A prospective longitudinal study of infant anxiety and sensory responsivity as early markers for infants with typical and elevated likelihood of autism and ADHD

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Abstract

This thesis explores the developmental pathways and consequences of differences in sensory responsivity and anxiety in early infancy. Alterations in different domains of sensory responsivity and anxiety may have differential developmental consequences. Identifying which early markers relate to later manifestations of autism and attention deficit hyperactivity disorder (ADHD) is important for understanding causal paths to symptom development. Since both of these conditions are highly heritable, tracking infants who have an older sibling with the condition, and thus are at an elevated likelihood (EL) of autism and ADHD themselves, from early in development, provides an essential insight into key developmental trajectories. The current study uses two cohorts of prospective longitudinal infant-siblings, who were followed from early infancy to toddlerhood, with parent-report assessments of sensory responsivity, anxiety and emerging autistic and ADHD traits at 10, 14, 24 and 36 months. The first cohort of the British Autism Study of Infant Siblings (BASIS) included infants with and without a family history of autism (N = 247; EL-autism N = 170 and Typical Likelihood (TL) N = 77). The second cohort consisted of children who took part in the Studying Autism and ADHD Risks (STAARS) study, which included EL-ADHD infants (N = 161; EL-autism N=80; EL-ADHD N=31; EL-autism/ADHD N=21 and TL N=29). Chapters 3 and 4 apply cross-lag panel modelling to these longitudinal datasets, with results suggesting 1) alterations in sensory responsivity are associated with later autistic traits, 2) taking into account different domains of sensory responsivity is key to understand specificity of effects, and 3) paths between anxiety and sensory responsivity did not replicate between cohorts. In Chapter 5, trajectory modelling indicated that sensory domains that associated with likelihood status (i.e., having an older autistic/ADHD sibling or not) were not the same as those associated with outcome traits. Alterations in early sensory responsivity are not unique to autism but also observed in ADHD. Taken together, this thesis indicates that further

work is needed to probe into construct overlap and account for the inter-dependence of different aspects of sensory responsivities in the same analytical model. It also highlights the importance of replication studies and the need for careful sample ascertainment. Given the developmental nature of these constructs, this thesis underscores the importance of subsequent investigations extending into mid-childhood.

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Statement of work

The data presented within this PhD thesis is from a collaboration study between King's College London and Birkbeck, University of London. The data was collected from two distinct phases of research projects: Phase 2 - cohorts of the British Autism Study of Infant Siblings (BASIS) (data used in Chapter 3) and Phase 3 - cohort of the Studying Autism and ADHD Risks Study (STAARS) (data used in Chapters 4 and 5).

In Chapter 3, the data used were derived from Phase 2 of the BASIS project, collected by the BASIS team before my PhD was commenced. However, I acquired permission from the study's Principal Investigators, Prof. Charman and Prof. Jones, to access and analyse this data under pre-existing ethical permissions.

My involvement in this study started during the data collection stage of Phase 3 and 3.1. I have been involved in the coordination and organising of testing sessions at the 2 and 3 year visits. Additionally, I was involved in testing the participants, collecting data, entering it, and subsequently analysing it. A testing day involved a range of experimental tasks, encompassing eye-tracking, EEG, and various behavioural assessments, including administration of developmental measures such as the Mullen Scale of Early Learning and clinical assessments such as ADOS-2. My contributions consist of data collection, data entry and analysis which was then used towards the content of Chapters 4 and 5.

A note on publications

Chapter 3 and 4 represents the publication detailed below. King's College London requires that, for a thesis incorporating publications, chapter text must be the same as the published paper, with any supplementary materials included in the thesis appendices.

Narvekar, N., Carter Leno, V., Pasco, G., Johnson, M. H., Jones, E. J., & Charman, T. (2022). A prospective study of associations between early fearfulness and perceptual sensitivity and later restricted and repetitive behaviours in infants with typical and elevated likelihood of autism. *Autism*, *26*(8), 1947-1958. https://doi.org/10.1177/13623613211068932

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List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
APA	American Psychological Association
B	Non-standardised Covariant
BAP	Broad Autism Phenotype
BASIS	British Autism Study of Infant Siblings
BI	Behavioural Inhibition
CBCL	Child Behaviour Check List
CBCL	Child Behaviour Checklist
CFA	Confirmatory Factor Analysis
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CFI	Comparative Fit Index
CSS	Calibrated Severity Scores
DSM	Diagnostic and Statistical Manual
ECBQ	Early Childhood Behaviour Questionnaire
EEG	Electroencephalogram
EL	Elevated Likelihood
FIML	Full Information Maximum Likelihood
fMRI	Functional Magnetic Resonance Imaging
IBQ-R	Infant Behaviour Questionnaire-Revised
ITSP	Infant Toddler Sensory Profile
LGC	Latent Growth Curve

MAR	Missing at Random
MCAR	Missing Completely at Random
MNAR	Missing Not at Random
MSEL-ELC	Mullen Scales of Early Learning – Early Learning Composite
p	Probability
PDD	Pervasive Developmental Disorder
RMSE	Root Mean Square Error
RMSEA	Root Mean Square Error of Approximation
RRB	Restricted Repetitive Behaviours
SA	Social Affect
SCI	Social Communication Interaction
SD	Standard Deviation
SEM	Structural Equation Modelling
SRMR	Standardised Root Mean Square Residual
SRS	Social Responsiveness Scale
STAARS	Studying Autism and ADHD Risks Study
TL	Typical Likelihood
TLI	Tucker Lewis Index
TLI	Tucker-Lewis Fit Index
VABS	Vineland Adaptive Behaviour Scale.
β	Standardised Covariant

Note on language

We acknowledge that language and terminologies used in autism studies are continually evolving and updating to reflect our growing understanding of this condition, as well as to promote more inclusive and respectful discourse within the field. There are a few terminologies used in this thesis that need a mention:

In this thesis, we have used identity first language throughout to reflect the community preference for this language (Bottema-Beutel, Kapp, Lester, Sasson, & Hand, 2021; Taboas, Doepke, & Zimmerman, 2023). However, Chapter 4 does not use this language because it was reproduced as it appears in the article published before this.

We are using the term 'elevated likelihood' in place of the previously more commonly used term 'high risk' (HR) in response to parental preferences reported in Fletcher-Watson et al. (2017). However, we acknowledge that in the recent past (during the course of my PhD), terminologies have shifted from elevated likelihood to family history, and we have tried to stay consistent in most places.

Lastly, considering the inconsistencies in the use of the terms to describe the sensory differences in autism, such as "sensitivity", "reactivity" and "responsivity (He et al., 2023), we have decided to use responsivity as an indicator of altered sensory experiences. As a concept, it is a description of behavioural responsivity to sensory input, which is the construct that the Infant Toddler Sensory Profile mostly measures. However, Chapter 3 and 4 may not reflect this choice as it was published before this thesis was written. Similarly, we have refrained from using atypical sensory processing with the exception of Chapters 3 and 4 as they were published before the printing of this thesis.

Chapter 1: Introduction

The overarching objective of this thesis is to understand the relationship between early infant anxiety, sensory responsivity, and later neurodivergent (e.g., autistic, ADHD) traits in infant siblings with a family history of autism and ADHD (i.e., older sibling or biological parent). This chapter offers an overview of autism encompassing its clinical history over time, epidemiological considerations, putative aetiological factors, along with a discussion on sensory responsivity challenges. It subsequently delves into examining co-occurring conditions, particularly emphasising anxiety and ADHD. Finally, it highlights the significance of using longitudinal and prospective study designs to capture and identify developmental pathways and mechanisms from very early in infancy.

1.1 Overview of autism

Autism spectrum disorder, hereafter referred to as autism, is a neurodevelopmental condition characterised by core features that involve a varying degree of difficulty in social functioning, communication, and the presence of restricted and repetitive behaviours and sensory differences (DSM-5-TR, 2022). There is evidence for genetic aetiologies as high as 64 to 91% (Tick, Bolton, Happe, Rutter, & Rijsdijk, 2016) and environmental influences (Geschwind & State, 2015; Hertz-Picciotto, Schmidt, & Krakowiak, 2018; Mandy & Lai, 2016). There is a consensus that autism is determined by a combination of gene-environment interplay where genes might have a more prominent role to play (Taylor et al., 2020). Hence, since no reliable biological marker exists, autism is diagnosed based on observed phenotypical criteria defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR, 2022).

1.2 Clinical history of autism:

Leo Kanner and Hans Asperger's contributions are often referred to as the cornerstone of the clinical history of autism. However, Eugen Bleuler (1911) first introduced the term 'autism' to describe the tendency of children with schizophrenia to exhibit social withdrawal and a disconnection from reality. New evidence suggests that Grunya Efimovna Sukhareva (1926) was a pioneer in the field and initially used the term "schizoid (eccentric) psychopathy" but subsequently replaced it with "autistic (pathological avoidant) psychopathy" to depict the clinical presentation of autism. She defined autism and characterize it more fully as a "flattened affective life," "lack of facial expressiveness and expressive movements", and "keeping apart from their peers", "talking in stereotypic ways," with "strong interests pursued exclusively", and sensitivities to specific noises or smells (Manouilenko & Bejerot, 2015). Kanner (1943) borrowed the term autism from Bleuler but defined it differently, where he did not consider infantile autism an early form of schizophrenia, nor was it a condition developed later in life but since birth. During the same time, Asperger (1944) described his clinical observations of cases who displayed deficiency in non-verbal communication, lack of empathy, eye contact, and had extraordinary talent. He also highlighted their capacity to maintain daily life functioning and their ability to pursue a successful career despite facing challenges in social and non-social interactions. He referred to these individuals as "little professors" who exhibited a strong fixation on a particular interest and faced difficulties engaging in reciprocal conversations. Over time, Kanner's definition of autism was used to define "lower functioning" individuals, and Aspergers's definition was used to describe what was previously described as "higher functioning" individuals or those with Asperger syndrome.

1.3 Current parameters and characteristics of the diagnosis

Previous diagnostic criteria DSM-III recognised infantile autism, which fell under the broader pervasive developmental disorder (PDD) (American Psychiatric Association, 1980), whereas DSM-IV in 1994 excluded the term infantile autism and substituted it with categories of Asperger's syndrome, autistic disorder, Rett disorder, pervasive developmental disorder (not otherwise specified), and childhood disintegrative disorder. In contrast, DSM-5 in 2013 established a cohesive autism spectrum based on two core domains, and Asperger syndrome was no longer a separate diagnostic category; instead, it was folded into the autism spectrum. Another big change was the move to official recognition of sensory symptoms as a part of the diagnostic criteria. Given that almost 74% of autistic children have some form of sensory differences and is one of the few traits that can be identified in the first few years of life (Sacrey et al. 2015). A new edition of the International Classification of Diseases, the ICD-11, a diagnostic manual produced by the World Health Organization (WHO) published in 2018, has also updated its diagnostic criteria, which now is in line with DSM-5. As of 2022, the DSM-5 manual has been updated to DSM-5-TR.

The current diagnostic criteria for autism by Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5-TR, 2022) is provided below (Table 1.1)

Table 1. 1 DSM-5-TR diagnostic criteria for autism spectrum disorder

Diagnostic Criteria **(F84.0)**

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by all of the following, currently or by history (examples are illustrative, not exhaustive; see text):

    1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

    2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

    3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

    1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

    2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).

3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

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

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

Specify current severity based on social communication impairments and restricted, repetitive patterns of behavior:

- **Requiring very substantial support**
- Requiring substantial support
- Requiring support

Specify if:

- **With or without accompanying intellectual impairment**
- **With or without accompanying language impairment**

Specify if:

- **Associated with a known genetic or other medical condition or environmental factor** (**Coding note:** Use additional code to identify the associated genetic or other medical condition.)
- **Associated with a neurodevelopmental, mental, or behavioral problem**

Specify if:

- **With catatonia** (refer to the criteria for catatonia associated with another mental disorder, p. 135, for definition) (**Coding note:** Use additional code F06.1 catatonia associated with autism spectrum disorder to indicate the presence of the comorbid catatonia.)

Even though these domains may be universally applicable, there is noted variability in the autism phenotype based on sex, income, maternal education, and race that play a role in the probability of getting a diagnosis of autism (Belcher, Morein-Zamir, Stagg, & Ford, 2023; Durkin et al., 2017; Rosenberg et al., 2018). To cater to the diverse array of behavioural manifestations and experiences of individuals with autism, the UK National Institute for Health and Care Excellence (NICE) guidance advises a multidisciplinary team approach equipped with access to appropriate physical, mental health, and social care services, to conduct assessments for individuals on the autism spectrum (National Institute for Health and Care Excellence, 2011, 2013).

The diagnostic manuals recognise that behavioural criteria of traits are needed to make an autism diagnosis, and these may not fully appear until later typically between 2 and 6 years of age (Boyd, Odom, Humphreys, & Sam, 2010; Brett, Warnell, McConachie, & Parr, 2016). Direct clinical evaluation and parental reports are important since autism traits may be subtle during toddlerhood and not fully observed during the assessment (Charman & Baird, 2002).

1.4 Epidemiology and developmental course of autism

1.4.1 Average age of diagnosis in children

The emergence of autism in the first two years of life is well-documented. The average age of diagnosis in the United Kingdom is 43 months (Salomone et al., 2018). However, in certain cases the emergence of autism symptoms in childhood is variable, with some children showing signs of autism very early and others not being identified until much later (M. Miller, Austin, et al., 2020). Many toddlers who are later diagnosed with autism are known to exhibit behavioural and neurological markers by their first birthdays (Hazlett et al., 2017; Ozonoff et al., 2010). Autism diagnoses are considered stable by 18–24 months though many children might not be diagnosed until later (Ozonoff et al., 2015). In recent times, children diagnosed with autism are getting their initial diagnosis, interventions, and developmental support at earlier stages in their lives compared to previous years (Hanley et al., 2021). A comprehensive review of studies from 2012 to 2019 indicated conflicting results in the age of diagnosis due to influencing factors such as types of autism, i.e. autism versus Asperger syndrome, delay in diagnoses due to the presence of cooccurring conditions such as ADHD, and gender differences (van 't Hof et al., 2021).

1.4.2 Prevalence rate of autism

Even though traits of autism may vary in intensity and presentation over time, autistic people make up 1% of the population in the UK (Baron-Cohen et al., 2009) and worldwide (Zeidan

et al., 2022). Reported childhood prevalence is ~1.5% (Elsabbagh et al., 2012; Maenner, Shaw, & Baio, 2020; Zeidan et al., 2022). Autism presents more often in males, with a ratio of 3:1 (Loomes, Hull, & Mandy, 2017), although more recent estimates have suggested that the male-to-female ratio ranged from 0.8 to 6 (Zeidan et al., 2022). Research consistently indicates that girls with autism tend to be diagnosed later in life, possibly because they are better at masking their traits (Kopp & Gillberg, 2011; Lai & Baron-Cohen, 2015).

A study focusing on developmental aspects of the Broader Autism Phenotype (BAP), indicated that 28% of those at an elevated likelihood to autism due to an autistic family member demonstrated different developmental patterns at 36 months (Ozonoff et al., 2014). Gaining insights into the development of non-autistic traits in elevated likelihood siblings at an early stage would allow us to explore the early emergence of characteristics associated with the BAP, which is more common in families with autistic individuals.

Over time, there has been a noticeable increase in the prevalence of autism, which primarily reflects the broadening of the diagnostic criteria and distinguishing it from overlapping conditions, as well as increased awareness and improved identification methods among children (Fombonne, 2020; Zeidan et al., 2022).

1.4.3 Understanding the recurrence rate of autism

The recurrence rate is the likelihood that the younger sibling of an autistic child, will also receive a diagnosis of autism. The variability in the statistics of prevalence and recurrence is thought to be influenced by factors such as stoppage, where many parents with one child diagnosed with autism chose not to have more children. This can bias estimates of sibling recurrence risk if not properly addressed (Grønborg, Hansen, Nielsen, Skytthe, & Parner, 2015; Hoffmann et al., 2014). The sibling recurrence rate in population cohorts is notably higher at ~10% (Hansen et al., 2019; Sandin et al., 2014), reflecting the substantial

heritability of the condition (Tick et al., 2016). In an infant sibling study, about 20% of the infants with an autistic older sibling will go on to receive a diagnosis of autism themselves (Messinger et al., 2015; Ozonoff et al., 2015), and another 20% will manifest subthreshold traits or different developmentalal patterns (Charman et al., 2017; Messinger et al., 2015). This puts the infant at "Elevated Likelihood" (EL) for autism. In an EL infant study design, younger siblings of an older autistic child are typically followed from the first year of postnatal life to at least 36 months. Using the infant study design approach, Ozonoff et al. (2011) found a recurrence rate of 18.7% among younger siblings of probands. In addition, this study found that infants from multiplex families, characterised by two or more diagnosed older siblings (probands), were twice as likely to receive an autism diagnosis compared to infants from simplex families, where only one older sibling had a diagnosis of autism. Another study found a significant difference in sibling autism recurrence likelihood by sex. Families with older autistic female siblings have a higher familial possibility for autism than older male autistic siblings (Hansen et al., 2019).

1.5 Aetiology of autism

In recent years, the increased understanding of how autism develops, its causes and how it impacts the individual has helped clarify some aetiological factors that underly the emergence of autism. This has also shown us that autism is complex and multiple factors can contribute to the same phenotypes.

1.5.1 Inherited factors and environmental influences

Twin and family studies show a considerable genetic influence on autism, with heritability estimates ranging from 60% to 90% depending on the study design and analytical method (Deng et al., 2015; Tick et al., 2016). Despite the high heritability, autism manifestations rarely result from a single gene or genetic mutation that is predictive of all diagnoses of

autism. (Zwaigenbaum et al., 2015). A study by Tick et al. (2016) confirmed a strong genetic influence in the causation of autism and rejected the claim that there is a strong shared environmental effect on autism; however, acknowledging the possibility of the influence of environmental, or nongenetic effects on autism. Overall, there is a consensus that a combination of largely genetic and to a certain extent environmental factors determines autism.

There has been a rise in prevalence (1/150 8 year olds had autism diagnoses in 2000 versus 1/36 8 year olds had autism diagnoses in 2020, (Maenner et al., 2023)), which could be attributed to the rise in autism awareness and public health response worldwide in addition to epidemiological studies offering objective indicators of the impact of autism (Fombonne, 2020). This rise has also led researchers to look at environmental causes. Findings suggest that environmental factors could account for approximately up to 40 % of the differences we see in autism diagnoses (Deng et al., 2015; Modabbernia, Velthorst, & Reichenberg, 2017). Geschwind and State (2015) note that environmental factors mainly affect the developing brain during the prenatal period. Air pollution, pesticides, plastics, prenatal vitamins, lifestyle and family factors, and maternal health during pregnancy have been shown to have an association with neurodevelopment and psychiatric conditions but have lacked specificity to autism (Hertz-Picciotto et al., 2018; Taylor et al., 2020). An ongoing debate exists on how environmental factors contribute to the likelihood of developing autism (Modabbernia et al., 2017).

1.6 Sensory responsivity differences in autism

Understanding the background, prevalence and aieteology is crucial to recognising the complex nature of autism. Especially those observed in children can provide important insight into the condition’s development to subsequently aid in identification, interventions,

and support. Autistic traits aren't unitary; sensory differences are a core characteristic of autism and are listed alongside restricted, repetitive patterns of behaviour, interests, or activities in the DSM-5, occurring in approximately 80-95% of cases of autism (Tavassoli et al., 2016; Tomchek & Dunn, 2007). Despite this, there's a tendency to look at sensory differences as being separate from autistic traits (Chen, Sideris, Watson, Crais, & Baranek, 2022; Feldman et al., 2020; Niedźwiecka, Domasiewicz, Kawa, Tomalski, & Pisula, 2019). However, questions remain about whether those connections are truly empirically motivated and whether they would also be consistent at different developmental stages. Knowing that sensory differences are inherent to autism helps in comprehensive understanding of autism, yet it is also important to examine whether it is specific to RRB or can also associate to other traits such as social communication interactions. Research suggests that sensory responsivity seems to influence development by impacting adaptive, cognitive, social, and linguistic skills (Cascio, Lorenzi, & Baranek, 2016). Additionally, exploring how sensory differences manifest in other non-autistic conditions such as anxiety disorders and ADHD increases our understanding and impact of sensory differences across various neurodevelopmental conditions. Some children who do not have a diagnosis of autism also display sensory hyperresponsivity (Carpenter et al., 2019). So even though sensory differences are a part of the diagnostic criteria, it is also a meaningful entity in their own right which deserves specific study. Given the diverse range of behaviours and cognitions within the autism diagnostic category, it's important to focus on specific domains and assess their predictive value for developmental outcomes. By doing so, we can better understand the nuanced nature of sensory differences and their implications across neurodevelopmental conditions. Hence, investigating sensory differences offers insight into the mechanisms underpinning autism symptoms.

Although the clinical field is not completely unified in how to define or categorise sensory responses. There are a few popular theories of differences in sensory responsivity. The sensory integration theory was proposed by Ayres in 1979 (Kilroy, Aziz-Zadeh, & Cermak, 2019). It refers to the ability to produce appropriate motor and behavioural responses to stimuli. The focus was on hyper and hypo responses in autistic individuals, where they exhibited sensory responsivity in 3 areas: *Registration* - detection and interpretation of sensory stimuli. *Modulation* - the ability to register sensory input and to regulate the input they do register. *Motivation* - desire or willingness to respond to a stimulus or ignore it.

Later, Dunn proposed another model that provided a theoretical framework for sensory processing (Dunn, 1997). The model includes neurological thresholds (low to high) and self-regulation strategies (passive to active). Dunn derived four basic quadrants of sensory processing: Low registration – missing or not noticing sensory stimuli; Sensation seeking – actively seeking sensory stimuli from the environment; Sensory sensitivity – discomfort with sensation; and Sensation avoiding – limits exposure to sensory stimuli. When adapted to measure sensory processing, this model covered several modalities such as oral, visual, tactile, vestibular, and auditory experiences (Dunn, 2002).

Later Miller proposed the Sensory Processing Disorder Model (SPD) (L. Miller, Anzalone, Lane, Cermak, & Osten, 2007; L. Miller, Nielsen, Schoen, & Brett-Green, 2009). This model underscores the significance of sensory differences in various developmental conditions like autism, ADHD, and developmental coordination challenges. According to Miller's theory, sensory differences stem from a disparity between an individual's altercations in sensory abilities and the environmental demands they encounter. The model identifies three main patterns of sensory differences: (i) Sensory modulation disorder (SMD): refers to difficulty regulating responses to sensory stimulation, and three subtypes are proposed: (a) Sensory

over-responsive (responds too much, for too long, or to stimuli of weak intensity); (b) Sensory under-responsive (responds too little, or needs extremely strong stimulation to become aware of the stimulus); and (c) sensory seeking/craving (responds with intense searching for more or stronger stimulation). All three modulation subtypes share the common difficulty of grading or regulating responses to sensory stimuli. (ii) Sensory-based motor disorder: within which two subtypes are proposed: (a) Postural disorder, which reflects problems in balance and core stability, and (b) dyspraxia, which encompasses difficulties in motor planning and sequencing movements. (iii) Sensory discrimination disorder: refers to difficulty interpreting the specific characteristics of sensory stimuli (e.g., the intensity, the duration, the spatial, and the temporal elements of sensations), and can be present in any of the seven sensory systems (i.e., vestibular, proprioceptive, and the five basic senses).

Another framework by He et al. (2023) proposes a classification that operationalises sensory experiences approach by categorizing sensory-relevant constructs into five hierarchical levels:

(i) Sensory-related neural excitability – degree of change in a measurable brain response following sensory stimulation, for example, mainly measured using fMRI, EEG.

(ii) Perceptual sensitivity – individual's ability to detect and discriminate between stimuli.

(iii) Physiological reactivity to sensory input – changes in bodily reaction to sensory input, for example, pupil dilation or skin conductance in response to stimuli.

(iv) Affective reactivity to sensory input – the way individuals evaluate and respond to sensory stimuli, can be measured using self-report or observational methods.

(v) Behavioural responsivity to sensory input - the manner in which the individual reacts to stimuli they find uncomfortable or pleasurable.

It is important to note that the inconsistencies in terminologies used in the extant literature to refer and describe sensory features (such as sensitivity, reactivity, responsiveness) complicates and obfuscates the understanding of sensory differences in autism. Hence, He et al. propose categories that broadly reflect the constructs - perception as sensitivity to sensory input; physiological and affective as reactivity to sensory input; and behavioural as responsivity to sensory input. Inconsistent terminology poses challenges not only in research concerning sensory differences in autism but also across various other fields, prompting the need for standardised taxonomies to address issues of interchangeable terminology used, facilitating structured and organised research that focuses on studying rather than assuming relationships. Since this thesis focuses largely on sensory traits measured at the behavioural level, we use the term sensory responsivity.

1.6.1 Emergence and impact

Many autistic individuals report that differences in sensory responsivity make daily life challenging for autistic people and can negatively impact their well-being (Pellicano, Dinsmore, & Charman, 2014; Sibeoni et al., 2022). Differences in sensory responsivity in autistic individuals become apparent during childhood (Feldman et al., 2020; Williams et al., 2018), though the timing of their emergence remains somewhat unclear. Sensory differences in infants with an elevated likelihood of autism tend to surface around the second year of life (Worthley et al., 2023). Additionally, demographic factors such as assigned sex at birth, race and maternal educational levels have been linked to these sensory responsivity differences, where it is reported that male white children with more highly educated mothers were more likely to have sensory differences documented (Kirby et al., 2022).

Multiple studies have noted the impact of sensory responsivity differences in development and daily life. The increased sensory seeking observed in infants with an elevated likelihood

of autism, later diagnosed with the condition, has been found to impact their social development at 36 months of age (Baranek et al., 2018; Damiano-Goodwin et al., 2018). Similarly, hyporesponsivity has been shown to have an influence on later communication skills in elevated likelihood infants (Grzadzinski et al., 2021). Both hyper and hypo sensory profiles have been associated with lower adaptive behaviour in areas such as socialization and daily living skills (Wolff et al., 2019). Moreover, sensory seeking profiles have been linked to less developed motor skills (Tomchek & Dunn, 2007; Travers et al., 2022). Nonetheless, our understanding of the contribution of early emerging sensory challenges in infancy and their lasting impacts on children's social and cognitive development remains limited. Investigating infants with sensory differences, with or without an autism diagnosis, can provide valuable insights into the intricate relationship between sensory responsivity and the core social and communication difficulties observed in autism. In particular, there is a critical need for longitudinal studies that trace the developmental trajectories of sensory manifestations from infancy and assess the influence of early sensory features on the emergence of autism traits during toddlerhood.

1.7 Co-occurring conditions in autism

Despite being characterised as a single condition, autism is highly individualised, mainly because of vast heterogeneity in trait presentation, functional level, and cognitive and linguistic abilities (Lai, Lombardo, Chakrabarti, & Baron-Cohen, 2013), but also due to the high prevalence and variety of accompanying co-occurring conditions.

Co-occurring conditions are one or more additional conditions or health challenges that coincide with a primary condition. A co-occurring condition represents a secondary diagnosis characterised by symptoms separate from the primary condition (Al-Beltagi, 2021). Some co-occurring conditions may persist throughout a lifetime, and some may resolve with time. In

all cases, they then impact behaviour, development, and health. In some cases, these impacts can resemble the traits of autism.

Autistic individuals have a high prevalence of multiple mental health challenges. Co-occurring mental health conditions in autism have been noted early in childhood (Salazar et al., 2015) and continue into adolescence (Simonoff et al., 2013). The prevalence of co-occurring conditions increases among adults with autism (Joshi et al., 2013), contributing to considerable long-term effects on health and quality of life (Lai et al., 2019).

Mental health conditions that occur alongside autism are more prevalent within the autism population compared to the general population. Some of the most prominent co-occurring conditions and their pooled prevalence found in conjunction with autism, as seen in the systematic review conducted by Lai et al. (2019), were – 28% for ADHD, 20% for Anxiety, 11% for Depressive disorders, 5% for Bipolar and related disorders, 4% for Schizophrenia spectrum and psychotic disorders and 9% for Obsessive-compulsive and related disorders.

In addition, other studies (Al-Beltagi, 2021; Amiet et al., 2008) noted common physical co-existing conditions in autism:

Epilepsy occurs in about 30% of the autism population. The risk of epilepsy in children increases to 50% when autism and intellectual disability are present.

Sleep Disorders- Approximately, 50% to 80% of autistic children experience sleep disorder, which encompasses challenges such as frequent, prolonged waking, trouble falling asleep, or extremely early rising.

Gastrointestinal (GI) issues affect approximately 46% to 84% of autistic children, challenges include food intolerance and sensitivities, vomiting, abdominal pain, chronic constipation and/or diarrhoea, gastroesophageal reflux, ulcers, etc.

In most cases, the association between autism and co-occurring conditions is more pronounced in females as compared to non-autistic males, suggesting that co-occurring conditions increases the likelihood of receiving an autism diagnosis compared to males. For instance, the autistic female/male ratio for anxiety is 2:2.1 and for ADHD is 1:1.6. The prevalence of co-occurring condition rates is also largely influenced by the age of initial autism diagnosis, possibly contributing to autism heterogeneity observed in autism research and clinical settings (Rødgaard, Jensen, Miskowiak, & Mottron, 2021). Recognizing the social repercussions is also important. The higher prevalence of mental health issues among individuals diagnosed with autism later in life can be attributed to the challenges of living without awareness and adequate assistance, particularly among women who are diagnosed with autism later in their lives (Pelton et al., 2020).

Co-occurring conditions can be especially difficult to diagnose since many of the symptoms can look like the core traits of autism, including difficulties with communication and expression, lack of engagement, inattention, lack of eye contact, repetitive behaviours, emotional regulation difficulties, or hyperactivity. Co-occurring conditions in relation to autism may contribute, overlap with traits, or coexist and share underlying mechanisms that crossover diagnostic criteria of autism and other conditions (Stefanik et al., 2018). Hence, gaining a clearer understanding helps address questions about the heritability of co-occurring traits and the relationships between their severity and autism traits for adequate evaluation and support services (Lai et al., 2019).

Anxiety and ADHD are commonly co-occurring conditions with autism, yet little is known about their typical development in infancy. The following section will provide a more detailed account of autism with co-occurring conditions of anxiety and ADHD, and outline

why examining them through a developmental lens is fundamental to unravelling the causal mechanisms leading to observable traits and symptoms.

1.7.1 Anxiety

According to DSM-5-TR (2022), anxiety is broadly categorised into separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder (social phobia), panic disorder panic attack specifier, agoraphobia, generalised anxiety disorder (GAD), substance/medication induced anxiety disorder, anxiety disorder due to another medical condition and other specified anxiety disorder unspecified anxiety disorder. It is not uncommon for an individual to experience multiple anxiety disorders simultaneously (Mohapatra, Agarwal, & Sitholey, 2013). For instance, co-occurring such as separation anxiety with GAD and specific phobias, selective mutism with social anxiety, and panic disorder with agoraphobia have been observed in children (Wolk et al., 2016). In this thesis, we focus on temperamental precursors, mainly a fearful temperament rather than a specific form of anxiety diagnosis in infant-siblings with elevated likelihood of autism and ADHD.

Some of the diagnostic criteria for anxiety are marked as fear or anxiety about one or more social situations, or specific objects or excessive fear or anxiety about separation from those to whom they are attached. In children, this is expressed by crying, freezing, tantrums or clinging behaviour. This display of behaviour must occur in peer settings and not just during interactions with adults. This fear, anxiety or avoidance must persist for at least 4 weeks.

1.7.1.1 Prevalence and age of onset of anxiety

Childhood anxiety occurs in about 1 in 4 children at some time between the ages of 13 and 18 years. The average peak onset for all anxiety disorders is estimated at five and a half years old (with a second, smaller peak at 15.5 years; Solmi et al., 2021). However, the lifetime prevalence of a severe anxiety disorder in children ages 13 to 18 is approximately 6%. The

general prevalence in children under 18 years is between 5.7% and 12.8% (Ströhle, Gensichen, & Domschke, 2018). Across all ages, women are approximately one and a half times more likely to be affected by anxiety disorders than men (Javaid et al., 2023).

1.7.1.2 Aetiology and intergenerational transmission

The anxiety disorders show heterogeneity, suggesting that the roles of these factors vary across conditions. Family studies have shed light on the hereditary aspect of these disorders, revealing that first-degree relatives of individuals with panic disorders face a three- to fivefold elevated risk of developing similar conditions compared to the general population (Ströhle et al., 2018).

The heritability of anxiety disorders, i.e., the extent to which genetic factors contribute to their development, is 30–67%, suggesting that genetic factors account for a large portion of the variability of anxiety disorder, and the remaining is accounted for by personal experiences of negative environmental factors, such as life events (Adwas, Jbireal, & Azab, 2019; Gottschalk & Domschke, 2016).

Parenting behaviour plays a pivotal role in the development of anxiety and has been extensively linked to its aetiology. Specifically, certain behaviours in the early stages of child development have been associated with the later emergence of anxiety symptoms. For instance, critical and cold parenting, emotional maltreatment, parental modelling of anxiety have all been associated with subsequent anxiety symptom development in children (Aktar & Bögels, 2017; Norton & Abbott, 2017). Moreover, it's worth noting that prenatal parental anxiety can serve as a predictive factor for infant hyperarousal, which can contribute to the development of a fearful child temperament—an early precursor to later anxiety (de Vente, Majdandzic, & Bogels, 2020). It is important to acknowledge the difficulty of demonstrating

evidence for parenting as a risk factor as it will nearly always be confounded with genetics (Ahmadzadeh et al., 2021; Cheesman et al., 2020).

1.7.1.3 Autism and co-occurring anxiety

Anxiety is one of the most frequently co-occurring conditions in autistic children with prevalence rates varying between 11 and 84% (White, Oswald, Ollendick, & Scahill, 2009). Co-occurring anxiety and autism traits may intensify the difficulties that children with autism experience. For instance, difficulties in social interaction may heighten social anxiety, ultimately leading to reduced social functioning (Chang, Quan, & Wood, 2012) and a diminished quality of life (van Steensel, Bögels, & Dirksen, 2012). In a twin study involving children aged 10 to 15 years, it was observed that non-autistic twin of an autistic twin, when compared to control subjects, exhibited notably elevated symptoms of social anxiety, generalized anxiety, and panic (Hallett et al., 2013). Kerns et al. (2014) study's results indicate that anxiety among autistic youth may exhibit both conventional characteristics (traditional anxiety) as defined by the DSM-5 and unconventional features (atypical anxiety) diverging from these criteria. This suggests that co-occurring anxiety may co-exist in individuals with autism due to the similarities observed between autism-related anxiety and DSM-defined anxiety. However, the differences observed raise questions about whether these unique expressions of anxiety are specific to autism or apparent across varied diagnostic groups, and hence warrant further investigation.

Link between sensory and anxiety in autism

Green and Ben-Sasson (2010) propose three theories regarding the relationship between sensory over responsivity (SOR) and anxiety in autistic children; SOR caused by anxiety, anxiety caused by SOR, and both SOR and anxiety not causally related but associated via a third variable such as a common risk factor or overlapping diagnostic criteria. Green, Ben-

Sasson, Soto, and Carter (2012) found that SOR predicts later development of anxiety in children at approximately 28 months of age, and not vice versa. Additionally, MacLennan, Rossow, and Tavassoli (2021), found that SOR predicts both anxiety and Intolerance of Uncertainty (IOU) in autistic preschool children aged 3- 5 years indicating that SOR could be an early factor in development of anxiety. Furthermore, adults reported that sensory experience has an impact on mental health and linked sensory differences to anxiety, self-harm and eating disorder. They further describe sensory stimuli and environments can become overwhelming and lead them to disengage or shutdown (MacLennan, O'Brien, & Tavassoli, 2022). Verhulst, MacLennan, Haffey, and Tavassoli (2022) looked at perceived causal relationships and noted that autistic adults further distinguish sensory differences as cause and effect of anxiety, where autistic adults reported to perceive anxiety to be more the effect of sensory hyperresponsivity than the cause and sensory seeking behaviours are a potential consequence of anxiety. Therefore, quantitative studies and voices of those with lived experience both suggests that sensory differences, particularly hyperresponsivity may play an important role in development and manifestation of anxiety across age groups in autistic individuals.

Fear an infant precursor to later anxiety

Anxiety as a term is commonly used in older children and adults, in young infants it is usually measured as a temperamental trait or fearfulness as seen in the diagnostic criteria. Anxiety disorders are typically diagnosed around the age of 11, but certain behaviours observed before this age could potentially serve as precursors to future anxiety. In toddlerhood, these children tend to avoid engaging with new objects and unfamiliar individuals. This avoidance of novel experiences may inhibit their social development, reduce their assertiveness, and consequently increase their susceptibility to developing

anxiety disorders (Buss, 2011). Parent-report is the most common method to measure infant anxiety and a few studies engage in observational assessment to measure infant fearfulness (Tang 2020). A meta-analysis focusing on children under six years of age revealed that early signs of anxiety, including behavioural inhibition, fearful reactivity to novel stimuli, and shyness, may serve as indicators of future childhood anxiety disorders (Möller, Nikolić, Majdandžić, & Bögels, 2016).

Fear in young children often arises in response to stimuli conveying threat or uncertainty, triggering self-protective responses. Behavioural inhibition is characterised by heightened fearfulness, shyness and wariness towards novel stimuli (Fox, Henderson, Rubin, Calkins, & Schmidt, 2001). Elevated fear responses in infancy have been linked to later behavioural inhibition and anxiety (Kagan, Snidman, Zentner, & Peterson, 1999; Schmidt et al., 1997). Longitudinal investigations using the parent-report Infant Behaviour Questionnaire (IBQ) fear subscale have consistently demonstrated that fearfulness assessed in infancy predicts subsequent anxiety symptoms (Shephard et al., 2019; Tonnsen, Malone, Hatton, & Roberts, 2013). Additionally, studies have shown that fearfulness and shyness in infants and toddlers can predict certain features of anxiety by the age of 7 (Shephard et al., 2017). Though the manifestation of fear and anxiety in infants with autism can be complex, it is highly prevalent among children and adolescents diagnosed with autism, indicating a possible link between infant anxiety and autism that may stem from similar developmental pathways originating in infancy.

1.7.2 ADHD

Although autism and ADHD are seen as separate conditions with different diagnostic criteria and traits, there is an overlap between certain symptoms and commonly associated or co-occurring factors. Studies have identified general developmental factors (e.g., motor

development), attention, temperament and affect regulation, and even social behaviour as potential overlapping early risk markers shared by both autism and ADHD (Johnson, Gliga, Jones, & Charman, 2015). These findings indicate a combination of overlapping and distinct early markers of preschool autism- and ADHD-like profiles which can be difficult to differentiate early in life (M. Miller, Austin, et al., 2020). Van Der Meer et al. (2012) noted that pure ADHD symptoms can occur independently but vice versa was not true, as autism symptoms always co-occurred with ADHD. Furthermore, both conditions showed certain overlapping (visuo-spatial and verbal attention) and differing (working memory) cognitive profiles. Findings from a twin study examining the overlap between autism and ADHD implied that more children with 1 condition exhibit features of the other condition rather than display complete co-occurrence. The focus is on symptom co-occurrence, rather than full overlap between conditions (Ronald, Larsson, Anckarsäter, & Lichtenstein, 2014).Some report that the limited explanatory capacity of the diagnostic labels doesn't fully explain the complex and diverse experiences of the diagnosed individual (Krakowski et al., 2020; Scheerer et al., 2022). Therefore, differentiating between autism and ADHD, maybe difficult as they may share distinct or partially overlapping early developmental markers and pathways, which this thesis aims to explore.

The DSM-5-TR (2022) describes ADHD as characterized by two core domains: 1) inattention; 2) hyperactivity and/or impulsivity. In order to receive an ADHD diagnosis before the age 17, the individual must demonstrate six or more traits in either the 1) inattentive domain - for example, fails to give close attention to details, has difficulty sustaining attention in play tasks, does not seem to listen when spoken to directly; or 2) hyperactive and impulsive core domains, for example, often fidgets, often runs about or climbs in situations where it is inappropriate, has difficulty waiting for their turn, often

interrupts. For an ADHD diagnosis, these traits must persist for a minimum of 6 months to an extent that is inconsistent with developmental level and that negatively disrupts social and academic functioning.

1.7.2.1 Prevalence and age of onset

Although ADHD is a lifelong condition, different developmental course seems to exist due to its later age of onset ~7 years as compared to autism (Rocco, Corso, Bonati, & Minicuci, 2021). Its prevalence is ~3%–5% in children and adolescents (Sayal, Prasad, Daley, Ford, & Coghill, 2018), and affects up to ~2 to 7% of children aged 3 to 12 years worldwide (Sayal et al., 2018).

1.7.2.2 Genetics and environmental influences

ADHD is highly heritable with heritability estimates in the range of 60%–90%. (Q. Chen et al., 2017; Thapar, 2018). The likelihood of developing ADHD is higher in siblings of children with ADHD or in those having a first degree relative clinically diagnosed with ADHD, with a recurrence estimate of approximately 13% (M. Miller et al., 2019). Further, twin and family studies suggest that ADHD may be best understood as a quantitative trait with equal heritability across various levels of trait severity, rather than as a distinct aetiologically category (Posner, Polanczyk, & Sonuga-Barke, 2020; Thapar, 2018).

Environmental factors linked to ADHD include maternal smoking and alcohol use, low birth weight, premature birth and exposure to environmental toxins (Banerjee, Middleton, & Faraone, 2007). Another approach to identifying environmental risk factors in ADHD is to focus on the complex gene-environment interactions and epigenetic effects (e.g., DNA methylation). Environmental toxins and stress can all induce epigenetic changes, thus the identification of genes that show epigenetic changes linked to ADHD, or in response to environmental risk factors is beneficial for future studies (Faraone et al., 2015).

1.7.2.3 Autism and co-occurring ADHD

Although autism and ADHD exhibit distinct core traits, prior research has suggested a notable genetic overlap between the two conditions. It is noteworthy that autism and ADHD frequently co-occur at clinical and trait levels (M. Miller et al., 2019). Twin and family studies have consistently demonstrated moderate shared heritability between these conditions (Ghirardi et al., 2019; Taylor et al., 2013). Moreover, there is a familial pattern to both conditions, with approximately 25 to 32% of individuals diagnosed with autism also presenting with ADHD (Lai et al., 2019). In line with these findings, siblings of autistic children tend to exhibit elevated rates of ADHD, and conversely, siblings of children with ADHD have an increased likelihood of autism (Ghirardi et al., 2019; M. Miller et al., 2019). This underscores the interconnectedness of autism and ADHD, particularly from a genetic perspective.

Nevertheless, our understanding of how common genetic factors translate into traits associated with autism and ADHD remains somewhat limited. Some common developmental mechanisms such as motor skills, attention and temperamental differences have been proposed as potential contributors to the emergence of autism and ADHD; however, specific pathways leading to these conditions have not been definitively identified (Johnson, Gliga, et al., 2015; Jones, Gliga, Bedford, Charman, & Johnson, 2014).

To delve deeper into the co-occurrence of these conditions, it is crucial to explore the developmental pathways that they share and those that differentiate them. By examining the early stages of development in infancy, prior to the clear manifestation of the behaviours associated with autism and ADHD, we may uncover shared and distinct neurodevelopmental pathways related to each condition, when considered separately and in combination (Johnson, Gliga, et al., 2015). This is important for the investigation of understanding early markers

such as sensory responsivity as potential infant indicators that could predict later traits of autism and ADHD.

1.8 Importance of longitudinal studies in development

Autism is a lifelong developmental condition; however, most studies on autism are cross-sectional in nature. As a result, they typically provide information on what it looks like at one single time point.

An increasing number of long-term studies are now following autistic individuals over a long period. Many of these studies include several hundred participants. When conducted with samples of individuals who enter the study as children, researchers can construct developmental pathways and trajectories associated with autism. Understandably, following autistic individuals over an extended period can be expensive, time consuming and require long term commitment from the families. However, it may be the sole means to understand which early life factors support autistic children over the long term.

For instance, a study on how autism traits changed in a sample of 155 children aged 2 to 25, found that most autistic individuals showed clinical challenges across the lifespan. However, there was a decrease in autism traits overall. The group that was undiagnosed showed significant changes over time, where the autism traits increased over time. This suggested that diagnoses of autism can change across development (Elias & Lord, 2022).

Another longitudinal study conducted by Colvert et al. (2022), on how autism and co-occurring mental health related to each other, tracked 135 autistic twins, 55 non-autistic co-twins, and 144 twins low in autistic traits from age 4 to age 13. Findings suggested that autistic twins experience higher co-occurring difficulties from childhood to early adolescence.

Meanwhile, a longitudinal study that examined language trajectories and outcomes in autistic children receiving early behavioural intervention from 6 months to 36 months found that children receiving early behavioural intervention showed a substantial increase in language relative to normative expectations (Frazier et al., 2021).

These results show the common approach researchers use in longitudinal studies to examine how changes in one development aspect influence another. Furthermore, data from longitudinal studies reveal how the interaction between autistic children and their families or environment can shape their outcomes.

1.8.1 Early development studies

Autistic children frequently achieve crucial milestones later than their non-autistic peers, although the specific timing can exhibit significant variability. One of the initial indications of divergent developmental patterns in a child's growth is often observed in their attainment of early developmental milestones (Jones et al., 2014). A study using an extensive dataset of developmental milestone achievement analysed data from previously collected parent-reported measures from 17,098 autistic individuals in a cross-sectional study. The results indicated substantial variability in average developmental milestones. These were contingent on varying factors, such as intellectual disability, genetic testing, timing of diagnosis, and study cohort (Kuo et al., 2022). Since autism diagnoses typically occur around or after the age of 3, any study relying solely upon autism diagnosis as a criterion may miss crucial developmental information that precedes the diagnosis. Additionally, such an approach may result in a non-random, selective sample, influenced by factors such as sex at birth, ethnicity, socioeconomic status, and access to local service providers, potentially limiting the generalizability of the study's findings.

1.8.2 Infant study design

Studies on infant siblings allow researchers to follow the elevated likelihood infants from birth to early identification or signs of autism. In an elevated likelihood infant study design, younger siblings of an older autistic child are typically followed from the first year of postnatal life through to at least 36 months, the age at which autism diagnosis is both highly reliable and stable (Woolfenden, Sarkozy, Ridley, & Williams, 2012). This is important due to the high recurrence rate in infant siblings of autistic children (Charman et al., 2017; Messinger et al., 2015; Ozonoff et al., 2014). This provides the opportunity to gain an enriched sample and thus increase one's statistical power whilst conserving resources.

Even though certain traits are noted before the age of 3, an official autism diagnosis is usually received at a much later age. Recent studies have used a prospective method to track the infant sibling from birth. This method overcomes the problem of stoppage, over reporting and capturing certain behaviour that only ever occurred once by clinically assessing the elevated likelihood of infants longitudinally and obtaining clinical assessments of autism at 36 months (Zwaigenbaum et al., 2005).

To increase knowledge about the emergence of autism, researchers first used retrospective study designs in which data were obtained from home videotapes, medical records or parent recall that focused on the early development of children already diagnosed with autism (Szatmari et al., 2016). These may be useful but also biased by recall bias, influenced by the older sibling, and the time gap between development and parent interview. The elevated likelihood design provided an opportunity to estimate the sibling likelihood more precisely and to explore the full range of variable expressivity of the risk genotype from a longitudinal perspective (Szatmari et al., 2016). Among other things, the infant sibling design allows one

to monitor developmental growth and trajectories, identify early brain differences and neural markers and contribute to understanding the gene-environment interactions.

As noted by Szatmari et al. (2016), infant sibling designs have some concerns:

The generalisability of the findings to autistic individuals is a concern, as all the results are derived from infant siblings who may or may not develop autism. It is necessary to acknowledge that not all autistic individuals will have an older autistic sibling. The experience of living with an autistic family member might influence how early presentation of the infant sibling is reported.

A common concern, shared by many longitudinal studies, relates to the potential impact or influence of repeated monitoring and exposure of the infant sibling to frequent assessments. Parents can also learn new ways to interact with their infant through observations during assessment by trained professionals. All these factors could influence the child's developmental trajectory.

Overall, prospective studies contribute greatly to the recognition of traits of autism that may begin to emerge before getting a diagnosis. Understanding the interplay between different neurodevelopmental domains across the first years of life and the influences these have will be important, both to understand the developmental mechanisms that lead to the autism behavioural phenotype and to design approaches to developing early interventions (J. Green et al., 2013). Additionally, examining these traits is important to identify for clinical purposes and identification of children at elevated likelihood and for understanding causal pathways to symptom development (Jones et al., 2014). These results carry important implications for early identification and likelihood signs of autism.

1.9 Chapter summary

Based on the presented evidence, it is observed that infant anxiety, sensory symptoms and ADHD frequently co-occur in autism. Additionally, the similarities in the traits of these constructs often overlap. These constructs of infant anxiety and sensory responsivity have the potential to provide insights into later developing traits. Hence, we need to understand the interaction between these constructs and identify the earliest signs of emerging autism. To explore these complicated relationships, the following studies use a prospective longitudinal model to investigate the relationship between autism, infant fear, and sensory responsivity in elevated and typical likelihood infant siblings.

Overall thesis aim:

This thesis aims to explore the relationship between infant anxiety and sensory responsivities and the role they play in understanding emerging markers of later autism and ADHD traits in an infant sibling sample enriched for elevated likelihood to autism and ADHD. The specific aims are:

- Test longitudinal associations between early fear/shyness, perceptual sensitivity and later RRB and SCI in a prospective infant-sibling cohort, which includes infants with an elevated likelihood of autism (Chapter 3).
- Examine the replicability of associations from Chapter 3 in an independent infant-sibling cohort and explore the contributions of different domains of sensory responsivity (hyper and hypo-responsivity) (Chapter 4).
- Estimate the developmental trajectories of hyper-responsivity, hypo-responsivity, sensation seeking between 10 and 36 months, and test associations between these

trajectories and autism/ADHD likelihood status as compared to 36 month autistic and ADHD traits (Chapter 5).

Chapter 2: Methodology - Structural Equation Modelling

This thesis investigates the developmental trajectories and associations of sensory responsivity and anxiety during the early stages of infancy with neurodivergent conditions of autism and ADHD at 36 months. In order to study this effectively, one requires to examine data over a period of time to understand developmental mechanisms and unpick the directionality of effects. A longitudinal study offers the advantage of identifying these developments or changes in the target population as a whole and at the individual level. The key point is that longitudinal studies extend beyond a single moment in time. A few statistical models can handle longitudinal data – repeated measures ANOVA, linear mixed effects models and Structural Equation Modelling (SEM), to name a few. To investigate constructs before the emergence of autistic traits and examine changes over time in autism, our target sample consisted of siblings with elevated likelihood of autism and ADHD. They were assessed at four time points, with visits ranging from 8-months to 36-months. This permitted the examination of trait continuity from infancy to toddlerhood. Prospective longitudinal studies of infant siblings of autistic children have provided important insights into the emergence of autism (Szatmari et al., 2016) (See Figure 2.1). Infants with elevated likelihood for autism are now the primary focus of research interested in exploring the early developmental markers of autism, given their potential to be identified prenatally and subsequently monitored from birth. The infant study design is motivated by findings that suggested that autism ran in the family and siblings were at an elevated likelihood of developing autism themselves (Smalley, Asarnow, & Spence, 1988) and the concerns about the time lag between parents noticing and reporting symptoms (Zwaigenbaum, Bryson, & Garon, 2013). The elevated likelihood design provides a unique opportunity to estimate the likelihood and examine the full range of traits expressed and study the sibling likelihood

longitudinally, thus enabling an exploration of the entire range of traits (Messinger et al., 2015) and deepen our understanding of autism over the earliest phases of life (Varcin & Jeste, 2017).

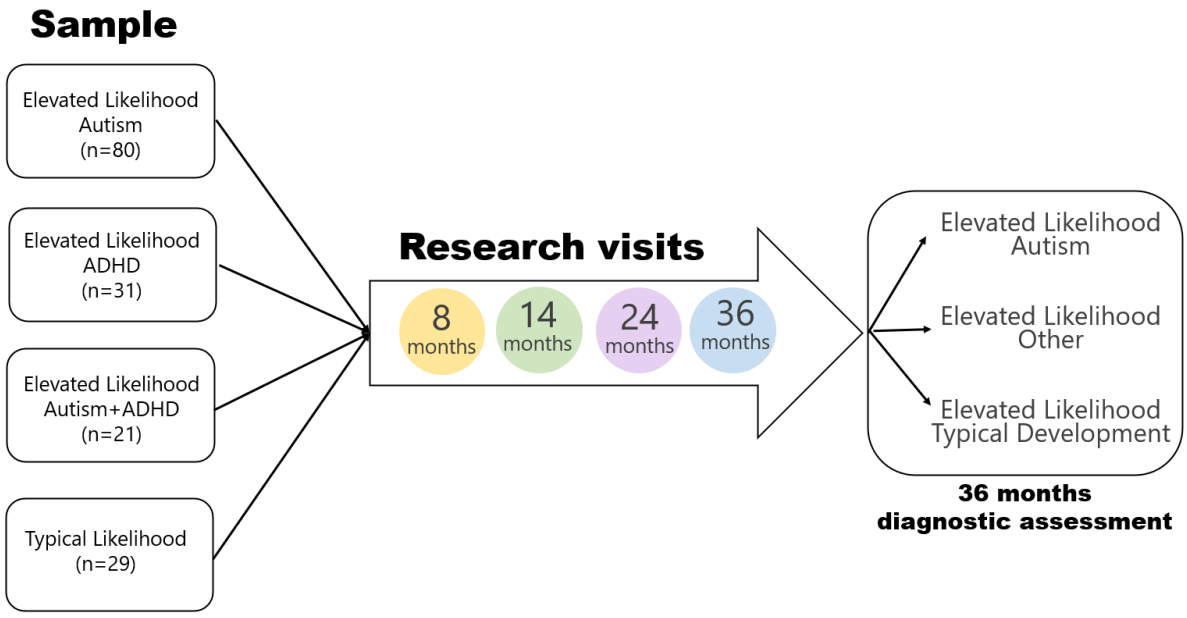

Figure 2. 1 Illustration of an infant study design (Virgina Carter Leno, Rianne Haartsen, 2023, *Alterations to Excitation/Inhibition Balance Are Associated with Increased Sensory Hyper Responsivity in Cohorts Enriched for Neurodivergent Outcome)*.

The primary aim of this thesis is to examine the developmental patterns and severity of these constructs over various timepoints and between groups. The secondary aim is to examine whether early infant anxiety and sensory symptoms can be an early marker of later autism traits. Given these criteria, we needed a model that directly addresses the traits and states the stability and influence of constructs in longitudinal research. A time series and multilevel models to analyse intensive longitudinal data do not explicitly consider measurement error (Castro-Alvarez, Tendeiro, Meijer, & Bringmann, 2022). Hence, structural equation models (SEM) help overcome these limitations and study the psychometric properties of the questionnaires used in intensive longitudinal data.

We will first define SEM and cover the considerations for fit indices, sample size and missing data, followed by types of models under SEM.

Structural Equation Modelling (SEM) is a statistical technique that allows researchers to investigate complex relationships between multiple variables in a single model. This approach is a very general and powerful multivariate technique that includes specialized versions of other analysis methods such as general linear model. SEM is an umbrella term that extends to many different types of models, such as path models, cross lagged design, and growth curve models. Typically, SEM involves specifying a model of interest, estimating parameters and assessing model fit to understand how well your theorised model fits to the real-life data you have. More broadly, SEM is particularly suited to study longitudinal data because of the following proposed reasons (Bijleveld et al., 1998; Farrell, 1994; Jeon, 2015):

- Longitudinal data often involve multiple variables that interact with each other over time. SEM enables researchers to model these complex relationships, including direct and indirect effects, mediating and moderating effects, and reciprocal relationships. SEM requires researchers to set up their model a priori to reflect their hypothetical underlying structure of the data, which can sharpen inference.
- SEM can help model latent variables, allowing researchers to capture underlying constructs that may change over time.
- Longitudinal data often has many missing observations, as participants may not always attend every single research visit. SEM can estimate models using full information maximum likelihood (FIML) estimators, which can handle missing data, such that participants with one research visit missing are not excluded from the total analysis.

- SEM provides various fit indices that help researchers assess how well their model fits the data. This is particularly useful for comparing different models and selecting the one that best represents the underlying longitudinal relationships.
- SEM can be used for growth curve modelling, where researchers analyse the trajectory of change in variables over time. This is particularly useful for understanding developmental processes.

Fit indices

Model fit or goodness of fit measures how well a statistical model fits a set of observations. When goodness of fit is high, the values expected based on the model are close to the observed values. There are many fit indices that can tell us whether the model we built is good or not. A few of them are listed below (Acock, 2013; Hu & Bentler, 1999; Kline, 2016; Schumacker & Lomax, 2004):

- *Chi-square with degrees of freedom and p-value* – Assesses the overall fit and the discrepancy between the sample and fitted covariance matrices. It is sensitive to sample size. It compares the differences between the data collected and what the model predicts. If the differences are small, this suggests the model is a good representation of the data. The chi-square compares our model to a saturated model that has no degrees of freedom. A *p-value*> 0.05. is considered a good fit.
- *CFI (Comparative Fit Index)* – This is a widely used measure. It compares our model with a baseline model, assuming no relationship exists among our observed variables. It compares the amount of departure from close fit for the model against that of the independent (null) model, i.e., compares the fit of a target model to the fit of an independent or null model. Its values range from 0 to 1.0, being the best result. The

recommended cutoff values should be either 0.90 or 0.95, with the 0.95 cutoff becoming more widely used today. It is not very sensitive to sample size.

- *RMSE (Root Mean Square Error)* – Is an absolute fit index scaled as a badness-of-fit statistic where zero indicates the best results. It also generally "rewards" models with more degrees of freedom or models analysed in the larger samples with lower values of RMSEA. Zero represents a good fit. It is recommended that this be 0.05 for a good fit and less than 0.08 for a reasonably close fit.

- *TLI (Tucker Lewis Index)* – This has the same cutoff values as the most commonly used CFI. The TLI imposes a greater relative penalty for model complexity than the CFI, but only one of these two statistics should be reported because their values are highly correlated. It is preferable for smaller samples.

- *SRMR (Standardised Root Mean Square Residual)* – Is an absolute fit index that is badness-of-fit statistics. The SRMR is computed as a square root of the average squared covariance residual in a standardised metric. Thus, it measures the means absolute correlation residual, the overall difference between the observed and predicted correlations. The value of SRMR > .10 may indicate poor fit, but the matric of correlation residuals should be inspected in an event.

Models can fit poorly because they may not have accounted for measurement error in the predictors. Failure to account for measurement error can make the wrong variables appear significant. If one model fits well it does not mean that another model with a different structure won't fit too.

Sample size (Bijleveld et al., 1998; Kline, 2016)

- SEM is generally a large sample technique, but attempts have also been made to adapt it to smaller samples.
- Certain estimates, such as standard errors for effects of latent variables, may need to be more accurate when the sample size is not large.
- Smaller sample sizes are required when outcome variables are continuous and normally distributed. The effects are linear, and there are no interactive effects. Versus analysis in which some outcomes are not continuous, have severely non-normal distributions or have curvilinear or interactive effects.
- More complex models with parameters require bigger sample sizes than simpler models with fewer parameters because models with more parameters require more estimates, and larger samples are necessary for the computer to estimate the additional parameters with reasonable precision.
- Large sample sizes are needed if score reliability is relatively low and less precise data requires larger samples to offset the potentially distorting effects of measurement error.
- Higher levels of missing data require larger sample sizes to compensate for loss of information.
- Overall, sample size requirements in SEM can be considered on the number of cases required for the results to have adequate statistical precision versus minimum sample sizes needed for significant tests in SEM to have reasonable power.

Types of missing data (Kline, 2016; Schumacker & Lomax, 2004):

- Missing Completely at Random (MCAR) assumes that everyone had the same probability of being omitted from the analysis. Listwise deletion of records with missing observations, and methods that first calculate summary statistics from observed data and fit models to these moments assume MCAR.
- Missing at Random (MAR) allows the probability of missingness to vary but only with the observed values of variables included in the model. This is what is assumed in Full-Information Maximum Likelihood (FIML).
- Missing Not at Random (MNAR or non-ignorable) allows the probability of missingness to vary with both observed and unobserved values of variables.

The assumptions, strengths, and limitations for these different types of models will be discussed below.

2.1 Path Models

Path models estimate multiple direct and indirect relationships between variables and how they influence each other by having variables arranged in a time order (concept of Path Model was initially used to build on the Models for Chapters 3 and 4). For example, if x occurs before y, then we can argue that y does not cause x. However, this also means that x does not necessarily cause y. Hence, many researchers prefer to say that "x influences y" or "x is associated with y" instead of asserting that "x causes y". Path models are used if all variables are observed (e.g., no latent factors are included in the model) (Acock, 2013).

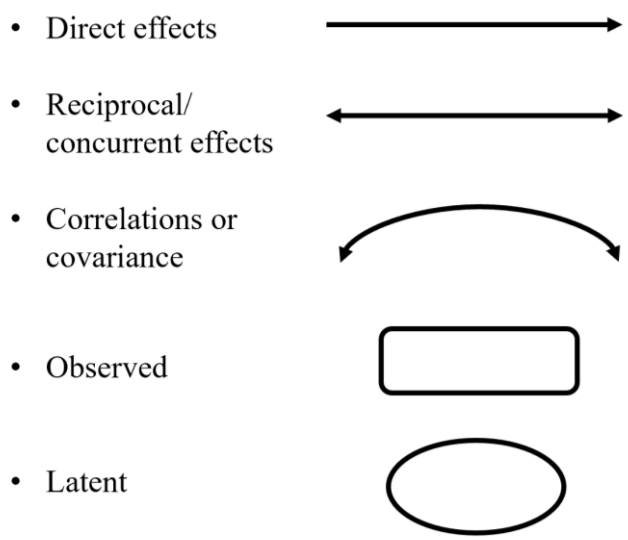

Figure 2. 2 Terms and symbols

SEM allows distinctions between observed and latent variables. Most experimental and non-experimental studies concern the relationship between two variables. In experimental studies, the researcher manipulates independent variables and the effect on the dependent variable is observed. In non-experimental studies, terms such as predictor and criterion (respectively) are used instead of independent and dependent, although some use them interchangeably. In SEM, we typically use the terms observed or manifest variables for any variables that are observed directly; these are indicated by a square or rectangle and latent variables or factors are indicated by a circle or oval (Figure 2.2 and 2.3).

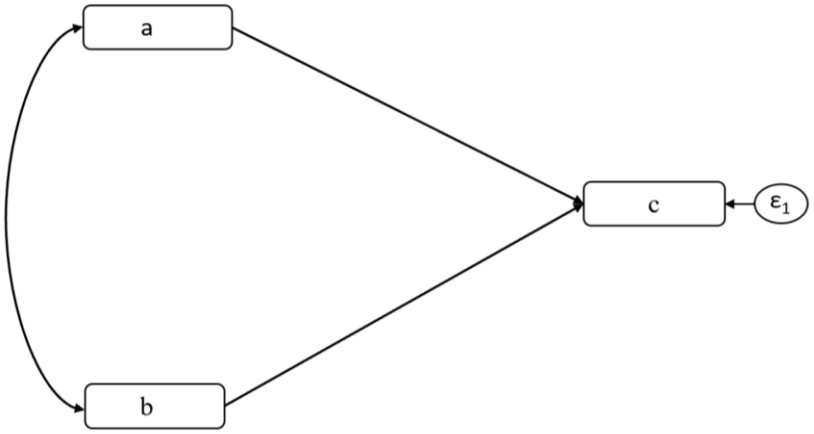

Figure 2. 3 Example of path model with two predictors (Independent Variables (IV)) a and b, and one outcome (Dependent Variable (DV)) c. Error (ε) is part of DV that is not explained by IV.

The path model is sometimes referred to as the causal model. The path analysis part of the structural equation model is known as the structural component, whereas the confirmatory factor analysis is known as the measurement component. With path analysis, we do not have randomisation of participants to groups, nor do we typically have experimenter controls over exposure to the independent variables. Few studies have used path analysis in autism research (S. J. Lane, Reynolds, & Dumenci, 2012; Leonardi et al., 2021).

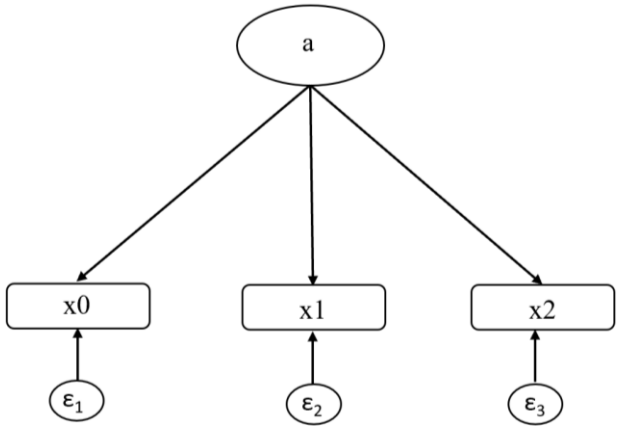

Figure 2. 4 Example of a measurement model

The measurement model in SEM is where the researcher assesses the validity of the indicators of each construct (Figure 2.4). It is that part of an SEM model that deals with the latent variables and their indicators. A pure measurement model is a confirmatory factor analysis (CFA) model in which there is unmeasured covariance (two-headed arrows) between each possible pair of latent variables, there are straight arrows from the latent variables to their respective indicators, there are straight arrows from the error and disturbance terms to their respective variables, but there are no direct effects (straight arrows) connecting the latent variables. The measurement model is evaluated like any other SEM model, using fit indices or measures. After showing the validity of the measurement model, the researcher can proceed to the structural model. Some are of the opinion to not proceed to the structural model until one is satisfied the measurement model is valid (Acock, 2013).

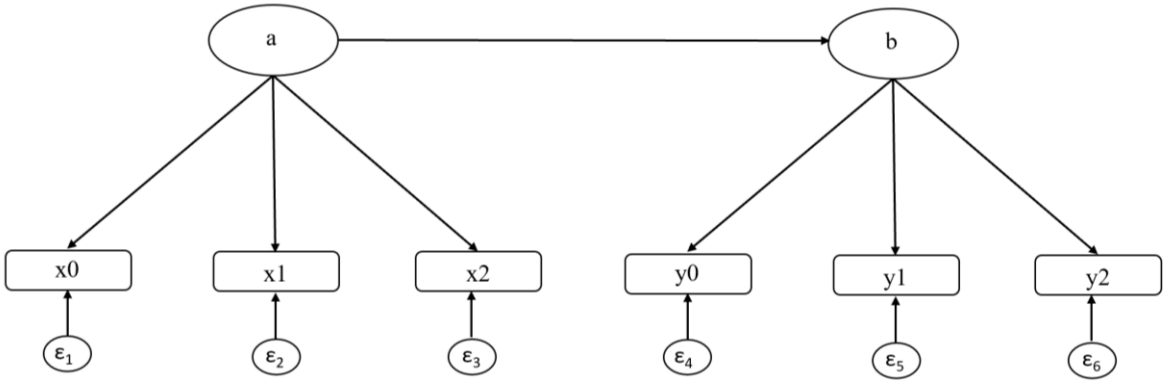

Figure 2. 5 Example of a structural model

The structural model may be contrasted with the measurement model. It is the set of exogenous and endogenous variables in the model, with the direct effects (straight arrows) connecting them and the disturbance and error terms for these variables (reflecting the effects of unmeasured variables not in the model). The structural model is concerned with the influence and significance between the constructs (Figure 2.5). The term "full structural model" means the measurement and structural relationships of each construct are included in the model testing.

Path models typically contain exogeneous predictors, endogenous and endogenous mediator variables which are described below (Acock, 2013):

Exogeneous variables are not causally dependent on any other variable in the model. They may correlate to one another, but no causal direction exists between them. All exogenous variables are independent variables, but not all independent variables are exogenous variables. Any explanation of these variables is external to the path model, i.e., outside the model. Any variable that is never on the left-hand side of the equation and is the target of an arrow from another variable or is predicted by another variable is often called exogeneous in SEM.

Endogenous variable is a dependent variable with respect to all other variables in the model, i.e., any variable on the left side in at least one equation is often called endogeneous in SEM. Any explanation of these variables is or internal origin, i.e., inside of the model.

Endogenous mediator variables can be either independent or dependent variables with respect to other variables. The mediator variable intervenes between exogenous variable and endogenous variable.

Listed are the assumptions, strengths and limitations of the path model (Jeon, 2015; Tomarken & Waller, 2005).

Assumptions:

- Relations among variables in the model are linear, additive, and causal.
- Each residual is not correlated with variables that precede it in the model.
- There is a one-way causal flow. The reciprocal causation between variables is ruled out.
- The variables are measured on an interval scale.
- The variables are measured without error. All these assumptions are hard to be satisfied in social science.
- Assumptions of normality apply to the dependent, and not the independent variable. Exogeneity assumes that predictor variables are not influenced by errors or disturbances from other variables in the model.

Strengths:

- This model forces you to think in terms of models, hypothesis and theories along with providing information on temporal ordering, directionality of effects, and what causes what.
- Path models do not rely on listwise deletion for handling missing data which can result in biased results and reduce statistical power.
- Path diagrams provide a clear visual representation of the relationships, making it easier for researchers to communicate their models to others.
- When modelling changes over time, path analysis is advantageous over 'simpler' methods of capturing change e.g., calculation of difference scores – as this estimates scores at T2, and variables that predict these scores accounting for scores at T1.
- Capturing individuals baseline level of constructs of interest is important due to the phenomenon of regression to the mean, path models also allow error variance to be different at each time point, difference score models assume variance is equal over time, which is unlikely to be true.

*Limitations***:**

- Limitation on Assumptions: Some of the assumptions are hard to satisfy in social sciences. Therefore, the assumptions themselves can be limitations.
- Co-linearity Issue: This is a common problem in path analysis as well as regression analysis. Co-linearity, prevalent in both path and regression analysis, arises from highly correlated independent variables. This impairs path coefficient estimation accuracy and effect detection.

- Meaning of Model fit: A significant fit of a path model to data doesn't prove causal relationships, as external factors can influence causation. Researchers might inadvertently use a posteriori approach, altering variables for better fit.
- Sample Size and Categorical Variables: Use of categorical variables, non-random sampling, and small sample size prevents the variance-covariance structure of the sample from matching the variance-covariance structure of the population. A sample size 20 times larger than estimated paths is recommended for reliability. Continuous variables are preferred over categorical ones to avoid inflated path coefficient estimates.

2.2 Cross-lagged Panel Model

The cross-lagged panel model is a variation of path model (used in Chapters 3 and 4). In this design, variables are measured at two or more time points, and the relationships between the variables at each time point are examined (Acock, 2013; Kearney, 2017). If we want to know the influence of x on y and the influence of y on x we use panel data where we have two waves of data. We have curved line between x1 and y1 because we assume these two will be correlated. Paths a and b are known as stability coefficients as they reflect how stable the constructs are over time. Paths labelled c and d tell us how early x1 influences y2, and how early y1 influences x2 (see Figure 2.6). Examples of this approach can usually be found in studies looking directional effects of traits (Ersoy et al., 2021; Green et al., 2012).

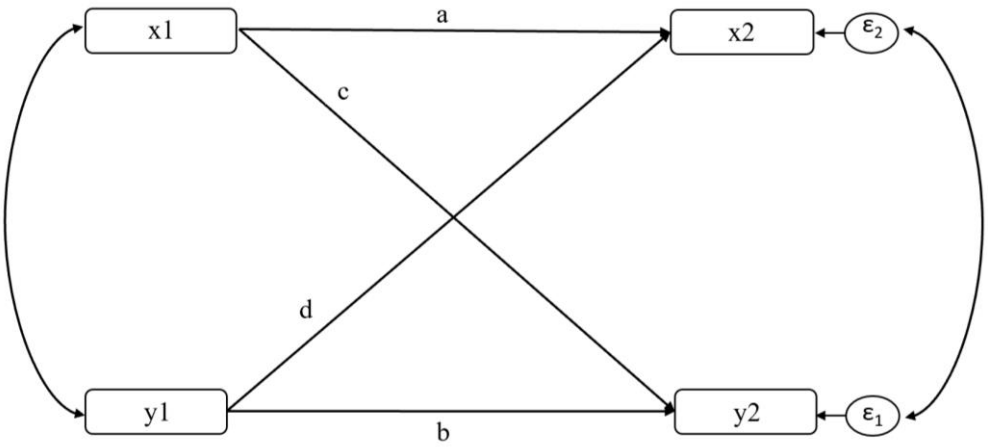

Figure 2. 6 Example of cross lagged panel design.

Strengths (Tomarken & Waller, 2005)*:*

- Cross-lag models can also incorporate latent variables, where multiple observed variables are used to infer the underlying latent construct of interest (see Figure 2.7).
- Cross-lagged model offers notable advantages, primarily attributed to its ability to address the influence of measurement error.
- This model enables a heightened precision in the measurement of constructs due to the incorporation of multiple indicators. Importantly, even in scenarios where an individual possesses only one of several indicators, an accurate score for the construct can still be derived.

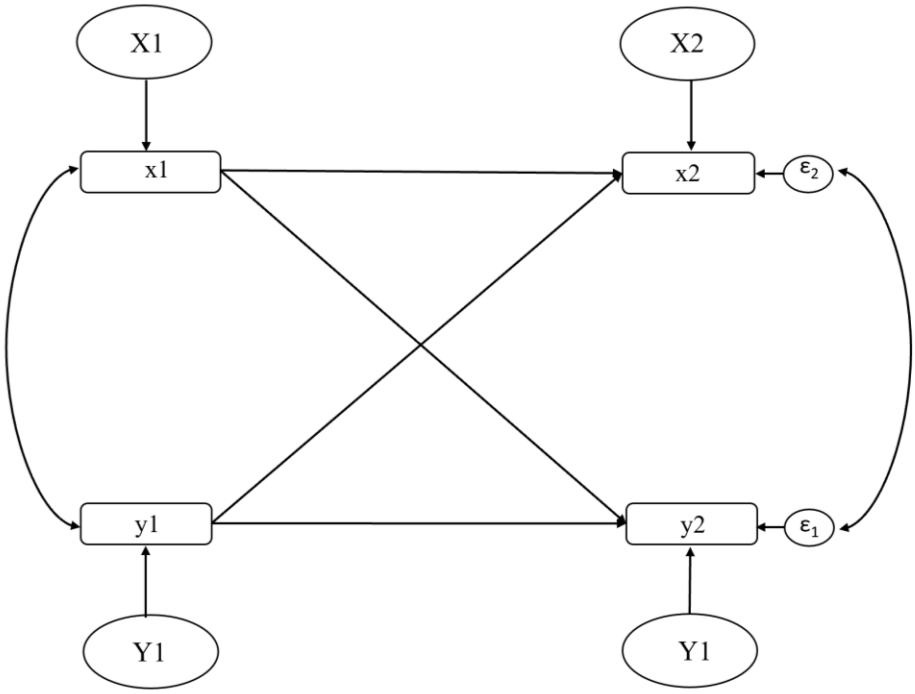

Figure 2. 7 Example of a cross lagged model with latent factors. Where X1. X2, Y1, Y2 are latent factors and x1, x2, y1, y2 are observed variables. For example, X1 is intelligence and x1 is a measure of intelligence.

Assumption and limitations (Hamaker, Kuiper, & Grasman, 2015; Kearney, 2017; Whittaker & Schumacker, 2022):

- Synchronicity: The first is the assumption of synchronicity, which assumes that measurements at each time point occurred at the exact same times. Although most studies are designed to measure variables simultaneously, complications during data collection mode frequently violate this assumption.
- Stationarity: Another assumption of cross-lagged panel analysis is that variables and relationships stay the same across time. There are varying degrees of stationarity, in models with three or more time points.

- Comparing Cross-Lagged Coefficients: To make claims about causal predominance, cross-lagged path analysis typically includes comparing relative sizes of cross-lagged coefficients. This is accomplished by standardising variables. In some cases, it may not be appropriate to assume the variables were measured on the same scale.
- Measurement Error: Many cross-lagged panel models assume that variables are measured without error. Some argue that measurement error may also be misidentified as real change when models have only two timepoints. In these cases, measurement error could still confound results of structural equation models.
- Stability: Cross-lagged panel models generally lack explicit theories of change. As such, autoregressive parameters are included to account for stability for everyone across time. This assumes there are no inter-individual differences, or differences between people, over time in stability. Inter-individual differences that do exist, such as unobserved trait-like influences or dependencies, may bias results.

2.3 Latent Growth Curve Model

Growth curve models are commonly used in longitudinal studies to visualize and analyse developmental or change over a period of time (used in Chapter 5). For instance, studies used growth curve model to explore the trajectories of sensory patterns from infancy to school age in children (Chen 2022, Ben-Sasson 2010). They are used to identify the trajectory and predict who has more positive or negative trajectory. The overall trajectory is referred to as fixed effect, i.e., when everyone has the same trajectory. The difference in individuals' trajectories from the overall trajectories is referred to as random effects. The SEM command does not estimate a different trajectory for each individual, but it does estimate the variance of the random effect (Acock, 2013). There are two possible random effects for the growth trajectory. The first is the intercept or initial level. A latent variable can be used to represent a

random intercept. This latent variable may also be called the latent intercept growth factor. When there is substantial variance in the intercept of different people, the covariates help explain this variance – for example do boys have higher intercept than girls? The second possible random effect is the slope or rate of change. The predictors explain trajectories rather than just scores at just one time point and the latent variables represent an intercept and a slope (Acock, 2013; Kline, 2016).

In a growth curve model, we need to identify the intercept to know where the growth curve starts, and then we need to identify the slope to know the rate of increase or decrease that occurs for each unit change in time. This is done by fixing the loadings for the intercept to one, and the loadings for the slope factor to reflect the amount of time passed since the first measurement point.

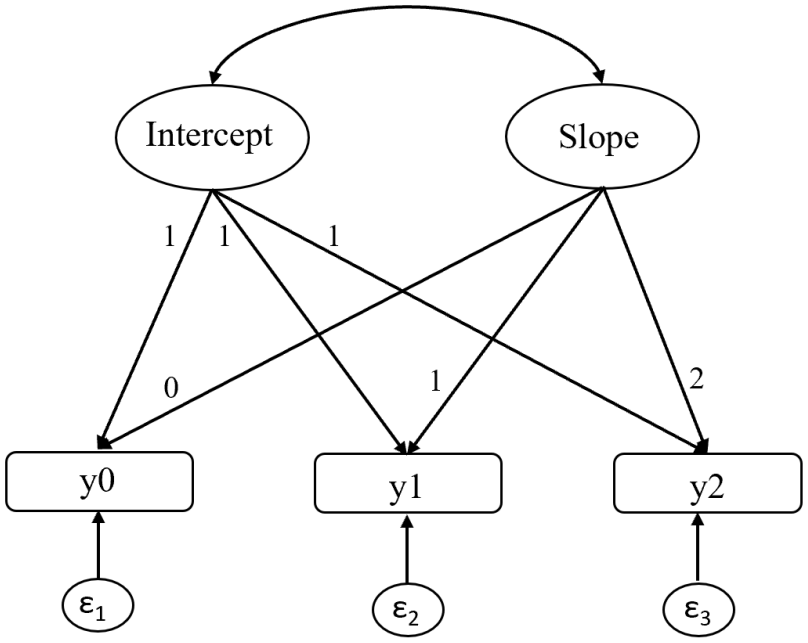

Figure 2. 8 Example of linear growth curve. The variables y0, y1, and y2 are observed variables. The y0 is the person's score at baseline/start reflecting their intercept.

With a single intercept and slope we are usually describing a linear growth curve. Timepoints added to the model add to degrees of freedom but also provide more information for the testing model. With two timepoints there is no relationship to test because two points determine only one line hence a need for at least three timepoints for a linear growth curve (see Figure 2.8) (Acock, 2013; Kline, 2016; McCormick, Byrne, Flournoy, Mills, & Pfeifer, 2023).

Listed are the strengths and limitations of the latent growth curve model (Acock, 2013; Duncan, Duncan, & Strycker, 2013; Tomarken & Waller, 2005).

Strengths:

- Latent growth curve model can be advantageous when you have multiple time points of measurement, because it captures change over time in two parameters – the intercept and the slope, thus lowering the number of parameters and thus statistical tests within an analysis.
- Models can include time variant (things specific to a given timepoint, e.g., anxiety) or time-invariant (things that don't change over time, e.g., family likelihood status) covariates.
- It is beneficial to assess developmental trajectories especially in elevated likelihood infant siblings, as opposed to evaluating different cross-sectional markers at different time points.

Limitations:

- It is often recommended to use large samples while using SEM, this can be hard with developmental data or clinical populations, especially with infant samples where

families might be overwhelmed with clinical needs and or may not have the time to commit to a longitudinal study.

- Latent growth curve requires a minimum of three time points for a linear growth curve. More time points are preferred.
- This model can be harder to converge as more complex models with greater number of parameters to estimate.
- The model assumes linear effects from covariate to intercept/slope unless otherwise specified.
- Although not unique to SEM, one of the common criticisms is that one way that SEM models are approximations is by omitting variables that are implicated in the causal processes of a model. Such omissions can distort the representation of measurement and/or causal framework, often leading to skewed parameter estimations and inaccurate estimates of standard error.

Despite SEMs over all limitations, the advantages of SEM for analysing longitudinal data are substantial. SEM's ability to model complex relationships, capture latent variables, and record growth trajectories make it a powerful tool in understanding prospective longitudinal data.

The next three empirical studies conducted for this thesis employ cross-lagged model in Chapter 3 and 4, while Chapter 5 applies latent growth curve model. This methodological approach provides a comprehensive understanding of the directionality and developmental trajectories between early emerging constructs and later neurodivergent traits.

Chapter 3: A prospective study of associations between early fearfulness and perceptual sensitivity and later restricted and repetitive behaviours in infants with typical and elevated likelihood of autism

This is the accepted version of the following article:

Narvekar, N., Carter Leno, V., Pasco, G., Johnson, M. H., Jones, E. J., & Charman, T. (2022). A prospective study of associations between early fearfulness and perceptual sensitivity and later restricted and repetitive behaviours in infants with typical and elevated likelihood of autism. *Autism*, *26*(8), 1947-1958. https://doi.org/10.1177/13623613211068932

Supplementary materials for this chapter, as detailed in the text, are attached in Appendix A.

Table and figure labels (e.g., Table 3.1) have been updated to be in line with the rest of the thesis.

3.1 Abstract

Autism is diagnosed based on social and communication difficulties, restricted and repetitive behaviours and sensory anomalies. Existing evidence indicates that anxiety and atypical sensory features are associated with restricted and repetitive behaviours, but cannot clarify the order of emergence of these traits. This study uses data from a prospective longitudinal study of infants with and without a family history of autism (N=247; Elevated Likelihood N=170 and Typical Likelihood N=77). Longitudinal cross-lag models tested bidirectional pathways between parent-rated infant fear/shyness and perceptual sensitivity at 8, 14 and 24 months, and associations between these domains and parent-rated restricted and repetitive behaviours and social communication scores at 36 months. In addition to within-domain continuity, higher levels of fear/shyness at 14 months were associated with higher levels of

perceptual sensitivity at 24 months. Higher levels of both fear/shyness and perceptual sensitivity at 24 months were associated with greater restricted and repetitive behaviours and social communication scores at 36 months. Results demonstrate the directionality of developmental pathways between fear/shyness and perceptual sensitivity in infancy and toddlerhood, but question theories that argue that these domains specifically underlie restricted and repetitive behaviours rather than autism. Identifying how early emerging anxiety and sensory behaviours relate to later autism is important for understanding pathways and developing targeted support for autistic children.

Lay Abstract

Restricted interests and repetitive behaviours are central to the diagnosis of autism and can have profound effects on daily activities and quality of life. These challenges are also linked to other co-occurring conditions such as anxiety and sensory sensitivities. Here, we looked at whether early emerging signs of anxiety and sensory problems appear before symptoms of autism by studying infants with a family history of autism, as these infants are more likely to develop autism themselves. Studying infant siblings provides an opportunity for researchers to focus on early developmental markers of autism as these infants can be followed from birth. This study found that early infant signs of anxiety (e.g. fear/shyness) predicted later perceptual sensitivity, and those infants who scored higher on fear/shyness and sensitivity were more likely to experience more persistent repetitive behaviours, but also social and communication difficulties in toddlerhood. Early signs of anxiety and perceptual sensitivity may thus relate to both later social difficulties and repetitive behaviours. These findings support the importance of further research exploring the causal links between these domains in relation to autism, resulting in increased understanding of children who go onto develop autism in the future and guiding early interventions and supports.

Keywords: autism, early development pathways, elevated likelihood, restricted and repetitive behaviours, temperament

3.2 Introduction

Autism spectrum disorder (ASD) (henceforth referred to as autism) is a neurodevelopmental condition with a childhood prevalence of ~1.5% (Maenner et al., 2020) which is typically diagnosed approximately around 6years of age (Brett et al., 2016). The core characteristics involve a varying degree of difficulty in social functioning, communication, and the presence of restricted and repetitive behaviours and sensory anomalies (APA, 2013). Although restrictive and repetitive behaviours (RRBs) are part of the diagnostic criteria for autism, historically more attention has been given to social and communication difficulties, and therefore, less is known about RRB despite their influence on daily activities (Leekam, Prior, & Uljarevic, 2011) and quality of life (Hochhauser & Engel-Yeger, 2010). RRBs are a mix of behaviours characterised by repetition and desire for sameness in the environment, preoccupation with parts of objects, restricted interests and ritualistic behaviours, and the most recent diagnostic criteria now includes hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment within the RRB domain (APA, 2013). RRBs are present at an early age (Wolff et al., 2014), including in typically developing infants (Leekam et al., 2007), and yet remain understudied compared to early social motivation and social attention (Elsabbagh & Johnson, 2016). A more comprehensive understanding of the infant characteristics associated with individual differences in RRB could identify individuals who may have more difficulty in this domain and inform the development of better targeted support.

The association between anxiety and RRB in autistic individuals

Recent research has reported associations between anxiety (which is highly prevalent in autistic youth; (Simonoff et al., 2008)) and RRB in autistic children (Gotham et al., 2013; Lidstone et al., 2014; Rodgers, Glod, Connolly, & McConachie, 2012). Studies of typically developing children with the anxiety-related condition obsessive–compulsive disorder (OCD) also suggest a link between anxiety and repetitive behaviours that may extend beyond autism. Indeed, children with OCD and autistic children are found to have comparable levels of sameness behaviours such as ritualistic habits and adherence to routines, and repetitive movements (Jiujias, Kelley, & Hall, 2017; Zandt, Prior, & Kyrios, 2007), although the drivers of RRB may differ between the two groups. One interpretation of these findings is that certain types of RRB could be useful for managing anxiety levels by allowing the child to impose control over their environment (Lidstone et al., 2014; Rodgers et al., 2012). Such frameworks assume that anxiety precedes RRB. However, a few studies have tested the directionality of the anxiety–RRB association; two studies that assessed RRB early in childhood found higher RRB was associated with greater anxiety later in development in autistic individuals (Baribeau et al., 2020; Ben-Itzchak, Koller, & Zachor, 2020), but the anxiety to RRB pathway was not tested.

An important factor to consider when examining associations between anxiety and RRB is sensory processing differences, broadly characterised as hypo- and hypersensitivity to sensory input and/or sensation-seeking, although others note that measurements of sensory sensitivity often conflate sensory sensitivity (i.e. differences in ability to detect differences in sensory input) and sensory reactivity (i.e. observable reactions to sensory input, which may be in part due to greater affective response) (Schulz & Stevenson, 2020). As noted above, while sensory processing atypicalities are now included as a subdomain of RRB symptoms in autism (APA, 2013), some suggest that sensory processing differences may themselves

directly contribute to individual differences in other aspects of the RRB domain (Boyd, Baranek, et al., 2010; Grzadzinski et al., 2020; Schulz & Stevenson, 2019). Sensory sensitivities are also positively associated with anxiety in autistic and typically developing children (Neil, Olsson, & Pellicano, 2016), and sensory over-responsivity (akin to hyper-sensitivity) is associated with longitudinal changes in anxiety in autistic toddlers (Green et al., 2012). Although most research has focused on direct pathways between sensory processing and RRB, or between sensory processing and anxiety, it is also possible, if not likely, that more complex associations exist. For example, it may be that the early emerging sensory aspects of the RRB domain trigger anxiety, which in turn triggers other behavioural RRB characteristics (e.g., repetitive and stereotypic behaviours, and insistence on sameness) in order to regulate arousal. Thus, it may be that motoric/behavioural RRB is a proximal response to both anxiety and sensory sensitivities (and the two cooccur), or that sensory sensitivities precede anxiety (or vice versa), which in turn prompt RRB (Joosten, Bundy, & Einfeld, 2009). Indeed, studies that have measured all three constructs in autistic children report that the association between anxiety and RRB may be partially mediated by sensory avoidance sensitivity (Black et al., 2017; Lidstone et al., 2014), or that sensory hypo- and hypersensitivity act upon RRB through anxiety (Wigham, Rodgers, South, McConachie, & Freeston, 2015), although all used a cross-sectional design.

Prospective infant sibling design

Most research on the interplay between anxiety, sensory processing and RRB in autism has been conducted with individuals with an existing diagnosis and is largely crosssectional. However, reported associations in older children are likely compounded by a history of interactions between these factors once they have emerged earlier in development (Johnson, Jones, & Gliga, 2015). Thus, focusing on these factors early in development allows one to

examine associations between domains as individual differences in factors of interest emerge. Teasing apart issues of directionality is required to build a more mechanistic model of pathways to RRB. This may be possible within prospective studies of infants with a family history of autism, which enable the measurement of particular phenotypes before diagnosis occurs (Constantino, Charman, & Jones, 2021; Jones et al., 2014). About 20% of infants with an older sibling with autism will go on to receive a diagnosis of autism themselves (Ozonoff et al., 2011), and another 20% will manifest subthreshold symptoms or developmental delay (Charman et al., 2017; Messinger et al., 2013). This recurrence rate allows the feasible study of emerging autism in siblings with (referred to as Elevated Likelihood; EL) and without (referred to as Typical Likelihood; TL) a first degree relative with an autism diagnosis followed from the first year of postnatal life to an age at which a diagnosis can be made. Although only a subgroup of these infants will go onto receive a diagnosis, on a whole these cohorts are characterised by substantial variation in autistic traits. Given that genetic studies find that aetiological influences on autism traits at the extremes are shared with aetiological underpinnings of traits in general population (Robinson et al., 2011) (i.e. that aetiology of the diagnosis is shared with aetiology of traits), studying precursors of continuous autistic traits can identify mechanisms relevant to autism as a diagnostic category.

When studying anxiety and sensory processing differences, it is necessary to identify appropriate developmental precursors to later clinically defined responses (Clifford et al., 2013; Macari, Koller, Campbell, & Chawarska, 2017; Schwichtenberg et al., 2013). In typically developing children, research suggests temperamental styles such as behavioural inhibition, fearful reactivity to novel stimuli and shyness precede childhood anxiety disorders (Möller et al., 2016). Although less is known about normative developmental patterns of sensory processing and manifestations of atypical perceptual processing in early infancy,

perceptual sensitivity has been conceptualised as a core component of models of infant temperament and appears to be stable between infancy and toddlerhood (Gartstein & Rothbart, 2003; Putnam, Gartstein, & Rothbart, 2006).

Present study

This study uses a prospective longitudinal design to examine associations between fear/shyness, perceptual sensitivity, RRB and social communication in EL and TL infant siblings in early infancy. This study has two aims: first, to test bidirectional associations between fear/shyness and sensory processing between 8 and 24 months using well validated measures of infant characteristics; second, to test if these constructs are associated with RRB and social communication at 36 months of age. We include social communication as an outcome to assess the specificity of associations with RRB; the constructs of interest (anxiety and sensory processing) are also reported to be longitudinally associated with social communication (Vlaeminck, Vermeirsch, Verhaeghe, Warreyn, & Roeyers, 2020).

3.3 Methods

Participants

As part of the British Autism Study of Infant Siblings (BASIS: http://www.basisnetwork.org), 247 infants were assessed four times, with visits at approximately 6–9, 12– 15, 24 and 36 months of age. Infants in the EL group (n=170; 85 male; 85 female) had at least one older sibling with a community clinical diagnosis of autism, which was confirmed based on parent report: using the Development and Wellbeing Assessment (DAWBA; (Goodman, Ford, Richards, Gatward, & Meltzer, 2000)), the Social Communication Questionnaire (SCQ; (Berument, Rutter, Lord, Pickles, & Bailey, 1999)) or parent confirmed community clinical autism diagnosis. Infants in the TL group (n = 77; 35

male and 42 female) had at least one older sibling with typical development and no known autism in first-degree family members (as confirmed through parent interviews regarding family medical history). The Mullen Scales of Early Learning (MSEL; (Mullen, 1995)) and Vineland Adaptive Behaviour Scale-II (VABS-II; (Sparrow, Cicchetti, & Balla, 2005)) were administered at each visit. All toddlers were assessed at 24 and 36 months with the Autism Diagnostic Observation Schedule-2 (ADOS-2; (Lord et al., 2012)), and at 36 months, parents were interviewed using the Autism Diagnostic Interview–Revised (ADI-R; (Lord, Rutter, & Le Couteur, 1994)). Best estimate clinical diagnosis of autism was made at age 3 informed by, but not dependent on outcomes from the ADOS-2, the ADI-R, the VABS-II and MSEL scores by experienced researchers (T.C. and G.P.). Thirty-four EL infants met the diagnostic criteria for autism at 36 months (see Supplementary Appendix Table A3.1). Participants were recruited from a volunteer database at the Birkbeck Centre for Brain and Cognitive Development. All parents included in the study completed written informed consent before each visit.

Measures

Fear and sensory sensitivity were assessed with the Infant Behaviour Questionnaire-Revised (IBQ-R; (Gartstein & Rothbart, 2003) at 8 and 14 months and Early Childhood Behavioural Questionnaire (ECBQ; (Putnam et al., 2006) at 24 months. Both measures are reliable and well-validated parent-reported questionnaires. Internal consistency and inter-rater reliability of the IBQ-R have been previously investigated by Gartstein and Rothbart (2003), where internal consistency was acceptable to excellent for all IBQ-R subscales in children aged 3–9 months (α=0.70–0.90). Parents rated their child on how often they exhibited each behaviour in the previous 2weeks. Items are scored on a Likert-type scale from 1 (Never) to 7 (Always). The IBQ-R is designed for infants aged 3–12 months and consists of 191 items. The ECBQ is

developed to assess temperamentrelated behaviours in children aged 18–36 months and consists of 201 items. The IBQ-R subscales of fear (16 items) and perceptual sensitivity (12 items), the ECBQ subscales of shyness (12 items) and perceptual sensitivity (12 items) were calculated. The perceptual sensitivity subscale refers to detection or perceptual awareness of slight, low-intensity stimulation from the external environment. In the IBQ-R, the fear subscale measures infant distress or inhibited approach to novel social and non-social stimuli. In the ECBQ, this collection of behaviours is separated into two subscales termed fear (indexing distress or inhabited approach to novel non-social stimuli) and shyness (indexing discomfort, slow or inhibited approach to novelty and uncertainty in social situations) – development work suggested the social and non-social components could not be reliably dissociated in infancy (Gartstein & Rothbart, 2003). We chose the IBQ-R fear and ECBQ shyness subscales as the closest measures to the construct of infant/ toddler behavioural inhibition that maps onto later childhood anxiety, as per previous research involving typically developing infants (Dyson, Klein, Olino, Dougherty, & Durbin, 2011) and in EL samples (Ersoy et al., 2021), and based on the observation that in the current sample, the correlation between 14-month IBQ-R fear and 24-month ECBQ shyness (r=0.52 and p<0.001) was greater than the correlation with 24-month ECBQ fear (r=0.46 and p<0.001). In the current sample, internal consistency was good for the fear/shyness (α=0.85–0.89) and the perceptual sensitivity subscales (α=0.85–0.86).

The Social Responsiveness Scale–2 (SRS-2; (Constantino & Gruber, 2012)) questionnaire designed to measure autistic traits consists of 65 items, each rated on a 4-point scale ranging from 1 (not true) to 4 (almost always true). Parents completed the Preschool forms of the SRS at 36 months and scores on the RRB (12 items) and Social Communication and Interaction subscales (indexing SCI; 53 items) subscales were calculated (henceforth referred to as RRB

and SCI). In our sample, both subscales of RRB and SCI showed excellent internal consistency (α=0.99 each). Due to skew, the RRB and SCI variables were log transformed.

3.4 Data analysis

Two cross-lagged structural equation models were estimated to test the directionality of pathways between fear/ shyness, perceptual sensitivity, RRB and SCI. Model 1 examined the autoregressive and cross-lagged pathways between the three measures of fear/shyness and perceptual sensitivity at 8, 14 and 24 months (Figure 3.1). Model 2 examined the direction of longitudinal relationships between each timepoint of fear/shyness, perceptual sensitivity measurement and later RRB and SCI (Figure 3.2). We included SCI as an outcome in Model 2 to assess the specificity of associations to RRB scores; post hoc tests compared the magnitude of the association for any significant predictors of RRB to the magnitude of the association for SCI. All models were estimated using maximum likelihood to account for missing data. For Model 2, robust standard errors were used to correct for any residual skew in RRB/SCI scores. In both models, EL/TL status was adjusted for by entering likelihood status as predictor of all variables in the model. To check that results were not unduly influenced by the subgroup of infants who received an autism diagnosis later in development, we re-ran models excluding these participants (the pattern of findings was largely similar; however, some associations were no longer statistically significant, see Appendix Table A3.3 and Figures A3.1 and A3.2). Model fit was assessed by the root means square error of approximation (RMSEA) and comparative fit index (CFI). Acceptable fit is indicated by RMSEA of 0.05–0.08 and CFI of 0.90–0.95, whereas good fit is indicated by RMSEA of 0.01–0.05 and CFI of 0.95– 1.00 (Hu & Bentler, 1999; Kline, 2016). Model fit indices are not available for models estimated with robust standard errors. We fit models sequentially for parsimony and clarity of interpretation. All models were estimated using observed (i.e. non-

latent) variables in STATA 16. For completeness, we also present unadjusted correlation coefficients between fear/shyness and perceptual sensitivity at 8, 14 and 24 months and RRB and SCI at 36 months (see Appendix Table A3.2).

Community Involvement

There was no specific community input from autistic individual or family members on the analysis presented in this study. However, the BASIS network views families as partners in our research programme. We regularly hold meetings with a Parent Consultation Group to discuss targeted ethical, procedural and strategic issues at all stages of our work. In 2019, we held a family 'expo' event including parents (some of whom had an autism diagnosis), older siblings with an autism diagnosis, and some of the infant siblings who were in mid-childhood, both to share our findings and to gain feedback on our proposed new studies. As part of our work in AIMS-2-TRIALS, we lead regular online meetings of the Ethics and Biomarkers Working Groups in which autistic people help us shape the directions of our research. Understanding co-occurring conditions like anxiety is often brought up by these teams as an important priority, consistent with the results of broader surveys of the community.

3.5 Results

Sample characteristics

Sample characteristics for all measures and likelihood group comparisons are shown in Table 3.1. The EL group had higher ADOS social affect scores at 24 months, higher ADOS RRB scores at 24 and 36 months and higher ADI-R scores at 36 months, as compared to the TL group. The TL group had higher scores on MSEL at 8, 24 and 36 months.

Table 3. 1 Sample characteristics by Typical and Elevated likelihood groups.

	EL group	TL group	Group difference
8-months			
Sex (N girls: N boys)	84:85	42:35	χ^2 (1) = 0.496, p = .481
Age in months	8.23 (1.14)	7.91 (1.34)	t(244) = -1.941, p = .053, d = *-0.27*
MSEL	102.46 (15.79)	107.25 (12.59)	t(244) = 2.344, p = .020, d = 0.32
IBQ-R-Fear	2.95 (1.15)	2.54 (0.88)	t(233) = -2.735, p = .007, d = -0.39
IBQ-R-Perceptual Sensitivity	3.79 (1.27)	3.81 (1.15)	t(186) = 0.109, p = .913, d = 0.02
14-months			
Sex (N girls: N boys)	82:84	41:34	χ^2 (1) = 0.450, p = .502
Age in months	14.51 (1.32)	14.35 (1.32)	t(239) = -0.870, p = .385, d = -0.12
MSEL	95.20 (15.57)	104.81 (15.26)	t(244) = -1.941, p = .053, d = 0.62
IBQ-R-Fear	3.47 (1.08)	2.99 (0.88)	t(225) = -3.3381, p = .001, d = -0.48
IBQ-R-Perceptual Sensitivity	3.74 (1.23)	4.13 (1.04)	t(198) = 2.178, p = .031, d = 0.33
24-months			
Sex (N girls: N boys)	79:79	38:35	χ^2 (1) = 0.346, p = .556
Age in months	25.39 (1.99)	24.21 (0.93)	t(229) = -4.822, p < .001, d = -0.68
MSEL	99.69 (20.13)	115.55 (14.14)	t(221) = 5.913, p < .001, d = 0.86
ADOS CSS SA	3.05 (2.05)	1.96 (0.60)	t(182) = -2.689, p = .008, d = -0.57
ADOS CSS RRB	4.09 (2.72)	2.54 (2.20)	t(182) = -2.773, p = .006, d = -0.59
ECBQ-Shyness	3.33 (1.05)	2.90 (0.82)	t(206) = -2.997, p = .003, d = -0.44
ECBQ-Perceptual Sensitivity	3.32 (1.18)	3.34 (1.13)	t(206) = 0.104, p = .917, d = 0.15
36-month			
Sex (N girls: N boys)	80:84	38:35	χ^2 (1) = 0.329, p = .566
Age in months	38.43 (2.21)	38.40 (2.65)	t(235) = -0.108, p = .914, d = -0.02
MSEL	103.39 (23.99)	117.04 (15.91)	t(234) = 4.440, p < .001, d = 0.63
ADOS CSS SA	3.54 (2.63)	3.33 (2.25)	t(235) = -0.603, p = .547, d = -0.08
ADOS CSS RRB	4.55 (2.64)	3.71 (2.47)	t(235) = -2.296, p = .023, d = -0.32
ADI-R Social	3.80 (4.97)	0.96 (1.49)	t(186) = -2.836, p = .005, d = -0.61
ADI-R Communication	4.07 (4.73)	0.48 (1.05)	t(186) = -3.777, p < .001, d = -0.81
ADI-R RRB	1.43 (2.40)	0.08 (0.28)	t(186) = -3.065, p = .003, d = -0.66
SRS-RRB	5.24 (7.19)	1.58 (2.19)	t(223) = -4.220, p < .001, d = -0.60
SRS-SCI	35.48 (26.25)	19.81 (9.24)	t(223) = -4.921, p < .001, d = -0.70

ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; ECBQ = Early Childhood Behavioral Questionnaire; IBQ-R = Infant Behavioral Questionnaire-Revised; MSEL ELC= Mullen Scales of Early Learning Early Learning Composite Standard Score; RRB = Restrictive and Repetitive Behaviors; SA = Social Affect; SCI = Social Communication Interactions; Difficulties; SD = Standard Deviation; SRS = Social Responsiveness Scale.

Model 1: associations between fear/shyness and perceptual sensitivity from 8 to 24 months

The cross-lagged model provided a good fit to the data ($\chi 2$ (2) =3.83, p=0.15; CFI=0.99, RMSEA=0.06) (Figure 3.1). There were significant associations between fear at 8 months and fear at 14 months (β=0.53 and p<0.001) and between fear at 14 months and shyness at 24 months (β=0.50 and p<0.001), but not between fear at 8 months and shyness at 24 months (β=0.01 and p=0.93). Similarly, there were significant associations between perceptual sensitivity at 8 and 14 months (β=0.50 and p<0.001) and 8 to 24 months (β=0.37 and p<0.001), and the association between 14 and 24 months (β=0.15 and p=0.06) scores fell just short of significance. Cross-sectional associations between fear and perceptual sensitivity were significant at 8 (β=0.25 and p<0.001), 14 (β=0.16 and p=0.02) and 24 (β=0.26 and p<0.001) months. Crosslagged paths indicated that higher levels of fear at 14 months were associated with higher levels of perceptual sensitivity at 24 months (β=0.18 and p=0.01). All other cross-lag pathways were non-significant (ps⩾0.38).

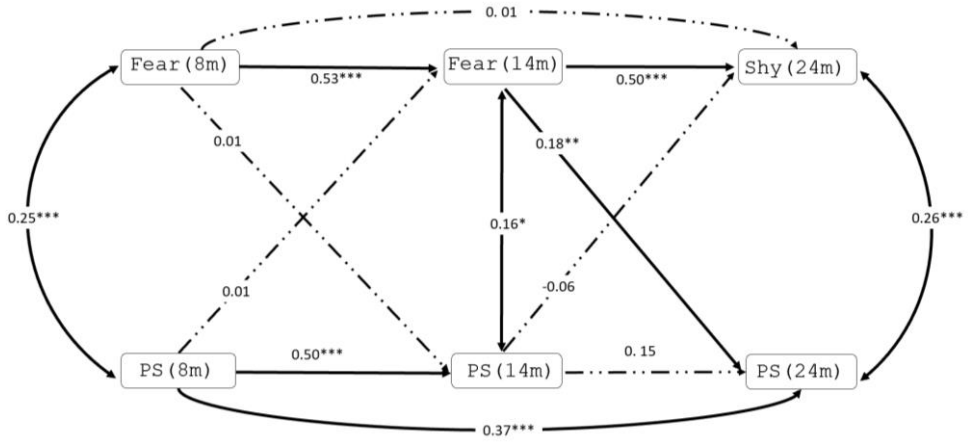

Figure 3. 1 Estimated model for cross lagged path related to Fear/Shyness and Perceptual Sensitivity (PS). Bold indicates significant association. (*p < .05, **p < .01, and *** p < .001)

Model 2: longitudinal association between fear/ shyness, perceptual sensitivity and RRB and SCI at 36 months

There was a concurrent positive association between RRB and SCI at 36 months (β=0.66 and p<0.001). Both higher levels of shyness and perceptual sensitivity at 24 months were significantly associated with heightened levels of RRB (β=0.20 and p=0.01; β=0.24 and p=0.004, respectively) and SCI (β=0.28 and p<0.001; β=0.23 and p=0.01, respectively) (Figure 3.2). Pairwise post hoc tests suggested no differences in the strength of these associations (all ps>0.21). Lower levels of perceptual sensitivity at 14 months were related to higher SCI only (β=−0.19 and p=0.02).

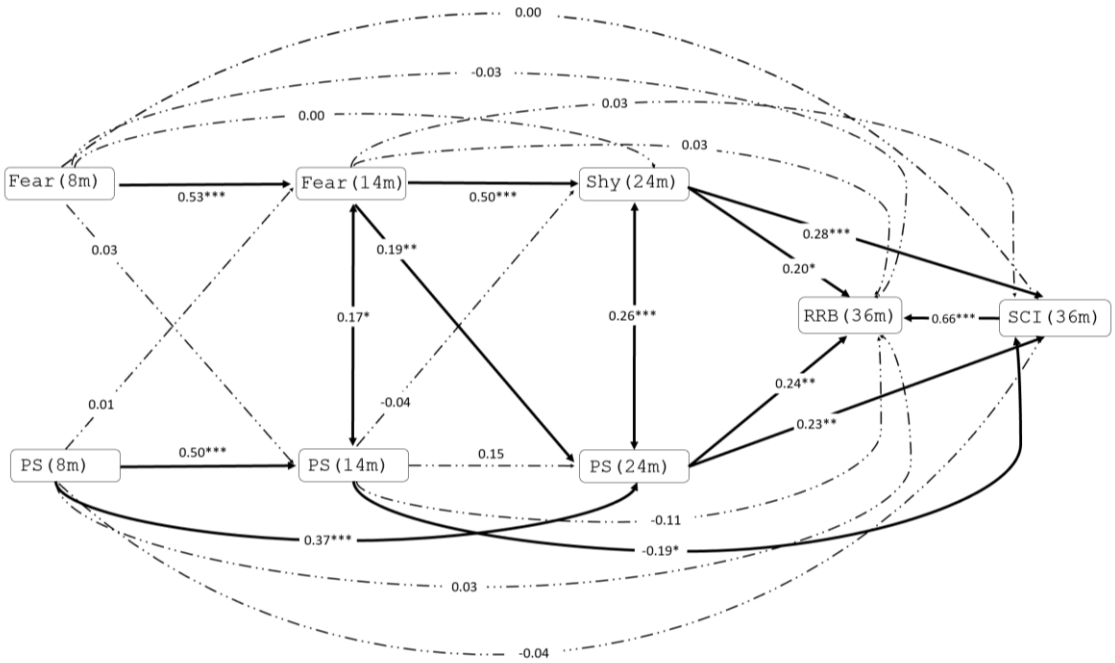

Figure 3. 2 Cross-lagged associations between Fear/Shyness, Perceptual Sensitivity (PS), restricted and repetitive behaviours (RRB) and social communication interactions (SCI) 8, 14, 24 and 36 months. Bold indicates significant association. (*p < .05, **p < .01, and *** p < .001).

Sensitivity analysis

When models were rerun excluding infants who received an autism diagnosis, the patterns mostly remained the same (see Supplementary Materials). The association between perceptual sensitivity at 8 months and SCI at 36 months became significant (β=−0.22 and p=0.023), such that lower levels of perceptual sensitivity were associated with higher levels of SCI. The associations between fear at 14 months and perceptual sensitivity at 24 months (β=0.16 and p=0.034), shyness at 24 months and SCI at 36 months (β=0.23 and p=0.001), perceptual sensitivity at 24 months and SCI at 36 months (β=0.30 and p<0.001) and perceptual sensitivity at 24 months and RRBs at 36 months (β=0.29 and p=0.001) remained significant. The associations between shyness at 24 months and RRB at 36 months (β=0.13 and p=0.140) and perceptual sensitivity at 14 months and SCI at 36 months were no longer statistically significant (β=−0.10 and p=0.294).

3.6 Discussion

This study investigated the directionality of associations between fear/shyness and perceptual sensitivity in the first 2 years of life and tested whether these two constructs were associated with later manifestations of RRB and SCI in a longitudinal cohort of infants enriched for autism outcomes. Cross-lag models indicated that at each timepoint, levels of fear/shyness and perceptual sensitivity positively predicted within-domain scores at the next time point, and higher levels of fear at 14 months were associated with higher levels of perceptual sensitivity at 24 months (but not vice versa). This suggests it is possible to measure temperamental fear/shyness and sensory sensitivity from the first years of life with some stability, and that the two domains may be interrelated. Results also showed that higher levels of shyness and perceptual sensitivity at 24 months were associated with heightened levels of

both RRB and SCI scores at 3 years, indicating that differences in anxiety and sensory processing may not be specific precursors of RRB but are shared with SCI.

Group differences and continuity in infant manifestations of anxiety and perceptual sensitivity

We found that those from the EL group scored higher on fear/shyness at all three age points as compared to TL group, highlighting that greater fear/shyness is associated with autism likelihood in infancy. With regard to perceptual sensitivity, the EL group scored lower than TL group on perceptual sensitivity at 14 months, with the direction of effect comparable to an earlier study in our cohort (with partly overlapping participants) (Clifford et al., 2013). Models showed significant autoregressive pathways, suggesting a substantial degree of within-domain continuity for both fear/shyness and perceptual sensitivity in the early infant period (aside from 14 to 24 months perceptual sensitivity which showed a non-significant trend). Our findings concur with research reporting significant within-person continuity in these constructs in young neurotypical and older autistic samples (Green et al., 2012; Putnam et al., 2006), which will be of interest to other researchers seeking to study early infant manifestations and developmental trajectories of these domains in typical and atypical populations. However, we highlight there is always a possibility that parents form a stable view of their child and may report consistency even if there is meaningful behaviour change; multi-respondent longitudinal designs are needed to test this hypothesis.

Longitudinal associations between fear/shyness and perceptual sensitivity

We extend cross-sectional findings (S. J. Lane et al., 2012; Lidstone et al., 2014; Neil et al., 2016; Wigham et al., 2015) by testing the directionality of associations between anxiety and sensory sensitivity in early infancy. Our results showed greater fear at 14 months was

associated with higher perceptual sensitivity at 24 months and not vice versa. One interpretation of this finding is that infants may be more likely to notice environmental sensory stimuli if they are hypervigilant of their environment, that is, being startled at sudden or loud noises (a core symptom of anxiety). Our findings are in contrast to previous work which found that sensory over-responsivity predicted anxiety 1 year later in autistic toddlers (Green et al., 2012) (and not vice versa). Differences in ages, sample and the measurement of sensory/perceptual processing may have contributed to these opposing sets of results. The mean age upon entry to the study by Green and colleagues was 28 months, and infants were followed up 1 year later, thus capturing a later developmental period (28–40 months) than that covered in this set of our analyses (8–24 months). Given that the early infant period is characterised by developmental change in how incoming information is processed and responded to, it is possible that the nature of the association between sensory processing and fear/ anxiety changes over development. In addition, all participants in the study by Green et al. had a diagnosis of autism, whereas the current sample was made up infants at TL and EL of developing autism, and only a small subset went on to receive a diagnosis themselves. Green and colleagues asked parents specifically about their child's negative emotional response to sensory stimuli (e.g. 'is bothered by loud noises or bright lights'), which may have included a more affective sensory response, whereas the current questionnaires were tapping infant's general sensitivity to the environment (e.g. 'How often during the last week did the baby appear to listen to even very quiet sounds'). Collecting information on both objective measures of sensory processing (e.g. discrimination thresholds) and affective response to different sensory inputs may help to disentangle the role of processing of, as compared to emotional reactivity to, different sensory inputs in elevating risk for anxiety.

Longitudinal association between fear/shyness, perceptual sensitivity, RRB and SCI

Results also show that higher levels of shyness and perceptual sensitivity at 24 months are associated with higher levels of parent-rated RRB at age 3. The finding of a positive association between infant manifestations of fearfulness and RRB extends previous cross-sectional studies that report positive associations between anxiety and RRB in older autistic individuals (Gotham et al., 2013; Lidstone et al., 2014; Rodgers et al., 2012) by establishing a longitudinal path from infant anxiety and perceptual processing to later RRB at 36 months. One idea put forward is that RRBs are employed as a strategy to regulate arousal levels and decrease anxiety by controlling environmental input (Lidstone et al., 2014), and our findings support this hypothesis. However, we highlight that we did not have a measure of RRB scores before 24 months (where fear/shyness and perceptual sensitivity were measured). Thus, it could also be possible that RRBs precede anxiety (as found in older samples by Baribeau et al. (2020)), or that bidirectional associations best characterise them over time.

Similar to fear/shyness, we also found greater perceptual sensitivity at 24 months was positively associated with RRB at 36 months. Similar results are found in other studies on EL (Wolff et al., 2019) and typically developing (Schulz & Stevenson, 2019) populations, where sensory related behaviours are significantly associated with a wide range of RRB. Similar to the interpretation for the association between fear/shyness and RRB, if a developing infant is especially sensitive to small changes in their sensory environment, they may develop a preference for sameness/ rigid pattern of behaviour to regulate incoming novel sensory information, although more precise measurement of sensory sensitivity as compared to sensory reactivity (as in Schulz and Stevenson (2019)) would help to better test this working hypothesis. Alternatively, in keeping with the fact that sensory processing differences are a subdomain of RRB, these may be among the earliest manifestations of RRB-type symptoms. A more parsimonious interpretation of our findings is that we see associations between these

two domains because we are measuring the same construct, which is especially pertinent given sensory processing differences are part of the RRB symptom domain (and thus are probed in the SRS-2 RRB items). However, it seems unlikely this could fully account for the observed association as only one SRS-2 RRB item specifically assessed sensory processing differences ('Shows unusual sensory interest or strange ways of playing with toys').

We further assessed whether the relations between fear/shyness and perceptual sensitivity with later RRB are specific to this domain. Contrary to this hypothesis, we found a similar pattern of associations existed with SCI, that is, higher levels of shyness and perceptual sensitivity at 24 months are also associated with higher levels of SCI at 36 months (in line with Vlaeminck et al. (2020)), and the pathways from fear/shyness and perceptual sensitivity to RRB and SCI were of comparable strength. This raises the question of specificity. Constructs such as anxiety and sensory processing have been proposed to specifically relate to RRB, but our results suggest they may also be important in understanding the emergence of SCI. These results challenge research that argues for fractionation of the different domains of autistic symptoms, in that they should be conceptualised as independent constructs with differential genetic and cognitive correlates (Happé & Ronald, 2008). Instead, our results suggest that there may be shared developmental pathways to RRB and SCI in toddlerhood (Constantino et al., 2021). It may be that the fractionation of domains of autistic symptoms is developmentally specific in that autistic symptoms manifest as one latent construct early in infancy, but the two domains become more differentiated as individuals become older (although see Beuker et al. (2013)). We also highlight that although this study focused on autistic traits as the outcome of interest; and it might be case that infant fear/shyness and perceptual sensitivity are associated with traits/characteristics beyond those indexing autism, such as emotional and behavioural difficulties. This requires investigation in future studies.

Finally, we found lower perceptual sensitivity at 14 months was associated with more persistent SCI (but not RRB). As the focus of this article was on infant precursors of RRB, we did not form specific predictions as to the nature of associations with SCI; this domain of autistic characteristics was only included to assess the specificity of associations to RRB. Therefore, we do not consider this result a confirmation of a specific hypothesis, but rather something to be explored further with relevant measures. However, we do note that our results concur with two other longitudinal infant sibling studies, where decreased sensory sensitivity is associated with decreased neural response to social stimuli and fewer social approach behaviours (Jones, Dawson, & Webb, 2018), and increased sensory seeking (indicative of hypo-sensitivity and/or reduced response to sensory input) is associated with greater social difficulties in toddlerhood through the mechanism of reduced social orienting (Baranek et al., 2018). As many of the items in the perceptual sensitivity measure used at 14 months ask about environmental awareness/noticing, one hypothesis is that if you are less sensitive to incoming sensory information (including social cues) at a critical developmental period, this could lead to atypical development of social cognition and consequent difficulties in social interactions (Jones et al., 2018). These results are interpreted as highlighting the importance of awareness of environmental changes for learning about social information (e.g. through social orienting) and adaptive social development. It may be that there are sensitive periods in early development where it is important for the developing infant to be acutely aware of changes in their ongoing environment to promote social learning whereas, conversely, the same level of sensitivity later in development impedes ongoing social interactions (e.g. as the infant is distracted from social situations by sensory hypersensitivities). Better understanding of the normative developmental trajectories of

sensory sensitivity and reactivity in infancy is necessary to delineate how atypical sensory development impacts emerging socio-cognitive abilities.

Finally, we highlight that in sensitivity analyses excluding infants who went onto be identified as autistic, most associations remained (aside from the associations between shyness at 24 months and RRB at 36 months, and perceptual sensitivity at 14 months and SCI at 36 months). The fact the pattern of findings largely remained (and even those that became non-significant had comparable coefficients of effect) suggests that the reported associations may represent mechanisms that are present across typical and atypical development, in line with studies suggesting the comparability of genetic influences on binary diagnostic status versus continuous variation in traits (Robinson et al., 2011).

Strengths and limitations

The main strengths of this study are the prospective longitudinal design, where infants are followed from birth to 36 months of age, giving a detailed picture of dynamic developmental changes in the first few years of life, and the moderate-to-large sample size for this type of study. This longitudinal approach is key to examining the directionality of early emerging associations in a reasonably large sample. However, we also note some limitations. As we solely used parent-report measures, shared method variance may have contributed to associations between the domains. In addition, the fact that in some families, there was already a first-degree relative with autism may have impacted how parents report on the behaviour of infant siblings. For example, parental perception of the older sibling with autism may influence their reporting on younger siblings' behavioural traits. Nevertheless, in previous study, parent report and direct observation ratings overlapped moderately for sensory over-responsivity (Tavassoli et al., 2019). It is also not well-known whether scores

on the IBQ are influenced by other autistic characteristics (e.g. social motivation and monotropism). Furthermore, we highlight a change in the questionnaire from IBQ-R at 14 months to its counterpart at 24 months (ECBQ) to ensure that items are age-appropriate. Despite this change in questionnaires, we found substantial within-domain continuity in fear/shyness and perceptual sensitivity over time, suggesting that the change of instrument did not have an overly large impact on construct measurement. Future research should focus on incorporating experimental and observational measures of infant anxiety (such as changes in heart rate and skin conductance), sensory processing (including brain measures to distinguish reactivity from detection and habituation) and autistic symptoms (e.g. observation and video coding methods; (Damiano, Nahmias, Hogan-Brown, & Stone, 2013; Harrop et al., 2014) to minimise the impact of shared method variance and measurement overlap and disentangle sensory sensitivity as compared to sensory responsiveness and affective reactivity. In addition, measures of anxiety and perceptual sensitivity that can be used across a wide developmental range (e.g. auditory oddball paradigms paired with psychophysiological recording; Haartsen, Jones, Orekhova, Charman, and Johnson (2019)) may be a useful source of complementary information to age-dependent questionnaires. Finally, although we have conceptualised fear/shyness and perceptual sensitivity as separable individual characteristics that are associated with later autism traits, it is unclear whether they represent constructs which influence the expression of autism traits later in development (e.g. the proposed hypothesis that being less sensitive to incoming sensory information impacts the development of social cognition), or are simply early markers of emerging autism (Constantino et al., 2021; Johnson, Charman, Pickles, & Jones, 2021).

3.7 Conclusion

This study found early infant manifestations of anxiety (e.g. fear/shyness) were associated with later perceptual sensitivity, and higher fear/shyness and perceptual sensitivity at 24 months were both associated with more RRB and SCI measured 1 year later. We also found lower perceptual sensitivity at 14 months was associated with greater SCI scores in toddlerhood. Findings build on cross-sectional work on the correlates of RRB, but also call into question theories that argue that these domains specifically underlie RRB rather than the broader range of autistic characteristics. Given the possible cascading effects of early anxiety and sensory atypicalities on autism symptoms, our findings support the importance of further research to increase our understanding of those children who are likely to develop autism, and to guide future attempts to develop mechanistically informed early intervention and supports.

Chapter 4: The roles of sensory hyperreactivity and hyporeactivity in understanding infant fearfulness and emerging autistic traits

This is the accepted version of the following article:

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Supplementary materials for this chapter, as detailed in the text, are attached in Appendix B.

Table and figure labels (e.g., Table 4.1) have been updated to be in line with the rest of the thesis.

4.1 Abstract

Background: Existing evidence indicates that atypical sensory reactivity is a core characteristic of autism, and has been linked to both anxiety (and its putative infant precursor of fearfulness) and repetitive behaviours. However, most work has used cross-sectional designs and not considered the differential roles of hyperreactivity and hyporeactivity to sensory inputs, and is thus limited in specificity.

Methods: 161 infants with and without an elevated likelihood of developing autism and attention-deficit hyperactivity disorder (ADHD) were followed from 10-36 months of age. Parents rated an infant precursor of later anxiety (fearfulness) using the Infant Behaviour Questionnaire at 10 and 14 months, and the Early Childhood Behavioural Questionnaire at 24 months, and sensory hyperreactivity and hyporeactivity at 10, 14 and 24 months using the

Infant Toddler Sensory Profile. Domains of autistic traits (restrictive and repetitive behaviours; RRB, and social communication interaction, SCI) were assessed using the parent-rated Social Responsiveness Scale at 36 months. Cross-lagged models tested 1) paths between fearfulness and hyperreactivity at 10-24-months, and from fearfulness and hyperreactivity to later autism traits, 2) the specificity of hyperreactivity effects by including hyporeactivity as a correlated predictor.

Results: Hyperreactivity at 14 months was positively associated with fearfulness at 24 months, and hyperreactivity at 24 months was positively associated with SCI and RRB at 36 months. When hyporeactivity was included in the model, paths between hyperreactivity and fearfulness remained, but paths between hyperreactivity and autistic traits became non-significant.

Conclusions: Our findings indicate that alterations in early sensory reactivity may increase the likelihood of showing fearfulness in infancy, and relate to later social interactions and repetitive behaviours, particularly in individuals with a family history of autism or ADHD.

Keywords

Autism; hyperreactivity; hyporeactivity; anxiety; early development; elevated likelihood; sensory reactivity.

4.2 Introduction

Autism is a neurodevelopmental condition characterised by differences in social communication and the presence of restricted interests and repetitive behaviours. Recent diagnostic frameworks have incorporated sensory atypicalities into the cluster of restricted and repetitive behaviours (RRB) as part of the core autism symptoms (DSM-5; American Psychological Association, APA, 2013). Sensory differences are experienced by almost 74%

of autistic children (Kirby et al., 2022). However, sensory differences are not unique to autism and are present in other neurodevelopmental conditions such as Down's Syndrome and Williams Syndrome (Baranek et al., 2013), intellectual disability (Posar & Visconti, 2018), and Attention Deficit Hyperactivity Disorder (ADHD) (Schulz et al., 2023); some report they are present in a significant proportion of typically developing children (Carpenter et al., 2019). Although not all alterations in sensory reactivity are experienced as negative, certain sensory differences can negatively impact daily activities, especially in situations where environments are less controlled (Posar & Visconti, 2018). Sensory challenges continue to present themselves in adulthood, making it an important consideration across the lifespan (Crane, Goddard, & Pring, 2009). Despite this, our knowledge of the developmental manifestation and impact of atypical sensory reactivity early on in life is limited.

Characterising Sensory Atypicalities

Progress in understanding the drivers and impact of sensory differences has been complicated by the broad range of terminologies used to describe differences in sensory functioning (e.g., hyper and hypo sensitivity/processing/reactivity/responsiveness, sensation seeking) (see He et al., 2022 for a review of nomenclature and theoretical frameworks) and the different modalities of sensory experience (e.g., visual, auditory, tactile). In this study, we use the terminology of hyperreactivity and hyporeactivity, with hyperreactivity representing greater behavioural reactivity to sensory inputs and hyporeactivity observed as lower behavioural reactivity to sensory inputs. A significant proportion of autistic children experience both hyperreactivity and hyporeactivity in multiple domains (Marco et al., 2012; Niedźwiecka, Domasiewicz, Kawa, Tomalski, & Pisula, 2019). Although data-driven approaches have had success in differentiating individuals with profiles of high and low sensory atypicalities, they do not find evidence for specificity of sensory reactivity profiles, again suggesting most

people with sensory differences experience both hyperreactivity and hyporeactivity (Tillmann et al., 2020).

Developmental Consequences of Early Alterations in Sensory Reactivity

One way to conceptualise the role of early alterations in sensory reactivity is through the developmental cascades framework (Bradshaw, Schwichtenberg, & Iverson, 2022), where early differences in specific domains (e.g., sensory reactivity) can have cascading and far-reaching effects on a variety of other, seemingly unrelated domains (e.g., autistic characteristics, mental health difficulties). Focusing early in development is particularly pertinent when thinking about sensory differences, given the early maturation of primary sensory systems in the brain. Indeed, infant-sibling designs (where infants with a family history of autism are recruited to give a sample enriched for neurodevelopmental outcomes, referred to as elevated likelihood; EL) find differences in sensory behaviour and brain function from as early as 6 months in infants who go onto receive an autism diagnosis (Sacrey et al., 2015; Shen & Piven, 2022). In terms of dimensional symptom profiles, RRB have been the primary focus since sensory atypicalities are located within this symptom domain according to DSM-5 criteria. In 14-month-old infants showing early autistic traits (as identified through community screening), parent-rated hyperreactivity, but not hyporeactivity, was associated with higher RRB at 3 – 5 years of age (Grzadzinski et al., 2020). However, there is evidence for a broader effect of early alterations in sensory differences and responsivity on autistic traits. In an infant-sibling cohort tracked from 10 to 36 months, perceptual sensitivity at 24 months were both positively associated with RRB and social communication and interaction (SCI) traits at age 3 years (Narvekar et al., 2022). Others find using a directly assessed play-based observational measure, hyporeactivity (but not hyperreactivity) at 14 months was associated with later SCI difficulties and RRB. In the

same cohort, greater directly-assessed atypical sensory behaviours (a combination of hyporeactivity and sensory seeking) was concurrently associated with lower joint attention at 12 and 22 months, and predictive of greater observer-rated social difficulties at 3 – 5 years (Nowell et al., 2020); hyperreactivity was not included as a predictor of interest. Similarly, studies from prospective infant-sibling cohorts report stronger correlations between RRB and hyperreactivity as compared to hyporeactivity between 12 and 24 months (Wolff et al., 2019). In the study by Wolff and colleagues (2019), although sensory atypicalities were not associated with observer-rated social affect, both hyperreactivity and hyporeactivity were associated with lower parent-rated socialization skills, and only hyporeactivity was associated with lower parent-rated communication skills. Similarly, higher parent-reported hyporeactivity is reported to be associated with lower communication skills in infant-siblings aged 12 to 18 months (Feldman et al., 2021). In autistic toddlers aged 2 years, parent-reported hyperreactivity was found to be a predictor of enhanced neural response to faces and increased social approach at age 4 (Jones, Dawson, & Webb, 2018), again suggesting differential effects for hyperreactivity as compared to hyporeactivity.

Although the extant evidence regarding the specificity of associations between the types of early sensory differences and later clusters of autism characteristics is mixed, likely due in part to variability in measurement of sensory reactivity and sample ascertainment, an emerging theme is that hyperreactivity is more closely related to RRB, whereas hyporeactivity is more closely linked to difficulties in socio-communication skills. With regards to the effect of hyperreactivity on RRB, some posit that RRB might reflect a compensatory strategy to reduce negative affect/arousal (Kapp et al., 2019). Further, research has reported associations between anxiety, sensory atypicalities and RRB (Gotham et al., 2013; Lidstone et al., 2014; Rodgers, Glod, Connolly, & McConachie, 2012; Williams,

Campi, & Baranek, 2021). Some have suggested that hyperreactivity acts upon RRB through anxiety (Wigham, Rodgers, South, McConachie, & Freeston, 2015) in autistic children. Indeed, hyperreactivity is reported to be predictive of longitudinal increases in anxiety in both autistic (Green, Ben-Sasson, Soto, & Carter, 2012) and typically developing (Carpenter et al., 2019; Schwarzlose, Tillman, Hoyniak, Luby, & Barch, 2022) children. In very young infants, anxiety per se is hard to measure and thus typically researchers focus on domains of temperament that are thought to be developmental precursors, namely behavioural inhibition/fearfulness (Gartstein et al., 2010; Shephard et al., 2019; Tonnsen, Malone, Hatton, & Roberts, 2013). Potentially suggestive of bidirectional cascading effects, in one infant sibling study greater fearfulness at 14 months predicts enhanced perceptual sensitivity at 36 months (characterized by enhanced detection of slight, low intensity environmental stimuli, conceptually close to hyperreactivity) (Narvekar et al., 2022). However, the field is limited by the lack of models that include both hyperreactivity and hyporeactivity. As hyporeactivity and hyperreactivity often co-occur in the same individual, studies which only focus on one domain of sensory atypicalities may be attributing phenotypic specificity (e.g., the proposed hyperreactivity to anxiety/RRB pathway) when global sensory alterations could explain the pattern of results.

The present study extends our previous work on infant fearfulness and sensory reactivity (Narvekar et al., 2022), by examining bidirectional associations between hyperreactivity and fearfulness in early infancy, and how these domains relate to later SCI and RRB traits in toddlerhood, using a more precise measure of sensory differences that distinguishes between hyperreactivity and hyporeactivity. Importantly, we examine the effect of including hyporeactivity on our findings to assess the specificity of associations between hyperreactivity and later fearfulness and SCI and RRB traits. We test these associations in a

prospective longitudinal cohort enriched for atypical neurodevelopmental outcomes through a family history design. This includes infants with family history of autism and/or ADHD. Both conditions are associated with early alterations in sensory reactivity (Shephard et al., 2022), have significant symptom overlap (Nijmeijer et al., 2008), and share aetiological underpinnings evidenced by twin studies (Ronald, Larsson, Anckarsäter, & Lichtenstein, 2014; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008). Furthermore, they have a high co-occurrence rate ranging from 40 to 70% (Antshel & Russo, 2019). Hence, we expect shared transdiagnostic pathways from early alterations to developmental outcomes to be common (although some may be distinct) in infants with a family history or autism and/or ADHD, due to common behavioural co-occurrence and moderate cross-condition heritability. We predicted that early hyperreactivity will be associated with infant fearfulness, and that both hyperreactivity and infant fearfulness will be associated with RRB traits. We also predicted that when we included hyporeactivity, effects of hyperreactivity on infant fearfulness and RRB traits would remain, and we would see a specific path from hyporeactivity to SCI traits. To maximise statistical power, and given that our sample is a heterogenous group spanning the clinical and nonclinical range, we focused on autistic traits rather than categorical diagnosis.

4.3 Methods

Participants

Participants were recruited for a longitudinal study as part of the Studying Autism and ADHD Risks Study (STAARS); for more details see Begum-Ali et al. (2022). Infants either had an elevated likelihood for autism (EL-autism; n=80; 42 male; 38 female), who had a first degree relative with a community clinical diagnosis of autism; elevated likelihood for ADHD

(EL-ADHD; n=31; 19 male; 12 female), who had a first degree relative with a community clinical diagnosis of ADHD or a probable research diagnosis of ADHD, and elevated likelihood for both conditions (EL-autism+ADHD, n=21; 12 male; 9 female), which consisted of the criteria of the previous two groups and diagnosed with both autism and ADHD; and lastly typical likelihood (TL; n= 29; 18 male; 11 female), who had at least one older sibling with typical development and no known autism or ADHD diagnosis in first-degree family members, which included the child's biological parents and full/half siblings (as confirmed through parent interviews regarding family medical history). Current analyses included infants who had at least one datapoint at the 10, 14, 24 or 36-month assessments, giving a final sample size of 161. See Table 4.1 for a breakdown of datapoints at each timepoint.

The Mullen Scales of Early Learning (MSEL; (Mullen, 1995)) and Vineland Adaptive Behaviour Scale-II (VABS-II; (Sparrow, Cicchetti, & Balla, 2005)) were administered at each visit. All toddlers were assessed at 24 and 36 months with the Autism Diagnostic Observation Schedule-2 (ADOS-2; (Lord et al., 2012)), and at 36 months parents were interviewed using the Autism Diagnostic Interview-Revised (ADI-R; (Lord, Rutter, & Le Couteur, 1994)). Best estimate DSM-5 clinical diagnosis of autism was made at age three informed by, but not dependent on outcomes from the ADOS-2, the ADI-R, the VABS-II, and MSEL scores by experienced researchers (TC, GP). 12 EL infants met the diagnostic criteria for autism at 36 months (9 in the EL-autism group, 3 in the EL-autism+ADHD group). All parents included in the study completed written informed consent before each visit.

Measures

Infant fearfulness was assessed with the fear subscale of the Infant Behaviour Questionnaire – Revised short form (IBQ-R; (Gartstein & Rothbart, 2003); fear subscale = 6 items) at 10 and 14 months and Early Childhood Behavioural Questionnaire – short form (ECBQ; (Putnam, Gartstein, & Rothbart, 2006); fear subscale = 8 items) at 24 months. The fear subscale measures infant/toddler distress or inhibited approach to novel social and non-social stimuli and higher fear scores in infancy are associated with greater child anxiety later in childhood (Gartstein et al., 2010; Shephard et al., 2019). Parents rated their child on how often they exhibited certain behaviours in the previous 2-weeks. Items are scored on a Likert scale from 1 (Never) to 7 (Always). The IBQ-R is designed for infants aged 3–12 months and the ECBQ for children aged 18 to 36 months. Both measures are reliable and well-validated parent-report questionnaires (Gartstein & Rothbart, 2003; Tomlinson, Harbaugh, & Anderson, 1996). The reliability of the fear subscale of the IBQ-R and ECBQ in our sample was assessed using Cronbach's alpha, which showed good internal consistency ($\alpha = 0.75$ - 0.83).

Infant sensory hyporeactivity and hyperreactivity were measured with the Infant Toddler Sensory Profile (ITSP; Dunn, 2002), a 48-item parent-caregiver questionnaire that measures sensory difficulties in children aged 7–36 months. Parents rate the frequency of their child's behaviour on a 5-point scale from 1 (almost always) to 5 (almost never). The ITSP scores assess sensory differences across five domains; auditory, visual, tactile, vestibular, and oral. Items are also grouped into four quadrants; low registration, sensation seeking, sensory sensitivity, and sensation avoiding. A composite low threshold score can be calculated by combining scores from the sensory sensitivity and sensation avoiding scales. Higher scores indicate the child shows less atypicality as compared to their peers. We used the total scores from the low registration quadrant as our index of hyporeactivity (11 items) and the total

scores from the low threshold quadrant as our index of hyperreactivity (25 items) (Germani et al., 2014; Vlaeminck, Vermeirsch, Verhaeghe, Warreyn, & Roeyers, 2020).

The ITSP showed high internal consistence for hyporeactivity ($\alpha = 0.81$ - 0.88 across 10, 14 and 24 months); and hyperreactivity ($\alpha = 0.90$ - 0.91 across 10, 14 and 24 months). In the current sample, correlations between the quadrants of sensory sensitivity and sensation avoidance subscales that form the low threshold/hyperreactivity scale were strong at each timepoint (10 months: $r = 0.834$; 14 months: $r = 0.807$; 24 months: $r = 0.812$, all $p < .001$) (see Appendix Table B4.2).

As analyses focused on traits rather than diagnostic symptoms, we used the preschool version of Social Responsiveness Scale – 2 (SRS-2; (Constantino & Gruber, 2012)) at 36 months to capture RRB (12 items) and SCI (53 items) traits. The SRS is a parent-rated questionnaire designed to measure autistic traits, consisting of 65 items, each rated on a 4-point scale ranging from 1 (Not True) to 4 (Almost Always True). In our sample, both subscales of RRB and SCI showed excellent internal consistency (α=0.90 and α=0.97 respectively).

Data Analysis

All analyses were run in Stata 16. Due to positive skewed distributions, the RRB and SCI variables were log transformed. For completeness, we present unadjusted correlation coefficients between all variables (see Appendix Table B4.1). To test our predicted hypotheses, 1) hyperreactivity will be associated with infant fearfulness, 2) hyperreactivity and infant fearfulness would be associated with RRB, 3) effects of hyperreactivity on infant fearfulness and RRB would remain with the inclusion of hyporeactivity, and 4) we would see a specific path from hyporeactivity to SCI, two cross-lagged structural equation models were estimated using maximum likelihood to account for missing data, and robust standard errors

were used to correct for any residual skew in RRB/SCI scores. Model 1 examined the direction of longitudinal associations between each timepoint of fear, hyperreactivity and later RRB and SCI (Figure 4.1). To test the specificity of the associations with hyperreactivity we re-ran Model 1, but also included measurement of hyporeactivity at 10, 14, and 24 months (Model 2; Figure 4.2). All models were adjusted for sex and group. Sex was included to account for actual sex-differences in reactivity, and potential gender-based differences in how parents rate their children's behaviour. Group status was accounted for by entering two binary variables (EL-Autism present/absent; EL-ADHD present/absent) as predictors of all variables in the model. We also specified an interaction between the two likelihood groups, but all interaction terms were non-significant and therefore not included in final models. We also ran additional follow-up sensitivity analyses to better understand the role of ADHD family history and co-occurring ADHD traits. This involved 1) excluding EL-ADHD infants and 2) including ADHD traits at 36 months (Child Behaviour Checklist (CBCL) ADHD subscale) as an outcome that correlated with SCI and RRB. We report unstandardised (B) and standardised (β) coefficients. As an additional robustness check, we used the Wald test to test whether constraining all significant coefficients to zero (i.e., leaving out these predictor variables) significantly reduced the fit of the model (conceptually equivalent to a Likelihood Ratio test for nested models). A significant p value indicates that the selected coefficients are not simultaneously equal to zero, meaning that including these paths create a statistically significant improvement in the fit of the model.

4.4 Results

Sample characteristics and likelihood group comparisons are shown in Table 1.

Table 4. 1 Sample Characteristics

Mean (*SD*)	N	EL-autism N=80	EL-ADHD N=31	EL-autism+ADHD N=21	TL N=29	Group differences	Direction of Effect
10 months							
Sex (n female:male)	149	38:38	12:14	8:12	11:16	p = .783	-
Age in months	149	10.03 *(0.52)*	10.23 *(0.91)*	10.15 *(0.49)*	10.00 *(0.62)*	p = .422	-
MSEL ELC	149	88.03 *(15.09)*	85.04 *(15.61)*	84.90 *(16.55)*	88.89 *(12.19)*	p = .660	-
IBQ-R Fear	123	3.67 *(1.43)*	3.03 *(1.14)*	3.77 *(1.39)*	3.14 *(0.84)*	p = .091	-
ITSP Hyporesponsivity	127	44.98 *(7.19)*	48.13 *(3.72)*	45.24 *(7.09)*	46.18 *(4.83)*	p = .213	-
ITSP Hyperresponsivity	128	93.75 *(15.29)*	95.65 *(7.46)*	93.57 *(13.93)*	95.98 *(8.40)*	p = .863	-
14 months							
Sex (n female: male)	138	35:38	7:16	7:12	10:13	p = .474	-
Age in months	138	14.30 *(0.64)*	14.22 *(0.80)*	14.37 *(0.60)*	14.26 *(0.62)*	p = .893	-
MSEL ELC	139	78.25 *(11.92)*	79.08 *(11.12)*	72.53 *(14.50)*	78.78 *(11.99)*	p = .259	-
IBQ-R Fear	127	3.87 *(1.29)*	3.83 (1.56)	4.07 (1.30)	3.42 (0.87)	p = .485	-
ITSP Hyporesponsivity	129	45.35 *(6.96)*	45.50 *(6.05)*	43.74 *(6.70)*	47.87 *(4.54)*	p = .294	-
ITSP Hyperresponsivity	129	92.41 *(14.82)*	93.56 *(9.82)*	89.28 *(13.23)*	94.82 *(7.99)*	p = .617	-

24 months							
Sex (n female:male)	128	33:33	9:13	5:11	11:13	p = .565	-
Age in months	128	24.92 *(1.55)*	24.68 *(1.09)*	24.38 *(0.72)*	24.58 *(1.14)*	p = .420	-
MSEL ELC	125	100.63 *(20.76)*	106.86 *(21.21)*	96.94 *(17.12)*	114.25 *(17.91)*	p = .017	EL-autism, EL-autism+ADHD <TL
ECBQ Fear	115	2.36 *(1.11)*	2.19 *(0.78)*	2.41 *(1.15)*	2.04 *(0.59)*	p = .570	-
ITSP Hyporesponsivity	118	47.53 *(7.12)*	45.18 *(6.86)*	44.47 *(8.40)*	48.95 *(3.15)*	p = .140	-
ITSP Hyperresponsivity	118	92.07 *(14.83)*	90.42 *(14.33)*	88.67 *(18.57)*	97.64 *(8.63)*	p = .251	-
ADOS CSS SA	127	3.32 *(1.95)*	2.95 *(2.01)*	4.13 *(2.19)*	2.29 *(1.00)*	p = .019	TL< EL-autism, EL-autism+ADHD
ADOS CSS RRB	127	3.53 *(2.54)*	4.05 *(2.48)*	2.88 *(2.36)*	2.79 *(2.19)*	p = .279	-
36 months							
Sex (n female:male)	119	33:28	11:12	5:11	7:12	p = .306	-
Age in months	119	37.21 *(1.46)*	37.35 *(2.69)*	37.19 *(1.52)*	36.79 *(1.78)*	p = .779	-
MSEL ELC	117	108.10 *(18.53)*	118.39 *(18.83)*	105.93 *(19.90)*	129.05 *(11.75)*	p < .001	EL-autism, EL-autism+ADHD < TL; EL-autism, EL-autism+ADHD < EL-ADHD
SRS RRB	107	5.48 *(6.38)*	4.05 *(5.22)*	9.00 *(9.53)*	1.16 *(1.61)*	p = .005	TL<EL-autism, EL-autism+ADHD; EL-ADHD<EL-autism+ADHD

SRS SCI	107	37.43 *(26.66)*	31.50 *(19.41)*	52.00 *(40.10)*	22.21 *(8.78)*	p = .013	TL<EL-autism, EL-autism+ADHD; EL-ADHD<EL-autism+ADHD
ADOS CSS SA	123	2.62 *(1.90)*	2.27 *(1.58)*	2.93 *(1.44)*	3.15 *(1.98)*	p = .425	-
ADOS CSS RRB	123	3.53 *(2.46)*	3.00 *(2.58)*	4.00 *(2.67)*	3.30 *(2.41)*	p = .666	-
ADI-R Social	122	3.89 *(5.33)*	2.55 *(4.04)*	5.69 *(8.15)*	0.94 *(1.00)*	p = .046	TL<EL-autism+ADHD
ADI-R Communication	122	3.53 *(4.65)*	1.55 *(2.69)*	3.38 *(4.10)*	0.67 *(0.97)*	p = .021	TL<EL-autism, EL-autism+ADHD; EL-ADHD<EL-autism
ADI-R RRB	122	1.42 *(2.03)*	0.73 *(1.49)*	1.69 *(2.12)*	0.39 *(0.61)*	p = .070	-

ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; CSS = Composite Standard Score; ECBQ = Early Childhood Behavioural Questionnaire; IBQ-R = Infant Behavioural Questionnaire-Revised; ITSP= Infant Toddler Sensory Profile; MSEL ELC= Mullen Scales of Early Learning Early Learning; RRB = Restrictive and Repetitive Behaviours; SA = Social Affect; SCI = Social Communication Interactions; Difficulties; SD = Standard Deviation; SRS = Social Responsiveness Scale. Note: Group differences were tested using one-way ANOVAs with group as a between-subject factor, followed by uncorrected post-hoc pairwise comparisons of means. Raw scoring was used where lower score indicated a greater severity for ITSP.

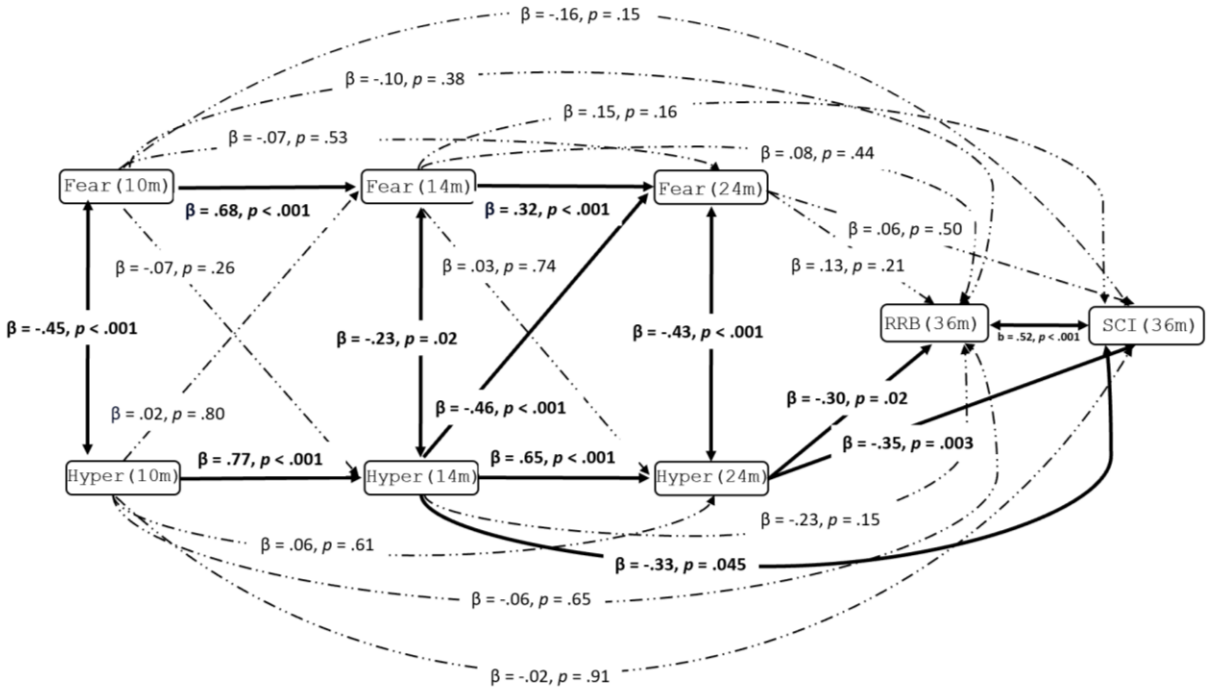

Figure 4. 1 Cross-lagged associations between Fear, Hyperresponsivity, Restricted and Repetitive Behaviours (RRB) and Social Communication Interactions (SCI) at 10 – 36 months of age. Bold indicates significant association. Raw scoring was used where lower score indicated a greater severity for ITSP.

Table 4.2. Model 1 with standardized coefficients.

		b	***p***	**[95% Confidence Interval**		**β**
Fear 14m	Fear 10m	0.67	0.000	0.51	0.83	0.68
	Hyperreactivity 10m	0.00	0.799	-0.01	0.02	0.02
Fear 24m	Fear 14m	0.25	0.001	0.10	0.39	0.32
	Fear 10m	-0.05	0.534	-0.22	0.12	-0.07
	Hyperreactivity 14m	-0.04	0.000	-0.05	-0.02	-0.46
Hyperreactivity 14m	Fear 10m	-0.72	0.268	-2.00	0.56	-0.07
	Hyperreactivity 10m	0.76	0.000	0.64	0.88	0.77
Hyperreactivity 24m	Fear 14m	0.31	0.737	-1.50	2.13	0.03
	Hyperreactivity 10m	0.07	0.566	-0.16	0.29	0.06
	Hyperreactivity 14m	0.74	0.000	0.50	0.99	0.65

RRB 36m	Fear 14m	0.06	0.446	-0.10	0.22	0.08
	Fear 10m	-0.08	0.379	-0.25	0.10	-0.10
	Hyperreactivity 10m	0.00	0.633	-0.02	0.01	-0.06
	Fear 24m	0.12	0.209	-0.07	0.32	0.13
	Hyperreactivity 14m	-0.02	0.143	-0.04	0.01	-0.23
	Hyperreactivity 24m	-0.02	0.018	-0.04	0.00	-0.30
SCI 36m	Fear 14m	0.08	0.161	-0.03	0.18	0.15
	Fear 10m	-0.08	0.146	-0.19	0.03	-0.16
	Hyperreactivity 10m	0.00	0.910	-0.02	0.01	-0.02
	Fear 24m	0.04	0.504	-0.08	0.17	0.06
	Hyperreactivity 14m	-0.02	0.040	-0.03	0.00	-0.33
	Hyperreactivity 24m	-0.02	0.003	-0.03	-0.01	-0.35
Covariance Fear 14m - Hyperreactivity 14m		-1.61	0.037	-3.12	-0.10	-0.23
Covariance Fear 10m - Hyperreactivity 10m		-7.34	0.000	-11.05	-3.63	-0.45
Covariance Fear 24m - Hyperreactivity 24m		-3.43	0.000	-5.17	-1.70	-0.43
Covariance SCI 36m – RRB 36m		0.16	0.000	0.10	0.23	0.52

SCI = social communication interaction; RRB = restrictive and repetitive behaviours

Model 1: Bidirectional associations between fear and hyperreactivity from 10 to 24 months and later autism traits at 36 months

The model fit was good ($\chi^2 = 1.73$, $p = .422$, CFI = 1.00, TLI = 1.01). The Wald test of combined coefficients was significant ($\chi^2 = 394.01$, $p < .001$). There was within-domain continuity for both constructs (see Figure 4.1, Table 4.2). As predicted, there was a negative association between hyperreactivity at 14 months and fear at 24 months (B = -0.04, β = -0.46, $p < 0.001$), with the negative scoring of the ITSP indicating that greater hyperreactivity was associated with higher levels of fear. Higher hyperreactivity at 14 months was also associated with higher SCI (B = -0.02, β = -0.33, p = .04) but not RRB (B = -0.02, β = -0.23, p = .14) at 36 months. Higher hyperreactivity at 24 months was significantly associated with higher RRB (B = -0.02, β = -0.30, p = .02) and SCI (B = -0.02, β = -0.35, $p < .01$) at 36 months. There was a concurrent positive

association between RRB and SCI at 36 months (B = 0.16, β = .52, p < .001). All other pathways were non-significant (see Figure 4.1).

As the association between hyperreactivity and fear was in the opposite direction to our previously published results in an independent infant-sibling cohort (where we found higher infant fear predicted enhanced perceptual sensitivity), to better understand the drivers of opposing results, we ran a comparable model using the same variables as in our previous work in the current sample. Results from modelling perceptual sensitivity (our previous marker of sensory reactivities) and fear/shyness (to mirror our previously used subscales) in the current cohort showed a negative association at the threshold of statistical significance between perceptual sensitivity at 14 months and shyness at 24 months, such that higher perceptual sensitivity at 14 months was associated with lower shyness at 24 months (β = -.19, p = .055). (see Appendix Figure B4.1). However, when we accounted for differences in the presence of ADHD family history between previous and current samples by excluding EL-ADHD infants (the previous cohort only recruited TL and EL-autism infants) this path became non-significant (β = -.13, p = .30) (see Appendix Figure B4.2). We also noted a significant drop in within-domain continuity for perceptual sensitivity between 14 and 24 months, regardless of the inclusion of EL-ADHD infants, which contrasted to the strong within-domain continuity observed for hyperreactivity in the current analyses. Based on these results, we infer that perceptual sensitivity may not be a stable measure across time points or cohorts, or that the transition from the IBQ to the ECBQ at 14 to 24 months impacted our ability to capture the same underlying construct over developmental time.

Given the lack of association between fear and RRB in our primary analysis was also unexpected (and goes against previous reports of associations between infant manifestations of anxiety and autism traits in a comparable developmental period; Ersoy et al., 2021), we ran an additional supplementary model testing whether fear in isolation (e.g., removing measurements of hyperreactivity from the model) predicted autistic traits (see Appendix Figure B4.3). We found fear at 24 months was positively associated with both RRB (B = 0.41, β = .42, p < .001) and SCI (B = 0.28, β = .43, p < .001) at 36 months, suggesting these associations may be in part driven by unmeasured effects of hyperreactivity.

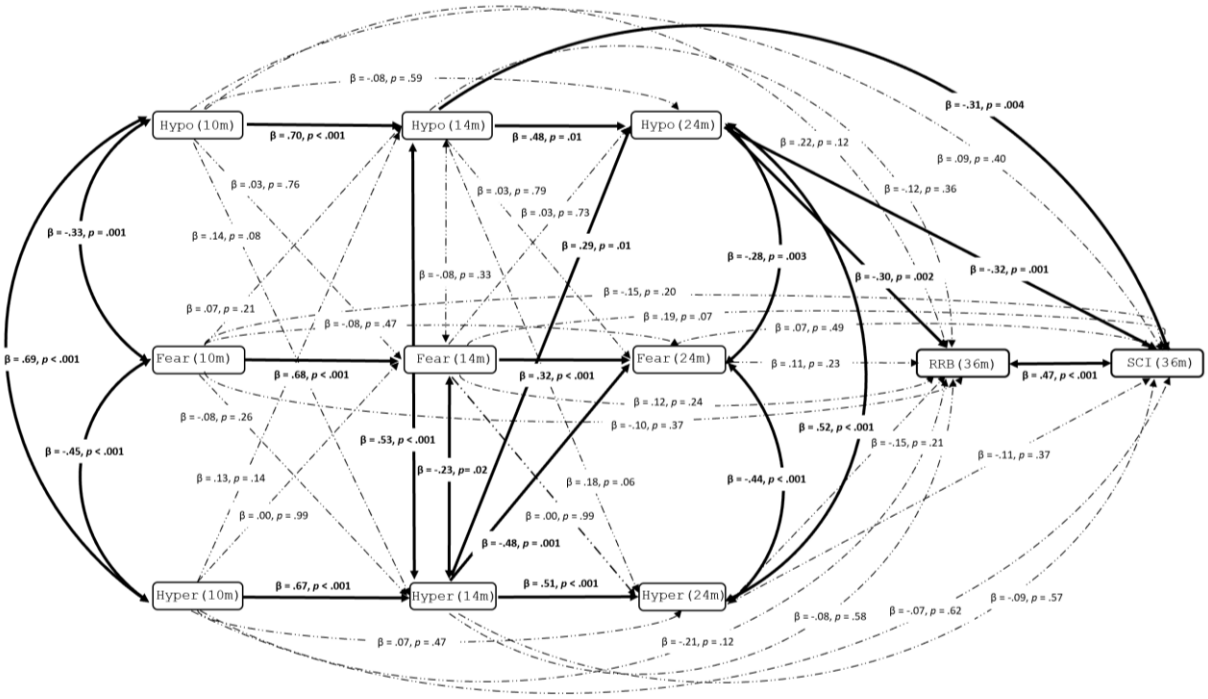

Figure 4. 2 Cross-lagged associations between Fear, Hyperresponsivity, Hyporesponsivity, Restricted and Repetitive Behaviours (RRB) and Social Communication Interactions (SCI) at 10 – 36 months of age. Bold indicates significant association. Raw scoring was used where lower score indicated a greater severity for ITSP.

Table 4.3. Model 2 with standardized coefficients.

		b	*p*	[95% Confidence Interval]		β
Fear 14m	Fear 10m	0.67	0.000	0.51	0.83	0.68
	Hyporeactivity 10m	0.01	0.756	-0.03	0.04	0.03
	Hyperreactivity 10m	0.00	0.987	-0.02	0.02	0.00
Fear 24m	Fear 14m	0.25	0.000	0.11	0.38	0.32
	Fear 10m	-0.06	0.467	-0.23	0.11	-0.08
	Hyporeactivity 14m	0.00	0.791	-0.03	0.04	0.03
	Hyperreactivity 14m	-0.04	0.002	-0.06	-0.01	-0.48
Hyporeactivity 14m	Fear 10m	0.33	0.210	-0.18	0.84	0.07
	Hyporeactivity 10m	0.70	0.000	0.56	0.83	0.70
	Hyperreactivity 10m	0.06	0.151	-0.02	0.15	0.13
Hyperreactivity 14m	Fear 10m	-0.74	0.262	-2.02	0.55	-0.08
	Hyporeactivity 10m	0.28	0.079	-0.03	0.59	0.14
	Hyperreactivity 10m	0.66	0.000	0.52	0.81	0.67
Hyporeactivity 24m	Fear 14m	0.14	0.732	-0.65	0.92	0.03
	Hyporeactivity 10m	-0.09	0.551	-0.39	0.21	-0.08
	Hyporeactivity 14	0.52	0.017	0.10	0.95	0.48
	Hyperreactivity 14m	0.16	0.006	0.04	0.27	0.29
Hyperreactivity 24m	Fear 14m	0.01	0.992	-1.79	1.81	0.00
	Hyperreactivity 10m	0.08	0.413	-0.11	0.26	0.07
	Hyporeactivity 14m	0.41	0.061	-0.02	0.84	0.18
	Hyperreactivity 14m	0.59	0.000	0.29	0.88	0.51
RRB 36m	Fear 14m	0.09	0.258	-0.07	0.26	0.12
	Fear 10m	-0.08	0.377	-0.25	0.09	-0.10
	Hyporeactivity 10m	0.03	0.119	-0.01	0.08	0.22
	Hyperreactivity 10m	-0.02	0.113	-0.04	0.00	-0.21
	Fear 24m	0.11	0.233	-0.07	0.30	0.11
	Hyporeactivity 14m	-0.02	0.340	-0.06	0.02	-0.12
	Hyperreactivity 14m	-0.01	0.576	-0.03	0.02	-0.08
	Hyporeactivity 24m	-0.04	0.001	-0.07	-0.02	-0.30
	Hyperreactivity 24m	-0.01	0.206	-0.03	0.01	-0.15
SCI 36m	Fear 14m	0.10	0.070	-0.01	0.20	0.19
	Fear 10m	-0.07	0.197	-0.18	0.04	-0.15
	Hyporeactivity 10m	0.01	0.400	-0.01	0.03	0.09
	Hyperreactivity 10m	0.00	0.619	-0.02	0.01	-0.07
	Fear 24m	0.05	0.488	-0.09	0.19	0.07
	Hyporeactivity 14m	-0.03	0.003	-0.05	-0.01	-0.31
	Hyperreactivity 14m	0.00	0.570	-0.02	0.01	-0.09
	Hyporeactivity 24m	-0.03	0.000	-0.05	-0.01	-0.32
	Hyperreactivity 24m	0.00	0.369	-0.02	0.01	-0.11

Covariance Fear 14m - Hyporeactivity 14m	-0.29	0.345	-0.89	0.31	-0.08
Covariance Fear 14m - Hyperreactivity 14m	-1.60	0.035	-3.09	-0.11	-0.23
Covariance Fear 10m - Hyporeactivity 10m	-2.63	0.002	-4.29	-0.96	-0.33
Covariance Fear 10m - Hyperreactivity 10m	-7.36	0.000	-11.07	-3.64	-0.45
Covariance Hyporeactivity 10m - Hyperreactivity 10m	55.27	0.000	37.71	72.83	0.69
Covariance Fear 24m - Hyporeactivity 24m	-1.07	0.004	-1.79	-0.34	-0.28
Covariance Fear 24m - Hyperreactivity 24m	-3.49	0.000	-5.16	-1.83	-0.44
Covariance Hyporeactivity 14m - Hyperreactivity 14m	15.20	0.000	8.04	22.36	0.53
Covariance Hyporeactivity 24m - Hyperreactivity 24m	25.97	0.000	14.37	37.57	0.52
Covariance RRB 36m - SCI 36m	0.12	0.000	0.06	0.19	0.47

SCI = social communication interaction; RRB = restrictive and repetitive behaviours

Model 2: Analyses testing specificity of hyperreactivity effects

When we included hyporeactivity measured at 10, 14 and 24 months as an additional variable in the model (see Figure 4.2), the model fit was good ($\chi^2 = 7.33$, $p = .292$, CFI = .99, TLI = .98). The Wald test of combined coefficients was significant ($\chi^2 = 536.28$, $p < .001$). Cross-lagged paths indicated higher hyperreactivity at 14 months remained associated with higher fear at 24 months (B = -0.04, $\beta = -0.48$, $p = .002$), and higher hyperreactivity at 14 months was also associated with higher hyporeactivity at 24 months (B = 0.16, $\beta = 0.29$, $p = .01$). Higher hyporeactivity at 24 months was significantly associated with higher RRB (B = -0.04, $\beta = -0.30$, $p = .001$) and SCI (B = -0.03, $\beta = -0.32$, $p < .001$) at 36 months, and the paths from

hyperreactivity at 24 months to RRB and SCI at 36 months both became non-significant (B = -0.01, β = -0.15, p = .21; B = 0.00, β = -0.11, p = .37 respectively). Higher hyporeactivity at 14 months was also associated with increased SCI (B = -0.03, β = -0.31, p < .01). The concurrent positive association between RRB and SCI at 36 months remained (B = 0.12, β = .47, p < .001). All other pathways were non-significant (see Figure 4.2 and Table 4.3). As an additional check, we excluded the two items from the low registration quadrant (our metric of hyporeactivity) that had clear overlap with autistic traits/symptomatology (Item 13 "It takes a long time for my child to respond to his/her name when it is called", Item 16 "My child avoids eye contact with me") (9 items total using this revised scoring) to prevent contamination when seeking to look at paths from hyporeactivity to later autistic traits. Results from the model using this amended scoring were largely unchanged (see Appendix Figure B4.4).

Sensitivity Analyses Accounting for ADHD Family History and Traits

First, we ran a sensitivity analysis excluding EL-ADHD infants to check that main findings were not only driven by the sub-group of infants with a family likelihood of ADHD (see Models, Appendix Figure B4.5 and B4.6, akin to Model 1 and Model 2). Model Appendix B4.5 largely replicates the paths found in Model 1, in that higher 14-month hyperreactivity is associated with higher 24-month fear (β = -.49, p < .001), and 24-month hyperreactivity remains associated with SCI (β = -.39, p = .001) and RRB with similar coefficient of effect, although at a trend level of significance (β = -.29, p = .06). Model S6, where we include hyporeactivity, again mostly replicates Model 2, in that higher 14-month hyperreactivity is associated with higher 24 months fear (β = -.50, p = .01) and higher 24 months hyporeactivity respectively (β = .31, p = .02) , and higher 24-month hyporeactivity is associated with greater 36-month SCI and RRB (β = -.32, p <

.001, β = -.24, p = .02 respectively). One new path became statistically significant; higher fear at 14 months was associated with higher SCI at 24 months (β = .28, p = .01), although the standardized coefficient of effect was similar to models run on the full sample (β = .19, p = .07).

Next, in the full sample, we then ran a second sensitivity analysis where we included ADHD traits (CBCL-ADHD subscale) as correlated outcome at 36 months (see Models, Appendix Figure B4.7 and B4.8, again akin to Model 1 and Model 2). When ADHD traits were included as well as autism traits at 36 months, the pattern of associations between 24-month fear, hyporeactivity and hyperreactivity and later SCI and RRB remained unchanged, but additional associations were identified between hyperreactivity at 10 months and hyporreactivity at 10 and 24 months with ADHD traits at 36 months. Thus, we found no clear evidence that unmeasured ADHD was driving observed associations with autistic traits, but it is possible that unmeasured ADHD could be masking some significant pathways that contribute to observed associations.

Finally, we re-ran Model 1 and 2 using a subset of IBQ/ECBQ items from the Fear and Shyness subscales that were more closely matched to check that differences in construct measurement between the two versions of the questionnaire was not driving the pattern of results (see Appendix Table B4.3 for item matching, Appendix Figure B4.9 and Figure B4.10 for results). Results were unchanged, with a marginal increase in within-domain continuity for Fear/Shyness.

4.5 Discussion

The current paper examined the developmental correlates of alterations in sensory reactivity on infant fearfulness and autistic traits in the first three years of life. Results showed a pathway from 14-month hyperreactivity to 24-month infant fearfulness, in line with previous research, which found sensory over-responsivity was positively associated with anxiety one year later in a cohort

of toddlers with a similar age to our later time points (mean age of 28 months upon study entry) (Green et al., 2012). The anxiety measure used by Green and colleagues (General Anxiety subscale of the ITSEA) includes items that tap fearfulness, similar to the current work, but also items that index more compulsive and ritualistic type behaviours. We also found that greater hyperreactivity at 14 months was associated with higher levels of SCI at 36 months, and greater hyperreactivity at 24 months was longitudinally associated with both more RRB and SCI traits at 36 months. When hyporeactivity was included in the model to assess specificity of effects, pathways between hyperreactivity and fear remained, but paths from hyperreactivity to SCI and RRB became non-significant, suggesting unmeasured hyporeactivity may have been driving observed effects. Thus, to comprehend the developmental pathways to autism and specificity of effects, we need to take into account different types of sensory reactivities.

The relationship between hyperreactivity, infant fearfulness and autistic traits

Our cross-lag models of infant fearfulness and hyperreactivity measured at 10, 14 and 24 months found associations between greater 14-month hyperreactivity and later fearfulness. This is in contrast to our previous report (Narvekar et al., 2022), where we found a path in the reverse direction between 14-month fearfulness and 24-month perceptual sensitivity (conceptually similar to hyperreactivity). Our additional supplementary analyses, using the same measures as in our previous work (i.e., moving from the ITSP hyperreactivity to the IBQ-R perceptual sensitivity subscale), did not replicate the fearfulness-sensitivity path in this new sample. This lack of replication, and the fact that other studies with overlapping age ranges (Green et al., 2012), including current results, report the opposite direction of effect, indicates that further work is needed to probe generalisability; factors that could have impacted our ability to replicate

previously reported effects include moving from pure EL-autism cohorts to other groups enriched for other atypical neurodevelopmental outcomes, in addition to unobserved differences in sample ascertainment and possible lack of stability in perceptual sensitivity measure with age. Finally, we note when we re-ran models with a novel fear/shyness subscale based on the subset of items that were more clearly matched between the IBQ and ECBQ, we found a decrease in the standardized coefficient for the association between 14 months hyperreactivity and 24 months fear/shyness (e.g., β = -.28 in item-matched Model S9 vs. β = -.46 in original Model 1). This change in coefficient suggests that the large effect may in part reflect incomplete adjustment of early fear/shyness levels due to a change in measure to match developmental level (although the effect remains relatively large in the item-matched models).

Although within diagnostic manuals sensory reactivities are included in the RRB domain, we found pathways from hyperreactivity to RRB and SCI. Some report evidence of specific associations between hyperreactivity and RRB (Black et al., 2017; Boyd et al., 2010; Chen, Sideris, Watson, Crais, & Baranek, 2022; Schulz & Stevenson, 2019), others report hyperreactivity also predicts social difficulties (Feldman et al., 2021; Wolff et al., 2019), including our own previous work on perceptual sensitivity (Narvekar et al., 2022). The degree to which hyperreactivity truly only impacts RRB remains unclear; current diagnostic frameworks may have inadvertently encouraged researchers to primarily consider the mechanisms by which atypical sensory reactivity can lead to RRB, rather than autistic traits more broadly. It is worth noting here the wide range of phenomena that fall under the umbrella term of atypical sensory differences (e.g., sensitivity, reactivity, and/or responsivity) (He et al., 2022). More precise definition of levels of meaning and measurement will support generation of empirical mechanistic hypotheses linking sensory reactivity to different domains of autism characteristics.

One interpretation of the observed path from hyperreactivity to RRB is that RRB represent a coping mechanism to regulate states of high arousal associated with fear and anxiety (Vlaeminck et al., 2020). If this was the case, we might also expect to see associations between infant fearfulness and RRB, such that fearfulness acts as a mediator between hyperreactivity and RRB (as in Wigham et al., 2015). However, in contrast to previous studies (Ersoy et al., 2020; Narvekar et al., 2022; Shephard et al., 2019), we did not find significant paths from infant fearfulness to RRB. One explanation is that these latter studies (Ersoy et al., 2020; Narvekar et al., 2022; Shephard et al., 2019) did not include a specific measure of hyperreactivity, and observed relations between fearfulness and RRB could thus reflect unmeasured hyperreactivity. In support of this hypothesis, our supplementary analyses (Figure S3) showed when we removed hyperreactivity from the model, we recover the association from infant fearfulness to later autism traits. The lack of path from fearfulness to RRB when we include hyperreactivity in the model suggests that at least at this developmental stage, RRB may not function as coping mechanism for high levels of fearfulness. It may be that over time, being more reactive leads to anxiety about encountering situations with aversive sensory stimuli in the future, but also use of RRB to manage in-the-moment arousal. Measures that can separate arousal from anticipatory anxiety and avoidance behaviours, and moment-to-moment dynamic data including direct capture of arousal, are required to test this working hypothesis. These analyses highlight the importance of carefully constructed multivariate analyses that can capture the different aspects of complex developmental systems present in the early infant period.

The specificity of hyperreactivity effects

We next examined whether the effects of hyperreactivity on infant fearfulness and autistic traits were specific to this type of sensory atypicality, or whether they were shared with hyporeactivity. As it is known that different types of atypical sensory reactivities are correlated, even within a given individual (Elwin, Ek, Kjellin, & Schröder, 2013; Niedźwiecka et al., 2019; Tillmann et al., 2020), it is important to include multiple types of sensory atypicalities in analytic models. When we also included hyporeactivity in our cross-lag models, we found strong bivariate correlations between hyporeactivity and hyperreactivity, in line with the idea that individuals who experience hyporeactivity are also more likely to experience hyperreactivity. However, the effect of hyperreactivity on fearfulness appeared relatively specific; no paths were seen from hyporeactivity to fearfulness, and hyperreactivity effects remained even in multivariate models. Thus, even though hyporeactivity and hyperreactivity share high variance, there may be specific variation in hyperreactivity that raises the likelihood of fearfulness. Since infant fearfulness has been proposed as an early precursor of child anxiety (Gartstein et al., 2010; Shephard et al., 2019) , this is in keeping with recent conceptualisations of 'sensory over responsivity' as a transdiagnostic risk factor for anxiety that is present even in typically developing populations (Carpenter et al., 2019; Schwarzlose et al., 2022). The current results demonstrate this may be true even in the first year of life, and much like the developmental cascade framework (Bradshaw et al., 2022), it is important to better understand the mechanisms by which heightened sensory reactivity increases anxiety, in order to develop targeted (and thus effective) support.

When considering the associations between hyperreactivity and later autism traits, when hyporeactivity was included in the model it was found to be predictive of later RRB and SCI, and

associations with hyperreactivity became non-significant. This pattern is different to results from a recent general population study which found even when hyperreactivity and hyporeactivity were both included as predictors of autism traits, hyperreactivity was still predictive of RRB (Chen et al., 2022). There are multiple possible interpretations of these findings. One possible explanation may be that hyporeactivity is on the pathway to autism outcomes, but hyperreactivity is not, and the latter is more relevant for understanding co-occurring features such as anxiety. Alternatively, it could be that the hyporeactivity scale used in the current study is capturing features of early autism, and that is why it 'trumps' the effects of hyperreactivity. Indeed, inspection of the ITSP hyporeactivity subscale suggests some items are very similar to the types of early social communication difficulties that are characteristic of autism. However, when we run the same model with a revised version of the ITSP hyporeactivity subscale, where we remove two items that most clearly overlap with the early autism phenotype ('it takes a long time for my child to respond to his/her name when it is called', 'my child avoids eye contact with me') from the scale to minimize construct overlap. (shown in Figure S4), we found most associations remained the same, including those between hyporeactivity and later autistic traits. This question of measurement relates to wider debates about what is a marker or manifestation of autism early in the developmental pathway, and what are factors that are causally involved in the aetiology of autism and associated characteristics. Unpicking these two possibilities is challenging; analytic models that can test directionality of within-person associations between aspects of sensory reactivity and autistic traits (Hamaker, Kuiper, & Grasman, 2015; Mund & Nestler, 2019), or delineate stability and change in statistically-defined classes of symptoms (McCulloch, Lin, Slate, & Turnbull, 2002), may help. Precise measurement of proposed markers/likelihood factors as compared to clinical outcomes is critical.

Finally, we note that additional supplementary analyses found that when ADHD traits were included as well as autism traits at 36 months, the pattern of associations between 24-month fear, hyporeactivity and hyperreactivity and later SCI and RRB remained unchanged. Thus, we found no clear evidence that co-occurring ADHD traits were driving observed associations with autistic traits, despite the SRS and other autism measures being confounded with other neurodevelopmental traits, including ADHD (as noted by Grzadzinski et al., 2011; Havdahl et al., 2016). One possibility is given the earlier age of autism onset than ADHD, the SRS may be less likely to be confounded at this young age. On the other hand, it appears that certain sensory reactivity measures that predicted autistic traits also predicted ADHD traits i.e., hyperreactivity at 24 months. Interestingly, the fact that when we include hyporeactivity in models with ADHD traits, this also 'overrides' previously observed associations from hyperreactivity, suggests the similar override effect to autistic traits is likely not solely due to our measure of hyporeactivity being contaminated with autism traits. Overall, our additional sensitivity analyses suggest the observed associations with autistic traits are unlikely to be purely due to the presence of unmeasured ADHD, and some associations were shared between autistic and ADHD traits. These findings highlight that sensory differences may function in a transdiagnostic manner and as such may not be specific to autism traits (Scheerer et al., 2022), although we also found some evidence of a limited number of specific associations (e.g., 10-month hyperreactivity and hyporeactivity to ADHD only).

Lastly, it is important to consider the implications of these findings for the broader infant population. One interpretation consistent with our findings is that alterations in early sensory reactivity may increase the likelihood of showing fearfulness in infancy, and presage later social interactions and repetitive behaviours, particularly in individuals with a family history of autism

or ADHD. Moreover, sensory differences are not exclusive to autism and ADHD; they may be a common feature of the neurodevelopmental pathways to a number of neurodevelopmental conditions (Baranek et. al., 2013; Posar & Visconti, 2018).

Strengths and Limitations

This study has several strengths. Although the field of autism research, and psychological research more broadly, often highlights the importance of replication (Asendorpf et al., 2016; Nosek et al., 2022), published examples are relatively lacking. We show here the value in replication and transparency, in terms of gauging the generalisability of past results, and the importance of variation in both measurement and sample design. We also collected detailed and repeated measurement of different aspects of sensory reactivity within a prospective longitudinal design. Most studies examine different aspects of sensory reactivity in isolation; our approach allows us to move towards a more precise mechanistic understanding of how differences in reactivity of incoming sensory input contribute to different types of autistic behaviours and mental health difficulties. However, we also acknowledge important limitations; all data was based on parent report, resulting in the possibility of shared method variance contributing to results. Additionally, even though we removed the two ITSP hyporeactivity items with the clearest overlap with the early autism phenotype, other items may overlap with early autistic social communication features. How we measure sensory differences independently from other autistic characteristics is a challenge for the field more broadly, and may require development of new measures in the future. Observational and experimental measures may be of use here (Baranek et al., 2018; Tavassoli et al., 2019). Additionally, we recognize that the lack of uniform measures across various time periods, even if it is meant to ensure that the questions are suitable

for a specific age group, may be considered a limitation. Agreement in the field as to appropriate instruments that capture relevant constructs and can be used in a comparable manner across a broad developmental range is required to support use of more advanced statistical models (e.g., random intercept cross lag panel models) and thus strengthen inference. Regardless of the change in questionnaire, we found within-domain continuity in all our constructs, indicating that the change in measurement scales did not have a large influence on our findings.

4.6 Conclusions

The results from this study have important methodological and clinical implications. First, hyperreactivity in early infancy may be one of clearest predictors of fearfulness in infancy, and thus may offer a potential target for future interventions. Second, the direction of relation between sensory atypicalities and early fearfulness appeared to vary across cohorts, highlighting the importance of replication studies and the need to carefully consider sample composition in infant-sibling studies. Third, it is crucial to measure independent but correlated aspects of sensory atypicalities, and include them in the same analytic model, to understand shared versus distinct mechanisms. An important goal for future studies is to unpick how these alterations in sensory reactivity translate to challenges in child development, with a focus on later anxiety.

Key points

- Most research on sensory reactivity does not account for the fact that different types of sensory atypicality often co-occur.
- We find a specific association between sensory hyperreactivity in early infancy and later fearfulness, even when accounting for the co-occurrence of hyperreactivity and hyporeactivity.

- Although there was some evidence hyperreactivity was associated with later autism traits, this appears to be driven by the co-occurrence with hyporeactivity.

- Results suggest alterations in different domains of sensory reactivity may have differential developmental consequences.

Chapter 5: Developmental trajectories of sensory differences from infancy to toddlerhood in elevated likelihood groups of autism and ADHD

5.1 Introduction

Sensory challenges was included as part of the diagnostic criteria for autism in DSM-5 and includes hyper- or hyporesponsivity to sensory input or unusual interests in sensory aspects of the environment within the restrictive and repetitive behaviour (RRB) domain (APA, 2013). Some studies report sensory differences being affiliated with attention deficit hyperactivity disorder (ADHD) as well (Bijlenga, Tjon-Ka-Jie, Schuijers, & Kooij, 2017; Ghanizadeh, 2011; Panagiotidi, Overton, & Stafford, 2018). Overall, there is consensus that sensory responsivity in autism and ADHD groups are more elevated as compared to typically developing (TD) groups (Baker, Lane, Angley, & Young, 2008; Kamath et al., 2020; A. Lane, Young, Baker, & Angley, 2010; Little, Dean, Tomchek, & Dunn, 2018; Shimizu, Bueno, & Miranda, 2014).

Studying sensory differences has been complex due to its multiple domains. Based on Dunn (1997) model of sensory processing, there are four quadrants, and as per Dunn, each quadrant is related to a response based on the individual's neurological threshold: The low registration – slow response to sensation, such as not noticing or reacting to sounds that other people notice. The sensation seeking – seeks out stimulating sensory environments, such as shiny or bright objects. The sensory sensitivity – distressed or discomforted by sensory stimuli for example, noisy environment or change in room temperatures. The sensation avoiding – distressed by exposure to certain stimuli and attempts to avoid it, such as avoiding certain foods or other children. Sensory sensitivity and sensation avoiding represent low threshold (hyperresponsivity)

i.e., they respond to sensory stimuli faster and more intensely, whereas low registration represents high threshold (hyporesponsivity) to sensory stimuli. These quadrants/domains of sensory responsivity are further divided into auditory, visual, audition, tactile, vestibular, and oral subscales. The most common framework for categorising of sensory patterns is hyperresponsivity, hyporesponsivity and sensation seeking (Baranek, David, Poe, Stone, & Watson, 2006).

Although autism and ADHD are both neurodevelopmental conditions that typically emerge early in life, they have distinct as well as some shared features. Autism is characterized by social communication difficulties, restricted and repetitive behaviours and sensory differences (APA, 2013), whereas the core features of ADHD include attentional control difficulties, hyperactivity and impulsivity (APA, 2013). Autism has a childhood prevalence of ~1.5% (Maenner et al., 2020) and is typically diagnosed around six years of age (Brett et al., 2016), and ADHD affects up to ~2 to 7% of the children aged 3 to 12 years worldwide (Sayal et al., 2018). Even though autism and ADHD have distinct trait profiles and share few overlapping diagnostic criteria, both conditions have some traits that overlap, such as difficulties with social interactions, attention and sensory differences (Little et al., 2018) and share aetiological underpinnings evidenced by twin studies (Nijmeijer et al., 2008; Ronald et al., 2014; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008). Furthermore, they have a high co-occurrence rate ranging from 40 to 80% (Antshel & Russo, 2019; Joshi et al., 2017). However, research has shown inconsistent patterns of associations between sensory responsivity domains (hyperresponsivity, hyporesponsivity, and sensation seeking) and autism and ADHD. The current understanding of these relations has been mainly based on observations with older children with a diagnosis, and it may not fully capture the types of sensory features, nor their developmental pathways and interactions, in infancy.

Patterns of associations between sensory domains in those diagnosed with autism or ADHD

There is substantial body of evidence in literature that autistic people experience sensory differences. In particular, they seem to show more hyperresponsivity and hyporesponsivity compared to non-autistic peers (Niedźwiecka et al., 2019; Robertson & Simmons, 2013). When examining these sensory responsivity differences as individual domains, higher rates of sensory over-responsivity (hyperresponsivity) appear to persist from early childhood throughout the lifespan (Ben-Sasson et al., 2009). Furthermore, autistic children who exhibit hyperresponsivity often also demonstrate elevated levels of anxiety (Green & Ben-Sasson, 2010; Uljarevic, Lane, Kelly, & Leekam, 2016). The presence of hyperresponsivity in autistic children can lead to functioning difficulties in the environment such as, gross motor movements of jumping and bouncing, unusual interests in one type of play (Kirby, Boyd, Williams, Faldowski, & Baranek, 2017). It has been found that autistic individuals show patterns of both hyperresponsivity and hyporesponsivity. This is highlighted in a study that compares autistic individuals with those who have a developmental delay, where autistic individuals are more likely to show patterns of high hyporesponsivity concurrent with high hyperresponsivity (Baranek et al., 2006). Other research also emphasised that higher parent-reported scores of early sensory hyperresponsivity predicted lower overall adaptive and daily living skills for autistic children in later childhood and higher scores of hyporesponsivity associated with lower socialization scores (Williams et al., 2018). A study focusing on children aged 11 to 105 months noted that a reduced or absence of response to sensory stimuli (hyporesponsivity) was linked to lower joint attention and language challenges in autistic children. It was also found that in contrast to hyperresponsivity, the severity of hyporesponsivity seemed to decrease as a function of mental age in young autistic children (Baranek et al., 2013).

Alterations of sensory responsivity in all domains are present for autistic individuals. Especially hyperresponsivity and hyporesponsivity has consistently been reported for children with or at elevated likelihood of autism, but the evidence of the presence of sensory seeking is comparatively weak. Decreased sensory seeking is often reported in infants with later autism diagnosis (Little et al., 2018). Additionally, a decrease in sensory seeking behaviours in autistic children was noted between 3 and 17 years of age (Lidstone et al., 2014).

As compared to autism, research into sensory responsivity and ADHD is limited. A study conducted with a non-clinical adult population showed that those who reported higher levels of ADHD traits also reported more sensory responses, mainly hyperresponsivity and hyporesponsivity (Panagiotidi et al., 2018). This was also supported by other studies on older samples which showed that adults with ADHD scored higher than a group of TD adults on questionnaire measures of hyporesponsivity and hyperresponsivity (Bijlenga et al., 2017; Kamath et al., 2020), but they also found that adults with ADHD scored lower on sensation seeking behaviours compared to TD adults (Bijlenga et al., 2017). When the Dunn (2002) model was applied to a study by Lufi and Tzischinsky (2014), they found that adolescents with ADHD scored higher in activity, hearing, and low registration (hyporesponsivity) than those without ADHD. The systematic review by Ghanizadeh (2011) among children with ADHD, shows that most of these studies reported increased sensory responsivity for all sensory modalities. Further research in support by Shimizu et al. (2014), reported that children with ADHD presented with sensory differences on all sensory domains (Low Registration, Sensation Seeking, Sensory Sensitivity and Sensation Avoiding). These findings demonstrate that sensory responsivity could be included as a feature of ADHD as well. Some studies lean towards the association of sensation seeking and hyporesponsivity and ADHD. Children with ADHD showed more sensory

challenges with low registration and sensation seeking than the control group. Sensory seeking and hyporesponsivity are associated with inattention, hyperactivity-impulsivity, and ADHD traits (Delgado-Lobete, Pertega-Diaz, Santos-Del-Riego, & Montes-Montes, 2020). It was also reported that children with ADHD are more likely to seek out sensory inputs and notice less sensory input (hyporesponsivity) than TD children (Little et al., 2018).

Exploring associations between sensory domains in autism and ADHD in the same sample

While many studies have examined sensory responsivity separately in the context of autism and ADHD, only a limited number of studies have looked at sensory differences in both autistic and ADHD participants within the same study. At the same time, there is consensus on significant group differences between TD control groups and autism and or ADHD groups (Bijlenga et al., 2017; Clince, Connolly, & Nolan, 2016). Findings on group differences between autism and ADHD are inconsistent. Some studies indicate a group difference between autism and ADHD with regard to sensory responsivity (with some exceptions on different domains), (Keating, Bramham, & Downes, 2021; Mattard-Labrecque, Amor, & Couture, 2013; Schulz et al., 2023), on the other hand, other studies report no difference between the two groups (Cheung & Siu, 2009; Little et al., 2018; Sanz-Cervera, Pastor-Cerezuela, Gonzalez-Sala, Tarraga-Minguez, & Fernandez-Andres, 2017; Scheerer et al., 2022). Whereas Schulz et al. (2023) noted that autistic children and those with ADHD differed on hyporesponsivity and hyperresponsivity but not on sensory seeking and that the autism group displayed more severe and frequent sensory differences than ADHD group. Also, hyporesponsivity and hyperresponsivity is higher in autistic individuals and those with ADHD as compared to ADHD alone (Dellapiazza et al., 2021; Mattard-Labrecque et al., 2013). With regards to sensation seeking, both autistic children and

those with ADHD scored more on sensory responsivity, motor and adaptive behaviours than ADHD only group (Mattard-Labrecque et al., 2013), but a few studies also noted that the ADHD group scored higher than the autism group (Clince et al., 2016; Dellapiazza et al., 2021). In contract, Schulz et al. (2023) reported no difference between the autism group and ADHD. These differences in patterns of associations between domains and groups noted in the studies above could be attributed to the differences in sample size, sample age, methodologies, terminologies, and questionnaires used. Some studies often have a narrow focus, concentrating on specific domains while disregarding the broader sensory responsivity profiles in their analysis. Consequently, these variations lead to multiple unanswered questions, thereby necessitating further research and investigation.

Longitudinal studies on sensory responsivity

Most studies looking at sensory responsivity are cross sectional, focusing on older children diagnosed with autism and/or ADHD. Hence, it is crucial to conduct prospective longitudinal studies on infant siblings to understand the early onset of these conditions and possible shared causal mechanisms. While sensory differences in autistic individuals are evident during childhood (Feldman et al., 2020; Williams et al., 2018), when these differences emerge is less clear. One infant sibling study found that at 12 months, children later diagnosed with autism showed elevated hyperresponsivity on a parent report measure compared with children who did not go on to develop autism (Wolff et al., 2019). Since most sensory measures are parent reports, at a practical level, identifying hyperresponsivity is easier to note than hyporesponsivity. The overt characteristics of hyperresponsivity capture observers' or parents' attention, whereas the absence of something or the subtle cue of hyporesponsivity is easier to miss or ignore (Jones et

al., 2014). In another study, parents reported sensory differences among infant siblings, some as young as six months of age, in children who later met the criteria for an autism diagnosis (Sacrey et al., 2015). Similarly, heightened parent-reported sensory responsivity at 12 months predicted later autism diagnosis at three years in a non-clinical sample (Turner-Brown, Baranek, Reznick, Watson, & Crais, 2013). Several studies have indicated that the level of sensory responsivity decreases over time. For instance, Cheung and Siu (2009), in their longitudinal study involving children from 2.7 months to 12 years, noted a decrease in responsivity to sensory stimuli amongst autistic children, whereas an increase in response, mainly in the auditory domain, among those with ADHD, as they aged. Similarly, Little et al. (2018) observed that, in 3 to 14 year olds, regardless of their diagnosis of autism or ADHD, a younger sample scored higher on sensation seeking versus an older sample. In summary, there is growing research that supports the relationship between early sensory responsivity and later autism diagnosis (Grzadzinski et al., 2020; Sacrey et al., 2015; Wolff et al., 2019). With regard to ADHD, much less research has been conducted in the early infant period. Even though there is overall evidence for early sensory differences in infants who receive an ADHD diagnosis the exact type of differences is unclear (Shephard et al., 2022). In a study of children between 6 months to 72 months, Keating et al. (2021) reported that children with a family history of ADHD (referred as Elevated Likelihood; EL) scored higher than TD children, even on domains of hyperresponsivity and hyporesponsivity. Although they did find group differences for hyperresponsivity and hyporesponsivity, no group difference was found for sensation seeking. It is evident that the amount of information available regarding the sensory responsivity of siblings with EL ADHD or EL autism is limited. Such studies are imperative in understanding early markers and developmental changes over time.

Current study

In our previous study (Narvekar et al., 2022), perceptual sensitivity (hyperresponsivity) was associated with autism traits at 36 months. However, in our partial replication, hyperresponsivity lost its association with autism traits at 36 months when hyporesponsivity was included in the model. Given that hyperresponsivity and hyporesponsivity are strongly correlated, even within the same individual, it is important to include different domains of sensory responsivity in the same analytic model to understand shared versus distinct mechanisms. The relations between sensory differences and autism traits appeared to vary across cohorts and domains.

Since we have already looked at fearfulness (infant anxiety) in Chapter 4 with very similar measures, we did not want to ask the same question twice, as it isn't good from a multiple testing viewpoint. Considering less is known about how sensory domains relate with each other and later autism/ ADHD traits, the focus of Chapter 5 was on core sensory domains and developmental trajectories and their association with 36 month outcomes before we explore its relation to co-occurring conditions such as anxiety. Secondly, the decision to not focus on fear in Chapter 5 was made to minimise the limitation of changing questionnaires from 14 months to 24 months timepoints. To maintain consistency, ITSP was used as a measure of sensory responsivity to ensure the same measure at all timepoints. Hence, Chapter 5 focused on the sensory domains in infancy and toddlerhood in relation to autism and ADHD traits as outcome, with plans to explore anxiety in future studies, and with possibility of including later timepoints such as mid-childhood.

Broadening the focus to neurodevelopmental traits as the primary outcome of interest in Chapter 5, it appeared important to include sensory seeking for examination. Even though, sensory

seeking is pertinent to sensory responsivities, it is a distinct construct and requires further examination. Given everything we have learnt from previous studies in this thesis, this study aims to examine the shared versus distinct associations of sensory domains (hyperresponsivity, hyporesponsivity, sensation-seeking) in infants with a family history of autism and/or ADHD (EL autism / EL ADHD) and autism and ADHD traits at 36 months. Additionally, the objective is to investigate the difference in the association between the developmental trajectories (intercept and slope) of sensory responsivity domains and later autism and ADHD traits at 36 months to understand when sensory differences emerge.

Previously, we used the cross-lagged model to examine whether sensory responsivity (hyperresponsivity and hyporesponsivity) between 10 to 24 months is associated with autism traits at 36 months. We noted the strengthening of associations over time, where we found associations between later time points of 24 months sensory responsivity and autism traits at 36 months; these associations persisted even when ADHD traits at 36 months were also included as a correlated outcome (e.g., suggesting associations with autistic traits were not driven by their overlap with ADHD traits). In the current study, we plan to further investigate these relations with Latent Growth Curve (LGC) modelling across assessments at 10, 14 and 24 months to estimate longitudinal growth trajectories over infancy (see Chapter 2). This analysis helps estimate change over time and account for individual-level changes to predict the outcome and allows us to examine the predictors and consequences of individual differences in development. We also include the subscale of sensation seeking, which might be related to ADHD and study whether we see any shared versus distinct patterns between later autism and ADHD traits at 36 months.

We address the research questions:

(i) Are differences in infant sensory behaviours associated specifically with later autism or ADHD traits, or are they broader neurodevelopmental factors that serve as shared early indicators of both?

(ii) Do the domains of sensory responsivities (hyperresponsivity, hyporesponsivity and sensation seeking) associate differently with autism and ADHD traits at 36 months?

(iii) Do early sensory differences predict later autism/ADHD traits or do emerging sensory responsivities differences predict later autism/ADHD traits?

(iv) Do children from different family history groups show distinct sensory pattern trajectories?

We hypothesize that sensation seeking will be associated with ADHD traits and not autism traits and that hyperresponsivity will be associated with autism traits and not ADHD traits. We further anticipate that hyporesponsivity will be associated with autism and ADHD traits.

Given the complexity of sensory responsivity in autism and ADHD and the limited research done in this area, particularly none utilizing this analytical model, we refrain from predicting the results of the intercept-slope findings in the three sensory domains of hyperresponsivity, hyporesponsivity, and sensation seeking, and two phenotypical outcomes of autism and ADHD traits at 36 months. Instead, we use the LGC model to examine if these associations differential relates to early marker, as reflected by the intercept (i.e., they are more likely to be a precursor to later autism/ ADHD traits), or growth in manifestations over time, as indicated by the slope (i.e., they are more likely to be an early emergence of autism/ADHD traits).

5.2 Methods

Participants

Participants were recruited for a longitudinal study as part of the Studying Autism and ADHD Risks Study (STAARS), based on their family history of Autism or ADHD. Community clinical diagnosis/probable research diagnosis were used to define the presence of autism and ADHD, respectively. Infants with a first degree relative (older sibling) with a diagnosis of autism, were considered at elevated likelihood of autism. Elevated likelihood of ADHD group has either older sibling or a parent with a diagnosis of ADHD. Elevated likelihood for both conditions (i.e., autism and ADHD) were also included. Lastly, infants with no familial likelihood of autism or ADHD, meaning at least one older sibling with typical development and no first-degree relatives with a diagnosis of autism or ADHD, were also included (as confirmed through parent interviews regarding family medical history). The current analysis consisted of a final sample of 161 infants. Each infant was given a rating for familial likelihood of autism and ADHD based on the presence of clinical diagnosis. A total of 80 (EL-autism 42 male; 38 female) infants with elevated likelihood of autism, 31 (EL-ADHD; 19 male; 12 female) infants with elevated likelihood of ADHD, 21 (EL-autism+ADHD, 12 male; 9 female) infants with elevated likelihood of both autism and ADHD, and 29 (TL; 18 male; 11 female) infants with typical likelihood for either autism or ADHD were included in the sample for this study. Participants entered the study at 5-months of age and were later seen at 10, 14, 24 and 36-months. Inclusion criteria included full-term birth and no known medical or developmental condition at the time of enrolment. During their visit, participants complete a series of lab-based tasks and behavioural assessments. Paper questionnaires were mailed to the parents in advance to provide sufficient time to complete

them before their visit. Written consent was obtained from the parent(s), and ethical approval was granted by the relevant committees. Families were reimbursed for expenses and infants were given a certificate and t-shirt after each visit. Testing was conducted only when infants were content and alert. See Appendix Figure C5.1 and C5.2 for flow chart of participants in each group, and diagram of number of participants for each measure at each time point.

Measures

At every visit, the Mullen Scales of Early Learning (MSEL; (Mullen, 1995)) and Vineland Adaptive Behaviour Scale-II (VABS-II;(Sparrow et al., 2005)) were administered to evaluate the participants' developmental abilities. The Autism Diagnostic Observation Schedule-2 (ADOS-2;(Lord et al., 2012) was administered to all toddlers at 24 and 36 months, while the Autism Diagnostic Interview-Revised (ADI-R; (Lord et al., 1994) was used to interview parents when their child turned 36 months. At 3 years and mid-childhood the clinical diagnosis of autism according to DSM-5 was influenced by, but not dependent on, scores on the ADOS-2, ADI-R, SCQ, Vineland, and Mullen/WASI, researcher observations on the visit, and additional parent-reported information, by experienced researchers. 12 infants with EL met the criteria for autism at 36 months.

Infant Toddler Sensory Profile

To assess sensory responsivity in children between 10 and 36 months of age, we used the Infant Toddler Sensory Profile (ITSP; (Dunn, 2002)). The ITSP is a 48-item questionnaire completed by parents or caregivers, which measures infant sensory patterns. Parents/caregivers rate their child's behaviour on a scale of 1 (almost always) to 5 (almost never) across five sensory domains: auditory, visual, tactile, vestibular, and oral. The items are also grouped into four

quadrants: low registration, sensation seeking, sensory sensitivity, and sensation avoiding. To calculate the composite low threshold score, scores from the sensory sensitivity and sensation avoiding scales are combined. ITSP is scored such that a lower score is more sensitivity to the sensory domain, i.e., a low score suggest that the child shows more sever responses to sensory stimuli and higher scores suggest the child shows less sever responses compared to their peers and a midpoint score would indicate an average response to sensory stimuli. In this study during growth curve analysis, we reverse the scoring such that a higher score would equal to higher sensitivity to help with the interpretability of results. In this study, the index of hyposensitivity is the total score from the low registration quadrant, which comprises 11 items, while the index of hyperresponsivity is the total score from the low threshold quadrant, which comprises 25 items (Germani et al., 2014; Vlaeminck et al., 2020) and sensation seeking consisted of 14 items. The internal consistency of the ITSP demonstrated strong reliability for hyporesponsivity (α = 0.81-0.88), hyperresponsivity (α = 0.90-0.91) and sensation seeking (α = 0.75 – 0.83) across 10, 14, and 24 months.

Measures of Autism and ADHD traits

Autistic traits were measured using the preschool version of Social Responsiveness Scale – 2 (SRS-2; (Constantino & Gruber, 2012). The SRS is a 65-item parent-rated questionnaire designed to measure autistic traits, with responses rated on a 4-point scale from 1 (Not True) to 4 (Almost Always True). Out of the 65 items only two items from the SRS-2 had an overlapped with sensory features; they were – “Shows unusual sensory interest (e.g., mouthing or spinning objects) or strange ways of playing with toys” and “Touches others in an unusual way (e.g., he or

she may touch someone just to make contact and then walk away without saying anything)". In our sample, SRS-2 showed excellent internal consistency ($\alpha = 0.97$) at 36 months.

ADHD traits were measured by the ADHD sub-scale of the Child Behaviour Checklist (CBCL; (Achenbach, 1991), which assesses inattention and hyperactivity in children aged 36 months based on parent observation in the past 2 months. Parents rate their child's behaviour using a 3-point Likert scale, and the scores are summed for a total score. The reliability of the CBCL-ADHD subscale in our sample showed good internal consistency ($\alpha = 0.87$) at 36 months. Neither SRS-2 nor CBCL were used for autism/ADHD diagnosis in this study, instead they were used to measure autism/ADHD-related traits at 36 months.

5.3 Data Analysis

Latent growth curve modelling of sensory patterns trajectories

Structural equation models were used to estimate three separate Latent Growth Curves (LGC) to examine the trajectories of hyperresponsivity, hyporesponsivity and sensory seeking in infant siblings from 10 to 24 months. The 36 months SRS-2 and CBCL variables were log transformed, due to a positive skew. The LGC model included an intercept and slope, and fixed effects for age, and were estimated using maximum likelihood to account for missing data. We used a two-step method, first univariate LGC modelling was performed separately on the three sensory patterns, where we fit each construct of hyperresponsivity, hyporesponsivity and sensation seeking individually over 3 timepoints (10, 14 and 24 months) without including the likelihood groups, gender and outcome variables of autism and ADHD traits at 36 months. Age at visit was entered as a time-varying covariate that could predict observed scores at each time point. From these models, we extract estimated scores for each participant for their intercept and slope for

each construct, which are adjusted for variance how old children were when they completed each visit. For such models, acceptable fit is indicated by RMSEA of 0.05–0.08 and CFI of 0.90–0.95, whereas good fit is indicated by RMSEA of 0.01–0.05 and CFI of 0.95– 1.00 (Hu & Bentler, 1999; Kline, 2016). In the subsequent model, the estimated intercept and slope scores for all three sensory domains (hyperresponsivity, hyporesponsivity and sensation seeking) were entered as multiple correlated mediators, predicted by likelihood group (autism and ADHD) and sex (male vs. female), and predicting SRS-2 total scores and CBCL's subscale of ADHD at 36 months (see Figure 5.1 conceptual model). This longitudinal mediation model was set up to reflect the developmental timing of heritable characteristics, emerging sensory differences and autism and ADHD traits at toddlerhood. We report unstandardised (B) and standardised (β) coefficients (see Appendix Table C5.3). To facilitate with clearer interpretation of change over time, we revered ITSP scores during LGC analysis, such that higher scores represented more of the construct of interest.

As additional analysis, we re-ran the models with amended ITSP scores for hyporesponsivity subscale and another model correcting the skew in the distribution for hyperresponsivity and hyporesponsivity. To ensure our findings were not unduly influenced by the subgroup of infants who subsequently received an autism diagnosis later in development, we conducted additional analysis by excluding these participants.

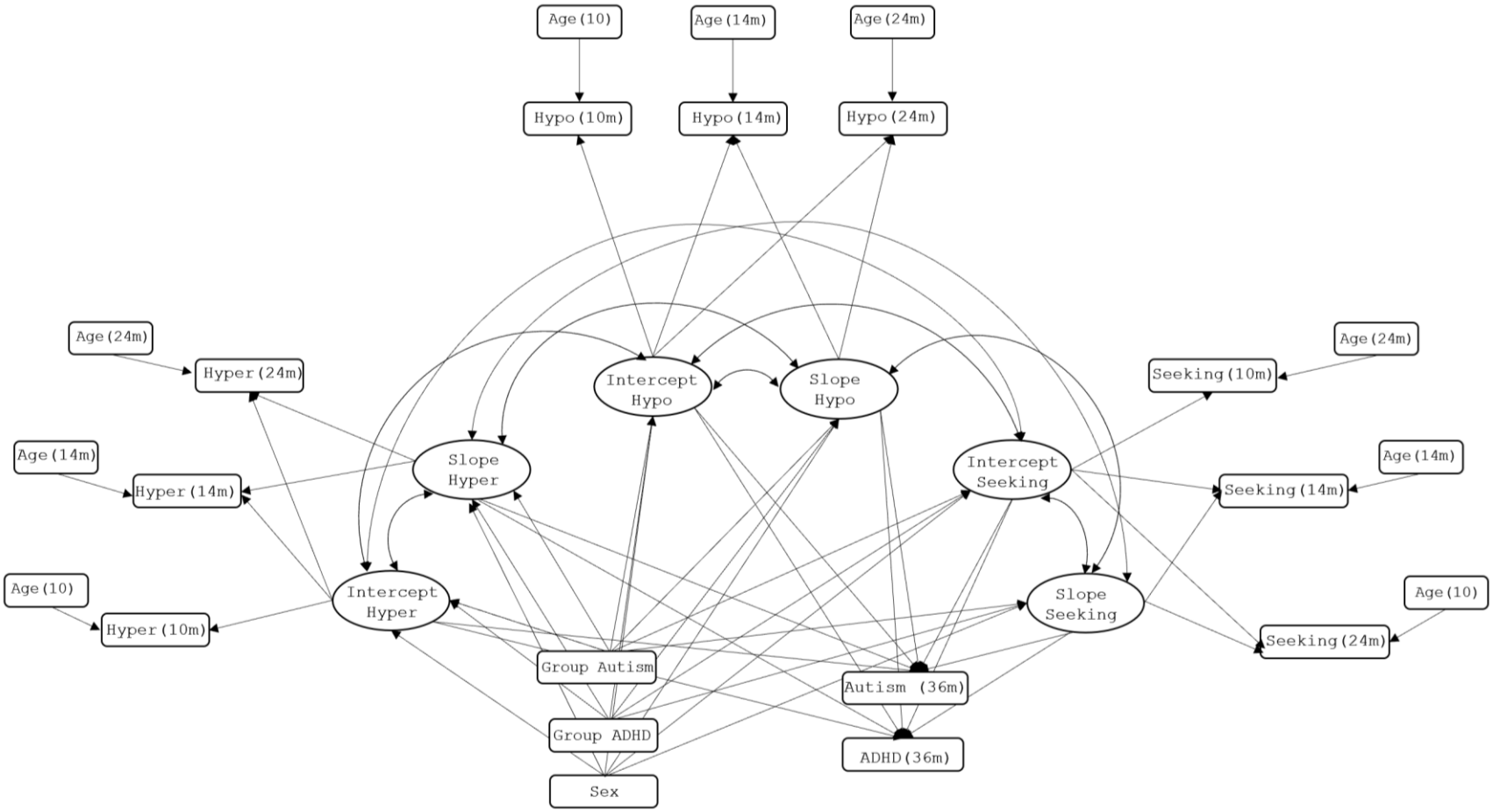

Figure 5. 1 Conceptual model

Table 5. 1 Sample Characteristics of infant questionnaires

Mean (*SD*)	N	EL-autism N=80	EL-ADHD N=31	EL-autism+ADHD N=21	TL N=29	Group differences	Direction of Effect
10 months							
ITSP Hyporesponsivity	127	44.98 *(7.19)*	48.13 *(3.72)*	45.24 *(7.09)*	46.18 *(4.83)*	p = .213	-
ITSP Hyperresponsivity	128	93.75 *(15.29)*	95.65 *(7.46)*	93.57 *(13.93)*	95.98 *(8.40)*	p = .863	-
ITSP Sensation Seeking	128	29.98 (6.40)	22.98 (5.08)	26.80 (7.89)	25.35 (3.19)	p < .001	TL<EL-autism; EL-ADHD<EL-autism, EL-autism+ADHD
14 months							
ITSP Hyporesponsivity	129	45.35 *(6.96)*	45.50 *(6.05)*	43.74 *(6.70)*	47.87 *(4.54)*	p = .294	-
ITSP Hyperresponsivity	129	92.41 *(14.82)*	93.56 *(9.82)*	89.28 *(13.23)*	94.82 *(7.99)*	p = .617	-
ITSP Sensation Seeking	130	32.46 (6.98)	27.63 (6.08)	29.58 (7.25)	30.38 (5.15)	p = .021	EL-ADHD<EL-autism
24 months							
ITSP Hyporesponsivity	118	47.53 *(7.12)*	45.18 *(6.86)*	44.47 *(8.40)*	48.95 *(3.15)*	p = .140	-
ITSP Hyperresponsivity	118	92.07 *(14.83)*	90.42 *(14.33)*	88.67 *(18.57)*	97.64 *(8.63)*	p = .251	-
ITSP Sensation Seeking	119	40.27 (8.35)	34.05 (7.41)	38.44 (9.54)	37.59 (6.65)	p = .037	EL-ADHD<EL-autism
36 months							
SRS	107	42.91 *(32.39)*	35.55 *(24.19)*	61 *(48.52)*	23.37 *(9.46)*	p = .008	TL<EL-autism, EL-autism+ADHD; EL-ADHD< EL-autism+ADHD
CBCL ADHD	116	4.22	5	5.79	3.05	p = .076	-

	(3.28)	*(3.58)*	*(3.93)*	*(2.16)*

CBCL = Child Behaviour Checklist; CSS = Composite Standard Score; ITSP= Infant Toddler Sensory Profile; SD = Standard Deviation; SRS = Social Responsiveness Scale. Note: Group differences were tested using one-way ANOVAs with group as a between-subject factor, followed by uncorrected post-hoc pairwise comparisons of means. Raw scoring was used where a lower score indicates a greater severity for ITSP.

5.4 Results

Sample characteristics

The developmental sample characteristics are presented in Appendix Table C5.1. Sample characteristics of the questionnaires used, and likelihood group are presented in Table 5.1. The EL ADHD had lower scores than EL autism on ITSP sensation seeking across all timepoints, at 14 and 24m, indicating greater severity of sensation seeking behaviours in the EL-ADHD group. At 10 months EL autism scored higher than TL, indicating greater severity in TL group; and EL autism and EL autism+ADHD group had higher scores than EL ADHD, indicating greater severity in EL ADHD group. At 14 and 24 months EL autism scored more than EL ADHD, demonstrating greater severity in EL ADHD group. Both EL autism and El autism+ADHD scored higher than TL and EL autism+ADHD scored higher than EL ADHD at 36 months on SRS. The bivariate correlations between hyperresponsivity and hyporesponsivity at most time points were highly associated with each other at p=.001. Sensation seeking was correlated with hyperresponsivity and hyporesponsivity at later timepoints. Whereas SRS and CBCL at 36 months correlated with each other and hyperresponsivity, hyporesponsivity and sensation seeking. The correlation results are reported in Appendix Table C5.2.

Patterns of associations of sensory behaviours for hyperresponsivity, hyporesponsivity and sensation seeking.

Indices of model fit were not available for univariate LGCs as all models were fully saturated. A significant association was found for the intercept and slope of hyporesponsivity ($\beta = .37$, $p = .001$) suggesting significant individual differences at initial levels and change over time for

hyporesponsivity only. No significant associations were found for hyperresponsivity and sensation seeking (see Appendix Figure C5.3).

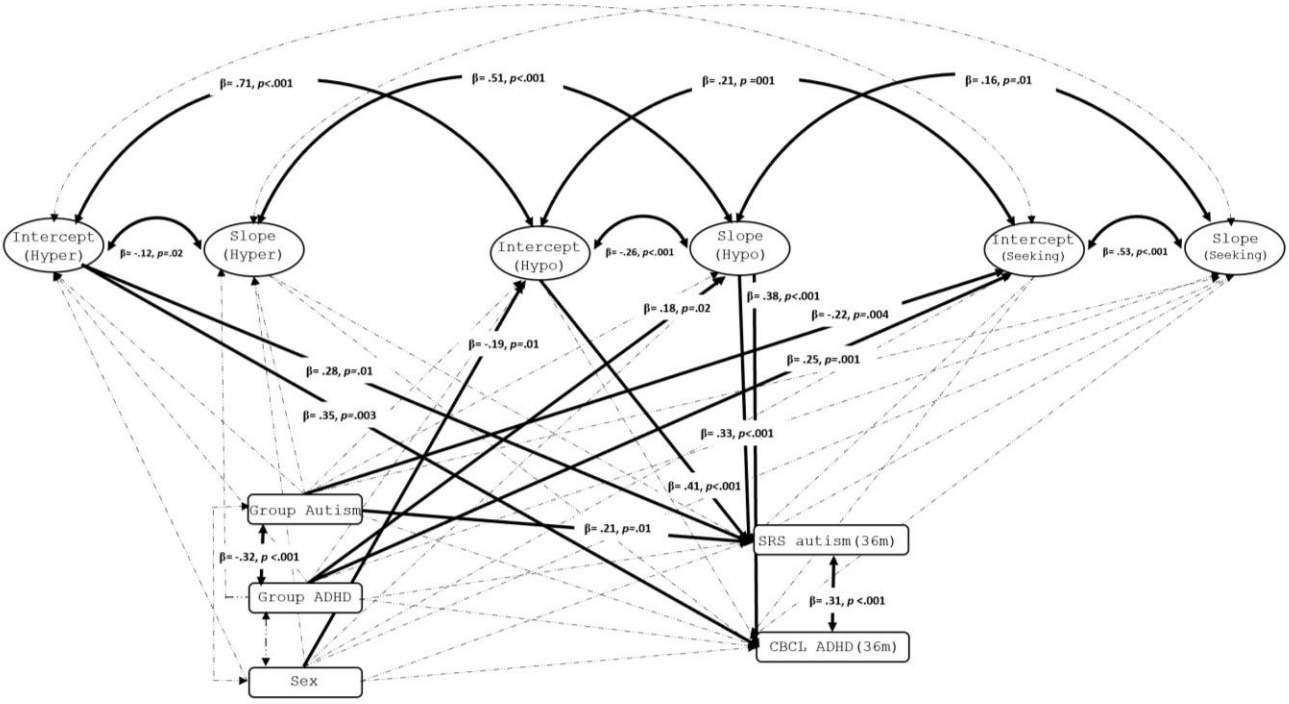

Figure 5. 2 Latent growth curve association between sensory pattern trajectories of hyperresponsivity, hyporesponsivity, sensation seeking and likelihood groups and sex on later autism and ADHD traits at 36 months. Bold indicates significant associations. Reverse scoring was used where a higher score indicated greater severity for ITSP.

Latent growth factor associations

In the final model (see Figure 5.2) the multivariate correlated growth curve model provided a moderate fit for data ($\chi^2(6) = 14.34$, $p = 0.026$; CFI = .983; RMSEA = .093). Positive correlations were found between the intercepts of hyperresponsivity and hyporesponsivity (β = .71, $p < .001$), and between the intercepts of hyporesponsivity and sensation seeking (β = .21, p = .001). The slopes of hyperresponsivity and hyporesponsivity (β = .51, $p < .001$), as well as

hyporesponsivity and sensation seeking (β = .16, *p* =.01) were positively correlated with each other respectively, indicating that these trajectories travelled together in the same direction over time. Most of the significant intercept-slope correlations were negative (hyper: β = -.12, *p* = .02; hypo: β = -.26, *p* < .001). The only positive correlations were found between the intercept and slope for sensation seeking (β = .53, *p* < .001).

Influence of likelihood groups and sex on sensory patterns

EL autism was positively associated with autism traits at 36 months (β = .21, *p* = .01), and at a non-significant trend level with ADHD traits at 36 months (β = .15, *p* = .065). Neither autism nor ADHD traits at 36 months were associated with EL ADHD. EL autism negatively associated with intercept of sensation seeking (β = -.22, *p* = .004) while EL ADHD was positively associated with a higher intercept of sensation seeking, (β = .25, *p* = .001) indicating that children with EL ADHD tended to engage in more frequent seeking behaviours at baseline. EL ADHD was also positively associated with steeper slopes of hyporesponsivity (β = .18, *p* = .02). Child's sex was significant predictor of intercept of hyporesponsivity (β = -.19, *p* = .014), such that boys had higher hyporesponsivity scores than girls at baseline.

Sensory patterns trajectories and autism and ADHD traits at 36 months

Intercept of hyperresponsivity (β = .28, *p* = .01) and hyporesponsivity (β = .41, *p* < .001) were both positively associated with 36 months autism traits, i.e., early hyperresponsivity and hyporesponsivity relates to later autism traits. Intercept of hyperresponsivity was also positively associated with ADHD traits at 36 months (β = .35, *p* = .003), and a steeper slope of hyporesponsivity was positively associated with 36 months autism and ADHD traits (β = .33, *p* <

.001; β = .38, $p < .001$) i.e., change over time in hyporesponsivity related to manifestation of later autism or ADHD traits at 36 months. However, neither the slope (change over time) of hyperresponsivity (β = .09, $p = .21$; β = -.02, $p = .78$) nor sensation seeking over time (β = -.04, $p = .63$; β = .07, $p = .38$) associated with autism or ADHD traits at 36 months.

We re-ran the model on the same sample with the amended scoring of ITSP hyporesponsivity subscales. Two items from the hyporesponsivity subscales ("It takes a long time for my child to respond to his/her name when it is called" and "My child avoids eye contact with me") were excluded from the analysis due to their overlap with early autism phenotypes. The results of this model mainly replicated the original model where all the associations remained the same (see Appendix Figure C5.4).

Sensitivity analysis

In order to account for the skew in hyperresponsivity and hyporesponsivity we used square root transformation for the hyperresponsivity and hyporesponsivity scores then ran sensitivity analysis to check that the findings were not influenced by the negative skew in distribution of the hyperresponsivity and hyporesponsivity (Appendix Figure C5.5). We found that this model largely replicated the Model 1, Figure 5.2), except that a new association from the intercept of hyperresponsivity and sensation seeking was formed (β =.15, $p = .03$) and the association between the intercept and slope of hyporesponsivity was lost (β = -.08, $p = .10$). All previous associations with likelihood groups, sex and 36 months outcomes remained. Lastly, models were re-run excluding infants who later received a diagnosis of autism, to check their influence on the results (Appendix Figure C5.6). The patterns of associations largely remained the same. The association between sex and intercept of hyporesponsivity (β = -.14, $p = .08$), slope of

hyporesponsivity and autism traits at 36 months (β = .20, p = .08) and EL autism and autism traits at 36 months (β = .16, p = .08) were non-significant.

5.5 Discussion

This study investigated the developmental trajectories of sensory responsivity across the first two years of life, focusing on hyperresponsivity, hyporesponsivity and sensation seeking in siblings with and without an EL of autism and ADHD and how these trajectories are associated with emerging autism and ADHD traits at 36 months.

There was observed heterogeneity in the developmental trajectories of sensory patterns in this early period. Notably, sensory patterns of infants with high hyperresponsivity and hyporesponsivity scores at 10 months decreased over time, and those with high sensation seeking scores at 10 months increased over time. There is some consistency with previous qualitative evidence on a small sample of children from birth to 2 years, where sensation seeking may emerge from more typical infant repetitive behaviour (Thelen, 1979) but intensify with age. Which is contrary to findings that suggest a decline in sensation seeking over time (Lidstone et al., 2014; Little et al., 2018). Similar to our results, another study also found a decrease in hyporesponsivity over time in autistic children, developmental delay and typical development aged 11 to 105 months (Baranek et al., 2013). In contrast, findings from Freuler, Baranek, Watson, Boyd, and Bulluck (2012) indicated that hyporesponsivity was relatively stable from infancy to preschool or school age, whereas stability of hyperresponsivity was less evident in infancy. Due to limited research in this area, it is difficult to draw firm conclusions about the associations of precursors and early manifestations of sensory patterns based on these results alone and would need further investigation.

Sex effects

The results of our analysis indicated that likelihood group and infant sex were associated with variation in developmental trajectories of sensory response. Specifically, male infants were likely to exhibit higher initial levels of hyporesponsivity compared to female infants in early development. Our findings align with a previous prospective study that examined sensory responsivity in children aged 6 months – 7 years, where they also found sex differences in the whole sample, where male infants show more hyporesponsivity than female infants (Chen et al., 2022). In another study on autistic children, males were reported to have more sensory responsivity (in the domains of auditory, visual, tactile, gustatory and olfactory) than females (Jussila et al., 2020). No sex differences were found in hyperresponsivity and sensation seeking in our study, which contrasts with findings on comparable samples of 2 to 14 year olds, where autistic females displayed more hyperresponsivity and other sensory altercations (A. Lane et al., 2022; Osorio et al., 2021). Some studies also found no sex differences in any sensory domains in samples of autistic children and those with ADHD (Cheung & Siu, 2009; Dellapiazza et al., 2021). Our results emphasise the potential role of sex in the development of early sensory trajectories and how crucial it is to reduce potential gender biases in samples overrepresenting males (Pender, Fearon, Heron, & Mandy, 2020). It also highlights that any differences in sensory domains for males and females with EL of autism or ADHD are still understudied or restricted to a certain sensory domain.

Sensory domains and associations with family history of autism and ADHD

Our study found that those with EL ADHD predicted higher initial levels of sensation seeking. In contrast, infants with EL autism showed lower initial levels of sensation seeking, i.e., those with

a family history of ADHD are more likely to show sensation seeking patterns early on in development than those with a family history of autism. Previous studies have shown an increased incidence of the sensory seeking pattern in children (Mimouni-Bloch et al., 2018; Shimizu et al., 2014) and adults (Kamath et al., 2020) with ADHD than TD. In addition, these studies suggest that features, especially those seeking stimulation, may be found relatively rarely in children with EL autism and more frequently in children who have EL ADHD. This may indicate that an increased genetic likelihood for ADHD may be associated with developmental differences in sensory responsivity, such as sensation seeking. Furthermore, findings from earlier studies note where adults with ADHD score higher than those with autism on sensation seeking (Clince et al., 2016), this association was largely explained by the presence of attention problems in those with ADHD than autism in the 6 to 12 years sample (Dellapiazza et al., 2021). A cross-sectional study on 3 to 14 years found that younger children are more likely to show more seeking behaviours towards sensory stimuli they want to experience than older children, irrespective of their diagnosis of autism or ADHD (Little et al., 2018). Our findings suggest, at least at the likelihood level, that these differences might be present from very early on in development. As most previous studies were conducted with children with existing diagnoses of autism or ADHD, current findings underscore the need to assess the impact of an infant's likelihood of autism and ADHD on sensation seeking and sensory development.

We observed that EL ADHD was associated with a steeper slope of hyporesponsivity compared to EL autism. Therefore, infants with EL ADHD showed greater increases over time in hyporesponsivity. A study by Keating et al. (2021) on EL ADHD sample aged 6 to 72 months, reported that over 50% of EL ADHD displayed extreme patterns of hyporesponsivity as

compared to less than 30% of TD. Although differences in sensory responsivity early in infancy have typically been thought of as associated with autism, results here show they may be a marker of other forms of neurodevelopmental conditions; as also noted in a sample with a larger age range from 1 to 18 years diagnosed with autism and ADHD (Scheerer et al., 2022). Hyporesponsivity and EL ADHD are still understudied, and the current understanding of the relations between sensory responses and ADHD are limited to draw definitive conclusions about the directions of these associations.

Relationships between slopes and outcomes at 36 months

In addition to being associated with EL of autism and ADHD, we also found developmental trajectories of sensory responsivity were associated differently with later neurodevelopmental traits. Particularly, the greater change in hyporesponsivity patterns over time predicted both later autism and ADHD traits at 36 months. These results align with previous studies which showed a subsequent increase in hyporesponsivity in those diagnosed with autism in the first two years of their life. It was found that during toddlerhood, hyporesponsivity and hyperresponsivity increased among EL infants who got the diagnosis but decreased in those EL infants who did not meet the diagnosis (Grzadzinski et al., 2020). Moreover, in a similar age group with EL infants who are later diagnosed with autism, these differences are magnified over the second year of life (Wolff et al., 2019). A comparison of autistic toddlers with TD groups, noted a high frequency of underresponsiveness and avoiding behaviours in autistic toddlers (Ben-Sasson et al., 2007). A cross-sectional study on 3 to 14 years also finds evidence that hyporesponsivity may be present in both autistic and ADHD children (Little et al., 2018). Additional evidence showed that in children (aged 3 to 10 years) with a diagnosis, sensory responsivity showed an increase in

ADHD children, whereas those diagnosed with autism showed a decrease in sensory responsivity (Cheung & Siu, 2009). Hyporesponsivity behaviours are primarily linked to reduced attention and disengagement, as researchers have noted behaviours such as slower attention disengagement and decreased orienting, which reflect greater hyporesponsivity, are observed in autistic children (Sabatos-DeVito, Schipul, Bulluck, Belger, & Baranek, 2016). Since some of the traits of autism such a slow response, could be attributed to lack of attention rather than hyporesponsivity, and considering inattention is a core feature of ADHD, it would be interesting to examine the role attention plays in relation to the pathways from sensory responsivity to autism and ADHD traits.

Relationships between intercepts and outcomes at 36 months

We found that higher initial levels of hyporesponsivity and hyperresponsivity (with our first time point at 10 months) were associated with autism traits at 36 months. These findings align with earlier evidence from prospective longitudinal studies on EL siblings where early hyporesponsivity and hyperresponsivity at 14 months were indicators of more overall later autistic severity (Chen et al., 2022; Grzadzinski et al., 2020). These findings suggest that increased hyperresponsivity and hyporesponsivity in early infancy may act as a marker for later autism diagnosis. As supported by our previous study (Narvekar et al., 2022) where we noticed strengthening of association between hyperresponsivity at 24 months and autism traits at 36 months. Our study's strong correlations between hyperresponsivity and hyporesponsivity, evident in both the intercept and slope, imply a degree of shared variance of these constructs. However, hyporesponsivity may also align more with early autism traits due to trait overlap, such as decreased response to name and avoiding eye contact (Grzadzinski et al., 2020). Our

sensitivity analysis showed that the associations remained the same ever after we removed the items from the hyporesponsivity subscales that overlapped with autism traits, i.e., delayed response to name and avoids eye contact. However, we did note that children who go on to get a diagnosis might be the ones contributing most to these associations, which is understandable in the case of those associations with autistic traits at 36 months because those infants will likely be scoring higher on autistic traits. These children are clearly contributing to the association, but it is unclear the extent to which these types of relations are relevant to nonautistic children.

Results from the current study found that early hyperresponsivity also acts as a precursor to later ADHD traits at 36 months. Previous research has demonstrated a strong link between ADHD with both hyporesponsivity and hyperresponsivity, with emphasis on sensitivity, seeking and low registration, and that these issues impact everyday function and social behaviour (Little et al., 2018; Mimouni-Bloch et al., 2018; Piccardi et al., 2021). Although our results did find that both hyperresponsivity and hyporesponsivity predicted ADHD traits, interestingly, they were at different times in development. We found that early hyperresponsivity predicted ADHD traits at 36 months, but later emerging hyporesponsivity predicted ADHD traits at 36 months. Possibly due to different causal mechanisms. Cross sectional studies previously done are inadequate for investigating such developmental effects, which is possible due to use of longitudinal data.

We did not find that sensation seeking acts as a precursor or early manifestation of later autism diagnosis. It was observed that sensory seeking behaviour prior to two years was not significantly related to autism trait severity during the preschool years in an elevated likelihood sample (Grzadzinski et al., 2020). Baranek et al. (2018) noted that sensory seeking behaviours around 24 months of age might be more strongly related to later autism diagnoses and traits

compared to traits at 14 months or alterations between 14 and 23 months. This suggests that sensation seeking appear to associate at a later age in infancy thus there is a need to follow infants at later timepoints to examine their developmental trajectories. However, contrary to other findings, we found no associations between sensation seeking and ADHD traits either. A cross sectional study on children aged 6 to 12 years diagnosed with autism and ADHD showed that an increase in sensory seeking was related to attention problems more in ADHD groups than in autism (Dellapiazza et al., 2021). This is also seen in students with ADHD, scoring higher on sensation seeking than those with autism (Clince et al., 2016). These studies were done on samples with longer age ranges. Hence, later onset of ADHD diagnosis could be a factor for our lack of association between sensation seeking and ADHD.

Strengths and limitations

This study contributes to the underexplored area of studying sensory responsivity in autism and ADHD during the developmental period of infancy to toddlerhood, in the same sample. Using a prospective longitudinal design and repeated measurement of different sensory responsivity aspects allows us to examine sensory differences between autism and ADHD. Using the LGC model, we can explore the developmental trajectories of sensory differences across time. This study also has some limitations. The study solely relies on parental questionnaires to assess sensory differences and autism and ADHD traits, this can lead to potential for shared method variance influencing the results. Additionally, most families had a first degree relative with autism or ADHD diagnoses, which could have impacted their responses. Having an older child with an autism diagnosis might affect the parental judgement for the younger child. Hence, parental perspective might be influenced by informant bias. A study showed minimal agreement

between parent report and self-report in slightly older sample (MacLennan, Roach, & Tavassoli, 2020), highlighting the need for objective measures. Future studies should consider objective and experimental measures of early-life marker, such as Electroencephalogram (EEG) (Damiano-Goodwin et al., 2018) or heart rate (Nuske et al., 2019) as they provide valuable objective and quantifiable data which are direct physiological indicators of brain activity (EEG) and autonomic nervous system responses (heart rate). These are less susceptible to biases or subjective reporting. In addition, the use of multi-informant assessment for example where data is gathered from multiple sources such as parent, teachers, and clinicians (Makin, Hill, & Pellicano, 2017) and or observational method (Kirby et al., 2017) to gain more comprehensive insight could also be employed to overcome parental biases.

5.6 Conclusion

To summarise, altercations in sensory responsivity are not unique to autism but are also associated with ADHD likelihood and outcome traits at 36 months. A key takeaway from this study is that sensory domains associated with EL autism and EL ADHD are not the same as those associated with autism and ADHD outcome traits at 36 months. This highlights the role that developmental trajectories play in the growth of sensory domains. Certain sensory domains start as a precursor but, over time, may become an indicator of the manifestation of autism or ADHD. The associations observed in the growth curve of different trajectories of sensory responses suggest that these domains are interconnected. Therefore, individual children might display behaviours characterised by one or more sensory responsivity across different contexts and developmental stages (Chen et al., 2022). It is important to capture the broader spectrum of developmental alterations in sensory patterns and behavioural manifestations across autism and

ADHD. These findings can improve our understanding of how sensory responsivity and EL factors correlate across various diagnoses. The current study's observations of distinct associations between sensory responsivity domains during infancy and later autism and ADHD have significant implications for early identification and understanding of the impact of genetic and environmental influences and stressors on the developmental trajectories of these infants. By identifying these factors targeted supports can promote positive development in such infants. By understanding these associations, we may be better equipped to address potential cascading effects on other aspects of development and ultimately improve long term outcomes.

Chapter 6. General Discussion

This chapter summarises the three empirical studies conducted for this thesis. The interpretation of the thesis findings in the context of broader literature is then discussed, followed by the strengths and limitations of the work. The implications of the work for research and clinical practice are considered, and finally recommendations for future research are presented.

6.1 Synopsis

In the general introduction chapter, perspectives on the aetiology, sensory responsivity, co-occurring psychopathology of anxiety (captured in this thesis through the construct of infant fearfulness) and ADHD in autism were outlined. Currently, there are no clear diagnostic biomarkers for autism. It is defined by its observable behavioural manifestations. Sensory responsivity differences are a key characteristic of autistic people but are not well understood. Anxiety is a highly co-occurring condition (White et al., 2009), and infant anxiety (fearfulness) may be an early predictor of later anxiety in children. As noted in the review by Fox et al. (2023), longitudinal studies of infants to mid-childhood/adolescents showed behavioural inhibition (a component of fear) identified in first year of life increased the chances of anxiety in late childhood and adolescence in a non-autistic sample. This was also noted in children with and without autism (Ersoy et al., 2021). Existing research acknowledges that both infant anxiety and sensory responsivity are prevalent among autistic individuals. However, the type of relationship that exists between them is underexplored. This thesis sought to understand the causal mechanism of these constructs and their role not only in emerging autistic traits but also in co-occurring anxiety and ADHD.

Three empirical studies were conducted examining the directionality and effect of the constructs and traits from infancy to toddlerhood. In the first of these (Chapter 3), the aim was to examine the relationship between infant anxiety and perceptual sensitivity in the first two years of life and test whether these were associated with later manifestations of RRB and SCI traits in a sample consisting of infant siblings with an elevated and typical likelihood of autism.

Next (Chapter 4), attention is turned to examining whether the associations found in the earlier study replicated in a different cohort and exploring the developmental consequences of alterations in sensory responsivity on emerging infant anxiety and autistic traits in the first three years of life. For this, sensory responsivity was categorised as hyperresponsivity and hyporesponsivity in a sample enriched for elevated likelihood for both autism and ADHD and examined on the basis that autism and ADHD often co-occur.

Finally (Chapter 5), to address the developmental trajectories from infancy to toddlerhood and to inform its relationship with later autism and ADHD traits at 36 months, it was important to consider the developmental course of sensory responsivity in an elevated likelihood sample. The study aimed to examine how sensory responsivity develops over time, specifically during the first two years, and its association with later autism and ADHD traits at 36 months.

All the chapters of this thesis used a prospective longitudinal design and examined early markers of autism in infant siblings. Chapter 3 explored this in the context of sensory responsivity and infant anxiety in an elevated likelihood of autism sample, and Chapter 4 examined and expanded on these findings in a sample enriched with an elevated likelihood of autism and ADHD. Chapter 5 investigates the growth curve pattern of sensory responsivity in a sample consisting of elevated

likelihood of autism and ADHD. In this way, the different chapters all sought to demonstrate the directionality and trajectory of infant anxiety, sensory patterns, autism and ADHD.

6.2 Summary of findings

The first empirical study (Chapter 3) examined the bidirectional associations between infant fear and perceptual sensitivity between 10 – 24 months. Firstly, it was found that there was within-domain continuity of constructs of fear/shyness and perceptual sensitivity. Higher fear at 14 months was also found to be associated with higher perceptual sensitivity at 24 months, whereas the reverse association was not found. Subsequently, it was seen that higher levels of fear/shyness and perceptual sensitivity at 24 months were associated with higher levels of RRB at 36 months and SCI at 36 months. Taken together, the pattern of results indicated that infant anxiety and perceptual sensitivity may not only be a precursor to RRB but shared with SCI.

The second empirical study (Chapter 4) built upon these results, which are discussed here in systematic steps for parsimony and clarity of interpretation:

(i) To further build on the findings from the previous analysis, a more precise measure of sensory responsivity that distinguishes between hyperresponsivity and hyporesponsivity was used. Hyporesponsivity was included in the analysis to test the specificity of the associations between hyperresponsivity, fear and later autism traits of RRB and SCI. As predicted, higher levels of hyperresponsivity at 24 months was associated with both higher levels of RRB and SCI at 36 months. However, fearfulness lost its association with RRB and SCI. It was also expected that the paths would remain with the inclusion of hyporesponsivity in the model. However, it was noted that with the inclusion of hyporesponsivity, hyperresponsivity lost its association with

RRB and SCI and new associations were formed where higher levels of hyporesponsivity associated with higher levels of RRB and SCI.

(ii) An association of higher hyperresponsivity at 14 months to higher fear at 24 months was found. A replication study to confirm this association on a similar but independent cohort was conducted. Although the previous study (Chapter 3), found an association between fear/shyness at 14 months and perceptual sensitivity at 24 months, there was no such association in the replication in Chapter 4. However, there was a trend-level negative association between perceptual sensitivity at 14 months and fear/shyness at 24 months, which was lost when EL ADHD group was excluded from the analysis.

(iii) An exploratory post hoc analysis found that when tested for fear along with RRB and SCI in isolation, fear at 24 months positively associated with RRB and SCI at 36 months.

(iv) In addition, given the lack of association between hyperresponsivity and RRB and SCI with the inclusion of hyporesponsivity, models were re-run with an amended version of the hyporesponsivity subscale, which dropped the items that directly overlapped with autism traits. The results remained unchanged. There was no evidence to suggest that items from the subscale of hyporesponsivity influenced the pathways of association with autism traits.

(v) Further investigaton was conducted to examine if the exclusion of the EL ADHD group would impact the associations found in the earlier analysis, results found that the associations largely remained the same.

(vi) An exploratory post hoc sensitivity analysis where ADHD traits were included at the 36 months outcomes along with autism traits of RRB and SCI indicated that the pathways of hyporesponsivity to autism traits remained unchanged. Furthermore, new associations were

formed where higher levels of hyporesponsivity at 24 months and hyperresponsivity at 10 months associated with higher levels of ADHD traits at 36 months and lower levels of hyporesponsivity at 10 months associated with higher levels of ADHD traits at 36 months.

Following these studies, Chapter 5 explored the developmental trajectories of sensory responsivity over time. Findings report that male infants were likely to exhibit higher initial levels of hyporesponsivity than female infants in early development. However, an elevated likelihood of ADHD predicted higher initial levels of sensation seeking. Whereas an elevated likelihood of autism showed lower initial levels of sensation seeking. It was noted that elevated likelihood of ADHD is associated with a steeper slope of hyporesponsivity over time. When examining how sensory responsivity related to later autism and ADHD traits, it was found that higher initial levels of hyperresponsivity and hyporresponsivity were associated with autism traits at 36 months, and the slope of hyporesponsivity associated with autism at 36 months and showed a steeper growth over time. Higher early hyperresponsivity acts as a precursor to ADHD at 36 months, while the slope of hyporesponsivity associated with ADHD at 36 months and showed an increase over time.

6.3 Interpretations of the main findings

Having detailed the findings in previous chapters of the thesis, consideration is now given to the key findings and how these relate to the existing literature. First, an interpretation is provided of the findings of the association between infant anxiety and sensory differences, after which infant anxiety and sensory responsivity are looked at with outcome measures of autism and ADHD. Lastly, the overlapping nature of autism and ADHD are discussed.

6.3.1 Associations between infant markers of anxiety and perceptual sensitivity/hyperresponsivity

The findings outlined in this thesis regarding the associations between fearfulness and perceptual sensitivity/hyperresponsivity can be examined through the lens of Green and Ben-Sasson (2010)'s Theory. Findings in Chapter 3 reported higher infant fearfulness at 14 months associated with higher perceptual sensitivity at 24 months. These are suggestive that infants are more likely to notice environmental sensory stimuli if they are hypervigilant of their environment. One interpretation is that because fearfulness is characterised by increased arousal and vigilance, individuals tend to be more conscious of stimuli in their surroundings. These results are in line with the theory proposed by Green and Ben-Sasson (2010), where anxiety predicts Sensory Over Responsiveness (SOR), suggest that anxiety disorders involve being overly hyperaroused, which leads to constantly scanning for potential threats and preparing for them. This heightened state of vigilance and difficulty in controlling negative feelings through focus might play a role in SOR. When children are on high alert, searching for threat, they're more likely to pick up on and respond to sensory stimuli in their environment. However, in Chapter 4, these associations were reversed, where higher hypersensitivity at 14 months was associated with higher fearfulness at 24 months. Individuals who are hypersensitive to sensory stimuli may detect stimuli at a lesser intensity, resulting in a greater number of perceivable stimuli in their environments. This may lead an individual to be overloaded by their sensory environment (Green 2012). The findings from Chapter 5 are consistent with Green and Ben-Sasson (2010) other theory, which suggests association between SOR and subsequent anxiety. They suggested that the link between SOR and anxiety can be explained by fear and conditioning. Unpleasant sensations like a loud noise (unconditioned stimuli) get connected with specific things or situations, like a balloon.

Consequently, these objects become conditioned stimuli, capable of eliciting a conditional response, such as fear or anxiety. So, for example, the sight of the balloon might trigger anxiety even without the loud noise. The constant, unpredictable, and uncontrollable exposure to these conditioned stimuli can make the child hyperresponsive to anything that might seem threatening, keeping them in a state of high alert and leading to general fear and worry. This state includes constantly scanning the environment for threat-related cues and preparation for potential threats. This heightened reaction to the sensory stimulus may extend to the entire environment due to context conditioning, thus contributing to hypervigilance and anxiety (Green & Ben-Sasson, 2010). Therefore, it is possible that hyperresponsivity can lead to more fearfulness in infants which can subsequently influence their social interactions and repetitive behaviours negatively.

One of the reasons for the lack of replication could be that the scale used to measure hyperresponsivity was a subscale of temperament and was not meant for measuring sensory differences alone. This underscores the importance of precise measurement to target the domain of interest. It also highlights the need for replication. Few studies have focused on the associations of infant anxiety and sensory differences, and even fewer studies have been done to replicate results. Replication of findings with different samples is essential for fostering confidence in scientific conclusions and necessary for generalisability across populations (Asendorpf et al., 2016; Nosek et al., 2022). With the exception of a few studies (Baranek et al., 2013; Haartsen et al., 2019; West, Leezenbaum, Northrup, & Iverson, 2019), the current field is limited in its replication of prospective infant studies.

Even though the associations in Chapter 3 did not replicate in Chapter 4, we found that the association between higher hyperresponsivity at 14 months with higher fearfulness at 24 months

remained in all sensitivity analyses. This indicates that the measure for hyperresponsivity is a more robust and precise measure of sensory responsivity, even when hyporesponsivity was included in the model and the elevated likelihood of ADHD group was excluded. This direction of association has also been observed in other studies involving autistic individuals across different age groups (MacLennan et al., 2022; MacLennan et al., 2021; Verhulst et al., 2022). Hence given the empirical studies mention here, this relationship from hyperresponsivity to fearfulness has stronger evidence in support of the direction of the association.

The results of these findings and other evidence should be reviewed, considering that the discrepancies in design, measures, age range, and diagnosed versus undiagnosed samples limit comparability with other studies. More investigation is needed to confirm these results in order to probe the generalizability of this finding. Examining the emergence of infant anxiety and sensory responsivity as well as their relationship over time in very young children with autism, can increase our understanding of potential reciprocal relationships between these two conditions and construct overlap.

Infants undergo significant developmental changes, and around 24 months, they can communicate and express their source of distress verbally or non-verbally. This aids parents in linking their child's emotions with a particular sensory input, leading to increased accuracy in the parent report of these behaviours (Ben-Sasson, Carter, & Briggs-Gowan, 2010). Regardless of whether anxiety emerges later than sensory differences or vice versa, future studies should examine the relationship between anxiety and sensory patterns over a longer period of time, especially given elevated rates of anxiety (40%) in autistic adolescents and young adults (Malow,

Qian, Ames, Alexeeff, & Croen, 2023) which tends to impact functioning and mental health over time negatively (Uljarević et al., 2020) emphasises the need for timely assessment and support.

6.3.2 Infant anxiety and later autism and ADHD traits

In Chapter 3, findings showed that infant anxiety at 24 months was not only associated with RRB at 36 months but also SCI at 36 months. This was supported by another study with partly overlapping sample of infant siblings (Ersoy et al., 2021), where infant anxiety is associated with later autism traits. Our finding of higher infant anxiety being associated with increased later autism traits contributes to the idea that RRB is a useful coping mechanism used as a means to manage anxiety and exert control over their environment (Kapp et al., 2019). Similarly, heightened fearfulness and shyness increase the chance of avoiding novel stimuli and thus limiting learning opportunities. This could in turn impact the development of social cognition and subsequently lead to higher social communication challenges (Fox & Pine, 2012).

On the contrary, in Chapter 4, we found that in the presence of hyperresponsivity, this association between infant anxiety and later autism traits was not significant but became significant when the model was run in isolation. Overall, infant anxiety predicted later autism traits; however, when studied with other constructs, it might be accounted for by the presence of other co-occurring features. In order to examine the complex relationships among multiple variables simultaneously, more studies using multivariate analysis would provide a comprehensive and accurate understanding of the different underlying developmental patterns and factors at play during early infancy. The interconnectedness of emerging infant anxiety and sensory responsivity constructs in development calls for constructing developmentally informed

theoretical models to decipher the construct that is the marker or manifestation cause versus the construct that is the mediator on the causal path.

6.3.3 Longitudinal association between sensory responsivity, autism and ADHD

(a) Autism traits and sensory patterns of hyperresponsivity and hyporesponsivity

Sensory differences are a heterogeneous condition at the behavioural level that includes various sensory domains. These domains play significant roles in shaping behaviours, with various theories outlining their functions and manifestations. These theories provide frameworks for understanding how sensory experiences influence behaviour and contribute to the complexities of sensory differences in individuals. The results in this thesis can be explored via two similar theoretical perspectives. Both theories propose that autistic individuals show more than one type of sensory differences and have been classified into subtypes that differ in their severity and domains. Dunn's theory of sensory processing (Dunn, 1997) suggests that individuals may differ in how they respond to sensory input, which in turn impacts their behaviour. At 36 months, children with autism traits may exhibit unique sensory responsivity patterns, such as hyperresponsivity or hyporesponsivity, which can influence their interactions and experiences in their environment. Similarly, Lucy Miller's theory of Sensory Processing Disorder (SPD) theorises that individuals may have difficulty processing and integrating sensory information, leading to challenges in daily functioning. Miller’s classification is based on previously proposed model by Dunn (1997). At 36 months, children with autism traits may exhibit symptoms of SPD, such as sensory seeking or avoidance behaviours, which can contribute to their overall profile of sensory differences and impact their social interactions and adaptive behaviours. Understanding and addressing these sensory differences is crucial for providing tailored support for autistic

children and children with autism traits. Results of the association between sensory responsivity and later autism traits reported in all three empirical chapters indicate that increased perceptual sensitivity/hyperresponsivity is associated with higher levels of later autism traits. Although studies on sensory differences have typically focused on different domains of sensory responsivity, they report associations with autism traits, and these associations may be present in infants with an elevated likelihood of developing autism before receiving a diagnosis (Sacrey et al., 2015; Turner-Brown et al., 2013; Wolff et al., 2019). We found that patterns of these associations differed when we looked at them in the same model that distinguished sensory responsivity as hyperresponsivity and hyporesponsivity. In Chapter 5, we looked at developmental trajectories; it was observed that initial hyperresponsivity is associated with autism traits at 36 months. These results concur with reports from longitudinal studies showing that hyperresponsivity in early childhood, particularly in infancy, can be a predictive factor for later challenges in RRB and SCI in school-aged children (Chen et al., 2022; Grzadzinski et al., 2020). This could be because hyperresponsivity is easy to identify as it is an external manifestation of behaviour and can be more prominent than hyporesponsivity. As also seen in the theories proposed by Miller's Sensory Processing Disorder Model and Dunn's Sensory Processing model, where hyperresponsivity refers to traits of responding too much for too long, hence being easier to identify in infancy as due to limited behaviours.

However, in Chapter 4 we found that hyperresponsivity lost its association to later autism traits in the presence of hyporeactive and in Chapter 5, hyperresponsivity did not seem to be an early manifestation (have a steeper slope of growth) of later autism traits, i.e., hyperresponsivity behaviours do not become much stronger or more noticeable as the child gets older. This could be because as the child grows, majority of the stimuli encountered are multisensory (Kirby et al.,

2017). As proposed by Ayres (1979), who based her intervention on one of the key principles that activities must engage in more than one sensory system simultaneously, they concluded that multisensory stimulation is often more effective than unisensory stimulation in changing behaviour. She emphasis that typically developing individuals automatically sort and organize messages from numerous sensory neurons before transmitting this information to motor neurons, despite the constant and disorganised nature of neural activity. This allows the person to stay regulated and organise actions (L. Miller et al., 2009). Therefore, other behaviours become more noticeable and might compensate for or overlap with hyperresponsivity. By contrast, EL children later diagnosed with autism showed increased hyperresponsivity by 6 months of life and continuing into the second year of life (Clifford et al., 2013; Zwaigenbaum et al., 2005).

We also noted that EL autism group did not associate with either intercept or slope of hyperresponsivity. This indicates that the causal mechanism of hyperresponsivity to EL autism group and autism traits may differ.

Findings from Chapters 4 and 5 demonstrate that hyporesponsivity did not associate with EL autism. However, hyporesponsivity is associated with later autism traits, and hyporesponsivity acts as a precursor as well as an early manifestation of autism traits., i.e., not only is it possible to identify hyporesponsivity early in infancy, but it also remains a noticeable part of infant's behaviour as they continue to grow. This trend is also observed in other studies (Chen et al., 2022), especially in those children who receive a diagnosis of autism later (Wolff et al., 2019).

The findings from Chapter 4 showed the specificity of the association between hyporesponsivity at 14 months and SCI at 36 months. Sensory disturbances could influence the development of social and communication skills in children with more autistic traits (Jones et al., 2018; Szatmari

et al., 2016). Hyporesponsivity is characterised as a slow response to environmental stimuli, not noticing things in the environment. Hence, infants with increased hyporesponsivity can tend to avoid novel situations. Therefore, it is plausible that these can hinder learning social skills.

The development and differences of these associations found can be approached from a few viewpoints. Firstly, autism may result from a typical developmental trajectory that is derailed over later infancy and toddlerhood (Ozonoff et al., 2010). Secondly, challenging behaviour in infants might be subtle or transient due to their limited skills and fall outside the core dimensions of autism (Varcin & Jeste, 2017). Thirdly, associations between early behaviours and later outcomes tend to become more apparent, primarily after 24 months. This could be attributed to behavioural manifestations and phenotypical continuity, especially concerning later autism traits that typically begin to emerge during the second year of life (Gammer et al., 2015).

Having addressed the findings from Chapters 3,4 and 5, it is essential to consider to what extent the scales used measure sensory responsivity and infant fearfulness instead of autistic traits. For instance, the SRS can be inflated by other types of psychiatric issues (Grzadzinski et al., 2011; Havdahl et al., 2016). With regard to specificity, there is limited work in this area. As to whether our measure of sensory responsivity is picking up early signs of autism, we ran a sensitivity analysis where items that seemed to overlap with autism traits were removed from the analysis. Results showed that these items did not seem to influence the overall patterns of sensory responsivity and later autism and ADHD traits. To be certain that fearfulness/shyness measures are truly a reflection of early anxiety as opposed to autism, previous studies have demonstrated that measurements from the fearfulness subscale of the IBQ/ECBQ predict later anxiety but not autism symptoms (Shephard et al., 2019; Tonnsen et al., 2013). However, we acknowledge that

the extent to which autism symptomatology influences scores on temperament or sensory responsivity questionnaires in young childhood is not well explored.

(b) ADHD and sensory patterns of hyperresponsivity and hyporesponsivity

Findings from Chapters 4 and 5 report that hyperresponsivity and hyporesponsivity were both related to later ADHD traits. However, the timing of the development of sensory patterns seems to differ. Hyperresponsivity acts as an early marker of later ADHD traits, whereas hyporesponsivity acts as an early manifestation of later ADHD traits, which becomes more noticeable over time. The co-occurrence of differences in sensory responsivity and ADHD has been documented by several other investigators (Bijlenga et al., 2017; Shimizu et al., 2014). A review by Shephard et al. (2022) stated that sensory responsivity associated with ADHD and presented specific vulnerability during initial 5 years of life. Within the existing literature on ADHD, hyperresponsivity has been more widely studied (Reynolds & Lane, 2008). ADHD tends to co-occur with hyperresponsivity, and both continue to develop over time (Ben-Sasson et al., 2007).

We noted that EL ADHD group had a steeper slope of growth of hyporesponsivity during infancy. It has been consistently observed that there are significant differences in hyperresponsivity based on the likelihood groups of ADHD (M. Miller, Iosif, et al., 2020; Wood, Asherson, Rijsdijk, & Kuntsi, 2009). ADHD can be identified as early as 12 months and behavioural indicators of likelihood for later ADHD may be present early in development, which may improve earlier detection and support for the condition (M. Miller, Iosif, Young, Hill, & Ozonoff, 2018). A key characteristic of ADHD is inattention, which can make it difficult to distinguish whether sensory responsivity is a result of inattention leading to missing cue or

heighten sensitivity to stimuli. Identifying early indicators for ADHD in infancy and early childhood is complex, given that high levels of inattention, hyperactivity, and impulsivity are developmentally typical in young children. Consequently, measuring and determining clinically meaningful differences in these constructs at a young age becomes a challenging task (Miller 2020).

There is a need for mainstreaming the identification of sensory differences in ADHD as a core feature in children undergoing diagnostic evaluation to rule out misdiagnosis and determine co-occurrence. Sensory differences in ADHD can have a larger effect on the child's life, such as social interactions and academic performance. Using a sensory responsivity perspective in respect to ADHD offers a way to broaden the options for supporting children with ADHD to perform successfully at home, school, and in the community (Dunn & Bennett, 2002).

A notable limitation within the existing body of literature is the focus on investigating sensory responsivity within ADHD only groups, often limited to individuals with existing diagnoses and rarely on likelihood groups. Our study noted that infants in different likelihood groups demonstrated different sensory pattern trajectories. Most studies done frequently concentrate on certain sensory domains like hyperresponsivity, making it harder to draw insights across the broader field. In order to test the associations of sensory patterns and their developmental trajectories, more infant and toddler longitudinal studies are needed, which are currently limited in the field of ADHD and overlapping samples with autism.

6.3.4 Shared versus distinct developmental mechanism from sensory responsivity to autism and ADHD

Studies of older siblings and family members show not only that autism and ADHD commonly co-occur (M. Miller et al., 2019) but also that in siblings of children with autism and ADHD, other neurodevelopmental and neuropsychiatric conditions, including anxiety, conduct disorder, intellectual disability and language delay are also common (Jokiranta-Olkoniemi et al., 2019). This could mean that reported associations between autism and sensory responsivity differences could be in part driven by unmeasured ADHD. However, results from Chapters 4 and 5 of this thesis suggest this is not the case, as associations between sensory responsivity differences and autistic traits remained even when ADHD traits were included in the model. Previous studies investigating sensory patterns in autism and ADHD cohorts have shown both results that build up support, but also results that are less consistent with these findings. For instance, the sensory responsivity examined in a sample of those with autism and ADHD found that patterns of phenotypical traits of sensory responsivity were similar across both diagnosed groups of autism and ADHD. Therefore, sensory responsivity was transdiagnostic in nature (Scheerer et al., 2022). Other studies highlight that sensory responsivity patterns may differ on sensory domains with autism and ADHD. For instance, autism group showed more severe hyporesponsivity and hyperresponsivity than ADHD group, ADHD group showed more seeking behaviour than autism group (Dellapiazza et al., 2021). Our results were similar in context to seeking behaviour, where EL ADHD group showed more seeking behaviour compared to EL autism.

There are several possible explanations for the differences in evidence. Firstly, autism and ADHD diagnostic labels have poor explanatory power (Krakowski et al., 2020; Scheerer et al., 2022). Secondly, in line with this evidence, researchers have proposed that the earliest features

of autism may lie outside the core dimension of diagnostic manifestation, such as motor and visual-perceptual function (Di Giorgio et al., 2016; Varcin & Jeste, 2017). Thirdly, it can be argued that when parents report on observable behaviour, it remains unclear whether the behaviour within the contexts of autism and ADHD represents the same underlying processes. For example, seeking behaviour might serve the purpose of self-soothing, or it could also serve the purpose of self-arousal. Likewise, hyporesponsivity, especially in the context of auditory responsivity in autism, could be the habituation of stimuli, whereas in ADHD it could mean inattention (Johnson, Gliga, et al., 2015). It is possible that autism and ADHD are difficult to differentiate because they result from shared early developmental pathways or due to convergence in early behavioural manifestations of these conditions. Therefore, we need objective and specific markers for sensory responsivity rather than only relying on parent inference, which can be biased based on what they know of their child's or infant sibling's diagnostic status.

Keeping the framework proposed by He et al. (2023) on sensory experiences in mind, we have focused on sensory responsivity using behavioural markers as an indicator of our associations with later autism and ADHD traits. It would be recommended in the future to study sensory reactivity related neural excitability and physiological reactivity to sensory input as an objective index of sensory differences that could help understand how EL or autistic children and those with ADHD respond to sensory stimuli. These measures are relatively free of human error compared with reports by caregivers. One such objective index of brain response to sensory stimuli is electroencephalography (EEG). The neurobiological data from the brain represents a potential marker of aspects of autism and is particularly useful in understanding behavioural and cognitive challenges (Sarmukadam, Sharpley, Bitsika, McMillan, & Agnew, 2018). EEG is

relatively non-invasive, with lower sensitivity to physiological and environmental artefacts and higher temporal resolution than the functional magnetic resonance imaging (fMRI) techniques (Webb et al., 2015). Another objective measure of autism is eye-tracking, which is unobtrusive, can be rapidly collected, cross a wide range of ages and cognitive levels, and is relatively less expensive than EEG or fMRI. It helps directly assess the core social attention deficits contributing to autism (Frazier et al., 2017; Sabatos-DeVito et al., 2016). A combination of parent report and clinician administered observation also serve as valuable tools to inform clinical judgment when assessing trait identification and severity, overcoming the inherent limitations associated with just parental reports (Baranek et al., 2013; Tavassoli et al., 2016).

Previous studies have typically investigated autism and ADHD manifestation separately, particularly research on infant markers of later autism and ADHD remains limited. Further studies should consider focusing on data driven profiles rather than categorical diagnosis. This approach can potentially facilitate the differentiation between shared and unique causal pathways. Additionally, it can shed light on autism and ADHD's concurrent nature and aetiology.

6.4 Strengths and Limitations

The core strength of this study is the use of a prospective longitudinal design based on infant siblings of autistic children. As noted in Chapters 3, 4 and 5, this design allows investigations into behavioural markers that indicate early expression of neurodevelopmental and other co-occurring conditions (Shephard et al., 2019). Additionally, one can use samples who are enriched for autistic traits to ask questions about developmental mechanisms underpinning autism as a diagnostic category (Constantino et al., 2021). Understanding the mechanism that occurs before

a diagnosis is important for early intervention, support planning and improving the overall well-being and quality of life for individuals with autism and their families. Evidence suggests that core behavioural signs of autism do not appear until the second year of life (Johnson, Gliga, et al., 2015) and the age of diagnosis is typically around 3 years (Jones et al., 2014; Szatmari et al., 2016). However, early markers such as sensory differences are known to appear by infant's first year (Clifford et al., 2013; Jones et al., 2014). Infants with an elevated likelihood of autism provide an opportunity to investigate early signs and markers of autism before overt traits appear. Early markers such as these may help to identify early support for very young autistic children and their families. In addition, collecting data over numerous ages allows for studying developmental trajectories. The use of SEM aids to examine the complex relationships between various constructs and provide insight into development over time. This helps to facilitate a developmentally plausible, dynamic, and interactive models of causation. In this way, the study design allowed the exploration of cascade-like patterns of these constructs over time (Bradshaw, Schwichtenberg, & Iverson, 2022). Furthermore, a number of the aspects explored are topics that have limited research or have shown less consistent results in autism and mainly ADHD studies. In particular, this applies to building on our findings, especially replicating on a different cohort, using a more precise sensory measure and later investigating its developmental influence. The novel use of methods and their findings provide a foundation for future research in these areas.

In addition to these strengths, a few limitations are worth noting. Infant studies have a concern of generalizability of findings, which arises because all children in these samples have an older sibling, but not all autistic children in the wider population have an older autistic sibling (Szatmari et al., 2016); which can affect how we interpret early signs in the infant sibling. Additionally, infants who have older siblings with autism and later develop autism themselves

may not represent all children with autism. There is a lack of information on how parental expectations and concerns might influence autism expression, especially concerning infant temperament (Clifford et al., 2013). Furthermore, multiplex families tend to exhibit more characteristics associated with autism, especially in sensory traits among parents compared to children and parents from simplex families. Indicating that sensory responsiveness might play a role in the genetic vulnerability to autism (Donaldson, Stauder, & Donkers, 2017; Schwichtenberg, Young, Sigman, Hutman, & Ozonoff, 2010).

While the study's overall sample size is moderate, limitations arise from unequal group sizes, particularly with the relatively small typical likelihood groups. To address this, the study combined both EL and TL groups, and the likelihood groups were predictors on all constructs, a common approach in the field (Shephard et al., 2019). However, this method may constrain the ability to investigate whether developmental mechanisms are consistent in both EL and TL groups.

Another consideration is that infants have a limited range of behaviours, which may restrict the credibility of parental reports. Research suggests that parents become more adept at detecting and reporting on their infants' behaviour as the child develops (Ben-Sasson et al., 2010). Observable signs (such as those of hyperresponsivity) tend to capture the attention of observers or parents, on the other hand the absence of certain behaviours or subtle cues (such as those of hyporesponsivity) can easily go unnoticed or be disregarded (Jones et al., 2014). In addition to parent questionnaires, researchers can employ various methods to measure fearfulness and sensory responsivity differences and their relationship to later autism and ADHD traits in childhood. One common approach is direct observation, where trained observers assess a child's

behaviour and physiological responses in various situations (Delehanty & Wetherby, 2021). Another technique involves psychophysiological measures, such as heart rate and skin conductance, which offer objective insights into a child's physiological responses to measure and sensory responsivity (Billeci et al., 2018). Techniques could also include the multi-rater approach, i.e., using examiner rating from an experimental paradigm as well as parent rating, this methods helps avoids relying on parent report alone (Palmer et al., 2023) and the multimethod approach, where the study uses a combination of observational method (for example video coding), EEG, eye tracking along with parent report (Rossow, MacLennan, & Tavassoli, 2021; Tang et al., 2020). Hence, a combination of parent report and use of experimental and observational measures could be used to minimised shared method variance and provide a comprehensive understanding of the directionality and trajectory on construct of interest.

6.5 Research and clinical implications

Heterogeneity in autism reflects a developmental process that can be variable in timing but one that unfolds and stabilises over the first few years of life (Constantino, Charman, & Jones, 2020). This highlights the complexity of mapping initial brain function to later outcomes in developmental psychopathology (Johnson et al., 2021). The infant sibling design enables the selection of infants enriched for specific traits of interest, offering valuable insights into early markers and developmental trajectories associated with these traits, enhancing our understanding of the condition's early manifestations. Although currently limited, research has initiated to prospectively follow co-occurring conditions, such as anxiety and ADHD (Cervin, 2022; M. Miller, Austin, et al., 2020).

Combining parent-reported data with experimental measures (Lory, Kadlaskar, McNally Keehn, Francis, & Keehn, 2020) can enrich the depth and generalizability of research results. This approach provides a more comprehensive view of a child's development and behaviour, allowing for a more accurate assessment of their challenges. The findings also emphasise the need for replication and improved measurement tools to identify and assess conditions at their onset, especially in infants. As a result, continuous refinement of assessment methods is essential to ensure early detection and intervention.

Regarding clinical implications, selecting the most appropriate intervention for children with autism symptoms who show anxiety and sensory differences depends on which causal pathway is supported. Despite their potential connections, the two conditions are currently treated independently, with distinct approaches (Green et al., 2012).

As for treating anxiety in children, the popular approach is Cognitive Behavioural Therapy, which has shown some positive research outcomes on certain types of anxiety (J. Wood et al., 2020). Then there are interventions such as family-based intervention (Del Rosario, Gillespie-Lynch, Johnson, Sigman, & Hutman, 2014) which focus to support the development of effective emotional regulation strategies and improve the quality of a child’s later social skills. As the children age, there are different types of anxiety and the relationship between sensory responsivity and these anxiety types may vary. Therefore, these differences should be considered while devising specific interventions for anxiety (MacLennan et al., 2020).

The most common intervention for differences in sensory responsivity is sensory integration therapy, i.e., aimed to increase participation by reducing negative responses to sensation, which was noted to be more beneficial for boys aged 4 to 11 years with co-occurring ADHD (Randell

et al., 2022). Other interventions include Occupational Therapy, Ayers Sensory Integration therapy – a play-based intervention proving sensory motor engagement (Parham et al., 2011), touch therapy (Silva, Schalock, Ayres, Bunse, & Budden, 2009), and sensory diet (Fazlioğlu & Baran, 2008). However, the empirical support for the efficacy of these interventions still needs to be more conclusive, primarily due to the absence of randomised controlled trials in the majority of these research studies. Given the interconnectedness between sensory responsivity and infant anxiety in children with autistic traits, the information from studies like those conducted in this thesis can be used to develop a combined intervention that can address both sensory and anxiety related aspects, as it may offer potential advantages.

In summary, infant sibling studies provide a unique window into early development and the emergence of features associated with conditions like autism and ADHD. These studies offer opportunities to enhance our understanding of early markers and improve measurement methods, identify children at higher likelihood, and develop early intervention strategies that can positively impact the lives of individuals with the condition and their families.

6.6 Future directions

There are many directions future studies can focus upon. To further our understanding of the mechanisms of emerging autism traits, future work can consider addressing how variability in sensory responsivity impacts the development and emergence of autism and ADHD traits. It would be helpful for studies to combine parent reports with objective/experimental measures of sensory detection (e.g., EEG to distinguish responsivity from detection and habituation). This would allow for conclusions to be drawn regarding the limitations of parental reporting.

There have been mixed findings on how sensory responsivity develops over time, with some evidence noting that differences in sensory responsivity lessen with age and others observing that they become more severe with age (Cheung & Siu, 2009; Little et al., 2018). Future research should conduct more replication studies as they are essential to establish the robustness and reliability of findings, particularly in the context of conflicting evidence on the directional relationship between sensory responsivity and infant anxiety. Importance should be given to include multiple constructs within the same analytical model to investigate overlap of construct effectively. Researchers should also consider conducting longitudinal analysis examining outcomes in mid-childhood. This approach allows us to capture developmental changes and provide nuanced understanding of emerging constructs and their relation to outcomes over time.

Lastly, more research is needed to explore to what extend sensory responsivity and anxiety are not also present in other developmental conditions. This would help distinguish whether these constructs are specific risk factors for autism, as opposed to markers found in children with an array of challenges in general.

6.7 Concluding remarks

This thesis focused on exploring the early mechanisms of infant anxiety and sensory responsivity in infants at an elevated likelihood of autism and ADHD. Considering the complex interactions of the construct, the three empirical studies explored the directionality and extent to which infant anxiety and sensory differences interact with each other and their association with later autism and ADHD traits. This study adds a longitudinal perspective to our understanding of sensory responsivity by looking at the developmental trajectories of the infant and their traits. The

findings highlight the importance of tracking early emerging traits during the initial years of life, indicating that traits noted in later toddlerhood may have antecedents early in development.

Appendix A

Supplementary Materials for Chapter 3

Table A3. 1 Sample characterization by phase and outcome groups.

	EL Autism	EL Atypical	EL Typical	TL
Phase 1				
Sex (N girls: N boys)	6:11	9:3	17:7	29:21
Phase 2				
Sex (N girls: N boys)	2:15	12:20	36:28	13:14

Table A3. 2 Whole Sample Correlations between Fear/Shyness, Perceptual Sensitivity, RRB and SCI.

	IBQ Fear 8 months	IBQ Fear 14 months	ECBQ Shyness 24 months	IBQ PS 8 months	IBQ PS 14 months	ECBQ PS 24 months	SRS RRB 36 months	SRS SCI 36 months
IBQ-R Fear 8m	1.000 (235)							
IBQ-R Fear 14m	0.563* (219)	1.000 (227)						
ECBQ Shy 24m	0.300* (202)	0.515* (196)	1.000 (208)					
IBQ-R PS 8m	0.251 (186)	0.144 (178)	0.088 (159)	1.000 (188)				
IBQ-R PS 14m	0.105 (194)	0.179 (195)	0.042 (174)	0.514* (163)	1.000 (200)			
ECBQ PS 24m	0.292* (201)	0.252 (195)	0.306* (203)	0.488* (161)	0.357* (173)	1.000 (208)		
SRS RRB 36m	0.159 (213)	0.219 (208)	0.326* (197)	0.141 (172)	-0.015 (186)	0.254* (197)	1.000 (225)	
SRS SCI 36m	0.181 (213)	0.256*(208)	0.411* (197)	0.018 (172)	-0.112 (186)	0.203 (195)	0.729* (225)	1.000 (225)

() sample size
* Correlation is significant at the p<.01 level

ECBQ = Early Childhood Behavioral Questionnaire; IBQ-R = Infant Behavioral Questionnaire-Revised; PS = Perceptual Sensitivity; RRB = Restrictive and Repetitive Behaviors; SCI = Social Communication Interaction; SRS = Social Responsiveness Scale.

Table A3. 3 Summary of selected path analysis results. Standardised beta coefficient and their p-values

	Standardised beta coefficient, p-values
Fear 8m – Fear 14m	β = 0.52, p < .001
Fear 14m – Shyness 24m	β = 0.47, p < .001
Shyness 24m – SCI 36m	β = 0.23, p = .001
Perceptual Sensitivity 8m - Perceptual Sensitivity 14m	β = 0.52, p < .001
Perceptual Sensitivity 8m - Perceptual Sensitivity 24m	β = 0.39, p < .001
Perceptual Sensitivity 24m – SCI 36m	β = 0.30, p < .001
Perceptual Sensitivity 8m – SCI 36m	β = -0.22, p =.023
Fear 14m – Perceptual Sensitivity 24m	β = 0.16, p = .034

SCI = Social Communication Interaction

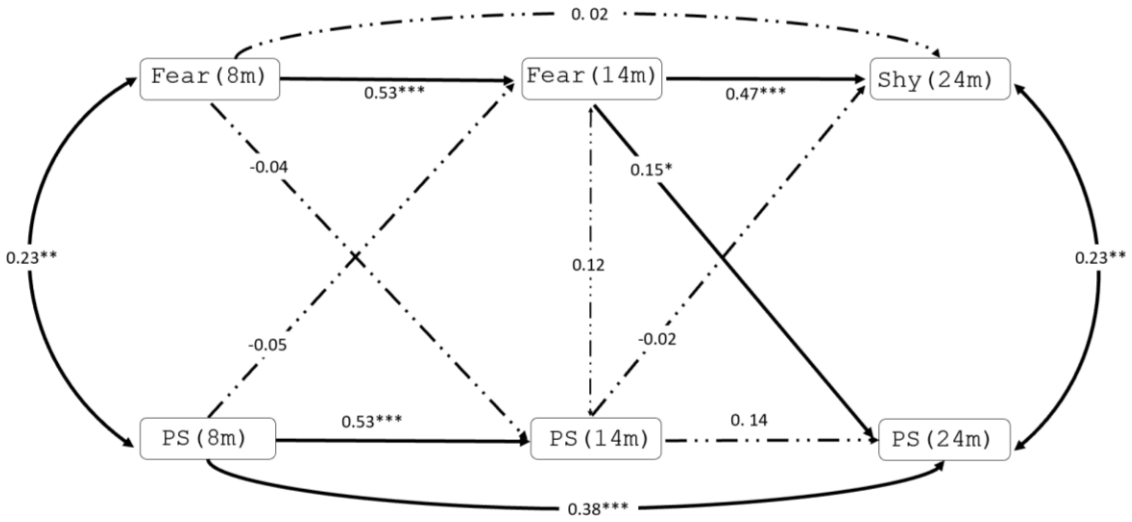

Figure A3. 1 Estimated model for cross lagged path related to Fear/Shyness and Perceptual Sensitivity (PS) in infants without autism outcomes. Bold indicates significant association. (*p < .05, **p < .01, and *** p < .001)

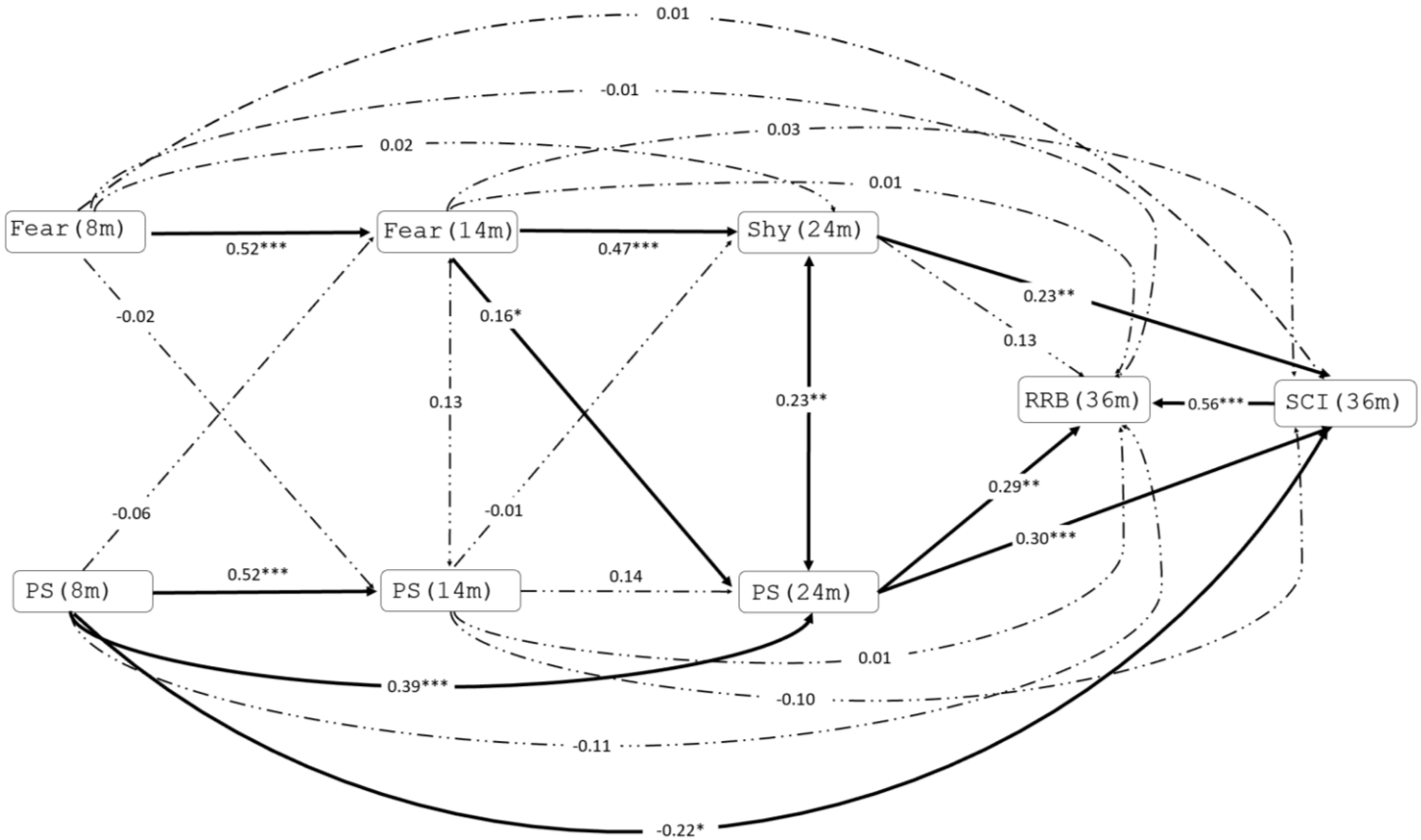

Figure A3. 2 Cross-lagged associations between Fear/Shyness, Perceptual Sensitivity (PS), restricted and repetitive behaviours (RRB) and social communication interaction (SCI) 8, 14, 24 and 36 months in infants without autism outcomes. Bold indicates significant association. (*p < .05, **p < .01, and *** p < .001).

Rational for using IBQ-R at 14 months:

While IBQ-R is validated up to 12 months, many behavioural traits assessed by IBQ-R often continue across infancy. It is important to note that the IBQ-R and ECBQ were explicitly designed to tap comparable constructs across development (e.g., the ECBQ was specifically developed as an 'upwards extension' of the IBQ; (Putnam et al., 2006). In order to accurately capture age-appropriate behavioural manifestations of common underlying constructs over time, slightly different questions are required to match the child's developmental level but tap the same underlying domain. This is evident in our cross lagged models, particularly with the IBQ-R fear subscale demonstrating stability of traits from 8-10 months to 14 months and from 14 months to 24 months. Secondly, the decision to use the IBQ for slightly older infants was also made due to practical considerations, where consistency in measurement tools is desired especially in longitudinal studies and due to limited availability of alternative validated measures for assessing sensory differences in older infants (e.g., ECBQ is only validated for 18 months upwards). Although there is limited work in this area of infant siblings, studies on partially overlapping samples (e.g. Ersoy et al., 2021; Shephard et al., 2019) and studies on general population (Braithwaite, Sharp, Pickles, Hill, & Wright, 2021; Gensthaler et al., 2013), also have used IBQ-R in similar age range. Therefore, using already established measures ensures that not only is it consistent with our longitudinal study it makes it more comparable to previous infant temperament literature.

Understanding IBQ-R subscale of perceptual sensitivity:

Perceptual sensitivity in IBQ-R assesses infants' responsivity to sensory stimuli from the environment such as sound, lights, texture or movement. It focuses on infants noticing these behaviours and their ability to detect slight, low intensity stimuli from external environment (Putnam et al., 2006). Therefore, it refers to the trait that distinguishes small changes in the immediate environment.

Directionality in SEM:

Directionality in SEM requires two or more time points. It involves indicating the direction of influence and not causality between variables, as it helps understand the direction of relationship between the variables within the models (Acock, 2013). However, we include participants who only contributed data at one time point to improve precision of measurement of means, and using maximum likelihood means their likely score, and the uncertainty with which it was estimated, are included within broader analyses (Huberty et al., 2021). This study had only 0.81% of participants with one timepoint. Given this relatively small proportion, it does not significantly influence the study's conclusion.

Appendix B

Supplementary Materials for Chapter 4

Table B4. 1 Pearson correlation coefficients between key variables

	IBQ Fear 10m (1)	IBQ Fear 14m (2)	ECBQ Fear 24m (3)	ITSP Hypo 10m (4)	ITSP Hypo 14m (5)	ITSP Hypo 24m (6)	ITSP Hyper 10m (7)	ITSP Hyper 14m (8)	ITSP Hyper 24m (9)	SRS RRB 36m (10)	SRS SCI 36m (11)
1	-										
2	0.70*	-									
3	0.33*	0.45*	-								
4	-0.30*	-0.14	-0.30*	-							
5	-0.16	-0.17	-0.33*	0.77*	-						
6	-0.14	-0.11	-0.43*	0.50*	0.65*	-					
7	-0.43*	-0.26*	-0.46*	0.68*	0.60*	0.45*	-				
8	-0.40*	-0.39*	-0.54*	0.65*	0.72*	0.59*	0.81*	-			
9	-0.24	-0.22	-0.62*	0.56*	0.58*	0.72*	0.59*	0.70*	-		
10	0.18	0.24	0.46*	-0.34*	-0.57*	-0.59*	-0.41*	-0.62*	-0.57*	-	
11	0.16	0.22	0.47*	-0.47*	-0.70*	-0.71*	-0.47*	-0.66*	-0.64*	0.88*	-

* p<.01. ECBQ = Early Childhood Behavioural Questionnaire; IBQ-R = Infant Behavioural Questionnaire-Revised; ITSP = Infant Toddler Sensory Profile; RRB = Restrictive and Repetitive Behaviours; SCI = Social Communication Interaction; SRS = Social Responsiveness Scale. Raw scoring was used where a lower score indicated a greater severity for ITSP.

Table B4. 2 Pearson correlation between sensory sensitivity and sensation avoiding

	Sensory Sensitivity 10m (1)	Sensation Avoiding 10m (2)	Sensory Sensitivity 14m (3)	Sensation Avoiding 14m (4)	Sensory Sensitivity 24m (5)	Sensation Avoiding 24m (6)
1	-					
2	0.83*	-				
3	0.80*	0.73*	-			
4	0.70*	0.77*	0.81*	-		
5	0.65*	0.54*	0.69*	0.60*	-	
6	0.50*	0.47*	0.59*	0.67*	0.81*	-

* $p < .001$ Raw scoring was used where a lower score indicated a greater severity for ITSP.

Table B4.3. Matching of IBQ-R and EBCQ items on fear domain.

IBQ-R	ECBQ Fear	ECBQ Shyness
Startle at a sudden change in body position (e.g., when moved suddenly)? (Q22)	While at home, how often did your child show fear at a loud sound (blender, vacuum cleaner, etc.)? (Q25)	
When introduced to an unfamiliar adult, how often did the baby cling to a parent? (Q76)		When approached by an unfamiliar person in a public place (for example, the grocery store), how often did your child cling to a parent? (Q3)
When introduced to an unfamiliar adult, how often did the baby refuse to go to the unfamiliar person? (Q77)		When approached by an unfamiliar person in a public place (for example, the grocery store), how often did your child pull back and avoid the person? (Q2)
When introduced to an unfamiliar adult, how often did the baby never "warm up" to the unfamiliar adult? (Q78)		When approaching unfamiliar children playing, how often did your child seem uncomfortable? (Q32)
When in the presence of several unfamiliar adults, how often did the baby continue to be upset for 10 minutes or longer? (Q87)	No match, item not included	No match, item not included
When an unfamiliar person came to your home or apartment, how often did your baby cry when the		In situations where s/he is meeting new people, how often did your child turn away? (Q50)

visitor attempted to pick her/him up? (Q89)		
	During everyday activities, how often did your child seem frightened for no apparent reason? (Q38)	No match, item not included
	While at home, how often did your child seem afraid of the dark? (Q26)	No match, item not included
	While in a public place, how often did your child seem uneasy about approaching an elevator or escalator? (Q57)	No match, item not included
	While in a public place, how often did your child cry or show distress when approached by an unfamiliar animal? (Q58)	No match, item not included
	While in a public place, how often did your child seem afraid of large, noisy vehicles? (Q59)	No match, item not included
	While in a public place, how often did your child show fear when the caregiver stepped out of sight? (Q60)	No match, item not included
	When visiting a new place, how often did your child not want to enter? (Q99)	No match, item not included
	No match, item not included	When approaching unfamiliar children playing, how often did your child watch rather than join in? (Q31)

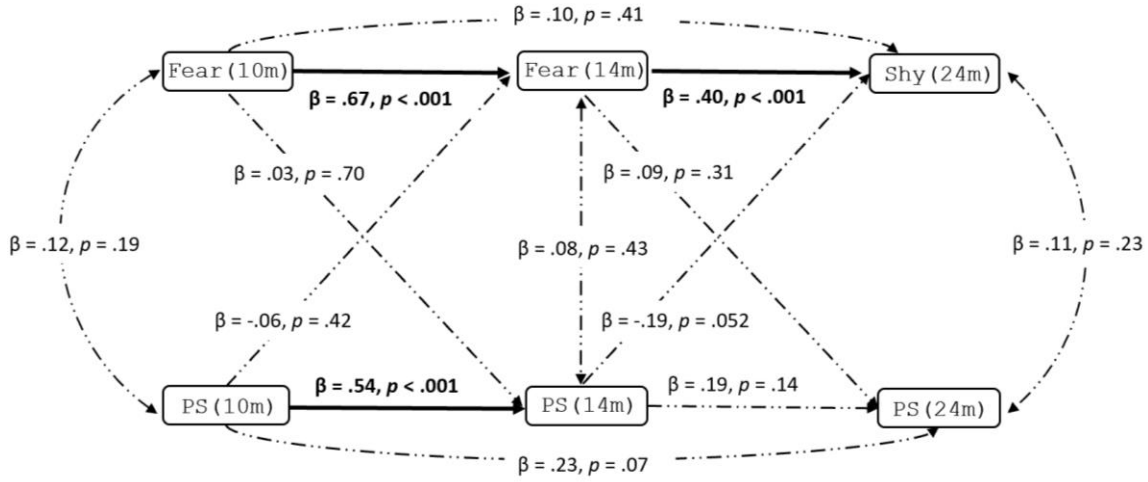

Figure B4. 1 Cross-lagged replication model related to Fear/Shyness and Perceptual Sensitivity (PS) at 10, 14 and 24 months in infants from the whole sample. Bold indicates significant association.

Note: Perceptual Sensitivity was measured using the 6-item perceptual sensitivity subscale of the Infant Behaviour Questionnaire – Revised short form (IBQ-R; Gartstein & Rothbart, 2003) at 10 and 14 months and Early Childhood Behavioural Questionnaire – short form (ECBQ; Putnam et al., 2006) at 24 months.

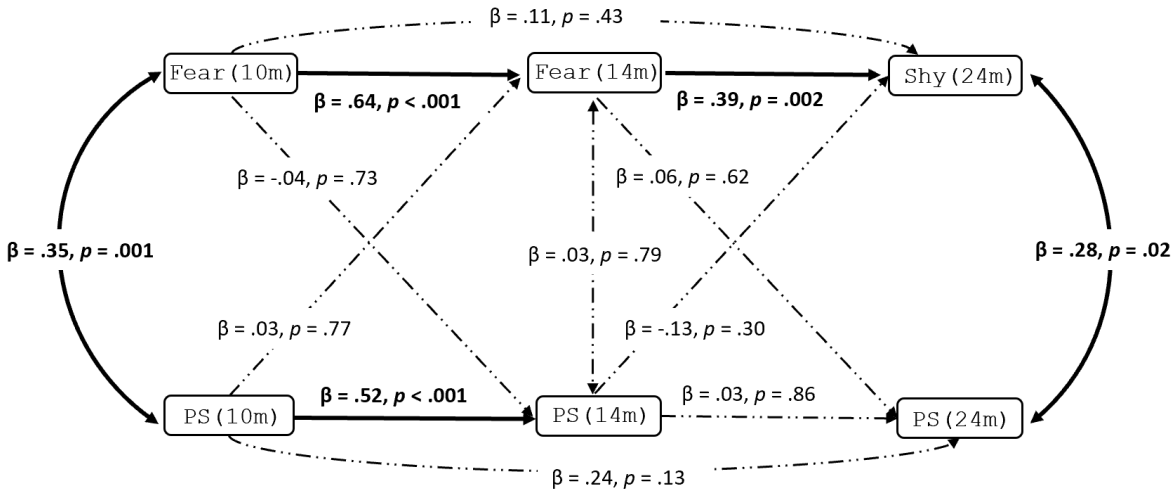

Figure B4. 2 Cross-lagged replication model excluding infants with family history of ADHD (EL-ADHD) at 10, 14 and 24 months. Bold indicates significant at p < .05.

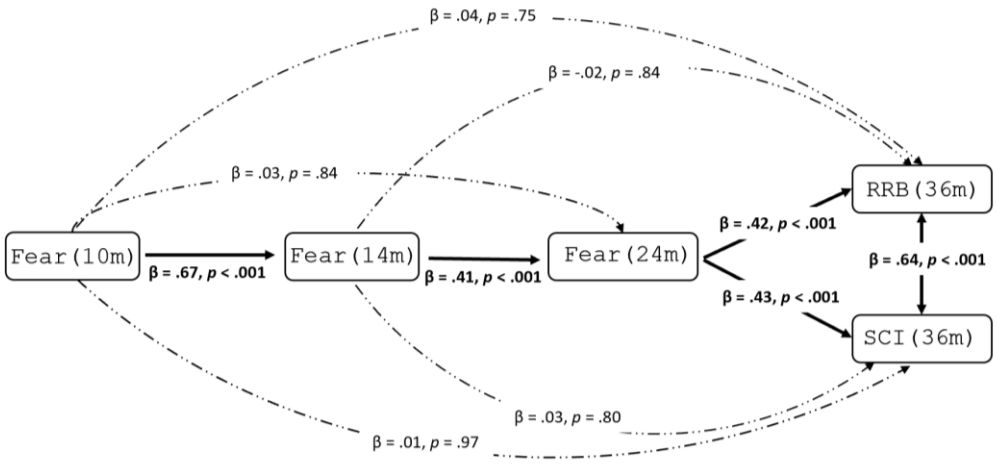

Figure B4. 3 Path analysis between Fear at 10,14,24 months and Restricted and Repetitive Behaviours (RRB) and Social Communication Interaction (SCI) at 36 months in infants from the whole sample. Bold indicates significant at p < .05.

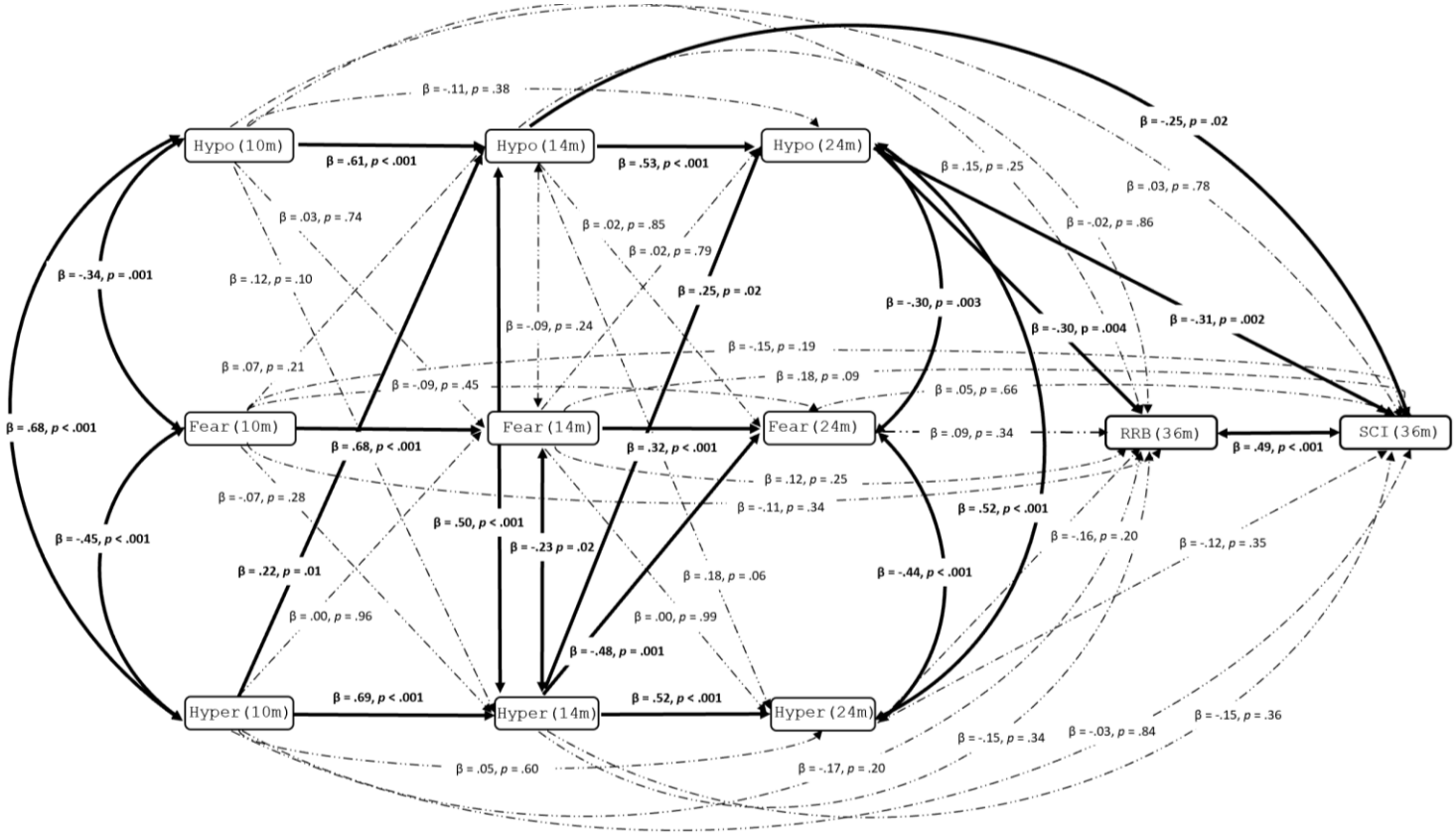

Figure B4. 4 Cross-lagged associations between Fear, Hyperreactivity, Hyporeactivity, Restricted and Repetitive Behaviours (RRB) and Social Communication Interactions (SCI) at 10 – 36 months of age using amended scoring of ITSP Hyporeactivity subscale. Bold indicates significant at $p < .05$.

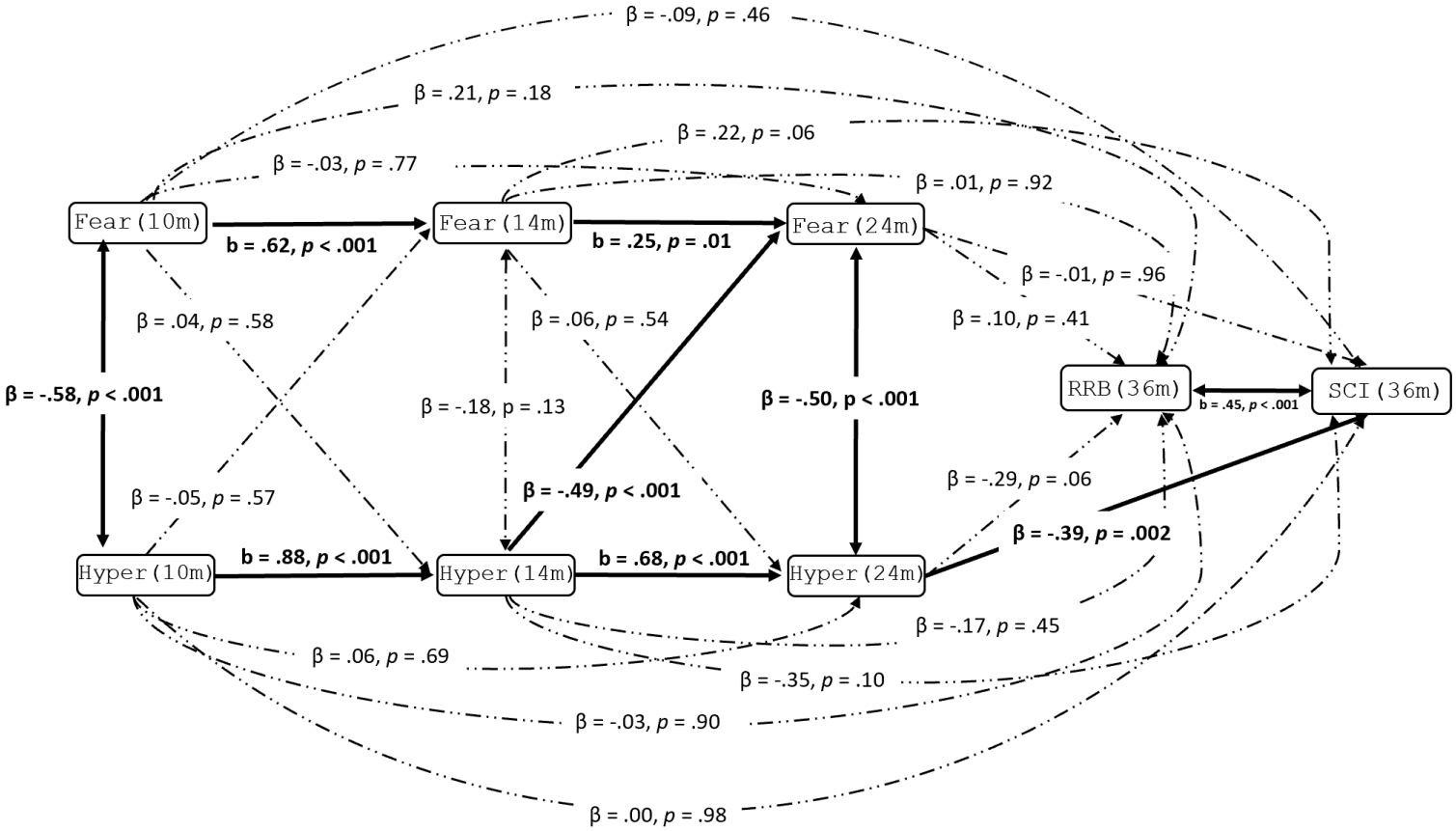

Figure B4. 5 Cross-lagged association between Fear, Hyperreactivity, Restricted and Repetitive Behaviours (RRB) and Social Communication Interactions (SCI) at 10 -36 months of age in sample excluding infants with family history of ADHD. Bold indicates significant at p < .05.

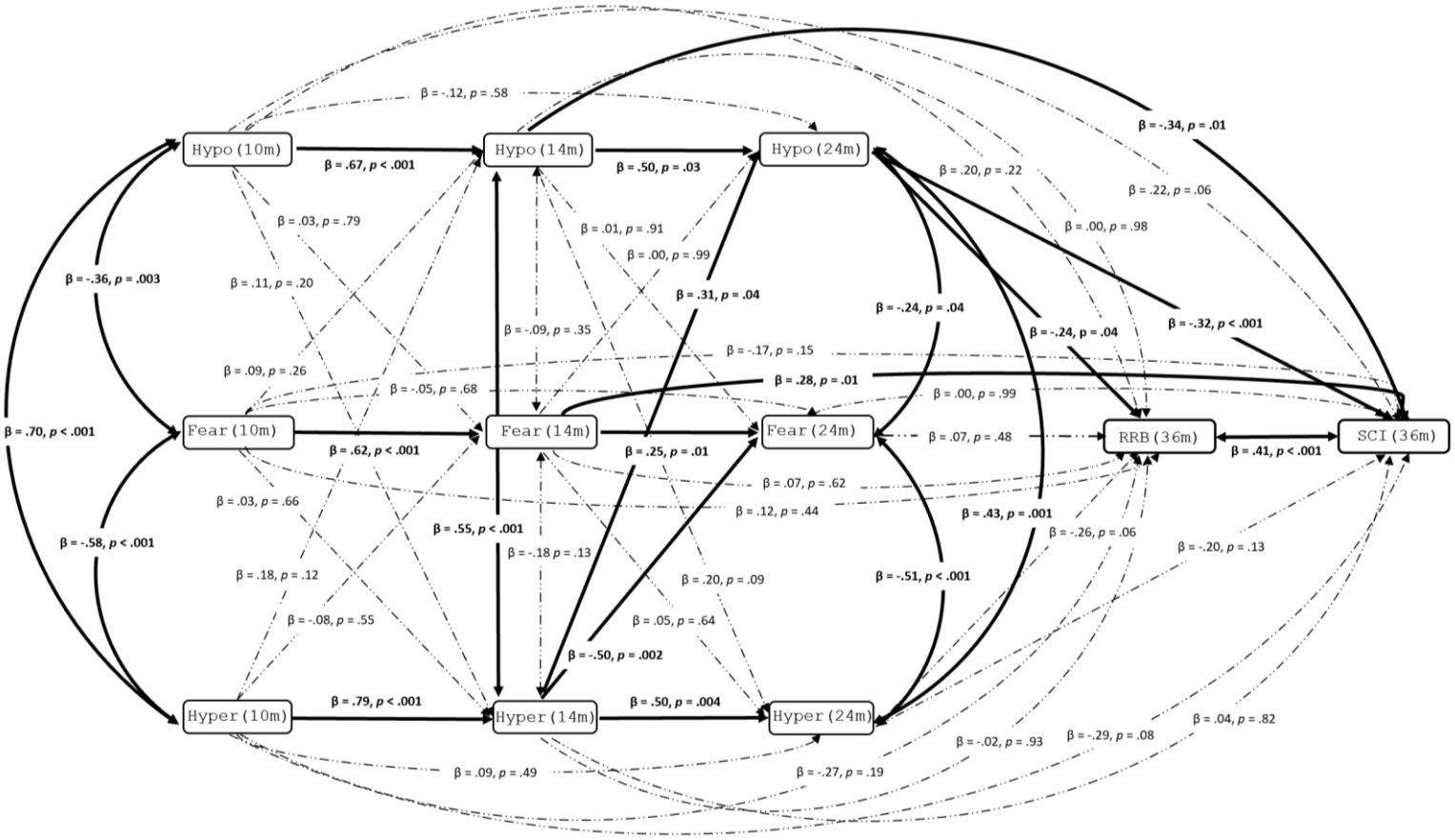

Figure B4. 6 Cross-lagged association between Fear, Hyperreactivity, Hyporeactivity, Restricted and Repetitive Behaviours (RRB) and Social Communication Interactions (SCI) at 10 -36 months of age in sample excluding infants with family history of ADHD. Bold indicates significant at p < .05.

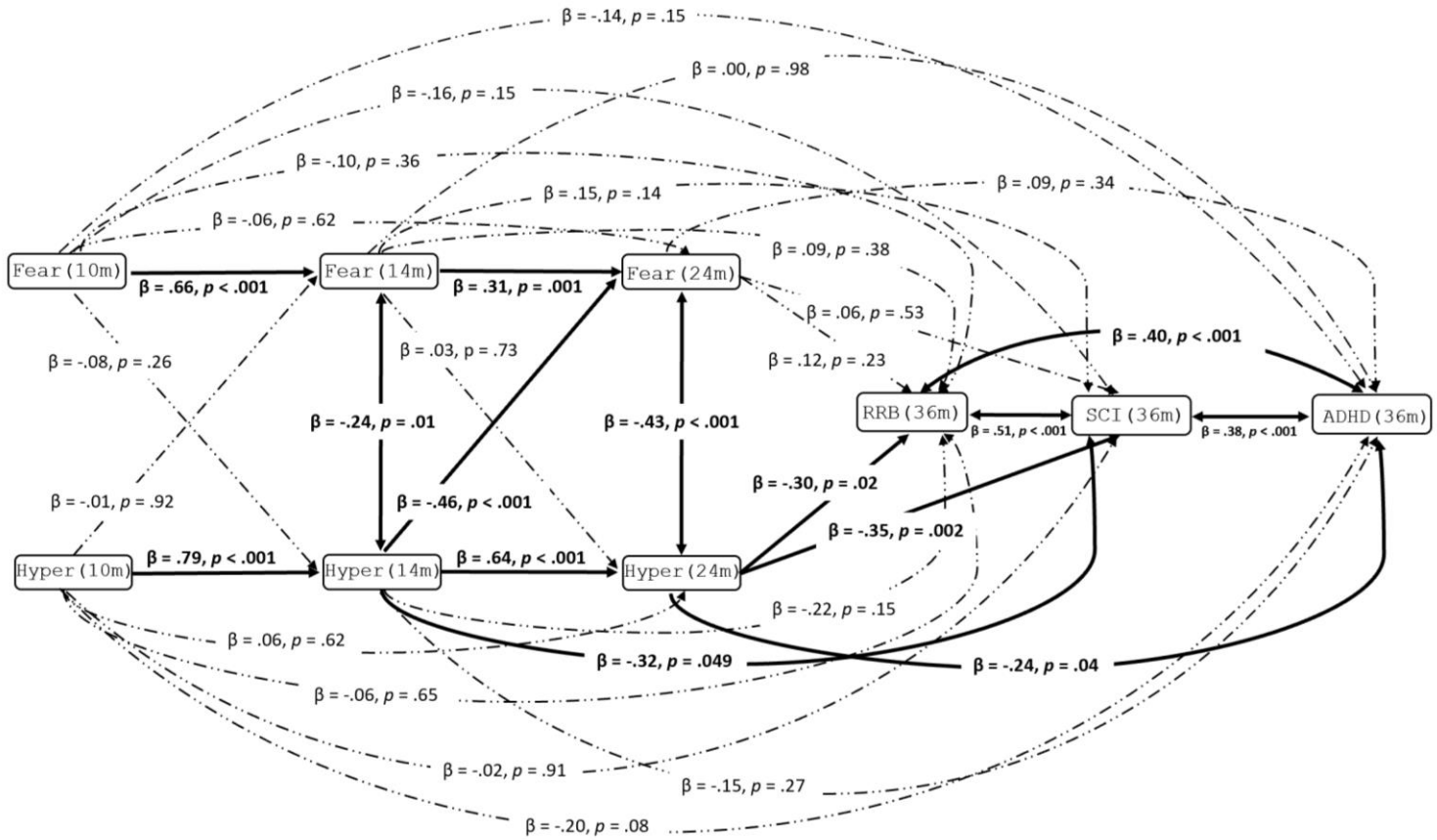

Figure B4. 7 Cross-lagged association between Fear, Hyperreactivity, Restricted and Repetitive Behaviours (RRB), Social Communication Interactions (SCI) and ADHD traits at 10 -36 months of age in infants from the whole sample. Bold indicates significant at $p < .05$.

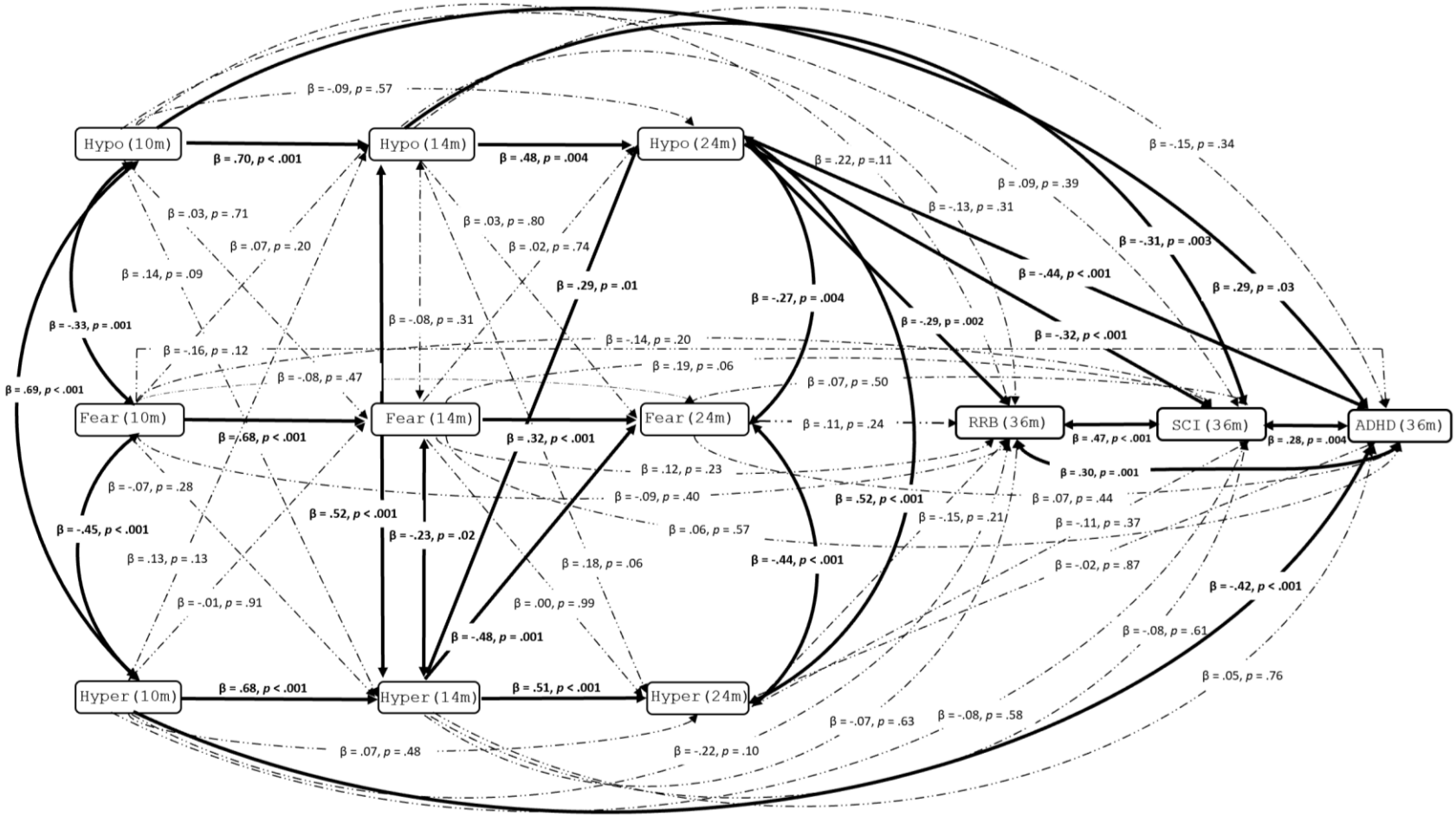

Figure B4. 8 Cross-lagged association between Fear, Hyperreactivity, Hyporeactivity, Restricted and Repetitive Behaviours (RRB), Social Communication Interactions (SCI) and ADHD traits at 10 -36 months of age in infants from the whole sample. Bold indicates significant at $p < .05$.

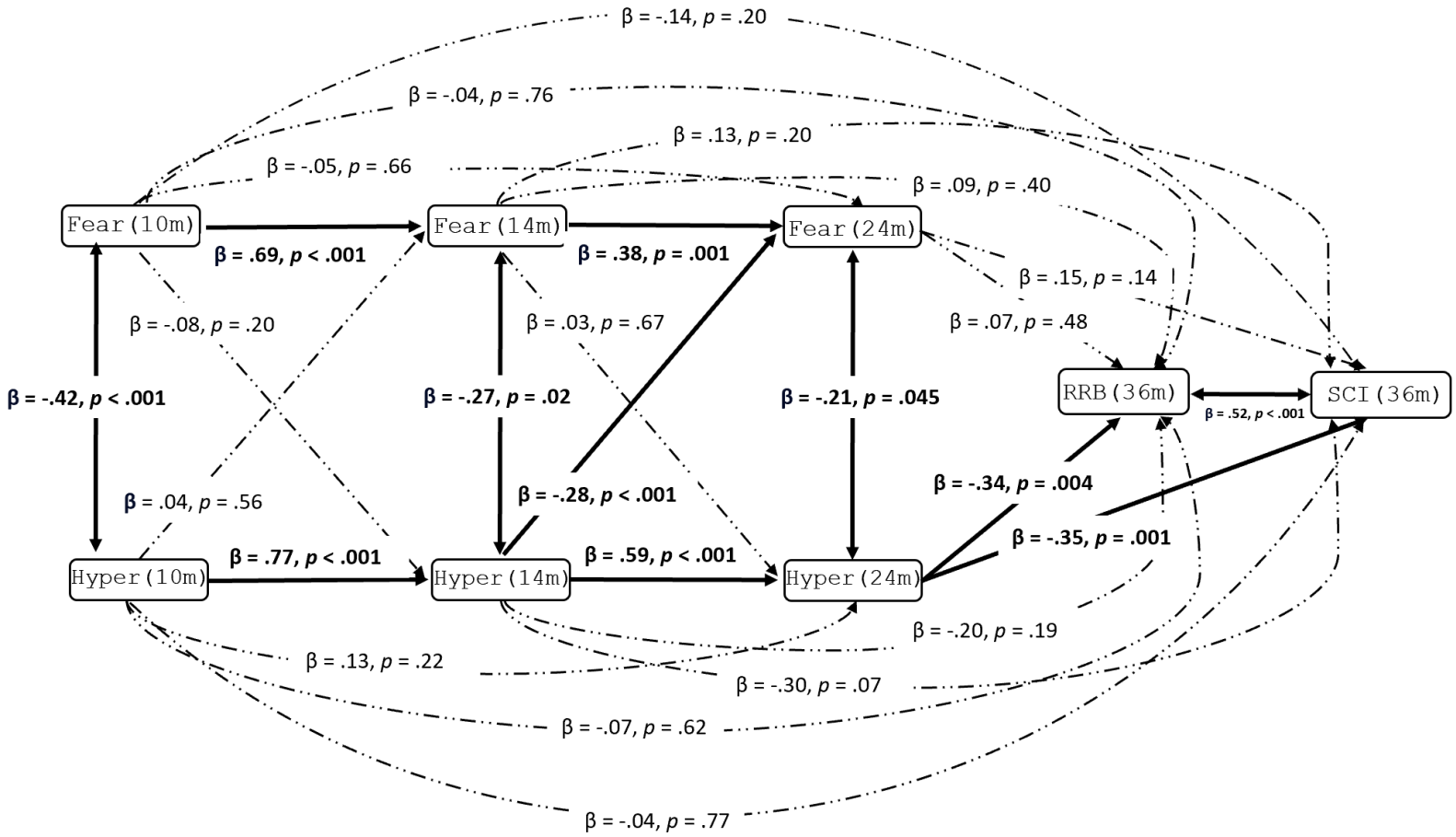

Figure B4.9 Cross-lagged associations between Fear, Hyperreactivity, Restricted and Repetitive Behaviours (RRB) and Social Communication Interactions (SCI) using subset of matched IBQ/ECBQ items. Bold indicates significant at p < .05.

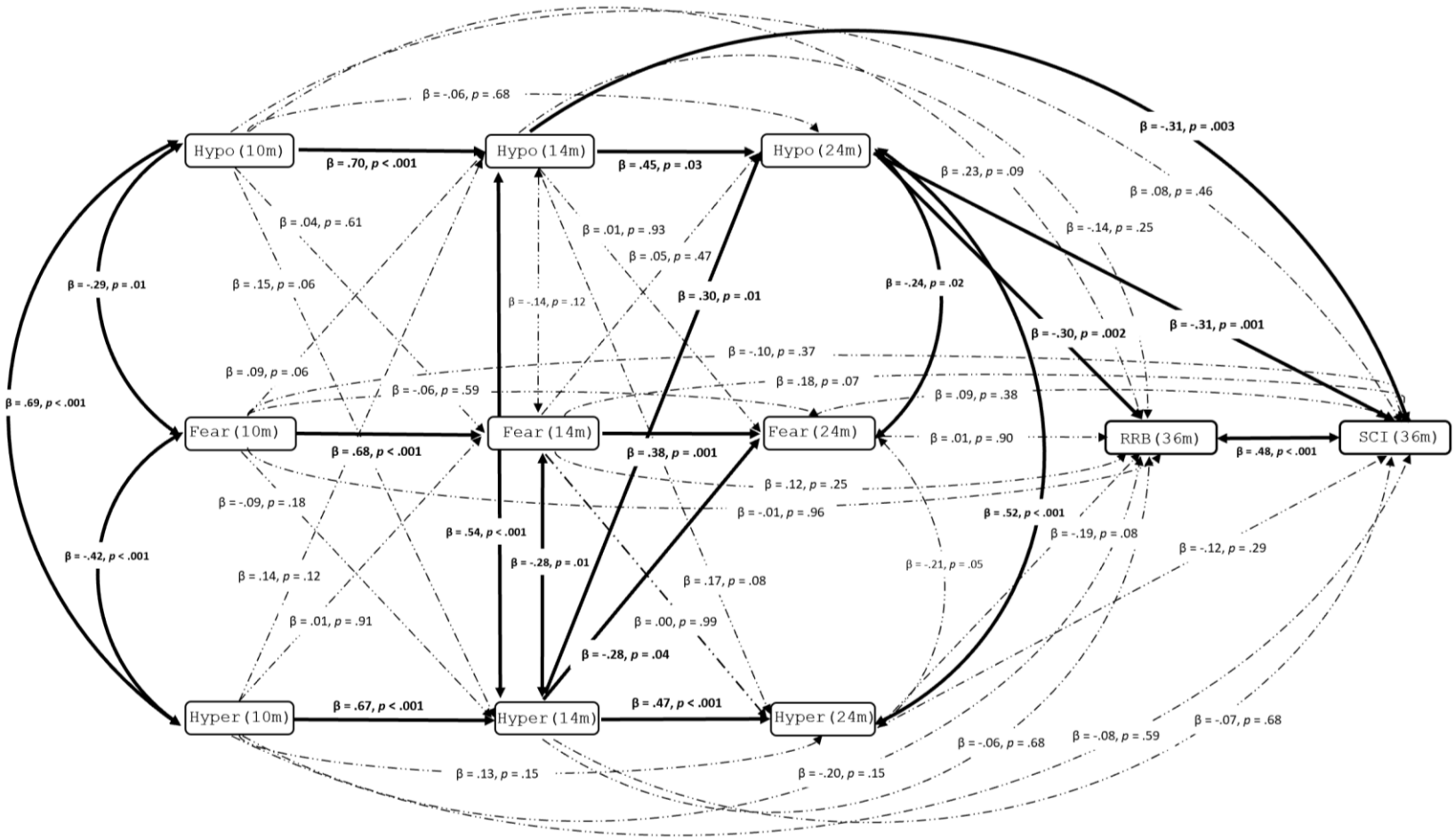

Figure B4.10 Cross-lagged associations between Fear, Hyperreactivity, Hyporeactivity, Restricted and Repetitive Behaviours (RRB) and Social Communication Interactions (SCI) using subset of matched IBQ/ECBQ items. Bold indicates significant at p < .05.

Studies on anxiety and sensory in autistic cohorts:

Several studies conducted on autistic youth and adults highlight the different mechanisms in the association between anxiety and sensory domains. Hyperresponsivity predicted traditional anxiety, similar to anxiety in typically developing youth, and traditional anxiety, along with autism traits predicted atypical anxiety (Kerns et al., 2014). Additionally, hyperresponsivity is associated with phobia-related symptoms, while sensory hyporesponsivity correlates with social anxiety, with no association found between sensory seeking and anxiety (MacLennan et al., 2020). Verhulst et al. (2022) emphasise the significance of identifying sensory domains that act as causes and effects of anxiety in autistic adults. Their research suggests that while sensory hyperreactivity has been identified as a cause of anxiety in autistic individuals, anxiety may also influence sensory seeking behaviour. These findings collectively underscore the importance of considering sensory domains and differences when developing targeted research studies and supports for specific anxiety and sensory related conditions.

Rational for now including sensory seeking:

The decision not to include sensation seeking in the initial chapters of the thesis was mainly because we were particularly interested in anxiety, which has been more strongly linked to hyperresponsivity, and thus this was the primary focus in Chapters 3 and 4, as also seen in previous work done in the field (Grzadzinski et al., 2020; Vlaeminck et al., 2020). In earlier Phases 1 and 2, we did not have the ITSP but only the IBQ, so the Perceptual Sensitivity subscale was the only sensory trait measure available to us. Hence, Chapter 4 (Phase 3) aimed to further expand and investigate these associations found in Chapter 3 using ITSP, a more specific measure of

sensory responsivity. In order to check for specificity of the associations, hyposensitivity was included in the models, as hypo- and hyperresponsivity are the most commonly studied domains of sensory responsivity (Chen et al., 2022; Wolff et al., 2019). Including sensation seeking at this point would complicate the model with too many constructs and lead to model convergence issues. While sensation seeking is relevant to sensory responsivity, it is a distinct construct that warrants separate investigation beyond the current objectives of Chapter 4. Finally, considering neurodevelopment traits more broadly as the outcome of interest and not focusing on anxiety, it seemed relevant to include in sensory seeking for examination in Chapter 5.

Exclusion of ADHD only model:

The decision to not run model with ADHD only group was mainly due to the small sample size of the cohorts, especially since it would pose challenges in running SEM for our analysis, which requires substantial sample sizes (Bijleveld et al., 1998; Kline, 2016). Models with fear and hyporesponsivity only along with 36 month autism traits were initially run (see Figure B4.11. added in the appendix) but not included in Chapter 5 (as Chapter 5 is now a published paper). The results were similar to that we see in the combined models. Hence, priority was given to other analysis such as replicating results, excluding EL-ADHD cohort, and including ADHD traits at 36 months.

Given the high level of covariance between constructs, interpreting nonsignificant associations requires careful considerations. Additionally, sensitivity analyses were performed to further confirm the nuances of the associations in such complex SEM models.

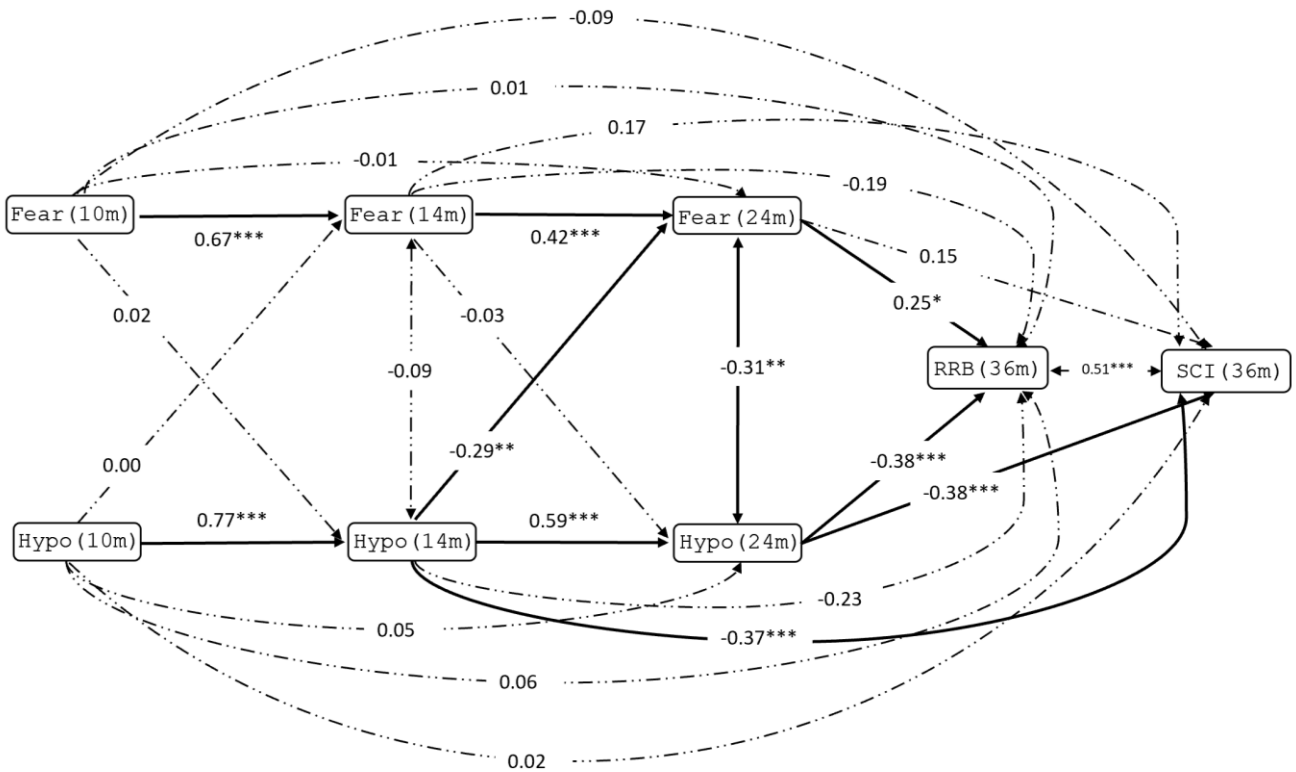

Figure B4.11 Cross lagged association between fear, hypo responsivity restricted and repetitive behaviours (RRB) and social communication interaction (SCI) at 10 to 36 months of age. Bold indicates significant associations (*p < .05, **p < .01, and *** p < .001).

Questionnaires:

In Chapter 4 we use ITSP to focus on the domains of hyper- and hyporesponsivity. In the previous Chapter 3 we focused on the perceptual sensitivity which is a subscale of IBQ-R, which is a measure of temperament in infancy. When compared at the item levels, perceptual sensitivity from IBQ-R/ECBQ and hyperresponsivity from ITSP allows us to capture behavioural responsivity to sensory input from the environment as opposed to affective reactivity that only measured observable reactivity in response to sensory input (The Infant Toddler Social and Emotional Assessment; ITSEA used in Green's et.al., study), where children who are more sensitivity but do not become obviously upset maybe missed. So, the two aspects of sensory differences are related but distinct constructs. However, we saw different results, where in Chapter 3 fear at 14 months associated with perceptual sensitivity at 24 months whereas in Chapter 4 hyper-responsivity at 14 months associated with fear at 24 months. This later finding has more supporting evidence in other studies such as Green et al. (2012), where they measured affective reactivity in autistic children aged 28 months. This lack of replication could be due to change in cohort from pure EL autism to EL autism and ADHD cohort, change in measurement from 14 months to 24 months and IBQ-R being a temperamental measure instead of a sensory responsivity measure. Lastly, it is not very well known whether the scores on IBQ are influenced by other autistic traits.

Addition to discussion:

Similar results of SOR/hyper-responsivity preceding anxiety are found in other studies ranging from preschool children to autistic adults (MacLennan et al., 2022; MacLennan et al., 2021; Verhulst et al., 2022) providing strong evidence of hyperresponsivity contributing to later anxiety in autistic population across ages.

Appendix C

Supplementary Materials for Chapter 5

Table C5. 1 Sample Characteristics

Mean (*SD*)	N	EL-autism N=80	EL-ADHD N=31	EL-autism+ADHD N=21	TL N=29	Group differences	Direction of Effect
10 months							
Sex (n female:male)	149	38:38	12:14	8:12	11:16	p = .783	-
Age in months	149	10.03 *(0.52)*	10.23 *(0.91)*	10.15 *(0.49)*	10.00 *(0.62)*	p = .422	-
MSEL ELC	149	88.03 *(15.09)*	85.04 *(15.61)*	84.90 *(16.55)*	88.89 *(12.19)*	p = .660	-
14 months							
Sex (n female: male)	138	35:38	7:16	7:12	10:13	p = .474	-
Age in months	138	14.30 *(0.64)*	14.22 *(0.80)*	14.37 *(0.60)*	14.26 *(0.62)*	p = .893	-
MSEL ELC	139	78.25 *(11.92)*	79.08 *(11.12)*	72.53 *(14.50)*	78.78 *(11.99)*	p = .259	-
24 months							
Sex (n female:male)	128	33:33	9:13	5:11	11:13	p = .565	-
Age in months	128	24.92 *(1.55)*	24.68 *(1.09)*	24.38 *(0.72)*	24.58 *(1.14)*	p = .420	-
MSEL ELC	125	100.63 *(20.76)*	106.86 *(21.21)*	96.94 *(17.12)*	114.25 *(17.91)*	p = .017	EL-autism, EL-autism+ADHD <TL
ADOS CSS SA	127	3.32 *(1.95)*	2.95 *(2.01)*	4.13 *(2.19)*	2.29 *(1.00)*	p = .019	TL< EL-autism, EL-autism+ADHD

ADOS CSS RRB	127	3.53 *(2.54)*	4.05 *(2.48)*	2.88 *(2.36)*	2.79 *(2.19)*	p = .279	-
36 months							
Sex (n female:male)	119	33:28	11:12	5:11	7:12	p = .306	-
Age in months	119	37.21 *(1.46)*	37.35 *(2.69)*	37.19 *(1.52)*	36.79 *(1.78)*	p = .779	-
MSEL ELC	117	108.10 *(18.53)*	118.39 *(18.83)*	105.93 *(19.90)*	129.05 *(11.75)*	p < .001	EL-autism, EL-autism+ADHD < TL; EL-autism, EL-autism+ADHD < EL-ADHD
ADOS CSS SA	123	2.62 *(1.90)*	2.27 *(1.58)*	2.93 *(1.44)*	3.15 *(1.98)*	p = .425	-
ADOS CSS RRB	123	3.53 *(2.46)*	3.00 *(2.58)*	4.00 *(2.67)*	3.30 *(2.41)*	p = .666	-
ADI-R Social	122	3.89 *(5.33)*	2.55 *(4.04)*	5.69 *(8.15)*	0.94 *(1.00)*	p = .046	TL<EL-autism+ADHD
ADI-R Communication	122	3.53 *(4.65)*	1.55 *(2.69)*	3.38 *(4.10)*	0.67 *(0.97)*	p = .021	TL<EL-autism, EL-autism+ADHD; EL-ADHD<EL-autism
ADI-R RRB	122	1.42 *(2.03)*	0.73 *(1.49)*	1.69 *(2.12)*	0.39 *(0.61)*	p = .070	-

ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; MSEL ELC= Mullen Scales of Early Learning Early Learning; SA = Social Affect; SD = Standard Deviation. Note: Group differences were tested using one-way ANOVAs with group as a between-subject factor, followed by uncorrected post-hoc pairwise comparisons of means. Raw scoring was used where a lower score indicates a greater severity for ITSP.

Table C5. 2 Pearson correlation coefficients between key variables

	Hypo 10m (1)	Hypo 14m (2)	Hypo 24m (3)	Hyper 10m (4)	Hyper 14m (5)	Hyper 24m (6)	Sensation seeking 10m (7)	Sensation seeking 14m (8)	Sensation seeking 24m (9)	SRS 36m (10)	CBCL ADHD 36m (11)
1	1										
2	0.73*	1.00									
3	0.45*	0.64*	1.45*								
4	0.67*	0.61*	0.59*	1.00							
5	0.62*	0.72*	0.72*	0.81*	1.00						
6	0.54*	0.59*	0.07	0.59*	0.70*	1.00					
7	0.09	0.08	0.23	0.08	-0.05	0.10	1.00				
8	0.15	0.28	0.42*	0.16	0.16	0.17	0.59*	1.00			
9	0.27	0.28	-0.42	0.31	0.20	0.35*	0.55*	0.60*	1.00		
10	-0.41*	-0.67*	-0.70*	-0.47*	-0.66*	-0.64*	0.02	-0.23	-0.39*	1.00	
11	-0.32	-0.57*	-0.70*	-0.46*	-0.57*	-0.57*	-0.15	-0.30	-0.49*	0.73*	1.00

*$p < 0.001$. Raw scoring was used where a lower score indicates a greater severity for ITSP.

Table C5. 3 Model 1 with non standardized coefficients

		b	***p***	**[95% confidence Interval]**		**β**
Hyperresponsivity intercept	Group Autism	1.61	0.382	-2.00	5.22	0.07
	Group ADHD	1.65	0.386	-2.08	5.37	0.07
	Gender	-0.94	0.581	-4.28	2.40	-0.04
Hyperresponsivity slope	Group Autism	0.77	0.232	-0.49	2.04	0.10
	Group ADHD	0.86	0.196	-0.44	2.17	0.11
	Gender	-0.18	0.762	-1.35	0.99	-0.02
Hyporesponsivity intercept	Group Autism	1.60	0.060	-0.07	3.27	0.15
	Group ADHD	0.40	0.651	-1.33	2.12	0.04
	Gender	-1.94	0.014	-3.48	-0.39	-0.19
Hyporesponsivity slope	Group Autism	-0.21	0.618	-1.02	0.61	-0.04
	Group ADHD	0.97	0.023	0.13	1.81	0.18
	Gender	0.15	0.705	-0.61	0.90	0.03
Sensation seeking intercept	Group Autism	-1.92	0.005	-3.24	-0.59	-0.22
	Group ADHD	2.24	0.001	0.87	3.60	0.25
	Gender	0.36	0.559	-0.86	1.59	0.04
Sensation seeking slope	Group Autism	-0.21	0.131	-0.49	0.06	-0.12
	Group ADHD	0.20	0.160	-0.08	0.49	0.11
	Gender	-0.04	0.731	-0.30	0.21	-0.03
Autism traits	Hyperresponsivity intercept	0.02	0.010	0.00	0.03	0.28
	Hyperresponsivity slope	0.02	0.212	-0.01	0.04	0.09
	Hyporesponsivity intercept	0.05	0.000	0.03	0.08	0.41
	Hyporesponsivity slope	0.09	0.000	0.04	0.13	0.33
	Sensation seeking intercept	0.02	0.163	-0.01	0.04	0.11
	Sensation seeking slope	-0.03	0.635	-0.14	0.09	-0.04
	Group Autism	0.28	0.006	0.08	0.49	0.21
	Group ADHD	0.04	0.683	-0.15	0.23	0.03
	Sex	-0.03	0.696	-0.20	0.13	-0.03
ADHD traits	Hyperresponsivity intercept	0.02	0.004	0.01	0.04	0.35

	Hyperresponsivity slope	0.00	0.783	-0.04	0.03	-0.02
	Hyporesponsivity intercept	0.03	0.124	-0.01	0.06	0.18
	Hyporesponsivity slope	0.11	0.000	0.06	0.17	0.38
	Sensation seeking intercept	0.03	0.084	0.00	0.06	0.16
	Sensation seeking slope	0.06	0.381	-0.08	0.21	0.07
	Group Autism	0.23	0.065	-0.01	0.47	0.15
	Group ADHD	0.02	0.879	-0.22	0.25	0.01
	Sex	-0.18	0.082	-0.39	0.02	-0.12
Covariance Hyperresponsivity intercept-Hyperresponsivity slope		-4.75	0.028	-8.99	-0.51	-0.12
Covariance Hyperresponsivity intercept-Hyporesponsivity intercept		37.72	0.000	27.89	47.56	0.71
Covariance Hyperresponsivity intercept-Sensation seeking intercept		5.13	0.077	-0.56	10.81	0.12
Covariance Hyperresponsivity slope-Hyporesponsivity slope		4.58	0.000	3.03	6.13	0.51
Covariance Hyperresponsivity slope-Sensation seeking slope		-0.04	0.853	-0.44	0.36	-0.01
Covariance Hyporesponsivity intercept-Hyporesponsivity slope		-3.06	0.000	-4.31	-1.80	-0.26
Covariance Hyporesponsivity intercept-Sensation seeking intercept		4.03	0.001	1.55	6.52	0.21
Covariance Hyporesponsivity slope-Sensation seeking slope		0.31	0.015	0.06	0.56	0.16
Covariance Senseeking intercept-Sensation seeking slope		1.68	0.000	1.13	2.24	0.53
Covariance Autism traits-ADHD traits		0.07	0.002	0.03	0.12	0.31
Covariance Group Autism-Group ADHD		-0.07	0.000	-0.11	-0.04	-0.32
Covariance Group Autism-Sex		0.02	0.312	-0.02	0.06	0.08
Covariance Group ADHD-Sex		-0.01	0.585	-0.05	0.03	-0.04

Reverse scoring was used where a higher score indicated a greater severity for ITSP.

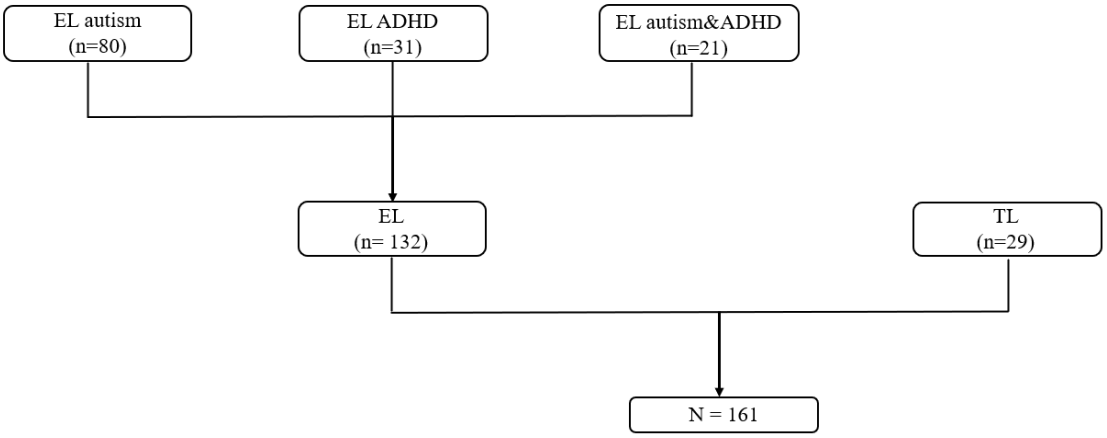

Figure C5. 1 Flow chart of participants in each group.

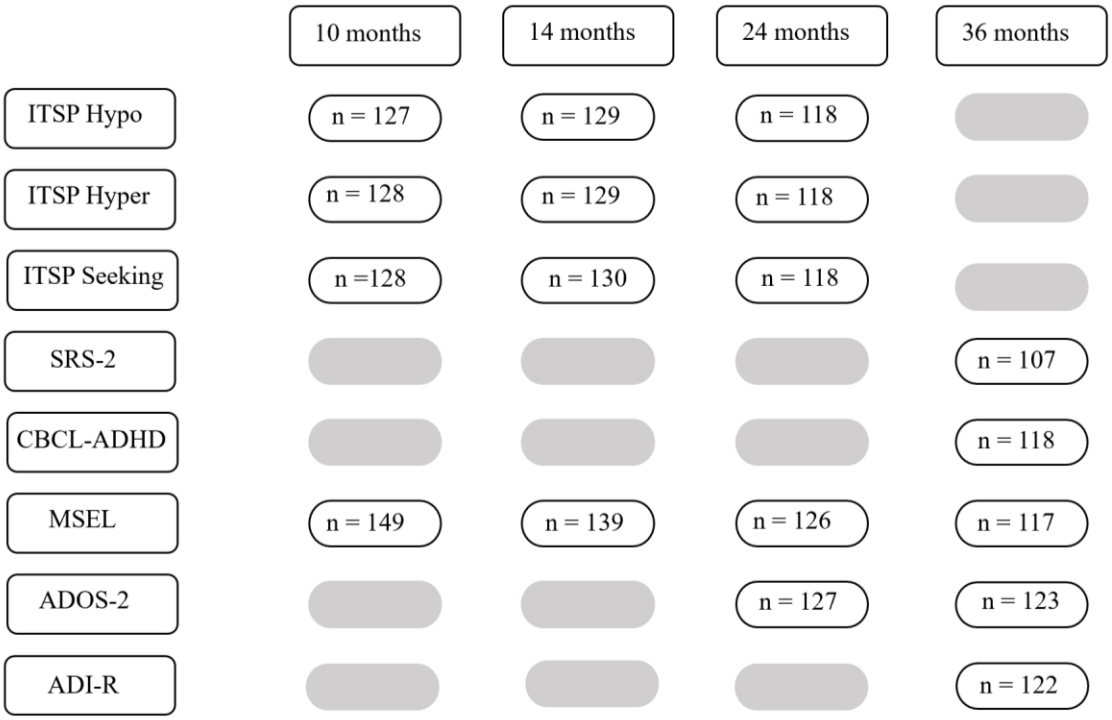

Figure C5. 2 Diagram of number of participants for each measure at each time point. ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; CBCL = Child Behaviour Checklist; CSS = Composite Standard Score; ITSP= Infant Toddler Sensory Profile; MSEL ELC= Mullen Scales of Early Learning Early Learning; SRS = Social Responsiveness Scale.

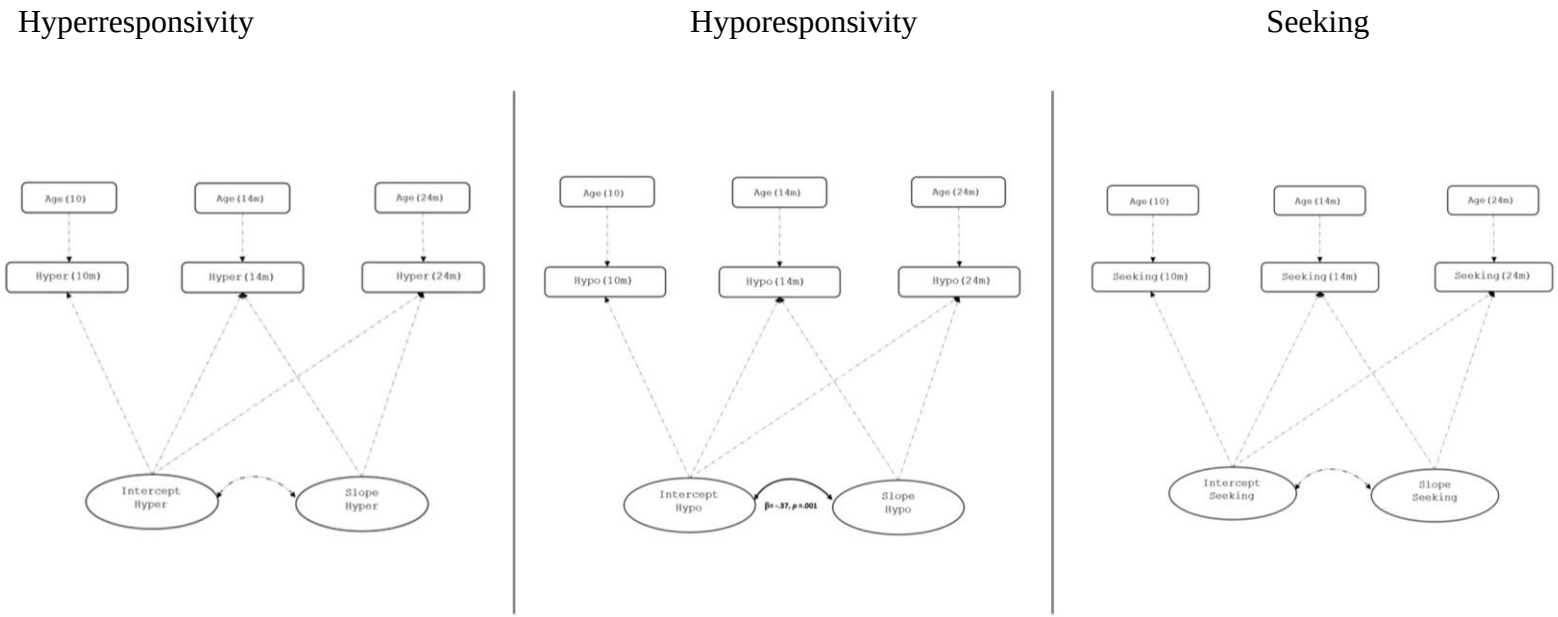

Figure C5. 3 Univariate linear LGCMs for each of the three sensory domains. Reverse scoring was used where a higher score indicated a greater severity for ITSP.

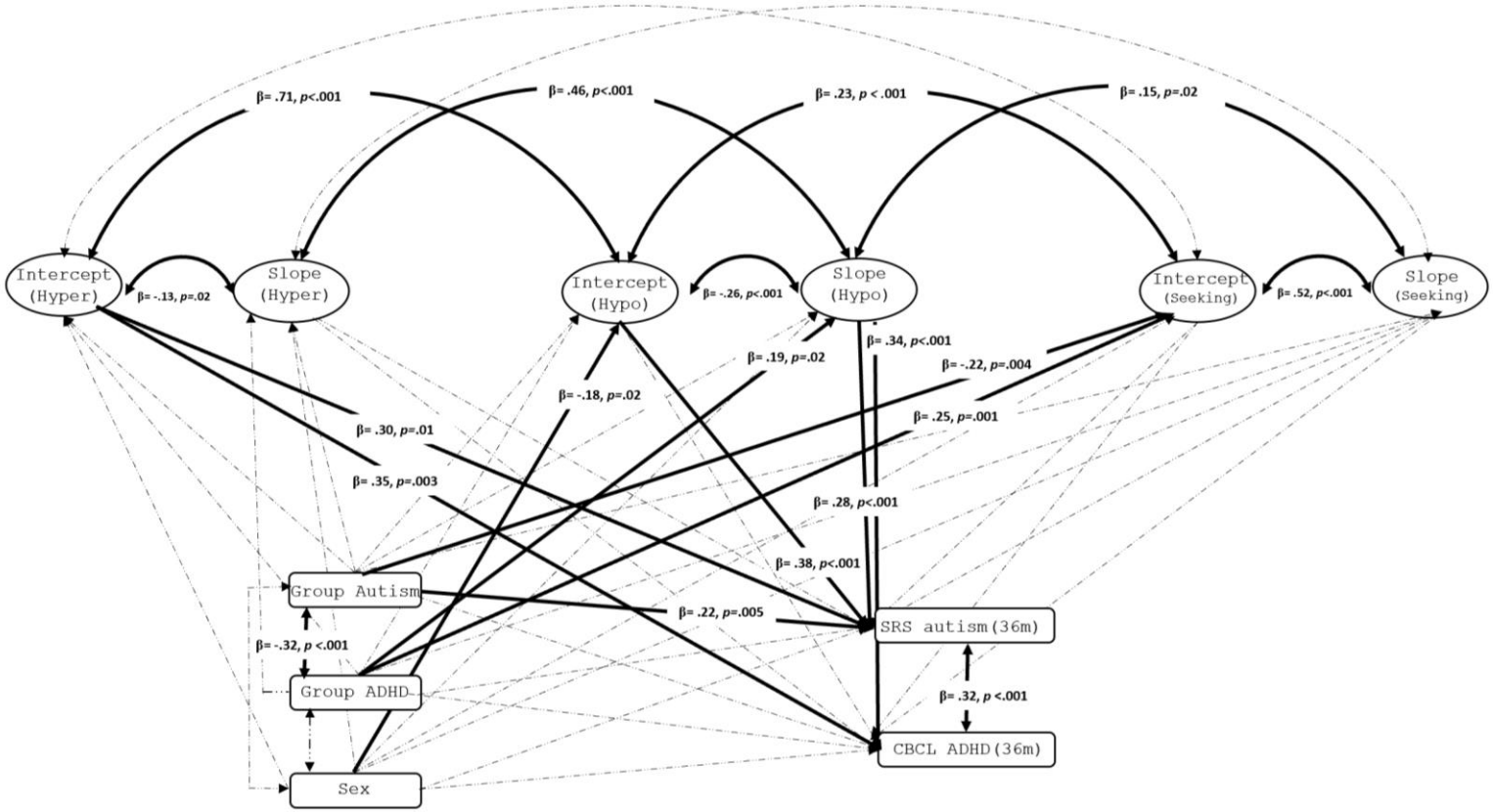

Figure C5. 4 Latent growth curve association between sensory pattern trajectories of hyperresponsivity, hyporesponsivity, sensation seeking and likelihood groups and sex on later autism and ADHD traits at 36 months using amended scoring of ITSP hyporesponsivity subscale. Note: Two items from the Hyporesponsivity subscale were excluded from the analysis due to their overlap with early autism phenotypes. Bold indicates significant associations. Reverse scoring was used where a higher score indicated a greater severity for ITSP.

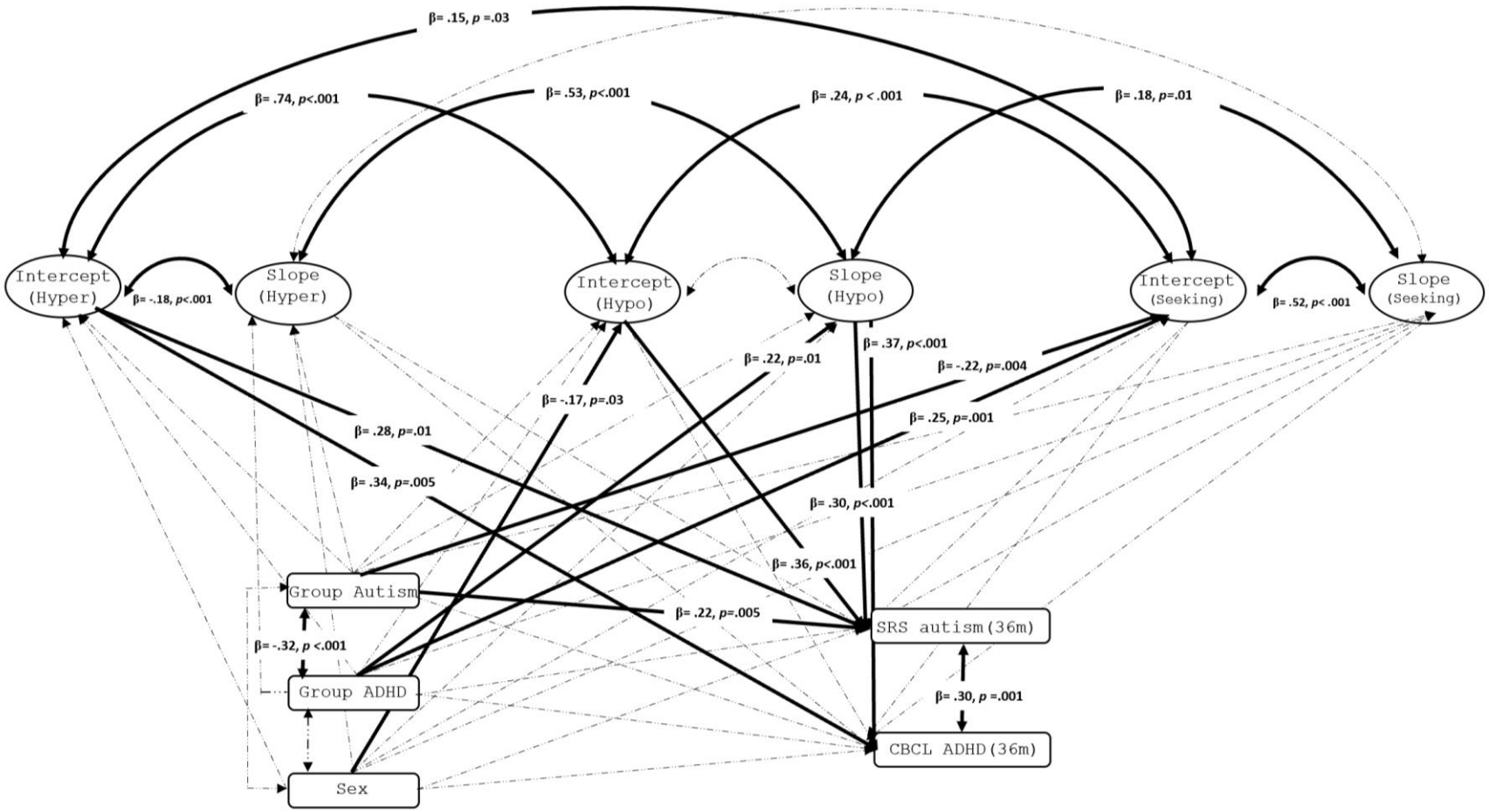

Figure C5. 5 Sensitivity analysis correcting for the skew in sensory domains of hyperresponsivity and hyporesponsivity. Bold indicates significant associations. Reverse scoring was used where a higher score indicated a greater severity for ITSP.

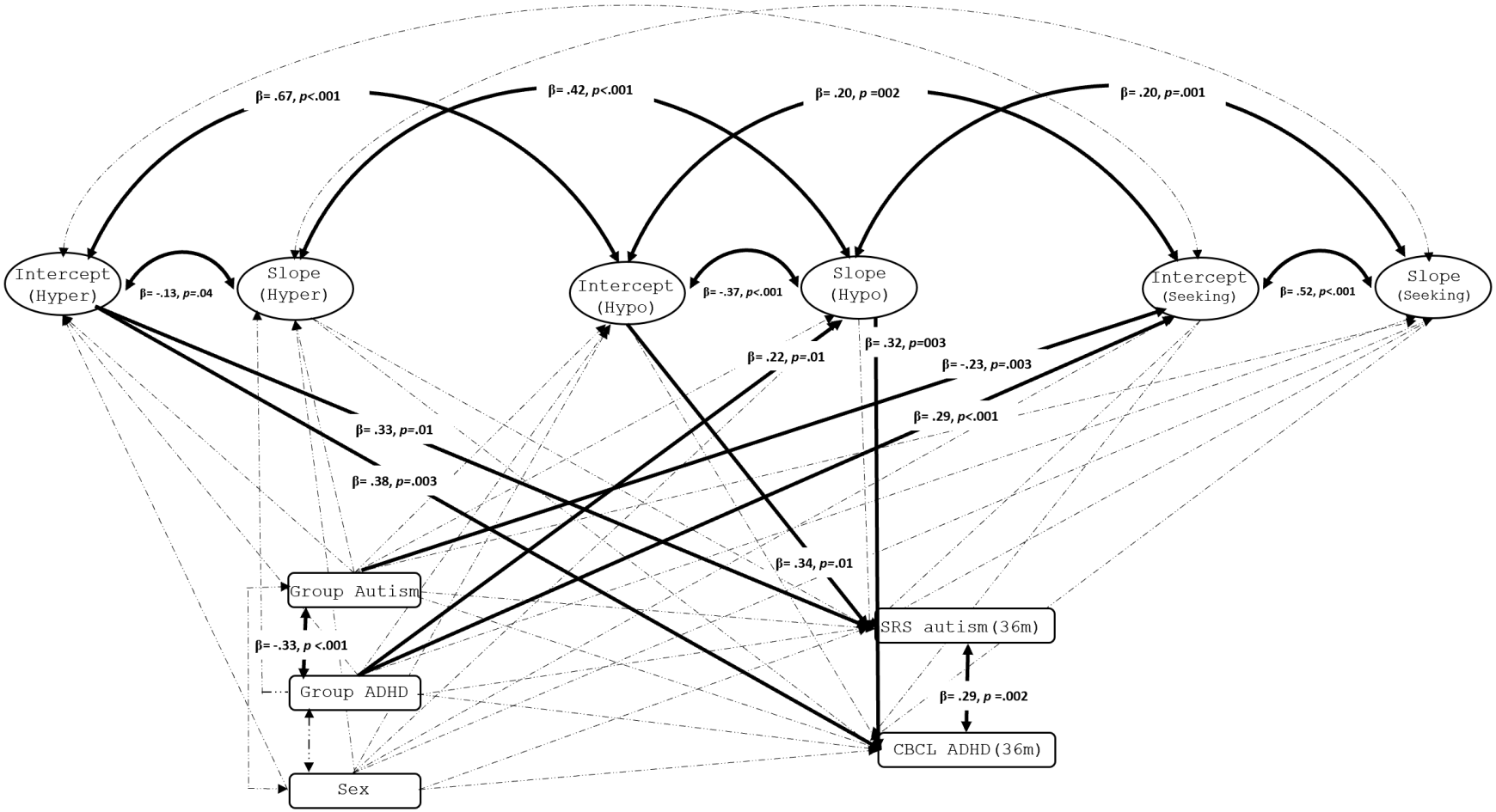

Figure C5. 6 Latent growth curve association between sensory pattern trajectories of hyperresponsivity, hyporesponsivity, sensation seeking and likelihood groups and sex on later autism and ADHD traits at 36 months in infants without autism outcomes. Bold indicates significant associations. Reverse scoring was used where a higher score indicated a greater severity for ITSP.

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