anterior cingulate cortices, and the amygdalae. In contrast, decreased functional connectivity was observed in

dorsal ‘executive’ brain systems such as the frontal and anterior cingulate cortices and the posterior insulae. These findings suggest that functional connectivity anomalies in DS are most prominent in frontal and anterior temporal brain regions.

This is consistent with the literature on structural alterations to brain anatomy in DS and the associated cognitive phenotype (Lott & Dierssen, 2010). The DS brain is microcephalic; yet differentially greater volume reductions have been observed in the hippocampi and fronto-temporal cortices (Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993; Nadel, 1999). Volumetric reductions to the hippocampi, and the microstructural and functional disturbances that are implied, are consistent with episodic memory impairments in children and adults with DS (Carlesimo, Marotta, & Vicari, 1997; Pennington, Moon, Edgin, Stedron, & Nadel, 2003; Raz et al., 1995; Vicari, 2001).

Another brain region implicated in the neuropathology of DS is the cerebellum. Significantly reduced cerebellar volumes have been documented in foetuses and adults with DS (Aylward et al., 1997; Baxter, Moran, Richtsmeier, Troncoso, & Reeves, 2000; Guidi, Ciani, Bonasoni, Santini, & Bartesaghi, 2011; Rotmensch et al., 1997; Winter, Ostrovsky, Komarniski, & Uhrich, 2000). Visuo-spatial and sensory-motor difficulties in DS may be attributed to cerebellar dysfunction (Konczak & Timmann, 2007; Savelsbergh et al., 2000; Yang, Conners, & Merrill, 2014). Furthermore, cerebellar outputs have been found to extend to cortical systems and limbic circuits that are involved in attention, executive control, language and working memory processes (Manto, 2006; Strick, Dum, & Fiez, 2009), all of which are implicated in the DS phenotype. Linguistic and visuospatial deficits in DS may, for instance, be partially explained by impaired connectivity of frontocerebellar structures involved in articulation and verbal working memory (Lott & Dierssen, 2010).

DS is associated with delayed cognitive development and intellectual disability with a neuropsychological profile that includes specific deficits in motor, language and memory domains (Chapman & Hesketh, 2000; Jarrold, Baddeley, & Hewes, 2000; Jarrold, Baddeley, & Phillips, 2002; Laws & Gunn, 2004; Martin et al., 2009; Silverman, 2007; Vicari, 2006). There is research to suggest that social abilities are a relative strength in DS (Fidler, Hepburn, & Rogers, 2006; Kasari & Freeman, 2001; Loveland & Kelley, 1991; Rosner, Hodapp, Fidler, Sagun, & Dykens, 2004). For instance, Fidler and colleagues (2008) examined emergent cognitive profiles in infants with DS relative to those with idiopathic intellectual disability at 12 and 30 months of age.[4] According to their data, social orienting and engagement behaviours emerged with greater relative competency in young children with DS. Still, a significant minority of individuals with DS (approximately 18%) have been found to reach screening thresholds for ASD (DiGuiseppi et al., 2010; Moss, Richards, Nelson, & Oliver, 2013; Richards et al., 2015).

Reports of ASD comorbidity in DS populations have sparked considerable debate with regard to the precise nature of the observed socio-communicative deficits and RRBs. Empirical enquiry into the behavioural profiles of autistic-like impairment observed in children and adults with DS has uncovered evidence of a distinct phenotype. Hepburn and colleagues (2008) conducted a longitudinal examination of autistic-like trait expression in toddlers with DS. They found that deficits in communication and play were accompanied by a number of developmentally appropriate social skills that included sharing, engaging in joint attention and directing vocalisations to others.

[4] The Bayley Scales of Infant Development (Bailey, 1993) were administered a both time points yielding scores on motor, linguistic and socio-communicative sub-domains.

Moss and colleagues (2013) examined SCQ data derived from adults with DS who met screening thresholds for ASD on this measure relative to adolescents with idiopathic ASD who were matched according to symptom severity and level of adaptive functioning. They reported broadly similar phenotypic presentations. However, ASD in DS was associated with less environmental withdrawal suggesting subtle differences in the nature of the observed socio-communicative difficulties. Warner and colleagues (2014) examined behavioural presentations of ASD comorbidity in 6- to 15-year-olds with DS relative to a reference sample of individuals with idiopathic ASD.[5] Symptomatic profiles were evaluated according to children's scores on Social Communication Questionnaire (SCQ) items (Rutter, Bailey & Lord, 2003; Warner, Moss, Smith, & Howlin, 2014). Despite reaching screening thresholds for ASD on this standardised measure, the results revealed that children and adolescents with DS were significantly less likely to show impairment in several aspects of non-verbal communication including use of gesture and imitation. They were also significantly less likely to demonstrate impairment on items corresponding to social exchange and reciprocity. The authors hypothesised that relatively high levels of social competency in DS may function as a protective factor against the socio-communicative deficits typically observed in children with idiopathic ASD.

Channell and colleagues (2015) examined autistic trait expression in individuals with DS aged between 10 and 21 years. Here, data derived from the Social Responsiveness Scale (Constantino & Gruber, 2005) revealed an uneven profile, with greatest difficulty

[5] Of note, the study by Warner and colleagues (2014) referenced an idiopathic ASD comparison cohort detailed in an earlier study by Berument, Rutter, Lord, Pickles and Bailey (1999). No direct comparisons were made between children with DS and this idiopathic ASD sample. Moreover, the suitability of this reference group is questionable on account of a much wider age range (i.e., 4 – 40 years) and a lack of information concerning the dimensional distribution of IQ data within this idiopathic ASD cohort (Berument et al., 1999).

recorded on items relating to RRB and social cognition, and the least difficulty noted on items relating to social awareness and social motivation.

A more recent examination of SCQ data in 6- to 15-year-olds with DS revealed a broadly similar symptomatic profile relative to an idiopathic ASD group matched on chronological age and verbal ability (Warner, Howlin, Salomone, Moss, & Charman, 2017). However, children with DS who reached thresholds for ASD on this autistic trait measure were found to demonstrate fewer problems with reciprocal social exchange and lower rates of emotional and peer-related problems. These results are consistent with the idea that phenotypic expressions of autistic-like impairment in DS differ from that which is observed in cases of idiopathic ASD.

In terms of interpreting these differences in behavioural symptomatic expression, it has been proposed that autistic-like traits in DS emerge primarily on account of general cognitive impairment. Skuse (2007), for instance, has suggested that intellectual disability diminishes the brain's capacity to compensate for the presence of independently inherited genetic risk variants. In the case of DS, a number of genes that are located on chromosome 21 (e.g., BTG3, CXADR and NCAM2) have been implicated in the emergence and expression of idiopathic ASD (see Molloy, Keddache, & Martin, 2005); hence, increased gene dosage that is engendered by a third copy of chromosome 21 might place the individual with DS at elevated risk of ASD.

As in the case of FXS, high rates of intellectual disability have been proposed to account for the increased prevalence of ASD in DS. DiGuiseppi and colleagues (2010) examined the prevalence of ASD in children with DS aged between 2 and 11 years and found that the likelihood of reaching screening thresholds for comorbidity was greater

in cases of increased intellectual disability.[6] Similarly, Molloy and colleagues (2009) conducted a study to identify the cognitive correlates of ASD status in children with DS (age range: 4 - 16 years). According to their findings, cases of comorbidity were differentiated from cases of DS-ASD according to poorer performance on measures of general cognitive ability, receptive and expressive language ability and adaptive behaviour. Of note, when the authors adjusted for variability in general cognitive functioning, mean scores on indices of autistic trait severity remained higher in children with DS and ASD relative to DS controls. They concluded that intellectual disability cannot account in full for the manifestation of ASD in DS populations.

Phenotypic heterogeneity is a key feature of ASD, and formal diagnostic systems are designed to tolerate this symptomatic variability (APA, 2013; WHO, 1994). Still, it is becoming increasingly apparent in the literature that syndromic forms of ASD manifest distinctly in terms of behavioural symptomatic profile. The following section outlines the clinical relevance of this topic with reference to the prospective impact of this doctorate research.

1.4.3. Clinical Implications

When faced with the challenge of discerning whether a child with a genetic syndrome is presenting with ASD, clinicians deliberate on the extent to which the behavioural traits exhibited by the child resemble that of idiopathic ASD. Yet there is a growing body of

[6] A functional E-I imbalance in DS offers a possible mechanistic interpretation for elevated rates of ASD in conjunction with increased intellectual disability; synaptic dysfunction is a neurophysiological feature of idiopathic ASD (Coghlan et al., 2012; Tabuchi et al., 2007; Uzunova, Pallanti, & Hollander, 2016), and a number of genetic syndrome groups characterised by high rates of intellectual disability (Fiala, Spacek, & Harris, 2002; Kaufmann & Moser, 2000; Purpura, 1974; for review, see Valnegri, Sala, & Passafaro, 2012). Similarly, in the case of DS, dendritic irregularities have been documented (Contestabile, Magara, & Cancedda, 2017). For instance, there have been reports of decreased glutamatergic synaptic density in pluripotent stem cell neurons derived from human cases (Hibaoui et al., 2014; Weick et al., 2013).

evidence to suggest that idiopathic and syndromic forms of ASD manifest differentially (e.g., DiGuiseppi et al., 2010; McDuffie et al., 2015; Moss et al., 2013).

Indeed, there is ongoing clinical uncertainty surrounding the nature and validity of autistic-like presentations in high-risk genetic syndrome groups, often resulting in prolonged diagnostic decision making and delayed access to intervention services. Empirical efforts to elucidate the neurocognitive processes underpinning autistic-like deficits in FXS and DS are necessary to inform and improve the clinical management of those who reach diagnostic thresholds for ASD, and there is clinical incentive to do so; in FXS, comorbidity carries increased risk of psychological dysfunction and behavioural delinquency (Smith, Barker, Seltzer, Abbeduto, & Greenberg, 2012). Similarly, in the case of DS, high ASD trait levels have been associated with greater emotional and behavioural impairments (Carter, Capone, Gray, Cox, & Kaufmann, 2007; DiGuiseppi et al., 2010; Warner et al., 2014). Insights gained may tell us something about whether intervention practices designed to ameliorate the symptoms associated with idiopathic ASD are applicable to these high-risk genetic syndrome groups. For example, the Early Start Denver Model is a parent-mediated intervention in which children's exposure to faces is increased via meaningful interpersonal exchange, with an emphasis on positive affect (Dawson et al., 2010; Estes et al., 2015). It aims, in this way, to facilitate the development of neural reward systems specific to social interaction and, in doing so, elevate children's social motivation. Long-term participation in this programme has been found to yield significant socio-communicative improvements in children with idiopathic ASD. Moreover, these behavioural improvements are mirrored in the post-treatment normalisation of electrophysiological brain activity associated with social information processing (Dawson et al., 2012). It remains unknown, however, whether application of the Early

Start Denver Model to children with syndromic forms of ASD would generate similar improvements.

Moreover, there is an ongoing international effort to develop pharmacological treatment methods that target the molecular and pathophysiological mechanisms implicated in the emergence and expression of ASD. Due to the significant aetiological heterogeneity that is associated with idiopathic forms of ASD, monogenic disorders at high risk of comorbidity, like FXS, are being used to model the biological and neural system pathways underpinning phenotypic presentations of socio-communicative impairment and RRB (for review, see Green & Garg, 2018). However, these fine-grained empirical endeavours work off the premise that monogenic models are analogous to idiopathic forms of phenotypic expression and this is problematic considering the growing body of evidence to suggest that this is not the case.

In order to better understand the nature of the autistic-like deficits observed in high-risk genetic syndrome groups, fine-grained analyses of the neurocognitive processes underpinning these profiles are required. In the following section, visual attention is introduced as a means of bridging behavioural and neurophysiological levels of phenotypic description in the context of syndromic ASD.

1.5. Visual Attention

Attention is the means through which we selectively perceive and process, with an aim to navigating, our external worlds. Posner and colleagues were the first to propose a conceptual model of attention; it detailed three attentional processes: alerting, spatial orienting and executive attention (Petersen & Posner, 2012; Posner & Petersen, 1990). According to this model, alerting is an elicited state of arousal or readiness; it is, in its most basic form, evident in neonates. Spatial orienting, then, is the shifting of attention between targets in a visual field (Robert Desimone & Duncan, 1995); it involves three

discrete operations: disengaging, shifting, and re-engaging attention (Posner & Petersen, 1990; Posner, Walker, Friedrich, & Rafal, 1984). Finally, executive attention references the processes by which conflict between competing visual inputs is resolved for the purpose of goal-directed action (Miller & Cohen, 2001).

Spatial orienting in early infancy is supported by simple processes that enable the infant to orient towards perceptually salient information in their visual fields; it is, in this way, stimulus-bound (Atkinson & Braddick, 2011; Atkinson, Hood, Wattam-Bell, & Braddick, 1992; Butcher, Kalverboer, & Geuze, 2000; Johnson, Posner, & Rothbart, 1991). In these early developmental stages, the executive system has yet to come online. This is evidenced by empirical observations of looking behaviour in the postnatal period; according to performance on gap-overlap tasks, young infants struggle to disengage and shift their attention flexibly from one visual stimulus to another (Colombo, 2001; Hood & Atkinson, 1993).[7] More complex orienting mechanisms become functional between 4 and 6 months of age as evidenced by the increased efficiency with which infants shift attention to the onset of visual targets (Johnson, 1995). Additionally, around this time, the ability to suppress competing visual information during attentional orienting shifts begins to emerge (Amso & Johnson, 2008; Hood, 1993; Johnson & Tucker, 1996). These developmental changes in looking behaviour likely reflect increases in processing speed on account of the neural and synaptic maturation of relevant brain systems (Csibra, Johnson, & Tucker, 1997; Deoni et al., 2011; for review, see Ross-Sheehy, Schneegans, & Spencer, 2015).

[7] Gap-overlap tasks are commonly employed to test visual orienting abilities. In these tasks, participants are required to fixate on a central stimulus before reacting with a gaze shift to the onset of a peripheral stimulus (Fischer & Breitmeyer, 1987; Saslow, 1967; for more detail, see pages 32-33).

This developmental progression from stimulus-bound (exogenous) visual attention toward a more complex endogenous system that supports goal-directed action is closely linked to the developmental maturation of oculomotor control systems (Johnson, 1990). A sub-cortical pathway from the retina to the superior colliculi is first to emerge,[8] followed by projections from the primary visual and temporal cortices to the superior colliculi later in development. In the first month of infancy, difficulties disengaging visually from salient stimuli are experienced on account of reduced inhibitory input from the basal ganglia to the superior colliculus in conjunction with poor cortical control (Hikosaka, Takikawa, & Kawagoe, 2000; Johnson, 1990). At approximately 3 months of age, anticipatory eye movements are enabled by inputs from the frontal eye fields, located in the prefrontal cortex (Canfield & Marshall, 1991; Canfield & Kirkham, 2001; Haith & McCarty, 1990).[9] Soon after, functional connections between the prefrontal and parietal cortices develop, forming the basis of a feedback circuitry that continues to mature cortically throughout childhood and adolescence supporting increasingly more advanced oculomotor control functions (e.g., Konrad et al., 2005; Luna et al., 2001; Rueda et al., 2004).

The developed visual system is composed of two anatomically distinct neural circuits that support specific mechanisms for attentional control (Goodale & Milner, 1992; Simic & Rovet, 2017). The ventral network originates in the primary visual cortex and extends to the temporo-parietal junction and the ventral frontal cortex; this circuit is primarily involved in the perception of colour and form, allowing for complex object

[8] The superior colliculi are located on the roof of the midbrain and participate in the production of saccadic eye movements via projections to the premotor circuits of the brain stem (Lee, Rohrer, & Sparks, 1988; Moschovakis, 1996).

[9] The other major cortical eye fields, the supplementary eye fields, are located within the medial frontal cortex and participate in the control of eye movements by regulating oculomotor excitability (for review, see Stuphorn, 2015).

recognition (Perrett & Oram, 1993; Tanaka, 1996; Van Essen & Maunsell, 1983). The dorsal network, conversely, extends from the primary visual cortex to the intraparietal sulcus and superior parietal lobule, as well as to the frontal eye fields. This dorsal circuitry is critical for spatial/motion processing; moreover, it functions to integrate and resolve competing exogenous inputs and, in doing so, allows for visuo-spatial selection (e.g., Pammer, Hansen, Holliday, & Cornelissen, 2006). While each circuit is specialised for distinct attentional subprocesses, it is becoming increasingly apparent in the literature that flexible attentional control requires dynamic exchange between the two (Asplund, Todd, Snyder, & Marois, 2010; Maurizio Corbetta & Shulman, 2011; for review, see Vossel, Geng, & Fink, 2014).

Conceptually, visual attention has traditionally been defined as a single, discrete 'spotlight' that navigates visual space, enhancing the processing of what is attended to at the expense of what is not (Posner & Petersen, 1990; Treisman & Gelade, 1980). Analogously, attention may be understood as the means through which organisms select a subset of information from that which is available for selective processing. This is often referenced in the literature as a signal-to-noise ratio (e.g., Briggs, Mangun, & Usrey, 2013; Luo, Zhihao Luo, & Maunsell, 2015). These conceptual descriptions have evolved in recent years according to contemporary empirical insights. Visual attention is now understood to be a dynamic process governed by top-down and bottom-up inputs and modulated by neural interactions (for review, see Wilimzig, Schneider, & Schöner, 2006). Much of this conceptual and scientific progress has derived from research employing gap-overlap paradigms to study saccadic eye movement behaviour and its neural correlates in monkey and human subjects (Dorris, Olivier, & Munoz, 2007; Dorris & Munoz, 1998; Fischer & Breitmeyer, 1987; Johnson et al., 1991).

1.5.1. The Gap-Overlap Task

Gap-overlap tasks are designed to assess the speed at which eye movements are initiated in contexts of sequentially presented, and often times overlapping, visual stimuli. Specifically, they measure latency to disengage from an original central stimulus in order to orient to the onset of a novel peripheral target. Research has shown that on such tasks, saccadic reaction time (SRT) is reduced when the central fixation stimulus offsets prior to the onset of the peripheral target (i.e., 'gap' trials) compared to when the offset of the central fixation point and the onset of peripheral stimuli occur simultaneously (i.e., baseline trials) and to when the central fixation stimulus remains onscreen (i.e., 'overlap' trials; Saslow, 1967; Van der Stigchel, Hessels, Van Elst, & Kemner, 2017). Interpretations of decreased SRTs on gap trials describe the manner in which a temporal inter-stimulus interval may act as a warning sign, increasing the viewers readiness to respond to the prospective onset of a visual target (Kingstone & Klein, 1993; Paré & Munoz, 1996). Similarly, it has been proposed that the temporal gap reduces SRT as it releases the oculomotor system from its previous state of fixation, eliminating this necessary step in the initiation of a saccade (Fischer & Breitmeyer, 1987).

The neural correlates of these visual orienting processes have been the focus of much empirical enquiry, particularly with regard to the role of the superior colliculus (for review, see Krauzlis, Lovejoy, & Zénon, 2013). The superior colliculus is a sub-cortical formation that integrates inputs from the retina and the primary visual cortex in order to generate a topographical map of receptive visual fields. Localised distributions of neurons are activated according to these inputs; patterns of activation are stabilised by a dynamic intercourse of excitatory and inhibitory cellular processes. During fixation, neurons representing the central visual field are activated (Munoz & Wurtz, 1993). Mediated in part by the reticular formation in the brainstem, saccadic eye movements

require a temporary reduction in the discharge rates of these 'fixation' neurons and a corresponding increase in the excitability of saccade-related neurons within the superior colliculus (Dorris & Munoz, 1998; Dorris, Paré, & Munoz, 1997).

In terms of interpreting the performance profile typically observed on gap-overlap tasks, SRT reductions on gap trials have been found to occur according to two processes; the first is a reduction in the neural activity of the relevant fixation neurons in the saccade map of the superior colliculus (Dorris & Munoz, 1995); the second is an increase in the activity of pre-saccadic neurons in the frontal eye fields (Dias & Bruce, 1994). It has been proposed that a preparatory response to stimulus offset is projected to the superior colliculus as a signal to disengage from the current fixation point and prepare for a yet-to-be-designated eye movement. This signalling mechanism, then, yields a relative reduction in SRT on gap trials; on baseline trials, the signalling mechanism is sharply curtailed by the immediate onset of the peripheral target (Dias & Bruce, 1994).

The SRT difference observed between gap and baseline trials is commonly labelled a 'gap effect' (Saslow, 1967) or in this thesis, a temporal facilitation (FAC) effect. Studies have shown that the size of this FAC effect is greater in children than in adults (Cohen & Ross, 1977, 1978). As such, it is considered to index the maturity and efficiency of corresponding visual and attentional brain systems. While the superior colliculus is a sub-cortical structure known to mature early in development, the frontal eye fields are located within the frontal cortex which is characterised by a protracted developmental time-line that extends into early adulthood (Konrad et al., 2005; Luna et al., 2001; Rueda et al., 2004). Therefore, shorter FAC effects in adulthood are a likely manifestation of a more advanced neural infrastructure characterised by elevated functional connectivity within and between frontal and parietal brain regions allowing for enhanced visuo-spatial selection (Pammer et al., 2006).

In overlap trials of the gap-overlap task, the central fixation point remains onscreen during peripheral stimulus onset and, typically, throughout the duration of the trial. Overlap trials have been shown to elicit longer disengagement latencies relative to gap and baseline performance levels in children and in adults (Hood & Atkinson, 1993; Johnson et al., 1991; Kulke, Atkinson, & Braddick, 2015). This relative SRT difference is commonly referred to as a disengagement (DIS) effect. On baseline and gap trials, fixation is released by the offset of the central stimulus which allows for express or visually guided saccadic shifting to take place in response to the onset of peripheral stimuli. Longer relative SRTs on overlap trials, then, are considered to reflect additional oculomotor and/or endogenous (cortical) processes that are required to voluntarily disengage and shift attention away from persisting central fixation points (Hanes & Schall, 1996; Munoz & Everling, 2004; Müri et al., 1999).

Studies employing gap-overlap paradigms have shown that in the first 4 months of life, young infants struggle to flexibly disengage and shift attention in contexts of competing visual stimuli. Beyond this early time window, visuo-spatial orienting becomes less sticky with observed decreases in DIS effect size with increasing chronological age. This kind of disengagement difficulty or 'sticky attention' rarely persists beyond this time frame in NT infants, but it has been observed in older children with idiopathic ASD.

1.5.2. Visual Orienting in Idiopathic ASD

Beyond formal diagnostic classification, idiopathic ASD is characterised by a profile of visuo-perceptual irregularity that includes disengagement deficits on tasks assessing visuo-spatial orienting capacities (for review, see Sacrey, Armstrong, Bryson, & Zwaigenbaum, 2014). These difficulties have been found to emerge early in the development of the phenotype. This is according to research employing gap-overlap

paradigms to examine early visuo-spatial orienting abilities in infants at familial risk of ASD in reference to subsequent socio-communicative outcomes.[10] In one study, disengagement latencies in high-risk infants at 12 months of age (*n*=27) were found to correlate significantly with ASD symptom severity at 24 months (Zwaigenbaum et al., 2005). In another study, high-risk infants aged between 9 and 10 months (*n*=16) were reported to exhibit longer disengagement latencies compared to NT low-risk infants (Elsabbagh et al., 2009). Considered in tandem, these findings provide support for the notion of such studies, early disengagement deficits on trials characterised by competing visual stimuli (i.e., overlap trials) have been found to predict socio-communicative outcomes. More recently, Elsabbagh and colleagues (2013) examined attentional disengagement performance in infants at high and low familial risk of idiopathic ASD relative to diagnostic outcome at 36 months. They found that high-risk infants who went on to receive a clinical diagnosis of ASD at 3 years of age exhibited significantly increased baseline corrected SRTs on overlap trials at 14 months relative to all other groups. Considered in tandem, the results of these studies support the notion that impaired visuo-spatial orienting is an early phenotypic feature of idiopathic ASD.

Similar disengagement deficits have been documented in toddlers and young children with idiopathic ASD. Landry and Bryson (2004) administered a gap-overlap task to five-year-olds with idiopathic ASD and examined performance profiles relative to NT controls of similar non-verbal intelligence according to the Leiter International Performance Scale (Leiter, 1948). They found that, on average, children with idiopathic ASD took significantly longer to disengage and shift visual attention on overlap trials. Similarly, higher mean SRTs on baseline-corrected overlap trials have been documented

[10] Familial risk in prospective longitudinal studies of this kind is defined by the presence of an older sibling carrying a clinical diagnosis of idiopathic ASD; there is an 18% likelihood of ASD in infant siblings of older children with a diagnosis (Ozonoff et al., 2011).

in 6-year-olds with idiopathic ASD relative to NT controls of a similar chronological age and intellectual ability level (Kleberg, Thorup, & Falck-Ytter, 2017). These findings suggest that, at these ages, idiopathic ASD is associated with disengagement difficulty in contexts of competing visual stimuli.

By contrast, Wilson and Saldaña (2018) administered the gap-overlap task to slightly older (7-year-old) children with idiopathic ASD and chronological age-matched NT controls; no significant group differences were observed on trials characterised by competing visual stimuli (i.e., overlap trials). Rather, those with idiopathic ASD were differentiated from their NT peers in demonstrating significantly decreased SRTs on gap trials that featured a brief inter-stimulus interval. The authors interpreted this increased gap effect as an increased susceptibility to the cueing effects of stimulus offset in this ASD cohort (Wilson & Saldaña, 2018).

With increasing age, the presence and nature of visual orienting deficits in idiopathic ASD become less clear. In one study, administration of the gap-overlap task to 10-year-olds with and without idiopathic ASD revealed no significant group differences in performance according to SRT (Van der Geest, Kemner, Camfferman, Verbaten, & Van Engeland, 2001). In adolescents with idiopathic ASD, conversely, Goldberg and colleagues (2002) observed significantly increased SRTs across all gap-overlap trial types relative to NT controls suggesting a gross reduction in disengagement efficiency at this age (i.e., not specific to overlap trials). These results were replicated in a subsequent gap-overlap assessment of visuo-spatial orienting in 12-year-olds with and without ASD (age range 9-15 years; Todd, Mills, Wilson, Plumb, & Mon-Williams, 2009). Here, idiopathic ASD status was, again, associated with increased SRT across multiple gap-overlap trial types. When interpreting the findings of these studies (Goldberg et al., 2002; Todd et al., 2009), it is worth considering the nature of the

stimuli employed (i.e., static and consistent across central and peripheral locations). It has more recently been shown that when it comes to eliciting visuo-attentional irregularities in ASD, stimulus type matters (Chevallier et al., 2015). Gap-overlap paradigms featuring dynamic, colourful stimuli that differ between central and peripheral locations are more ecologically valid and may, consequently, be more sensitive in terms of their capacity to elicit meaningful group differences (Elsabbagh et al., 2013; Landry & Bryson, 2004; Zwaigenbaum et al., 2005).

Studies applying gap-overlap paradigms to adults with and without idiopathic ASD have reported no group differences, but again issues surrounding stimulus saliency warrant consideration. In one study, the central stimulus was programmed as a white cross and the peripheral stimulus was a while square (Kawakubo, Maekawa, Itoh, Hashimoto, & Iwanami, 2004). Similarly, Masconi et al. (2009) presented adults with ASD and NT controls matched on age and intellectual ability with a gap-overlap task that employed equally low-interest stimuli (i.e., white dots). Again, no significant group effects were observed.

While there is evidence to suggest that disengagement deficits are a robust visuo-perceptual marker of ASD in infancy and early childhood, inconsistencies regarding the presence and nature of these difficulties in later years may reflect variations in task design, particularly stimulus type (Sacrey et al., 2014). Alternatively, the nature of the relationship between visuo-spatial orienting efficiency and phenotypic outcome may vary with chronological age. The idiopathic ASD phenotype emerges and is expressed in the first two-three years of life; this may represent a sensitive developmental period wherein any disruption or delay to the maturation of visual and attentional brain systems and, subsequently, to the child's ability to orient flexibly, may directly impact their socio-communicative development (Johnson, 2001). This would be due to the fact that

the brain structures and functions implicated in the development of certain social capacities may be particularly sensitive to experience-dependent growth and refinement during this time window. In the subsequent years, then, children with idiopathic ASD may eventually reach NT levels of visuo-spatial orienting via compensatory mechanisms or, if the system was delayed, via a developmental catch-up.

1.5.2.1. Neural Correlates of Irregular Visual Orienting in Idiopathic ASD

Idiopathic ASD is characterised by a widespread neuropathology that includes structural and functional variations to subcortical brain regions implicated in visuo-spatial orienting (Dommett, Overton, & Greenfield, 2009; Johnson, Jones, & Gliga, 2015). Irregularities in the composition of GABAergic cells within the superior colliculus have been noted in animal models of ASD, suggesting an imbalanced synaptic ratio between excitatory and inhibitory mechanisms (Dendrinos, Hemelt, & Keller, 2011).[11] In human subjects, fMRI has revealed suppressed neuronal activation of the bilateral superior colliculi in adults with idiopathic ASD relative to NT controls (Kleinhans et al., 2011).[12] While gap-overlap assessments of visuo-orienting ability have documented equivalent SRTs in adults with and without idiopathic ASD, the results of this fMRI study suggest that similar-looking performance profiles may reflect different underlying mechanisms (Karmiloff-Smith, 1997).

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[11] In this study, Dendrinos and colleagues (2011) administered a single injection of valproic acid to pregnant rats. Prenatal exposure to this teratogen generated an animal model of ASD characterised by sensory hyposensitivity* and reduced sociability. Post-mortem examination revealed a significantly reduced number of parvalbumin-positive neurons, a subset of GABAergic cells, in the superior colliculi of the offspring.

* Hypo-responsivity to sensory input is an established phenotypic feature of idiopathic ASD (APA, 2012; for reviews, see Bogdashina, 2016; Rogers & Ozonoff, 2005).

[12] fMRI data were collected from adults with and without idiopathic ASD during a fearful face processing task (Kleinhans et al., 2011).

Variations to the structure and function of cortical networks implicated in visual and attentional processes have been observed in cases of idiopathic ASD. Hazlett and colleagues (2017) conducted a longitudinal structural MRI study to look at developmental change in cortical surface area in infants between 6 and 12 months of age. They found that total brain increased significantly in infants at high familial risk of ASD who later received a clinical diagnosis relative to their non-clinical high and low risk counterparts, with the most robust increases observed in brain regions linked to the processing of sensory information, such as the middle occipital cortex.

Lewis and colleagues (2014) used diffusion-based tractography to examine differences in white matter connectivity in infants at high and low familial risk of idiopathic ASD. Their results revealed reduced local and global connectivity (i.e., fewer, smaller or dysmyelinated white matter fibres) across temporal, parietal and occipital brain regions in high-risk infants who, at 24 months of age, exhibited high ASD trait levels; moreover, this reduction was inversely related to trait severity ratings. In particular, brain regions implicated in visual information processing systems were found to be affected; these included the inferior temporal (Gross, 2008; Rolls, Aggelopoulos, & Zheng, 2003) and medial occipital lobes, wherein lies the primary visual cortex (Hinds et al., 2009; Jancke et al., 1999; Roelfsema, Lamme, & Spekreijse, 1998).

Elison and colleagues (2013) used diffusion tensor imaging to examine the neural correlates of visuo-spatial orienting abilities in 7-month-old infants at high and low familial risk for idiopathic ASD.[13] They noted a unique neuropathological profile in high-risk infants who went on to exhibit elevated levels of autistic trait severity at 2

[13] Diffusion tensor imaging is a neuroimaging technique used to measure white matter connectivity patterns according to water diffusion in vivo, providing sensitive indices of axonal integrity (Alexander, Lee, Lazar, & Field, 2007)

years of age; greater disengagement difficulty was associated with increased radial diffusivity in the splenium of the corpus callosum.[14] In terms of interpreting this result, there is research to suggest that increased radial diffusivity is indicative of disordered myelination (Song et al., 2002) with negative consequences for axonal firing rates and speeds of information transmission (Wake, Lee, & Fields, 2011). Moreover, with regard to these findings by Elison and colleagues (2013), it is worth considering that splenial connective fibres link primary and secondary visual areas to temporal and parietal brain areas (e.g., Dougherty, Ben-Shachar, & Bammer, 2005; Saenz & Fine, 2010); it may, therefore, be the case that a reduction in the structural and functional integrity of these fibres decreases the rate at which information is transferred between these brain regions, with implications for the visuo-attentional processes that rely on these neural networks.

Wolff and colleagues (2015), more recently, published MRI data which showed that morphological overgrowth of the corpus callosum between 6 and 12 months of age was significantly positively associated with RRB severity at 2 years of age. The authors concluded that callosal overgrowth may constitute an early neuropathological feature of idiopathic ASD. This complex behavioural phenotype appears, therefore, to emerge according to a progressive neuropathology that is localised, in part, to the corpus callosum, a commissure known to mediate the maturation of neural systems implicated in the development of basic-level visuo-spatial orienting capacities (Pietrasanta, Restani, & Caleo, 2012).

[14] The corpus callosum is the main fibre tract connecting the left and right hemispheres of the brain (for review, see Frazier & Hardan, 2009). It mediates information transfer between the cortical representations derived from each visual hemifield (Choudhury, Whitteridge, & Wilson, 1965; Hubel & Wiesel, 1967) and in doing so, modulates visual response properties, like orientation and direction of movement, across the midline (Schmidt, Lomber, & Innocenti, 2010).

In conclusion, gap-overlap paradigms, in conjunction with brain imaging methods, are continuing to yield valuable insights into the processes and mechanisms underlying visuo-spatial orienting deficits in children and adults with idiopathic ASD. In the following section, visual search is introduced as a second paradigm commonly employed in the study of visuo-perceptual processes in idiopathic ASD.

1.5.3. Visual Orienting and Search Paradigms

Visual search paradigms typically involve presenting a viewer with stimulus arrays that feature one or multiple target items and instructing the viewer to locate these items (Treisman & Gelade, 1980). Performance is often indexed according to the time it takes the viewer to locate target items. If the target item is identifiable according to a single feature dimension, it 'pops out' and is captured by visual attention, for instance, a red square within an array of yellow squares (Corbetta & Shulman, 2002; Desimone & Schein, 1987; Theeuwes, 1992). Consequently, larger set sizes (i.e., increased numbers of distractors) do not result in longer search times.[15] Conversely, when target and distractor items share a conjunction of features, locating the target item requires effortful shifts in attention, for example, locating a red square within a field of red triangles, yellow triangles and yellow squares. In such instances, larger set sizes yield longer target detection latencies.

[15] There is an ongoing debate about the degree to which attentional capture on single feature search trials is governed by exogenous (bottom-up) or endogenous (top-down) processes. According to stimulus-driven theories, performance is uniquely governed by bottom-up attentional mechanisms; the saliency of the target stimulus - established by its unique physical attribute –is proposed to capture visual attention regardless of task-relevant goals (Franconeri & Simons, 2003; Hickey, McDonald, & Theeuwes, 2006; Theeuwes, 1992; Yantis & Jonides, 1984). In opposition to this theoretical perspective, however, studies have shown that under certain task conditions, top-down process may be actively employed to suppress saliency signals and successfully avoid attentional capture (Gaspelin, Leonard, & Luck, 2017, 2015a; Lookadoo, Yang, & Merrill, 2017; Sawaki & Luck, 2010).

Distinct mechanistic processes are involved in the detection and recognition of target items (Eimer, 2015; Ghorashi, Enns, Klein, & Lollo, 2010); it is generally believed that selective attention is the means through which target items are detected, while object recognition requires the integration of the local features that comprise each target item (e.g., Wolfe, 2007; Xu & Chun, 2009).

Selective attention is an umbrella term used to reference the process that enables salient information to be brought into focus while irrelevant information is filtered out (Driver, 2001). The degree to which selective attention draws on exogenous and endogenous inputs varies throughout development; this maturational timeline is evident in studies of visual search performance across different chronological ages. Exogenous attentional processes mature early in development, as illustrated by a plateauing in single feature search abilities at about 2 years of age (Woods et al., 2013). Conjunction search performance, by comparison, continues to improve throughout childhood and adolescence (Brennan, Bruderer, Liu-Ambrose, Handy, & Enns, 2017; Donnelly et al., 2007; Woods et al., 2013). This progression is due to the age-related maturation of endogenous attentional control mechanisms, the neural correlates of which likely include the neuronal maturation of frontoparietal brain regions, in conjunction with an increasingly more distributed network architecture (Fair et al., 2009; Farrant & Uddin, 2015; Supekar, Musen, & Menon, 2009).

Immature endogenous control mechanisms in childhood mean that selective attention is vulnerable to attentional capture by task-irrelevant stimuli, with implications for visual search efficiency (Gaspelin, Margett-Jordan, et al., 2015). In adulthood, conversely, the neural systems required to support the employment of top-down attentional control are up and running, enabling the viewer to actively suppress overt shifts of attention to salient but irrelevant search items (Folk, Remington, & Johnston, 1992; Gaspelin,

Leonard, & Luck, 2015; Lien, Ruthruff, & Johnston, 2010). These systems include a frontoparietal network featuring the frontal eye fields, inferior frontal junction, superior frontal and angular gyri, and the precuneus (e.g., Couperus & Mangun, 2010; Payne & Allen, 2011; Ruff & Driver, 2006; Sylvester, Jack, Corbetta, & Shulman, 2008; for review, see Zanto & Rissman, 2015).

1.5.4. Visual Search Performance in Idiopathic ASD

Visual search is another task domain in which visuo-spatial orienting in individuals with idiopathic ASD manifests atypically, often yielding enhanced performance outcomes relative to NT controls (for reviews, see Dakin & Frith, 2005; Simmons et al., 2009). Reduced target detection times on odd-one-out visual search tasks have been documented early in the emergence of the phenotype; prospective longitudinal research by Gliga and colleagues (2015) revealed a significant positive association between visual search efficiency at 9 months and ASD symptom severity at 2 years of age in a familial risk sample. Moreover, a follow-up study referencing diagnostic outcome at 3 years of age confirmed this association, establishing superior visual search performance as an antecedent of idiopathic ASD (Cheung, Bedford, Johnson, Charman, & Gliga, 2018). This perceptual advantage is well replicated in paediatric ASD cohorts, though more often in reference to conjunction, as opposed single, search trials (e.g., Kaldy, Kraper, Carter, & Blaser, 2011; O'Riordan, 2000; O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001; Plaisted, O'Riordan, & Baron-Cohen, 1998; but see Keehn et al., 2013). Additionally, group differences have been more reliably revealed on visual search trials characterised by increased levels of difficulty.[16]

[16] Task complexity may be manipulated by changing the number of distractor stimuli featured in a given conjunction search trial, for instance, and/or by altering the featural characteristics of distractor stimuli to influence the conspicuousness of targets.

Theoretical interpretations of this phenotypic advantage posit that idiopathic ASD is characterised by anomalies in the top-down modulation of visuo-perceptual inputs, presumably on account of irregularities in the functional architecture connecting frontoparietal and primary sensory brain areas. Weak central coherence (Happé & Frith, 2006) and enhanced perceptual functioning (Caron, Mottron, Berthiaume, & Dawson, 2006) models maintain that decreased target detection speeds are due, at least in part, to a local processing bias; this is in reference to the proposed tendency for individuals with idiopathic ASD to preferentially process the local featural properties of a stimulus over its global form. Alternatively, superior search abilities have been theorised to emerge in children with idiopathic ASD on account of an irregular alerting system (Keehn et al., 2013). As originally described by Posner and Petersen (1990), this system is responsible for achieving and maintaining a homeostasis in terms of sensitivity/arousal levels in response to incoming sensory information. Liss and colleagues (2006) proposed that early irregularities in the development of this system result in an overly-focused attentional style. Moreover, they posited that this increased signal-to-noise ratio facilitates superior processing of stimulus features at the locus of attention which, in turn, may manifest as superior visual search performance.

The supposition that superiority on visual search tasks in individuals with idiopathic ASD is due to enhanced perceptual functioning has gained empirical support from eye-tracking studies focused on elucidating underlying process. Joseph and colleagues (2009) administered a visual search task to children with and without idiopathic ASD who were matched according to chronological age and non-verbal IQ. In keeping with the literature, they documented significantly reduced target detection times in those with idiopathic ASD. Furthermore, they found that groups were differentiated according to mean fixation latencies on search items; children with idiopathic ASD spent

significantly less time fixating on search items on route to locating the target stimuli. This was interpreted by the authors as an indication that enhanced search performance in idiopathic ASD reflects an ability to process stimulus features more efficiently at the locus of attention which, in turn, facilitates more rapid attentional shifting between search items.

Blaser and colleagues (2015) examined visual search performance in toddlers with and without idiopathic ASD in terms of pupillary responsivity, considered by many to be a sensitive index of arousal and attentional engagement (Hess & Polt, 1960; Jackson & Sirois, 2009; Kahneman & Beatty, 1966). According to their results, task-evoked pupillary dilation was significantly greater in toddlers with idiopathic ASD who outperformed age-matched NT controls. The authors concluded that superior visual search performance in idiopathic ASD manifests on account of a highly focused visuo-perceptual style, as opposed the employment of alternative search strategies.

1.5.4.1. Neural Correlates of Superior Search Performance

The significance of enhanced pupillary dilation in idiopathic ASD may be considered in reference to the neural systems associated with the regulation of arousal and associated attentional mechanisms. Fluctuations in pupil diameter reflect change in autonomic arousal which, in turn, is regulated by the locus coeruleus, a nucleus located within the pons of the brainstem. This nucleus is the cerebrum's main source of the noradrenaline (also called norepinephrine), a neuro-modulator that regulates levels of arousal and attentional responsivity (Devauges & Sara, 1990; McGaughy, Ross, & Eichenbaum, 2008; for review, see Sara & Bouret, 2012). Direct manipulation of the locus coeruleus has been shown to enhance performance on perceptual tasks in a manner that is indicative of greater attentional engagement and reduced distractibility (Usher, Cohen, Servan-Schreiber, Rajkowski, & Aston-Jones, 1999). Consequently, researchers have

proposed that a hyperphasic locus coeruleus may account for the visuo-perceptual profile typically observed in cases of idiopathic ASD (Aston-Jones et al., 2007); individuals with idiopathic ASD often excel on tasks that require a highly focused attentional state (e.g., serial search) but struggle on tasks that require flexible attentional shifting. In support of this supposition, the noradrenaline locus coeruleus system has been implicated in animal models of ASD (Darling et al., 2011), as well as in humans (Mehler & Purpura, 2009). Moreover, pharmacological intervention studies have illustrated the efficacy of noradrenaline re-uptake inhibitors as a means to suppress the neuronal activity of the locus coeruleus and to, consequently, ameliorate the behavioural and attentional features associated with idiopathic ASD (Béïque, De Montigny, Blier, & Debonnel, 2000; Carminati et al., 2016; Hollander, Kaplan, Cartwright, & Reichman, 2000).

Further insight into the neural mechanisms underpinning visual search efficiency in idiopathic ASD can be gained by referencing the work that has been done using fMRI methods. Keehn and colleagues (2008) were the first to investigate the neurofunctional correlates of visual search performance in children and adolescents with idiopathic ASD (n=9). Using an event-related fMRI design, they examined blood-oxygen-level dependent (BOLD) responses in a cohort of 10- to 17-year-olds with idiopathic ASD relative to NT controls (n=13) matched on mean chronological age and non-verbal intellectual ability. According to their data, children and adolescents with idiopathic ASD recruited a more distributed network of superior parietal and frontal brain regions brain areas when engaged in visual search. More specifically, they observed increased activation in the superior frontal gyrus, suggesting that visual search performance in

idiopathic ASD relies more heavily on the involvement of the frontal eye fields.[17] Moreover, children and adolescents with idiopathic ASD demonstrated atypically enhanced activation of occipital regions, consistent with the hypothesis that superior search abilities are underpinned by enhanced discriminatory capacities in idiopathic ASD. This, in conjunction with increased frontoparietal activation, suggests that enhanced search performance in idiopathic ASD is due to greater top-down modulation of serial search processes, in addition to the increased bottom-up processing of exogenous input.

More recently, Keehn and colleagues (2013) used functional connectivity MRI methods to examine activation levels within and between dorsal and ventral attentional networks in children and adolescents with idiopathic ASD (*n*=19). Relative to NT controls (*n*=19) matched according chronological age and intellectual ability, 8- to 18-year-olds with idiopathic ASD demonstrated increased functional connectivity between occipital and frontal brain regions during a visual search task. This finding is consistent with previous reports of increased functional connectivity (Noonan, Haist, & Müller, 2009) and EEG coherence (Léveillé et al., 2010) between visual occipital and frontal brain regions in individuals with idiopathic ASD. It runs contrary, however, to theoretical models and observations of reduced long-range connectivity in idiopathic ASD (e.g., Belmonte et al., 2004). In interpreting this disparity, Keehn and colleagues (2013) propose that task-evoked BOLD responses in frontoparietal brain regions are likely to vary according to the nature of a given task. As such, tasks that elicit functional underconnectivity are

[17] In addition to generating saccade commands (Dias & Bruce, 1994), the frontal eye fields play a central role in the allocation of spatial attention in monkeys (Moore, Armstrong, & Fallah, 2003; Moore & Fallah, 2004) and in humans (Grosbras & Paus, 2002). Magnetic stimulation over the frontal eye fields has been shown to modulate conjunction search performance in NT adults, for instance (Muggleton, Juan, Cowey, & Walsh, 2003).

likely to be related to domains of impairment, as in the case of language processing (Just, Cherkassky, Keller, & Minshew, 2004).

While the precise neural mechanisms underpinning enhanced visual search performance in children and adults with ASD remain unclear, it is a well-documented visuo-perceptual feature of this neurodevelopmental disorder in idiopathic forms. The fact that this performance strength pre-empts the symptomatic expression of idiopathic ASD (Cheung et al., 2018; Gliga et al., 2015) supports the notion that atypical visual perception is intrinsically linked to the emergence of the phenotype. It is important to note, however, that manifestations of idiopathic ASD are by no means homogenous; it is not a distinct neurodevelopmental condition, but rather a collection of complex disorders that share common behavioural deficits. While, on average, idiopathic forms of ASD may be identifiable according to performance on gap-overlap and visual search paradigms, within-group heterogeneity colours all empirical work seeking to classify the phenotype across any and all levels of description.

1.6. Neurodevelopmental Perspectives and Theories

There are several theoretical accounts of ASD, many of which place distinct cognitive or neural mechanisms at the root of this neurodevelopmental disorder. The theory of mind account of ASD maintained that an inability to attribute mental states to others was a principal deficit, driving the behavioural expression of the phenotype (Baron-Cohen, Leslie, & Frith, 1985). A noteworthy shortcoming of this theory is that it is somewhat modular in its perspective and fails to account for the non-social features of the disorder. More contemporary theoretical descriptions assume a neuro-constructivist position; the phenotype is believed to unfold via the cascading effects of early genetic and/or environmental disruption to basic-level processes (Karmiloff-Smith, 1998). Jarrold et al. (2000) proposed that theory of mind problems in ASD may arise via early

perceptual integration problems that limit the child's capacity to form a cohesive understanding of his or her social world. In support of this supposition, longitudinal research has revealed a unidirectional association between atypical (i.e., local) information processing in children aged 4 to 7 and theory of mind performance scores three years later (Pellicano et al., 2010). Uta Frith (1989) argued that due to this observed local processing bias, individuals with ASD are incapable of forming coherent and meaningful representations of the world around them. Her weak central coherence account of ASD maintained that such featural processing biases were the result of a global information processing impairment. This has been challenged by evidence of developmentally appropriate performance levels on global processing tasks in individuals with idiopathic ASD (Lopez & Leekam, 2003; Mottron, Burack, Iarocci, Belleville, & Enns, 2003; Ozonoff, Strayer, McMahon, & Filloux, 1994). Consequently, Mottron and colleagues (2001, 2006) proposed an enhanced perceptual functioning model of ASD. Here, they retain the notion of a local processing bias, but this local orientation is not considered to function at a cost to global information processing systems.

Pellicano and Burr (2012) proposed that perceptual atypicality in ASD may be understood in reference to how sensory and perceptual systems deal with uncertainty. In an effort to tap into mechanism (i.e., the nature of the computations) underlying basic-level visuo-perceptual irregularity in ASD, they suggest that attenuated Bayesian priors or 'hypo-priors' may be responsible; consequently, the degree to which perceptual events are influenced or modulated by previous experience is reduced, leading to more accurate representations of the world.

Alternatively, Keehn and colleagues (2013) suggest that early difficulties self-regulating arousal levels in response to incoming sensory information may constitute a primary

deficit in ASD. More specifically, they proposed that basic-level deficits in visuo-spatial orienting may be a potential means through which an infant's ability to self-regulate is disrupted; this perspective emerged on the basis of previous observations that typically developing infants self-regulate their arousal levels by intermittently disengaging and shifting their gaze away from faces that present in their visual field (Field, 1981). Keehn and colleagues (2013) posited that early difficulties disengaging and shifting attention away from faces may prompt a compensatory narrowing of the visuo-attentional spotlight (i.e., an increased signal-to-noise ratio), in an effort to self-regulate arousal levels. Consequently, idiopathic ASD is considered to be associated with an enhanced capacity to process stimulus features at the locus of attention which manifests as a phenotypic advantage on visual search tasks. This theoretical model of phenotypic emergence is attractive in that it bridges the apparent dichotomy between visuo-spatial orienting deficits and enhanced visual search performance in idiopathic ASD.

The notion of an elevated signal-to-noise ratio in idiopathic ASD has been considered in greater depth. Davis and Plaisted-Grant (2015) suggest that the phenotypic features of idiopathic ASD develop as a consequence of atypically low levels of neural noise. They begin by differentiating between endogenous (externally present in a stimulus) and exogenous (inherent in neural mechanisms) sources of noise; both are considered to influence signal-to-noise ratio and the subsequent detection of perceptual signals. This may be understood in reference to neural signalling thresholds. 'Stochastic resonance', crudely, is the idea that subthreshold signals benefit from the addition of noise, which can be either endogenous or exogenous (McDonnell & Ward, 2011). According to Davis and Plaisted-Grant (2015), atypically low levels of endogenous noise in idiopathic ASD means that higher levels of exogenous noise are required for signalling thresholds to be reached, enabling perceptual detection and discrimination. This would

explain why children and adults with idiopathic ASD excel at visuo-perceptual tasks that are characterised by high levels of exogenous noise, for example, in the case of conjunction visual search. Moreover, the authors offer a possible explanation for low levels of neural noise in ASD suggesting that hyperphasic noradrenergic activity within the cortex, originating from the locus coeruleus, may play a role (e.g., Aston-Jones et al., 2007; Usher et al., 1999).

Single-deficit models of ASD are problematic in that each is unlikely to account for the broad range of phenotypic features observed in cases of idiopathic ASD (Happé, Ronald, & Plomin, 2006). Johnson (2017) offers a novel theoretical perspective that endeavours to account for the complex phenotypic heterogeneity associated with this neurodevelopmental disorder. Here, ASD is conceptualised as the phenotypic outcome of compensatory brain processes that occur in response to early signal-processing irregularities. To exemplify this proposed process, he uses the analogy of a fever; a common adaptive neurophysiological response to a wide variety of causal factors (bacterial, viral, etc.). In a similar vein, Johnson (2017) suggests that ASD is the product of a common adaptive brain response to any environmental and/or genetic disruption to early neural processes, most likely at the level of the synapse. Corresponding to this notion, computational models of brain development have illustrated the manner in which many different starting states can give rise to considerably fewer phenotypic end states (Oliver, Johnson, Karmiloff-Smith & Oliver, 2000).

According to this theoretical model, disruptions to early information processing systems are likely to negatively impact a child's capacity to reliably sample information from the environment (Johnson, 2017); as a direct result, these systems might impose sensory restrictions via an increased signal-to-noise ratio. Moreover, in a process termed niche

construction, the child is likely to develop an information processing bias corresponding to an emergent preference for repetitive, mechanical and self-led forms of stimulation. In essence, then, Johnson (2017) postulates that expressions of socio-communicative impairment and RRB emerge as an adaptive response to early processing deficits that bias attentional systems against dynamic, complex and, often times, social sensory inputs.

While there is no one accepted neurodevelopmental framework for the emergence and expression of ASD, theoretical frameworks enable the conceptual amalgamation of diverse and seemingly disparate empirical observations. Moreover, they can provide useful platforms on which to generate novel testable hypotheses. Johnson's (2017) adaptive brain theory is attractive in that it considers the phenotypic heterogeneity observed in cases of ASD. For instance, it may be applied to syndromic forms of ASD. Many genetic syndromes considered to be at high risk of ASD, including FXS and DS,[18] are characterised by defective GABAergic systems. According to Johnson's (2017) model, an early disruption to information signalling processes on account of an imbalanced E-I ratio would increase the likelihood of phenotypic expression via the adaptive systemic response detailed in the previous paragraph. While this is just one theoretical perspective on the neurodevelopment of syndromic and idiopathic forms of ASD, it offers a useful framework on which to conceptualise comorbidity in high-risk populations.

[18] Also including Rett Syndrome (Coghlan et al., 2012; Medrihan et al., 2008), Schizophrenia (Lewis et al., 2012), Tourette Syndrome (Di Cristo, 2007; Kalanithi et al., 2005) and Neurofibromatosis type 1 (Costa et al., 2002; Diggs-Andrews and Gutmann, 2013).

1.7. Visuo-Perceptual Profiles in FXS and DS

Genetic syndromes that feature high rates of autistic-like impairment are considered useful models for the study of phenotypic emergence and expression when genetic aetiology is well-defined (Karmiloff-Smith, 1998; Karmiloff-Smith et al., 2016). There is, however, ongoing debate surrounding the precise nature of the observed socio-communicative deficits and RRB in DS and FXS populations.

There is a growing body of evidence to suggest that expressions of autistic-like symptomatology in these high-risk genetic syndrome groups arise via disparate neurocognitive mechanisms (e.g., McDuffie et al., 2015; Moss et al., 2013; Warner et al., 2017). Yet despite these empirical advances, we know little about the visuo-perceptual correlates of autistic-like traits in children with DS or FXS. The need to address this knowledge gap is clear in light of the research implicating visuo-perceptual irregularity in the emergence and expression of idiopathic forms of ASD.

There is only one published study to date that has examined the visuo-perceptual correlates of autistic trait expression in FXS or DS cohorts. In this study, Roberts and colleagues (2012) examined gaze behaviour in infants with FXS at 9, 12 and 18 months of age relative to 12-month-old NT controls. The experimental task involved presenting infants with a toy and visually coding look duration and disengagement latency (referencing the time spent looking at the toy prior to an initial disengagement). The results revealed a significant group difference in mean latency to disengage and shift visual attention away from a toy following a period of sustained attention; longer latencies were observed in infants with FXS. However, this effect was found to be driven by the presence of an outlier and once removed, the effect was no longer significant. No other group differences emerged in terms of looking behaviour. The merit of this study lies in its focus with regard to identifying visuo-perceptual features

associated with autistic-like trait expression in infants with FXS. However, it has several limitations including its crude analysis of looking behaviour based on retrospective video coding and its misrepresentation of the data; the output variable of interest, 'disengagement latency', may be more appropriately conceived of as an index of sustained attention duration.

More generally (i.e., not in relation to autistic-like trait expression), inattention is a key phenotypic feature of FXS and irregularities in visuo-attentional orienting and executive eye-movement control have been observed. Scerif and colleagues (2005) examined oculomotor control in toddlers with FXS on a task that measured children's ability to inhibit saccadic shifts towards boring stimuli that predicted the onset of more visually rewarding peripheral stimuli. They found that relative to mental-age matched NT controls, toddlers with FXS were impaired in their ability to inhibit reactive gaze shifts to the onset of predictive stimuli. This was interpreted by the authors as demonstrating an inability to use learned information about the contingency between cue and target location to adaptively modify behaviour in the same way as NT children.

Visual search abilities have also been examined in children with FXS. Scerif and colleagues (2004) administered a touch-screen search task to 4-year-olds with FXS and documented equivalent target detection times relative to chronological age-matched NT controls. Examination of performance indices concerning accuracy and error data revealed significant group differences, however. Toddlers with FXS produced a significantly greater number of immediate repetitive errors, also termed dysexecutive perseverative errors, and distractor errors, compared to their NT peers. These results were considered to signal a selective attention deficit in FXS (Scerif et al., 2004).

Munir and colleagues (2000) administered a computer-based visual search task to older boys with FXS aged between 8 and 15 years. Performance was compared against a DS

control group matched according to chronological and mental age, and two mental age-matched NT cohorts, one characterised by high levels of inattention and hyperactivity, and another characterised by age-appropriate levels of inattention and hyperactivity. The results supported a selective attention deficit in FXS; relative to boys with DS, those with FXS made an increased number of incorrect clicks, interpreted by the authors as a deficit in their ability to select relevant information. In sum, there is evidence to suggest that visual orienting is atypical in FXS, with children exhibiting selective attention deficits evidenced by reactive gaze shifts to stimulus onset. In terms of a possible underlying mechanism, there is evidence to suggest that sensory processes in FXS are characterised by a decreased signal-to-noise ratio which, in turn, is likely to manifest as selective attentional difficulty (Buschman & Kastner, 2015; Franco, Okray, Linneweber, Hassan, & Yaksi, 2017; Golovin & Broadie, 2017).

Studies to date examining visual orienting and visual search abilities in children with DS reveal a different visuo-attentional profile. Brown and colleagues (2003) examined sustained attention in infants with DS relative to two mental age-matched comparison groups: infants with William Syndrome and NT controls. They presented infants with toys and measured latencies of sustained attention. In line with long-standing reports of sustained attention deficits in children with DS (Green, Dennis, & Bennets, 1989; Krakow & Kopp, 1982), the authors observed significantly reduced latencies in the DS cohort relative to both NT and WS comparison groups.

By extension, Steele and colleagues (2011) examined visual search data collected from these same participant samples and found that the infants with DS were slower to locate visual targets amidst distractor stimuli. The search paradigm that was employed was presented on a touch-screen device; target identification required a finger press. The authors interpreted the observed group difference as an artefact of slowed motor

processing in DS. They also examined attentional orienting data derived from a double-step saccade task (Gilmore & Johnson, 1997; Steele et al., 2011). According to these data, infants with DS performed similarly to NT controls in terms of their ability to disengage visually from fixated stimuli and orient to the onset of secondary stimuli. This finding adhered to previous reports of developmentally appropriate visual orienting abilities in adults (Randolph & Burack, 2000) and adolescents with DS (Goldman, Flanagan, Shulman, Enns, & Burack, 2005).

In conclusion, DS and FXS are associated with syndrome-specific profiles of visuo-attentional irregularity. Despite the high-risk status of these genetic syndrome groups, there has been only one investigation of visuo-perceptual performance in reference to autistic trait severity, and this was a crude examination based on retrospective video coding of infant behaviour in FXS (Roberts et al., 2012). Fine-grained analyses are necessary to the determine whether these syndromic forms of ASD are similar or dissimilar to idiopathic forms in terms of associated visuo-perceptual mechanism.

1.8. Doctorate Research

This thesis presents an empirical investigation into the visuo-perceptual processes underpinning autistic trait variation in children with idiopathic ASD, FXS and DS. Following this introductory chapter, Chapter 2 provides a comprehensive account of the project's design and methodology. In light of the inconsistencies in the literature, Chapter 3 presents an eye-tracking study of attentional disengagement and visual search abilities in children with idiopathic ASD relative to NT controls matched on indices of verbal and non-verbal intellectual ability. By extension, this study examines the degree to which general cognitive capacities are implicated in idiopathic and non-clinical expressions of socio-communicative difficulty and RRB. It is worth noting that the idiopathic ASD cohort considered here is low functioning, an often-neglected and

understudied population within the field of ASD research (Jack & Pelphrey, 2017; Stedman, Taylor, Erard, Peura, & Siegel, 2019).

Chapter 4 details a cross-syndrome investigation into the intellectual and visuo-perceptual correlates of autistic trait variation in children with idiopathic ASD, FXS and DS, with a specific focus on the SRT output variables derived from a gap-overlap task. In keeping with the reports in the literature of distinct behavioural symptomatic profiles, attentional disengagement abilities and their associations with expressions of autistic-like impairment were expected to manifest in syndrome-specific ways. Moreover, the contribution of verbal and non-verbal intelligence factors to expressions of autistic-like impairment was examined across these three clinical cohorts. It was hypothesised that in both high-risk genetic syndrome groups, children with greater deficits on measures of verbal and non-verbal ability would exhibit higher levels of autistic trait expression.

Chapter 5 presents a cross-syndrome study of visual search ability in children with idiopathic ASD, FXS and DS. Within- and between-group variation in autistic trait severity was examined according to visual search efficiency (i.e., target detection latency) on single feature and conjunction search trials. Children with idiopathic ASD were expected to outperform their peers with DS and FXS. Moreover, higher autistic trait levels in association with exhibiting increased target detection times (poorer performance) were anticipated in children with FXS, in accordance with the selective attention deficits that have been documented previously in this clinical population. In the case of DS, a significant positive association between autistic trait severity ratings and visual search times was anticipated on account of generally delayed motor processing, a well-established phenotypic feature of the genetic syndrome (for review, see Horvat, Croce, & Fallaize, 2016).

A final empirical study is presented in Chapter 6. Here, the relationship between attentional disengagement and visual search abilities is examined in reference to indices of autistic trait severity across idiopathic ASD, FXS and DS cohorts. Hypotheses were formed according to the results of the previous chapters.

The final chapter in this thesis, Chapter 7, is a general discussion of the results of this doctoral work with reference to theoretical, conceptual and clinical implications. Avenues for future research are presented so that the results of this research may be extended to further our understanding of ASD risk and expression in these high-risk genetic syndrome groups.

Chapter 2. Methodology

2.1. Overview

This chapter provides an umbrella account of the methodology employed in the current project. First, participant recruitment methods and sample demographics are presented. Next, the experimental procedure is outlined, preceding a comprehensive overview of the measures employed in the data collection process. Finally, a data analysis plan is presented that details the prospective management and analysis of the data.

2.2. Participants

Eighty-eight children ranging in age between 3 and 12 years were recruited to take part in the current project. This total number of children was subdivided into four participant groups: NT, idiopathic ASD, FXS and DS. Participation was conditional on children having no history of epilepsy and no previous incidences of acquired brain injury.

Groups were recruited via distinct networks and channels. NT participants were recruited via the Birkbeck Babylab database of registered families. Participants were classified as NT in the absence of any clinically diagnosed conditions. Children with a formal clinical diagnosis of idiopathic ASD were recruited via the Autism Spectrum Database – UK. Official application for access to this database was submitted and subsequently accepted in January 2017. This recruitment effort focused specifically on children with idiopathic ASD who would be classified as low functioning (i.e., those who are severely affected by the phenotype and display general cognitive impairment).

Children with FXS were recruited with the support of the Fragile X Society, a registered UK-based charity organisation with an emphasis on facilitating and disseminating research. Formal application for recruitment support was submitted, and subsequently accepted, in November 2016. Additional recruitment opportunities were obtained

through pre-existing connections with a number of FXS families by virtue of the research conducted by Dr. Dean D'Souza within the Birkbeck Centre for Brain and Cognitive Development (e.g., D'Souza, D'Souza, Johnson, & Karmiloff-Smith, 2016).

Families of children with DS were recruited with the help of the Down Syndrome Association. This registered UK-based charity organisation advertised the current project across a variety of social media platforms for a duration of 6 months, commencing in November 2017. Prior to this, formal application for assistance with recruitment was submitted and approved. In addition, connections to the London Down Syndrome Research Consortium via the work of my late supervisor, Professor Annette Karmiloff-Smith, enabled access to a small community of children with DS who fell within our age bracket of interest.

With regards sample demographics, groups varied significantly in terms of age and standardised IQ but were matched according to raw verbal and non-verbal intellectual ability ratings (Table 2.1). The NT cohort (n=50) spanned a broader and, on average, a younger age range than each of the other participant groups and was exclusively male to match the gender bias observed within the idiopathic ASD cohort (n=16). Seven children with FXS participated in this doctorate research, one of whom was female and two of whom carried clinical diagnoses of ASD (see tables 2.1 and 2.2). Finally, fifteen children with DS were recruited, seven of whom were female and seven of whom carried clinical diagnoses of ASD.

Table 2.1

Demographics and IQ Data with ANOVA Outputs

	NT (*n*=50)	**ASD** (*n*=16)	**FXS** (*n*=7)	**DS** (*n*=15)		
Variable	*m / f*	*m / f*	*m / f*	*m / f*		
Gender	50/0	16/0	6/1	8/7		
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	**Sig.**	**Bonferroni Post-Hoc**
Age $_{years}$	4.6 (1.6)	8.5 (1.6)	7.5 (1.2)	8.9 (2.0)	<.001	All > NT
Range	3-9	6-11	6-9	6-12		
Leiter-3 IQ*	98.1 (8.2)	72.7 (24.7)	71.3 (18.5)	51.9 (11.6)	<.001	NT> All >DS
Range	81-120	36-128	49-103	32-70		
Leiter-3 Raw**	53.8 (18.4)	56.4 (22.3)	47.1 (5.6)	39.9 (18.8)	.06	---
Range	30-108	17-91	40-56	6-65		
BPVS-3 IQ*	95.4 (11.5)	71.6 (3.7)	80.3 (13.1)	71.1 (2.8)	<.001	NT > All
Range	74-132	70-82	70-103	70-80		
BPVS-3 Raw**	60.4 (30.1)	51.2 (29.7)	69.6 (29.7)	45.3 (37.2)	.21	---
Range	23-134	3-102	37-125	5-107		

***** Age-normed intelligence quotient (IQ) scores re non-verbal (Leiter-3) and verbal (BPVS-3) ability

****** Raw Scores re non-verbal (Leiter-3) and verbal (BPVS-3) ability

Table 2.2

Demographics and IQ Data in children with FXS with (+) and without (-) ASD and children with DS ± ASD

	FXS		DS	
	- ASD (*n*=5)	**+ ASD** (*n*=2)	**- ASD** (*n*=8)	**+ ASD** (*n*=7)
Variable	*m / f*	*m / f*	*m / f*	*m / f*
Gender	4/1	2/0	4/4	4/3
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*
Age $_{years}$	7.0 (0.9)	8.8 (0.1)	9.1 (2.1)	8.7 (1.8)
Leiter-3 IQ	69.4(11.4)	76.0 (38.2)	59.4 (7.2)	43.4 (9.8)
Leiter-3 Raw	49.2 (5.1)	42.0 (2.8)	48.9 (15.1)	29.7 (18.1)
BPVS-3 IQ	77.8 (9.6)	86.5 (23.3)	72.1 (3.6)	70.0 (0.0) *
BPVS-3 Raw	64.0 (18.1)	83.5 (58.7)	62.4 (25.9)	25.9 (31.1)

***** A mean standardised score of 70 is indicative of floor effects on the BPVS-3.

2.3. Measures and Procedure

The current project was approved by the Ethics Committee within the Birkbeck Department of Psychological Sciences in September 2016. Recruitment and data collection commenced shortly after and continued for an approximate duration of 18 months.

All data collection took place at the Birkbeck Babylab within the Centre for Brain and Cognitive Development. Prior to testing, a detailed information sheet and a selection of parent-report questionnaires were distributed to families for completion as detailed below. Preliminary phone conversations were held with the parents of children with idiopathic ASD, DS and FXS to build rapport and acquire information that would enable the specialised catering of sessions in accordance with children's needs.

Participation involved approximately 3-4 hours of contact time. During this time, children were engaged in an 80-minute behavioural assessment, a 15-minute eye-tracking session and twenty-minutes of electroencephalogram (EEG) data acquisition.[19] All sessions began with parental briefing and the acquisition of informed written consent. Participant travel and accommodation costs were reimbursed on the day of testing.[20] These costs were covered by departmental research funds, and supplementary funding awarded to the project by The Waterloo Foundation.

[19] EEG data were collected to examine whether syndromic presentations of ASD were characterised by the same neural signatures as have been documented in children with idiopathic ASD (e.g., a reduced N170 response to faces). These data were collected as part of this doctorate research but are excluded from the current thesis due to funding-imposed time constraints. Departmental funds have recently been acquired will enable examination of these EEG data following the submission of this thesis.

[20] An offer of a night's accommodation at a local Premier Inn was offered to families living a considerable distance from London.

2.3.1. Parent-Report Questionnaires

Parents/caregivers of all participants completed a selection of questionnaires intended to capture children's behavioural characteristics and ability levels across a variety of key cognitive and behavioural domains. The selection process via which this questionnaire battery was formed was influenced by the primary research questions of the project, in addition to the psychometric properties of each in relation to both clinical and non-clinical populations, and the age ranges for which they were intended.

2.3.1.1. Social Communication Questionnaire

The Social Communication Questionnaire (SCQ) is a standardised screening tool for ASD (Rutter, Bailey, & Lord, 2003). This 40-item, parent-report questionnaire was developed as a companion screening measure for the Autism Diagnostic Interview-Revised (ADI-R, Couteur et al., 1989) and, as such, is closely aligned to the diagnostic criteria of The Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV; American Psychiatric Association, 2000) and The International Classification of Diseases (10th ed.; ICD-10; World Health Organisation, 1992).

Originally designed to assess degree of autistic symptomology in children aged 4 years and above, the application of the SCQ has since been extended to include children as young as 2 years of age, contingent on age-appropriate intellectual ability levels. In terms of its output, the SCQ generates a total score indicative of general autistic trait severity, and three sub-scores reflecting the triadic conceptualisation of ASD that was dominant at the time of its development. A total cut-off score of 15 is generally considered indicative of ASD (Rutter et al., 2003). The reliability and sensitivity of the SCQ is well-documented, with the caveat of low specificity (e.g., Allen, Silove, Williams, & Hutchins, 2007).

In the current project, the Lifetime version of the SCQ was administered to parents/primary caregivers of all participants. This version addresses a child's entire developmental history, in contrast with the Current version which examines children's behaviour in the context of the previous 3 months (Rutter et al., 2003).

2.3.1.2. Social Responsiveness Scale, Second Edition

Parents/caregivers of participants aged 4 years and above received the school-aged version of the Social Responsiveness Scale, second edition (SRS-2; Constantino & Gruber, 2012). The parents/caregivers of younger children received the pre-school version of the questionnaire. The SRS-2 is a 65-item parent-report questionnaire that provides a dimensional measure of autistic trait severity. Total scores index degree of impairment with scores in the range of 60 and 65 signalling mild to moderate deficits, and scores of 66 and higher signalling clinically significant levels of impairment (Constantino & Gruber, 2012). Total scores may be sub-divided and considered in reference to five subscales: social awareness, social cognition, RRB, communication and social motivation. The SRS-2 is both a validated screening tool for ASD and a validated measure of autistic trait expression in non-clinical populations (Bölte, Poustka, & Constantino, 2008; Moody et al., 2017; Wigham, McConachie, Tandos, & Le Couteur, 2012). Strong internal consistency (Cronbach's α = .95) and high sensitivity and specificity values (both .92) have been documented (for test review, see Bruni, 2014).

2.3.1.3. Repetitive Behaviour Questionnaire, Second Edition

The Repetitive Behaviour Questionnaire, second edition is a 20-item questionnaire that measures the frequency and severity of a wide range of RRBs (RBQ-2; Honey, McConachie, Turner, & Rodgers, 2012; Leekam et al., 2007). Each item is scored on a 3 or 4-point Likert scale, with higher scores indicating an increased rate and severity of

RRB. Total RBQ-2 scores may be broken down and considered in reference to four symptomatic sub-domains: unusual sensory interest, repetitive motor movement, rigidity/adherence to routine and preoccupation with restricted patterns of interest. The RBQ-2 is a validated measure of RRB expression for both NT children (Arnott et al., 2010; Leekam et al., 2007) and children with idiopathic ASD (Lidstone et al., 2014), with reports of good internal consistency for total RBQ-2 scores in reference to both (Cronbach's α = .85 and .86 respectively).

2.3.2. Standardised Behavioural Assessment

All participants were engaged in a behavioural assessment that incorporated the following standardised measures. These measures were selected on account of their well-cited suitability for use with clinical populations characterised by high rates of intellectual disability.

2.3.2.1. Leiter International Performance Scales, Third Edition

The Leiter International Performance Scales, third edition (Leiter-3) is a norm-referenced measure of non-verbal intelligence (Roid, Miller, Pomplun, & Koch, 2013). Administered non-verbally, this measure is specifically designed to cater for individuals with ASD, intellectual disability and attentional deficit.

A cognitive battery of four subtests are administered to generate non-verbal intelligence quotient (IQ) scores. These subtests are: (1) figure ground (i.e., identifying embedded figures within complex pictorial stimuli), (2) form completion (i.e., recognising 'whole objects' from fragmented visual representations, (3) classifications/analogies (i.e., object and/or geometric design classification, followed by classical matrix analogies), and (4) sequential order (i.e., pattern completion). Scores for each sub-test are added to

generate total raw score values which may be cross-referenced with chronological age data to generate standardised composite IQ scores.

2.3.2.2. British Picture Vocabulary Scales, Third Edition

The British Picture Vocabulary Scales, third edition (BPVS-3) is a standardised measure of receptive vocabulary designed for use with children between the ages of 3 and 16 years of age (Dunn, Dunn, & Styles, 2009). The task requires participants to demonstrate their comprehension of a variety of spoken words by selecting the correct corresponding image from a selection of four. The BPVS-3 provides a raw score of receptive language ability, in addition to an age-normed verbal IQ composite score. It is a well-cited means of indexing verbal abilities in both clinical and non-clinical populations (e.g., Annaz, Karmiloff-Smith, Johnson, & Thomas, 2009; Conti-Ramsden & Durkin, 2012; Currie & Cain, 2015).

2.3.2.3. Autism Diagnostic Observation Schedule, Second Edition

The Autism Diagnostic Observation Schedule, second edition (ADOS-2) is a semi-structured standardised assessment of autistic symptomology (Lord, Luyster, Gotham, & Guthrie, 2012; Lord, Rutter, DiLavore, Risi, Gotham, & Bishop, 2012). There are five administrative module options, each of which is designed to cater for different chronological ages and different levels of expressive language ability. The ADOS-2 is often employed as a diagnostic tool in clinical contexts to facilitate and inform the decision-making process (Kanne, Randolph, & Farmer, 2008). In the current project, it was used as a means of confirming the presence of ASD in children carrying an idiopathic or syndromic ASD diagnostic label and, equally, to confirm the absence of ASD within the NT sample.

Participants in the current study received modules 1, 2 and 3: module 1 was administered to individuals aged 31 months and older in the absence of phrase speech; module 2 was administered to children presenting with flexible phrase speech; and module 3 was administered in cases of verbal fluency. All modules encompassed a variety of activities, each designed to elicit developmentally appropriate signatures of socio-communicative ability. The psychometric properties for the ADOS-2 were recently reviewed by Dorlack, Myers and Kodituwakku (2018). According to their data, pooled sensitivity estimates for these modules 1, 2 and 3 were .89, .83 and .82, respectively, while pooled specificity estimates were .71, .84 and .72, respectively.

All ADOS-2 assessments were administered, recorded and coded/scored by the author who received formal administration and coding training (Nov 30th – Dec 4th, 2015; BeginningwithA: Autism Consultancy and Training; Oxford, England).

2.3.3. Concordance between Measures of Autistic Trait Expression

Multiple measures were employed to collect data in relation to autistic trait expression. These were the SRS-2, the RBQ-2, the SCQ and the ADOS-2 (see Tables 2.3 and 2.4). The two primary output measures that feature in this thesis are the SRS-2 and RBQ-2. The SRS-2 was selected in consideration of my research questions and planned statistical analyses (Section 2.4); it provides a broader dimensional scale than the SCQ and the ADOS-2 with regard to autistic trait severity. The RBQ-2 was selected to compliment the SRS-2, which is skewed in the degree to which it captures the social and non-social features of ASD; despite representing one half of the phenotypic dyad, RRB severity accounts for only 20% of variance in total SRS-2 scores. The RBQ-2 was required to capture RRB expression more comprehensively.

Table 2.3.

Means and Standard Deviations of Total Scores from all Autistic Trait Measures

	ADOS-2	**SRS-2**	**SCQ**	**RBQ-2**
NT *M(SD)*	3.5 (2.8)	46.1 (6.3)	6.1 (4.1)	26.2 (5.2)
ASD *M(SD)*	13.3 (5.6)	76.5 (12.8)	24.7 (8.4)	35.6 (8.4)
DS *M(SD)*	11.2 (6.6)	66.8 (14.1)	14.8 (10.6)	33.1 (11.3)
FXS *M(SD)*	10.1 (2.1)	72.3 (11.3)	19.4 (10.3)	33.0 (6.4)

Table 2.4.

Means and Standard Deviations of Total Scores from all Autistic Trait Measures for children with DS+/-ASD and FXS+/-ASD

	ADOS-2	**SRS-2**	**SCQ**	**RBQ-2**
DS+ASD *M(SD)*	17.4 (5.4)	77.7 (12.2)	24.7 (5.3)	40.6 (10.8)
DS-ASD *M(SD)*	0.7 (2.3)	57.3 (7.1)	6.1 (3.9)	25.7 (5.7)
FXS+ASD *M(SD)*	10.5 (1.0)	67.0 (17.1)	20.5 (12.0)	33.0 (11.3)
FXS-ASD *M(SD)*	10.0 (2.3)	74.4 (9.9)	19.0 (11.1)	33.0 (5.4)

To evaluate the concordance between these four measures of autistic trait expression, correlation coefficients were generated (see Table 2.5). Within the complete dataset, significant positive correlations emerge between the total score data derived from each measure. Correlation coefficients are presented for each participant cohort for reference. It is important to note that these analyses are differentially powered on account of varying sample sizes. It is also worth noting that ADOS-2 total score data is limited to a scale of 0-10; low variability within each cohort is likely to have impacted the results.

Table 2.5.

Correlation Coefficients for Indices Autistic Trait Severity

		ADOS-2	SRS-2	SCQ	RBQ-2
ALL	ADOS-2	1	.71**	.69**	-.49**
	SRS-2		1	.91**	.76**
	SCQ			1	.74**
	RBQ-2				1
NT	ADOS-2	1	.15	.21	.15
	SRS-2		1	.65**	.60**
	SCQ			1	.65**
	RBQ-2				1
ASD	ADOS-2	1	.41	.23	.13
	SRS-2		1	.77**	.67**
	SCQ			1	.48
	RBQ-2				1
DS	ADOS-2	1	.34	.62*	.37
	SRS-2		1	.89**	.81**
	SCQ			1	.78**
	RBQ-2				1
FXS	ADOS-2	1	.51	.72	.51
	SRS-2		1	.89**	.75
	SCQ			1	.75
	RBQ-2				1

Note: * p <.05, ** p <.001.

Cohen's kappa values were generated to look at the agreement between the ADOS-2, SRS-2 and SCQ in terms of their ability to differentiate children who had received clinical diagnoses of ASD from non-ASD cases. According to the results, there was substantial agreement (.84) between clinical diagnostic status and ADOS-2 cut-off data within the complete dataset; $\kappa = .65$, $p<.001$. Agreement within each participant cohort was as follows: NT: 91%, ASD: 93%, DS:87% FXS: 29%. While only 2 of the total

number of children with FXS (*n*=7) carried formal clinical ASD diagnoses, all reached ADOS cut-offs for ASD, hence the low level of agreement observed here.

Next, concordance estimates were evaluated between clinical diagnostic status and the SRS-2 cut-off for ASD (total scores ≥ 75). There was substantial agreement within the complete dataset (.86); $\kappa = .62$, $p<.001$. For each participant cohort, percentage agreement was as follows: NT: 100%, ASD: 100%, DS:87% FXS: 43%. Three of the five children classified as FXS-ASD received a total score of 75 or above on the SRS-2, hence the low level of agreement.

Finally, concordance between clinical diagnostic status and the SCQ (total scores ≥ 15) was evaluated. According to the results, agreement was excellent (.91); $\kappa = .78$, $p<.001$. Percentage agreement in each participant cohort was as follows: NT: 100%, ASD: 100%, DS:100% FXS: 29%. Within the FXS cohort, 3 of the 5 children classified as FXS-ASD received a total score of 75 or above on the SRS-2. For a discussion on the theoretical and clinical significance of these concordance estimates, see Section 7.5.

2.3.4. Eye-Tracking Paradigms

All participants engaged in a 12-minute eye tracking session. They were seated in front of a 23-inch Liquid-crystal display (LCD) monitor at a distance of 60 cm. Children were seated either in close proximity to, or on the lap of, their parent/caregiver. In the case of the latter, the parent/caregiver in question was instructed to keep their eyes closed for the duration of the session to ensure that the system collected data from the participating child only.

Before commencing with the data collection, an operator-controlled calibration was run. This consisted of coloured spirals that expanded and contracted in each of the four corners, and in the centre, of the screen. A ‘boing’ sound accompanied the onset of each

of these spirals. Following this brief five-point calibration, participants were presented with a battery of eye-tracking tasks. Data were collected using a Tobii TX300 eye tracking system. A webcam was used to monitor behaviour and sessions were video recorded for prospective analytic reference.

2.3.4.1. Gap-Overlap

Used in the study of attentional orienting, gap-overlap paradigms function by measuring SRT from a central to a peripheral stimulus (Fischer & Breitmeyer, 1987; Saslow, 1967). The current gap-overlap task (adapted from Elsabbagh et al., 2013; Landry & Bryson, 2004) was obtained through collaborative engagement with members of the British Autism Study of Infant Siblings (BASIS) consortium. For this task, participants observed a gaze-contingent central stimulus (i.e., a dynamic colourful clock) that, when fixated upon, was replaced by a peripheral target (i.e., a white cloud); these stimuli were unchanging (see Figure 2.1). The peripheral target was presented randomly either to the left or to the right of the central fixation stimulus at an eccentricity of 19° and was gaze-contingent for 2.5 seconds. After this brief period and/or when the target peripheral stimulus was fixated upon, each white cloud was replaced with an attractive animation (e.g., dog, teddy, star) accompanied by a rewarding sound effect (e.g., a car horn, an exclamation of 'yeow!')

This gap-overlap task consisted of 60 trials presented in blocks of 12 and featured three trial types or conditions. In *baseline* trials, the central stimulus disappeared as a peripheral stimulus simultaneously appeared. In *gap* trials, a 200ms inter-stimulus interval separated the offset of the central stimulus from the onset of the peripheral stimulus. Finally, in *overlap* trials, the central stimulus remained on screen, overlapping in time with the peripheral stimulus.

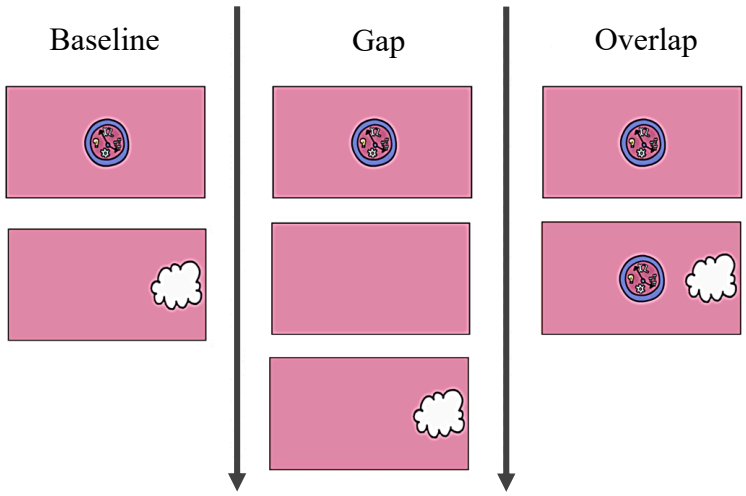

Figure 2.1. Gap-overlap task stimuli and trial types/conditions. Gap trials are characterised by a 200ms temporal delay in peripheral target onset.

A minimum of 6 valid trials per condition was necessary in order for data to be retained in subsequent analyses (Table 2.6). Trials were considered valid according to several criteria: (1) data quality was acceptable to form SRT estimates; (2) there were no periods of missing data greater than 200ms following central fixation or 50ms on either side of the peripheral stimulus onset; (3) gaze did not move in the opposite direction after leaving the central stimulus, and (4) SRT was between 150ms and 1200ms. Any trials in which these criteria were not met were excluded from subsequent analysis.

With regards task output, mean disengagement latency/SRT data in milliseconds (ms) were obtained for each of these three conditions. In addition, calculating the mean SRT difference between baseline and overlap trials provided a difference value often referred to as a DIS effect. Larger DIS effect sizes were considered an index of greater disengagement difficulty on baseline-corrected overlap trials. Moreover, a FAC effect was quantified by calculating the mean SRT difference between baseline and gap trials.

Larger FAC effect sizes reflected increased temporal facilitation in terms of disengagement efficiency on gap relative to baseline trials.

Table 2.6.
Number of Trials and Mean Reaction Times Retained for Analysis

		Valid Trials				**Serial Reaction Time (ms)**		
		Baseline	Gap	Overlap	Total	Baseline	Gap	Overlap
	n	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
NT	47	15.1 (2.4)	15.3 (2.6)	14.6 (2.7)	45.0 (6.2)	314 (51)	254 (46)	354 (74)
ASD	13	15.8 (2.5)	13.3 (3.2)	13.8 (3.3)	42.9 (8.0)	265 (38)	233 (44)	320 (77)
FXS	6	15.8 (2.2)	14.8 (1.7)	12.7 (2.1)	43.3 (4.5)	306 (38)	230 (42)	345 (97)
DS	10	13.6 (2.8)	11.5 (2.7)	12.6 (3.5)	37.7 (8.3)	302 (60)	286 (43)	375 (106)
Overall	83	15.1 (2.5)	14.5 (3.0)	14.1 (3.0)	43.7 (7.1)	297 (47)	251 (44)	349 (89)

2.3.4.2. Visual Search

The visual search task employed here was designed to assess the speed at which participants could visually locate a target stimulus amidst a number of distractor stimuli (adapted from Kaldy et al., 2011; Treisman & Gelade, 1980). Additionally, it was designed to illustrate the special status of the target stimulus implicitly (i.e., in the absence of any verbal instruction).[21]

Here, participants were presented with 20 visual search trials/displays; each featured a target stimulus (i.e., a red apple) and one or two kinds of distractor stimuli (i.e., blue

[21] Kadly and colleagues (2011) designed this task with an aim to catering for children with weak receptive language abilities. The task establishes the target status of the red apple, nonverbally, by (1) using a familiar object (i.e., red apple), (2) incorporating visual pop-out effects, (3) using the target in pre-trial animations that direct attention to the centre of the screen, and (4) by ending each trial with a rewarding spinning animation. In their pilot study, Kaldy and colleagues (2011) confirmed that both children with ASD and NT controls noted the special status of the target according to longer look durations relative to distractor stimuli.

apples and red rectangles. Prior to the onset of the task, participants were instructed to 'find the red apple'. While the task was designed to cater for children with low levels of receptive language, the verbal instruction was provided as an additional participatory aid.

Of the total number of trials, eight were single feature and twelve were conjunction. Single feature search trials were presented as set size 5 or 9 in equal amount and in random order (Figure 2.2). Conjunction search trials were presented as set size 5, 9 or 13 in equal amount and in random order (Figure 2.3).

Prior to the onset of each trial, participants were presented with a central fixation point (i.e., a cross) which remained on screen for one second and was then replaced by the target stimulus (i.e., the red apple) for 2 seconds. This pre-trial presentation of the target stimulus was intended by the authors who designed the paradigm (Kaldy et al., 2011) to establish the special status of the red apple prior to the onset of each search display. The primary output variable for this task was target detection latency (i.e., the time taken to locate/fixate upon the target stimulus from the initial presentation of the display). Each search display remained on screen for a maximum of 4 seconds, or until the target stimulus (i.e., the red apple) was fixated upon. Missing visual search data were recorded for only one participant on account of a skewed calibration; this was a NT child, dropping the sample size to forty-nine in subsequent visual search analyses.

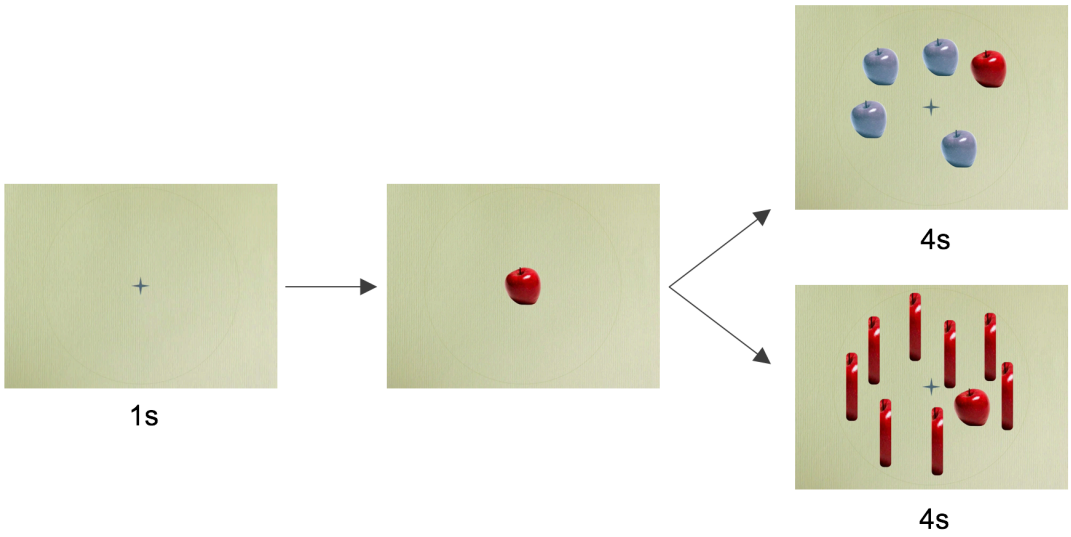

Figure 2.2. Visual representation of stimulus presentation for single feature search trials, with a sample display for each set size (5 and 9).

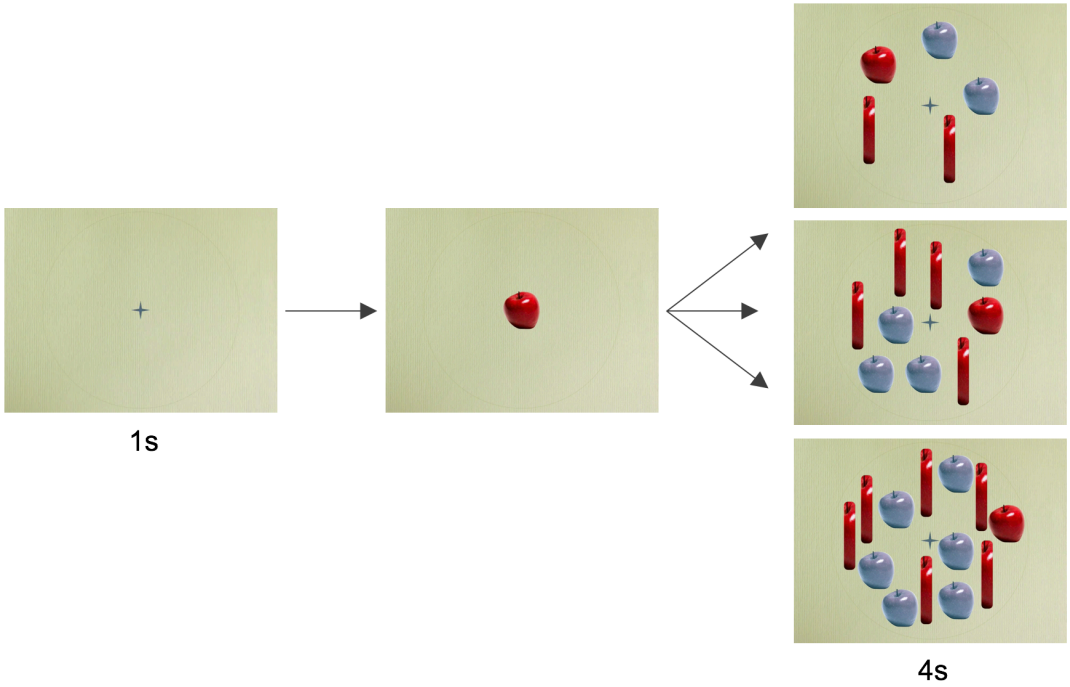

Figure 2.3. Visual representation of stimulus presentation sequence for conjunction search trials, with sample displays for all set sizes (5, 9 and 13).

2.4. Planned Statistical Analyses

Data were plotted and analysed using Microsoft Excel and IBM SPSS software (version 24), respectively. Statistical test selection was informed by whether or not parametric test assumptions were met within and across participant groups.

Bivariate and partial correlation analyses were applied to the data to explore linear associations as informed by the primary research questions outlined in Chapter 1. Cross-sectional trajectory analyses were employed to further examine performance trajectories within and between-groups in relation to one another (Thomas et al., 2009). This method was akin to standard analyses of variance (ANOVA), but instead of testing group mean differences, performance was examined in relation to linear intercepts and gradients.

Trajectories were plotted for all key visuo-perceptual outputs according to intellectual ability and autistic trait severity. Independent samples t-tests and univariate ANOVA's were employed to assess mean group differences in attentional disengagement and visual search performance. Group comparisons were reported with an understanding that at times they carried limited weighting; for instance, on account of a small FXS sample. These were complemented by a case series approach in which performance profiles were examined at the level of the individual.

This chapter detailed the participant samples, measures and procedures, and planned statistical analyses of the research presented hereafter. The following chapter presents the first of four eye-tracking studies, examining the visuo-perceptual processes underpinning autistic trait variation in children with idiopathic ASD relative to NT controls matched on intellectual ability.

Chapter 3: Visuo-Perceptual Markers of Idiopathic ASD in Middle Childhood

3.1. Overview

Visuo-spatial orienting difficulties and strengths in visual search performance have been implicated in the emergence and early phenotypic expression of idiopathic ASD. There is, however, ongoing uncertainty surrounding the nature and presence of these visuo-perceptual irregularities in mid to late childhood.

This chapter details an eye-tracking study in which visual orienting and search abilities are examined in a novel cohort of children with idiopathic ASD (n=16) and NT controls matched on indices of intellectual ability (n=50). Based on the previous literature, it was hypothesised that children with idiopathic ASD would demonstrate less efficient visuo-spatial orienting according to performance on a gap-overlap task, and a phenotypic advantage on a visual search task as evidenced by shorter target detection latencies.

According to the results, target detection latencies were significantly reduced on conjunction search trials in children with idiopathic ASD; moreover, this phenotypic advantage was greater in those who rated more highly on measures of symptom severity. Contrary to my original hypotheses, children with idiopathic ASD were quicker to orient visually in response to peripheral target onset on baseline trials of the gap-overlap task. Within the NT sample, higher overlap SRTs were associated with increased autistic trait expression; this association was moderated by chronological age. Finally, inquiry into the relationship between attentional disengagement and visual search abilities revealed a significant three-way interaction effect reflecting a unique profile in children with idiopathic ASD; higher SRS-2 scores were associated with decreased FAC effect sizes and decreased conjunction search latencies.

This chapter details the visuo-perceptual profile associated with autistic trait variation in the current sample of children with idiopathic ASD and in doing so, sets the necessary foundation for subsequent comparative analyses incorporating DS and FXS datasets.

3.2. Introduction

Beyond clinical classification, idiopathic ASD is characterised by a wide range of visuo-perceptual irregularities. Visuo-spatial orienting deficits are particularly well documented (Sacrey et al., 2014). Longitudinal, prospective analyses of early visual orienting abilities in infants at familial risk of idiopathic ASD have documented attentional disengagement deficits in those who progress to a clinical diagnosis (Elsabbagh et al., 2013; for review, see Keehn et al., 2013). In older children (5-year-olds) with idiopathic ASD, Landry and Bryson (2004) reported significantly increased disengagement latencies/SRTs on overlap trials of a gap-overlap task compared to children with DS of a similar chronological and mental age and younger mental age-matched NT controls. Similarly, higher mean SRTs on baseline-corrected overlap trials have been documented in 6-year-olds with ASD relative to NT controls matched on both age and intellectual ability (Kleberg et al., 2017). These findings suggest that idiopathic ASD at these ages are associated with difficulties disengaging and shifting attention in contexts of competing visual stimuli.

More recently, Wilson and Saldaña (2018) administered a gap-overlap task to 7-year-olds with idiopathic ASD and noted increased mean SRT on gap trials only relative to age-matched NT controls. This was interpreted by the authors as reflecting an increased susceptibility to the cueing effects of stimulus offset at this age. Other studies have recorded increased disengagement latencies in older children and adolescents with idiopathic ASD across all gap-overlap trial types (i.e., baseline, gap and overlap) suggesting a gross disengagement deficit relative to NT controls (Goldberg et al., 2002;

Todd et al., 2009). By contrast, a number of studies have documented equivalent SRTs on gap-overlap paradigms in children with and without idiopathic ASD (Fischer et al., 2014, 2016; Van der Geest et al., 2001).

While there is evidence to suggest that disengagement deficits are a robust visuo-perceptual marker of ASD in infancy and early childhood, the literature is mixed with regard to the presence and nature of these difficulties in later years (Sacrey et al., 2014). It may be the case that the nature of the relationship between visuo-spatial orienting efficiency and phenotypic outcome changes with chronological age. It is possible, for instance, that visuo-spatial orienting abilities in idiopathic ASD develop according to an extended maturational timeline on account of early disruption to corresponding brain systems. This would mean that while visual orienting deficits are apparent in the early years, children with idiopathic ASD might eventually reach NT levels of visuo-spatial orienting via compensatory mechanisms or, if the system was delayed, developmental catch-up. As a result, older children with idiopathic ASD may be expected to perform similarly to their NT peers on gap-overlap paradigms.

Additionally, inconsistencies in the literature are likely due, at least in part, to variations in methodology and task design between studies. Disengagement latencies on gap-overlap tasks are known to be influenced by the featural properties (i.e., salience) of the stimuli employed (e.g., Blakely, Wright, Dehili, Boot, & Brockmole, 2012; Theeuwes, 2010), and there is research to suggest that idiopathic ASD is associated with a hyper-sensitivity to variations in stimulus saliency (Chevallier et al., 2015; Sasson, Elison, Turner-Brown, Dichter, & Bodfish, 2011). Greater methodological consistency is necessary to facilitate progression towards a more consistent account of visual orienting abilities in paediatric cases of idiopathic ASD. Moreover, examining visuo-spatial orienting abilities in the context of the broader visuo-perceptual profile that has been

documented in children with idiopathic ASD would likely advance our current understanding of this complex neurodevelopmental disorder. It is difficult, for instance, to reconcile visuo-spatial orienting deficits in idiopathic ASD with the phenotypic advantage on visual search tasks that has been reported in the literature.

Visual search is another task domain in which visuo-spatial orienting in individuals with idiopathic ASD manifests atypically (Dakin & Frith, 2005; Simmons et al., 2009). However, contrary to the early disengagement deficits observed on gap-overlap tasks, infants at high familial risk of idiopathic ASD have been shown to outperform their low-risk peers, in association with ASD trait levels at 24 months of age (Gliga et al., 2015) and clinical diagnostic status at 32 months of age (Cheung et al., 2018). These studies provide support for the notion that enhanced visual search abilities are intrinsically linked to the emergence of the phenotype.

Plaisted, O'Riordan and Baron-Cohen (1998) were the first to document superior visual search performance in children with idiopathic ASD. They administered a visual search task to 8-year-olds and found that, relative to a NT group matched on age and verbal ability, children with ASD were quicker to detect target stimuli on conjunction search trials. Of note, these groups differed significantly in terms of non-verbal mental age according to the block design sub-test of the Wechsler Intelligence Scale for Children (Wechsler, 1974); children with idiopathic ASD outperformed the NT controls on this measure, again illustrating a phenotypic advantage on tasks that draw on visuo-spatial abilities.

Conversely, O' Riordan (2000) administered a visual search task to 9-year-olds with idiopathic ASD and found that, relative to NT controls matched on chronological age

and non-verbal intellectual ability,[22] no phenotypic advantage emerged on conjunction trials involving the identification of present target stimuli. However, superior performance was noted on more difficult trials that required the identification of absent target stimuli.

In another study, Jarrold, Gilchrist and Bender (2005) recorded decreased target detection latencies (improved performance) on both single feature and conjunction search trials in an ASD cohort spanning 8 to 15 years of age. However, these differences emerged in reference to a significantly younger NT control group; age-related maturational effects may have influenced this result. No evidence of a phenotypic advantage was documented in a subsequent study looking at visual search efficiency in adolescents with and without ASD when groups were matched according to both age and non-intellectual ability, as derived from the second edition of the Kaufmann Brief Intelligence Test (Joseph, Keehn, Connolly, Wolfe, & Horowitz, 2009; Kaufmann & Kaufmann, 2004).

Kadly and colleagues (2011) designed and administered a visual search task that required no verbal instruction to toddlers with ASD and age-matched NT controls. Performance was assessed according to children's success rate in locating the target stimulus presented in each four-second search trial. They found that ASD status at this age was associated with superior performance on conjunction search trials. Moreover, this group differentiation was found to broaden with increasing set size; the greater the number of distractor items in a given conjunction search trial, the greater the observed phenotypic advantage in cases of idiopathic ASD. Further inspection of these data showed that children with idiopathic ASD scanned a greater number of items per search

[22] Non-verbal intelligence was indexed according to performance on the Raven's Coloured Progressive Matrices (Raven 1956; Raven, 2000).

trial than their NT counterparts. This was interpreted by the authors as reflecting enhanced perceptual discrimination allowing for more efficient guided search (O'Riordan & Plaisted, 2001; Wolfe, Cave, & Franzel, 1989), rather than a faster-paced serial scrutiny of conjunction search items.

A number of theoretical models have been proposed to account for enhanced visual search performance in idiopathic ASD populations (see Section 1.5.4). Liss and colleagues (2006) proposed that early irregularities in the development of a child's alerting system may result in an overly-focused attentional style or increased signal-to-noise ratio. They maintained that this is likely to facilitate superior processing of stimulus features at the locus of attention which may, in turn, manifest as superior visual search performance. Empirical support for this claim came, subsequently, from eye-tracking studies showing that children and adolescents with idiopathic ASD exhibit shorter fixation latencies on search items relative to NT controls (Joseph et al., 2009; Brandon Keehn et al., 2009). Furthermore, visual search performance has been found to evoke significantly increased pupillary dilation in toddlers with idiopathic ASD relative to age-matched NT controls (Blaser et al., 2015). Pupillary responsivity is considered by many to be a sensitive index of arousal and attentional engagement (Hess & Polt, 1960; Jackson & Sirois, 2009; Kahneman & Beatty, 1966); hence, the authors concluded that superior visual search performance in idiopathic ASD manifests on account of a highly focused visuo-perceptual style, as opposed the employment of alternative search strategies.

Keehn and colleagues (2013) introduced the notion that disengagement deficits early in development are a potential means through which an infant's ability to self-regulate is disrupted, resulting in a narrowing of their visuo-attentional spotlight and a consequential advantage on visual search tasks (see Section 1.6). This theoretical

account of phenotypic emergence is attractive in that it bridges the apparent dichotomy between disengagement difficulties and enhanced visual search performance in idiopathic ASD. Moreover, it yields a testable hypothesis: if both visuo-perceptual phenotypic features share a common underlying mechanism – an increased signal-to-noise ratio – performance profiles on visual search tasks will vary according to gap-overlap indices of visual orienting ability.

In sum, visual orienting deficits and superior search performance have been implicated in the early emergence and expression of idiopathic forms of ASD. In mid to late childhood, however, the literature is mixed. Progression towards a comprehensive account of visuo-perceptual irregularity in ASD is hindered by the empirical study of each phenomenon in isolation to date, and by the limited methodological overlap that is featured in the literature.

3.2.1. The Current Study

The current study utilised eye-tracking paradigms commonly cited in the ASD literature to examine visual orienting and search abilities in a novel cohort of 6- to 11-year-olds with idiopathic ASD relative to a younger NT cohort matched according to non-verbal intellectual ability. The contribution of verbal and non-verbal intelligence factors was examined in reference to idiopathic and NT forms of autistic trait expression, according to the BPVS-3 and Leiter-3 respectively. This was intended to facilitate the characterisation of clinical and non-clinical manifestations of socio-communicative impairment and RRB.

The decision to match groups according to non-verbal intellectual ability and not chronological age was based on the profile of the current idiopathic ASD cohort which was low functioning (for verbal and non-verbal IQ scores, see Table 2.1); in such instances, indices of non-verbal intellectual ability are considered a better predictor of

general cognitive ability than chronological age (Weiss, Weisz, & Bromfield, 1986). This was intended to ensure that differences on outcome variables could not be attributed to differences in general cognitive ability between the two groups. Non-verbal intelligence was indexed here according to performance on the Leiter-3. The use of this standardised measure of visuo-spatial ability was in keeping with the opinion that clinical groups characterised by specific areas of strength and weakness should be matched to NT controls on a domain of functioning that is relevant to target tasks (Burack, Iarocci, Flanagan, & Bowler, 2004; Thomas et al., 2009).

In terms of original hypotheses, children with idiopathic ASD were expected to exhibit deficits in visuo-spatial orienting; moreover, greater levels of disengagement difficulty were anticipated in children exhibiting more severe symptomatic profiles. Similarly, in terms of visual search performance, significant group differences were anticipated as children with idiopathic ASD were expected to demonstrate decreased target detection times on conjunction search trials; group differences have emerged more consistently in the literature for conjunction search, as opposed single feature search, performance, particularly in older children (e.g., Joseph et al., 2009; O'Riordan et al., 2001). Within the idiopathic ASD cohort, a significant negative association was anticipated between search latency and symptom severity. In line with dimensional phenotypic perspectives, indices of autistic trait expression within the current NT sample were expected to vary according to similar visuo-perceptual processes. Finally, in keeping with the notion of a common underlying mechanism (e.g., an increased signal-to-noise ratio), a relationship was anticipated between performance indices on gap-overlap and visual search paradigms.

3.3. Method

3.3.1. Participants

Sixteen children with a clinical diagnosis of idiopathic ASD and fifty NT children were recruited to take part in the current study (for details concerning recruitment process and inclusion criteria, see Chapter 2). Demographic data for both groups are presented in Table 3.1 with *t*-test coefficients corresponding to significant and non-significant group differences for variables of interest, all of which are detailed in the following section.

Table 3.1

Descriptive Statistics by Group and associated T-test Coefficients

	ASD		**NT**			
	n	*M (SD)*	*n*	*M (SD)*	*t*	*p*
Age $_{years}$	16	8.5 (1.6)	50	4.6 (1.6)	8.2	< .001
Leiter-3 Raw Scores	16	56.4 (22.3)	50	53.8 (18.4)	.47	.64
BPVS-3 Raw Scores	16	51.2 (29.7)	50	60.4 (30.1)	-1.1	.29
RBQ-2 Total Scores	15	35.6 (8.4)	49	26.2 (5.2)	4.1	.001
SRS-2 Trait Scores	15	76.5 (12.8)	48	46.1(6.3)	8.9	< .001

3.3.2. Measures and Procedure

Measures and data collection procedures were as previously described in Chapter 2. Data collection took place at the Birkbeck Babylab, CBCD. All testing sessions comprised an 80-minute behavioural assessment, followed by a 15-minute eye-tracking session. Prior to this, parents were briefed and written participatory consent was acquired.

Verbal intelligence was evaluated using the BPVS-3 (Dunn et al., 2009) and non-verbal intelligence was assessed using the Leiter-3 (Roid et al., 2013). The SRS-2 was employed as a dimensional measure of ASD trait severity; this has been established in the literature as a useful means of quantifying non-clinical trait variation (Bölte et al., 2008; Constantino & Gruber, 2012; Constantino & Todd, 2003; Takei et al., 2014). As the SRS-2 is predominantly concerned with the socio-communicative features of the phenotype, the RBQ-2 was incorporated as a means of considering rate and severity of RRB (Leekman et al., 2007).

All participants engaged in an eye-tracking session that featured two paradigms previously employed to differentiate idiopathic ASD from non-ASD populations: gap-overlap (adapted from Elsabbagh et al., 2013; Landry & Bryson, 2004) and visual search (adapted from Kaldy et al., 2011; Treisman & Gelade, 1980). As described in Chapter 2, the gap-overlap task provides a measure of disengagement latency on baseline, gap and overlap trials, while the visual search task measures target detection latencies on single feature and conjunction search trials.

3.3.3. Statistical Analyses

Shapiro-Wilks tests were run to check that data were normally distributed. Examination of skew and kurtosis values, in addition to the test output, revealed significantly positively skewed distributions for three variables: chronological age, Leiter-3 raw scores and total RBQ-2 scores. Log10 transformations were applied to improve the distribution of these data for analysis. Graphical illustrations of inferential outputs and references to raw data present these data as they were pre-transformation.

Mixed-design ANOVAs were conducted to analyse SRT and visual search data within and between idiopathic ASD and NT cohorts. A trajectory analysis approach (Thomas et al., 2009) was employed to examine autistic trait variation within and between-groups according to indices of intellectual function and visuo-perceptual ability. Performance trajectories were analysed in terms of the intercepts and gradients via a modified version of the traditional Analysis of Covariance (ANCOVA). For each analysis, the x-axes were re-scaled to ensure all main effects were calculated at the first point of group overlap and, of note, each ANCOVA model featured chronological age as a co-variate. In cases of multiple comparisons, statistically significant effects were considered against a Bonferroni corrected significance level.

3.4. Results

3.4.1. Autistic Trait Expression according to Indices of Verbal and Non-Verbal Intelligence

Bivariate correlation analyses were conducted to examine whether higher autistic trait levels were associated with lower verbal and non-verbal abilities, according to the BPVS-3 and Leiter-3 respectively, in NT and ASD cohorts. The results revealed that higher levels of autistic trait severity, according to both the RBQ-2 and SRS-2, were associated with lower Leiter-3 scores in NT children only (Table 3.2). Similarly, higher RBQ-2 scores were associated with lower raw BPVS-3 scores but only within the NT sample. No associations emerged between total SRS-2 scores and children's receptive language ability according to the BPVS in either cohort (Table 3.2).[23] When each significant association within the NT cohort was entered into partial correlation analyses controlling for differences in chronological age; only the significant association between SRS-2 and raw Leiter-3 scores remained (r =.50, p <.001).

Table 3.2.

Correlation Coefficients for Indices of Intellectual Ability and Autistic Trait Severity

		Leiter-3	BPVS-3	RBQ-2	SRS-2
NT	Leiter-3	1	.88**	-.44(**)	-.35*
	BPVS-3		1	-.43(**)	-.18
	RBQ-2			1	.68**
	SRS-2				1
ASD	Leiter-3	1	.76**	-.06	-.19
	BPVS-3		1	-.06	-.28
	RBQ-2			1	.58*
	SRS-2				1

Note: * p <.05, ** p <.001, (**) No longer significant when chronological age was partialled out.

[23] It is important to note that the absence of reliable effects in the idiopathic ASD cohort may be linked to the fact that the group is 3 times smaller than the NT cohort, thereby generating reduced statistical power.

3.4.2. Disengagement Latencies in Idiopathic ASD and NT Cohorts

Group differences in disengagement latency/SRT as derived from the gap-overlap task were examined using a 3 x 2 mixed-design ANOVA. The within-subjects factor was trial type (baseline, gap and overlap) and the between-subjects factor was group (NT and ASD). The results revealed a main effect of trial type; F (2, 116) = 50.13, $p < .001$, $\eta^2 = .46$. Bonferroni post-hoc tests revealed SRT differences in a manner in keeping with the literature; mean SRT was significantly increased on overlap relative to gap and baseline trials, and significantly reduced on gap relative to baseline and overlap trials (for mean raw data per condition, see Table 3.3). No trial type × group interaction effect emerged [F (2, 116) = 1.12, $p = .33$] but a significant main effect of group was observed [F (1,58) = 2.62, $p = .02$, $\eta^2 = .09$]. Independent samples t-tests revealed significantly decreased mean SRT on baseline trials only in children with idiopathic ASD (mean difference: 48.92ms; see Table 3.3).

As the current cohorts differed significantly according to chronological age (Table 3.1), chronological age was included as a co-variate in an ANCOVA model featuring mean baseline SRT as the dependent variable and group (ASD and NT) as the fixed factor.[24,25] The results revealed a significant main overall effect of age [F (1,56) = 6.11, $p = .02$, $\eta^2 = .10$], but no significant group × age interaction effect [F (1,56) = .69, $p = .41$].

[24] Chronological age was mean centred in this and subsequent ANCOVAs so that intercept differences were tested at the group mean value.

[25] Age and SRT data were visually inspected to ensure appropriate linearity for ANCOVA modelling.

Table 3.3

T-test Coefficients for all Gap-Overlap Output Variables by Group

	NT	**ASD**			
	M (SD)	*M (SD)*	*t*	*p*	Cohen's *d*
Baseline SRT	314 (51)	265 (39)	3.20	.002	1.12
Gap SRT	254 (46)	233 (46)	1.47	.15	---
Overlap SRT	354 (74)	320 (81)	1.43	.16	---
FAC effect*	61 (50)	33 (33)	1.89	.06	---
DIS effect**	40 (60)	56 (79)	-0.77	.45	---

* Difference score calculated by subtracting mean gap SRT from mean baseline SRT.

** Difference score calculated by subtracting mean baseline SRT from mean overlap SRT.

3.4.3. Autistic Trait Expression according to Disengagement Latency

A series of modified ANCOVAs was run to examine within- and between-group variation in indices of autistic trait severity according to mean SRT data derived from the gap-overlap task. The fixed factor in each model was group (ASD and NT). Total SRS-2 scores were entered as the dependent variable. The co-variate in each model was the mean disengagement latency/SRT data for one of three gap-overlap conditions (i.e., baseline, gap and overlap).

With baseline SRT as the co-variate, there was a significant main effect of group [F (1, 53) = 70.19, p<.001, η^2=.57] reflecting higher total SRS-2 scores in children with ASD relative to NT controls (see Figure 3.1). There was no main effect of baseline SRT [F (1, 53) = 0.05, p=.82] and no group × SRT interaction effect; F (1, 53) = 0.43, p=.51.

Examining variability in total SRS-2 scores according to gap SRT revealed a main effect of group [F (1, 53) = 43.86, p<.001, η^2=.45] and a main effect of gap SRT [F (1, 53) = 4.55, p=.04, η^2=.08] but no group × SRT interaction effect; F (1, 53) = 1.31, p=.31. Similarly, examining variability in total SRS-2 scores according to overlap SRT

revealed a similar main effect of group [F (1, 53) = 42.40, p<.001, η^2=.44] and a main effect of gap SRT [F (1, 53) = 5.45, p=.02, η^2=.09] but no group × SRT interaction effect; F (1, 53) = 0.41, p=.53 (see Figure 3.1). Neither of the main of effect of gap SRT nor the main effect of overlap SRT remained significant when Bonferroni correction for multiple comparisons was applied.[26]

Similar analyses were conducted to assess trajectories of socio-communicative ability according to each derivative gap-overlap variable (i.e., FAC and DIS). With group (ASD and NT) as the fixed factor and total SRS-2 scores entered as the dependent variable, a significant main effect of FAC emerged; F (1, 53) = 11.81, p=.001, η^2=.18 (see Figure 3.2). Moreover, a significant group × FAC interaction effect was observed [F (1, 53) = 9.93, p=.003, η^2=.16]; higher SRS-2 scores were associated with decreased FAC effect sizes in children with idiopathic ASD only (R=-.61, p=.04); no such association emerged within the NT sample (R=-.09, p=.58). Of note, partial correlation analyses showed that this association within the idiopathic ASD cohort remained significant when differences in chronological age and raw Leiter-3 scores were considered (R=-.65, p=.04).

Finally, total SRS-2 scores were plotted and analysed relative to children's DIS data (i.e., overlap-baseline SRT). A significant main effect of DIS emerged [F (1, 53) = 6.59, p=.01, η^2=.11]. Bivariate correlation analyses confirmed an association between SRS-2 scores and DIS effect size in NT children only (r =.29, p =.05). No interaction effect was observed; F (1, 53) = .66, p=.42 (Figure 3.1).

[26] Bonferroni correction was performed by dividing the critical p-value (.05) by the number of comparisons being made, in this case five: baseline SRT, gap SRT, overlap SRT, DIS and FAC effects. This yielded an adjusted p-value of .01.

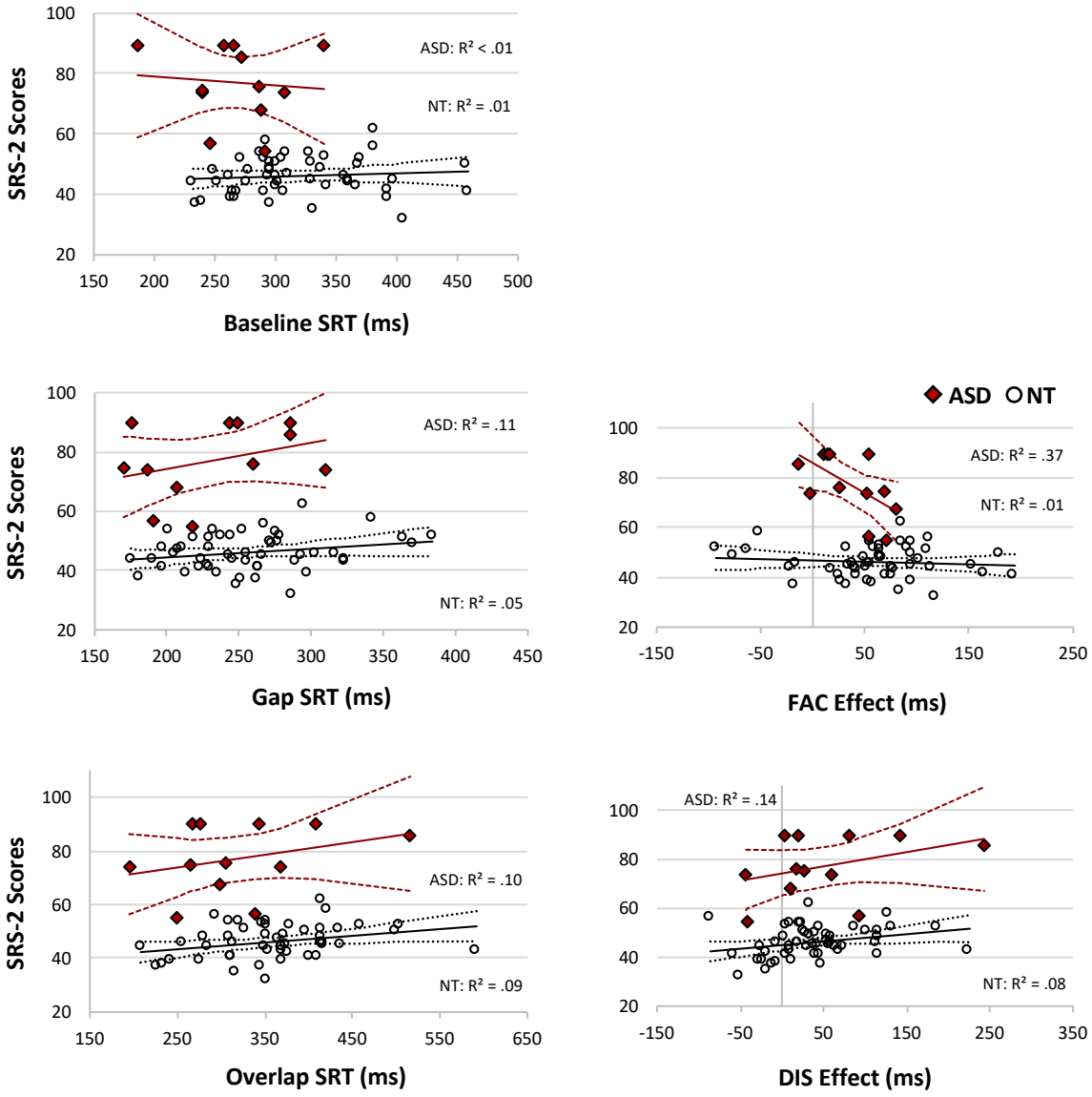

Figure 3.1. Total SRS-2 scores plotted against mean SRT data according to each gap-overlap output variable for ASD and NT cohorts.

Further ANCOVAs were run to examine within- and between-group differences in rate and severity of RRB, as indexed by the RBQ-2, relative to disengagement latency/SRT. The fixed factor in each model was group (ASD and NT). Total RBQ-2 score was entered as the dependent variable. The co-variate in each model was the mean disengagement latency/SRT data for one of three gap-overlap conditions (i.e., baseline, gap and overlap). The results revealed significant main effects of group for each model;

significantly higher total RBQ-2 scores were recorded for children with idiopathic ASD relative to NT controls (Figure 3.2)

With groups combined, a main effect of SRT was noted for gap trials suggesting an overall association with total RBQ-2 scores; F (1, 54) = 8.52, p=.005, η^2=.14. Bivariate correlation analyses were employed to examine this main effect in reference to each participant group. The output revealed a significant positive association between total RBQ-2 and gap SRT data in NT children only (r = .34, p =.02). Similarly, a main effect of SRT was observed for overlap trials also; F (1, 54) = 7.76, p=.007, η^2=.13. Again, this effect was driven by a significant positive association within the NT cohort (r = .42, p =.004); no significant association was documented in cases of idiopathic ASD. When chronological age differences were considered in a partial correlation analyses, this association between RBQ-2 scores and overlap SRT within the NT cohort fell below the level of statistical significance (r = .27, p =.08). No significant group × SRT interaction effects emerged (Figure 3.2).

Further ANCOVA models were run to analyse trajectories of RRB expression according to each derivative gap-overlap output (i.e., FAC and DIS). With group (ASD and NT) as the fixed factor and total RBQ-2 scores as the dependent variable, a significant main effect of FAC emerged; F (1, 59) = 18.75, p<.001, η^2=.24 (Figure 3.3). Moreover, a significant group × FAC interaction effect was found; F (1, 54) = 7.08, p=.01, η^2=.12; higher RBQ-2 scores were associated with smaller FAC effect sizes in children with ASD but not in NT controls. Again, this association within the idiopathic ASD cohort remained significant when the contribution of chronological age and non-verbal intellectual ability according to the Leiter-3 was examined in a partial correlation analysis.

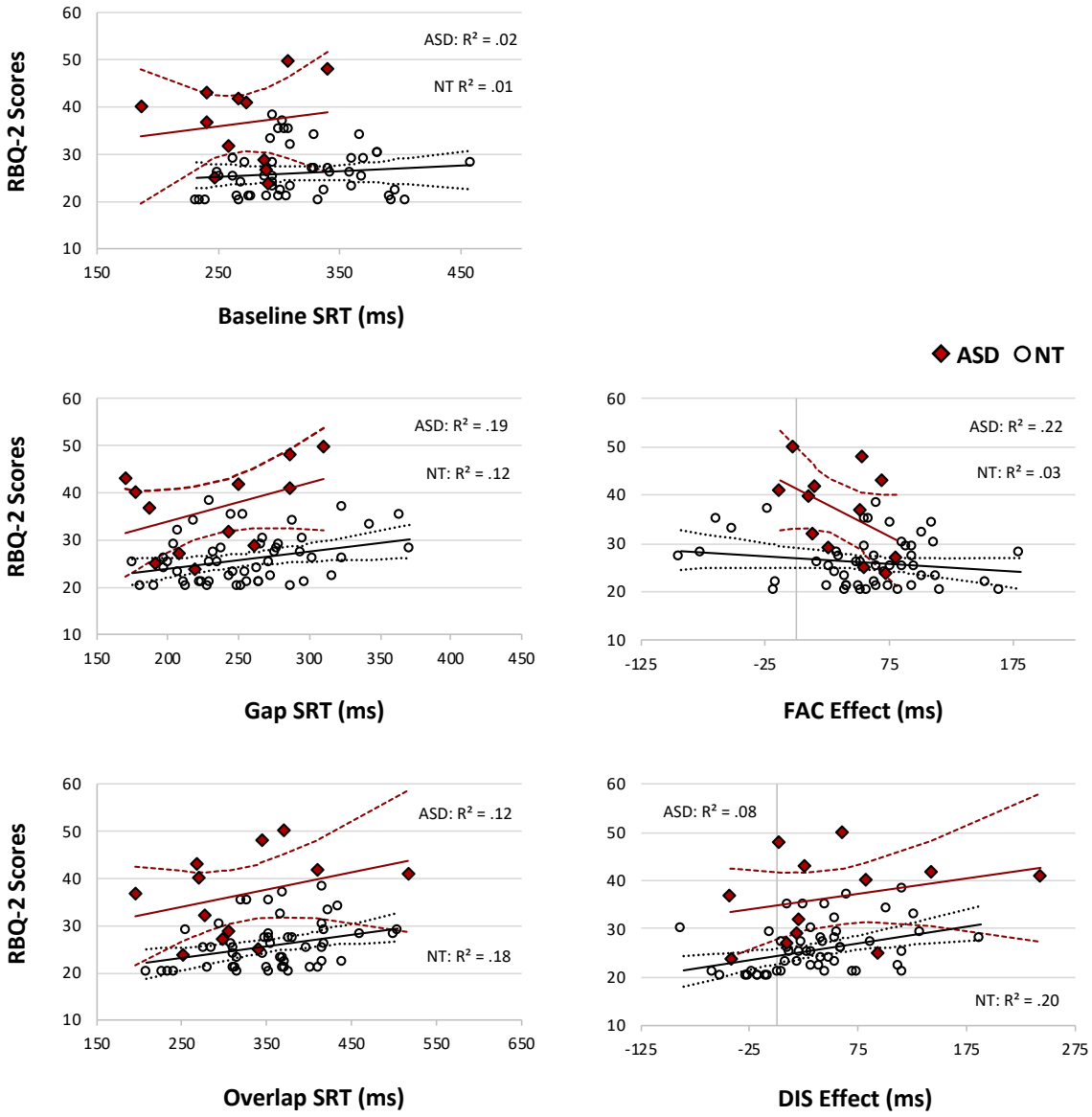

Figure 3.2. Total RBQ-2 scores plotted against mean SRT data according to each gap-overlap output variable for ASD and NT cohorts.

Similarly, I examined within and between-group variation in children's total RBQ-2 scores according to DIS effect size. ANCOVA outputs revealed a significant main effect of DIS; F (1, 54) = 7.63, p=.008, η^2=.12. Bivariate correlation analyses confirmed a significant positive association between total RBQ-2 scores and DIS within the NT cohort only (r =.45, p =.002); this effect was moderated by differences in chronological

age with partial correlation analyses yielding a non-significant result (r =.27, p =.08). No significant group × DIS interaction effect emerged; F (1, 54) = 0.09, p=.77.

3.4.4. Visual Search Performance in Idiopathic ASD and Neuro-typical Cohorts

A 2 x 2 mixed-design ANOVA was conducted to compare visual search performance within and across participant groups. The within-subjects factor was trial type (single feature and conjunction) and the between-subjects factor was group (NT and ASD). The results revealed a main overall effect of condition [F (1, 63) = 13.99, p < .001, η^2 =.18] reflecting significantly increased target detection times on conjunction relative to single feature search trials. Moreover, a significant main effect of group was noted [F (1,63) = 8.65, p = .005, η^2 =.12]. No trial type × group interaction effect emerged; F (1, 63) = 1.29, p =26.

An independent samples t-test was run to investigate this significant main effect of group in reference to single feature search performance; no significant group difference was found; t (63) =1.78, p=.08. A similar analysis was run to look at mean group data in reference to conjunction search performance. The results revealed significantly decreased target detection times on conjunction search trials in children with idiopathic ASD (M=803, SD=249) relative to NT controls (M=1077, SD=321); t (63) =3.12, p=.003, Cohen's d=.95. The impact of chronological age was tested in an ANCOVA, with group as the fixed factor and mean conjunction search latency as the dependent variable. The results revealed a significant overall effect of age [F (1,61) = 4.36, p =.04, η^2 =.07] but no significant group × age interaction effect [F (1,61) = 2.44, p = .12].

3.4.5. Autistic Trait Expression according to Visual Search Performance

Next, I investigated variation in idiopathic and non-clinical forms of autistic trait expression in reference to visual search performance. A series of modified ANCOVA

models was run with group (ASD and NT) as the fixed factor and children's total SRS-2 scores as the dependent variable. The co-variate in each model was the mean target detection time for either single feature or conjunction visual search trials. Outputs revealed significant main effects of group for each model, as higher SRS-2 scores differentiated cases of idiopathic ASD from NT controls (Figure 3.3a).

Examination of total SRS-2 scores according to target detection times on single feature trials revealed no main effect of performance [F (1, 58) = .18, p=.67] and no significant group difference in gradient; F (1, 58) = .1.03, p=.32. A different pattern of results was observed for target detection times on conjunction search trials; there was an overall main effect of conjunction search time [F (1, 58) = 6.15, p=.02, η^2=.10] and a significant interaction effect reflecting differential performance gradients for ASD and NT groups; F (1, 58) = 11.94, p=.001, η^2=.17. Of note, these effects persisted when the analysis was repeated with verbal and non-verbal intelligence ratings entered as co-variates.

Next, within and between-group variation in RRB expression was examined according to total RBQ-2 scores in relation to target detection latencies on single feature search trials (Figure 3.3b). No main effect of single feature search performance emerged [F (1, 59) = .43, p=.52] but there was a significant group × single feature search interaction effect reflecting differential ASD and NT gradients [F (1, 59) = 4.52, p=.04, η^2=.07]; this effect failed to retain significance when Bonferroni correction was applied.[27] Finally, a modified ANCOVA was conducted to examine within and between-group variation in total RBQ-2 scores according to target detection times on conjunction

[27] Bonferroni correction was performed by dividing the critical p-value (.05) by the number of comparisons being made, in this case four: single feature search time, conjunction search time, total SRS-2 scores and total RBQ-2 scores. This yielded an adjusted p-value of .0125.

search trials. No significant main effect of conjunction search performance and no significant group × conjunction search interaction effect emerged.

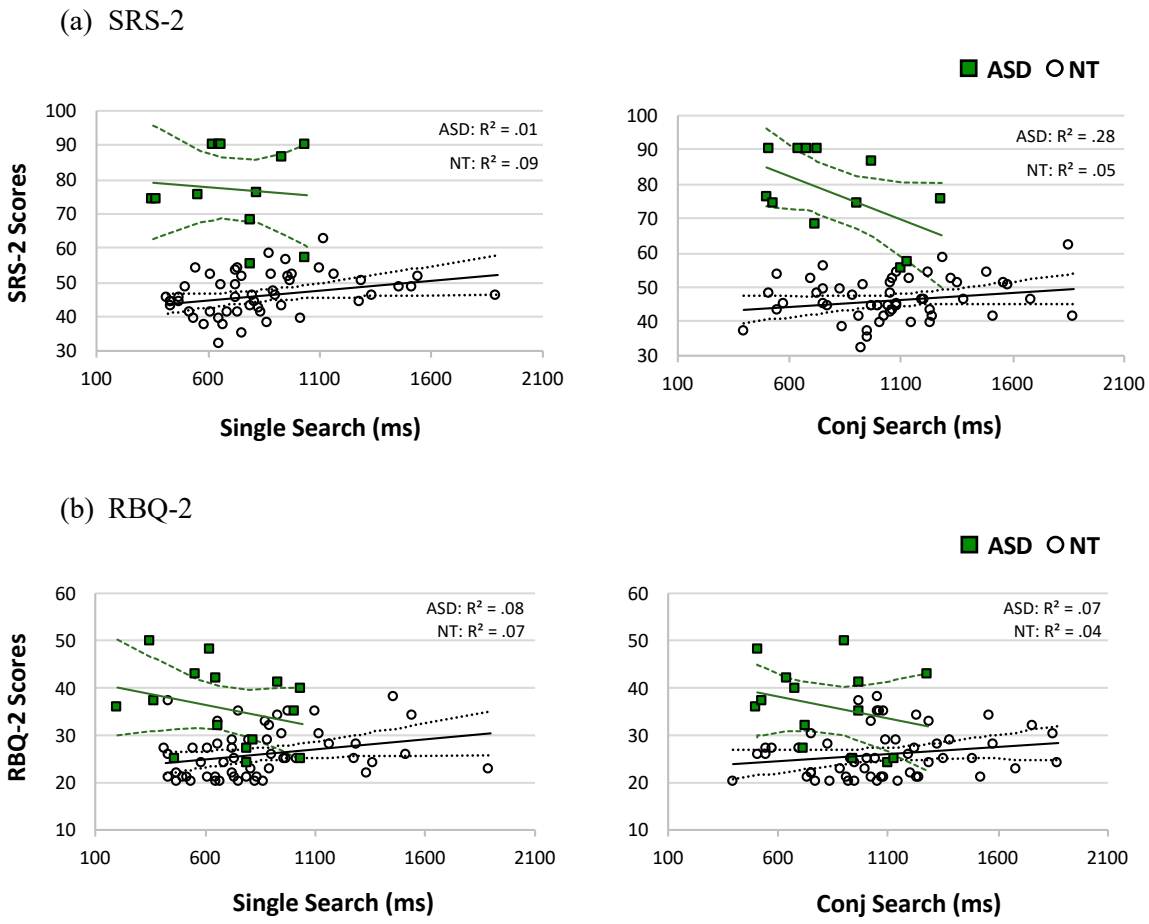

Figure 3.3. Autistic trait expression according to (a) total SRS-2 scores and (b) total RBQ-2 scores plotted against mean target detection times on single feature and conjunction search trials.

3.4.6. Visual Search Performance according to Disengagement Latency

Within and between-group variability in visual search performance was examined according to visuo-spatial orienting efficiency, as measured by the gap-overlap task. In the first set of ANCOVA models, group (ASD and NT) was entered as the fixed factor and mean target detection time on single feature trials was entered as the dependent

variable. In each model, the covariate entered was mean SRT for one of three gap-overlap conditions (i.e., baseline, gap and overlap). No statistically significant main or interaction effects were observed (see Figure 3.4). Next, these ANCOVA models were repeated with an adjusted dependent variable: mean target detection time on conjunction search trials. Again, no statistically significant main or interaction effects were observed (see Figure 3.5).

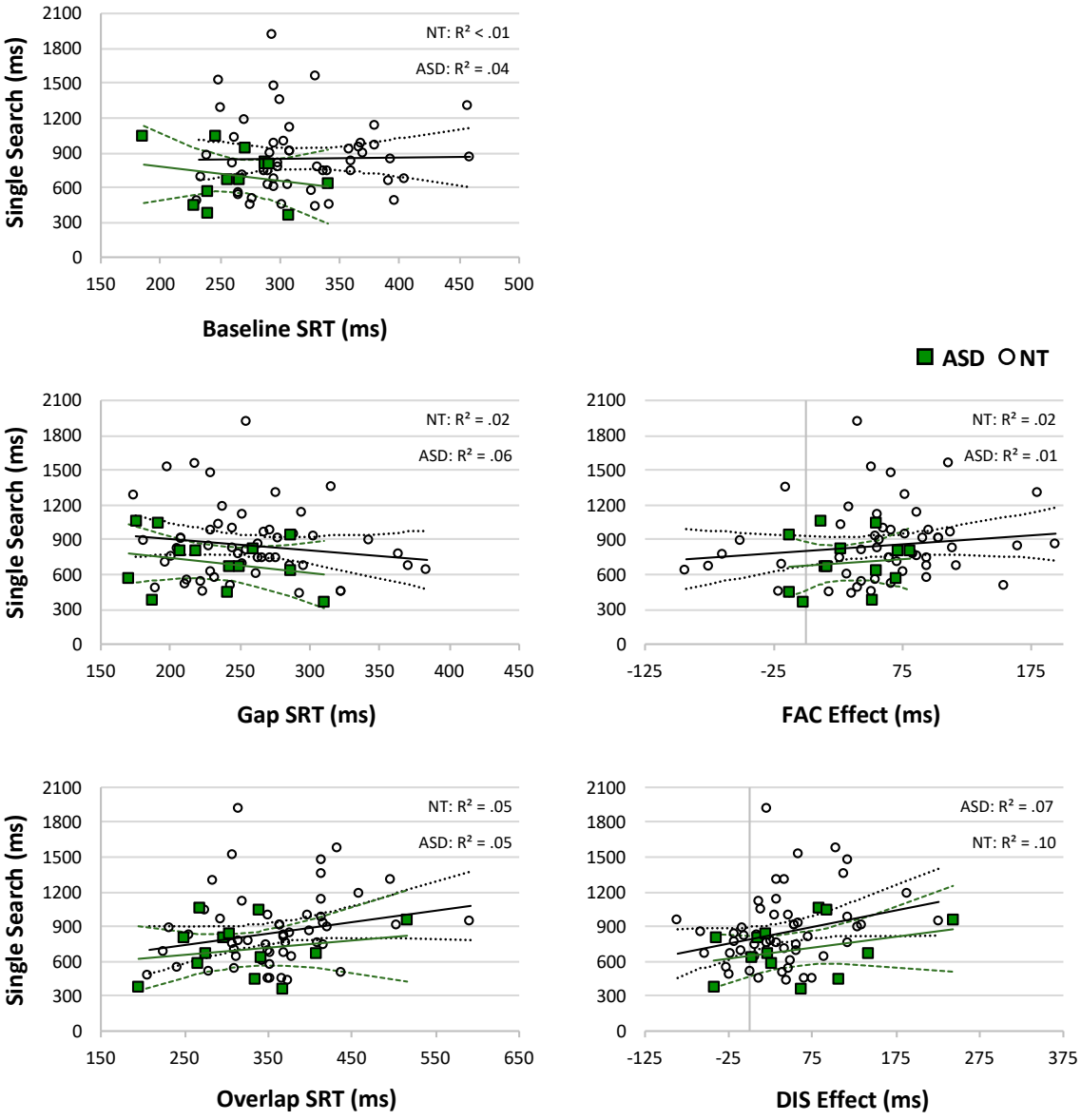

Figure 3.4. Mean target detection times on single feature search trials plotted for idiopathic ASD and NT participants against mean SRTs for each gap-overlap output variable.

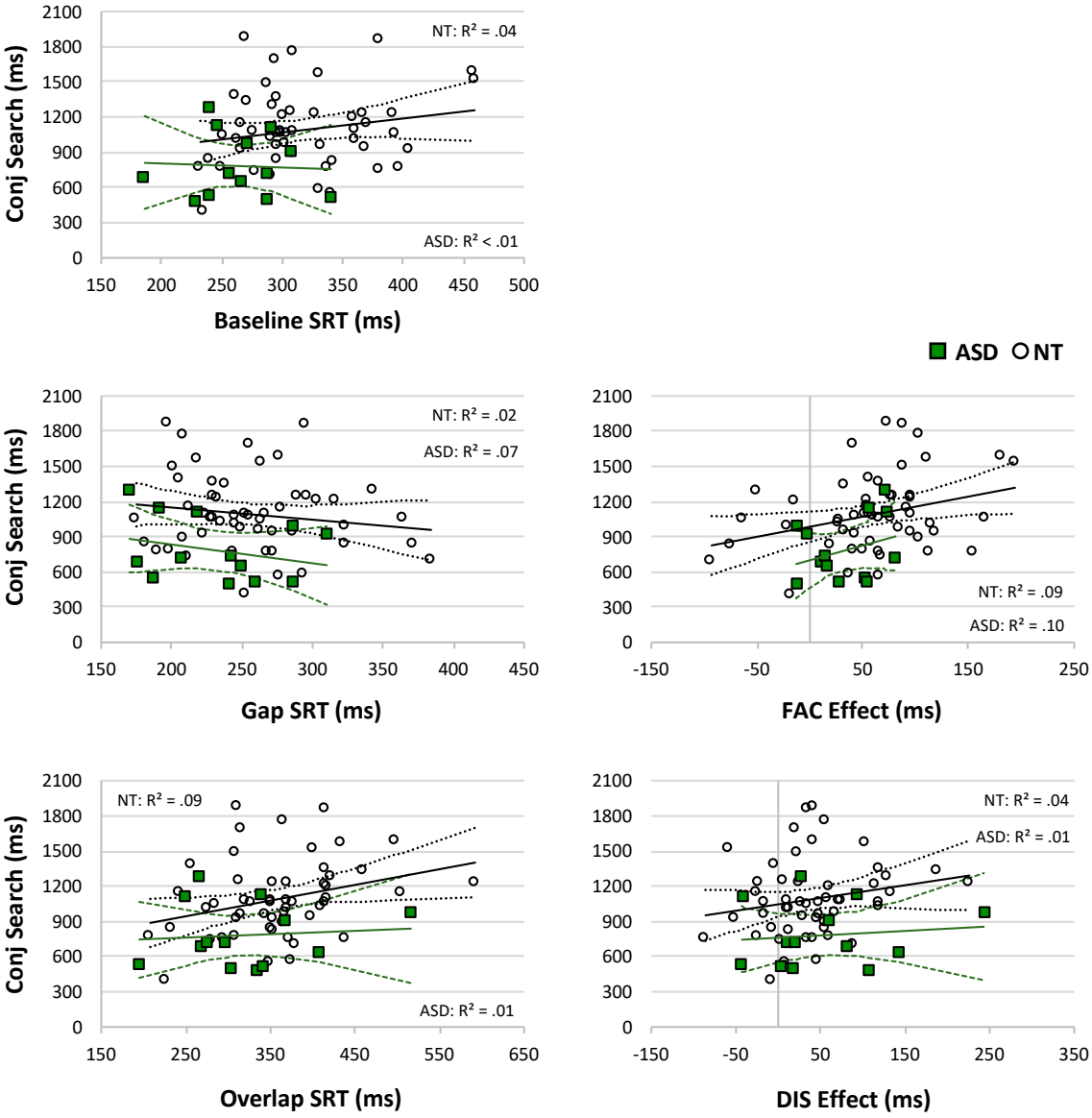

Figure 3.5. Mean target detection times on conjunction (conj) search trials plotted for idiopathic ASD and NT participants against mean SRTs for each gap-overlap output variable.

3.4.7. Visuo-Perceptual Profiling in relation to Autistic Trait Severity

Associations between indices of visual search and attentional disengagement efficiency were examined in reference to autistic trait severity. I focused specifically on the gap-overlap and visual search variables previously shown to relate independently to variability in indices of autistic trait severity (i.e., conjunction search latency and FAC). A modified ANCOVA was run with group as fixed factor and total SRS-2 scores as the dependent variable. Mean target detection latencies on conjunction search trials and mean FAC sizes were entered as co-variates. Main and interaction terms for the model were entered manually.

No significant main effects of conjunction search latency or FAC emerged in the model output; however, a significant three-way interaction effect emerged between group, conjunction search latency and FAC; F (1, 51) = 16.34, p <.001, η^2=.24. A schematic illustration of these data in the form of a grouped three-dimensional scatterplot confirmed overall higher SRS-2 scores in cases of decreased conjunction search latency and decreased FAC in cases of idiopathic ASD.

A second modified ANCOVA was run to assess within and between-group variation in total RBQ-2 scores according to conjunction search latency and FAC. No main or two-way interaction effects were observed; however, a similar group × conjunction search × FAC interaction effect was found; F (1, 52) = 4.29, p =.04, η^2=.08.

3.5. Discussion

Irregularities in attentional disengagement and visual search performance have been found to underpin, and even precede, the expression of idiopathic ASD (Cheung et al., 2018; Elsabbagh et al., 2013; Gliga et al., 2015; Zwaigenbaum et al., 2005). Beyond early childhood, however, the literature is mixed with regard to the presence and nature of these visuo-perceptual irregularities. The current chapter details an empirical investigation into the visuo-perceptual profile associated with idiopathic ASD status in middle childhood relative to NT controls matched on verbal and non-verbal intellectual ability, with a specific focus on attentional disengagement and visual search performance. By extension, variation in idiopathic and non-clinical forms of autistic trait expression was examined according to visuo-perceptual performance, with implications for the validity of dimensional phenotypic perspectives.

To facilitate the characterisation of idiopathic and non-clinical forms of autistic trait expression, and to elucidate the role of general cognitive ability in relation to each, associations between indices of intellectual ability and autistic trait severity were examined. In this regard, children with idiopathic ASD were differentiated from NT controls; shared variance emerged between indices of autistic trait severity and non-verbal intellectual ability in NT children only. For instance, rate and severity of RRB decreased with higher raw Leiter-3 scores in this NT cohort. This finding mirrors, to some extent, a previous study by Tregay, Gilmour and Charman (2009) which examined the cognitive correlates of RRB expression in NT 7 year-olds. They observed that children who rated more highly on the RRB items of the Childhood Routines Inventory (Evans et al., 1997) demonstrated reduced cognitive flexibility according to performance on a card-sorting task (e.g., Hughes, Dunn, & White, 1998). As this task featured explicit rule-switching cues to control for perseveration, it placed fewer

demands on children's representational flexibility (e.g., Perner, Stummer, Sprung, & Doherty, 2002; Zelazo et al., 2003). Consequently, the authors proposed that RRB expression in NT children manifests on account of impaired cognitive inhibition (i.e., the ability to inhibit previous rules; Diamond, Carlson, & Beck, 2005) and/or reduced representational flexibility (i.e., the ability to hold a given rule in working memory). In this study, chronological age moderated the observed negative association between children's total RBQ-2 scores and raw Leiter-3 data. This suggests that age-related improvements in non-verbal reasoning ability emerge in conjunction with an elevated degree of cognitive and behavioural flexibility, all of which are likely underpinned by an age-related neuronal maturation of corresponding executive brain systems.

The results of the current study also revealed a significant negative association between NT children's RBQ-2 scores and receptive language abilities according to the BPVS-3; no such association was observed within the current cohort of children with idiopathic ASD.[28] Again, this result in keeping with what has been documented previously, albeit in younger children. Harrop and colleagues (2014) reported a negative association between RRB and receptive language abilities according to the Preschool Language Scales (Zimmerman et al., 1992) in typically developing 2-year-olds. More recently, a longitudinal association was reported between degree of sensory-motor irregularity at age 2 and receptive language function at age 4, as derived from the BPVS-2 (Dunn, Dunn, Whetton & Burley, 1997; Larkin, Meins, Centifanti, Fernyhough, & Leekam, 2017). In interpreting this result, it may be the case that sensory-motor kinds of

[28] This finding is in keeping with previous reports of differential associations between RRB severity and indices of non-verbal intelligence in ASD and NT cohorts (Bishop et al., 2013; Bodfish, Symons, Parker, & Lewis, 2000; Lam, Bodfish, & Piven, 2008; Szatmari et al., 2006). Moreover, it adds to a growing body of literature to suggest that RRBs emerge and are expressed in children with idiopathic ASD via disparate mechanistic pathways.

repetitive behaviour function at a cost to children's social engagement with negative implications for language outcomes (Iverson, 2010).

The current findings suggest that symptom severity in idiopathic ASD varies independently of the contribution of verbal and non-verbal intelligence. This has been documented previously; Constantino and colleagues (2003) examined associations between SRS-2 scores and non-verbal IQ in a sample of children with idiopathic ASD spanning 4 to 14 years of age and found no significant correlations.[29] Similarly, Constantino, Przybeck, Friesen and Todd (2000) investigated socio-communicative abilities, according to the SRS, and full-scale IQ data in children with and without pervasive developmental disorders; no significant associations were observed.

While the results of this study must be considered in light of the phenotypic heterogeneity that is associated with idiopathic ASD and the modest sample size of the current cohort, they illustrate the manner in which idiopathic and non-clinical manifestations of socio-communicative impairment and RRB may vary according to the contribution of verbal and non-verbal intelligence factors. Moreover, in reference to subsequent chapters, they demonstrate the value of considering verbal and non-verbal abilities when endeavouring to characterise and elucidate the nature of manifestations of autistic-like impairment in high risk genetic syndrome groups.

This study was concerned with investigating the visuo-perceptual processes associated with idiopathic and non-clinical forms of autistic trait expression. Significant group differences emerged according to performance on a gap-overlap task assessing visuo-spatial orienting abilities. On baseline trials, the current idiopathic ASD cohort exhibited significantly reduced mean disengagement latencies; these children were

[29] Full-scale IQ data were acquired via a selection of assessment measures. These were the Wechsler Intelligence Scale for Children, the Stanford-Binet test and the Leiter International Performance scale.

quicker than NT controls at disengaging and shifting visual attention away from a central fixation point in response to peripheral target onset. The role of chronological age was examined to determine the extent to which decreased SRTs reflected age-related maturational effects in terms of visuo-spatial orienting efficiency; according to the data, chronological age did not account for this group difference on baseline trials. On gap and overlap trials, mean SRTs were equivalent in children with idiopathic ASD and NT controls. This is in keeping with previous reports of similar performance profiles in paediatric ASD and NT groups. Kelly, Walker and Norbury (2013), for instance, administered a gap-overlap task to 10-year-olds with and without ASD. No mean group differences in gap or overlap SRTs were noted. Similarly, Fischer and colleagues (2014) assessed visuo-attentional disengagement performance on gap and overlap trials in 9-year-olds with ASD relative to NT controls. No significant mean group differences emerged. Both studies featured participant groups that were matched according to chronological age and intellectual ability. Fisher and colleagues (2016) later investigated visuo-attentional disengagement in toddlers with and without ASD. More specifically, they examined mean group differences in what they termed 'disengagement cost', calculated by subtracting gap from overlap SRTs. They found that groups were undifferentiated according to this index of visual orienting efficiency. The authors interpreted this result as evidence in opposition to claims of a primary disengagement deficit in ASD.

Yet contrary to the current result, a number of studies have documented visuo-spatial orienting deficits in children with idiopathic ASD relative to NT norms (Sacrey et al., 2014). This dissonance may be due to variations in task design and methodology; in particular, the degree to which the stimuli employed in any gap-overlap task are salient to children with ASD is likely to influence the sensitivity of the paradigm in terms of its

capacity to elicit mean group differences. In Landry and Bryson's (2004) gap-overlap study, 5-year-olds with idiopathic ASD were found to exhibit significantly increased mean SRTs on overlap trials relative to NT controls. Of note, the central and peripheral stimuli employed in this gap-overlap task consisted of dynamic geometric imagery and since then, a visual preference for repetitive motion pertaining to geometric stimuli has been documented in children with idiopathic ASD (Pierce, Conant, Hazin, Stoner, & Desmond, 2011; Pierce et al., 2016). Similarly, Kleberg and colleagues (2017) demonstrated disengagement difficulties in 6-year-olds with ASD. Again, the stimuli employed consisted of a variety of geometric forms and everyday objects (e.g., toys and tools) that are considered to be particularly salient for children with ASD (Sasson et al., 2011). It may be case, then, that the central stimulus employed in the current gap-overlap task failed to reach the 'salience threshold' required to elicit group differences on gap or overlap trials.

It did, however, succeed in eliciting significant within-group effects, specifically with regard to performance on overlap trials of the gap-overlap task. Here, NT children were more likely to exhibit higher levels of autistic trait expression if they experienced increased difficulty disengaging and shifting visual attention flexibly in the presence of competing stimuli. Moreover, this association was moderated by the effects of chronological age. Age-related improvements (reductions) in SRT have been documented previously in typically developing children up until approximately 6 years of age (Boot, Pel, Evenhuis, & Van der Steen, 2012). The current data suggest that age-related maturation of ocular motor systems extends beyond 6 years of age. Moreover, they suggest that disengagement efficiency is tightly coupled to non-verbal reasoning ability, with implications for socio-communicative functioning.

While most studies examining disengagement efficiency focus on performance in the context of overlapping visual stimuli, the FAC effect provides a useful measure of the degree to which children's ability to disengage and shift visual attention is facilitated by the presence of a brief inter-stimulus temporal gap. Typically, SRT improves on gap relative to baseline trials (Saslow, 1967), and this is replicated here as a main effect. In terms of underlying mechanism, this improvement or FAC effect is considered to be the emergent property of two processes that function reactively to the offset of a visual fixation point. The first is reduced activation of the superior colliculus; more specifically, reduced activation of the relevant fixation location in the saccade map of the superior colliculus (Dorris & Munoz, 1995). This suppression is a well-documented prerequisite for the initiation of a saccade. The second is increased activity of pre-saccadic neurons in the frontal eye fields which projects a signal to the superior colliculus to disengage from the current fixation point and prepare for a yet-to-be-designated eye movement (Dias & Bruce, 1994). This signalling mechanism has been found to emerge only in trials characterised by this inter-stimulus temporal interval; in baseline trials, it is sharply curtailed by the immediate appearance of the peripheral target (Dias & Bruce, 1994).

Within the current idiopathic ASD cohort, increasing symptom severity was linked to a reduced FAC effect; children who rated more highly on the SRS-2 and RBQ-2 exhibited less of an SRT reduction on gap relative to baseline trials. In other words, SRT in children with idiopathic ASD who ranked highly on the severity spectrum benefited less from an inter-stimulus temporal interval. A reduced FAC effect size has previously been observed in infants at high familial risk of ASD, suggesting a role in the emergence of the phenotype (Elsabbagh et al., 2009). This implies that the mechanisms underpinning this FAC effect function atypically in infants at high risk of

ASD and, here, in older children with idiopathic ASD, according to their position on the clinical symptom severity spectrum.

It is interesting to note that an association between autistic trait severity and FAC effect size is seen here only in children formally diagnosed with idiopathic ASD. This suggests a differentiation between idiopathic and non-clinical forms of autistic trait expression according to irregularity in the mechanisms that react to the offset of a stimulus under fixation. It is important to note, however, that had the cohorts been matched on chronological age, a differentiation according to FAC effect size may not have emerged. The current result will need to be replicated against an age-matched NT sample to determine whether the visuo-perceptual profile observed here is characteristic of a particular chronological age bracket, generally, or whether it constitutes a phenotypic marker of idiopathic ASD, specifically.

This phenotypic differentiation between idiopathic and non-clinical forms of autistic-like trait expression is evidenced further according to the visual search data presented here. In keeping with the literature, the idiopathic ASD cohort demonstrated a phenotypic advantage (i.e., decreased target detection latencies) on conjunction search trials relative to NT controls. Moreover, a significant negative association emerged between total SRS-2 scores and target detection latencies on conjunction trials in children with idiopathic ASD only; those who exhibited increased levels of socio-communicative impairment were quicker to locate the target stimulus in conjunction search trials. Without a chronological age-matched NT cohort, the extent of this phenotypic advantage cannot be determined. Still, this result is in keeping with previous reports of a negative correlation between symptom severity in socio-communicative domains and visual search efficiency in adolescents with ASD (Joseph et al., 2009). Moreover, it ties in nicely with fMRI research documenting distinct neurofunctional

correlates of visual search performance in adolescents with ASD relative to NT controls (Keehn et al., 2008).[30] In terms of interpreting this finding, it is likely that whatever mechanistic irregularities underpin enhanced visual search performance operate to the detriment of socio-communicative skills development (Keehn et al., 2013; Liss et al., 2006). For instance, superior featural discrimination may function at a cost to the autistic child's ability to process global forms, like faces, which would inevitably disrupt the development of brain systems responsible for social reward learning and, by extension, the child's acquisition of regular socio-emotional processing capacities (Nomi & Uddin, 2015; Weigelt, Koldewyn, & Kanwisher, 2012).

Finally, I investigated the relationship between attentional disengagement and visual search performance. No significant degree of shared variance emerged between indices of visual search and disengagement efficiency independent of autistic trait severity. However, examining attentional disengagement and conjunction search latencies in reference to autistic trait severity and group revealed a significant three-way interaction. According to this result, autistic trait expression in children with idiopathic ASD was characterised by a unique visuo-perceptual profile according to increased search efficiency on conjunction trials (i.e., reduced target detection latencies) and decreased FAC on the gap-overlap task. This result is consistent with the notion that these visuo-perceptual features are expressed in children with idiopathic ASD via common phenotypic mechanisms.

This may be considered with regard to the neurofunctional correlates of both visuo-perceptual functions. Keehn and colleagues (2008) conducted an event-related fMRI

[30] Relative to their NT peers matched according to age and non-verbal intellectual ability, visual search performance in adolescents with ASD was associated with (1) increased occipito-temporal activation and (2) a wider activation network of superior parietal and frontal brain regions (Keehn et al., 2008).

study of visual search performance in children and adults with idiopathic ASD and found that, relative to NT control, participants with idiopathic ASD recruited a more distributed network of superior parietal and frontal brain regions. The authors observed increased activation in the superior frontal gyrus, which they interpreted as an increased reliance on the involvement of the frontal eye fields. Similarly, in reference to the FAC effect typically observed on gap-overlap tasks, the frontal eye fields are known to send saccade commands to the superior colliculus to facilitate disengagement on gap relative to baseline trials on gap-overlap tasks (Dias and Bruce, 1994). Moreover, it has been proposed that reductions in FAC reflect elevated functional connectivity broadly within and between frontal and parietal brain regions (Pammer et al., 2006). It may, therefore, be the case that the visuo-perceptual profile observed within the current idiopathic ASD cohort (i.e., enhanced conjunction search performance and decreased FAC on gap-overlap trials) reflects increased functional connectivity between relevant frontoparietal and occipital brain regions.

In conclusion, this chapter detailed a study of the visuo-perceptual correlates of idiopathic ASD status in middle childhood relative to NT controls matched on indices of intellectual ability. Significant group differences emerged as children with idiopathic ASD outperformed NT controls on conjunction search trials, in keeping with the literature. Further, decreased SRTs on baseline trials of the gap-overlap task were observed in cases of idiopathic ASD. Inquiry into the visuo-perceptual processes underpinning variation in autistic trait severity revealed a unique visuo-perceptual profile within the current idiopathic ASD cohort; higher levels of socio-communicative impairment were associated with reduced conjunction search times and smaller FAC effect sizes.

In the context of this thesis, this chapter provided a detailed account of the visuo-perceptual processes associated with autistic trait variation in children with idiopathic ASD. In doing so, it set the necessary foundation for cross-syndrome analyses incorporating FXS and DS cohorts.

Chapter 4: Autistic Trait Expression and Attentional Disengagement Abilities in FXS and DS

4.1. Overview

While there is a dense literature implicating visuo-perceptual irregularity in the emergence and expression of idiopathic ASD, there have been very few studies examining the visuo-perceptual correlates of autistic trait variation in children with DS and FXS. The current chapter presents an eye-tracking investigation into attentional disengagement abilities according to performance on a gap-overlap task in children with idiopathic ASD, FXS and DS, matched on chronological age, indices of verbal and non-verbal intellectual ability and autistic trait severity.

Attentional disengagement abilities were examined both in terms of between-group differences and in relation to autistic trait severity. Increased autistic trait severity was anticipated within the DS and FXS cohorts according to SRT indices of attentional disengagement performance; in keeping with reports in the literature of distinct behavioural symptomatic profiles, the nature of this association was expected to vary according to the visual and attentional profile observed previously in cases of FXS and DS. The results revealed significant between-group differences on gap-overlap trials characterised by an inter-stimulus temporal interval (gap trials); children with DS were significantly slower to disengage and shift attention on these trials than their peers with FXS or idiopathic ASD. Moreover, greater autistic trait expression within FXS and DS cohorts was associated with larger FAC effects, in contrast with the significant negative association observed in cases of idiopathic ASD. These findings provide evidence of a phenotypic differentiation according to indices of visuo-spatial orienting efficiency, in support of the notion that autistic-like deficits in DS and FXS emerge and are expressed via distinct neurocognitive mechanisms.

4.2. Introduction

Genetic syndrome groups that are characterised by high rates of autistic-like impairment, like FXS and DS, are considered to be useful models for studying the emergence and expression of ASD as genetic aetiology is well-defined (Doherty & Scerif, 2017; Farran & Karmiloff-Smith, 2012; Karmiloff-Smith, Doherty, Cornish, & Scerif, 2016). Yet, there is increasing evidence to suggest that these syndromic forms of ASD manifest distinctly in terms of behavioural symptomatic presentation (Glennon, Karmiloff-Smith, & Thomas, 2017).

In the case of FXS, autistic-like traits are extremely common; 90% of males display some form of behavioural irregularity that is phenotypically characteristic of ASD, with 30% reaching screening thresholds for comorbidity (Hernandez et al., 2009; Richards et al., 2015). Empirical enquiry into the nature of this comorbidity has provided evidence that is consistent with the idea of a distinct phenotype according to underlying neuro-cognitive mechanism (Gallagher & Hallahan, 2012; McDuffie, Thurman, Hagerman, & Abbeduto, 2015). Turk and Cornish (1998) examined face recognition and emotion perception in boys with FXS and documented developmentally appropriate performance levels, running contrary to observed deficits in idiopathic ASD cohorts. Similarly, symptomatic profiling in children and adults with FXS suggests a distinct behavioural phenotype characterised by increased rates of social reciprocity and higher levels of non-verbal communication (e.g., use of gesture, Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010). Furthermore, boys with FXS have been found to exhibit fewer compulsive and ritualistic behaviours than their idiopathic ASD peers (McDuffie et al., 2015; Wolff et al., 2012).

A significant minority of individuals with DS (approximately 18%) reach screening thresholds for ASD but, again, there is evidence to suggest that autistic-like traits

manifest distinctly (DiGuiseppi et al., 2010; Moss et al., 2013; Richards et al., 2015). Hepburn and colleagues (2008) examined socio-communicative abilities in toddlers with DS and found that deficits in communication and play were accompanied by a number of developmentally appropriate social skills which included sharing, engaging in joint attention and directing vocalisations to others. Similarly, Warner and colleagues (2014) studied behavioural profiles of autistic-like impairment in children with DS and noted that, relative to idiopathic ASD controls, children with DS+ASD were significantly less likely to show impairment in areas of social exchange, reciprocity and non-verbal communication, including use of gesture and imitation. More recently, children with DS who reached thresholds for ASD on the SCQ were found to demonstrate fewer problems with reciprocal social exchange and lower rates of emotional and peer-related problems relative to an idiopathic ASD group matched on chronological age and verbal ability (Warner et al., 2017).

It is apparent, therefore, that despite reaching screening thresholds for ASD, profiles of socio-communicative impairment and RRB manifest distinctly in children with DS and FXS. In order to gain a greater understanding of these comorbidities, it is necessary to progress beyond superficial behavioural levels of description and to assess, in a more fine-grained way, the nature of these phenotypic presentations in DS and FXS populations (Glennon et al., 2017).

4.2.1. Syndromic ASD: A Product of Intellectual Disability?

Additional information pertinent to the characterisation of syndromic forms of ASD can be obtained by examining the roles of verbal and non-verbal intelligence. It has been suggested that, on account of the high rates of intellectual disability associated with DS and FXS, cognitive factors play a greater role in the emergence and expression of these syndromic forms of ASD (Skuse, 2007). Indeed, there have been various reports of a

negative association between ASD symptom severity and indices of intellectual ability in FXS and DS populations (DiGuiseppi et al., 2010; Lewis et al., 2006; Molloy et al., 2009). A common underlying mechanism, such as a deficit in neuronal network connectivity, has been proposed to account for increased ASD risk in low functioning populations (Dierssen & Ramakers, 2006; Geschwind & Levitt, 2007). However, not all genetic syndrome groups characterised by intellectual disability feature high rates of ASD (Moss & Howlin, 2009). Moreover, in the case of DS, children with comorbid diagnoses of ASD have been found to exhibit significantly elevated ASD trait scores above and beyond the variance accounted for by differences in intellectual functioning. Molloy and colleagues (2009) differentiated between children with DS+/-ASD and found that significant group differences in autistic trait severity remained when variability in non-verbal intellectual ability was considered. While cognitive ability plays a clear role in phenotypic expression, it does not appear to account in full for the heightened prevalence of autistic-like traits in FXS and DS cohorts (Capone, Grados, Kaufmann, Bernad-Ripoll, & Jewell, 2005; Lee et al., 2016). Cross-syndrome studies looking at the relative contribution of intellectual factors to expressions of autistic-like deficit in FXS and DS cohorts may help to elucidate the precise nature of these comorbidities.

4.2.2. Visual Perception: Bridging the Gap between Genes, Brain and Behaviour

Visuo-perceptual irregularities have been implicated in the emergence and expression of idiopathic forms of ASD. Attentional disengagement deficits have been particularly well-documented in children with idiopathic ASD (e.g., Elsabbagh et al., 2013; Landry & Bryson, 2004; for review, see Sacrey et al., 2014). Whether autistic trait expression in the case of DS and FXS is associated with disengagement difficulty remains to be seen.

Chronic attention problems have been reported for both genetic syndrome groups, although FXS appears to be more severely impacted in terms of fulfilling clinical diagnostic criteria for attention deficit hyperactivity disorder (e.g., Sullivan et al., 2006).

To date, there has been only one empirical investigation into the visuo-perceptual correlates of autistic-like traits in either of these high-risk genetic syndrome groups (see Section 1.7). There have been a number of studies investigating visuo-attentional abilities in children and adults with FXS more generally (i.e., not considering performance in relation to autistic trait levels). Scerif and colleagues (2005) examined visuo-attentional orienting and executive eye movement control in infants and toddlers with FXS. They administered an oculomotor control task that measured children's ability to inhibit saccadic shifts towards uninteresting stimuli that predicted the onset of more visually rewarding peripheral stimuli. Their findings revealed that, relative to mental-age matched NT controls, toddlers with FXS were impaired in their ability to inhibit reactive gaze shifts to the onset of predictive stimuli. The authors interpreted this result as evidence to suggest that young children with FXS struggle to modify their behaviour adaptively according to learned information concerning contingencies between cues and target locations.

Visuo-perceptual abilities have been examined in children with DS also, though not in relation to ASD comorbidity. Brown and colleagues (2003) examined sustained attention in infants with DS relative to mental age-matched cohorts of children with Williams Syndrome and NT controls. They presented infants with toys and measured latencies of sustained attention. In line with long-standing reports of sustained attention deficits in children with DS (Gibson, 1978; Green et al., 1989; Krakow & Kopp, 1982), the authors observed significantly reduced latencies in the DS cohort relative to both comparison groups.

Landry & Bryson (2004) administered a gap-overlap task to 5-year-olds with idiopathic ASD, children with DS matched on chronological and mental age, and NT toddlers matched only in terms of mental age. On gap trials characterised by an inter-stimulus interval, they found no significant mean group differences in disengagement latency/SRT. However, on overlap trails characterised by competing visual stimuli, children with idiopathic ASD revealed a significant disengagement deficit (i.e., increased SRT) relative to both control groups. By extension, children with DS and NT toddlers were found to differ significantly in their disengagement efficiency on overlap trials, with the DS cohort demonstrating significantly decreased disengagement latencies. Moreover, these 5-year-olds with DS failed to show an advantage on gap relative to overlap trials. Taken together, these findings raised questions about the extent to which children with DS were engaged in the task (Miranda & Fantz, 1973).

The results of these studies suggest that children with DS may orient visually with similar efficiency to their mental age-matched NT peers, but demonstrate difficulties with sustained attention. By contrast, in FXS, children exhibit reactive gaze shifts to stimulus onset reflecting difficulties with selective attention (e.g., Munir et al., 2000; Wilding et al., 2002). Whether these visuo-attentional profiles are exacerbated in children exhibiting high levels of autistic trait expression remained to be seen. It could, for instance, be the case that ASD risk and expression in FXS is associated with degree of impairment in terms of selective attentional processes. This is in line with neuro-constructivist principles of neurodevelopmental disorder whereby atypical phenotypes unfold via the cascading effects of early perturbation to basic-level processes (Karmiloff-Smith, 1998). For instance, there is research to suggest that selective attentional deficits in FXS may reflect a reduced signal-to-noise ratio (Franco et al., 2017; Golovin & Broadie, 2017). An atypically diffuse visual attentional system could,

in theory, hinder a child's ability to reliably sample information from the environment resulting in ambiguous representations that, in turn, trigger adaptive attentional biases towards predictable, self-led, non-social forms of stimulation (Johnson, 2017).

4.2.3. The Current Study

This chapter presents an empirical investigation into the intellectual and visuo-perceptual correlates of autistic trait variation in children with FXS and DS relative to idiopathic ASD controls matched according to chronological age, receptive language ability, non-verbal intelligence and autistic trait severity. First, the contribution of verbal and non-verbal intelligence factors to expressions of autistic-like impairment are examined. It was hypothesised that in both high-risk genetic syndrome groups, children with greater deficits on measures of verbal and non-verbal ability would exhibit higher levels of autistic trait expression. Second, attentional disengagement abilities are evaluated across all three clinical groups, both in terms of between-group differences and in relation to autistic trait severity. It was hypothesised that increased autistic trait severity would be associated with greater visual orienting irregularity in children with DS and FXS; however, in keeping with reports of distinct behavioural symptomatic profiles, this irregularity was expected to manifest in syndrome-specific ways.

In addition to dimensional within-group analyses of autistic trait expression according to intellectual and visuo-perceptual factors, data from children who were clinically classified as having comorbid ASD were examined relative to cases of DS-ASD and FXS. I predicted that children with DS+ASD would be differentiated from their peers with DS-ASD according to indices of verbal and non-verbal intelligence; I expected children with comorbid ASD diagnoses to exhibit increased intellectual impairment due to the developmental weighting of clinical criteria. With regards to the FXS cohort, the sample size was too small (n=7) to differentiate according to ASD comorbidity for

analytic purposes. Consequently, this FXS cohort was treated as a case series allowing for more detailed examination of individual performance profiles.

4.3. Method

4.3.1. Participants

In addition to the idiopathic ASD cohort detailed in the previous chapter, fifteen children with DS and seven children with FXS were recruited to take part in this study (for details regarding recruitment process and inclusion criteria, see Chapter 2). Participant groups were matched according to chronological age, non-verbal intelligence (Leiter-3), receptive language ability (BPVS-3) and autistic trait severity (RBQ-2 and SRS-2; see Table 4.1). Demographics and behavioural data for children with FXS or DS with (+) and without (-) clinical diagnoses of ASD are presented in Table 4.2. Confirmation of clinical comorbidity was obtained via children's primary caregivers/parents and cross-checked in an ADOS-2 assessment administered by the author.

Table 4.1
*Means and Standard Deviations of Descriptive Statistics with ANOVA Outputs**

	ASD (*n*=16)		**FXS** (*n*=7)		**DS** (*n*=15)			
Gender	*m / f*		*m / f*		*m / f*			
	16/0		6/1		8/7			
	M (SD)	Range	*M (SD)*	Range	*M (SD)*	Range	*F*	*p*
Age $_{years}$	8.5 (1.6)	5.8-10.8	7.5 (1.2)	6.0-8.8	8.9 (1.9)	6.3 - 12	1.6	.21
Leiter-3	56.4 (22.3)	17-91	47.1 (5.6)	40-56	39.9 (18.8)	6 - 65	2.9	.07
BPVS-3	51.2 (29.7)	3-102	69.6 (29.7)	37-125	45.3 (37.2)	5 - 107	1.3	.28
RBQ-2	35.6 (8.4)	24-50	33.0 (6.4)	25-41	33.1 (11.3)	21 - 58	0.3	.73
SRS-2	76.5 (12.8)	55-90	72.3 (11.3)	55-86	66.8 (14.2)	48 - 90	2.0	.15

*With group (3 levels) as the fixed factor.

Table 4.2

Means and Standard Deviations of Descriptive Statistics in children with FXS ± ASD and DS ± ASD

	FXS				DS			
	- ASD (*n*=5)		**+ ASD** (*n*=2)		**- ASD** (*n*=8)		**+ ASD** (*n*=7)	
Gender	*m / f*		*m / f*		*m / f*		*m / f*	
	4/1		2/0		4/4		4/3	
	M (SD)	Range	*M (SD)*	Range	*M (SD)*	Range	*M (SD)*	Range
Age years	7.0 (0.9)	5.9-8.3	8.8 (0.1)	8.7-8.8	9.1 (2.1)	6.3-12	8.7 (1.8)	6.8-11.2
Leiter-3	49.2 (5.1)	43-56	42.0 (2.8)	40-44	48.9 (15.1)	19-65	29.7 (18.1)	6-55
BPVS-3	64.0 (18.1)	37-80	83.5 (58.7)	42-125	62.4 (37.1)	15-107	25.9 (28.2)	5-74
RBQ-2	33.0 (5.4)	27-41	33.0 (11.3)	25-41	25.7 (5.7)	21-38	40.6 (10.8)	27-58
SRS-2	74.4 (9.9)	60-86	67.0 (17.1)	55-79	57.3 (7.1)	48-69	77.7 (12.2)	59-90

4.3.2. Measures and Procedure

Measures and data collection procedures were as previously described in Chapter 2. Data collection took place at the Birkbeck Babylab, CBCD. All testing sessions comprised an 80-minute behavioural assessment, followed by a 15-minute eye-tracking session. Prior to this, parents were briefed and written participatory consent was acquired.

Receptive language abilities were assessed using the BPVS-3 (Dunn et al., 2009). Non-verbal intelligence was rated according to Leiter-3 (Roid et al., 2013). Autistic trait levels in terms of socio-communicative impairment were evaluated using the SRS-2 (Constantino & Gruber, 2012), while rate and severity of RRB was indexed according to the RBQ-2 (Leekman et al., 2007). Visuo-spatial orienting was assessed using a gap-overlap eye-tracking paradigm previously employed in studies of ASD risk and diagnostic status (adapted from Elsabbagh et al., 2013; Landry & Bryson, 2004).

4.3.3. Statistical Analyses

Shapiro-Wilks tests were run to check that all data were normally distributed. The results revealed a significant positive skew for disengagement latencies/SRTs on overlap trials. A Log10 transformation was applied to improve the distribution of these data for analysis. In inferential statistical analyses concerning overlap SRT, these Log transformed data were considered. All graphical illustrations of inferential outputs and references to raw data (e.g., mean and standard deviation) feature overlap SRTs pre-transformation.

Between-groups analyses were conducted to compare mean SRT data across idiopathic ASD, FXS and DS cohorts. In the case of DS, independent samples t-tests were used to test for differences in intellectual ability and SRT according to the presence or absence of comorbid ASD.

A trajectory analysis approach (Thomas et al., 2009) was employed to examine autistic trait variation within and between FXS, DS and idiopathic ASD groups according to indices of verbal and non-verbal intelligence, and attentional disengagement/SRT data as derived from the gap-overlap task. Performance trajectories were analysed in terms of intercepts and gradients. Main and interaction terms were manually entered into ANCOVA functions in SPSS. In all cases, the x-axes were re-scaled to ensure that main effects were calculated at the first point of group overlap. When necessary to correct for multiple comparisons, Bonferroni-adjusted significance levels were considered. Scatterplot representations of inferential outputs differentiate cases of comorbidity in DS and FXS cohorts by colour (presented in orange), for reference.

Due to the small size of the FXS sample, a complementary case-series analysis was conducted to examine patterns of individual variation with regard to autistic trait expression, intellectual ability and visuo-perceptual function. Moreover, for each

significant but statistically underpowered inferential output, children with FXS were detailed according to whether or not they performed within the confidence intervals of the associated idiopathic ASD trajectory. This allowed for a more precise description of these data concerning the degree to which groups overlapped with regard to trajectories of shared variance.

4.4. Results

4.4.1. Syndromic ASD and the Role of Intelligence

A series of independent samples t-tests were conducted to assess whether children with DS and ASD differed significantly from their peers with DS-ASD on measures of receptive language ability and non-verbal intelligence. The results revealed a significant group mean difference in raw BPVS-3 scores, indexing receptive language ability; $t(1,13)=4.49$, $p=.05$, $\eta^2=.26$. Here, significantly lower scores were noted in cases of comorbid ASD ($M=25.9$, $SD=28.2$) relative to children with DS-ASD ($M=62.4$, $SD=37.1$). Similarly, comorbidity in DS was associated with significantly lower raw Leiter-3 scores ($M=29.7$, $SD=18.1$) compared to DS-ASD ($M=48.9$, $SD=15.1$), reflecting greater non-verbal intellectual impairment; $t(1,13)=5.01$, $p=.04$, $\eta^2=.28$.

In the case of FXS, two of the total sample of seven children were clinically diagnosed with ASD. Examining these data at an individual level revealed distinct performance profiles in both cases of comorbidity (FX6 and FX7; see Table 4.3). One case, FX6, performed poorly on the BPVS-3 and the Leiter-3 reflecting impaired receptive language function and non-verbal intellectual ability, respectively. The other case, FX7, performed relatively well on the BPVS-3 but demonstrated a high-level of non-verbal intellectual impairment according to the Leiter-3. Of note, case FX7 was least impaired on measures of autistic trait severity relative to his peers with FXS; in fact, he scored below the clinical screening threshold of the SRS-2 (i.e., 60; see Section 2.3.1.1).

Chronological age was the only variable to differentiate both cases of comorbidity from their peers; both FX6 and FX7 placed at the higher end of the observed age range.

Table 4.3
Case-Series Description of FXS Data Points

	FX1	**FX2**	**FX3**	**FX4**	**FX5**	**FX6**	**FX7**
Age (months)	71	79	84	84	100	105	106
Gender (m/f)	m	m	m	f	m	m	m
Comorbid ASD	×	×	×	×	×	✓	✓
Leiter-3 Score	52	46	49	56	43	40	40
BPVS-3 Score	80	68	56	79	37	42	125
SRS-2	60	70	76	80	86	79	55
RBQ-2	27	29	41	34	34	41	25

4.4.2. Autistic Trait Expression and Intellectual Ability: Cross-Syndrome Analyses

A series of modified ANCOVAs were run to examine within and between-group trajectories of autistic trait expression relative to children's raw BPVS-3 and Leiter-3 data. First, total SRS-2 scores were plotted and analysed against children's receptive language abilities according to the BPVS-3. The fixed factor in this ANCOVA model was group with three levels (ASD, FXS and DS). The results revealed a significant main effect of raw BPVS-3 score [F (1,31) = 5.29, p=.03, η^2=.15]; greater receptive language abilities were linked to reduced autistic-like deficits according to the SRS-2 (see Figure 4.1). No significant group or group × BPVS-3 interaction effects emerged. Driven by a priori hypothesis regarding the increased role of receptive language ability in children with FXS (Abbeduto et al., 2018; Philofsky et al., 2004; Thurman, McDuffie, Hagerman, Josol, & Abbeduto, 2017), bivariate correlation analyses were

run to examine associations between autistic trait severity and raw BPVS-3 scores for each participant cohort. The results revealed a significant negative association in children with FXS only (r =-.84, p=.02). Cook's Distance values were inspected; no significant outliers were identified.

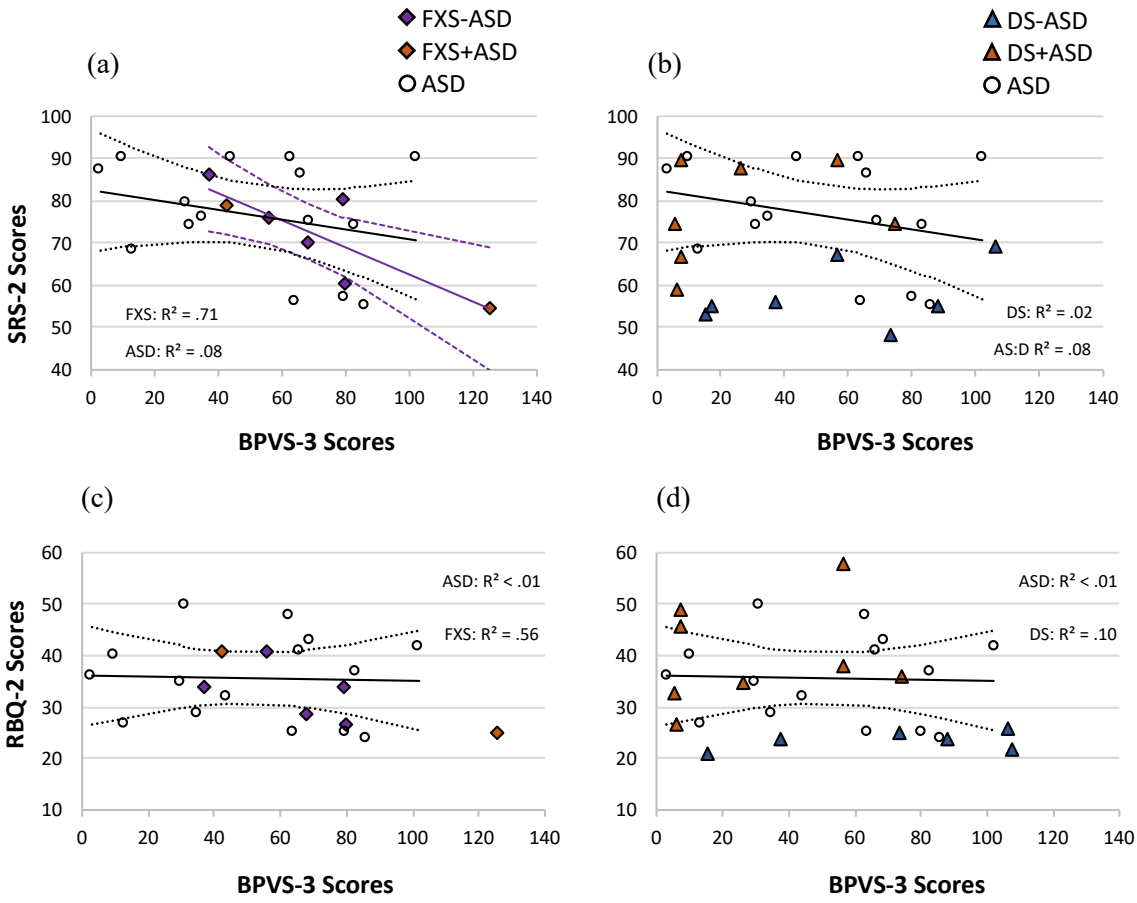

Figure 4.1. Autistic trait expression according to (a-b) SRS-2 and (c-d) RBQ-2 scores plotted against children's raw BPVS-3 scores. FXS and DS are plotted separately relative to idiopathic ASD controls. Trajectories for full DS or FXS cohorts are illustrated only when reliable.

A series of modified ANCOVAs were run to examine within and between-group trajectories of autistic trait expression relative to children's non-verbal intellectual ability according to the Leiter-3. Group was entered as the between-subjects factor

(ASD, FXS and DS) and total RBQ-2 scores as the dependent variable. Raw Leiter-3 scores were entered as a co-variate. No significant main or interaction effects emerged (Figure 4.2).

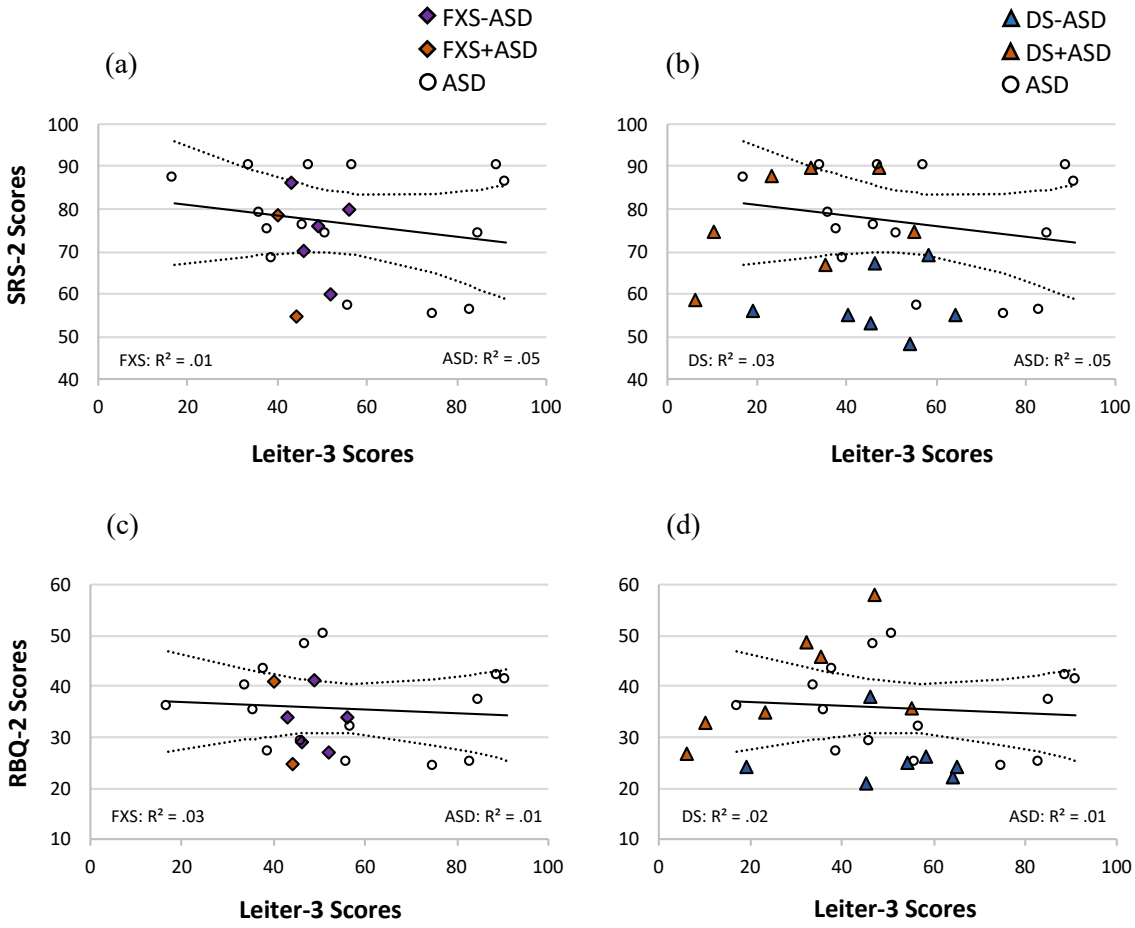

Figure 4.2. Autistic trait expression according to (a-b) SRS-2 and (c-d) RBQ-2 scores plotted against children's raw Leiter-3 scores. FXS and DS data points are plotted separately relative to idiopathic ASD controls.

Visual inspection of DS data points in Figure 4.2d revealed a distinct performance trajectory in children with comorbid ASD, identifiable by their orange colouring: a positive association was observed between total RBQ-2 and raw Leiter-3 scores (see Figure 4.2d). Bivariate correlation analyses confirmed a significant negative association

(r=.75, p=.05), differentiating these cases of comorbidity from their those with DS in isolation.

4.4.3. Group Differences in Attentional Disengagement Performance

A multivariate ANOVA was conducted to examine between-group differences in attentional disengagement performance. Group with three levels (ASD, FXS and DS) was entered as the fixed factor. Mean SRT data for each gap-overlap trial type (i.e., baseline, gap and overlap) were entered as dependent variables. The results revealed a significant main effect of trial type; F (1.3,35.6) =20.13, p<.001, η^2=.43.[31] Pairwise comparisons revealed significant mean SRT differences between trial types; participants took longer to disengage and shift attention on overlap trials (M=352, SD=105) relative to gap (M=253, SD=54, p<.001) and baseline trials (M=290, SD=53, p=.01) while mean SRTs were shortest on gap relative to baseline (p<.001) and overlap trials (p<.001).

A statistically significant difference in performance according to group was observed; F (6,50)=2.50, p=.03, Wilk's Λ=.592, η^2=.23. Tests of between-subjects effects showed that this difference was relevant to mean SRT on gap trials only; F (2,27) =5.87, p=.01, η^2=.30. According to Bonferroni post-hoc analyses, the group difference was driven by increased mean SRT in children with DS (M=291.7, SE=13.9) relative to those with FXS (M=229.8, SE=18.9) and idiopathic ASD (M=232.7, SE=12.8; see table 4.4). No significant condition × group interaction effect emerged; F (2.6,35.6) =0.62, p=.59.

Similar analyses were employed to assess between-group differences in attentional disengagement performance according to the derivative output variables of the gap-overlap task (i.e., FAC and DIS effects). No significant effects were observed.

[31] The assumption of sphericity was not met (Mauchly's W=.48, p<.001); Greenhouse-Geisser values are presented here, making an adjustment to the degrees of freedom (df) in this within-subjects analysis.

Table 4.4.

Pairwise Comparisons of Mean SRT data on Gap Trials

					95% CI for Difference	
		Mean Difference	**Std. Error**	**Sig.**	**Lower Bound**	**Upper Bound**
DS	FXS	61.94	23.47	.04	2.02	121.85
	ASD	59.08	18.95	.01	10.71	107.44

4.4.4. Autistic Trait Variation and Attentional Disengagement Performance

Separate ANCOVA models were run to analyse variability in SRS-2 scores according to children's mean SRT data for each gap-overlap condition (i.e., baseline, gap and overlap), with group (ASD, DS and FXS) as fixed factor. No significant main or interaction effects emerged (see Figure 4.3). Cook's Distance values were inspected to identify significant outliers; one emerged within the DS cohort, as can be seen in the plot illustrating SRS-2 scores according to baseline SRT (Figure 4.3). Removing this outlier and repeating the analysis had no impact on the results; no significant main or interaction effects were observed. By extension, independent samples t-tests were conducted to assess whether children with DS and ASD (n=7) differed significantly from their peers with DS-ASD (n=8) in terms of SRT for each gap-overlap condition; no significant group differences were observed.

Next, I assessed within and between-group variability in autistic trait severity according to attentional disengagement performance in contexts of competing visual stimuli, as indexed by the DIS effect (overlap-baseline SRT) derived from the gap-overlap task. I ran a modified ANCOVA with group as the between-subjects factor (ASD, FXS and DS) and total SRS-2 scores as the dependent variable. DIS effect size was entered as a co-variate in these models. No significant main or interaction effects emerged. These

data are illustrated in Figure 4.4, along with the corresponding baseline and overlap SRT data for reference.

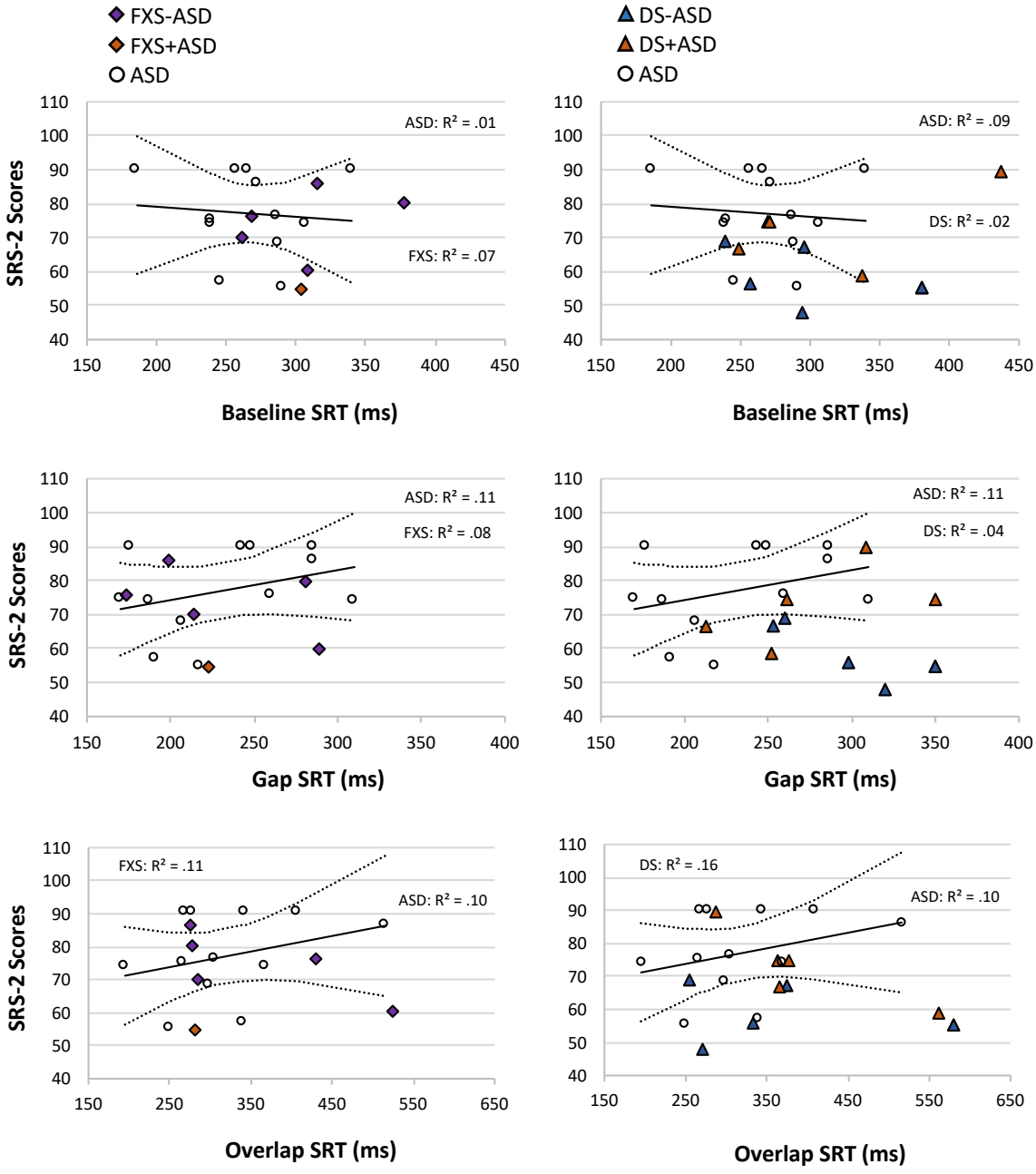

Figure 4.3. Total SRS-2 scores plotted against baseline, gap and overlap SRT data. FXS and DS data points are plotted separately relative to idiopathic ASD controls

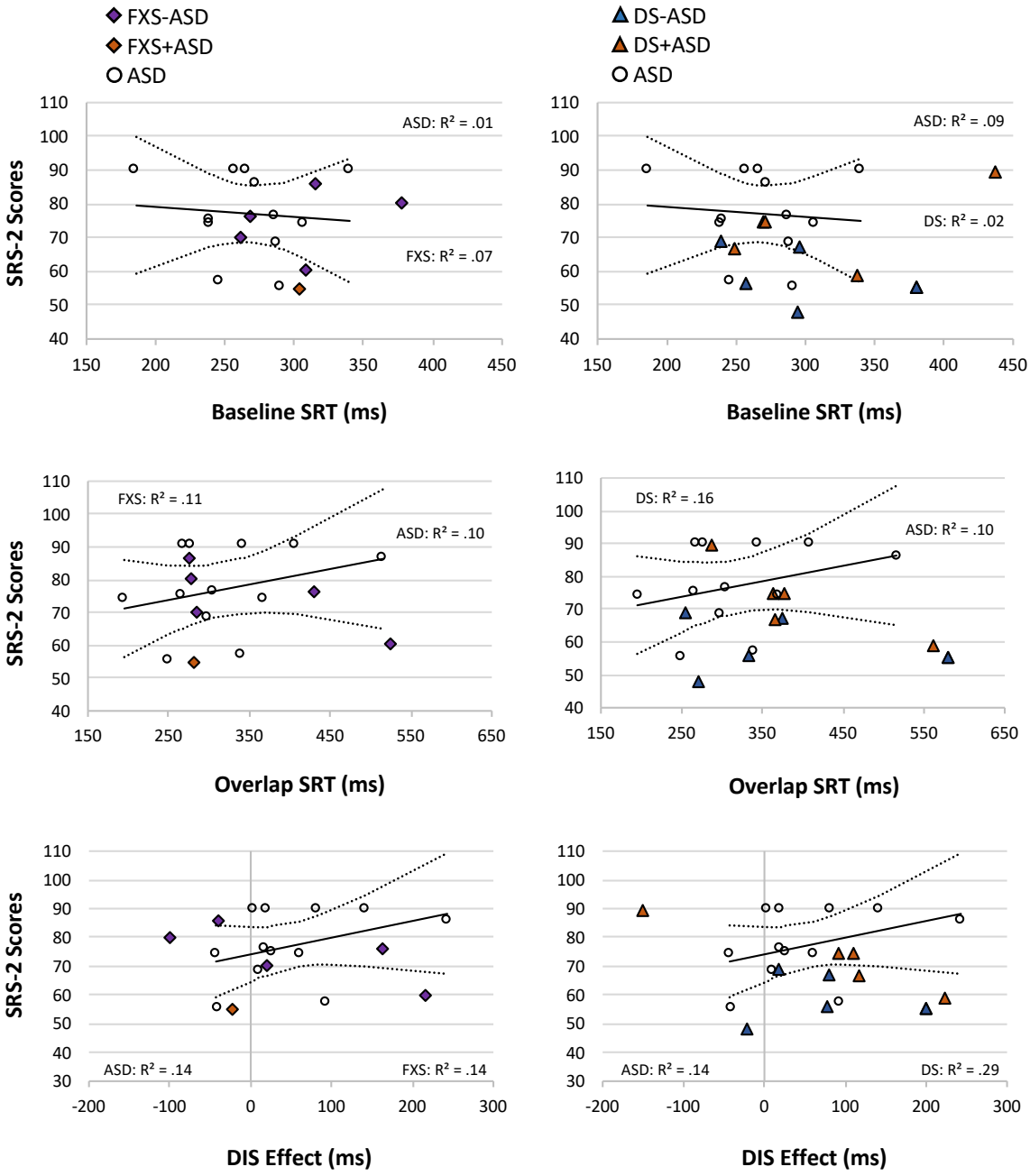

Figure 4.4. Total SRS-2 scores plotted against DIS effect data, preceded by the associated baseline and overlap SRT data. FXS and DS data points are plotted separately relative to idiopathic ASD controls.

Following this, within and between-group variation in autistic trait expression was examined according to FAC effect data (baseline-gap SRT). I ran a modified ANCOVA with group as the between-subjects factor (ASD, FXS and DS) and total SRS-2 scores as the dependent variable. FAC effect data were entered as a co-variate in this model. The results revealed a significant main effect of group [F (2, 23) = 6.35, p=.006, η^2=.36] and a significant group × FAC interaction effect [F (2, 23) = 4.55, p=.02, η^2=.28]. As can be seen in Figure 4.5, the performance gradients in both FXS and DS cohorts differ relative to that which is observed in children with idiopathic ASD (i.e., a significant negative association between SRS-2 scores and FAC effect size).

Re-running this ANCOVA model with chronological age entered as a co-variate revealed no main effects, but a significant group × age × FAC interaction effect; F (3, 21 = 6.50, p=.003, η^2=.48. Partial correlation analyses revealed that in the case of DS, the significant positive relationship between SRS-2 scores and FAC was moderated by chronological age within the current DS cohort only (r = .37, p = .31). In children with idiopathic ASD, the significant negative association between SRS-2 and FAC remained when differences in chronological age were considered (r = -.65, p = .03). Similarly, in the case of FXS, the significant positive association between SRS-2 and FAC remained when chronological age was considered (r = .91, p = .03).

Co-varying for children's raw BPVS-3 and Leiter-3 scores in separate ANCOVAs looking at within and between-group variation in SRS-2 scores according to FAC yielded no significant main or interaction effects.

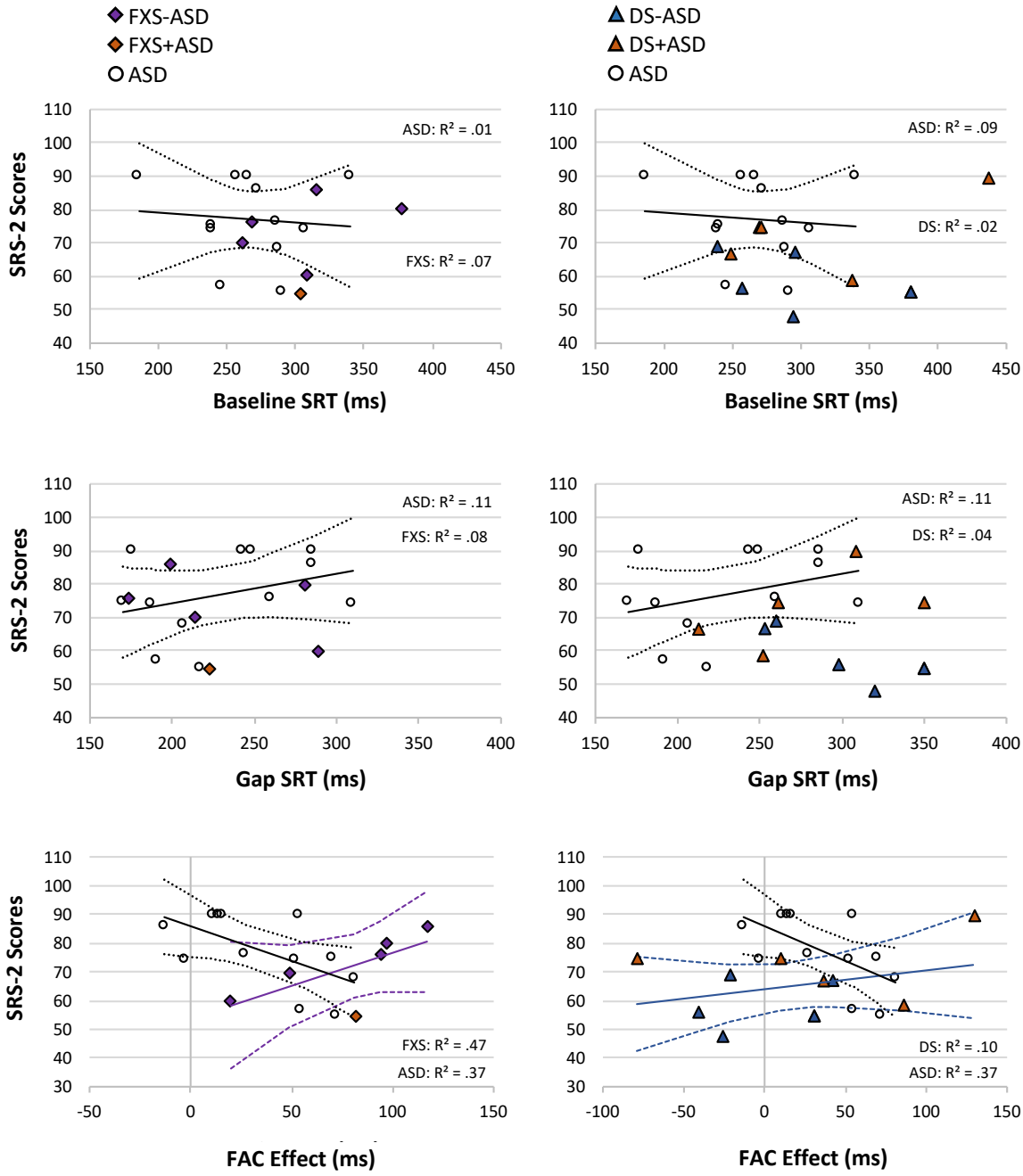

Figure 4.5. Total SRS-2 scores plotted against FAC effect data, preceded by the associated baseline and gap SRT data. FXS and DS data points are plotted separately relative to idiopathic ASD controls. Trajectories for full DS or FXS cohorts are illustrated only when reliable.

To compliment these trajectory analyses, I adopted a case-series approach to examine FXS data points in greater detail. This revealed that six of the seven FXS cases fell outside of the confidence intervals of the idiopathic ASD trajectory, supporting a distinct performance trajectory (Table 4.5). Inspecting the characteristics and performance profile of the single case (FX2) that fell within these confidence intervals revealed nothing to differentiate him from his peers.

Table 4.5.
Case-Series Description of FXS Data Points in Positive Association between SRS-2 scores and FAC effect size.

	FX1	**FX2**	**FX3**	**FX4**	**FX5**	**FX6**	**FX7**
Age (months)	71	79	84	84	100	105	106
Gender (m/f)	m	m	m	f	m	m	m
Comorbid ASD	×	×	×	×	×	✓	✓
Leiter-3 Score	52	46	49	56	43	40	40
BPVS-3 Score	80	68	56	79	37	42	125
Trajectory Data							
SRS-2	60	70	76	80	86	79	55
FAC effect (ms)	20	49	94	97	117	---	81
Within ASD CI	×	✓	×	×	×	×	×

Similarly, I examined within and between-group variation in children's total RBQ-2 scores relative to their performance on the gap-overlap task. Separate ANCOVA models were run to analyse variability in RBQ-2 scores according to children's mean SRT data for each condition (i.e., baseline, gap and overlap) with group (ASD, FXS and DS) as fixed factor. No significant main or interaction effects emerged (see Figure 4.6). Cook's Distance values were inspected to identify significant outliers; none emerged.

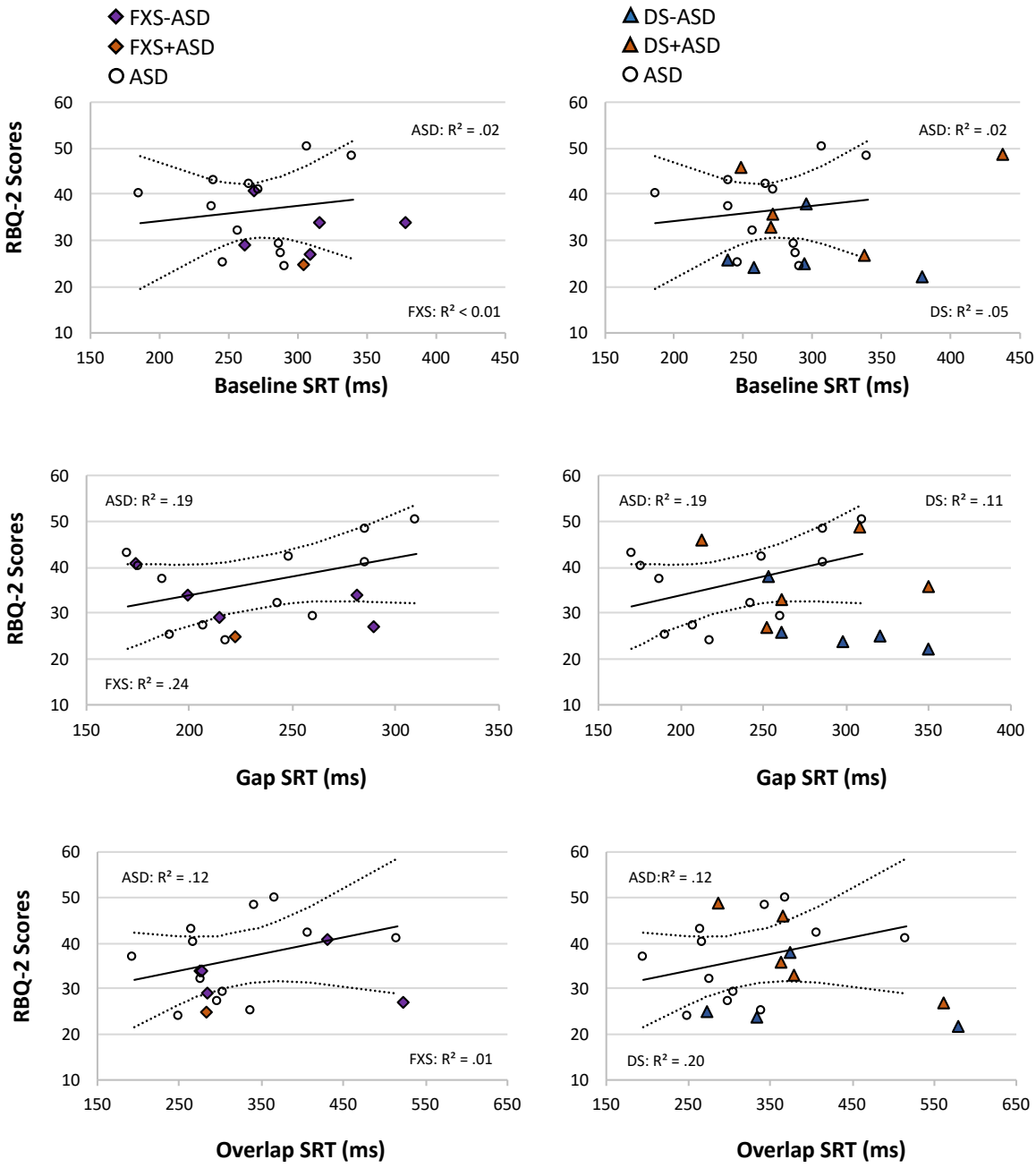

Figure 4.6. Total RBQ-2 scores plotted against baseline, gap and overlap SRT data. FXS and DS data points are plotted separately relative to idiopathic ASD controls.

Next, I assessed within and between-group variability in RRB expression according to attentional disengagement efficiency in contexts of competing visual stimuli, as indexed by the DIS effect (overlap-baseline SRT). I ran a modified ANCOVA with group as the between-subjects factor (ASD, FXS and DS) and total RBQ-2 scores as the dependent

variable. DIS effect size was entered as a co-variate in these models. No significant main or interaction effects emerged. These data are illustrated in Figure 4.7, along with the corresponding baseline and overlap SRT data for reference.

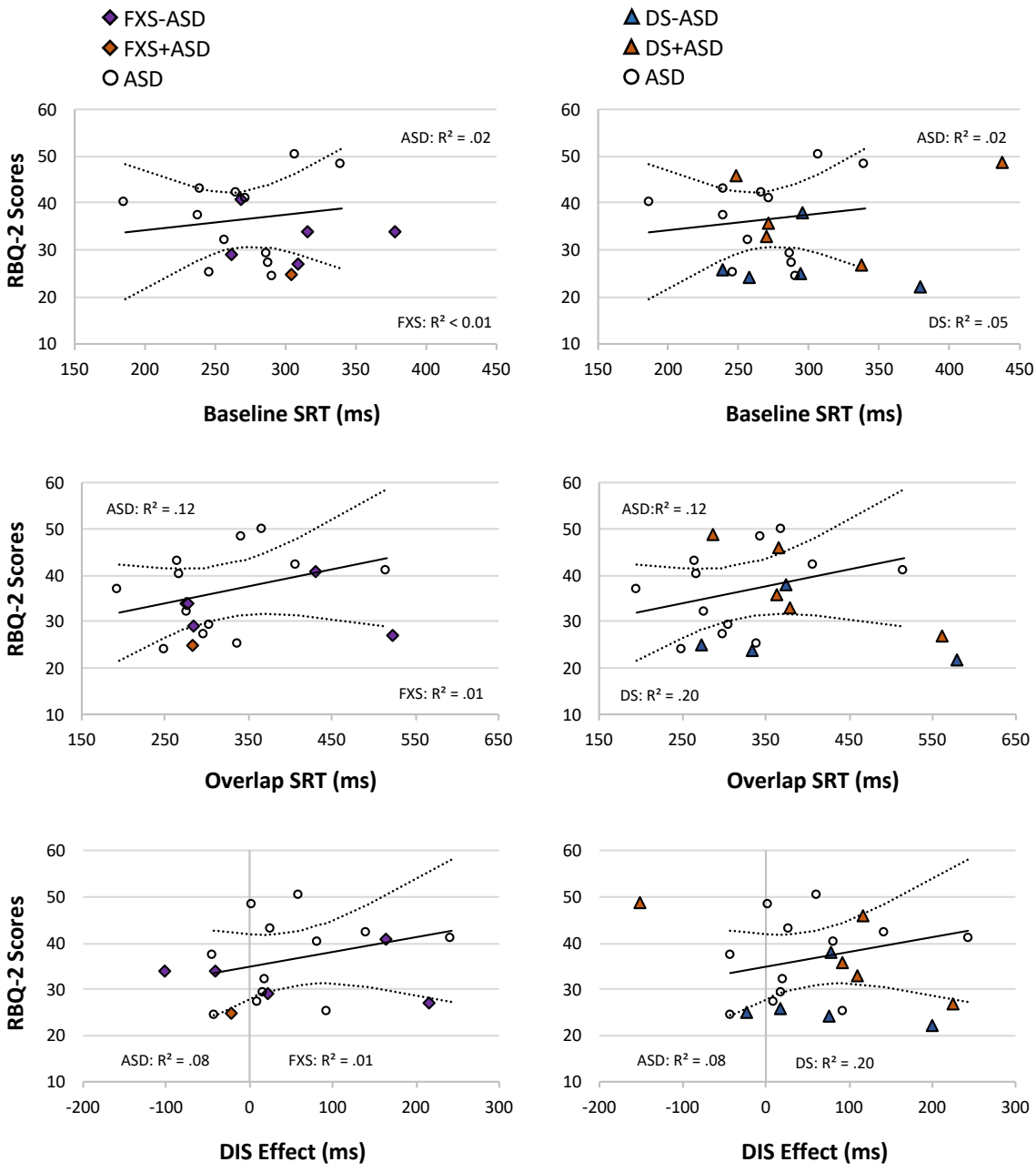

Figure 4.7. Total RBQ-2 scores plotted against DIS effect data, preceded by the associated baseline and overlap SRT data. FXS and DS data points are plotted separately relative to idiopathic ASD controls.

Following this, I examined within and between-group variability in RRB expression according to FAC (baseline-gap SRT). I ran a modified ANCOVA with group as the fixed factor (ASD, FXS and DS) and total RBQ-2 scores as the dependent variable. FAC effect data were entered as a co-variate in this model. No significant main group or FAC effects emerged. Further, no significant interaction effect was found; F (2, 22) = 2.68, p=.08, η^2=.21. Driven by a priori hypotheses that visuo-perceptual profiles in children with either DS or FXS would differ significantly from cases of idiopathic ASD, I re-ran this ANCOVA with group with only two levels (ASD and DS) as the between-subjects factor revealed a significant interaction effect; F (1, 18) = 4.66, p=.05, η^2=.21. This result suggests that, contrary to what was observed in cases of idiopathic ASD, greater trait expression in DS was associated with increased facilitation of disengagement on trials characterised by an inter-stimulus gap relative to baseline (Figure 4.8). Again, this effect was moderated by chronological age, as confirmed using partial correlation analyses (r = .43, p = .25).

Similarly, I investigated within and between-group trajectories in RRB expression according to FAC effect size in children with FXS relative to idiopathic ASD controls. No statistically significant main or interaction effects emerged; however, bivariate correlation analysis revealed a significant positive association between RBQ scores and FAC effect sizes in children with FXS (r=.83, p=.04). Of note, this association remained significant when chronological age differences were considered in a partial correlation analyses (r=.91, p=.03).

Co-varying for children's raw BPVS-3 and Leiter-3 scores in separate ANCOVAs looking at within and between-group variation in RBQ-2 scores according to FAC yielded no significant main or interaction effects.

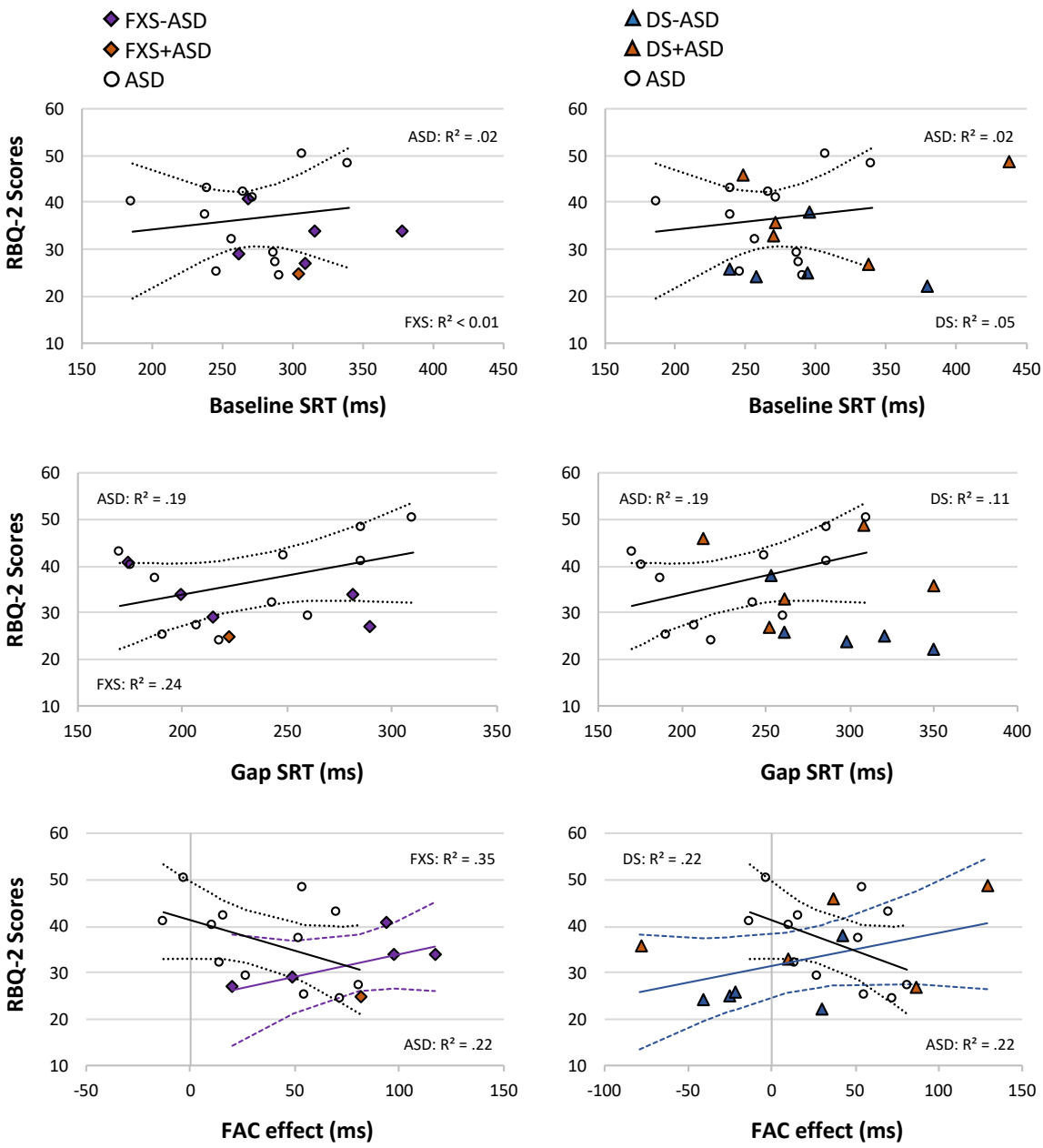

Figure 4.8. Total RBQ-2 scores plotted against FAC effect data, preceded by the associated baseline and gap SRT data. FXS and DS data points are plotted separately relative to idiopathic ASD controls. Trajectories for full DS or FXS cohorts are illustrated only when reliable.

In this instance, a case-series examination of individual FXS cases revealed that five of the total number of seven fell outside of the confidence intervals of the idiopathic ASD trajectory (Table 4.6). The two cases positioned within these confidence intervals were FX2 and FX7. Inspecting the characteristics and performance profile of case FX2 revealed nothing to differentiate this child from his peers. FX7, conversely, was one of two children with FXS to carry a clinical diagnosis of ASD. He displayed an uneven cognitive profile characterised by poor non-verbal intellectual functioning and a relative strength on the BPVS-3 measure of receptive language. No patterns of shared variance between cases FX2 and FX7.

Table 4.6

Case-Series Description of FXS Data Points in Positive Association between RBQ-2 Scores and FAC Effect Size.

	FX1	**FX2**	**FX3**	**FX4**	**FX5**	**FX6**	**FX7**
Age (months)	71	79	84	84	100	105	106
Gender (m/f)	m	m	m	f	m	m	m
Comorbid ASD	×	×	×	×	×	✓	✓
Leiter-3 Score	52	46	49	56	43	40	40
BPVS-3 Score	80	68	56	79	37	42	125
Trajectory Data							
RBQ-2	27	29	41	34	34	41	25
FAC effect (ms)	20	49	94	97	117	---	81
Within ASD CI	×	✓	×	×	×	×	✓

4.5. Discussion

This chapter details an empirical investigation into the intellectual and visuo-perceptual correlates of autistic trait expression in children with FXS, DS and idiopathic ASD, with a specific focus on attentional disengagement efficiency according to performance on a gap-overlap task. Moreover, as syndromic forms of ASD have been hypothesised to manifest largely on account of impaired cognitive function, I examined the degree of variance in autistic trait severity accounted for by verbal and non-verbal intelligence factors. In this regard, significant group differences emerged. Within the current DS cohort, children with a clinical diagnoses of ASD were differentiated from their peers with DS-ASD according to increased levels of non-verbal intellectual impairment. This finding is consistent with previous reports of a greater likelihood of ASD comorbidity in DS in cases of increased cognitive impairment (Capone et al., 2005; Moss & Howlin, 2009). Intellectual disability may increase the likelihood of ASD diagnoses partly on account of the fact that many of the clinical criteria and test measures used are developmentally weighted. Alternatively, it may be the case that a common underlying mechanism, such as a deficit in neuronal network connectivity, underlies increased ASD risk in low-functioning clinical populations (Dierssen & Ramakers, 2006; Geschwind & Levitt, 2007). Prospective longitudinal enquiry into the early risk markers associated with manifestations of ASD in DS will be necessary to elucidate neurodevelopmental pathways to comorbidity.

Further, in the current sub-sample of children with DS+ASD, a unique association emerged; RRB severity was increased in cases of higher non-verbal intellectual ability. In terms of interpreting this result, increased rates of RRB may reflect an elevated interest in and tendency towards engaging with the more predictable, non-social elements of a child's environment. Increased exposure to these particular kinds of

learning experiences, then, may facilitate a child's ability to engage with a task like the Leiter-3, designed to measure non-verbal reasoning ability in the absence of explicit social and linguistic exchange (Evans, Kleinpeter, Slane, & Boomer, 2014; Honey, McConachie, Randle, Shearer, & Couteur, 2008).

Similarly, autistic trait expression was found to vary significantly according to receptive language ability, as indexed by the BPVS-3, in children with FXS only; no association emerged in children with idiopathic ASD or DS. This finding mirrors the results of previous studies investigating language profiles in children with FXS and idiopathic ASD; these revealed that language functions are more closely linked to expressions of autistic symptomology in the case of FXS (Abbeduto et al., 2018; Philofsky et al., 2004; Thurman et al., 2017). Due to the small size of the current FXS sample, this result requires replication. Nevertheless, it points to a syndrome-specific phenotype that implicates receptive language abilities in expressions of autistic-like impairment to a greater degree than in cases of idiopathic ASD and DS. It may be that an attentional system characterised by a decreased signal-to-noise ratio in FXS functions at a cost to children's ability to process linguistic input with negative implications for receptive language outcomes. Cross-syndrome longitudinal studies are necessary in order to elucidate the degree to which verbal and non-verbal intelligence factors are implicated in syndrome-specific trajectories of phenotypic expression.

Empirical enquiry into the visuo-perceptual processes underpinning autistic-like trait expression in children with FXS and DS revealed further support for a phenotypic differentiation. No group differences emerged on baseline or overlap trials; however, mean SRTs on gap trials were significantly increased in children with DS relative to both FXS and idiopathic ASD cohorts. These data are inconsistent with the results of Landry & Bryson's (2004) study wherein the same gap-overlap task was administered

to 5-year-olds with idiopathic ASD and children with DS matched according to chronological age and intellectual ability. According to their data, groups performed equivalently on gap trials; however, on overlap trials, children with idiopathic ASD took significantly longer to disengage and shift attention in response to peripheral stimulus onset. The authors interpreted this result as illustrating a degree of syndrome-specificity in terms of early disengagement difficulty in contexts of competing visual stimuli as idiopathic ASD but not DS was associated with this kind of 'sticky attention'. In reference to the contrasting results of the current study (i.e., groups performed equivalently on overlap trials), age-related differences warrant consideration; our participant samples were older. Idiopathic ASD in early childhood may be marked by longer SRTs on overlap trials due to a delay in the maturation of corresponding oculomotor control systems; similar SRTs in older children may be indicative of a developmental catch-up following this initial period of delay and/or a reduced sensitivity of overlap trials to differentiate clinical cohorts with increasing chronological age.

Progressing beyond mean group comparisons, I examined SRT derived from the gap-overlap task according to within and between-group variability in autistic trait severity. The results revealed significant group differences only in reference to FAC (baseline-gap SRT). Within the current idiopathic ASD cohort, increased trait severity was associated with decreased FAC effect size. Conversely, increased autistic-like impairment in DS and FXS was associated with increased FAC indexing a greater SRT reduction on gap relative to baseline trials.

This result is consistent with the notion that visuo-attentional irregularity is implicated in expressions of autistic-like impairment in children with FXS and DS in a manner that is syndrome-specific. In the case of FXS, dorsal stream vulnerability to FMRP loss has

been proposed to underpin the visuo-spatial deficits observed in children and adults with FXS (Rais, Binder, Razak, & Ethell, 2018). Magnocellular neurons in the dorsal visual stream, for instance, have been shown to be particularly sensitive to Fmr1 deficiency (Kogan et al., 2004).[32] Additionally, abnormal synaptic circuitry on account of immature dendritic morphology has been noted in the visual cortical areas of FXS mouse models (Berman, Murray, Arque, Hunsaker, & Wenzel, 2012; Irwin et al., 2002). Moreover, before being integrated at the cerebral level, visual inputs are detected by and transmitted through the retina. Mouse modelling research has shown that Fmr1 deficiency impairs retinal function, resulting in a molecular and cellular phenotype characterised by synaptic dysregulation (Rossignol et al., 2014).

While the neuropathological mechanisms underpinning visual and attentional deficits in children with DS and FXS remain unclear, the results of this study suggest that, in both cases, the likelihood of autistic-like impairment is greater in children who experience increased visuo-perceptual irregularity. More specifically, autistic trait levels were elevated in children with FXS and DS exhibiting greater disengagement difficulty on a gap-overlap task. These data are consistent with the notion of syndrome-specific profiles of socio-communicative impairment and RRB in children with idiopathic ASD, FXS and DS according to underlying visuo-perceptual process. The clinical and conceptual implications of these findings are examined in Chapter 7. The following chapter presents a cross-syndrome study of visual search abilities in these idiopathic ASD, FXS and DS cohorts.

[32] The dorsal stream extends from the primary visual cortex to the intraparietal sulcus and superior parietal lobule, as well as the frontal eye fields. It functions to integrate and resolve competing exogenous inputs and, in doing so, allows for visuo-spatial selection (Pammer et al., 2006).

Chapter 5: Autistic Trait Expression and Visual Search Performance in Children with FXS and DS

5.1. Overview

Enhanced visual search performance is a well-established phenotypic feature of idiopathic ASD, as supported by the data presented in Chapter 3. Despite the high rates of autistic-like impairment observed in children with FXS and DS, there have been no empirical studies to date investigating visual search abilities in reference to expressions of autistic-like impairment in either of these high-risk genetic syndrome groups.

This chapter presents a cross-syndrome study of visual search abilities in children with idiopathic ASD, DS and FXS. Within- and between-group variation in autistic trait severity was examined according to search efficiency (i.e., mean target detection latency) on single feature and conjunction trial types. Children with idiopathic ASD were expected to outperform their peers with DS and FXS. Within the FXS cohort, higher autistic trait levels were anticipated with increased target detection latency, in accordance with the selective attention deficits previously documented in cases of FXS. In children with DS, a significant positive association was anticipated between autistic trait severity ratings and visual search latencies on account of generally delayed motor processing.

Contrary to these hypotheses, children with idiopathic ASD outperformed only their peers with FXS in terms of visual search efficiency, consistent with the notion of a syndrome-specific phenotype according to underlying visuo-perceptual mechanism. No significant group differences were observed between idiopathic ASD and DS cases. Yet within the DS cohort, ASD comorbidity was associated with significantly decreased target detection latency (improved search performance), suggesting a similar phenotypic advantage as that which is considered a robust phenotypic marker of idiopathic ASD.

5.2. Introduction

Eye-tracking paradigms are commonly employed to examine visual search abilities in clinical and non-clinical populations. Such paradigms typically involve presenting a viewer with stimulus arrays that feature one or multiple target items and instructing the viewer to locate these items (Treisman & Gelade, 1980). The identification of a target according to a single feature dimension, for instance, a red square within an array of yellow squares, is termed single feature search. In such cases, the saliency of the target stimulus established by its unique physical attribute - captures the viewer's attention (Corbetta & Shulman, 2002; Desimone & Schein, 1987; Theeuwes, 1992). Single feature search performance is, consequently, considered to be stimulus-driven / governed by exogenous attentional processes. This is somewhat illustrated by observations that larger set sizes (i.e., increased numbers of distractors) do not result in longer search times. Conjunction search performance, conversely, requires effortful shifts in attention. In these cases, the target item is identifiable according to a conjunction of features (e.g., a red square within a field of red triangles, yellow triangles and yellow squares) and larger set sizes yield longer target detection latencies.

Studies that have examined developmental trajectories of single feature and conjunction search performance in NT children offer valuable insight into the age-related maturation of selective attention processes. For instance, single feature search performance plateaus in NT children at approximately 2 years of age reflecting an early maturation of exogenous attentional control processes (Woods et al, 2013). Conjunction search performance, by comparison, continues to improve throughout childhood and adolescence (Brennan et al., 2017; Donnelly et al., 2007; Woods et al., 2013). This is due to a prolonged age-related maturation of endogenous attentional control mechanisms, likely associated with the protracted neuronal development of

frontoparietal brain regions, in conjunction with an increasingly more distributed network architecture (Fair et al., 2009; Farrant & Uddin, 2015; Supekar et al., 2009). Immature endogenous control mechanisms in childhood mean that selective attention is vulnerable to attentional capture by task-irrelevant stimuli, with implications for conjunction search efficiency (Gaspelin, Margett-Jordan, et al., 2015). In adulthood, the neural systems required to support the employment of top-down attentional control are fully developed, enabling an active suppression of attentional capture by salient but irrelevant search items (Folk et al., 1992; Gaspelin, Leonard, et al., 2015; Lien et al., 2010). These systems include a frontoparietal network featuring the frontal eye fields, inferior frontal junction, superior frontal and angular gyri, and the precuneus (e.g., Couperus & Mangun, 2010; Payne & Allen, 2011; Ruff & Driver, 2006; Sylvester, Jack, Corbetta, & Shulman, 2008; for review, see Zanto & Rissman, 2015)

The application of visual search tasks to children with idiopathic ASD has uncovered a phenotypic advantage whereby these children outperform their NT peers, more often on conjunction than single feature trials (Dakin & Frith, 2005; Simmons et al., 2009). Plaisted and colleagues (1998) were the first to note this advantage in children with idiopathic ASD. They administered a visual search task to 8-year-olds with and without idiopathic ASD matched according to chronological age and verbal ability and found that those with ASD look significantly less time to locate target stimuli amidst conjunction search arrays. This result has since been replicated in similar studies of visual search performance in idiopathic ASD and NT cohorts in mid-late childhood (e.g., Jarrold et al., 2005; O' Riordan, 2000).

Kadly and colleagues (2011) designed a visual search task that required no verbal instruction and was, consequently, suitable for administration to young children and clinical samples characterised by low levels of linguistic ability. They administered this

task to toddlers with idiopathic ASD and age-matched NT controls and found that ASD status was associated with superior performance on conjunction search trials. Moreover, the data showed that these toddlers with idiopathic ASD scanned a greater number of items per search trial than their NT peers. This was interpreted by the authors as reflecting enhanced perceptual discrimination facilitating more efficient serial search (O'Riordan & Plaisted, 2001; Wolfe, Cave, & Franzel, 1989).

The neural processes underpinning this phenotype advantage have been examined. Keehn and colleagues (2008) collected fMRI data (BOLD responses) from children and adolescents with idiopathic ASD and NT controls matched on age and non-verbal intelligence. Their data showed that during visual search performance, the ASD cohort demonstrated greater activation of occipital brain regions, consistent with the notion that this visuo-perceptual strength is due to enhanced discriminatory capacities. Moreover, the authors noted increased frontoparietal activation. Considered in tandem, these findings suggest that superior search performance in idiopathic ASD is due to greater top-down modulation of visuo-attentional processes, in conjunction with increased bottom-up processing of exogenous inputs. In keeping with this notion, Keehn and colleagues (2013) later observed enhanced functional connectivity between occipital and frontal brain regions during visual search performance in children and adolescents with idiopathic ASD relative to NT controls. These findings require replication. Still, they provide useful insight into the neural correlates of enhanced visual search performance in idiopathic ASD.

Genetic syndromes that feature high rates of autistic-like impairment are considered useful models to study phenotypic emergence and expression when genetic aetiology is well-defined (Karmiloff-Smith, 1998; Karmiloff-Smith et al., 2016). However, debate

in ongoing with regard to the precise nature of the autistic-like deficits observed in DS and FXS populations (McDuffie et al., 2015; Moss et al., 2013; Warner et al., 2017).

Despite the well-established visuo-perceptual profile observed in cases of idiopathic ASD, it remains to be seen whether manifestations of autistic-like deficits in DS or FXS cohorts are characterised by superior search abilities. More generally (i.e., not in relation to autistic-like trait expression), we know that irregular visual attention is a phenotypic feature of FXS; visual search paradigms offer a useful means of characterising this irregularity. Scerif and colleagues (2004) examined visual search abilities in 4-year-olds with FXS relative to chronological age-matched NT controls. They found that the speed at which children with FXS located target items was equivalent to NT controls; however, they produced a significantly greater number of immediate repetitive and distractor errors. This was interpreted by the authors as reflecting a selective attention deficit in young children with FXS.

Munir and colleagues (2000) examined visual search performance in older boys with FXS aged between 8 and 15 years. Performance was assessed relative to boys with DS matched according to age and intellectual ability, and two cohorts of mental age-matched NT boys; one of these cohorts was characterised by high (non-clinical) levels of inattention and hyperactivity, while the other was characterised by age-appropriate levels of both. Their results showed that relative to both NT control groups, both the DS and FXS groups took significantly longer to search for target items, found significantly fewer correct targets and made a significantly greater number of incorrect clicks on non-target items. These search data revealed weaknesses in task-irrelevant response inhibition for both FXS and DS cohorts, though these difficulties were most pronounced in boys with FXS (Wilding et al., 2002).

Steele and colleagues (2011) examined visual search data collected from infants with DS, William syndrome and mental age-matched NT controls. In addition to making more a greater number of search errors, infants with DS were slower than both other groups at locating target items. The authors interpreted this significant group difference as generally delayed motor processing in DS.

In conclusion, there is evidence to suggest that DS and FXS are associated with syndrome-specific profiles of visuo-attentional irregularity. Visuo-perceptual irregularity is considered by many a primary deficit in ASD. This raises the question as to whether syndromic forms of ASD arise on account of elevated visuo-perceptual irregularity in a manner that is consistent with idiopathic manifestations or whether autistic-like deficits are expressed according to elevated visuo-perceptual irregularity in a manner that is syndrome-specific.

5.2.1. The Current Study

Despite the high-risk status of these genetic syndrome groups, there have been no studies to date investigating visual search performance in reference to expressions of autistic-like impairment in children with FXS or DS. Documenting the visuo-perceptual features associated with autistic-like traits in these groups is necessary to inform prospective longitudinal enquiry into the early risk markers associated with syndromic manifestations of comorbidity, with clinical relevance with regard to the early identification of syndromic ASD-like impairments.

This chapter presents an empirical examination into visual search abilities in children with idiopathic ASD, FXS and DS matched according to chronological age, receptive language ability, non-verbal intelligence and autistic trait severity. Children with idiopathic ASD were expected to outperform their peers with DS and FXS. Moreover, it was hypothesised, contrary to what was observed in cases of idiopathic ASD, that

higher ASD trait levels in children with DS and FXS would be significantly positively associated with target detection latencies, indicative of poorer search performance. In the case of FXS, I anticipated this positive association on account of the selective attention deficits previously observed in FXS cohorts. By contrast, I predicted increased autistic trait severity with decreased search efficiency in children with DS on account of generally delayed motor processing. The phenotypic heterogeneity proposed here is consistent with empirical reports of distinct behavioural phenotypes of autistic-like impairment in these high-risk genetic syndrome groups. Moreover, it aligns with the literature illustrating syndrome-specific profiles of visuo-attentional irregularity in FXS and DS populations.

5.3. Method

5.3.1. Participants

As detailed in the previous chapter, sixteen children with idiopathic ASD, fifteen children with DS and seven children with FXS were recruited to take part in this study (for details regarding recruitment process and inclusion criteria, see Chapter 2). Participant groups were matched according to chronological age, non-verbal intelligence (Leiter-3), receptive language ability (BPVS-3) and autistic trait severity (RBQ-2 and SRS-2; see Tables 4.1 and 4.2).

5.3.2. Measures and Procedure

Measures and data collection procedures were as previously described in Chapter 2. Data collection took place at the Birkbeck Babylab, CBCD. All testing sessions comprised an 80-minute behavioural assessment, followed by a 15-minute eye-tracking session. Prior to this, parents were briefed and written participatory consent was acquired.

In a behavioural assessment conducted by the author, receptive language abilities were assessed using the BPVS-3 (Dunn et al., 2009) and non-verbal intellectual ability was rated according to the Leiter-3 (Roid et al., 2013). Data concerning autistic trait severity was acquired via two parent-report questionnaires: the SRS-2 (Constantino & Gruber, 2012) and the RBQ-2 (Leekman et al., 2007). The administration of both questionnaires ensured that both the social and non-social elements of the phenotype were considered.

A visual search eye-tracking paradigm was administered as a means of assessing target detection latencies on single feature and conjunction search trials (adapted from Kaldy et al., 2011; Treisman & Gelade, 1980).

5.3.3. Statistical Analyses

Shapiro-Wilks tests were run to assess the distribution of data for each variable of interest. Normal distributions were confirmed. Between-groups analyses were conducted to compare mean target detection latencies for single feature and conjunction trial types across idiopathic ASD, FXS and DS cohorts. Independent samples t-tests were employed to examine mean search latencies in children with DS according to the presence or absence of comorbid ASD. With regard to the FXS cohort, the sample size was too small (n=7) to differentiate according to comorbidity for analytic purposes. Consequently, this FXS cohort was treated as a case series allowing for more detailed examination of individual performance profiles.

Trajectory analyses (Thomas et al., 2009) were employed to assess autistic trait variation within- and between-groups according to visual search performance. Performance trajectories were analysed in terms of the intercepts and gradients. Main and interaction terms were manually entered into ANCOVA functions in SPSS. In all cases, the x-axes were re-scaled to ensure that main effects were calculated at the first point of group overlap. When necessary to correct for multiple comparisons, Bonferroni

adjusted significance levels were considered. Scatterplot representations of inferential outputs feature cases of ASD comorbidity in orange, for reference.

In the previous chapter, any statistically significant but underpowered inferential outputs derived from the FXS data set were accompanied by complementary case series analyses. These allowed for more precise description of individual FXS data points, particularly in reference to extent to which they fell within the confidence intervals of idiopathic ASD trajectories. Similar case series analyses were intended here, on the condition that significant trajectories were observed within the FXS cohort.

5.4. Results

5.4.1. Group Differences in Visual Search Performance

A multivariate ANOVA was conducted to examine between-group differences in visual search performance. Group with three levels (ASD, FXS and DS) was entered as the fixed factor. Mean target detection times for (i) single feature and (ii) conjunction search trials were entered as the dependent variables. The results revealed a statistically significant difference in performance according to group; $F(4,68)=2.80$, $p=.03$, Wilk's $\Lambda=.737$, $\eta^2=.14$. Tests of between-subjects effects revealed a significant group difference in mean target detection time for single feature trials only; $F(2,35)=4.37$, $p=.02$, $\eta^2=.20$. Bonferroni post-hoc tests showed that this effect was driven by significantly lower mean target detection times in children with idiopathic ASD (M=675, SD=263) relative to FXS (M=1085, SD=426; see table 5.1).

To determine whether increased single feature search latencies in children with FXS may be considered evidence of impaired selective attention, performance was compared with that of a NT cohort matched according to raw Leiter-3 scores, indexing non-verbal intellectual ability (see Section 2.2). An independent samples t-test was conducted to

test whether single feature search performance differed significantly between NT children (*M*=837, *SD*=328) and children with FXS (*M*=1085, *SD*=426). The result was non-significant; *t* (54) =1.80, *p*=.08.

Table 5.1
Pairwise Comparisons of Mean SRT Data on Single Feature Search Trials

					95% CI for Difference	
		Mean Difference	**Std. Error**	**Sig.**	**Lower Bound**	**Upper Bound**
ASD	FXS	-410	142	.02	-766	-54
	DS	-187	112	.32	-469	96

Further independent samples t-tests were conducted to test whether visual search abilities in children with DS varied significantly as a function of ASD comorbidity. No differences emerged in reference to single feature search performance. On conjunction search trials, a significant difference emerged [*t* (1,13) = 3.11, *p*=.009] as children with DS+ASD demonstrated significantly decreased target detection times (*M*=864, *SD*=127) relative to their peers with DS-ASD (*M*=1108, *SD*=172). Of note, this significant group difference remained when differences in an ANCOVA wherein differences in non-verbal intellectual ability were co-varied.

5.4.2. Autistic Trait Severity according to Visual Search Ability

Trajectory analyses were employed to examine within and between-group variability in autistic trait severity according to visual search performance. Modified ANCOVAs were run with group as the between-subjects factor (ASD, FXS and DS) and total SRS-2 scores as the dependent variable. Mean target detection times on single feature search trials were entered as a co-variate. No significant main or interaction effects emerged, as can be seen in Figure 5.1a.

Similar ANCOVA models were generated to explore variation in total SRS-2 scores according to mean target detection latencies on conjunction search trials. Again, the between-subjects factor was group (ASD, FXS and DS). No significant main effects emerged, but an interaction effect nearing significance was observed [$F(2,31)=4.10$, $p=.06$, $\eta^2=.17$] reflecting a positive association between SRS-2 scores and conjunction search times within the FXS cohort (Figure 5.1b). Finally, variation in autistic trait expression according to total RBQ-2 scores was examined in reference to children's single feature and conjunction search performance. No significant main or interaction effects emerged (Figure 5.2).

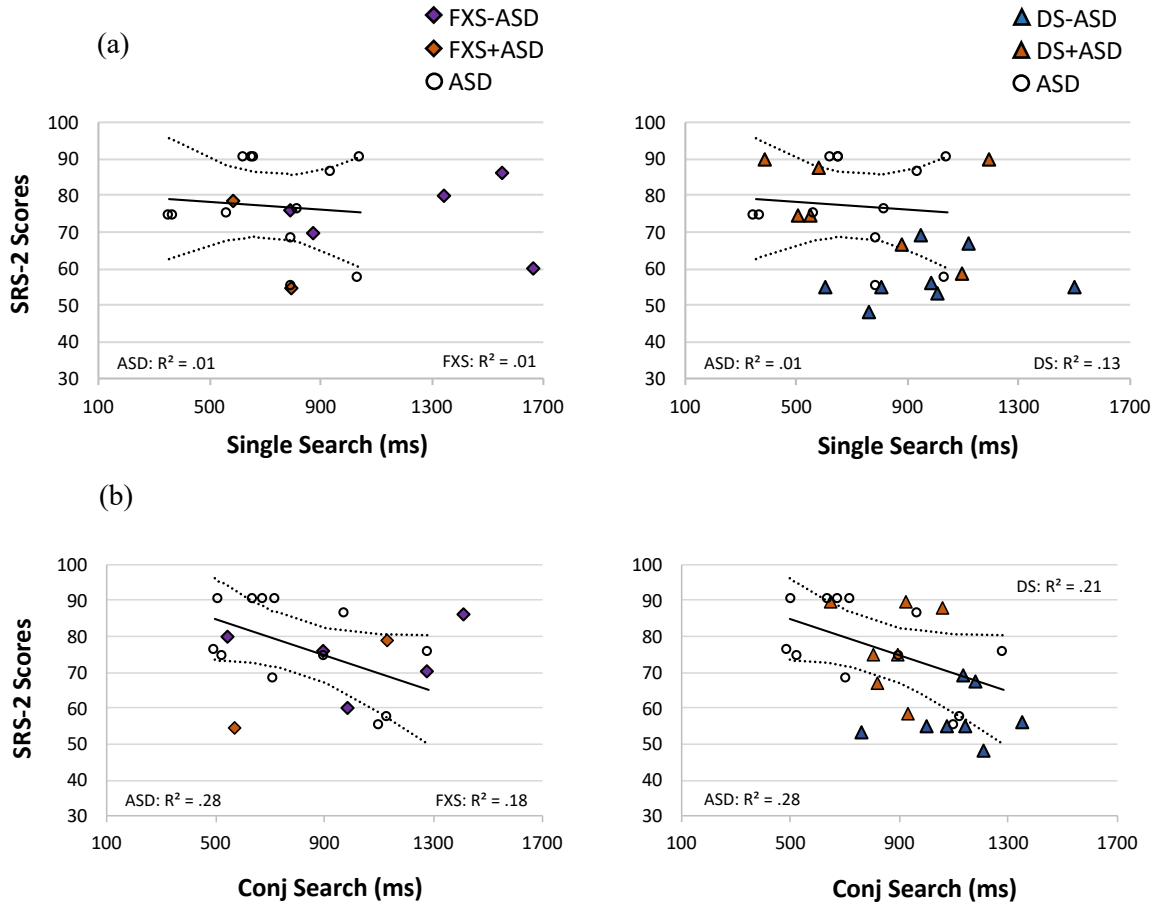

Figure 5.1. Total SRS-2 scores plotted against target detection times on (a) single and (b) conjunction (conj) search trials. FXS and DS data points are plotted separately relative to idiopathic ASD controls.

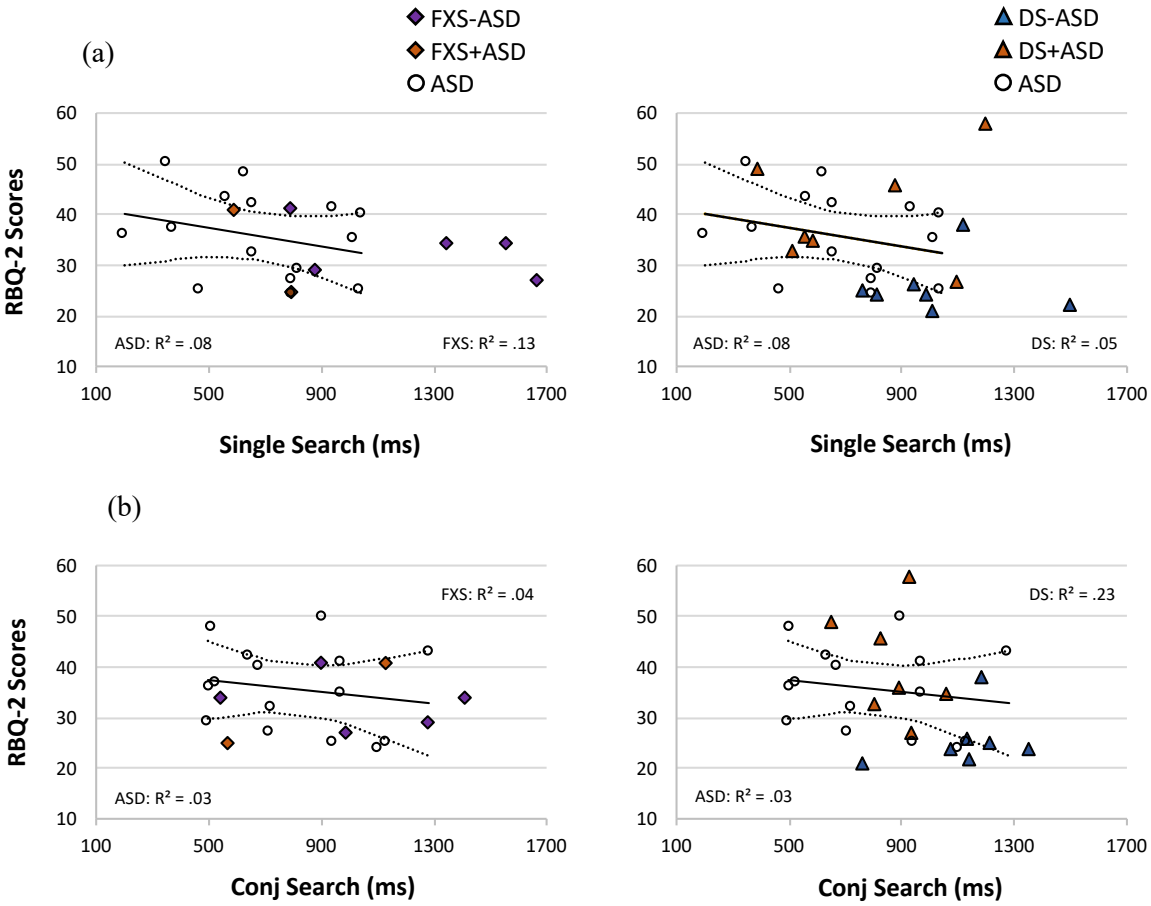

Figure 5.2. Total RBQ-2 scores plotted against target detection times on (a) single feature and (b) conjunction (conj) search trials. FXS and DS data points are plotted separately relative to idiopathic ASD controls.

5.5. Discussion

This chapter details a cross-syndrome investigation into visual search performance in children with idiopathic ASD, FXS and DS matched according to chronological age and intellectual ability. Despite similar mean levels of autistic trait severity, children with idiopathic ASD were found to take significantly less time to locate target items on single feature search arrays than children with FXS. This group difference suggests that while enhanced visual search performance is a well-documented phenotypic feature of

idiopathic ASD, it is not apparent in children with FXS. The size of the current FXS sample means that this result is suggestive only and requires replication; nevertheless, it is consistent with the notion that autistic-like deficits in FXS are characterised by distinct underlying visuo-perceptual processes.

This finding of phenotypic heterogeneity according to visuo-perceptual mechanism extends previous reports of a distinct behavioural profile of autistic symptomatology in FXS (McDuffie et al., 2015; Wolff et al., 2012). Moreover, it is in keeping with the profile of visuo-perceptual irregularity observed in cases of FXS (Cornish et al., 2004; Scerif et al., 2004; 2007). While superior search performance in idiopathic ASD cohorts is considered by many to reflect an overly-focused attentional style, often referred to as an increased signal-to-noise ratio (Joseph et al., 2009; Liss et al., 2006), there is evidence to suggest that attentional processes in FXS are characterised by a decreased signal-to-noise ratio, or diffuse attentional spotlighting (Franco et al., 2017; Golovin & Broadie, 2017).

The current result adds to the growing body of literature to suggest that profiles of autistic-like impairment in FXS differ to that which are observed in cases of idiopathic ASD. This phenotypic heterogeneity may be conceptualised according to neurodevelopmental frameworks that consider a gradual unfolding of clinical phenotypes via the cascading effects of early genetic and/or environmental disruption to basic-level processes (Karmiloff-Smith, 1998). Keehn and colleagues (2013) suggested that early difficulties self-regulating arousal levels in response to incoming sensory information may constitute a primary deficit in ASD. More specifically, they proposed that basic-level deficits in visuo-spatial orienting may be a potential means through which an infant's ability to self-regulate is disrupted; this perspective emerged based on previous observations that typically developing infants self-regulate their arousal levels

by intermittently disengaging and shifting their gaze away from faces present in their visual fields (Field, 1981). Keehn et al. (2013) posited that early difficulties disengaging and shifting attention away from faces may prompt a compensatory re-sizing of an infant's attentional spotlight as a means to self-regulate arousal levels. In application to FXS, Fmr1 deficiency has been shown to disrupt retinal structure and function early in development (Rossignol et al., 2014). One can theorise, then, that early oculomotor deficiency in cases of FXS may trigger the development of an information processing system characterised by a decreased signal-to-noise ratio. An atypically diffuse attentional system might, in turn, hinder infants' ability to reliably sample information from the environment, resulting in ambiguous representations that prompt emergent attentional biases such as a preference for predictable, self-led (i.e., non-social) forms of stimulation (Johnson, 2017). Moreover, a decreased signal-to-noise ratio may, in theory, give rise to the high rates of anxiety observed in samples of children and adults with FXS, as inadequate filtering of environmental noise may lead to elevated levels of arousal (Cordeiro et al., 2011; Ezell et al., 2018). While the current result provides preliminary support for a phenotypic differentiation on the basis visuo-perceptual mechanism, studies employing prospective longitudinal designs and infant cohorts are required to identify neurodevelopmental trajectories preceding behavioural expressions of autistic-like impairment in children with FXS relative to cases of idiopathic ASD.

Contrary to my original hypotheses, no significant group differences emerged between children with idiopathic ASD and the complete DS cohort on either single feature or conjunction search trials. However, considering visual search performance within the DS cohort according to the presence or absence of clinically diagnosed ASD revealed a significant differentiation; a phenotypic advantage emerged in cases of comorbidity as children with DS+ASD took significantly less time to locate target items on conjunction

search arrays than their peers with DS in isolation. Moreover, this differentiation remained significant when differences in non-verbal intellectual ability were taken into account. This finding is consistent with the notion that idiopathic forms of ASD and manifestations of ASD in DS share a common visuo-perceptual feature, namely enhanced performance on conjunction search trials. While this result requires replication, particularly as sample sizes were small, it implies that idiopathic forms of ASD and comorbid cases in children with DS may share common genetic risk factors and/or neuropathogenetic mechanisms. For instance, we know that certain genes located on chromosome 21 have been implicated in the emergence and expression of idiopathic ASD (e.g., BTG3, CXADR and NCAM2; Molloy et al., 2005). Comorbidity in DS may therefore be the result of the increased genetic dosage of common risk variants. Alternatively, different genetic risk factors may converge at the level of pathogenetic mechanism to produce similar visuo-perceptual profiles and phenotypic outcomes in children with idiopathic ASD and DS+ASD.

This finding prompts a number of conceptual considerations and novel testable hypotheses. Firstly, as superior search performance has been implicated early in the emergence of the idiopathic ASD phenotype (Cheung et al., 2018; Gliga et al., 2015), we might expect to observe this visuo-perceptual strength in infants with DS who later go on to receive clinical diagnosis of ASD. Prospective longitudinal research is necessary to determine whether or not enhanced search performance constitutes an early risk marker for ASD in children with DS.

Secondly, enhanced search performance in idiopathic ASD has been theorised to manifest on account of early disruption to the development of the alerting system which, in turn, prompts the emergence of an overly-focused attentional style, enabling stimulus features to be processed more efficiently at the locus of attention (Keehn et al.,

2013; Joseph et al., 2009). Support for this proposal comes from research by Blaser and colleagues (2015). They examined visual search performance and pupillary responsivity in toddlers with idiopathic ASD and NT controls. According to their results, task-evoked pupillary dilation was significantly greater in toddlers with idiopathic ASD who, incidentally, outperformed age-matched NT controls. As pupillary dilation is considered by many to be a sensitive index of arousal and attentional engagement (Hess & Polt, 1960; Jackson & Sirois, 2009; Kahneman & Beatty, 1966), the authors concluded that superior search performance in idiopathic ASD reflects a highly focused visuo-perceptual style. In light of the current results, it would be interesting to test whether search performance in children with DS+ASD elicits a similarly elevated level of pupillary dilation to imply a shared pathogenetic mechanism.

In conclusion, the results of this study are consistent with the notion of a syndrome-specific profile of autistic-like impairment in FXS according to underlying visuo-perceptual mechanism, extending the literature and elucidating the complex heterogeneity associated with this neurodevelopmental disorder. Conversely in the case of DS, ASD comorbidity is found to be associated with improved search performance, mirroring the phenotypic advantage observed in idiopathic forms of ASD. The theoretical, conceptual and clinical implications of this work are examined in Chapter 7.

Chapter 6: Visuo-Perceptual Profiles in Idiopathic ASD, FXS and DS

6.1. Overview

Chapter 3 illustrated the utility of examining performance profiles on gap-overlap and visual search paradigms in reference to one another. Here, the relationship between attentional disengagement and visual search abilities is examined in reference to syndromic forms of autistic trait expression, specifically in the context of FXS and DS.

Hypotheses were formed according to the results of the previous chapters. Similar visuo-perceptual profiles were anticipated in cases of DS and idiopathic ASD, with symptom severity levels increasing according to decreased FAC on the gap-overlap task and improved conjunction search performance. Conversely, it was hypothesised that increased trait severity in children with FXS would be associated with reduced visual search efficiency (i.e., increased target detection latencies) and increased FAC on the gap-overlap task.

Tracing and analysing these proposed three-dimensional trajectories confirmed a distinct visuo-perceptual profile in children with FXS, in a manner in keeping with the previously stated hypothesis. No coherent trend emerged to suggest a relationship between attentional disengagement and visual search efficiency according to autistic trait severity in children with DS. These results are consistent with the notion that, in the case of FXS, a syndrome-specific profile of visuo-attentional irregularity underpins expressions of autistic-like impairment. Moreover, they imply that the visuo-spatial deficits observed on gap-overlap and visual search paradigms may manifest on account of common phenotypic mechanism in children with FXS.

6.2. Introduction

A broad range of visuo-perceptual features have been documented in paediatric cases of idiopathic ASD. Typically, these features have been examined in isolation. This empirical tendency to focus discretely on individual phenotypic markers likely emerged in conjunction with a theoretical landscape formerly occupied by single deficit models of ASD. We have, as a result, acquired a rather fragmented understanding of visuo-perceptual irregularity in ASD.

There are two visuo-perceptual features of idiopathic ASD, in particular, that have, in theory, been difficult to reconcile. The first - inefficient attentional disengagement or 'sticky attention' - has been implicated in the early emergence and expression of the phenotype. The second - enhanced visual search performance – has been established in the literature as an early risk marker and robust visuo-perceptual feature of idiopathic ASD. Indeed, while disengagement deficits on gap-overlap tasks have been observed in children with idiopathic ASD, so too have performance strengths on visual search tasks. Moreover, there is evidence to suggest that the phenotypic advantage observed on visual search tasks is due to decreased fixation latencies on search items (Joseph et al., 2009); this begs the question 'how can children with idiopathic ASD disengage and shift their attention efficiently between visual search items but struggle to disengage and shift flexibly on gap-overlap trials?'.

Chapter 3 of this thesis set out to bridge this apparent dichotomy by investigating the relationship between attentional disengagement and visual search performance in children with idiopathic ASD and NT controls matched on indices of verbal and non-verbal intellectual ability. According to the acquired gap-overlap data, there was no evidence to suggest that visual attention was sticky in children with idiopathic ASD relative to NT controls. This echoed reports from a number of recent studies that

suggest that disengagement deficits in contexts of competing visual stimuli may not be as robust a marker of idiopathic ASD as previously implied (Fischer, Koldewyn, Jiang, & Kanwisher, 2014; Fischer et al., 2016; Van der Geest et al., 2001; Wilson & Saldaña, 2018). Instead, groups were differentiated according to a visuo-perceptual profile in idiopathic ASD that was characterised by decreased FAC on gap-overlap trials and increased conjunction search efficiency (i.e., reduced target detection latencies) with increased symptomatic severity.[33] In essence, increased symptomatic expression was associated with quicker baseline relative to gap SRTs and decreased target detection latencies on conjunction search trials. In terms of interpreting this result, evidence of increased visuo-spatial orienting efficiency on both gap-overlap and visual search eye-tracking tasks in children with idiopathic ASD may indicate a common underlying mechanism. It may, for instance, be the case that the neuropathological features associated with enhanced search performance in individuals with idiopathic ASD (e.g., elevated functional connectivity within and between frontoparietal and occipital brain regions; Keehn et al., 2008; 2013) allow for more efficient SRTs on the gap-overlap task.

Chapter 3 illustrated the utility of examining performance profiles on gap-overlap and visual search paradigms in reference to one another. Here, the relationship between attentional disengagement and visual search abilities was examined in reference to syndromic forms of autistic-like impairment, specifically in the context of FXS and DS.

[33] The FAC effect derived from this gap-overlap task was an SRT difference value representing the degree to which disengagement latency decreased, on average, on gap relative to baseline trials (for further information, see Section 2.3.3.1.).

6.2.1. The Current Study

The current chapter details a cross-syndrome investigation into the visuo-perceptual profiles underpinning expressions of autistic-like impairment in children with idiopathic ASD, FXS and DS. In particular, it considers the relationship between attentional disengagement and visual search performance, but only in reference to the variables previously shown to relate previously to indices of autistic trait severity (i.e., FAC). Hypotheses were formed according to the results of the previous chapters. A similar visuo-perceptual profile was anticipated in cases of DS and idiopathic ASD, with symptom severity levels increasing according to decreased FAC on the gap-overlap task and improved conjunction search performance. Contrary to the visuo-perceptual profile anticipated in cases of idiopathic ASD and DS, it was hypothesised that increased trait severity in children with FXS would be associated with reduced visual search efficiency (i.e., increased target detection latencies) and increased FAC on the gap-overlap task.

6.3. Method

6.3.1. Participants

Children with idiopathic ASD (*n*=16), DS (*n*=15) and FXS (*n*=7) were recruited to take part in the current study (for details concerning the recruitment process and inclusion criteria, see Chapter 2). Groups were matched according to chronological age, non-verbal intellectual ability (Leiter-3), receptive language ability (BPVS-3) and autistic trait severity (RBQ-2 and SRS-2; see Table 4.1). A subset of children with DS and FXS had been formally diagnosed with comorbid ASD prior to testing (see Table 4.2).

6.3.2. Measures and Procedure

Measures and data collection procedures were as previously described in Chapter 2. Participants were engaged in a behavioural assessment which featured the BPVS-3 (Dunn et al., 2009) and the Leiter-3 (Roid et al., 2013). Autistic trait severity was indexed according to two parent-report questionnaires: the SRS-2 (Constantino & Gruber, 2012) and the RBQ-2 (Leekman et al., 2007). Both questionnaires were necessary to ensure that symptom severity was considered in terms of socio-communicative impairment and in terms of RRB.

Participants took part in an eye-tracking session. They were presented with a gap-overlap task designed to capture SRT in ms across baseline, gap and overlap conditions (for further details, see Section 2.3.3.1) and a visual search task that measured target detection latencies in ms on both single feature and conjunction trial types (for further details, see Section 2.3.3.2).

6.3.3. Statistical Analyses

Shapiro-Wilks tests were run to assess the distribution of data for each variable of interest. Normal distributions were confirmed. A between-groups trajectory analysis

approach was employed to examine variation in total SRS-2 scores according to mean target detection latencies for single feature and conjunction search trials and the SRT data derived from the gap-overlap task according to group (Thomas et al., 2009). Performance trajectories were analysed in terms of the intercepts and gradients. Main and interaction terms were manually entered into ANCOVA functions in SPSS. In all cases, the x-axes were re-scaled to ensure that main effects were calculated at the first point of group overlap. Data were plotted in the forms of three-dimensional scatterplots to allow for complementary descriptive analysis in awareness of the small size of the participant samples considered here.

Due to the small size of the FXS sample, a complementary case-series analysis was conducted to examine patterns of individual variation with regard to autistic trait expression and visuo-perceptual function. This allowed for a more precise description of individual FXS data points in reference to the degree to which they overlapped with idiopathic ASD profiles.

6.4. Results

A modified ANCOVA was run with group (ASD, FXS and DS) as the fixed factor and total SRS-2 scores as the dependent variable. Target detection latencies on single feature search trials and FAC effect sizes were entered as co-variates. Main and interaction terms for the model were entered manually. The results revealed a significant group × single feature search × FAC interaction effect; F (3, 21) = 4.96, p =.009, η^2=.43. To examine this significant interaction effect further, the ANCOVA model was repeated with an adjusted two-level fixed factor (ASD and DS); no such effect was observed; F (2, 17) = 1.44, p =.26. By contrast, a third model featuring group (ASD and FXS) as fixed factor revealed a similar three-way interaction effect; F (2, 12) = 8.38, p =.005, η^2=.58. A schematic illustration of these data in the form of a grouped

three-dimensional scatterplot showed that higher SRS-2 scores in children with FXS were associated with increased single feature search latencies and increased FAC effect sizes, while a contrary trend was observed in cases of idiopathic ASD; higher SRS-2 scores were associated with decreased single feature search latencies and decreased FAC (Figure 6.1).

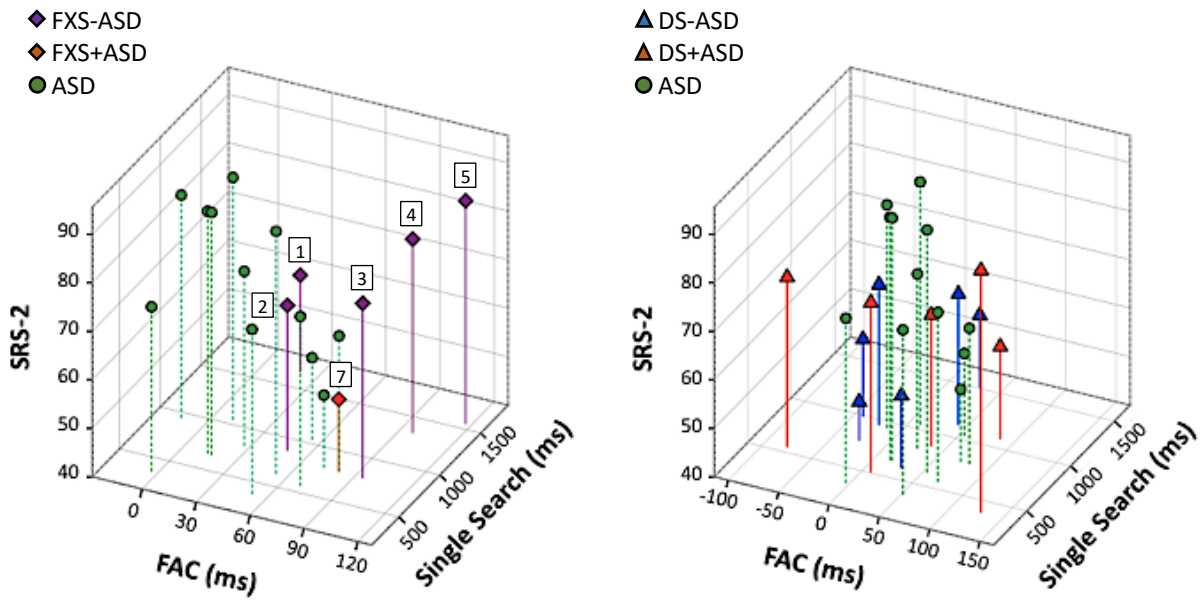

Figure 6.1. Three-dimensional scatterplots showing the relationship between FAC effect size (ms) and mean target detection latency on single feature search trials (ms) according to total SRS-2 scores for each clinical cohort. FXS and DS data points are plotted separately relative to idiopathic ASD. Note, the FAC scale on the two plots is different, while the ASD data are identical.

A case-series examination of individual FXS data points revealed that, while three-dimensional scatterplots did not support the application of confidence intervals, the majority of FXS cases appeared to fall outside of the range of the idiopathic ASD

trajectory (Table 6.1).[34] Two exceptions, FX2 and FX7, were noted. Inspecting the characteristics and performance profile of case FX2 revealed nothing to differentiate this child from his peers. Case FX7, conversely, carried a clinical diagnosis of ASD and demonstrated an uneven cognitive profile of low non-verbal intelligence according to the Leiter-3, and relatively high receptive language ability according to the BPVS-3.

Table 6.1.
Case-Series Description of FXS Data Points: SRS-2 scores according to FAC effect size and Single Feature Search Latency

	FX1	**FX2**	**FX3**	**FX4**	**FX5**	**FX6**	**FX7**
ASD Comorbidity	×	×	×	×	×	✓	✓
Age (months)	71	79	84	84	100	105	106
Leiter-3 Score	52	46	49	56	43	40	40
BPVS-3 Score	80	68	56	79	37	42	125
Trajectory Data							
SRS-2	60	70	76	80	86	79	55
FAC effect (ms)	20	49	94	97	117	---	81
Single Search (ms)	1662	874	791	1341	1553	582	791
Within ASD Trajectory	×	✓	×	×	×	---	✓

Note: No clear patterns of shared variance link cases FX2 and FX7.

Visual examination of DS data points in Figure 6.1 showed no clear three-dimensional trend; that is, aside from the observed variability in FAC effect size at the higher end of the SRS-2 scale (y-axis) and the lower of the single feature search latency scale (z-axis). Further examination of the two polar data points noted here revealed a noteworthy difference in chronological age: the child with DS+ASD who displayed a negative FAC

[34] Missing gap-overlap data for case FX6 means that only one FXS+ASD data point (case FX7) is present in the schematic illustration of these data (see Section 2.3.3.1 and Table 2.3 for further details).

effect (i.e., reduced SRTs on baseline relative to gap trials) was 11 years of age, while the child with DS+ASD who displayed the largest FAC effect size within this cohort was just 7 years of age.

By extension, a modified ANCOVA was run with group (ASD, FXS and DS) as the fixed factor and total RBQ-2 scores as the dependent variable. Target detection latency on single feature search trials and FAC effect size were entered as co-variates. No significant main or interaction effects emerged.

Next, autistic trait variation was examined within- and between-groups according to conjunction search performance and FAC. A modified ANCOVA was run with group (ASD, FXS and DS) as the fixed factor and total SRS-2 scores as the dependent variable. Target detection latency on conjunction search trials and FAC effect size were entered as co-variates. The results revealed a significant group × conjunction search × FAC interaction effect; F (3, 21) = 4.73, p =.04, η^2=. 32. To examine this effect further, the ANCOVA model was repeated with an adjusted two-level fixed factor (ASD and DS); no significant interaction effect was observed; F (2, 17) = 0.64, p =.54. By contrast, in a third model featuring group (ASD and FXS) as fixed factor, a similar three-way interaction effect emerged; F (2, 12) = 4.14, p =.04, η^2=.41. Mirroring the effects observed in relation to single feature search performance, a grouped three-dimensional scatterplot revealed higher SRS-2 scores in association with increased conjunction search latencies and increased FAC effect sizes in children with FXS, contrary to the trend observed in idiopathic ASD (Figure 6.2).

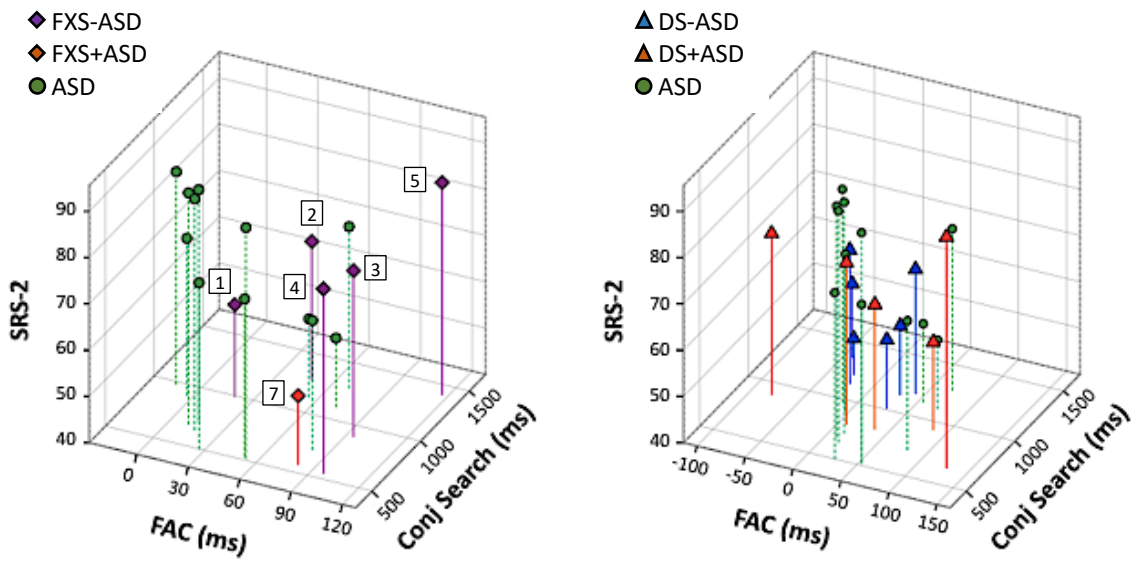

Figure 6.2. Three-dimensional scatterplots showing the relationship between FAC effect size (ms) and mean target detection latency on conjunction (conj) search trials (ms) according to total SRS-2 scores for each clinical cohort. FXS and DS data points are plotted separately relative to idiopathic ASD.

Performance trajectories for the idiopathic ASD and FXS cohorts are much less clearly defined in Figure 6.2. This suggests that single feature search performance may be more sensitive than conjunction search performance at differentiating these groups. Again, the FXS cohort was treated as a case series to allow for more detailed examination of individual performance profiles (Table 6.2). Based on a visual inspection of the relevant three-dimensional scatterplot, it was difficult to discern which FXS cases might be considered within the range of the idiopathic ASD trajectory; only case FX7 emerged as a possible point of overlap, albeit towards the low end of the SRS-2 scale.

Aside from the observation of increased variability in FAC effect size at the higher end of the SRS-2 scale, no clear trend was observed in the DS cohort (Figure 6.2).

Table 6.2.

Case-Series Description of FXS Data Points: SRS-2 scores according to FAC effect size and Conjunction Search Latency

	FX1	**FX2**	**FX3**	**FX4**	**FX5**	**FX6**	**FX7**
ASD Comorbidity	×	×	×	×	×	✓	✓
Age (months)	71	79	84	84	100	105	106
Leiter-3 Score	52	46	49	56	43	40	40
BPVS-3 Score	80	68	56	79	37	42	125
Trajectory Data							
SRS-2	60	70	76	80	86	79	55
FAC effect (ms)	20	49	94	97	117	---	81
Conj Search (ms)	987	1276	898	543	1411	1122	564
Within ASD Trajectory	×	×	×	×	×	---	✓

Following this, a modified ANCOVA model was run with group (ASD, FXS and DS) as the fixed factor and total RBQ-2 scores as the dependent variable. Target detection latency on conjunction search trials and FAC effect size were entered as co-variates. No significant main or interaction effects emerged.

6.5. Discussion

This study examined the relationship between attentional disengagement and visual search performance according to indices of autistic trait severity in children with idiopathic ASD, FXS and DS. The results confirmed a distinct visuo-perceptual profile in children with FXS according to degree of socio-communicative impairment relative to children with DS and idiopathic ASD. Within this FXS cohort, higher SRS-2 scores were associated with increased visual search latencies and increased FAC effect sizes; those who took longer to locate the target item on search trials and who, by association, demonstrated a larger SRT reduction on gap relative to baseline trials reported higher rates of socio-communicative impairment. This result is consistent with the notion that visuo-attentional irregularity is implicated in expressions of autistic-like impairment in children with FXS in a manner that is syndrome-specific. Moreover, it suggests that the visuo-perceptual profile observed in cases of FXS, according to performance on gap-overlap and visual search paradigms, may manifest on account of common underlying phenotypic mechanism.

Empirical efforts to build connections between the neurophysiological or mechanistic components of FXS and the observed clinical profile have commonly relied on animal models of this monogenic disorder. A study by Franco and colleagues (2017) examined sensory processing deficits according to underlying neuronal circuit mechanisms in a drosophila (i.e., fly) model of FXS. Building on the knowledge that FMRP loss results in alternations in GABAergic transmission and a subsequent increase in circuit excitability, the authors documented reduced stimulus selectivity in association with decreased inhibitory input, or lateral inhibition, from interneurons to projection neurons within corresponding sensory circuits. Moreover, they provided the first in vivo evidence to suggest that reduced FMRP impacts sensory processes and behaviour via a

broadening in the response tuning of principal neurons on account of this reduction in lateral inhibitory connections. The authors postulated that similar deficits in lateral inhibition may underlie the sensory discrimination deficits that have been observed in mouse models of FXS in visual, tactile and auditory modalities (Rotschafer & Razak, 2013; Zhang et al., 2014). [35]

In application to the current results, reduced lateral inhibition in FXS may manifest as diffuse attentional spotlighting, or a reduced signal-to-noise ratio, in sensory processing domains. This provides a possible mechanistic explanation for the visuo-perceptual profile documented here; autistic trait expression was greater in children with FXS who took longer to locate target items on search trials and who demonstrated a greater SRT reduction on gap relative to baseline trials on the gap-overlap task.

According to the current analyses, autistic trait variation in children with DS was undifferentiated from cases of idiopathic ASD and FXS in terms of associated visuo-perceptual profile; no clear trend emerged to suggest a relationship between attentional disengagement and visual search efficiency according to autistic trait severity. In accordance, and in keeping with the results of the previous chapters, autistic-like impairment does not appear to vary dimensionally according to underlying visuo-perceptual mechanism in children with DS, at least in reference to visual search and attentional disengagement efficiency.

[35] Drosophila models of FXS are attractive to researchers in that they are easier to maintain and are less costly both in terms of both time and money (for review, see Drozd, Bardoni, & Capovilla, 2018). Flies display complex behaviours, like olfactory learning and memory, for analysis. Moreover, it has been proposed that the neuropathological features associated with FMRP loss can be studied at a deeper level in flies than in any other animal model (Drozd, 2018). However, there have been no studies to date linking data from drosophila models to human FXS cases and, as in the case of most animal modelling, the applicability of findings to humans is questionable and must be interpreted with serious caution until empirically demonstrated.

Visual inspection of the DS data points, as illustrated in each of the three-dimensional scatterplots (Figures 6.1 and 6.2), revealed considerable variation in FAC effect size with increasing trait severity and decreased search latency. This was specifically in reference to two DS+ASD cases; further examination of these data points revealed a considerable age gap (i.e., 4 years) between the two children, suggesting that the wide age range of the current DS cohort may be problematic when examining visuo-perceptual performance profiles that are likely influenced by the age-related maturation effects.

In conclusion, the current study revealed a syndrome-specific visuo-perceptual profile underpinning expression of autistic-like impairment in children with FXS. It is interesting to note that while a three-way association emerged in reference to total SRS-2 scores, no such effects were observed in relation to rate and severity of RRB according to the RBQ-2. This may reflect what has been acknowledged in the literature with regard to the lack of syndrome specificity in relation to RRBs in children and adults with idiopathic ASD (Moss et al., 2009). The FXS sample that featured here was small, however; all associated inferential outputs must be considered tentatively until confirmed with larger samples. The following chapter considers the clinical and conceptual implications of the work presented here, in conjunction with the empirical investigations presented previously.

Chapter 7: General Discussion

7.1. Overview

This thesis examined the visuo-perceptual correlates of autistic trait variation in non-clinical, idiopathic and syndromic forms, with a specific focus on attentional disengagement and visual search performance. Chapter 3 tested the hypothesis that idiopathic ASD in middle childhood is characterised by visual orienting deficits and superior visual search performance relative to NT controls matched on indices of intellectual ability. Chapters 4, 5 and 6 investigated whether profiles of socio-communicative impairment and RRB in children with idiopathic ASD, FXS and DS are expressed via similar or dissimilar visuo-perceptual processes.

The current chapter presents a summary of the results of the studies that were run to test these hypotheses, with reference to theoretical, conceptual and clinical implications. Limitations and avenues for future research are presented so that the findings of the current thesis may be extended to further our understanding of ASD risk and expression in these high-risk genetic syndrome groups.

7.2. Characterising Idiopathic ASD according to Visuo-Perceptual Process

The research question that formed the basis of this doctoral work was: ‘Are syndromic forms of ASD characterised by the same visuo-perceptual features that have been documented in cases of idiopathic ASD?’. This relates to a broader question of whether idiopathic and syndromic forms of ASD are, in accordance with current classification and diagnostic practices, the same clinical entity.

While a range of visuo-perceptual features had been reported in children and adults with idiopathic ASD, two were particularly well documented in paediatric cohorts: enhanced visual search performance and irregular attentional disengagement (Cheung et al., 2018;

Elsabbagh et al., 2013; Gliga et al., 2015; Zwaigenbaum et al., 2005). Despite receiving considerable empirical attention, there was little consistency with regard to the precise nature of these visuo-perceptual irregularities, proposedly due to methodological disparities between studies and/or a phenotypic heterogeneity between samples.

In light of these inconsistencies, visuo-perceptual performance profiles were examined in an original cohort of children with idiopathic ASD (Chapter 3). Profiles were analysed in reference to a NT control group matched on indices of verbal and non-verbal intelligence according to the BPVS-3 and Leiter-3, respectively. On the gap-overlap task, groups differed only in the degree to which their ability to disengage and shift attention was facilitated by the presence of a brief inter-stimulus temporal gap. More specifically, children with idiopathic ASD demonstrated a reduced FAC effect with increasing symptom severity; those who rated more highly on measures of autistic trait expression exhibited less of an SRT reduction on gap relative to baseline trials. This implied that idiopathic ASD at the higher end of the spectrum was associated with a diminished reactivity to stimulus offset effects and, by extension, that the mechanisms underpinning this reactive process functioned atypically in children who were more severity affected.[36] No group difference emerged with regard to overlap SRTs, adding to a growing literature which suggests that disengagement deficits in contexts of competing visual stimuli, often termed 'sticky attention', may not be as robust a marker of idiopathic ASD as previously implied (Fischer, Koldewyn, Jiang, & Kanwisher, 2014; Fischer et al., 2016; Van der Geest et al., 2001; Wilson & Saldaña, 2018).

[36] In terms of underlying mechanism, the FAC effect is considered to be the emergent property of two processes that function reactively to the offset of a visual fixation point. The first is reduced activation of the SC (Dorris & Munoz, 1995) and the second is increased activity of pre-saccadic neurons in the frontal eye fields (Dias & Bruce, 1994).

Performance profiles on a conjunction visual search trials revealed a similar group differentiation; higher levels of autistic trait expression were associated with reduced target detection latencies in children with idiopathic ASD only. This result was consistent with previous reports of a phenotypic advantage on visual search tasks (Joseph et al., 2009; Brandon Keehn et al., 2009), providing empirical support for the theoretical supposition that enhanced search performance in cases of idiopathic ASD is due, at least in part, to an enhanced featural processing capacity (Caron et al., 2006; Happé & Frith, 2006). This is supported by empirical observations that children and adolescents with idiopathic ASD exhibit shorter fixation latencies on search items relative to NT controls (Joseph et al., 2009; Brandon Keehn et al., 2009). Additionally, it was proposed that children with idiopathic ASD develop an overly focused visuo-attentional style that enables enhanced featural discrimination and superior search performance on account of early disengagement difficulties and a subsequent inability to self-regulate arousal levels (Keehn et al., 2013). This was based on research showing that typically developing infants self-regulate their arousal levels by intermittently disengaging and shifting their gaze away from faces that present within their visual fields (Field, 1981). This led me to hypothesise that disengagement difficulties and enhanced visual search performance in children with idiopathic ASD share a common underlying mechanism, such as an increased signal-to-noise ratio. I examined the relationship between attentional disengagement and visual search performance in reference to autistic trait severity and observed a unique performance profile in children with idiopathic ASD: increased search efficiency on conjunction trials (i.e., reduced target detection latencies) and decreased FAC on the gap-overlap task with increased trait severity. This result was consistent with the idea that both visuo-perceptual features manifest, at least partly, on account of common phenotypic mechanisms. It may, for

instance, be the case that the neurofunctional correlates of search processes in cases of idiopathic ASD, namely increased activation of the frontal eye fields and elevated functional connectivity between associated frontal and occipital brain regions (Keehn et al., 2008; 2013) allow for more efficient attentional disengagement according to decreased FAC effect sizes on the gap-overlap task.

7.3. Syndrome-Specific Phenotypes according to Visuo-Perceptual Process

Having established a visuo-perceptual profile in children with idiopathic ASD, a series of cross-syndrome analyses were conducted to examine visuo-perceptual profiles in children with DS and FXS. Chapter 4 featured a cross-syndrome study of attentional disengagement performance according to SRT indices derived from a gap-overlap task. Significant group differences emerged. Contrary to the trend observed within the idiopathic ASD cohort, higher levels of autistic-like traits were associated with larger FAC effect sizes (i.e., greater SRT improvements on gap relative to baseline trials) in children with FXS and DS. As dorsal stream dysfunction is considered a neuropathological feature of FXS (Kogan et al., 2004; Rais et al., 2018), it may be the case that larger FAC effect sizes are indicative of greater underlying dorsal stream deficiency. While the neuropathological mechanisms underpinning visuo-spatial orienting deficits in children with FXS remain unclear, this result aligns with the notion that visuo-attentional irregularity is implicated in expressions of autistic-like traits in children with FXS in a manner that is syndrome-specific.

Chapter 5 presented a cross-syndrome study of visual search abilities in children with idiopathic ASD, FXS and DS. Despite similar mean levels of autistic trait severity, children with idiopathic ASD took significantly less time to locate target items on single feature search arrays when compared to children with FXS. This finding was consistent with the notion that attentional processes in FXS are characterised by diffuse attentional

spotlighting or a decreased signal-to-noise ratio (Franco et al., 2017; Golovin & Broadie, 2017). Further, it implied that while enhanced visual search performance is a well-documented phenotypic feature of idiopathic ASD, it is not apparent in children with FXS. No group differences emerged between children with idiopathic ASD and the complete DS cohort in terms of visual search performance; however, considering this DS cohort according to the presence or absence of comorbid ASD revealed a significant effect: a phenotypic advantage in cases of comorbidity as children with DS+ASD took significantly less time to locate target items on conjunction search arrays than their peers with DS-ASD. According to this finding, idiopathic forms of ASD and manifestations of ASD in DS share a common visuo-perceptual feature that may, by extension, reflect common genetic and/or neuropathological mechanisms.

Finally, Chapter 6 examined the relationship between attentional disengagement and visual search performance according to indices of autistic trait severity within and between these clinical cohorts. Relative to children with DS and idiopathic ASD, the results confirmed a distinct visuo-perceptual profile in children with FXS; within this cohort, higher SRS-2 scores were associated with increased search latencies and increased FAC effect sizes; those who took longer to locate the target item on search trials and who demonstrated a larger SRT reduction on gap relative to baseline trials experienced a higher level of socio-communicative impairment. This result suggests that the visuo-perceptual profile observed in cases of FXS, according to performance on gap-overlap and visual search paradigms, may manifest on account of common underlying phenotypic mechanisms, such as a decreased signal-to-noise ratio. No coherent trend emerged within the DS cohort to suggest a relationship between attentional disengagement and visual search efficiency according to autistic trait severity. Considered in tandem, these data provided further support for the notion of

syndrome specific expressions of autistic-like impairment according to associated visuo-perceptual process in children with idiopathic ASD, DS and FXS.

7.4. Phenotypic Specificity: The Contribution of Intellectual Factors

Additional information regarding the nature of syndromic forms of autistic trait expression can be gained by examining the roles of verbal and non-verbal intelligence. In Chapter 4, a significant degree of shared variance was observed between receptive language abilities and autistic trait severity in children with FXS; no such association emerged in children idiopathic ASD or DS. This finding echoed the results of previous research investigating language profiles in children with FXS and idiopathic ASD, showing that language functions are more closely linked to expressions of autistic symptomology in the case of FXS (e.g., Abbeduto et al., 2018; Thurman et al., 2017). Due to the small size of the current FXS sample, this result is suggestive only. Nevertheless, it points to a syndrome-specific phenotype that implicates receptive language abilities in expressions of autistic-like impairment to a greater degree than in cases of idiopathic ASD and DS. It may be the case that an attentional system characterised by a decreased signal-to-noise ratio functions at a cost to children's ability to process linguistic inputs with negative implications for receptive language outcomes. Longitudinal research is required to elucidate causal mechanism and cross-syndrome designs are necessary if we are to differentiate syndrome-specific trajectories of phenotypic expression.

Idiopathic and syndromic forms of ASD were further differentiated according to the contribution of non-verbal intelligence. Here, differentiating the DS cohort into those with and without comorbid ASD revealed significantly lower Leiter-3 scores in cases of clinical comorbidity. Moreover, a unique pattern emerged, with children with DS+ASD demonstrating higher rates of RRB with increasing non-verbal intelligence. It may be

the case that ASD comorbidity in DS is associated with particular strengths on tasks assessing visuo-spatial performance. Indeed, interacting with the environment in a repetitive manner may reflect a tendency to engage in certain kinds of learning opportunities (e.g., non-social) that place children in a stronger position to engage with a task like the Leiter-3, designed to measure non-verbal reasoning ability in the absence of explicit social and linguistic exchange (Evans et al., 2014; Honey et al., 2008). Understanding why ASD in DS implicates non-verbal intellectual ability to a greater degree than in the case of FXS or idiopathic ASD requires further research. Nevertheless, in the context of this doctoral research, these data provide additional empirical support for syndrome-specific phenotypes at a cognitive level of description in DS and FXS cohorts.

7.5. Conceptual and Theoretical Implications

The validity of ASD diagnoses in children with DS is a topic of ongoing empirical and clinical debate. There is a consensus within the literature that intellectual disability plays a clear role, as was illustrated here in Chapter 4; children with DS and comorbid ASD were found to demonstrate significantly lower levels of non-verbal intellectual ability, according to the Leiter-3, than their peers with DS-ASD. This aligns with the notion that, at least in the context of DS, increased intellectual disability is associated with increased ASD risk. It has been proposed that this association may be partly due to the fact that many of the diagnostic criteria for ASD are developmentally weighted, increasing the likelihood that a low-functioning child with DS will tick a greater number of boxes and be given a clinical diagnosis. Skuse (2007) proposed that intellectual disability may diminish the brain's capacity to compensate for the presence of independently inherited genetic risk variants, facilitating the expression of autistic-like deficits. In theory, the data presented in this thesis are consistent with this supposition;

not only were children with DS+ASD differentiated from their peers with DS-ASD according to lower levels of intellectual ability, they exhibited a visuo-perceptual strength on single feature search trials, mirroring the phenotypic advantage observed in cases of idiopathic ASD (Chapter 5). This clear differentiation in terms of intellectual ability and the absence of any linear relationship between dimensional autistic-like trait distributions and these indices of visuo-perceptual performance suggests a categorical differentiation between children with DS who are and are not affected by ASD.

Conversely, in the case of FXS, there appears to be no clear distinction between children who received clinical diagnoses of comorbid ASD prior to testing, and those who did not. Two of the seven children with FXS that feature in this doctorate research carried clinical diagnoses of ASD. While it is impossible to draw conclusions from a sample of this size (see Section 7.8 for further details pertaining to this study limitation), case series analyses showed no clear distinction between these cases of comorbidity and children with FXS only according to non-verbal intellectual ability or visuo-perceptual function. The only notable difference between children with FXS with and without ASD was the fact that both cases of comorbidity fell at the higher end of the chronological age range within this sample.[37] This suggests, in keeping with the literature, that autistic-like traits are a phenotypic feature of FXS and are dimensionally distributed within paediatric FXS cohorts.

This project employed multiple measures of autistic trait severity, enabling an examination of the concordance between each of these and clinical diagnostic status

[37] This observation mirrors previous reports by Lee and colleagues (2016) who conducted a longitudinal study of autistic-like behavioural deficits in children with FXS. According to their findings, symptomatic expression worsened with increasing chronological age; moreover, this increase was most prominently observed in terms of socio-communicative functions as opposed RRB.

(see Section 2.3.3). This examination revealed that the cut-off values for ASD according to each of these measures (i.e., ADOS-2, SRS-2, SCQ and RBQ-2) was highly consistent with clinical diagnostic provision within the DS cohort. By contrast, all children with FXS scored above the scoring threshold for ASD according to the ADOS-2 regardless of whether or not they had a clinical diagnosis of ASD. Additionally, children with FXS-ASD frequently scored above the cut-off values for ASD according to the SCQ and SRS-2. This highlights the importance of moving beyond superficial behavioural measures to examine the true nature of autistic-like behavioural traits in children with FXS whereas in the case of DS, these measures appear to be relatively effective at differentiating children with DS with and without ASD.

The data reported in this thesis support a distinct profile of visuo-perceptual irregularity in children with FXS. Moreover, within this cohort, increased irregularity was observed in cases of elevated autistic-like trait expression. Presentations of socio-communicative impairment and RRB in FXS may be considered within a neurodevelopmental framework. According to Johnson's (2017) adaptive brain theory, ASD is the phenotypic outcome of compensatory brain processes that occur in response to early signal-processing irregularities. While it is just one mechanistic account of ASD emergence and expression, it offers a useful framework with which to interpret the results of this doctoral work and, more broadly, to conceptualise syndromic forms of neurodevelopmental disorder. In application to FXS, irregularities in synaptic structure and function that arise on account of the absence of FMRP may trigger the development of an information processing system characterised by a decreased signal-to-noise ratio. An atypically diffuse attentional system may hinder the child's ability to reliably sample information from the environment, resulting in ambiguous representations that, in turn, are likely to yield adaptive attentional biases such as a preference for predictable, self-

led forms of stimulation. Moreover, a decreased signal-to-noise ratio may, in theory, give rise to the high rates of anxiety observed in samples of children and adults with FXS (Cordeiro et al., 2011; Ezell et al., 2018); inadequate filtering of environmental noise may lead to elevated levels of arousal.[38]

7.6. Clinical Implications for High-Risk Genetic Syndrome Groups

Elucidating the precise nature of autistic-like impairments in children with DS and FXS is necessary to inform and improve the clinical management of those who reach diagnostic thresholds for ASD; this is important as prognostic outcomes are worse for children exhibiting this comorbidity (see Section 1.4.3).

This doctoral work shows that expressions of autistic-like impairment in children with DS and FXS are associated with syndrome-specific profiles of intellectual difficulty and visuo-perceptual irregularity when compared to cases of idiopathic ASD. Behavioural intervention programmes designed to target particular neurocognitive features observed in children with idiopathic ASD may not be suitable for application to high-risk genetic syndrome groups. A recent case-series analysis by Vismara and colleagues (2018) examined the efficacy of a parent-mediated intervention programme (i.e., the Early Start Denver Model) to children with FXS.[39] Their pilot study to assessed the feasibility and utility of this intervention programme in four cases of FXS, three with clinically diagnosed ASD, over a time period of 6 to 9 months. These were young children with

[38] Clinically high levels of anxiety have been linked to difficulty differentiating signal from noise (Huang, Thompson, & Paulus, 2017). Mechanistic interpretations of this association vary; most reference Bayesian principles of inferential learning (e.g., Huang et al., 2017).

[39] This programme functions by facilitating meaningful dyadic exchange, with an emphasis on positive affect (Dawson et al., 2010; Estes et al., 2015). It aims, in this way, to facilitate the development of neural reward systems specific to social interaction and, in doing so, elevate children's social motivation. It has been found to improve socio-communicative outcomes in young children with idiopathic ASD, with these improvements reflected in post-treatment electrophysiological brain function in response to social information processing (Dawson et al., 2012).

FXS ranging in age from 25 to 40 months. Baseline and outcome measures included standardised tests[40] and a quality assessment of a parent-child interaction session that was coded blindly by four independent raters with 85% reliability. No post-intervention improvements were observed in children's social behaviour, which was partly indexed according to rates of spontaneous word production and joint attention initiation. While this pilot study represents an important first step towards the targeted treatment of autistic-like deficits in children with FXS, behavioural intervention strategies must take into consideration the unique cognitive profile that is associated with FXS and the syndrome-specific nature of the comorbidity, as illustrated in the current thesis.

Moreover, the findings presented in this thesis pose a challenge to the common practice of using high-risk genetic syndrome groups to model ASD emergence and expression as insights gained may not necessarily translate to idiopathic cases of ASD (for more information, see Section 1.4.3). This doctoral work illustrates a need to extend current therapeutic foci to include a greater emphasis on neurocognitive mechanism. This will elucidate distinct pathways to phenotypic expression and, in turn, facilitate a necessary bridging between psychological and biological intervention strategies (Green & Gard, 2018).

7.6. Strengths, limitations and Avenues for Future Research

The studies presented in this thesis provide novel insight into the visuo-perceptual processes associated with expressions of autistic-like traits and clinical comorbidity in children with DS and FXS. The cross-syndrome design enabled valuable group comparisons to be made, uncovering syndrome-specific profiles of visuo-perceptual

[40] These included the ADOS-T (for toddlers; Lord, Luyster, Gotham, & Guthrie, 2012) and the ADOS-2 (Lord et al., 2012), the Mullen Scales of Early Learning (Mullen, 1995) and the Vineland Adaptive Behaviour Scales (second edition; Sparrow, Cicchetti, & Balla, 2005).

irregularity. Further, the novelty of this research is apparent in its examination of the relationship between performance indices derived from gap-overlap and visual search paradigms. The studies presented here demonstrate the utility of moving beyond single task designs to examine visuo-perceptual data in multi-dimensional ways; this shift is necessary if we are to form holistic conceptualisations of visuo-perceptual irregularity in children with FXS, DS and/or ASD.

An additional merit of this work is that it includes children with low-functioning idiopathic ASD. Despite a 24-fold increase in the number of published papers relating to ASD in the past 30 years (Chakrabarti, 2017), individuals who are severely affected by the phenotype - typically those with general intellectual impairment - are referenced infrequently within this literature. A survey of relevant research outputs in 2017 revealed that 11% of participants with idiopathic ASD had an IQ of under 85 and even fewer were categorized as minimally verbal (Jack & Pelphrey, 2017). On account of this underrepresentation, the field is at risk of presenting a skewed account of this neurodevelopmental disorder, as those in greatest need are being left behind (Stedman et al., 2019). It is often the case that researchers exclude low-functioning individuals on account of the perceived challenge and difficulty of acquiring data from these populations. The work presented in this thesis shows that it is possible to include these often-neglected individuals provided appropriate consideration is granted to the needs of the individual as reflected in the selection of measures, the behavioural management strategies that are employed and the general flexibility of the testing set-up.

In light of the phenotypic heterogeneity that is well documented in cases of idiopathic ASD, and also in genetic syndrome groups of known aetiology, the findings presented here require replication in future studies incorporating larger samples. Small sample sizes are a major limitation of the studies presented in this thesis. Particularly in the case

of FXS, all relevant findings must be considered tentatively due to the size of the sample. While a cross-syndrome comparative approach was required to address questions of syndrome specificity (Oliver, Berg, Moss, Arron, & Burbidge, 2011), it set an ambitious target with regard to the sample sizes required to power to the necessary inferential statistics. Larger sample sizes were unable to be obtained on account of the rarity of FXS and DS and the restricted amount of time allocated to this doctoral work. Studies incorporating larger, potentially pooled, samples are necessary to examine whether the inferential outputs specified here are indeed representative of this clinical population.

It is worth noting that many of the correlations that were examined throughout this thesis were between standardised test scores and response times, the latter of which are known to be noisy (i.e., characterised by increased reaction time variability) in children (Dykiert, Der, Starr, & Deary, 2012; Mella, Fagot, Lecerf, & De Ribaupierre, 2015) and in various clinical cohorts, including ASD and attention deficit hyperactivity disorder (Baisch, Cai, Zongming, & Pinheiro, 2017; Karalunas, Geurts, Conrad, Bender, & Nigg, 2014). With regard to the findings of this doctoral work, the absence of statistically significant correlations ought to be considered within this context, while the presence of statistically significant associations, as derived from Bonferroni corrected comparisons, may be considered equivalently more powerful.

There are other cognitive and phenotypic markers of idiopathic ASD that may be investigated in high-risk genetic syndrome groups to further elucidate the nature of these comorbidities. For instance, impaired theory of mind (i.e., the ability to attribute mental states to others) is a robust characteristic of idiopathic ASD (Baron-Cohen et al.,

1985; Yirmiya, Erel, Shaked, & Solomonica-Levi, 1998).[41] Originally, theory of mind was indexed according to performance on the classic Sally-Anne false belief task. In more recent years, anticipatory looking paradigms have established themselves as more sensitive measures of theory-of-mind ability (Senju, Southgate, White, & Frith, 2009; Southgate, Senju, & Csibra, 2007). It would be interesting to know whether administering such eye-tracking paradigms to children with FXS or DS with comorbid ASD would reveal developmentally appropriate theory of mind abilities or a deficit in line with what has been observed in cases of idiopathic ASD.

More meaningful insights will be gained from longitudinal designs examining phenotypic trajectories over developmental time with an emphasis on individual variation. This is particularly the case in FXS where there is research to suggest a large degree of change in phenotypic expression according to chronological age (e.g., Hernandez et al., 2009). Moreover, genetic syndrome groups at high risk of ASD offer a valuable means to study early markers of phenotypic risk and expression when genetic aetiology is constrained (Doherty & Scerif, 2017; Farran & Karmiloff-Smith, 2012; Green & Garg, 2018; Karmiloff-Smith et al., 2016).[42] Applying longitudinal designs to study ASD risk in high-risk genetic syndrome groups, like DS and FXS, is necessary to

[41] The nature of theory-of-mind dysfunction in idiopathic ASD is a topic of debate (for review, see Belmonte, 2009). Traditionally, it was conceived of as a principal deficit in ASD, driving the behavioural expression of the phenotype (Baron-Cohen et al., 1985). Alternatively, it may be understood as a symptom of earlier domain-general deficits in complex information processing systems (Minshew & Goldstein, 1998). Jarrold and colleagues (2000) proposed that theory-of-mind problems arise from early perceptual integration problems that limit the child's capacity to form a cohesive understanding of his or her social world. A longitudinal study by Pellicano and colleagues (2010) provided support for this notion, revealing a unidirectional association between atypical (i.e., local) processing in children aged 4- to 7-years of age and theory-of-mind performance scores three years later.

[42] Alternatively, infants at familial risk of ASD may be examined longitudinally and prospectively to identify early precursors in terms of cognition and brain function (Johnson et al., 2015); there is an 18% likelihood of ASD in infant siblings of older children with a diagnosis (Ozonoff et al., 2011). In these idiopathic cases, however, it can be difficult to elucidate distinct cognitive and neuropathological pathways to ASD on account of considerable phenotypic and aetiological heterogeneity.

identify the pathological mechanisms that lead to socio-communicative deficits and RRB in these clinical populations. Doing so will enable the identification of shared and distinct trajectories of phenotypic risk and expression over the course of child development, providing translational insights for clinical research and practice (Farran & Karmiloff-Smith, 2012; Johnson et al., 2015).

Furthermore, there is a need to consider all facets of attentional function in the context of emergent neurodevelopmental disorders (i.e., auditory domains and the holistic integration of visual and auditory sensory inputs). In a longitudinal study looking at predictors of autistic symptomatology in boys with FXS (mean age: 8, range: 3–10), Cornish and colleagues (2012) found evidence to suggest that auditory inattention is a greater marker of ASD risk than visual inattention. Moreover, social and communication skills development is critically reliant on an ability to process and synthesise information from different sensory modalities, for instance, as in the case of audio-visual speech perception (Bahrick, 2010; Bahrick & Todd, 2012). There is a substantial body of research illustrating that children and adults with idiopathic ASD are impaired in their ability to integrate sensory signals from visual and auditory modalities (for reviews, see Brock, Brown, Boucher, & Rippon, 2002; Wallace & Stevenson, 2014). For instance, the latency required to perceive paired visual-auditory stimuli as originating from a single event is longer in individuals with idiopathic ASD than in NT cases (Bebko, Weiss, Demark, & Gomez, 2006; De Boer-Schellekens, Eussen, & Vroomen, 2013; Foss-Feig et al., 2010; Kwakye, Foss-Feig, Cascio, Stone, & Wallace, 2011; Stevenson et al., 2014). It has been proposed that extended temporal binding of multisensory inputs, for instance, as in the case of idiopathic ASD, may yield ‘hazy’ or ambiguous perceptual representations (Wallace & Stevenson, 2014). In support of this idea, Stevenson and colleagues (2012; 2014) have documented associations between

latency to bind multisensory input and the strength of children's perceptual binding of speech information. Additionally, in a cohort of children with idiopathic ASD, the ability to perceptually bind audio-visual information that is presented concordantly has been linked to degree of communicative impairment according to the ADOS, with greater impairment in cases of reduced perceptual binding (Woynaroski et al., 2013). These studies illustrate an increasing need to consider attention in a manner that is more ecologically valid than examining two-dimensional eye-tracking data in isolation; applying multi-sensory integration paradigms to the study of syndromic ASD risk and expression is warranted and likely to yield insights that translate more readily into clinical and education practices.

Finally, the studies presented in this thesis illustrate the insensitivity of standardised behaviour measures in terms of their capacity to differentiate between different kinds of socio-communicative difficulty and different manifestations of RRB, mirroring a growing sentiment in the literature regarding the comorbidity of neurodevelopmental disorders in genetic syndrome groups. Measures that were initially designed to determine a range of functions within the typically developing population are particularly inappropriate; task assumptions (e.g., that reaching a screening threshold points to the presence of a neurodevelopmental disorder) are likely to be challenged as poor performance on the part of a child or adult with a genetic disorder can occur for a variety of reasons, including degree of cognitive impairment, an inability to focus for the complete duration of the task and/or low motivation to engage. There is, by extension, an increased risk of floor effects on behavioural measures designed and normed with NT populations in mind, such that variation in terms of ability level may be greatly constrained. This doctoral research highlights the need to progress, as a field, beyond the use of superficial behavioural measures and to focus empirical efforts

instead on more fine-grained behavioural measures, like eye tracking, to tackle enduring questions about the nature of these proposed comorbidities.

Furthermore, brain imaging technologies offer an objective means of quantifying neurodevelopmental dysfunction in terms of brain structure and function. Neural markers of idiopathic ASD have been uncovered using EEG, for instance. Perhaps the most robust neural marker of idiopathic ASD is the diminished and sometimes absent face-sensitive N170 component derived from event-related potential (ERP) analyses. In NT individuals, the N170 component demonstrates distinct topographical variation (i.e., increased latency and amplitude) in response to inverted facial stimuli (Eimer, 2011; Puce, Smith, & Allison, 2000; Rebai, Poiroux, Bernard, & Lalonde, 2001; Rossion et al., 2000); in individuals with idiopathic ASD, however, ERP component analyses have revealed that this N170 facial inversion response is significantly reduced and/or absent (Dawson, Webb, & McPartland, 2005; Hileman, Henderson, Mundy, Newell, & Jaime, 2011; McPartland, Dawson, Webb, Panagiotides, & Carver, 2004). Whether a similar neural marker exists in cases of syndromic ASD remains to be seen. Future research efforts to elucidate the nature of syndromic forms of autistic-like trait expression will benefit from a shift in emphasis away from superficial behavioural measures and towards brain imaging methods that may be better equipped to differentiate between idiopathic and syndromic forms of behavioural impairment.

If we define ASD strictly according to current diagnostic standards, we may conclude that any child with FXS or DS who reaches the clinical threshold on standardised behavioural assessment measures, has ASD. However, as evidenced in this doctoral research, the visuo-perceptual profiles associated with expressions of autistic-like impairment in children with FXS are dissimilar to that which is observed in cases of idiopathic ASD. Further insight into the nature of these comorbidities can be gained by

extending definitions of idiopathic ASD to include the visuo-perceptual and neurophysiological markers known to be associated with the disorder and testing whether this extended definition holds in high-risk genetic syndrome groups. Empirical efforts to further elucidate the nature of these behavioural phenotypes must progress from a reliance on insensitive behavioural measures of socio-communicative function and RRB towards more fine-grained analytic frameworks incorporating sensory processing and neuroimaging modalities.

7.7. Conclusion

This doctoral research examined the visuo-perceptual processes underpinning autistic trait variation in children with idiopathic ASD, DS and FXS, focusing specifically on attentional disengagement and visual search performance. The results revealed syndrome-specific phenotypes according to associated visuo-perceptual processes, extending the literature and elucidating the complex heterogeneity associated with this neurodevelopmental disorder. In doing so, this research showed that while high-risk genetic syndrome groups offer an attractive means of studying ASD expression in cases of well-defined aetiology, it is problematic to assume that empirical insights gained are generalisable to idiopathic ASD. Moreover, these data illustrate the value of looking beyond superficial behavioural indices of ASD to examine, in a more fine-grained way, the neurocognitive features underpinning comorbid expressions of autistic-like deficit.

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