Early development of sensory perception in Autism Spectrum Disorders and Attention Deficit Hyperactivity Disorder

Early Development of Sensory Perception in Autism Spectrum Disorders and Attention Deficit Hyperactivity Disorder

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Declaration

'I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at Birkbeck, University of London or any other educational institution, except where due acknowledgment is made in the thesis. Any contribution made to the research by others, with whom I have worked at Birkbeck, University of London or elsewhere, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.'

This thesis includes work that appears in the following articles:

1. Piccardi, ES., Johnson, MH., Gliga, T. (2020). Explaining individual differences in infant visual sensory seeking. *Infancy*
2. Piccardi, ES., Begum Ali, J., Jones, EJH., Mason, L., Charman, T., Johnson, MH., Gliga, T. & BASIS/STAARS Team (2021). Behavioural and neural markers of tactile sensory processing in infants at elevated likelihood of Autism Spectrum Disorder and/or Attention Deficit Hyperactivity Disorder. *Journal of Neurodevelopmental Disorders*.

Dedication

This thesis is dedicated to my Family.

For their love, support and encouragement.

Abstract

Autism Spectrum Disorders (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are co-occurring neurodevelopmental disorders emerging early in development. Molecular genetics research suggests that common sensory vulnerabilities underlie the emergence of both disorders, yet no research examined the same sensory markers as potential infant predictors of ASD or ADHD traits in toddlerhood. This thesis examines the early development of sensory perception in infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the disorders.

Chapters 1-2 present, respectively, a theoretical introduction and methodological considerations for the investigation of sensory perception in these conditions.

Chapter 3 presents evidence from an EEG tactile repetition suppression task administered to 10-month-old infants, prospectively re-assessed at 24 months. Results indicate that reduced repetition suppression is a marker of ASD in infancy and predicts ASD traits in toddlerhood. Results further suggest that early enhanced parent-reported tactile sensory seeking mitigates the association between tactile atypicality and later ASD traits.

Chapter 4 presents evidence from an EEG visual task administered to 10-month-old infants, prospectively re-assessed at 24 months. Results indicate that enhanced responsiveness to visual input is a marker of ASD or ADHD in infancy and predicts concurrent parent-reported visual sensory seeking. Results further

indicate that enhanced responsiveness to incoming stimulation in infants with later higher ASD traits results from reduced prioritization of ongoing information.

Chapter 5 presents a proof-of-concept demonstration that variation in responsiveness to visual input also reflects variation in engagement with ongoing information in an independent cohort of 10-month-old infants at typical likelihood of the conditions.

Chapter 6 adopts an *individual differences approach* and reports on the concurrent/longitudinal associations between markers of information prioritization emerged from Chapter 5 and parent-reported sensory seeking, ASD and ADHD traits in the same participant sample, prospectively re-assessed at 16 months.

Chapter 7 discusses contributions and implications for research on the early development of sensory perception in ASD and ADHD.

Acknowledgments

I wish to express my deepest gratitude to my supervisors for welcoming me at the Centre for Brain and Cognitive Development (CBCD) – an incredibly rich, collaborative and mentally stimulating research environment.

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List of Abbreviations

ADHD = Attention Deficit Hyperactivity Disorder

ADI-R = Autism Diagnostic Interview-Revised

ADOS-2 = Autism Diagnostic Observation Schedule, Second edition

ADOS-2 CSS = ADOS-2 Calibrated Severity Scores

AHRR = Aryl-Hydrocarbon Receptor Repressor

AOSI = Autism Observation Scale for Infants

ASD = Autism Spectrum Disorder

BASIS = British Autism Study of Infant Siblings

BOLD = Blood-Oxygen-Level-Dependent

CAARS = Conners Adults ADHD Rating Scale

CBCL = Child Behaviour Checklist

CI = Confidence Interval

CH = Electrode Channel

CNVs = Copy Number Variations

DAWBA = Development and Well-Being Assessment

DMN = Default Mode Network

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition

DZ = Dizygotic

ECBQ = Early Childhood Behaviour Questionnaire

EEG = Electroencephalography

EF = Executive Functions

EL-ADHD = Elevated likelihood of Attention Deficit Hyperactivity Disorder

EL-ASD = Elevated likelihood of Autism Spectrum Disorder

EL-ASD+ADHD = Elevated likelihood of Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder

EPSP = Excitatory post-synaptic potential

EROs = Event-Related Oscillations

ERPs = Event-Related Potentials

fNIRS = Functional Near Infrared Spectroscopy

fMRI = Functional Magnetic Resonance Imaging

FYI = First Year Inventory

GABA = Gamma-Aminobutyric Acid

GEE = Generalised Estimated Equations

IBQ = Infant Behaviour Questionnaire

IBQ-R = Infant Behaviour Questionnaire Revised

ICA = Independent Component Analysis

ICC = Intra-Class Correlation Coefficient

ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th revision

IPSP = Inhibitory post-synaptic potential

ISI = Inter-Stimulus Interval

ITSC = Infant Toddler Symptom Checklist

ITSP = Infant Toddler Sensory Profile

MMN = Mismatch Negativity Paradigms

MRI = Magnetic Resonance Imaging

MRS = Magnetic Resonance Spectroscopy

MSEL EL = Mullen Scales for Early Learning Expressive Language

MSEL ELC = Mullen Scales for Early Learning Early Composite Score

MSEL FM = Mullen Scales for Early Learning Fine Motor Score

MSEL GM = Mullen Scales for Early Learning Gross Motor Score

MSEL RL = Mullen Scales for Early Learning Receptive Language Score

MSEL VR = Mullen Scales for Early Learning Visual Reception Score

MZ = Monozygotic

PCA = Principal Component Analysis

Q-CHAT = Quantitative CHecklist for Autism in Toddlers

S1 = First vibrotactile stimulus

S2 = Second vibrotactile stimulus

SCQ = Social Communication Questionnaire

SEQ = Sensory Experience Questionnaire

SensOR = Sensory Over-Responsivity Inventory

SNPs = Single Nucleotide Polymorphisms

SPS = Sensory Processing Scale

SRS = Social Responsiveness Scale

SWAN = Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour Scale

TDDT-R = Tactile Defensiveness and Discrimination Test Revised

TL = Typical likelihood of Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder

TSI = Tactile Suppression Index

VEP = Visual Evoked Potentials

Chapter 1: Introduction

1.1. Motivating the current PhD project

Autism Spectrum Disorders (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are heritable neurodevelopmental disorders emerging early in life. ASD affects up to 1.9% of the population (Maenner, Shaw, Baio, & others, 2020) and core features of the condition are social communication difficulties, restricted and repetitive behaviours and sensory atypicalities (DSM-5; American Psychiatric Association, 2013). ASD is more common in males than females, with ratios ranging from 2:1 to 5:1 in community-based and epidemiological studies (Lord et al., 2020). ADHD affects up to 3.4% of the population (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015) and core features of the condition are attentional control difficulties, hyperactivity and impulsivity (DSM-5; American Psychiatric Association, 2013). ADHD is more common in males than females, with a ratio of 3:1 documented in community-based studies (Arnett, Pennington, Willcutt, DeFries, & Olson, 2015). Both disorders substantially impact the quality of life of diagnosed individuals and their families. Evidence indicates that educational attainment is low in individuals with ASD (Fleury et al., 2014) or ADHD (Loe & Feldman, 2007). Further, unemployment rates are high in adults with ASD (Gotham et al., 2015) or ADHD (Barkley, 2006) and independent living can be a challenge for individuals with both conditions (Lord et al., 2020; Michielsen et al., 2015; Orsmond, Shattuck, Cooper, Sterzing, & Anderson, 2013). These findings emphasize the need to support individuals with ASD or ADHD diagnoses.

Reliable diagnoses for ASD or ADHD can be made in the presence of clinically significant behavioural manifestations, which typically appear between 2 and 3 years in children with ASD (Charman & Baird, 2002) and between 5 and 6 years in children with ADHD (Posner, Polanczyk, & Sonuga-Barke, 2020). The stability of an ASD diagnosis from the pre-school years to mid-childhood is high, with 84% of children receiving an ASD diagnosis at 2 years continuing to manifest ASD symptoms at 9 years (Lord et al., 2006). Similarly, the stability of an ADHD diagnosis from the pre-school years to mid-childhood is relatively high, with 70% of children receiving a diagnosis of the disorder at 5 years continuing to manifest ADHD symptoms at 12 years (Law, Sideridis, Prock, & Sheridan, 2014).

In addition to diagnostic longitudinal stability, ASD and ADHD also manifest substantial heterogeneity and frequently co-occur. The specific set of emerging traits and symptoms often varies widely between children with these disorders. For example, heterogeneity in intellectual functioning, sensory manifestations and the severity of social symptoms is reported in ASD (Lord et al., 2020). Thus, while some individuals with ASD may manifest a profile of low intellectual functioning, elevated sensory atypicalities and severe social symptoms, other individuals with the disorder may exhibit the opposite profile. Similarly, heterogeneity in attentional control difficulties, hyperactivity and impulsivity is reported in ADHD (Posner et al., 2020). Added heterogeneity is conferred to both conditions by co-occurring manifestations. In particular, co-occurrence rates between ASD and ADHD range between 40% and 80% (Antshel & Russo, 2019;

Joshi et al., 2017) and later born siblings of children with a diagnosis of ASD or ADHD appear to be at elevated likelihood to develop both conditions (Miller et al., 2019). Furthermore, ASD and ADHD are comorbid with additional psychiatric disorders, including anxiety, depression, Obsessive-Compulsive Disorder (OCD) and sleep difficulties (Lord et al., 2020; Posner et al., 2020). One promising approach to understanding the heterogeneity and complexity of ASD and ADHD is through the investigation of the trajectories of development of these disorders over time. By mapping the associations between early infant markers of ASD or ADHD and later manifestations, this approach can distinguish shared and distinct causal pathways between the conditions, highlight risk and protective factors and enhance our understanding of the nature of the co-occurrence and aetiology of ASD and ADHD (Johnson, Gliga, Jones, & Charman, 2015; Jones, Gliga, Bedford, Charman, & Johnson, 2014). Better understanding of the developmental trajectories of ASD and ADHD will inform mechanistic-based explanations, which are fundamental to lay the translational foundations for early intervention protocols.

Prospective longitudinal studies of infants at elevated likelihood of ASD and/or ADHD follow infant siblings of children with the disorders from infancy until 3-5 years, when diagnoses are possible. A control group of infant siblings of children with no family history of the disorders is followed in parallel. Evidence from these studies highlights similarities and differences in the early markers of ASD and ADHD. In particular, commonalities are seen in early sensory vulnerabilities (Gliga, Jones, Bedford, Charman, & Johnson, 2014; Johnson et al.,

2015; Thye, Bednarz, Herringshaw, Sartin, & Kana, 2018). Despite evidence that sensory vulnerabilities manifest in the early development of ASD and ADHD, no prior research investigated the same sensory markers as potential infant predictors of later ASD and/or ADHD traits in toddlerhood. The aim of the current PhD project is to fill this gap in our knowledge of these disorders by examining the early development of sensory perception in infants at elevated familial likelihood of ASD and/or ADHD relative to infants at typical likelihood of the disorders. The current chapter will provide a more detailed account by introducing 1) ASD and ADHD - symptomatology, diagnosis, aetiology and comorbidity; 2) Sensory perception in the early development of ASD and ADHD; 3) Theoretical models of sensory perception in neurotypical populations and populations with ASD and/or ADHD.

1.2. ASD and ADHD: symptomatology and diagnosis

1.2.1. ASD

The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5; American Psychiatric Association, 2013) describes ASD as a disorder characterized by two core domains: 1) difficulties in social communication and interaction; 2) restricted and repetitive behaviours or interests, including sensory hypersensitivity or hyposensitivity and/or unusual sensory interest. For core domain 1, the DSM-5 specifies that an individual must manifest evidence of difficulty across multiple contexts of the following subdomains: 1.1) social reciprocity; 1.2) non-verbal communication; 1.3) developing, maintaining and understanding relationships. For

core domain 2, the DSM-5 specifies that an individual must manifest evidence of difficulty in two of four subdomains: 2.1) stereotyped, repetitive behaviours; 2.2) insistence on sameness; 2.3) highly restricted and fixed interests; 2.4) hypersensitivity or hyposensitivity or interest in sensory inputs. Alongside core difficulties, the DSM-5 specifies additional criteria for a diagnosis of ASD, including an early emergence of symptoms, difficulties in daily living and absence of general intellectual disability or delay explaining the symptomatology. See Figure 1.1.

Behavioural manifestations are necessary for an ASD diagnosis to be made and the DSM-5 recognises that symptoms may not fully appear until social demands exceed the current abilities of the individual, typically at 4 or 5 years of age. However, early diagnoses are accepted and they can be made in toddlers aged 2 years. Early diagnoses are also described as "working diagnoses" and they are subjected to refinement over time, in consultation with parents (Charman & Baird, 2002). A multidisciplinary assessment of the toddler's developmental history, adaptive functioning and specific social interaction style is required for an early diagnosis to be made. Direct clinical evaluation is necessary given that many ASD core symptoms (e.g. repetitive and restricted behaviours or interests) may be subtle during toddlerhood and not fully emerge until later in development (Charman & Baird, 2002). Further, informants from parents can clarify current behaviours that may not be fully observed during the assessment (Pasco, 2011).

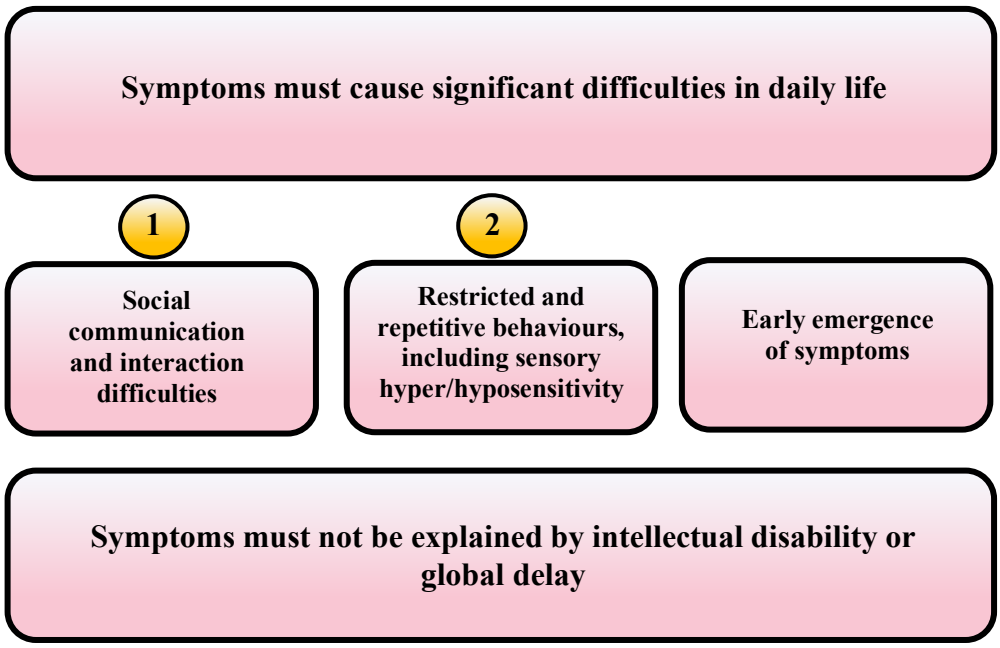

Figure 1.1. ASD as defined by DSM-5

ASD core symptoms span across sensory and social domains, they appear early in development and they cause significant difficulty in everyday life. An ASD diagnosis can be made only if these symptoms are not explained by global delay or intellectual disability.

1.2.2. ADHD

The DSM-5 describes ADHD as a disorder characterized by two core domains: 1) inattention; 2) hyperactivity and/or impulsivity. In order to receive and ADHD diagnosis before the age 17, the individual must manifest evidence of six or more symptoms in either the inattentive or hyperactive and impulsive core domains for six months or longer. For core domain 1, manifestations may include troubles

holding attention on tasks or play activities, trouble organising tasks, distractibility and forgetfulness in daily life. For core domain 2, manifestations may include fidgety behaviours, excessive talking, trouble with turn-taking and inability to take part in leisure activities quietly. Alongside these manifestations, the DSM-5 specifies additional criteria for a diagnosis of ADHD, including the presence of difficulties in daily living, an early emergence of symptoms and absence of other psychiatric conditions explaining the symptomatology. See Figure 1.2.

Although ADHD is a lifelong condition, different developmental trajectories exist. ADHD symptoms may exhibit an early onset (3-5 years), a middle childhood onset (6-14 years), a middle childhood onset with adolescent offset (6-14 years) or an adolescent/adult onset (>16 years). These different forms are currently not distinguished in diagnostic approaches. However, clinicians are increasingly recognising that alternative courses of the disorder may have different prognoses and require different treatment planning (Posner et al., 2020). Further, while in some individuals the first manifestations of ADHD may appear during the pre-school years, there are currently no clinical guidelines to diagnose ADHD before the age 4 (Homer et al., 2000). Thus far, research on the early precursors and predictors of ADHD is limited. However, researchers are increasingly recognizing the importance of identifying earlier markers of ADHD to plan for the effective screening of children at elevated likelihood of the disorder (e.g. Gurevitz, Geva, Varon, & Leitner, 2014; Miller, Iosif, Young, Hill, & Ozonoff, 2018).

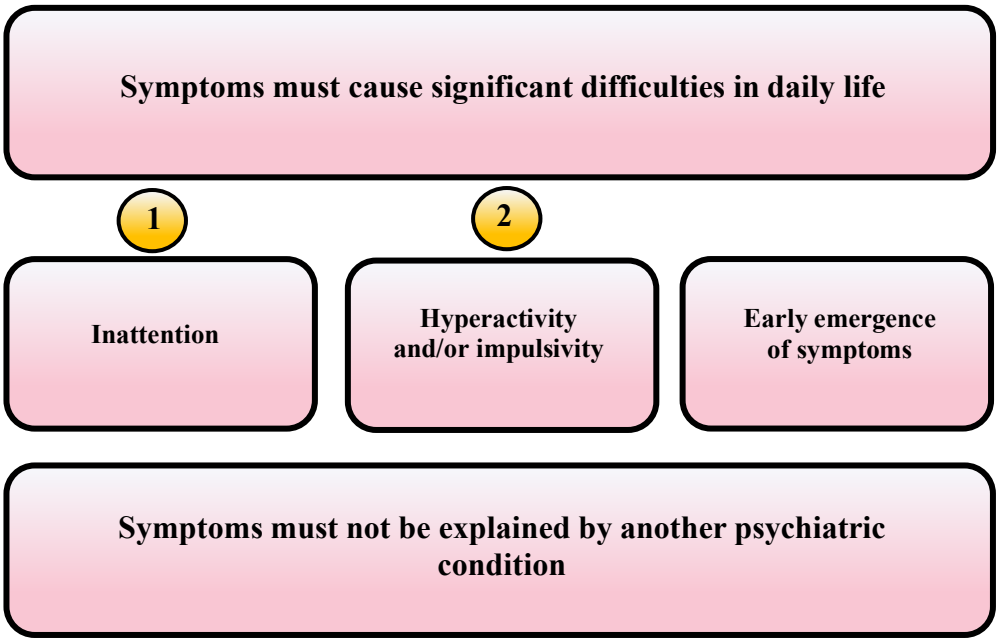

Figure 1.2. ADHD as defined by DSM-5

ADHD core symptoms include inattention and hyperactivity/impulsivity and they cause significant difficulty in everyday life. An ADHD diagnosis can be made only if these symptoms are not explained by other psychiatric conditions.

1.3. ASD and ADHD: Aetiology

Scientific progress in our understanding of the pathogenesis, causes, and pathophysiology of ASD and ADHD has occurred over the last two decades. While these advances clarified some aetiological factors underlying the emergence of symptoms in ASD and ADHD, they also highlighted the complexity of these disorders, whereby multiple pathways may lead to the same observable phenotype (i.e. equifinality). The following section reviews evidence for putative mechanisms

involved in the aetiology of ASD and ADHD. Research focused on genetic and environmental factors will be considered, alongside studies focusing on cognitive and neurobiological explanations.

1.3.1 ASD - Genetics

Twin and family studies concur in suggesting that genetic contributions are large in ASD, with heritability estimates ranging from 40% to 90% depending on the study design and analytical method (Gaugler et al., 2014; Lee et al., 2013; Sandin et al., 2017). Further, ASD manifests one of the highest heritability rates when compared to other common medical conditions (Wang, Gaitsch, Poon, Cox, & Rzhetsky, 2017). The likelihood of developing ASD is elevated in infant siblings of children with a diagnosis of the disorder and recurrence estimates range from 6.9% to 18%, depending on the study design (Grønborg, Schendel, & Parner, 2013; Miller et al., 2018; Ozonoff et al., 2011; Risch et al., 2014). Despite the high heritability, ASD manifestations are rarely the consequence of a single gene or genetic mutation.

Currently, more than 100 different genes have been linked to ASD and the contribution of de novo mutations is small (Courchesne, Gazestani, & Lewis, 2020; Gaugler et al., 2014; Catherine Lord et al., 2020). Thus, only in rare cases, a single genetic mutation gives rise to ASD manifestations, such as in individuals with tuberous sclerosis, neurofibromatosis or Fragile X syndrome (i.e. rare monogenic syndromes cumulatively account for less than 10% of ASD cases; Devlin & Scherer, 2012). Conversely, in most cases, ASD results from several cumulative

risk genes whose peak expression occurs at prenatal ages across brain regions (see Figure 1.3A) and which fall into two main groups: 1) broadly expressed regulatory genes and 2) brain-specific genes (Courchesne et al., 2020). Broadly expressed regulatory genes represent the majority of ASD risk genes and are expressed early in prenatal development (i.e. first to third trimesters of gestation). These genes are implicated in chromatin modelling, signalling pathway modulation and can perturb transcriptional programs in tissues and organs other than the brain (Courchesne et al., 2020, 2019). On the other hand, brain-specific genes are expressed at a later developmental stage (i.e. third trimester to early postnatal life) and they impact neurite outgrowth, synaptogenesis and the "wiring" of cortical functional networks (Courchesne et al., 2020, 2019), see Figure 1.3B and 1.3C.

Many of these brain-specific genes are enriched in glutamatergic projection neurons during the midfetal period, they exhibit the most significant co-expression in the prefrontal and primary motor and somatosensory cortex and impact several areas of functioning, including sensory perception, locomotion and sleep, see Figure 1.4 (Krishnan et al., 2016; Parikshak et al., 2013; Willsey et al., 2013). Further, about two-third of ASD risk genes are pleiotropic, thus influencing different areas of functioning at multiple stages of developmental. This property explains the multifaceted nature of ASD manifestations during the prenatal and early postnatal life, which begin with atypical cell number, neurogenesis, cell migration and differentiation and progress to later synaptic perturbations and cortical "wiring" mediated by experience-dependent postnatal factors (Courchesne

et al., 2020). Additionally, due to their pleiotropic nature, ASD risk genes do not act through a single mechanistic pathway but rather impact the development of the brain and other organs through multiple and complex pathways (Courchesne et al., 2019; Kasah, Oddy, & Basson, 2018).

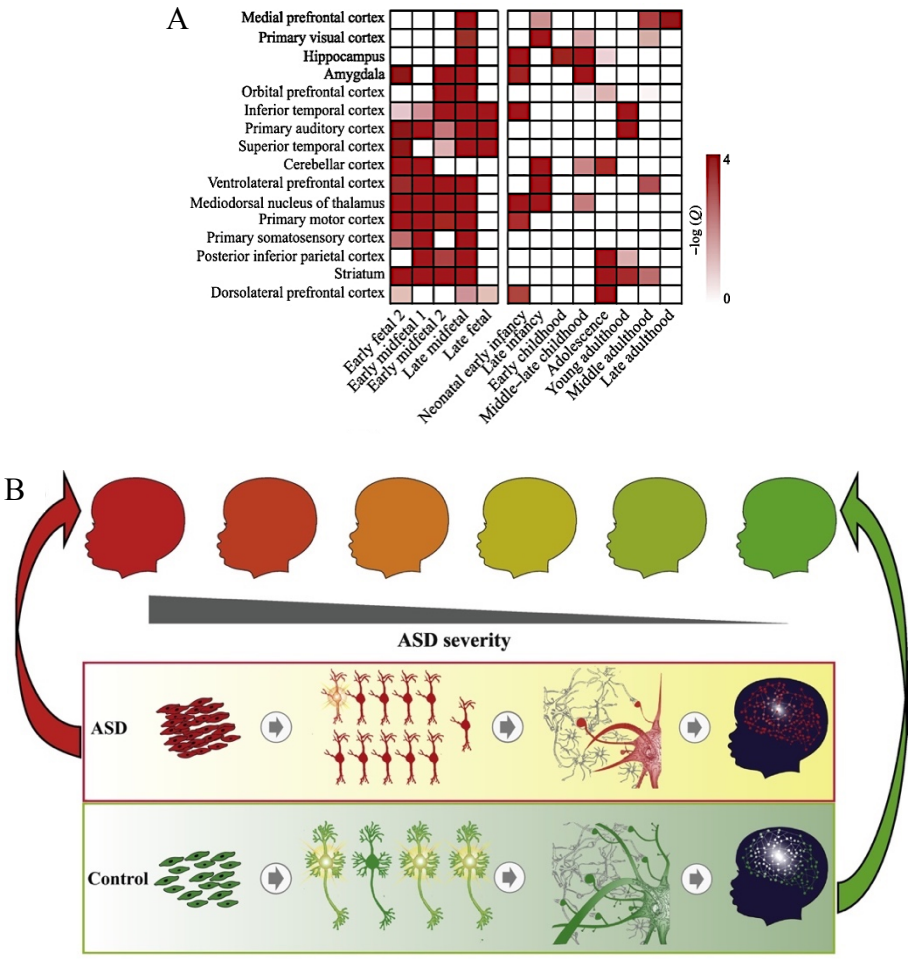

Figure 1.3. Expression and impact of ASD risk genes during development

A) Heat map of the expression of ASD risk genes during development across brain regions. Each cell in the heat map indicates a spatiotemporal signature: a set of genes highly expressed in a region at a specific developmental stage. The intensity

of the colour represents the log-transformed significance of the ASD-association of that signature. B) ASD risk genes impact multiple stages of prenatal and postnatal development. Prenatal stages include cell proliferation, migration and differentiation; postnatal stages include synaptogenesis, atypical cortical "wiring" and atypical neural synchronization. The severity of the ASD outcome is likely impacted by each of these perturbations. Adapted from Courchesne et al., (2020) and Krishnan et al., (2016).

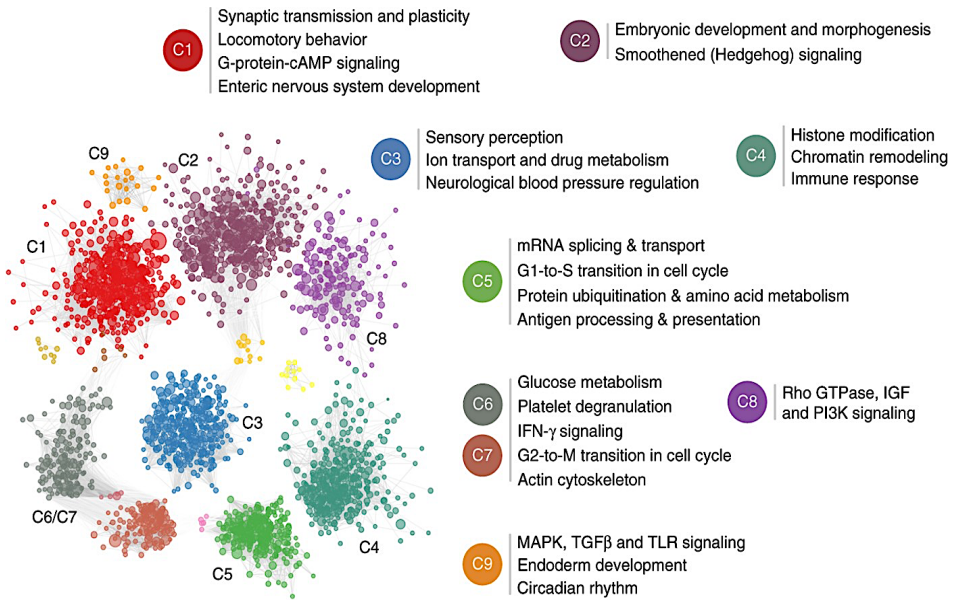

Figure 1.4. Modules of ASD risk genes and their functions

Genetic analyses aimed at identifying modules of functional ASD risk genes point to a landscape of functions dysregulated by ASD-associated mutations. These include sensory perception, locomotion and sleep. Adapted from Krishnan et al., (2016).

1.3.2. ASD - Environmental factors

Alongside genetic contributions, environmental factors have been proposed to influence the ASD liability (De La Torre-Ubieta, Won, Stein, & Geschwind, 2016; Modabbernia, Velthorst, & Reichenberg, 2017). Earlier twin studies reported little contribution of the environment on the ASD liability. However, recent evidence indicates that up to 40-50% variance in the ASD liability may be due to environmental contributions (Deng et al., 2015; Modabbernia et al., 2017). Environmental factors linked to elevated ASD likelihood include advanced parental age (Wu et al., 2017), birth trauma (particularly hypoxia; Modabbernia et al., 2017), maternal obesity (Windham et al., 2019), valproate use during pregnancy (Christensen et al., 2013), gestational diabetes mellitus (Xiang et al., 2015) and a short interval between pregnancies (Cheslack-Postava, Liu, & Bearman, 2011). Pre-natal stress during pregnancy has also been linked to elevated ASD likelihood (for a review, Kinney, Munir, Crowley, & Miller, 2008). In contrast, pre-natal folic acid intake has been shown to act as a protective factor (Schmidt et al., 2012), reducing the ASD likelihood for the offspring. Finally, clear evidence exists that ASD is not associated with vaccination (Taylor, Swerdfeger, & Eslick, 2014).

The mechanisms through which environmental contributions may affect the ASD liability remain debated (Modabbernia et al., 2017). However, it is likely that multiple and complex pathways involving genetic and epigenetic effects underlie the impact of environmental contributions. One example of such pathways may be the Aryl-Hydrocarbon Receptor Repressor (AHRR) DNA methylation,

which appears to mediate the association between maternal obesity and later adverse neurodevelopment in the offspring by influencing the placental environment (Bölte, Girdler, & Marschik, 2019; Godfrey et al., 2017).

1.3.3. ASD - Cognitive theories

Although clinical and experimental evidence indicates that ASD is a highly heterogeneous condition, substantial efforts have been made to channel the multiple manifestations of the disorder into one explanatory cognitive phenotype. Several cognitive accounts were generated from these efforts, including the: 1) Theory of Mind deficit; 2) Social Motivation theory; 3) Executive Dysfunction theory; 4) Weak Central Coherence theory; 5) Enhanced Perceptual Functioning theory; 6) Predictive coding theories.

The Theory of Mind (ToM) Deficit account proposes that individuals with ASD have difficulties in reflecting on their own and others' thoughts and emotions (Baron-Cohen, Leslie & Frith, 1985). In their seminal proposal, Baron-Cohen and colleagues (1985) presented the account as a universal explanation of the broad spectrum of social difficulties experienced by individuals with ASD. Following the observation that some individuals with ASD could perform typically in first-order belief tasks (e.g. "I think he thinks") but struggle with second-order belief tasks (e.g. "I think he thinks she thinks"), the account was revised to suggest that individuals with ASD may experience delayed development of their ToM abilities (Baron-Cohen, 1989). Later studies failed to replicate these results, leading

researchers to reformulate the theory in terms of mindblindness (Baron-Cohen, 1997; Hamilton, 2009; Rajendran & Mitchell, 2007). The mindblindness hypothesis suggests that individuals with ASD may not be invariably impaired in ToM tasks; rather, they may exhibit different degrees of mind reading ability, defined as the capacity to impute mental states and attribute beliefs. It follows that while some individuals with ASD may consistently fail belief-attribution tasks, others may manifest typical performance. This theoretical revision enabled researchers to better account for the variable degree of social atypicalities in ASD. However, the domain specificity of the theory limited its capability to explain the non-social manifestations of the disorder.

The Social Motivation theory proposes that individuals with ASD may lack social interest, therefore manifesting reduced social motivation (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012). The theory was initially elaborated following observation that individuals with ASD may experience reduced social orienting, reduced joint attention, reduced eye contact, infrequent pointing and lower drive to seek out social opportunities. Underlying this theory is the proposal that reduced social motivation in ASD may result from attribution of a lower reward value to social stimuli or contexts. In turn, lower reward attribution may be mediated by atypical functioning of the brain reward network, which is thought to include the amygdala, the ventral striatum, the orbitofrontal cortex and the ventromedial cortex (Chevallier et al., 2012). Further, this theory predicts reduced social motivation to manifest early in life, detrimentally impacting the development of later social skills.

Despite its developmental nature, the Social Motivation theory also represents a domain specific account of ASD symptoms, therefore being unable to explain many non-social atypicalities of the condition, including sensory symptoms and restricted and repetitive behaviours. In a later re-formulation of the theory, Jaswal & Akhtar, (2018) challenged some of its core assumptions, including the notion that individuals with ASD may lack social motivation. Thus, according to this re-formulation, individuals with ASD may not universally lack social motivation; rather, they may just "appear" socially uninterested.

The Executive Dysfunction theory proposes a domain general account according to which atypical manifestations in ASD (including social atypicalities) may be consequent to weak executive functioning (Hill, 2004; Pennington & Ozonoff, 1996). "Executive functions" (EF) is an umbrella term which refers to skills supporting planning, working memory, set shifting, inhibition and impulse control (Roberts, Robbins, & Weiskrantz, 1998). These skills are thought to be mediated by the prefrontal cortex and assumed by this account to be atypical in individuals with ASD. In particular, this theory proposes that ASD individuals may experience difficulties in tasks mediated by frontal cortical networks, leading to stereotyped behaviours, perseveration, rigidity and overall reduced social functioning. There is evidence that ASD individuals may experience difficulties with EF, manifested as reduced cognitive flexibility and set shifting (Ozonoff, 1997), although these results have not always been replicated (Rajendran & Mitchell, 2007). Generally, atypicalities in EF neither appear universal in

individuals with ASD, nor do they appear specific to the disorder, given that many individuals with Tourette syndrome, OCD or ADHD report similar difficulties (Rajendran & Mitchell, 2007). Indeed, Johnson (2012) proposed that weak EF early in development may represent a risk factor shared across conditions and limit the capacity for compensation in the face of pre-existing vulnerabilities.

The Weak Central Coherence theory also proposes a domain general account to explain social and non-social atypicalities in ASD (Frith, 2003; Frith, Happé, & others, 1995; Happe, 1999). This theory suggests that individuals with ASD may exhibit a weak drive for global coherence and a stronger drive for local information. The Weak Central Coherence theory was first elaborated following observation that individuals with ASD may outperform typically developing individuals in tasks requiring to locate a target among distracters (e.g. Embedded Figure Task, Block Design Task, Visual Search Tasks), in tasks requiring perceptual processing of hierarchical stimuli (e.g. Navon Task) and in visual illusion tasks (e.g. Titchener Task). Thus, the advantage exhibited by ASD individuals was initially interpreted as resulting from a reduced cognitive drive to attend to global information. However, later studies did not replicate advantages in visual illusion and hierarchical processing tasks (Plaisted, Swettenham, & Rees, 1999; Ropar & Mitchell, 2001). Thus, the theory was revised to suggest that individuals with ASD may manifest a perceptual profile characterised by both reduced global processing and enhanced local processing (Happé & Frith, 2006). Furthermore, rather than representing a dysfunction, the pattern of reduced global

processing and enhanced local processing was proposed to represent a *cognitive style* or *bias* (Happé & Frith, 2006).

The Enhanced Perceptual Functioning theory proposes that perception in ASD individuals may be driven by local content (Mottron, Burack, Dawson, Soulières, & Hubert, 2001; Mottron, Dawson, Soulières, Hubert, & Burack, 2006). However, rather than attributing this profile to weak top-down central coherence, the Enhanced Perceptual Functioning theory maintains that a bottom-up processing style may underlie the strength or preference for local information in individuals with ASD. Therefore, global processing may be intact in ASD subjects and it could be recruited when necessary. Notwithstanding, the local perceptual bias would improve their performance across tasks assessing sensory sensitivity, perceptual discrimination and processing of first-order static information (Mottron et al., 2006). A number of studies reported superior local processing and typical global processing in individuals with ASD, although these results have not always been replicated (for a meta-analysis see, der Hallen, Evers, Brewaeys, den Noortgate, & Wagemans, 2015). For example, Hadad and Ziv (2015) reported enhanced local processing and reduced sensitivity to global information, conveyed by Gestalt grouping laws, in adults with ASD. Conversely, reduced sensitivity to Gestalt laws was documented in children with the disorder (Brosnan, Scott, Fox, & Pye, 2004). Results from a meta-analysis of 56 studies and more than 1000 participants with ASD indicate that individuals with the disorder may neither manifest reduced global processing, nor enhanced local processing. Rather, individuals with ASD

may be slower than age-matched controls in global processing and their performance may be sensitive to task-specific effects (der Hallen, Evers, Brewaeys, den Noortgate, & Wagemans, 2015).

More recently, increased attention has been gained by *Predictive coding theories* (see section 1.6 for an in-depth examination of these theories and related evidence). These theories describe the brain as an active inference organ which is constantly trying to predict the sensory input it receives to infer the most plausible representation of the world. According to Predictive coding theories, each region of the sensory hierarchy represents both these predictions and the mismatch between predictions and sensory input (i.e. *prediction error*) (Friston & Kiebel, 2009; Kok & De Lange, 2015). Individuals with ASD would experience difficulty with predicting events or situations due to their reduced active inference capacity, i.e. their reduced ability to integrate prior experience with incoming sensory input. Reduced active inference capacity would lead individuals with ASD to prefer predictable contexts or actions, especially under conditions of environmental uncertainty (Lawson, Rees, & Friston, 2014; Pellicano & Burr, 2012; Sinha et al., 2014). This would explain the tendency of individuals with ASD to perform repetitive and ritualistic behaviours. These behaviours would require less active inference capacity given that sensory expectations and motor plans are pre-existent (Lawson et al., 2014; Pellicano & Burr, 2012). Further, adopting repetitive and ritualistic behaviours under conditions of environmental uncertainty would help individuals with ASD to fulfil their expectations in a consistent manner (Lawson et

al., 2014). Social situations are arguably uncertain and complex since the many-to-one mappings between causes and sensory input are increased and difficult to predict (Lawson et al., 2014). Thus, individuals with ASD would struggle dealing with social contexts due to their unpredictable nature and would prefer more predictable repetitive and ritualistic behaviours.

Overall, several cognitive theories have been advanced to explain the behavioural profile of individuals with ASD. Progress in this field has supported a transition from "social-first" explanations to "sensory-first" accounts, whereby sensory manifestations are considered responsible for higher-level social and cognitive atypicalities. Nonetheless, fewer accounts managed to explain the behavioural profile of ASD individuals with high level of sensitivity and specificity. Furthermore, among these accounts, only Predictive coding theories provided a biologically plausible instantiation of the context-sensitive behavioural atypicalities in ASD.

1.3.4. ASD - Neurobiological explanations

Research testing neural circuitry theories of ASD has fostered progress in our understanding of the mechanisms underlying the emergence of symptoms in this disorder. Broadly, this research indicates that atypical trajectories of whole brain development are present in ASD since the prenatal stages.

One line of research assessed the possibility that ASD may be characterised by *an initial phase of brain overgrowth, followed by a later phase of arrest of*

growth, neural loss and degeneration (Courchesne et al., 2007, 2019). Evidence in support of this prediction has emerged from post-mortem studies which reported neuron overabundance in the prefrontal cortex of children with ASD (Courchesne, Mouton, et al., 2011). Since neural proliferation occurs prenatally, between 10 and 20 weeks of gestation, this evidence supports the notion of early brain overgrowth in ASD. Additional post-mortem studies of individuals with ASD reported widespread atypicalities in neurogenesis and neuronal migration, including reduced growth of neuronal cell size and dendritic arbors and, in severe cases, incomplete removal of the subplate (i.e. which occurs during the third trimester) (Courchesne et al., 2019). Thus, in line with genetic evidence, results from post-mortem studies support the notion that widespread structural atypicalities in brain development have an early onset in ASD. These structural atypicalities may detrimentally impact later synaptogenesis and synaptic functioning, leading to atypical network synchronization (Courchesne et al., 2019).

The possibility that ASD may be characterised by *atypical network synchronization* has been explored by research focused on assessing functional connectivity in individuals with the disorder (Just, Cherkassky, Keller, & Minshew, 2004). Functional connectivity is a measure of the degree of synchronization of cortical responses. An initial report documented lower functional connectivity in language cortical areas in adults with ASD relative to control participants (Just et al., 2004). Later studies provided mixed evidence by documenting reduced, elevated or co-existent reduced and elevated functional connectivity in individuals

with ASD (Ecker, Bookheimer, & Murphy, 2015). It is possible that both under-connectivity and over-connectivity may be a characteristic of ASD, with the former dominating long-range neural connections and the latter dominating short-range neural connections (Belmonte et al., 2004). However, while long-range under-connectivity is a replicated finding in ASD, evidence regarding short-range functional connectivity in ASD is inconclusive (O'reilly, Lewis, & Elsabbagh, 2017; Vissers, Cohen, & Geurts, 2012). Further, it is possible that functional connectivity may undergo developmental changes (Uddin, Supekar, & Menon, 2013). Indeed, assessment of the cross-sectional developmental trajectory of functional connectivity indicates that over-connectivity may be present in toddlers with ASD but under-connectivity may characterise older children and adults with ASD (Hoppenbrouwers, Vandermosten, & Boets, 2014). Conversely, the longitudinal trajectory of functional connectivity from infancy to childhood remains unexplored.

A third line of research investigated the possibility that ASD may be characterised by *atypical excitation/inhibition (E/I) balance* in putative cortical areas (Lee, Lee, & Kim, 2017; Nelson & Valakh, 2015; Rubenstein & Merzenich, 2003). This prediction originated from the observation that ASD individuals develop epilepsy at a rate up to 25 times higher than the general population (Bolton et al., 2011) and that E/I imbalances are frequently observed in animal models of ASD (Gonçalves et al., 2017; Lee et al., 2017; Yizhar et al., 2011). In particular, factors hypothesized to contribute to E/I imbalances in ASD include atypical

excitatory and inhibitory synapse development, atypical synaptic transmission and plasticity, atypical downstream signalling and intrinsic neuronal excitability (Lee et al., 2017; Tatti, Haley, Swanson, Tselha, & Maffei, 2017). Atypical synaptic and neuronal signalling, in turn, would be mediated by altered balance in the synthesis of the neurotransmitters glutamate and GABA (Bejjani et al., 2012; Naaijen et al., 2017; Rojas, Becker, & Wilson, 2015) – a proposal consistent with genetic evidence suggesting that many brain-specific ASD risk genes are enriched in glutamatergic projection neurons during prenatal development (see section 1.3.1). Glutamate is the most important excitatory neurotransmitter in the brain, it regulates synaptic transmission, neuronal migration, excitability, plasticity and long-term potentiation (Naaijen et al., 2017; Nakanishi et al., 1998) and it is implicated in the synthesis of GABA (Bak, Schousboe, & Waagepetersen, 2006). On the other hand, GABA is the most abundant inhibitory neurotransmitter in the brain (although it switches from excitatory to inhibitory in early development; Ganguly, Schinder, Wong, & Poo, 2001) and it is implicated in long-range neuronal signalling (Naaijen et al., 2017).

There is evidence that E/I imbalances may contribute to sensory and social atypicalities in ASD. For example, studies using magnetic resonance spectroscopy (MRS) reported reduced GABA concentrations in the auditory and somatosensory cortex of adults and children with ASD (Puts et al., 2017; Rojas, Singel, Steinmetz, Hepburn, & Brown, 2014). Richardson and collaborators (2013; 2016) further investigated the role of GABA and glutamate in mediating the visual perceptual

phenomenon of binocular rivalry in adults with ASD and age-matched control participants. First, the authors documented slower rate of binocular rivalry in adults with ASD, which associated with the severity of ASD symptoms as assessed through standardized clinical assessment (i.e. Autism Diagnostic Observation Schedule, ADOS; Lord et al., 2000). No differences between the groups emerged in total GABA concentrations in the visual cortex; however, control participants manifested a positive association between GABA concentrations and binocular rivalry rate, which was absent in ASD participants (Robertson, Kravitz, Freyberg, Baron-Cohen, & Baker, 2013; Robertson, Ratai, & Kanwisher, 2016).

Overall, this evidence supports the prediction that alterations in the E/I balance of the brain may contribute to ASD manifestations. However, the exact mechanism underlying the link between E/I imbalances and sensory or social symptoms is unclear. Indeed, E/I imbalances could lead to elevated cortical excitability, or reduced cortical inhibition which could, in turn, impact cortical noise, signal-to-noise ratios or neural tuning sharpness (Rubenstein & Merzenich, 2003). Different mechanisms may also be present in early infancy compared to later childhood and adulthood (Rojas et al., 2015). Similarly, different mechanisms may exist in various subtypes of individuals with ASD (Uzunova, Pallanti, & Hollander, 2016).

1.3.5. ASD – Interim summary

Research into the pathogenesis, causes and pathophysiology of ASD has expanded over the last two decades. Concurring genetic and neurobiological evidence has revealed that ASD manifestations appear early in prenatal life and progress during later postnatal development. These manifestations are driven by hundreds of ASD-risk genes whose expression impacts several areas of phenotypic functioning, including sensory perception, motor functioning and sleep. At the same time, progress in our understanding of ASD phenotypic manifestations has been granted by advances in cognitive research. A paradigmatic shift has occurred in this field, leading researchers to move from "social first" to "sensory first" accounts, whereby sensory atypicalities are considered responsible for social symptoms in ASD. The emergence of Predictive coding theories has further given researchers the opportunity to link the context-sensitive behavioural atypicalities in ASD to atypical neural functioning, integrating brain and behaviour levels of explanation. The current PhD project will embrace this paradigmatic shift and adopt an integrated approach to the investigation of the early development of sensory perception that draws on Predictive Coding theories.

1.3.6. ADHD - Genetics

Heritability estimates for ADHD are high, ranging from 70% to 80% (Faraone et al., 2005) and the disorder manifests one of the highest heritability rates when compared to other medical conditions (Wang et al., 2017). The likelihood of

developing ADHD is elevated in siblings of children with ADHD or having a first degree relative with a clinical diagnosis of ADHD and the recurrence estimate is approximately 13% (Miller et al., 2018, 2019). Further, twin and family studies suggest that ADHD may be best understood as a quantitative trait equally heritable across different levels of symptoms severity, rather than as an aetiologically distinct category (Posner et al., 2020; Thapar, 2018). Thus, ADHD manifestations are rarely the consequence of a single gene or genetic mutation.

Evidence from genome-wide association studies indicates that 40% of the heritability in ADHD can be attributed to common genetic variants (Faraone et al., 2015). Specifically, common genetic variants associated to ADHD symptoms are linked to genes regulating dopamine, noradrenaline, serotonin and neurite outgrowth systems (Faraone et al., 2015; Neale et al., 2010). One replicated finding across molecular genetics studies is the over-representation of the DRD4 gene 7-repeat form in children with ADHD (La Hoste et al., 1996). Children with this form appear to be 1.5 times more likely to develop ADHD symptoms, including extreme sensory seeking manifestations (Comings et al., 1999; Swanson et al., 1998). Molecular genetics studies have also reported associations between the DAT110-repeat form and clinically ascertained ADHD (Cook et al., 1995; Curran et al., 2001). Further, it is known that this transporter gene is the main source of action of methylphenidate, which is commonly used to ameliorate ADHD symptoms (Castellanos et al., 2005). Differences in portions of the DNA (i.e. single nucleotide polymorphisms, SNPs) and rare genetic insertions and deletions (i.e. copy number

variations, CNVs) have also been documented in individuals with ADHD and mainly affect regions regulating nicotinic, glutamatergic and γ-aminobutyric acidergic (GABAergic) signalling pathways (Dark, Homman-Ludiye, & Bryson-Richardson, 2018; Dorval et al., 2007; Elia et al., 2012; Naaijen et al., 2017; Williams et al., 2012). Many of these genetic variations are shared with other neurodevelopmental disorders such as ASD and are implicated in several stages of prenatal and postnatal brain development, including early neuronal formation, migration, differentiation and later synaptogenesis and the "wiring" of cortical functional networks (Dark et al., 2018). Further, similar to ASD, also for ADHD many implicated genes are pleiotropic, thus influencing brain development through multiple and complex pathways which are further impacted by postnatal experience-dependent contributions.

1.3.7. ADHD - Environmental contributions

Environmental factors linked to elevated ADHD likelihood include maternal smoking and alcohol use, low birth weight, premature birth and exposure to environmental toxins (Banerjee, Middleton, & Faraone, 2007; Faraone et al., 2015). Early severe maternal deprivation was also found to be a significant predictor of later ADHD in a study following Romanian adoptees, such as the longer the deprivation experienced, the higher the likelihood of developing ADHD symptoms (Stevens et al., 2008). Similar to ASD, also for ADHD environmental contributions are proposed to influence liability through complex non-causal mechanisms,

including gene X environment interactions (e.g. serotonin and dopamine transporter linked polymorphisms), epigenetic effects (e.g. DNA methylation), oxidative stress, inflammation, and general interference with brain signalling pathways (Faraone et al., 2015).

1.3.8. ADHD - Cognitive theories

ADHD is a disorder characterized by substantial heterogeneity. Nonetheless, multiple efforts have been made to canalise the manifestations of ADHD into one explanatory cognitive phenotype. Several cognitive accounts were generated from these efforts, including the: 1) Executive Dysfunction theory; 2) Motivational Dysfunction theory; 3) Delay Aversion theory; 4) Response Variability theory; 5) Processing Speed theory.

The Executive Dysfunction theory proposes a domain general account according to which atypical manifestations of ADHD may be consequent to weak executive functions (EF) (Pennington & Ozonoff, 1996). According to this theory, weak EF would result from atypical prefrontal cortical networks and would represent an atypicality shared with other conditions, including ASD. Neuropsychological studies have provided evidence for this theory. These studies indicate that adults and children with ADHD experience difficulties in tasks of EF, including inhibitory control, sustained attention, working memory and behavioural flexibility (Weyandt & Gudmundsdottir, 2015). However, meta-analyses also suggest that EF difficulties account for no more than 10% of variance in ADHD

symptoms, thus suggesting that none of these atypicalities may be necessary or sufficient to cause ADHD (Willcutt, 2015).

The Motivational Dysfunction theory proposes that the behaviours of individuals with ADHD may be driven by enhanced sensitivity to reward and punishment contingencies (Luman, Oosterlaan, & Sergeant, 2005). Accordingly, individuals with ADHD would choose an immediate reward irrespective of previous reinforcements or relatively large delayed rewards and they would only manifest reinforcement learning when rewards are received immediately and frequently. This theoretical account was initially elaborated following observation that individuals with ADHD frequently manifest impulsive behaviours (Rapport, Tucker, DuPaul, Merlo, & Stoner, 1986; Tripp & Alsop, 2001). Further, elevated sensitivity to reward and punishment contingencies in individuals with ADHD was proposed to result from lower levels of tonic dopamine which, in turn, could be consequent to enrichment of the DRD4 gene 7-repeat form (Sagvolden, Johansen, Aase, & Russell, 2005). Mixed evidence in support of this proposal exists in the literature. In particular, while some reports documented differences in performance on reinforcement tasks in individuals with ADHD relative to control participants (Slusarek, Velling, Bunk, & Eggers, 2001), others documented comparable performance (Shanahan, Pennington, & Willcutt, 2008). Thus, whether ADHD may be partly attributed to motivational factors is still under debate.

The Response Variability theory proposes that individuals with ADHD may manifest frequent, transient and impairing fluctuations in cognitive functioning

(Castellanos & Tannock, 2002; Willcutt, 2015). This account was elaborated following observation that children and adults with ADHD frequently manifest slower and more variable reaction times on speeded, effortful tasks (Castellanos & Tannock, 2002; Johnson et al., 2007; Kofler et al., 2013). More variable responses in ADHD were linked to the dopamine transporter gene DAT1, which is the main site of action of methylphenidate (Castellanos et al., 2005). Despite this evidence, several issues underlie models of response variability in ADHD. In particular, it is currently unclear whether elevated response variability in ADHD may be a core atypicality of the condition or result from difficulties in other cognitive domains, including attention control, working memory and arousal regulation.

The Processing Speed theory suggests that slow processing speed may be a primary characteristic of ADHD, affecting performance across a variety of tasks (Willcutt, 2015). This account was initially proposed following observation that individuals with ADHD frequently report difficulties on reading measures of processing speed (e.g. naming speed task) (McGrath et al., 2011; Rucklidge & Tannock, 2002; Shanahan et al., 2006). Further, evidence indicates that individuals with ADHD manifesting higher processing speed are more responsive to interventions aimed at mitigating the severity of their symptoms (Shanahan et al., 2006). However, slower processing speed in reading tasks could also be explained as resulting from difficulties retrieving content from memory and/or planning motor output. Thus, if slower processing speed is indeed a core feature of ADHD, it should occur across tasks. Results from a meta-analysis of 319 studies disconfirmed this

prediction, indicating that slow processing speed in individuals with ADHD does not consistently manifest across experimental tasks (Kofler et al., 2013).

More recently attempts have been made to utilise *Predictive Coding theories* to explain core ADHD manifestations. I direct the reader to sections 1.3.3 and 1.6 for a discussion of the cornerstones of these theories. In general, Predictive Coding theories propose a domain general explanation of the context-sensitive human behaviour that is grounded in neurobiology and neuroanatomy (Friston & Kiebel, 2009; Kok & De Lange, 2015). Thus, these theories offer a framework for understanding behaviour in both individuals with typical or atypical developmental outcomes. In the context of ADHD, Predictive Coding theories hypothesize putative atypicalities in building top-down predictions to foster increased reliance on incoming and novel sensory input. In turn, reduced reliance on top-down predictions and increased reliance on incoming sensory stimulation would explain attention and inhibition difficulties, distractibility and elevated sensory seeking in individuals with ADHD. Preliminary evidence supporting this theoretical proposal exists (Gonzalez-Gadea et al., 2015). However, research in this field is in its infancy and more empirical studies are needed to confirm or falsify Predictive Coding hypotheses in the context of ADHD.

In summary, several cognitive theories have been proposed to explain the behavioural profile of individuals with ADHD. Each of these models has fostered progress in our understanding of the condition. However, none of these accounts has revealed capable of explaining the whole spectrum of behavioural atypicalities

in ADHD. Indeed, many of these theoretical explanations may not be mutually exclusive. Predictive Coding theories may offer a route towards integration of various levels of explanation, although more empirical research is necessary to corroborate this notion.

1.3.9. ADHD - Neurobiological explanations

Early brain insult was initially proposed as chief cause of ADHD symptoms and a few studies documented a link between hypoxic brain damage and later ADHD manifestations (Barkley, 2015). However, further research indicated that the vast majority of children with an ADHD diagnosis does not have a history of brain insult. In fact, brain insult accounts only for a small proportion of cases diagnosed with the disorder (Rutter, 1977). Progress had been made since this original formulation and ADHD is now understood as a disorder resulting from atypical trajectories of whole brain development. As reviewed in section 1.3.6, this conceptualization of the disorder is supported by molecular genetics studies, which indicate that many genes implicated in ADHD directly impact neurodevelopment from the prenatal stages.

Aligning to the Executive Dysfunction theory proposed in the cognitive domain, a first line of investigation assessed the possibility that ADHD may be characterised by *structural and functional atypicalities in brain regions mediating EF* (i.e. prefrontal cortex, basal ganglia and cerebellum) (Barkley, 2015). This investigation was prompted by evidence that children and adults suffering injuries

to those brain regions display atypical inhibitory control, emotion regulation and motivation – a cluster of symptoms sometimes described as "dysexecutive syndrome" and resembling those manifesting in individuals with ADHD. Neuropsychological studies have provided indirect evidence for this prediction by indicating that adults and children with ADHD experience difficulties in tasks of EF (Weyandt & Gudmundsdottir, 2015). Structural MRI studies have provided more direct evidence by revealing reduced brain volume in the brain regions mediating EF including the prefrontal cortex, the basal ganglia and the cerebellum of adults and children with ADHD (Barkley, 2015; Valera, Faraone, Murray, & Seidman, 2007). Direct evidence also exists that the size of frontal cortical regions and basal ganglia predicts the degree of difficulty experienced by children with ADHD in tasks of inhibitory control and sustained attention (Casey et al., 1997; Semrud-Clikeman et al., 2000). Thus, this evidence suggests that atypicalities in brain regions mediating EF may underlie ADHD manifestations. However, the extent to which such atypicalities may be present in early development and/or change over time remains unexplored.

A second line of research investigated the possibility that ADHD may be underpinned by *atypical trajectories of whole brain development since early in life*. Studies attempted to investigate this prediction by collecting longitudinal MRI scans from children with ADHD and control children over many years. Results from this research suggested that cortical maturation, defined as the age at which peak cortical thickness is achieved, is delayed in children with ADHD relative to

control children – a result that could be driven by mechanisms such as delayed dendritic spine growth and formation of supporting glia and vasculature (Shaw et al., 2007). Furthermore, delayed cortical thinning manifests in children with ADHD (Shaw et al., 2007) and in typically developing children with varying levels of hyperactive and impulsive symptoms (Shaw et al., 2011). Thus, evidence from this line of research indicates that altered brain development underlies the progressive emergence of ADHD symptoms and may explain the dimensionality of many ADHD manifestations.

Building on evidence of atypical trajectories of whole brain development in ADHD, a third line of research investigated the possibility that the disorder may be characterized by *atypical brain structural and/or functional connectivity* (Konrad & Eickhoff, 2010). Results from studies assessing structural connectivity in ADHD are mixed, with some reports documenting under-connectivity (as indexed by reduced white matter volume and axonal density of frontal lobes white matter fiber tracts) (Wu et al., 2019; Castellanos et al., 2002), and others documenting over-connectivity (as indexed by elevated white matter volume and fractional anisotropy) (Li et al., 2010; Peterson et al., 2011; Seidman et al., 2006). It is possible that developmental changes may underlie these manifestations, given that under-connectivity in ADHD is mainly reported in children and over-connectivity in adults. Studies investigating functional connectivity in individuals with ADHD mainly focused on disturbances of resting-state networks, in particular the default mode network (DMN). The DMN is a network of brain regions

exhibiting higher activity and stronger functional connectivity when people are not engaged in particular tasks. Lower attenuation of the DMN was proposed to underlie many ADHD manifestations, including difficulties in attention control and elevated response variability. However, reports on the functional connectivity of the DMN in ADHD are inconsistent, with some studies documenting under-connectivity (Castellanos et al., 2008) and other studies reporting over-connectivity (Konrad & Eickhoff, 2010). Further, it was proposed that the DMN in individuals with ADHD may be typical at rest, whilst exhibiting reduced attenuation in the transition from rest to task-dependent activities (Castellanos et al., 2008). Currently, evidence for this prediction remains scarce. Fewer studies investigated functional connectivity in individuals with ADHD during cognitive tasks, indicating that under-connectivity may be present during childhood while over-connectivity may exist during adulthood (Konrad & Eickhoff, 2010). Taken together, evidence regarding structural and functional connectivity in ADHD is inconclusive and these contrasting results may be consequent to developmental changes.

Finally, drawing on evidence from ASD research, a fourth line of investigation assessed the possibility that ADHD may be characterised by *atypical E/I balance in putative cortical networks* (Edden, Crocetti, Zhu, Gilbert, & Mostofsky, 2012; Naaijen et al., 2017; Purkayastha, Malapati, Yogeeswari, & Sriram, 2015). This prediction originated from the observation that E/I imbalances exist in several neurodevelopmental disorders comorbid with ADHD, including ASD (Naaijen et al., 2017). As in other disorders, also in ADHD factors

hypothesized to contribute to E/I imbalances include atypical excitatory and inhibitory synapse development, atypical synaptic transmission and plasticity, atypical downstream signalling and intrinsic neuronal excitability (Tatti et al., 2017). These atypicalities would be mediated by altered balance in the synthesis of the glutamatergic and γ-aminobutyric acidergic (GABAergic) neurotransmitters. Studies using MRS suggest that GABA concentrations are lower and glutamate concentrations are higher in individuals with ADHD relative to control participants (Purkayastha et al., 2015). Molecular genetics studies and animal models further suggest that an association exists between elevated functioning of the glutamatergic system in putative cortical areas (i.e. prefrontal cortex and basal ganglia) and symptoms of inattention, hyperactivity and impulsivity (Burton & Fletcher, 2012; Miller, Pomerleau, Huettl, Gerhardt, & Glaser, 2014; Naaijen et al., 2017). On the other hand, atypical functioning of the GABAergic system in the prefrontal cortex appears to be linked to inhibitory control difficulties. Despite this evidence, the extent to which atypical GABA and glutamate concentrations may be a primary characteristic of ADHD, or secondary to comorbid conditions and/or atypical functioning of other neurotransmitter systems remains unclear (e.g. dopamine is known to regulate the glutamatergic pathway; thus, reduced dopamine neurotransmission in ADHD could lead to overproduction of glutamate and consequent E/I imbalances; Naaijen et al., 2017; Purkayastha et al., 2015). Further, the exact mechanisms underlying the link between E/I imbalances and symptoms of inattention, hyperactivity and impulsivity are currently unknown.

1.4. ASD and ADHD: Comorbidity

The use of the term "comorbidity" is relatively new in the field of neurodevelopmental disorders, with the first descriptions appearing in the 1980s (Gillberg, 1983; Gillberg & Rasmussen, 1982). Since these formulations, the expression has been increasingly used to emphasize that many neurodevelopmental disorders rarely present in isolation.

ASD and ADHD are neurodevelopmental disorders manifesting substantial overlap in traits and symptoms (Leitner, 2014; Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010). These disorders co-occur more often than expected based on their individual incidence, with co-occurrence rates ranging between 40% and 80% (Antshel & Russo, 2019; Joshi et al., 2017). Co-aggregation is reported in individuals and families (Ghirardi et al., 2018) and later-born siblings of children with ASD or ADHD appear to be at elevated likelihood to develop both conditions (Miller et al., 2019).

Twin studies have been employed to investigate the aetiological link between ASD and ADHD. The twin study design is based on the fact that monozygotic twins (identical, MZ) share the entire DNA code, whereas dizygotic twins (fraternal, DZ) share only 50% of their DNA. Given that twins raised in the same family share the same environment and all or part of the DNA code, comparing the within-pair similarity of MZ and DZ twins on a specific trait enables researcher to establish overlap linked to genetic factors (Plomin, DeFries, & McClearn, 2008). Research employing the twin study design has confirmed an

aetiological link between ASD and ADHD (Nijmeijer et al., 2008; Ronald, Larsson, Anckarsäter, & Lichtenstein, 2014; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008) and indicated that correlated genetic variances are present between the conditions (Ronald et al., 2008; Stergiakouli et al., 2017). Thus, some common developmental mechanisms are proposed to underlie the emergence of ASD and ADHD but specific pathways are yet to be identified (Johnson et al., 2015; Jones et al., 2014).

Common genes with copy number variations or single nucleotide polymorphisms have been identified in ASD and ADHD. Many of these common genes are expressed early in prenatal development and are involved in regulating a variety of functions linked to neurodevelopment (Courchesne et al., 2020, 2019; Dark et al., 2018). Crucially, the vast majority of these common risk genes are pleiotropic and affect multiple functions at different developmental stages. This property explains why common genetic contributions may lead to shared and distinct manifestations in ASD and ADHD. However, despite increasing knowledge of the shared genetic factors between ASD and ADHD, our understanding of the pathways from common genes to traits and symptoms remains limited. Limited understanding of the mechanisms behind comorbid ASD and ADHD manifestations is likely a consequence of the complexity of these conditions, whereby multiple genetic factors interact in the context of several environmental factors to give rise to the observable phenotypes (Cristino et al., 2014; Dewey, 2018). One potential route to better understanding the comorbidity

between ASD and ADHD is through the investigation of the common and distinct developmental pathways between the disorders. This investigation can be conducted by assessing early markers as potential infant predictors of later ASD and/or ADHD traits. The following section will provide a more detailed account by presenting theoretical models of comorbidity and by clarifying why studying ASD and ADHD through a developmental lens is fundamental to unravel the causal mechanisms leading to observable traits and symptoms.

1.4.1. Theoretical models of comorbidity

Several theoretical models have been proposed to explain comorbidity between multifactorial disorders (Dewey, 2018; Neale & Kendler, 1995). As reported in Table 1, these models include: 1) *alternate forms*, where two disorders have the same underlying continuum of liability, thus sharing genetic and environmental risk factors; 2) *random multiformity*, where two disorders have different dimensions of liability but the presence of one disorder can increase the chance of developing the other disorder; 3) *three independent disorders*, where two disorders have different dimensions of liability and comorbidity is caused by a third, unrelated liability; 4) *one disorder as the early manifestation of the other*, where the second condition results from compensatory and compounding effects of the first disorder; 5) *overlapping liability*, where two disorders manifest together due to overlapping genetic and environmental risk factors; 6) *potentiation*, where a general susceptibility to psychopathology drives the emergence of the conditions; 7) *cross-*

assortative mating, where non-random mating causes heritability and comorbidity of two conditions.

Table 1 summarises predictions and evidence for/against each of these theoretical models in the context of ASD and ADHD. Overall, evidence suggests that ASD and ADHD are likely not alternate forms of a common liability dimension, nor they should be considered independent disorders. Conversely, evidence supports the notion that comorbidity between ASD and ADHD may result from some overlapping liabilities. Overlapping liabilities in ASD and ADHD would explain the existence of common genetic factors, the presence of common *and* distinct infant markers predicting later ASD and/or ADHD manifestations and both concurrent and successive comorbidity. Indeed, while it is usually assumed that comorbidity should manifest concurrently (i.e. comorbid manifestations appearing together), longitudinal research indicates that individuals with ASD or ADHD frequently manifest successive comorbidity (i.e. comorbid manifestations appearing at different points in time) (Dewey, 2018). Thus, children may meet diagnostic criteria for ASD or ADHD at one point in time but develop comorbid manifestations over time (Gotham, Pickles, & Lord, 2012; Olsson et al., 2016). It follows that prospective longitudinal studies examining the developmental trajectories of ASD and ADHD from infancy are essential to determine the long-term effects of concurrent and successive comorbid manifestations, to clarify the aetiology of the disorders and to better understand the causal antecedents linked to the emerging phenotypes.

Table 1. *Predictions and evidence for/against theoretical models of comorbidity in the context of ASD and ADHD*

Model	Genetics: Predictions and evidence	Early markers: Predictions and evidence	Support
Alternate Forms One dimension of liability gives rise to different manifestations	*Prediction*: 1-Common genes confer liability for ASD or ADHD. *Evidence (+)*: 1-Shared de novo and rare genetic CNVs identified in ASD and ADHD (Ronald et al., 2008; Stergiakouli et al., 2017). *Evidence (-)*: 1-Distinct loads of genetic variants associated with either ASD or ADHD (Solberg et al., 2019).	*Prediction:* 1-Absence of disorder-specific infant markers. *Evidence (-)*: 1-Early differences in certain infant markers, i.e. head circumference, motor milestones, activity and inattention (Johnson et al., 2015).	Scarce
Random multiformity Two disorders result from different dimensions of liability but one disorder can increase the chance of developing the other disorder.	*Prediction*: 1-Different genes should confer major liability for either ASD or ADHD. *Evidence (+)*: 1-Distinct loads of genetic variants associated with either ASD or ADHD (Solberg et al., 2019). *Evidence (-)*: 1-Shared *de novo* and rare genetic CNVs identified in ASD and ADHD (Ronald et al., 2008; Stergiakouli et al., 2017).	*Prediction:* 1-Absence of common infant markers. 2-Additive effects of ASD and ADHD in comorbid ASD+ADHD *Evidence (+)*: 1-Evidence for early additive effects of comorbid ASD+ADHD (Gliga, et al., 2015; Shephard et al., 2019; Tye et al., 2014, 2013). *Evidence (-)*: 1-Common infant markers between ASD and ADHD, i.e. similarities in achieving language milestones (Johnson et al., 2015).	Scarce
Three independent disorders Two disorders result from different liabilities. The comorbid condition is a	*Prediction*: 1-Different genes should confer major liability for ASD, ADHD or ASD+ADHD. *Evidence (-)*: 1-Shared *de novo* and rare genetic CNVs identified in ASD and ADHD (Ronald et al., 2008; Stergiakouli et al., 2017).	*Prediction:* 1-Absence of common infant markers; specific and independent infant markers associated with comorbid ASD+ADHD. 2-Comorbidity between ASD and ADHD should appear at chance rate.	Null

different disorder and results from an independent liability.	2-no report of specific genetic CNVs only associated to comorbid ASD+ADHD.	*Evidence (-)*: 1-Common infant markers between ASD and ADHD, i.e. similarities in achieving language milestones (Johnson et al., 2015). 2-Comorbidity between ASD and ADHD ranges from 40% to 80% (Antshel & Russo, 2019; Joshi et al., 2017). 3-Evidence for early additive effects of comorbid ASD+ADHD (Gliga, et al., 2015; Shephard et al., 2019; Tye et al., 2014, 2013).	
One disorder as the early manifestation of the other disorder The second disorder is a result of compensatory and compounding effects of the first disorder.	*Prediction:* 1-Common genes should confer liability for ASD and ADHD. *Evidence (+)*: 1-Shared *de novo* and rare genetic CNVs identified in both ASD and ADHD (Ronald et al., 2008; Stergiakouli et al., 2017). *Evidence (-)*: 1-distinct loads of genetic variants associated with either ASD or ADHD (Solberg et al., 2019).	*Prediction:* 1-Successive stages of early markers, traits and symptoms presentation. *Evidence (+)*: 1- ADHD age of onset (12 years) is later than ASD age of onset (3 years) according to DSM-5. *Evidence (-)*: 1- Concurrent presentation of infant markers specifically predicting ASD or ADHD (Johnson et al., 2015). 2-Mixed evidence concerning which of the two disorders would appear first – possibly driven by diagnostic bias (Antshel & Russo, 2019; Sokolova et al., 2017; Stevens, Peng, & Barnard-Brak, 2016).	Scarce
Overlapping Liability Two disorders can manifest together due to overlapping liabilities. This implies presence of common and distinct liability factors.	*Prediction:* 1-Common genes should confer liability for ASD and ADHD. 2-Overlap in genetic and environmental factors linked to ASD and ADHD should be present. *Evidence (+)*: 1-Shared *de novo* and rare genetic CNVs identified in both ASD and ADHD (Ronald et al., 2008; Stergiakouli et al., 2017). 2- distinct loads of genetic variants associated with either ASD or ADHD (Solberg et al., 2019).	*Prediction:* 1-Common *and* distinct infant markers associated to ASD and ADHD. 2-Additive effects of ASD and ADHD in comorbid ASD+ADHD. 3-Co-occurrence of correlated features rather than complete overlap in symptomatology. *Evidence (+)*: 1-Similarities and differences within and across developmental domains emerging from *infant sibling designs* (i.e., differences: head circumference, motor milestones, activity and inattention; similarities: language development) (Johnson et al., 2015).	Strong

		2-Significant evidence for early additive effects of comorbid ASD+ADHD (Gliga, et al., 2015; Shephard et al., 2019; Tye et al., 2014, 2013).	
Potentiation A general susceptibility to psychopathology drives emergence of the disorders.	*Prediction:* 1-A general genetic factor (*p factor*) should underlie all psychopathology; *Evidence (+)*: 1-General genetic factor that influences major psychiatric disorders reported (Pettersson et al., 2019). 2-Common genetic variants associated to ADHD also influence genetic liability towards broad childhood psychopathology (Brikell et al., 2018). 3- Associations documented between general factors, including pre-term birth and pre-natal stress exposure, and both ASD and ADHD (Bora, Pritchard, Chen, Inder, & Woodward, 2014; Johnson & Marlow, 2011).	*Prediction:* 1-Early markers for ASD and/or ADHD present but symptoms can wax and wane. 2-Possibility to develop ASD and/or ADHD later in life; *Evidence (+)*: 1-Late-onset ADHD reported and explained as consequent to susceptibility to general psychopathology (Manfro et al., 2019). *Evidence (-)*: 1-No convincing evidence that ASD or ADHD symptoms wax and wane or disappear with development (Ronald, 2019). 2-Most prominent studies on *p factor* have not included ASD (Ronald, 2019).	Moderate
(Cross) assortative mating Distinct liabilities exist but non-random mating causes the heritability and comorbidity of disorders.	*Prediction:* 1-Bias for pairing of individuals with the same (or complementary) disorders increases genetic variance in the offspring and determines high within/between conditions genetic correlations. *Evidence (+)*: 1-Non-random mating reported to occur in psychiatric conditions but not in non-psychiatric conditions (Nordsletten et al., 2016). 2-Moderate genetic correlations operating between ASD and ADHD (Ronald et al., 2008; Stergiakouli et al., 2017).	*Prediction:* 1-Early emergence of symptoms due to high heritability. 2-Familial environment contribute to symptoms emergence. *Evidence (+)*: 1-Disorders exhibiting the highest degree of non-random mating are those emerging in early development (i.e., ASD and ADHD) (Nordsletten et al., 2016). *Evidence (-)*: 1- no explanation for concurrent presence of common and distinct markers associated to ASD and ADHD; 2-one report that cross-assortative mating does not provide an explanation for the comorbidity between ASD and ADHD (van Steijn et al., 2012).	Moderate

1.4.2. The current approach – Studying ASD and ADHD through a developmental lens

Johnson and colleagues proposed that neurodevelopmental conditions such as ASD and ADHD may be better understood by embracing a developmental lens (Johnson et al., 2015). According to this theoretical perspective, "*taking development seriously"* (Karmiloff-Smith, 1999) would enhance understanding of the aetiology, heterogeneity and mechanisms of change underlying these conditions. This elaboration is based on the notion that ASD and ADHD symptoms may result from complex interactions between early emerging vulnerabilities and multiple aspects of the child's prenatal and postnatal environment. Thus, while certain symptoms may reflect vulnerabilities linked to genetic or environmental contributions, other symptoms may be the output of compensatory or cascading effects following atypical interaction with the environment (Gliga, Jones, Bedford, Charman, & Johnson, 2014; Johnson et al., 2015). It follows that studying early developmental pathways to later traits and symptoms is crucial to clarify how ASD and ADHD unfold from birth.

In accordance with evidence from molecular genetics studies, this framework poses early vulnerabilities, including E/I imbalances and alterations in synaptogenesis, synaptic functioning and cortical "wiring", to cause atypical neural functioning during critical periods which would, in turn, trigger adaptive or compensatory responses shaping the final observable phenotypes. Early vulnerabilities would result from broadly expressed genetic risk factors and would

be shared across many neurodevelopmental conditions. These vulnerabilities would initially impact sensory and motor system, given that such systems are the first to undergo specialization during development (Chomiak & Hu, 2017; Gao, Lin, Grewen, & Gilmore, 2017). Thus, temporally sensitive phenotypes would characterise these conditions and early manifestations would appear in domains qualitatively different from core diagnostic domains (Thomas, Davis, Karmiloff-Smith, Knowland, & Charman, 2016). However, due to the hierarchical progression of brain development, early-emerging sensory and motor atypicalities would impact later developmental stages, including the specialization of social and cognitive systems.

Importantly, this theoretical account proposes that mechanisms of whole-brain adaptation may underlie the emergence of observable phenotypes in these conditions (Johnson, 2017). Mechanisms of whole-brain adaptation proposed to underlie the emergence of observable phenotypes include 1) *recruitment of redundant neural pathways* to compensate for the loss of efficiency in other systems; 2) *reorganization of neural pathways* to optimize neural functioning; 3) *changes in the timing of developmental trajectories*, which could be driven by altered plasticity or developmental delays; 4) *niche construction*, whereby individuals may choose environments optimally suiting their neural processing styles. By acknowledging the existence of mechanisms of whole-brain adaptation this framework emphasizes the developmental nature of ASD and ADHD and highlights two major points: 1) most later symptoms of the disorders may not reflect

their original causes; 2) most risk genes linked to later manifestations may code for compounding or compensatory manifestations in these disorders.

In summary, the theoretical account proposed by Johnson and colleagues (2015, 2017) emphasizes the importance of embracing a developmental lens to study neurodevelopmental disorders such as ASD and ADHD, as well as comorbid manifestations between these conditions. Studying how ASD and ADHD unfold from birth would enable researchers to characterize the causal antecedents linked to alterations in early brain development, thus clarifying the aetiology, heterogeneity and developmental pathways underlying these complex and multifactorial conditions. Better understanding of the early developmental pathways of these disorders within a trans-diagnostic framework would, in turn, guide precision therapeutics and provide insights into the timing of early interventions (Finlay-Jones et al., 2019).

1.5. Sensory perception in the early development of ASD and ADHD

As reviewed in section 1.4.2, a developmental approach to the investigation of ASD and ADHD leads to the prediction that the earliest atypicalities in these disorders should manifest in the sensory and motor domains.

Sensory atypicalities, manifested as either increased or decreased sensitivity or as atypical seeking of sensory input, are reported in 90% of children with ASD (Jasmin et al., 2009; Leekam, Nieto, Libby, Wing, & Gould, 2007) and 50% of children with ADHD (Yochman, Parush, & Ornoy, 2004). The

developmental trajectory of sensory atypicalities in these disorders remains largely unknown, although some evidence suggests that chronological age plays a role in children's sensory features (Ben-Sasson et al., 2009). Evidence further suggests that sensory atypicalities may have detrimental effects on the development of motor skills (Ting, 2013) and on later social and adaptive functioning (Jasmin et al., 2009; Mattard-Labrecque, Ben Amor, & Couture, 2013). For example, a child who is hypersensitive to tactile stimulation may refrain from seeking contact with caregivers, limiting early opportunities for socialization. Similarly, a child who is hypersensitive to bright lights or noises may refrain from everyday activities, limiting motor exploration of the environment and spending less time interacting with peers. The few studies addressing the impact of sensory atypicalities in ASD and ADHD support first-hand and anecdotal accounts, indicating that elevated sensory manifestations relate to more severe social symptoms (Damiano-Goodwin et al., 2018; Hilton et al., 2010a; Jasmin et al., 2009; Mattard-Labrecque et al., 2013) and affective symptoms (Ben-Sasson et al., 2008), more disrupted classroom behaviour (including inattention and oppositional behaviour) and academic underachievement (Ashburner, Ziviani, & Rodger, 2008; Davis, Pass, Finch, Dean, & Woodcock, 2009; Sanz-Cervera, Pastor-Cerezuela, González-Sala, Tárraga-Mínguez, & Fernández-Andrés, 2017). Further, there is evidence that sensory manifestations in children with these conditions may impact the family environment (i.e. by limiting participation in work or leisure activities and by leading families to adopt strategies minimising children's distressing reactions to

sensory experiences; Bagby, Dickie, & Baranek, 2012; Schaaf, Toth-Cohen, Johnson, Outten, & Benevides, 2011). However, our knowledge of the role played by early emerging sensory atypicalities in infancy and their long-term effects on children's social and cognitive development is limited. In particular, there is a fundamental need for longitudinal studies mapping the developmental trajectories of sensory manifestations from infancy, as well as the impact of early sensory features on ASD and/or ADHD traits emerging in toddlerhood. The following section reviews methodological considerations and key evidence emerged from prospective longitudinal studies investigating the early development of sensory perception in infants at elevated familial likelihood of ASD and/or ADHD.

1.5.1. Prospective longitudinal studies of infants at elevated likelihood of ASD and/or ADHD – Design and methodology

Research investigating the early manifestations of ASD and/or ADHD may use retrospective or prospective study designs (Jones et al., 2014; Szatmari et al., 2016; Zwaigenbaum, Bryson, & Garon, 2013). Retrospective study designs rely on caregiver reports or video recordings and investigate the early markers of the conditions after a diagnosis has been made. These designs enable assessment of the early manifestations of the disorders in clinically ascertained samples but have several limitations. While caregiver reports and home video recordings can highlight the early behavioural markers of ASD and ADHD, their correlational nature limits the ability to disentangle the mechanisms underlying the observed

manifestations. Furthermore, caregiver reports may be undermined by recall bias and home videos may have limited accuracy due to lack of standardized procedures.

In contrast to retrospective study designs, prospective study designs enable investigating the early markers of ASD and/or ADHD before a clinical diagnosis is made. These studies follow infant siblings of children with ASD and/or ADHD from infancy until 3-5 years, when diagnoses are possible. A control group of infant siblings of children with no family history of the disorders is followed in parallel. Current evidence indicates that the within-condition recurrence rate for ASD is 12.03% and for ADHD is 12.47% (Miller et al., 2019). Furthermore, infant siblings of children with ASD or ADHD manifest elevated cross-condition recurrence rates. The recurrence of ADHD in siblings of children with ASD is estimated to be 3.8% and the recurrence of ASD in siblings of children with ADHD is estimated to be 1.92%, in both cases higher than the population rate of up to 3.4% for ADHD and up to 1.9% for ASD (Maenner et al., 2020; Polanczyk et al., 2015; but see Miller et al., 2019). Thus, by comparing prospective data collected from infants who later do or do not meet criteria for ASD and/or ADHD, researchers can identify early markers of later traits and symptoms. Further, comparing early markers between the disorders can clarify common and distinct developmental pathways to later manifestations.

Several practical considerations are worth noting in regard to the implementation of prospective study designs. Firstly, these designs require multiple assessments of the same participants from an early age. Assessments are usually

conducted in laboratory-based settings and enable researchers to collect high-quality and objective measures of children's neural, cognitive and social functioning. Alongside objective measures, researchers may collect caregiver reports and may administer multiple standardized developmental and/or clinical assessments. It follows that the families' compliance is fundamental for prospective longitudinal studies to be successful, as attrition may detrimentally impact the completion of these investigations. However, successful prospective longitudinal studies enable collection of unique datasets, which can invaluably enrich researchers' understanding of the developmental pathways within and between conditions, support the development of screening tools for early markers of the disorders and lay the translational foundations for early interventions protocols (Finlay-Jones et al., 2019; Jones et al., 2014).

1.5.2. Prospective longitudinal studies of infants at elevated likelihood of ASD and/or ADHD - Key evidence

Over the past 15 years, several studies investigated the early development of infants with an older sibling with ASD. Evidence from this research suggests that core diagnostic manifestations in ASD do not appear until the second year of life. Rather, the earliest detectable markers in ASD are related to sensory and motor functions (Gliga et al., 2014; Johnson et al., 2015; Jones et al., 2014). Sensory and motor atypicalities manifest from 6 months of age and predict later emerging traits and symptoms. In contrast, relatively fewer studies assessed the early development of

infants with an older sibling with ADHD. However, current evidence suggests that also in ADHD the earliest detectable markers may not pertain to core diagnostic domains (Johnson et al., 2015; Sullivan et al., 2015).

1.5.2.1. Early development of ASD – Observational evidence

Observational research on the early development of ASD has been conducted through early detection/monitoring instruments and parental reports. Both approaches have identified atypical behavioural manifestations appearing in infancy or toddlerhood. In the context of prospective longitudinal studies on the early development of ASD, these approaches have been applied, alone or in combination, to predict later symptoms or diagnostic outcome assessed at 24 or 36 months.

Much observational research in this field has been conducted using the *Autism Diagnostic Observation Schedule - Toddler Module* (ADOS-Toddler; Lord, Rutter, DiLavore, & Risi, 2008). The ADOS-Toddler is designed for infants/toddlers aged 12-30 months and it is reported to have 88% sensitivity (i.e. the ability to detect a true positive) and 91% specificity (i.e. the ability to detect a true negative). The ADOS-Toddler evaluates behavioural manifestations spanning language and communication, reciprocal social interaction, play and stereotyped or restricted behaviours. Generally, studies assessing the early development of ASD using the ADOS-Toddler have indicated that scores on the instrument at 12 months are predictive of diagnostic outcomes assessed with standardized measures at 36

months (Rowberry et al., 2014). However, contrasting results highlighting the heterogeneity of ASD manifestations since early in development exist in the literature. For example, Macari and collaborators (2012) reported scores on the ADOS-Toddler at 12 months to have limited utility for predicting a clinical best estimate diagnosis of ASD at 24 months (i.e. scores on the instrument at 12 months revealed to be highly overlapping between children with later typical relative to atypical developmental outcomes).

Observational research on the early development of ASD has also employed the *Autism Observation Scale for Infants* (AOSI; Bryson, Zwaigenbaum, McDermott, Rombough, & Brian, 2008). The AOSI is appropriate for infants aged 6-18 months and it is reported to have 38% sensitivity and 86% specificity. The AOSI provides an assessment of early ASD manifestations in the domains of social functioning, imitation and sensory-motor functioning. Since its standardization, the AOSI has been used in various prospective longitudinal studies on the early development of ASD (for a review see Bryson & Zwaigenbaum, 2014). Evidence from this research suggests that total scores on the AOSI at 6 months do not predict ASD symptoms at 24 months (as assessed by the ADOS; Lord et al., 2012). However, by 12 months, scores on the AOSI are predictive of ASD traits at 24 months and of diagnostic outcomes at 3 years (Gammer et al., 2015; Zwaigenbaum et al., 2005). Recently, Bedford and collaborators further reported scores on the AOSI at 14 months to significantly predict an ASD diagnosis during mid-childhood (Bedford et al., 2017). Despite this evidence, research also indicates that many

infants manifesting high AOSI scores at 12 months may not progress towards an ASD diagnosis but rather show resolution of symptoms (Macari et al., 2012), thus emphasizing the need for a cautious clinical interpretation of the instrument.

Alongside early monitoring/assessment instruments, researchers interested in studying the early development of infants at elevated likelihood of ASD have employed parental reports. Parental reports are relatively inexpensive observational tools and enable quick data collection. However, parental reports may be limited by recollection bias (Ben-Sasson & Carter, 2012; Dietz, Swinkels, van Daalen, van Engeland, & Buitelaar, 2006). A common parent-reported measure for the assessment of early ASD manifestations in toddlers aged 18-24 months is the *Quantitative Checklist for Autism in Toddlers* (Q-CHAT; Allison et al., 2008). The instrument assesses the frequency of occurrence of behaviours across several domains, including attention, pretend play, language development, repetitive behaviours and social communication. A shortened version of the Q-CHAT consisting of the ten most discriminative items is also available (Q-CHAT 10). The instrument is reported to have sensitivity up to 91% and specificity up to 89%. Preliminary studies with the Q-CHAT 10 reported the instrument to be effective in retrospectively discriminating pre-school children with ASD from community control children (Allison, Auyeung, & Baron-Cohen, 2012). However, more recent investigations suggested that while the Q-CHAT 10 may be appropriate for detecting ASD signs at 18 and 24 months in children receiving an ASD diagnosis

at 3 years, the specificity of the instrument may be too low for its clinical application (Raza et al., 2019).

Another common parent-reported instrument to investigate ASD manifestations at 12 months of age is the *First Year Inventory* (FYI; Baranek, Watson, Crais, & Reznick, 2003). The FYI is reported to have 92% sensitivity and 78% specificity. The instrument assesses the frequency of occurrence of behaviours within the social-communication and sensory-regulatory domains. In particular, the FYI taps into domains similar to those of the ADOS-Toddler and convergence is reported between the two instruments for the detection of ASD manifestations at 12 months (Macari et al., 2018). Further, evidence indicates that the FYI may provide information converging with the AOSI, such that 12-month-old infants scoring high on the FYI also display high scores on the AOSI (Ben-Sasson & Carter, 2012). Since the FYI is composed of two domains, it enables independent quantification of social-communication and sensory-regulation atypicalities. Studies employing this instrument have indicated that 12-month-old infants reporting sensory-regulation atypicalities on top of social-communication difficulties display higher rates of persisting developmental difficulties and lower levels of gross motor development at 3 years (Ben-Sasson & Carter, 2013). Additionally, utilisation of a dual cut-off score (including both social and sensory domains) may increase the specificity of the instrument up to 98% (Ben-Sasson & Carter, 2013).

Beside using the FYI, researchers have used the *Infant-Toddler Sensory Profile* (ITSP; Dunn, 2002) and/or unstandardized semi-structured parental interviews to characterise sensory manifestations in the early development of ASD. The ITSP is a parent-reported measure of children's sensory processing and it exists in two forms: the 0-6 months version and the 7-36 months version (see Chapter 2 for an in-depth discussion of the instrument). In one of the first investigations using the ITSP, Mulligan and White (2012) reported infants at elevated likelihood of ASD aged 11-13 months to manifest significantly lower sensory seeking behaviours compared to age-matched control infants – a result interpreted as indicative of a reduced capacity or motivation to explore the surrounding environment. Germani and colleagues (2014) investigated sensory manifestations using the ITSP in 24-month-old toddlers at elevated likelihood of ASD. Results indicated that toddlers later receiving an ASD diagnosis were rated by parents as manifesting elevated auditory and low registration atypicalities. More recently, Van Etten and collaborators (2017) investigated ITSP scores in infants at elevated likelihood of ASD undergoing repeated assessment at regular intervals from 3 to 36 months of age. While an analysis of age-related effects was not possible due to high attrition rates, the authors compared the distribution of ITSP scores between infants at elevated likelihood of ASD and age-matched control infants across ages. Elevated unusual sensory behaviours (i.e. atypically high or low) manifested in infants at elevated likelihood of ASD in all sensory modalities, with the visual, auditory and tactile modalities being particularly affected. This evidence aligns to

unstandardized parental interviews, whereby concerns about sensory behaviours are reported in infants later diagnosed with ASD from an early age. In particular, evidence indicates that parental concerns about infants' sensory manifestations at 6 months are predictive of an ASD diagnosis at 3 years, whereas concerns about social-communication and repetitive behaviours predict an ASD diagnosis only from 12 months of age (Sacrey et al., 2015).

Taken together, observational evidence on the early development of ASD indicates that heterogeneity in manifestations characterises the disorder since infancy. Observational research further suggests that the earliest manifestations of ASD may not appear in the social-communication domain but rather impact sensory functions. It is possible that early-emerging sensory atypicalities may detrimentally impact the development of social-communication skills in infants with later higher ASD traits. However, given the lack of studies assessing the potential link between sensory and social manifestations in the early development of ASD, this proposal remains speculative.

1.5.2.2. Early development of ADHD – Observational evidence

Research on the early behavioural manifestations of ADHD is in its infancy and limited by a lack of standardized early detection/monitoring instruments. Despite this limitation, evidence from unstandardized assessment and parent-reported measures concurs in suggesting that the first behavioural signs of ADHD may not appear until 12 months of age.

Based on the aetiological overlap between ASD and ADHD, Miller and collaborators (2018) investigated the early signs of ADHD in a sample of infants at elevated likelihood of ASD prospectively assessed from 3 to 36 months and whose diagnostic outcome was determined at 8-10 years of age. Infants later diagnosed with ADHD manifested sustained attention difficulties at 12 months and signs of inattention, hyperactivity and impulsivity were noticed by the examiners during an unstandardized observational assessment at 18 months. Parental concerns about their child's behaviour and temperament further emerged at 36 months. In a recent study, Miller and colleagues (2020) prospectively assessed infants at elevated likelihood of ADHD from 12 to 24 months. Unstandardized observational assessment indicated that infants with an older sibling or parent with ADHD manifested signs of hyperactivity and impulsivity as early as 12 months. Further, parents of infants at elevated likelihood of ADHD reported behavioural and temperamental concerns at 12 months.

Beside unstandardized observational assessments, the standardized *Infant Behaviour Questionnaire Revised* (IBQ-R; Putnam, Helbig, Gartstein, Rothbart, & Leerkes, 2014) and *Early Childhood Behaviour Questionnaire* (ECBQ; (Putnam, Gartstein, & Rothbart, 2006) have recently been adopted for ADHD early surveillance. The IBQ-R is a parent-reported measure of temperament appropriate for use with infants aged 3-12 months. The instrument exists in two forms, the short version and the very short version. The ECBQ serves the same purpose as the IBQ-R but it is appropriate for use with toddlers aged 18-36 months. The instruments

assess various areas of temperament including but not limited to activity, fear, approach and distress to limitation. Additional areas of temperament linked to EF are assessed by the ECBQ (e.g. inhibitory control). There is evidence that high activity at 7, 14 and 24 months and low inhibitory control at 24 months predict more severe inattention and hyperactivity/impulsivity symptoms during mid-childhood (Shephard et al., 2018).

Observational research with infants at elevated likelihood of ADHD has not yet been conducted to assess whether sensory atypicalities may exist in the early development of the disorder. Parental reports of sensory processing indicate that older children diagnosed with ADHD display sensory atypicalities, particularly in the tactile, visual and vestibular modalities (Ghanizadeh, 2011). Heterogeneity in sensory manifestations is also documented, given that children with ADHD may manifest hypersensitivity, hyposensitivity or atypical sensory seeking (Ghanizadeh, 2011). Despite significant heterogeneity, studies suggest that associations exist between atypical sensory processing and core ADHD manifestations, including externalizing behaviours. For example, Mangeot et al., (2001) reported a positive association between parent-reported sensory modulation difficulties in the tactile modality and aggressiveness in children with ADHD. However, evidence also indicates that sensory modulation difficulties may be more prominent in children with ADHD concurrently manifesting comorbid conditions, such as anxiety (Reynolds & Lane, 2009). Thus, given the lack of studies assessing the early development of sensory perception in ADHD, it is currently difficult to establish

whether sensory atypicalities in this disorder should be considered a primary manifestation or a secondary consequence of comorbid conditions.

In conclusion, limited observational research has been conducted to detect early behavioural markers of ADHD in infancy or toddlerhood. Current evidence suggests that the first behavioural signs of the disorder may appear at 12 months. On the other hand, assessment of potential sensory atypicalities in the early development of ADHD has yet to be conducted. Given that sensory atypicalities are reported in older children with ADHD, it is possible that these manifestations may already exist in infancy and impact later core ADHD manifestations.

1.5.2.3. General issues

While considerable observational research on the early development of ASD exists, observational research into the early behavioural signs of ADHD is in its infancy. Atypical sensory features may be present from early in development in both conditions, manifest across modalities, and underlie some of the behavioural manifestations reported later in development. In particular, parental reports and observational studies concur in suggesting that early sensory difficulties may be prodromal to core ASD manifestations. Despite this evidence, several areas warrant further investigation. Firstly, the extent to which atypicalities in sensory perception may underlie core ADHD manifestations from an early age is unclear. Secondly, the putative mechanism underpinning sensory atypicalities in ASD and/or ADHD

is unknown. Finally, our understanding of the potential trajectories linking early sensory features to later observable phenotypes in these disorders remains minimal.

1.5.2.4. Early development of ASD – Experimental evidence

Experimental research on the early signs of ASD has been conducted through a variety of methods, including brain-based assessments and behavioural investigations. Altogether, this research contrasts the notion that ASD may manifest as a disorder tied to one brain network (e.g. "social brain network"). Conversely, accumulating evidence indicates that atypical trajectories of whole-brain development characterise ASD since early in life, impacting first sensory and motor systems and later leading to social manifestations (Johnson, 2017; Lord et al., 2020).

Brain-based assessments concur in suggesting that subtle disturbances to multiple neural structures manifest in the early development of ASD. There is evidence that the developmental trajectory of total brain volume in ASD is marked by a significant overgrowth occurring during the first year of life. Early brain overgrowth is followed by a later slowed or arrested phase of growth, manifesting between childhood and adolescence, and by accelerated decline in brain volume occurring between adolescence and mid-adulthood (Courchesne, Campbell, & Solso, 2011). Structural MRI studies further indicate that cortical surface area hyper-expansion manifests in infants aged 6-12 months with later ASD and precedes brain volume overgrowth appearing at 24 months of age and predicting an

ASD categorical diagnosis and the severity of social symptoms at 2 years (Hazlett et al., 2017; Shen et al., 2017). The exact mechanism behind early brain overgrowth in ASD is unknown, although it is possible that over-proliferation of cortical progenitor cells during prenatal development may impact later mechanisms of post-natal development, including dendritic arborization and synaptic pruning (Hazlett et al., 2017). Further, differences in parameters of fractional anisotropy, axon diameters, fiber density and organization are documented in the first 6 months of life in infants with later ASD (Wolff et al., 2012).

In addition to atypicalities in the structural organisation of the brain, multiple brain functional atypicalities have been identified in the early development of ASD. For example, 6-month-old infants at elevated likelihood of ASD manifest lower spectral EEG power in all frequency bands compared to infants at typical likelihood of the disorder (Tierney, Gabard-Durnam, Vogel-Farley, Tager-Flusberg, & Nelson, 2012). Additionally, developmental trajectories of spectral EEG power between 6 and 24 months of age significantly differ between infants at elevated likelihood of ASD and infants at typical likelihood of the disorder (Tierney et al., 2012). Although the mechanism behind early differences in EEG spectral power remains debated, it is possible that these differences may reflect an early maturational delay in infants at elevated likelihood of ASD. Additional studies into early brain function in ASD have revealed atypicalities in functional connectivity and in neural mechanisms assumed to underlie sensory perception from infancy. For example, there is evidence that EEG frontal and central global connectivity in

the alpha (α) frequency band in 14-month-old infants at elevated likelihood of ASD may predict later ASD categorical diagnosis and the severity of restricted and repetitive behaviours at 3 years (Haartsen et al., 2019; Orekhova et al., 2014). Further, atypical event-related potentials (ERPs) and event-related oscillations (EROs) in EEG tasks assessing early sensory functions in infants with later ASD have been reported as early as 8-9 months of age (Guiraud, Kushnerenko, Tomalski, Davies, Ribeiro, & Johnson, 2011; Kolesnik et al., 2019). Taken together, evidence from brain-based assessments indicates that widespread atypicalities in brain structure and function manifest in ASD since infancy. These atypicalities are not tied to one functional brain system, thus contrasting the notion that ASD may result from early-onset perturbations of the "social brain network". On the contrary, early-emerging neural atypicalities may first impact sensory systems and only later lead to social manifestations that may be further compounded by atypical interaction with the environment.

Aligning to brain-based assessments, *behavioural investigations* have provided additional support for the notion that the earliest manifestations of ASD do not pertain to the social domain. Evidence from this research converges in suggesting that interest and pleasure in responding to others manifest during the first 6 months of life in infants with later ASD (Bryson et al., 2007). Further, 6-month-old infants with later ASD manifest typical social motivation, as assessed

through the *still face paradigm*[1] (Rozga et al., 2011; Young, Merin, Rogers, & Ozonoff, 2009). Eye-tracking evidence also indicates that infants with later ASD are indistinguishable from control infants on a variety of measures of early social orienting (Gliga, Jones, Bedford, Charman, & Johnson, 2014; Johnson, 2014). For example, 6-month-old infants with later ASD exhibit typical scanning of faces and preferential looking to the eyes (Elsabbagh et al., 2014). Similarly, 6 and 12-month-old infants with later ASD manifest spontaneous orienting and engagement with static faces (Elsabbagh, Gliga, et al., 2013). Only after 12 months of age, infants later diagnosed with ASD manifest a decrease in spontaneous orienting to social stimuli (Ozonoff et al., 2010), leading to the profile of reduced orienting to faces and eyes, as well as atypical scanning of social content, reported in older children and adults with the disorder (Jones, Carr, & Klin, 2008; Klin & Jones, 2008; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Rice, Moriuchi, Jones, & Klin, 2012). Altogether, these results challenge the notion that ASD may result from reduced social motivation and consequent social orienting early in development (Johnson, 2014).

While behavioural investigations on early social abilities in ASD do not support the notion that social atypicalities may manifest in infants later diagnosed with the disorder before 12 months of age, consistent support exists for the notion

[1]The *still face paradigm* quantifies the effort made by the infant to re-establish contact with the parent or an experimenter who is looking away. Evidence suggests that when the adult maintains the still face for a few seconds, the infant manifests a negative reaction (Toda & Fogel, 1993; Weinberg & Tronick, 1996).

that sensory and motor atypicalities may be present as early as 6 months of age in infants with later ASD. Transient delays in achieving motor milestones are some of the earliest atypicalities reported in experimental assessments of infants with later ASD. In particular, from 6 months of age, infants with later ASD manifest head lag (Flanagan, Landa, Bhat, & Bauman, 2012), performance delays on measures of fine and gross motor skills (Bolton, Golding, Emond, & Steer, 2012; Libertus, Sheperd, Ross, & Landa, 2014), asymmetric movements and reduced movement maturity (Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998; but see Ozonoff et al., 2008). Further, evidence indicates that motor atypicalities, including atypical fine and gross motor skills, atypical body posture and reduced movement maturity, may persist in ASD throughout the first two years of life (Johnson et al., 2015). Early-emerging motor difficulties in ASD may be underpinned by sensory atypicalities, given that motor skill performance is dependent on appropriate processing of sensory input (Ting, 2013; Whyatt & Craig, 2013). Zwaigenbaum and colleagues (2005) were the first to notice that sensory behaviours, including visual fixations on objects, reduced orienting to name and "hand rubbing" on surfaces or objects, could differentiate 6-month-old infants with later ASD from age-matched typically developing controls. Similarly, Loh and collaborators (2007) noticed that 18-month-old toddlers later diagnosed with ASD tended to cover their ears with hands more frequently than typically developing toddlers during standardized behavioural assessments. Since these reports, a few controlled studies have been conducted to evaluate sensory processing in the early development of ASD, indicating that

sensory atypicalities may manifest from an early age and across modalities. I review below key evidence emerged for each sensory modality.

1.5.2.4.1. Visual modality

There is evidence that infants with later ASD manifest superior visual search abilities at 9 and 15 months (but not at 24 months) (Cheung et al., 2016; Gliga et al., 2015). Further, 9-month-old infants later diagnosed with ASD present a hypersensitive pupillary light reflex (Nyström et al., 2018). Visual fixations and atypical visual engagement with objects (i.e. driven towards the peripheral visual field) have also been reported in infants with later ASD at 6 and 12 months of age (Kaur, Srinivasan, & Bhat, 2015; Ozonoff, Macari, et al., 2008). Atypicalities in the development of visual attention, including longer visual orienting latencies, were also reported at 7 and 14 months in infants with later ASD (Elsabbagh, Fernandes, et al., 2013; Paterson et al., 2013) and further linked to atypical functional specialization of posterior cortical circuits, as indexed by radial diffusivity in white matter fiber tracts (Paterson et al., 2013). Taken together, this evidence suggests that early atypicalities in visual perception manifest in infants with later ASD. However, the exact mechanism behind these atypicalities is unclear. For example, superior visual search in infants with later ASD may result from increased arousal, enhanced perceptual discrimination or elevated reliance on incoming sensory input relative to prior information.

1.5.2.4.2. Tactile modality

Tactile perception remains understudied in the early development of ASD, with no published report investigating this sensory modality in infants with later higher ASD traits through controlled experimental designs or direct assessment of brain function. The available evidence on tactile perception in the early development of ASD comes from observational research and parental reports, which concur in suggesting that infants with later ASD manifest atypicalities in tactile perception (i.e. tactile hypersensitivity) from 3 months of age (Van Etten et al., 2017) and reduced orienting to caregiver touch from 12 months of age (Kadlaskar, Seidl, Tager, Charles, & Keehn, 2019). Given that touch is the first sense to develop (Bremner & Spence, 2017) and the primary modality through which infants and caregivers communicate and interact (Cascio, 2010; Ferber, Feldman, & Makhoul, 2008; Mammen et al., 2016), further experimental assessment of tactile perception in the early development of ASD is needed.

1.5.2.4.3. Auditory modality

There is evidence that infants at elevated likelihood of ASD manifest reduced suppression of repeated auditory stimulation from 8-9 months of age, as assessed through ERPs and EROs in the gamma (γ) band (Guiraud, Kushnerenko, Tomalski, Davies, Ribeiro, Johnson, et al., 2011; Kolesnik et al., 2019). Furthermore, 9-month-old infants at elevated likelihood of ASD manifest reduced audio-visual speech integration (Guiraud et al., 2012). Despite this evidence, the impact of early

auditory atypicalities on later ASD manifestations remains unclear. In particular, only Kolesnik and collaborators (2019) reported results of the associations with 36-month outcome measures. While evidence for an association between early reduced auditory repetition suppression and later poor expressive language emerged in the entire sample, no evidence emerged for an association with ADOS scores at 36 months. Taken together, these results suggest that early atypicalities in auditory perception, including poor auditory repetition suppression, may exist in infants at elevated likelihood of ASD. Poor auditory repetition suppression in the early development of ASD may result from increased reliance on incoming sensory input relative to prior information and be further underlined by E/I imbalances in putative cortical areas. However, the extent to which these atypicalities may causally contribute to later atypical developmental trajectories in ASD remains unclear.

1.5.2.4.4. Oral and olfactory modalities

There is very limited research investigating the early development of the oral modality in infants with later ASD and no report has been published on olfactory perception in the early development of the disorder. Kaur and collaborators (2015) reported reduced oral exploration of objects in 6-month-old infants later diagnosed with ASD. Further, while infants with later typical development manifested a decrease in oral exploration of objects from 9 to 15 months, this decrease was absent in infants with later ASD. Considerable evidence indicates that, over time, typically developing infants manifest a decline in their oral exploration of objects, which

underlies the emergence of more refined manual exploratory strategies (e.g. fingering, transferring and rotating objects) (Belsky & Most, 1981; Ruff, 1984). Thus, limited decline in mouthing in the early development of ASD may signal delayed trajectories of exploratory behaviours which could, in turn, detrimentally impact the development of later social and cognitive skills.

1.5.2.5. Early development of ADHD – Experimental evidence

Experimental research investigating the early signs of ADHD is limited and findings are heterogeneous. Despite this heterogeneity, evidence supports the notion that atypical trajectories of whole-brain development may characterise ADHD since early in life, impacting first sensory and motor systems and later leading to core ADHD manifestations including inattention, hyperactivity and impulsivity.

Preliminary *brain-based assessments* suggested that 3-month-old infants with later ADHD may have smaller head circumference, which could persist until 4 years of age (Gurevitz et al., 2014; Heinonen et al., 2011). Smaller head circumference in early development was also linked to the severity of ADHD symptoms at 4 years (Heinonen et al., 2011), although other studies failed to replicate this result (Johnson et al., 2015). Debate on the utilisation of head circumference measures to infer early-emerging atypicality was later prompted by research suggesting that use of inappropriate norms and failure to control for body size may represent significant confounds (Jones et al., 2014). Evidence from

structural MRI investigations indicates that a smaller corpus callosum at 6 weeks of age may associate with EF difficulties at 4 years (including inhibitory control and emotion regulation difficulties) but not with parental reports of ADHD symptoms (Ghassabian et al., 2013). Further, research on very pre-term infants, who manifest a fivefold increased likelihood to develop ADHD symptoms compared to infants born full-term, suggests that a link exists between total cerebral tissue in infancy and ADHD manifestations in childhood (Bora et al., 2014).

While early-emerging atypicalities in brain function are likely a characteristic of ADHD, there is currently very limited research assessing potential functional neural markers linked to an ADHD likelihood status and/or predicting later ADHD traits and symptoms. One study investigating task-dependent functional brain responses suggested that reduced repetition suppression, indexed by limited reduction in early ERP responses to repeated auditory stimulation, manifests in 2.5 month-old-infants at elevated likelihood of ADHD and predicts ADHD symptoms, alongside anxiety and depression at 3 years (Hutchison et al., 2017). Poor auditory repetition suppression in the early development of ADHD may result from increased reliance on incoming sensory input relative to prior information and be further underlined by E/I imbalances in putative cortical areas. Despite research being scanty in this field, progress is expected given that several groups are currently pursuing research programs aimed at identifying the early markers of neurodevelopmental conditions (including ADHD) within a trans-

diagnostic framework (Charman & Jones, 2018; Finlay-Jones et al., 2019; Johnson et al., 2015).

Controlled *behavioural investigations* have provided some evidence for the notion that the earliest signs of ADHD may not pertain to core diagnostic domains but rather impact sensory and motor functions. In particular, evidence indicates that core ADHD manifestations, including inattention, hyperactivity and impulsivity, do not become apparent until 12 months of age in infants with later ADHD (Miller et al., 2020). In contrast, subtle atypicalities in achieving motor milestones may be apparent from 3 months of age in infants with later ADHD, although results have not been consistently replicated. For example, Gurevitz and colleagues (2014) reported atypical gross motor skills in 3-month-old infants with later ADHD, whereas Johnson and colleagues (2014) failed to document an association between early-onset motor atypicalities and later ADHD diagnoses. Subtle atypicalities in visuo-motor coupling have also been reported as early as 3 months in infants with later ADHD. For example, Friedman and colleagues (2005) reported reduced body movement suppression and greater rebound of body movement at look onset at 3 months to predict parental reports of inattention at 8 years. Thus, preliminary evidence suggests that subtle atypicalities in motor functioning may be prodromal to core ADHD manifestations. It is possible that early-emerging motor difficulties in ADHD may be underpinned by perturbations in sensory processing. However, at present, only one report on sensory functioning in the early development of ADHD has been published (Hutchison et al., 2017).

Thus, given the lack of experimental research assessing sensory manifestations in the early development of ADHD, this proposal remains speculative.

1.5.2.6. General issues

Experimental research has fostered advancements in our understanding of the early-emerging neural and behavioural atypicalities in ASD and ADHD. Despite this progress, a full characterization of the multiple associations between neural vulnerabilities, early-emerging sensory-motor atypicalities and later core manifestations in ASD and ADHD remains limited. It is possible that early brain structural and functional atypicalities may reflect shared vulnerabilities in these disorders. These atypicalities may contribute to common sensory and motor difficulties in infancy which could, in turn, cascade into later core diagnostic symptoms of the conditions through mediated or moderated pathways. More research investigating precursors and predictors of ASD and ADHD within a trans-diagnostic and developmental framework will be able to confirm or falsify this prediction and further advance our understanding of these disorders from infancy.

1.6. Theoretical models of sensory perception in neurotypical populations and populations with ASD and/or ADHD

For a long time, sensory perception has been conceptualised as a feedforward process aimed at accurately representing the environment through detection and filtering of stimulus features (Heeger, 2017). In fact, most computational accounts

of sensory processing adopt a feedforward (or bottom-up) approach towards explaining sensory perception. These models assume neurons' selectivity to depend on a weighted sum of their inputs, followed by a squaring output nonlinearity (Heeger, 2017). However, evidence indicates that feedback connections are a prominent feature of cortical anatomy and they are likely to play a significant functional role in information processing (Spratling & Johnson, 2004). Sensory cortical regions have a typical structure dominated by repeated sets of canonical microcircuits (Douglas, Koch, Mahowald, Martin, & Suarez, 1995; Douglas & Martin, 1991). Each of these microcircuits possesses a laminar organization with anatomically distinct feedforward and feedback connections (Felleman & Van Essen, 1991; Shipp, 2016; Shipp, Adams, & Friston, 2013; Spratling & Johnson, 2004), see Figure 1.5. The repeated presence of canonical microcircuits with a laminar organization in different sensory cortices suggests that common sets of neural computations relying on feedforward and feedback signals may underlie sensory perception across modalities. Indeed, the existence of common mechanisms involving both cortical feedforward and feedback pathways would explain many top-down perceptual effects documented across sensory modalities, including attentional selection, expectation, perceptual learning, repetition suppression, memory, familiarity and stimulus context influences (Auksztulewicz & Friston, 2016; Gilbert & Sigman, 2007; Kok & De Lange, 2015; Spratling & Johnson, 2004). I review in the following sections core assumptions and predictions of theoretical models explaining sensory perception as resulting from an integration

between feedforward and feedback signals. I discuss the variety of theories present in the literature and evaluate the implications of these theories for understanding sensory perception in populations with ASD and/or ADHD. In particular, I critically assess the status of Predictive coding as a testable framework and conclude by presenting evidence from key areas of investigation suggesting that an integrated approach to sensory perception that draws on the core assumptions of Predictive coding theories may be ideal to uncover the mechanisms underlying sensory manifestations in typically developing populations and in populations with later ASD and/or ADHD.

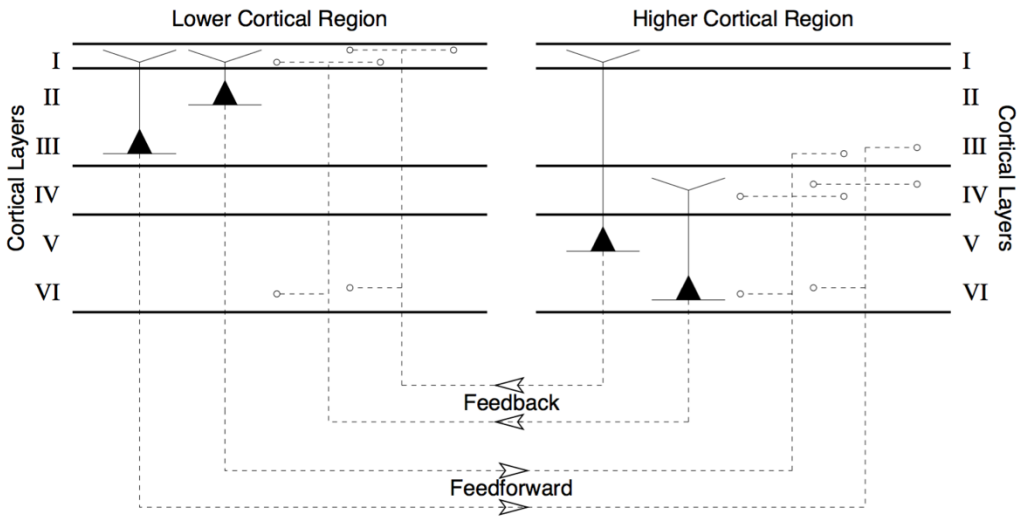

Figure 1.5. Laminar organization of sensory cortices

Representation of pyramidal cells within the six layers of the cortical sheet. Pyramidal cell bodies are depicted as filled triangles, dendrites as solid lines and axons as dashed lines. The cortical sheet is divided in two regions corresponding to different levels within an information processing hierarchy. Axon projections

connecting the two regions are represented. Feedforward connections link lower to higher cortical regions. Feedback connections link higher to lower cortical regions. Adapted from Spratling and Johnson (2004).

1.6.1. Integrated theories of sensory perception – mechanisms

Predictive coding theories provide an integrated, modality-independent theoretical explanation of sensory perception in neurotypical individuals as resulting from a synergistic relationship between feedforward and feedback mechanisms (Friston, 2005; Rao & Ballard, 1999). According to Predictive coding theories, sensory perception should be conceptualised as a generative (or iterative) process of active inference relying on feedback components named *predictions* and feedforward components named *prediction errors*. Feedback predictions can be understood as signals descending the cortical hierarchy via backward connections. Predictions act as top-down signals that may be recruited to reduce perceptual uncertainty and limit the computational resources needed to elaborate an accurate representation of the environment. Conversely, feedforward prediction errors can be understood as signals ascending the cortical hierarchy via upwards connections. Prediction errors act as bottom-up sources of information and result from the comparison between the state of a current sensory representation at a specific neural level and the descending feedback prediction. The sensory representation, at any given level of the cortical hierarchy, attempts to predict the representation at the level below. The resulting process is a set of iterations minimizing prediction errors and refining

sensory perception over time. From a computational standpoint, Predictive coding theories assume refinement of sensory perception to result from the progressive optimization of three parameters: 1) *causes*, 2) *states*, 3) *precision* (Kanai, Komura, Shipp, & Friston, 2015; Shipp, 2016). Causes are invariant properties of the environment that give rise to sensory regularities. States refer to the momentary fluctuations of the environment and are consequent to dynamic interactions between multiple causes. Lastly, precision refer to the reliability of both causes and states. Progressive optimization of these parameters is hypothesized to occur through a Bayesian set of iterations which involve both feedforward and feedback neural connections. To fully support this iterative process, feedforward and feedback connections are thus assumed to mediate distinct information contents – an assumption that appears supported by anatomical evidence indicating that distinct neural populations contribute to feedforward and feedback signal transfer (Berezovskii, Nassi, & Born, 2011; Markov et al., 2014).

The assumptions underlying Predictive coding theories lead to several testable predications (Kok & De Lange, 2015). Firstly, if sensory perception reflects a synergistic integration between feedforward and feedback signals, then the same bottom-up sensory input may lead to different responses depending on the strength of top-down predictions. For example, repetition suppression paradigms, whereby repeated pairs of sensory stimuli are presented over time, should lead to progressive refinement of predictions, causing suppression of expected sensory input over time (Auksztulewicz & Friston, 2016; Kok & De Lange, 2015). Secondly, pre-existent

and established top-down predictions should activate representations in sensory cortices even when bottom-up sensory input is absent (e.g. in working memory and mental imagery tasks, or when anticipating sensory events). Thirdly, if sensory perception manifests as a set of iterations to minimize prediction errors and maximise perceptual inference, then attention should operate by boosting the precision of prediction errors at each level of the sensory hierarchy.

1.6.2. Integrated theories of sensory perception – implications for understanding ASD and/or ADHD

Predictive coding has been proposed as a framework to understand sensory perception across neurodevelopmental disorders, including ASD and ADHD. As reviewed in section 1.5, atypicalities in sensory perception are documented in ASD and ADHD since the earliest developmental stages. Currently, several Predictive coding theoretical variants dominate the literature. These theories share the assumptions presented in section 1.6.1 and broadly hypothesize atypical sensory perception in individuals with ASD or ADHD to result from absent of reduced integration between feedforward and feedback signals, limiting refinement of sensory predictions over time. However, each of these theories also possesses unique features, leading to some differences in the specific set of emerging hypotheses.

An initial formulation was advanced by Pellicano and Burr (2012) in an attempt to explain the spectrum of sensory manifestations in individuals with ASD.

Following observation that many individuals with the disorder perform more accurately than controls in perceptual tasks, the authors suggested that they may perceive the world more accurately than neurotypical individuals due to their perception being less modulated by prior experience. Reduced influence of feedback signals (or priors) would explain many sensory manifestations in individuals with ASD. Firstly, limited reliance on feedback information and elevated reliance on feedforward sensory input could explain the profile of sensory hypersensitivity documented in individuals with ASD. Secondly, reduced reliance on priors could limit the ability to predict forthcoming events, explaining the experience of sensory overload in individuals with ASD. Thirdly, limited reliance on priors could explain the tendency of individuals with ASD to perform restricted and repetitive behaviours, which would require less active inference capacity, given that sensory expectations and motor plans are pre-existent.

In its original formulation, the theory was proposed to explain only sensory manifestations in ASD. However, later commentaries on the theory highlighted that sensory and social symptoms are intertwined in ASD and appropriate usage of prior information lies at the core of typical social interaction (Brock, 2012). Lawson and colleagues (2014) expanded on this conceptualization proposing that both sensory and social symptoms in ASD may result from elevated sensory precision (i.e. the precision of feedforward signals). Elevated sensory precision in individuals with ASD would result from reduced influence of feedback signals and be particularly visible under situations of high environmental uncertainty, in which prior

knowledge would be essential for resolving ambiguity. Given that social situations are dominated by uncertainty and are complex and difficult to predict, it follows that behavioural atypicalities in individuals with ASD would be especially notable in social contexts. Expanding on Lawson and colleagues' formulation (2014), Van de Cruys and collaborators (2013, 2014, 2017) proposed the "HIPPEA" (i.e. "High, Inflexible Precision of Prediction Errors in Autism") account, according to which individuals with ASD would assign a high and inflexible precision to incoming prediction errors, leading to difficulties separating signal from noise and learning from expectations, particularly in unstable environments. Thus, in contrast to Pellicano and colleagues' account (2012), the "HIPPEA" account does not assume individuals with ASD to manifest reduced influence of priors. Rather, individuals with ASD would rely on priors similarly to individuals without the condition. However, given the high and inflexible precision of their prediction errors, they would also tend to generate overfitted priors, leading to an incomplete and uninformative generative model of the world.

Attempts to employ Predictive coding theories to explain sensory manifestations in ADHD have also been made, although research in this area is limited. Preliminary elaborations propose that reduced influence of feedback signals may underlie novelty-seeking behaviours and elevated sensitivity to sensory input in individuals with ADHD (Gonzalez-Gadea et al., 2015). Further, atypical integration between feedforward and feedback signals could explain executive functioning difficulties in individuals with ADHD.

Predictive coding theories also provide insight into the potential developmental origins of ASD and/or ADHD. At the core of these approaches is the notion that sensory perception is iteratively refined, leading to progressive strengthening of predictions. Given the recurrent nature of sensory perception, it is possible that early-emerging atypicalities in integrating feedforward and feedback signals may gradually cascade into higher-level atypicalities. Cascading effects would, in turn, explain the link between sensory, social and cognitive difficulties reported in individuals with ASD and/or ADHD. However, this scenario goes beyond the corpus of assumptions and predictions of Predictive coding theories, as its exploration would require a developmental approach embracing the notions of context, mechanisms of change and longitudinal relations since early in life.

1.6.3. Integrated theories of sensory perception – key evidence

Predictive coding theories provide a comprehensive description of brain function. These theories integrate several levels of explanation, from neuroanatomy and neurophysiology, to perception and cognition. Besides offering a framework to explain mechanisms of sensory perception in neurotypical individuals, Predictive coding theories have the potential of illuminating the nature of atypicalities in sensory perception in ASD and/or ADHD. Despite this potential, empirical studies testing core assumptions and predictions of Predictive coding theories remain scarce (Egner & Summerfield, 2013; Heilbron & Chait, 2018). Further, the

capability of these theories to explain early-onset sensory manifestations and their potential cascading effects in ASD and/or ADHD remains unexplored.

1.6.3.1. Animal models

Animal research has mainly assessed the predictions of Predictive coding theories through repetition suppression experiments. These experiments rely on the repeated presentation of sensory stimuli and typically yield a selective attenuation of brain responses over time (but see section 1.6.3.2). Repetition suppression is reported to manifest across several time scales, in multiple brain regions (including the visual, auditory and tactile sensory cortices), and it is observed for low-level stimulus features and higher-level perceptual properties (Grill-Spector, Henson, & Martin, 2006). Results from animal studies concur in suggesting that repetition suppression should not be considered a simple neural adaptation (or fatigue) effect (Grill-Spector et al., 2006; Heilbron & Chait, 2018). In fact, studies extending traditional repetition suppression paradigms to investigate the effect of longer stimulus history on neural responses indicate that repetition suppression manifests over prolonged time frames (i.e. beyond the order of seconds at which adaptation occurs) and it is modulated by stimulus probabilities (i.e. higher stimulus probabilities yield stronger dampening of neural responses) (Rubin, Ulanovsky, Nelken, & Tishby, 2016; Ulanovsky, Las, Farkas, & Nelken, 2004) and predictability (Rummell, Klee, & Sigurdsson, 2016).

Thus, evidence from animal models suggests that the progressive refinement of predictions may drive sensory perception across modalities and underlie neural phenomena, such as repetition suppression, in several species.

1.6.3.2. Research with neurotypical adults

Predictive coding theories have received growing attention by research investigating the mechanisms underlying sensory perception in neurotypical adults. I review below key results emerged from this research, focusing on studies employing the EEG methodology and linking neural evidence to psychobehavioural factors (a look-up table with a summary of the discussed evidence is also presented in Appendix to Chapter 1).

Much research in this field has been conducted in the auditory modality using versions of repetition suppression experiments called *mismatch negativity paradigms* (MMN). In traditional MMN paradigms, sequences of tones establishing a regularity are violated by the sudden presentation of a deviant tone. These paradigms yield a neural response visible in the ERPs as a pronounced mismatch (i.e. a negativity in auditory MMN paradigms) to deviant relative to standard stimuli. Predictive coding theories describe this effect as resulting from a mismatch between a descending prediction and an incoming prediction error (Garrido et al., 2008). Evidence also indicates that the MMN response increases with the number of standard tone repetitions, further supporting the notion that MMN responses may depend on the progressive refinement of sensory predictions (Garrido et al., 2008;

Haenschel, Vernon, Dwivedi, Gruzelier, & Baldeweg, 2005). From a psychobehavioural perspective, a few studies have used the MMN response to characterise the mechanisms underlying perceptual learning. For example, Tremblay and colleagues (1998) showed that training-associated changes in neural activity, as indexed by the MMN response, precede behavioural discrimination of speech. Further, the MMN was found to correlate with gains in auditory discrimination, such as the higher the MMN response, the higher the accuracy and the shorter the reaction times in response to the presentation of the deviant stimulus (Kujala et al., 2001).

An extension of MMN paradigms are *roving paradigms*, whereby the deviant stimulus is replaced with a variable standard (i.e. stimulus deviancy is not defined on the basis of physical identity properties but it is defined on the basis of repetition frequency). This replacement may occur at predictable or unpredictable inter-stimulus intervals (ISI). Evidence from studies employing roving paradigms indicates that the repetition of standard stimuli induces neural suppression and that this effect is modulated by predictability (Costa-Faidella, Baldeweg, Grimm, & Escera, 2011). Furthermore, computational modelling suggests that the neural responses observed in roving paradigms are better explained by progressive refinement of predictions (i.e. learning), rather than neural adaptation (i.e. fatigue). For example, Lieder and collaborators (2013) compared the explanatory power of learning and adaptation in an EEG roving paradigm. Following computation of the MMN response, the authors fitted alternative models to explain trial-by-trial

fluctuations in the amplitude of the MMN response. A neural adaptation model embodying trial-by-trial fluctuations in neural responses was compared to a learning model which tracked the transition probabilities by means of prediction error minimization. Results suggested that the learning model better explained trial-by-trial fluctuations in MMN responses than the adaptation model.

Stimulus omission paradigms have also been employed to assess Predictive coding theories. These paradigms rely on the repeated presentation of sensory stimuli, followed by a sudden stimulus omission. Neural responses time-locked to the omitted stimulus are reported in these paradigms (Hughes et al., 2001; Raij, McEvoy, Mäkelä, & Hari, 1997; Yabe, Tervaniemi, Reinikainen, & Näätänen, 1997), suggesting that pre-existent and established predictions can exercise a top-down influence on perception, even in the absence of incoming sensory input. Crucially, stimulus omissions are reported to elicit neural activation only when omissions are unexpected (Chennu et al., 2016; Wacongne et al., 2011) and when sequences are prospectively predictable (Bendixen, Schröger, & Winkler, 2009), thus indicating that predictive mechanisms underlie these manifestations. From a psychobehavioural perspective, evidence suggests that active imagery may mediate the generation of neural responses time-locked to the omitted stimulus. This notion was supported by Janata (2001) who reported the stimulus-omission potentials to be visible when participants turned their expectations into active imagery (i.e. when they were internally singing the sequences of prospectively predictable tones themselves). Further, the topography of the ERPs time-locked to the omitted

stimulus significantly correlated with the topography of the same responses elicited by the actual presentation of the stimulus.

An important determinant of the predictive effects documented across several versions of repetition suppression paradigms is attention (Heilbron & Chait, 2018). In Predictive coding theories, attention is conceptualised as precision, i.e. the reliability of causes and states. In the presence of high sensory precision, sensory input will be up-weighted and predictions will be quickly updated based on the input received. Conversely, in the presence of low sensory precision, sensory input will be down-weighted and predictions will not be updated or they will be updated more slowly. Fast and slow updating of predictions may both be adaptive, depending on the nature of the environment. Precisely, fast updating of internal sensory models would be preferable in rapidly changing environments, whereas slow updating of internal sensory models to infer the longer-term accumulation of stimulus statistics would be preferable in more stable environments. Evidence suggests that the shaping of perception by past stimuli in neurotypical individuals is influenced by both recent stimuli and the overall stimulus distribution (Lieder et al., 2019). Evidence also suggests that, under particular conditions, predictability may enhance rather than suppress neural responses (Barascud, Pearce, Griffiths, Friston, & Chait, 2016). Response enhancement may be explained by considering that attention may initially up-weight incoming and relevant sensory input, leading to fast updating of internal sensory models. However, as the sensory information becomes redundant, attention may shift to down-weighting incoming sensory input,

supporting the longer-term accumulation of stimulus statistics. Thus, a conceptualisation of attention as precision may explain both the phenomena of repetition suppression and enhancement. The contribution of additional factors, including stimulus properties and the number of repetitions, should also be considered when evaluating the phenomena of repetition suppression and enhancement (Muïler et al., 2013). Indeed, evidence suggests that repetition suppression mainly manifests in response to the repeated presentation of simple stimuli (e.g. a tone or a vibration), whereas repetition enhancement is reported during an initial encoding phase of complex and/or unfamiliar stimuli (e.g. a repeated video scene) (Grill-Spector et al., 2006; Muïler et al., .2013; Segaert, Weber, De Lange, Petersson, & Hagoort, 2012). Thus, when complex stimuli are repeatedly presented, repetition enhancement may first appear (indexing initial strengthening of neural representations) and be followed by later repetition suppression (indexing a later phase of sharpening of neural representations) (Grill-Spector et al., 2006).

Taken together, evidence from studies with neurotypical adults aligns to animal models and supports the notion that prediction may be a crucial component of perception across sensory modalities.

1.6.3.3. Developmental research

Limited research has been conducted to assess the explanatory power of Predictive coding theories in early development. However, current evidence suggests that

signatures signalling prediction mechanisms may exist in the developing brain (Nordt, Hoehl, & Weigelt, 2016a; Trainor, 2012). Research indicates that effects similar to those observed in adults manifest in infancy, including repetition suppression (Emberson, Boldin, Robertson, Cannon, & Aslin, 2019; Nordt et al., 2016a), MMN effects (Leppänen et al., 2004; Sambeth et al., 2009; Tew, Fujioka, He, & Trainor, 2009), stimulus omission effects (Emberson, Richards, & Aslin, 2015) and response to unexpected visual events (Kouider et al., 2015). For example, Emberson and collaborators (2019) investigated the contribution of feedback signals in an auditory repetition suppression paradigm administered to 6-month-old infants. Infants were exposed to two conditions, one in which variability in stimulus presentation was expected (75% of the time) and a control condition where variability and repetition were equally likely (50% of the time). Reduced frontal cortical activation (as measured by functional Near Infrared Spectroscopy, fNRIS) was observed in response to variable auditory stimuli presented in the expected relative to control condition. The same research group also documented early-emerging difficulties in building predictions and using feedback signals to modulate responsiveness to incoming sensory input in infants born pre-term compared to infants born-full term from 6 months of age (Boldin, Geiger, & Emberson, 2018; Emberson, Boldin, Riccio, Guillet, & Aslin, 2017). Altogether, this evidence indicates that, from early in development, the brain can build predictions and use feedback signals to guide the selection and processing of incoming sensory input. Further, this evidence suggests that atypicalities in the integration of feedback and

feedforward signals may characterise infants at elevated likelihood of adverse neurodevelopmental outcomes.

Crucially, paradigms investigating infants' predictive abilities (e.g. repetition suppression paradigms) share principles with classic habituation paradigms (Nordt et al., 2016a). In classic habituation paradigms, infants are repeatedly presented with a certain stimulus, until habituation occurs. Following habituation, infants are presented simultaneously with two stimuli – the habituated and the novel stimulus. Sensitivity to the properties of the novel stimulus manifests as a novelty preference, i.e. increased looking to the novel compared to the habituated stimulus (Colombo & Mitchell, 2009). Similar to repetition suppression paradigms, also in classic habituation paradigms, attention acts as a determinant of the observed effects. If exposure is too short for infants to build a complete representation of the repeated stimulus, infants will continue attending at the repeated rather than novel stimulus, thus exhibiting a familiarity preference, see Figure 1.6.

Thus, developmental research suggests that mechanisms of prediction may be present since early in life, underlie infants' learning and be atypical in infants with later adverse neurodevelopmental outcomes. Nonetheless, no research has so far been conducted to evaluate the developmental trajectory of infants' predictive abilities as well as their long-term cascading impact on social and cognitive development in both typically developing infants and infants at elevated likelihood of ASD and/or ADHD.

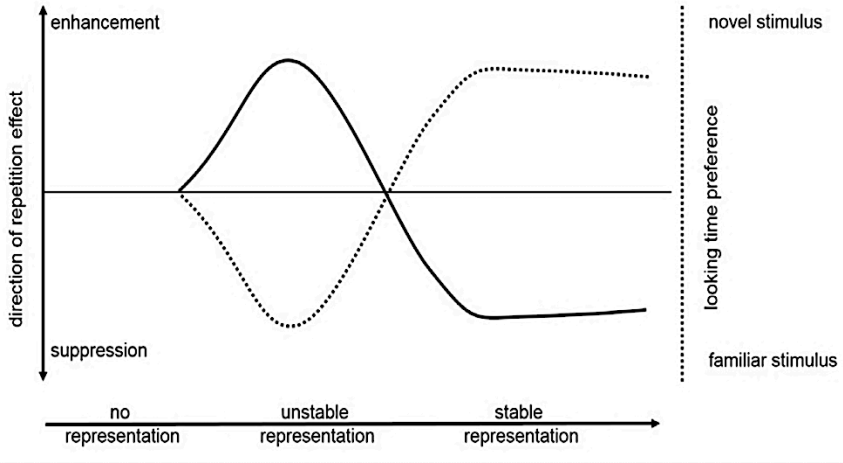

Figure 1.6. Illustration of the relationship between repetition suppression and looking time preference in classic habituation paradigms

The repeated presentation of a complex sensory stimulus (e.g. a video scene) can lead to enhancement or suppression of responses. Repetition enhancement manifests whilst a representation of the repeated stimulus is being created. Attention is supposed to up-weight sensory input during repetition enhancement. Repetition suppression manifests after a representation of the repeated stimulus is created. Attention is supposed to down-weight sensory input during repetition suppression. Repetition enhancement should lead to familiarity preference. Repetition suppression should lead to novelty preference. Adapted from Nordt et al., (2016).

1.6.3.4. Research with individuals with ASD and/or ADHD

Predictive coding theories have been proposed as a framework for understanding neurodevelopmental disorders, including ASD and/or ADHD. Despite this proposal, evidence assessing the predictions of Predictive coding theories in these conditions remains limited and mostly focused on adults with ASD. Behavioural, neuroimaging and eye-tracking studies concur in suggesting that, on average, adults with ASD display manifestations consistent with atypical predictive abilities, including enhanced perceptual functioning, sensory hypersensitivity, sensory overload, reduced repetition suppression and insensitivity to context (Lawson, Friston, & Rees, 2015; Lawson et al., 2014; Lieder et al., 2019; Sinha et al., 2014). Further, studies coupling empirical data and computational modelling indicate that adults with ASD may manifest reduced distinction between repeated and novel sensory stimuli which could, in turn, detrimentally impact their ability to learn about probabilistic relationships in the environment (Lawson, Mathys, & Rees, 2017). Predictive coding theories have alternatively explained these manifestations in ASD as resulting from limited influence of feedback signals (priors), leading to elevated reliance on feedforward sensory input (Lawson et al., 2014; Pellicano & Burr, 2012), or as consequent to high, inflexible precision of prediction errors, leading to overfitted priors (Van de Cruys et al., 2013, 2014, 2017). Support for the notion that adults with ASD may manifest atypical predictive abilities and up-weight incoming sensory input has emerged from studies investigating low-level sensory perception (Goris et al., 2018) and higher-level effects of social

manipulations (Chambon et al., 2017) or contextual influences on motor function (Palmer, Paton, Kirkovski, Enticott, & Hohwy, 2015). For example, Goris and collaborators (2018) employed a traditional MMN paradigm to test the hypothesis that incoming prediction errors in individuals with ASD may be less modulated by descending predictions. While the MMN response manifested in both neurotypical adults and adults with ASD, this response was significantly reduced in the latter group, supporting the notion that sensory perception in adults with ASD may favour feedforward information due to reduced reliance on feedback signals. Chambon and collaborators (2017) extended this notion to the social domain by demonstrating that difficulties in mentalizing in individuals with ASD may be explained by an unbalanced interplay between top-down prior knowledge and bottom-up sensory input. In particular, the authors reported adults with ASD to rely less on prior knowledge and more on incoming sensory input in a task requiring to infer the most likely social motor intention (i.e. cooperative or defective) of actors engaged in a game. Further, the lower the reliance on social priors in adults with ASD, the higher the severity of social symptoms and restricted/repetitive behaviours quantified through standardized assessment (i.e. Autism Diagnostic Interview, ADI; Lord, Rutter, & Le Couteur, 1994). Palmer and colleagues (2015) reported differences in the influence of the preceding sensory context on motor function in adults with ASD relative to controls. The authors recorded reach-to-grasp movements following an inactive period in which illusory ownership of a prosthetic limb was induced. While neurotypical adults showed disrupted reaching movement

following the illusion, this interference was absent in adults with a clinical diagnosis of ASD and adults with high ASD traits. Further studies have replicated the notion that reduced integration between feedback and feedforward signals may characterise sensory perception in individuals with high ASD traits (Skewes, Jegindø, & Gebauer, 2015). Altogether, this research suggests that, on average, adults with ASD manifest atypical integration between feedback and feedforward signals and this atypicality may explain sensory and social symptoms, as well as the strong desire for routine and predictability typical of the condition.

In contrast to research with ASD individuals, research assessing the explanatory power of Predictive coding theories in individuals with ADHD is limited. The only published report focuses on children with ADHD and documents elevated reliance on incoming sensory input in this group (Gonzalez-Gadea et al., 2015). Further, the authors report an association between enhanced responsiveness to sensory input and elevated set-shifting in children with ADHD. These results could explain the commonly reported novelty-seeking behaviours in this disorder.

In sum, research assessing the applicability of Predictive coding theories to explain sensory, social and cognitive manifestations in ASD confirms the notion that atypical integration between feedback and feedforward signals may lie at the core of these manifestations. Conversely, the ability of Predictive coding theories to explain ADHD manifestations has only been superficially investigated. Further, whether and to what extent these theories may explain early-emerging sensory

atypicalities in infants with later higher ASD and/or ADHD traits remains unexplored.

1.6.3.5. Concluding remarks

An integrated approach to sensory perception, which recognises the contribution of feedforward and feedback signals, may be ideal to characterise the nature and potential cascading effects of early-onset sensory atypicalities in infants with later ASD and/or ADHD. Over the past years, this approach has proved fruitful for understanding mechanisms of sensory processing in animal models, research with neurotypical adults and research with adults with neurodevelopmental conditions, mainly ASD. However, its potential for understanding the early development of ASD and/or ADHD remains unexplored. Adopting this approach within a developmental framework may yield deeper understanding of the nature, role and mechanisms of change underlying sensory manifestations from early in development, enabling researchers to move from static to dynamic descriptions of sensory perception and to embrace complexity across levels of explanations. At the same time, researchers wishing to adopt an integrated approach to study the early development of sensory perception should consider that, over the years, a variety of theories have flourished. Despite sharing a common set of assumptions (i.e. the notion that sensory perception results from a synergistic relation between feedback and feedforward signals), these theories also possess fundamental differences. For example, both Pellicano and colleagues' account (2012) and Van de Cruys and

collaborators' account (2013, 2014, 2017) predict ASD manifestations to result from atypical *relative* balance in the integration of feedback and feedforward signals. However, while the former account explains this atypical balance to result from reduced reliance on feedback signals (or priors), the latter account assumes this atypical balance to be consequent to heightened precision of feedforward signals (or prediction errors), causing feedback signals to be overfitted. Teasing apart between these explanations may be challenging, given that both reduced influence of priors and elevated precision of prediction errors may shift the processing balance in favour of incoming sensory stimulation. However, both ways of shifting the balance in inference should be, at least in principle, dissociable. This could be done by adopting paradigms designed to track the dynamics of learning over long time frames or multiple trials, including repetition suppression paradigms and/or habituation paradigms whereby the exposure to a repeated stimulus is experimentally manipulated.

1.7. Aim of the current project

The aim of the current PhD project is to examine the early development of sensory perception in infants at elevated familial likelihood of ASD and/or ADHD relative to infants at typical likelihood of the disorders. I conduct my investigation by adopting an integrated approach to sensory perception that draws on Predictive coding theories applied within a developmental framework. In particular, I aim with this PhD project to investigate whether atypicalities in sensory perception may

manifest in the early development of ASD and/or ADHD and hold predictive power in relation to later-emerging traits of the conditions. Further, drawing on the core assumptions of Predictive coding theories, I aim to investigate the extent to which early-emerging atypicalities in sensory perception in these conditions may result from atypical balance in the integration between feedforward and feedback signals, limiting refinement of sensory predictions over time.

Following the theoretical introduction provided in Chapter 1, Chapter 2 discusses methodological considerations relevant for the investigation of the early development of sensory perception in ASD and ADHD. Chapter 3 presents results from an EEG tactile repetition suppression task administered to infants aged 10 months, prospectively re-assessed at 24 months. I investigate whether atypical repetition suppression, indexed by limited reduction in alpha desynchronization with repeated tactile stimulation, may represent a marker of ASD and/or ADHD in infancy and significantly predict ASD and/or ADHD traits in toddlerhood. I further assess the role of parent-reported tactile sensory seeking as a mediator or moderator of the relationship between early atypical repetition suppression and later disorder-specific traits. This study fills a fundamental gap in our knowledge of ASD and ADHD by investigating putative mechanisms underlying atypical tactile perception from infancy and their potential cascading effects on later social and cognitive development. Chapter 4 presents results from an EEG visual sensory processing task administered to infants aged 10 months, prospectively re-assessed at 24 months. I investigate whether atypical responsiveness to incoming visual input,

indexed by elevated early visual-evoked potentials to black-and-white checkerboards overlaid on top of a continuous videoclip, may be a marker of ASD and/or ADHD in infancy/toddlerhood and predict ASD and/or ADHD traits in toddlerhood. I explore the possibility that enhanced responsiveness to incoming visual input in ASD and/or ADHD may result from reduced prioritization of ongoing over incoming visual stimulation. I conduct this investigation by assessing the mutual associations between background EEG theta oscillations and early visual-evoked potentials to incoming stimulation. Finally, I assess the potential associations between early markers of visual perception and parental reports of sensory seeking. This study furthers our knowledge of early-emerging visual profiles in ASD and ADHD, contemporarily uncovering candidate mechanisms underlying these manifestations. Chapter 5 extends on evidence discussed in Chapter 4 and provides a proof-of-concept demonstration that variation in responsiveness to incoming visual stimulation reflects variation in engagement with ongoing information in an independent sample of 10-month-old infants at typical likelihood of ASD or ADHD. This demonstration is laid out through characterization of the non-linear modulatory profiles of change manifested by background EEG theta oscillations during the repeated presentation of the videoclip and early visual-evoked potentials to checkerboards overlaid on top, as well as through assessment of the mutual associations between these measures. By elucidating the nature and characteristics of visual perception in infants at typical likelihood of ASD or ADHD, this study clarifies mechanisms that may underlie

atypical visual perception in these disorders. Chapter 6 adopts an *individual differences approach* and reports on the concurrent and longitudinal associations between markers of information prioritization emerged from Chapter 5 and parent-reported measures of sensory seeking, ASD traits and ADHD traits collected from the same sample of 10-month-old infants at typical likelihood of ASD or ADHD, prospectively re-assessed at 16 months. Chapter 7 discusses contributions and implications for research on the early development of sensory perception in ASD and/or ADHD.

Overall, this research will enhance our understanding of the mechanisms behind atypical sensory perception in ASD and ADHD from infancy. By mapping the longitudinal associations between infant sensory features and later ASD and/or ADHD traits, this project will help in distinguishing shared and distinct causal pathways between the conditions, thus highlighting risk and protective factors and furthering our knowledge of the nature of the co-occurrence and aetiology of these disorders. Better understanding of the developmental trajectories of sensory perception in ASD and ADHD will inform mechanistic-based descriptions relevant to lay the translational foundations for early intervention protocols.

1.8. Summary of Chapter 1

ASD and ADHD are heritable neurodevelopmental disorders emerging early in life. These disorders co-occur more often than expected based on their individual incidence and later-born siblings of children with ASD or ADHD are at elevated

likelihood to develop both conditions. Some common developmental mechanisms are proposed to underlie the emergence of ASD and ADHD but specific pathways have not been identified. Molecular genetics research and prospective longitudinal studies of infants at elevated likelihood of ASD or ADHD indicate that common sensory vulnerabilities may be present in the early development of these conditions. Despite this evidence, no prior research investigated the same sensory markers as potential infant predictors of later ASD and/or ADHD traits in toddlerhood. Mapping the associations between early infant markers of sensory perception and later ASD and/or ADHD traits in toddlerhood may help in distinguishing shared and distinct causal pathways between the conditions, thus highlighting risk and protective factors and enhancing our understanding of the nature of the co-occurrence and aetiology of ASD and ADHD. The aim of the current PhD project is to investigate the early development of sensory perception in infants at elevated likelihood of ASD and/or ADHD relative to infants at typical likelihood of the conditions. I conduct my investigation by adopting an integrated approach to sensory perception that draws on Predictive coding theories applied within a developmental framework. Chapter 2 will discuss methodological considerations relevant for the investigation of the early development of sensory perception in ASD and ADHD.

Chapter 2: Methodology

2.1. Introduction

This chapter aims to provide an overview of methodological considerations relevant for the investigation of the early development of sensory perception in ASD and ADHD. The first part of the chapter will introduce the concept of neural oscillations and highlight the role that these dynamics play in sensory perception. I will then discuss the suitability of electroencephalography (EEG) as a technique to measure these dynamics in developing populations. Thus, I will present approaches and analytical pipelines for the assessment of EEG in infancy.

The second part of the chapter will present complementary approaches to study the early development of sensory perception. I will critically review a common parent-reported measure, the *Infant-Toddler Sensory Profile* (ITSP), and discuss the potential of an approach combining EEG measures and parental reports. I will further highlight the importance of incorporating clinical measures in prospective studies of infants with later typical or atypical developmental outcomes. The chapter will conclude by discussing the implications of a multi-method, integrated approach to the investigation of the early development of sensory perception in infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the conditions.

2.2. Neural oscillations and their contribution to sensory perception

Neural oscillations are rhythmic fluctuations in the excitability of neural ensembles. These neural dynamics manifest across several temporal and spatial scales (Varela,

Lachaux, Rodriguez, & Martinerie, 2001) and have been implicated in long-range neural communication and signal broadcasting across brain networks (Buzsaki, 2006; Buzsáki & Watson, 2012). Neural oscillations have been shown to mediate several neurophysiological and cognitive phenomena, including long-term neural potentiation, sensory perception and higher level cognition (Buzsaki, 2006; Buzsáki & Watson, 2012; Cohen, 2014). Furthermore, neural oscillatory dynamics have been shown to play an active role for the specialization of brain functional networks since the earliest developmental stages (Chiu & Weliky, 2002; Colonnese et al., 2010; Katz & Shatz, 1996; Sur, Angelucci, & Sharma, 1999; Thompson, 1997). Indeed, changes in synchronized neural activity have been linked to changes in myelination and to the experience-dependent re-organization of cortical networks underlying sensory perception during infancy, childhood and adolescence (Colonnese et al., 2010; Dubois, Kostovic, & Judas, 2015; Uhlhaas et al., 2009_a; Uhlhaas et al., 2009_b). These properties make neural oscillations optimal for characterising the early development of sensory perception in populations with later typical or atypical developmental outcomes.

Evidence from animal and human research concurs in suggesting that neural oscillations are directly involved in mediating sensory functions. In particular, research indicates that background oscillatory dynamics can actively bias the selection and processing of sensory input, thus exercising a top-down influence on perception and enabling active parsing of incoming information over time (Buzsáki & Watson, 2012; Schroeder, Wilson, Radman, Scharfman, &

Lakatos, 2010). In a set of elegant studies conducted on anesthetized cats, Arieli and collaborators demonstrated that neural oscillatory dynamics can determine perceptual processing of incoming visual stimulation and shape the evoked neural activity over time (Arieli, Shoham, Hildesheim, & Grinvald, 1995; Kenet, Bibitchkov, Tsodyks, Grinvald, & Arieli, 2003; Tsodyks, Kenet, Grinvald, & Arieli, 1999). By employing optical imaging, the authors examined the relationship between the spiking activity of a single neuron and spontaneous oscillations of the surrounding network in the presence or absence of visual stimulation. Results demonstrated comparable oscillatory activity of the surrounding network both when the neuronal spikes were generated by the visual input and when they occurred spontaneously. In particular, the visual stimulus did not induce and arbitrary oscillatory state but rather brought about a pre-existent state of the network. The implication of these results is that a match between the spontaneous oscillatory state of a network and features of the stimulus can enhance perception, whereas an oscillatory state far from the input can lead to degraded perception of that input (Buzsaki, 2006; Buzsáki & Watson, 2012). Similar results emerged from studies investigating the contribution of neural oscillatory dynamics in regulating sensory perception in monkeys and humans (Buno Jr & Velluti, 1977; Busch & VanRullen, 2010; Han & VanRullen, 2017; VanRullen, Busch, Drewes, & Dubois, 2011).

Taken together, this evidence suggests that neural oscillations are actively involved in regulating neuronal signal transfer and the specialization of functional

brain networks since early in development. Furthermore, neural oscillations are directly implicated in the top-down selection and processing of sensory input throughout the lifespan and across multiple species. Thus, investigating the role that neural oscillations play in mediating sensory perception from early in development may shed light on the mechanisms underlying emerging sensory atypicalities in infants at elevated likelihood of ASD and/or ADHD. This research can be conducted with electroencephalography (EEG) – a methodology optimally suited to be used with developing populations and capable of providing information about the underlying neural events with excellent temporal resolution (i.e. millisecond time-scale).

2.3. The methodology of EEG

2.3.1. EEG recording and experimental set up

Electrical changes detectable at the scalp are consequent to ionic currents between neurons. EEG can measure these electrical changes through a set of sensors (i.e. electrodes) placed in direct contact with the participant's scalp. EEG research with infant populations typically utilises a cap with 128 or 256 electrodes (i.e. high-density EEG nets, see Figure 2.1), although EEG caps with fewer electrodes are available. Since air is a poor conductor of electricity, electrodes must be placed in direct contact with the participant's scalp either using conductive gel (i.e. *Biosemi* or *Acticap* systems) or by previously soaking the cap in a saline solution (i.e. *Hydrocel Geodesic Sensor* system) (Cohen, 2014; Johnson et al., 2001). EEG

systems utilising dry electrodes exist and enable quicker experimental set up and data acquisition. However, systems using conductive gel or saline solutions can significantly improve the quality of the collected data. Thus, research with developing populations typically relies on "wet" rather than "dry" systems. Different EEG systems also differ in their sampling rate for data acquisition. Sampling rate refers to the number of times per second that the data is acquired from all the electrodes and defines the temporal resolution of the recorded signal. In accordance with the Nyquist theorem, the sampling rate for data acquisition needs to be at least twice the highest frequency of interest (e.g. 100Hz if the researcher wants to recover 50Hz activity). In practice, the majority of EEG systems can acquire data with a sampling rate varying between 500Hz and 2000Hz (Cohen, 2014).

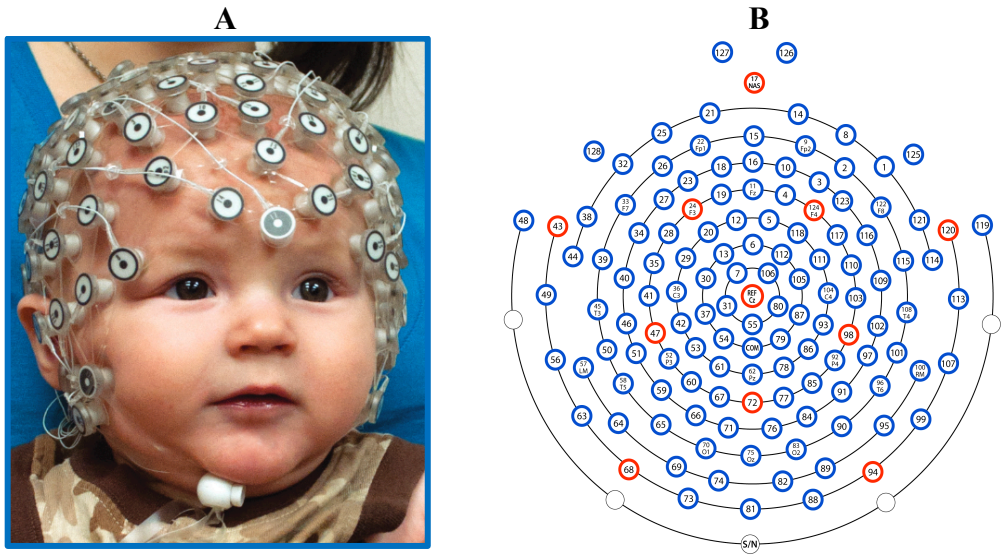

Figure 2.1. Hydrocel Geodesic Sensor net and montage properties

A) Picture of an infant participant wearing a Hydrocel Geodesic Sensor net with 128 electrodes. B) Representation of the electrode montage displaying the number and location of each channel.

A typical experimental set up for EEG acquisition includes a stimulus presentation computer, an EEG system and a recording computer, see Figure 2.2. Research with developing populations may also use a recording camera situated above or below the monitor used for stimulus presentation. This additional piece of equipment enables researchers to acquire and store video recordings to use for later behavioural coding. EEG signal acquisition commonly occurs in a shielded room to prevent intrusion from external electromagnetic fields. During the experimental session, EEG markers are sent from the stimulation computer to the recording computer. These markers signal the onset and offset of relevant events, thus

enabling researchers to appropriately segment the EEG signal during data processing.

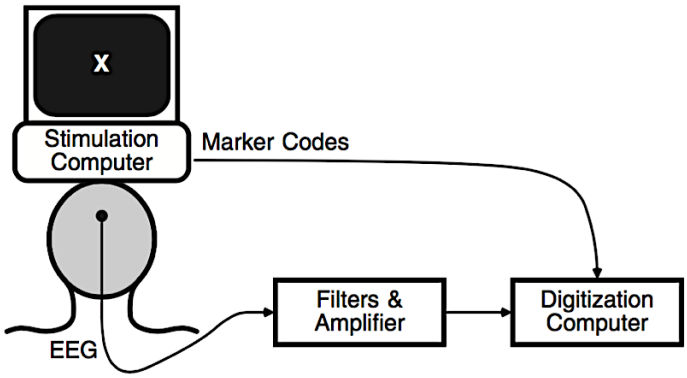

Figure 2.2. EEG experimental set up

The EEG signal in response to a set of stimuli is filtered and amplified and later digitized. Markers sent from the stimulation computer to the recording computer enable researchers to segment the EEG based on the onset and offset of the events of interest. Adapted from Luck (2014).

2.3.2. Volume conduction and its relation to the inverse and forward problems

While EEG has high temporal resolution, enabling the characterization of neural dynamics at a millisecond time-scale, the spatial resolution of this methodology is poor. The low spatial resolution of EEG is caused by volume conduction, i.e. the transmission of an electrical field from a primary neural source through several biological tissues towards the measurement electrodes. Volume conduction causes the tangential propagation of an electrical field between the skull and the scalp. As

a consequence, determining the generator of a neural signal is a complicated problem because the number and orientation of different neural sources are difficult to determine. It follows that EEG researchers may be able to characterise the broad topography of a signal but may not be able to locate the neural generators underlying the EEG. Researchers interested in locating the neural sources of a signal should employ techniques with higher spatial resolution, such as functional Magnetic Resonance Imaging (fMRI) or functional Near Infrared Spectroscopy (fNIRS), see Figure 2.3.

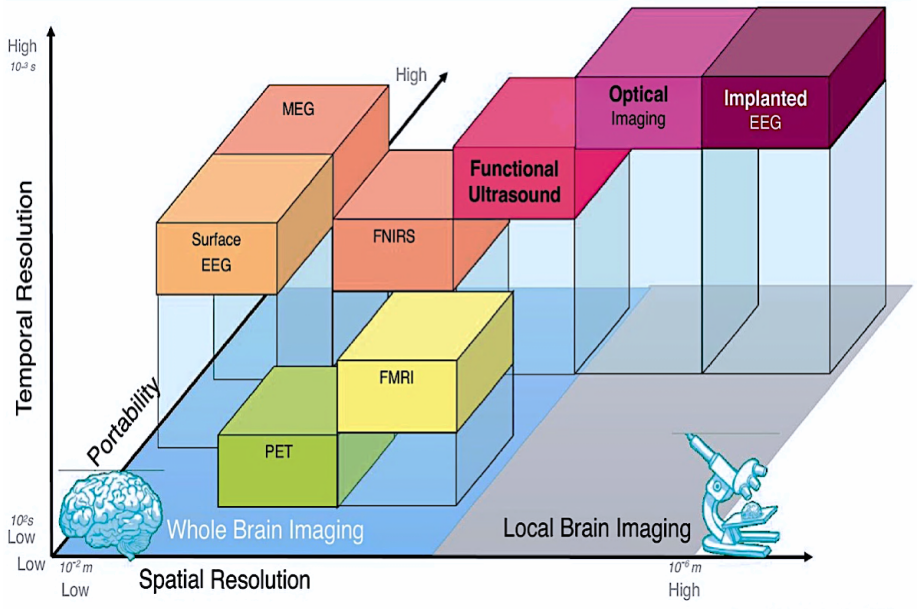

Figure 2.3. Comparison of neuroimaging techniques

Schematic representation of neuroimaging techniques. Spatial resolution is represented across the x-axis; temporal resolution is represented across the y-axis; portability is represented across the z-axis. EEG has high temporal resolution but

low spatial resolution. Researchers interested in characterising the neural sources of a generated signal with developing populations should use techniques with higher spatial resolution such as fNIRS and fMRI. Adapted from Deffieux, Demene, Pernot, & Tanter (2018).

Despite the limited spatial resolution of EEG, spatial localization techniques to infer the neural generators of electrical signals exist (Asadzadeh, Rezaii, Beheshti, Delpak, & Meshgini, 2019; Hallez et al., 2007). Spatial localization techniques enable researchers to solve the inverse problem (i.e. establishing which neural sources underlie a recorded EEG), through combination of several mathematical modelling approaches (including principal component analysis, independent component analysis and usage of realistic head models for source estimation; for additional details on these techniques see, Makeig, Debener, Onton, & Delorme, 2004; Alexander et al., 2017; Richards, Sanchez, Phillips-Meek, & Xie, 2016).

2.3.3. Approaches to the analysis of EEG in developmental research

Various approaches to the analysis of EEG data can be applied in developmental research. These approaches can be categorised in three groups: 1) time domain analyses; 2) frequency domain analyses; 3) time-frequency domain analyses. Each of these approaches requires researchers to perform preliminary processing stages. Many of these stages are common to EEG research with adults. Additional

processing stages must, however, be conducted in developmental research. These include performing video-coding of the infant's looking and/or moving behaviour and performing hand-editing of individual trials and electrodes contaminated by artifacts. A typical analytical pipeline to prepare and process infant EEG data for later time, frequency or time-frequency analyses is reported in Table 2. I adopt this pipeline for processing the EEG data in the following experimental chapters (note: I report below preliminary steps; following time, frequency or time-frequency analyses researchers may perform additional re-referencing, baseline correction and signal averaging across conditions and/or participant groups). I review in the following sections each of these analytical approaches and evaluate their practical implications for infant research.

***Table 2**. Typical EEG data preparation and processing steps for later time, frequency and time-frequency domain analyses*

EEG acquisition	**Behavioural video coding**	**EEG mark-up**	**Filtering**	**Segmentation**	**Baseline correction**	**Artifact detection**	**Hand-editing**	**Bad channel replacement**
○ Net preparation ○ Data recording ○ Data storing for later processing	○ Code infant's looking/movement ○ Code behavioural inference Reliability required to perform this step. Common software for video coding: *EGI Player* and *Mangold Interact*	○ Apply offline events signalling looking/movement ○ Apply offline events signalling behavioural interference	○ 0.3-40Hz band-pass filter Parameters vary based on requirements for later analyses	○ Segment trials	○ Apply baseline correction (100ms)	○ Mark eye electrodes as bad ○ Bad electrode: min-max > 200μV ○ Bad trial: >18 bad electrodes	○ Examine individual electrodes for blinks, saccades, movement artifacts and 50Hz noise ○ Perform the examination for each trial ○ Mark additional electrodes and/or trials as bad Reliability required to perform this step	○ Replace bad electrodes ○ Spherical spline interpolation

2.3.3.1. Time domain analyses – Event-related potentials (ERPs)

Event-related potentials (ERPs) enable analysing the EEG signal in the time domain, thus providing a window into the timing of neural processes underlying sensory perception. Following preparation and processing of the EEG recordings, ERPs can be computed by averaging the EEG data over multiple trials. The output of this computation is an average waveform for each participant. Statistical analyses can then be performed by extracting parameters for relevant components at chosen electrode sites. The principle underlying ERPs is that each trial contains both signal and noise; however, while the signal is similar across trials, noise varies randomly. Thus, by averaging over multiple trials, researchers can leave the signal and cancel the noise.

ERP analyses have several advantages. First, ERPs have high temporal resolution and accuracy since their extraction requires limited processing and gentle filters (Cohen, 2014; Luck, 2014). This property makes ERPs ideal to characterise the timing of neural events underlying sensory perception. Secondly, ERPs have a long history and offer a wide literature for interpreting and contextualising results. Despite these advantages, ERPs also have a few limitations. First, interpreting null results with ERP data can be difficult since ERPs contain little information about background EEG dynamics (Cohen, 2014). Secondly, ERPs do not allow researchers to make strong inferences about the underlying neurophysiological mechanisms since the exact neural dynamics leading to the emergence of ERPs remain under debate (Cohen, 2014; Luck, 2005; Sauseng et al., 2007). In particular,

it is not clear whether ERPs result from evoked responses with fixed latency and polarity additive to the ongoing EEG or from a superposition of ongoing EEG oscillations that reset their phases in response to sensory input (Sauseng et al., 2007). Finally, reliable quantification of ERPs requires averaging across multiple trials, making it difficult (especially with infant data) to estimate single-trial measures (Luck, 2014).

The statistical analysis of ERPs can be conducted by selecting relevant components and quantifying amplitude and/or latency measures. By convention, an ERP component is described as the electrophysiological correlate of an information processing stage produced by an underlying neural source (Fabiani, Gratton, & Federmeier, 2007; Luck, 2014). In practice, each component likely corresponds to more than one information processing stage and some processing stages may not temporally correspond to a clear ERP component. ERP components are given labels such as P1 or N1 to refer to their polarity and position within the average ERP waveform. A common nomenclature is used to refer to components across sensory modalities but this does not indicate that a functional link exists between them. A vast amount of research has been conducted to assess the characteristics of ERP components in the visual modality, namely the C1, P1, N1 and P2, see Figure 2.4. Chapters 4 and 5 report results of studies assessing the neural correlates of visual perception and the influence of top-down modulatory factors on such correlates in infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the disorder. Thus, I review below key properties of visual ERP components,

particularly discussing their link with psychobehavioural factors and highlighting the influence that top-down modulatory factors have on these ERP components.

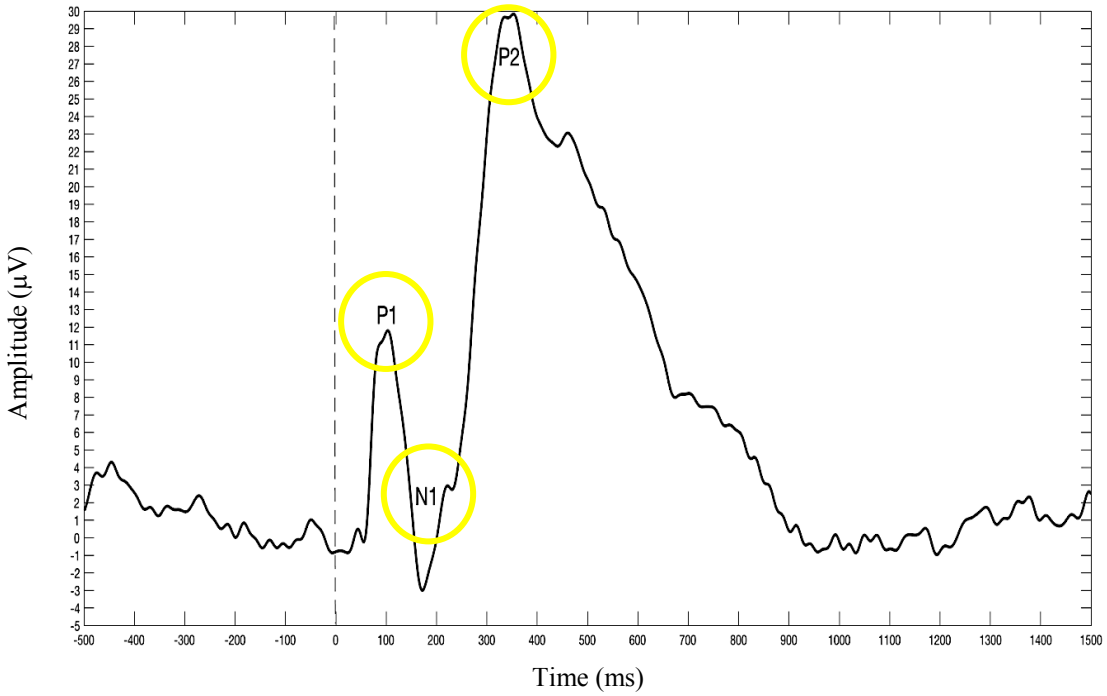

Figure 2.4. Average infant ERP waveform in response to visual stimulation

Average ERP waveform in response to visual stimulation (black-and-white checkerboard) extracted from a cluster of occipital electrodes in a 10-month-old infant. The visual ERP components P1, N1 and P2 are visible in successive order and highlighted with yellow circles. The visual component C1 is not visible since the visual stimulus was presented along the horizontal midline in this study. See Chapters 4 and 5 for further details.

The C1 is the first visual component and manifest its peak at 80-100ms after stimulus presentation. This component can have a positive or negative polarity and it is usually undetectable in response to stimuli presented along the horizontal

midline. C1 manifests a positive polarity in response to stimuli appearing in the lower visual field and a negative polarity in response to stimuli appearing in the upper visual field. The primary visual cortex (V1) is considered the neural generator of the C1 (Luck, 2014). Studies assessing the link between the C1 and psychobehavioural factors suggest that this component is enhanced in tasks requiring participants to allocate their attention to specific spatial locations. For example, Kelly and collaborators (2008, 2018) reported the C1 component to be enhanced in amplitude in a spatial cueing task whereby participants were cued on each trial to direct attention toward one of two locations in anticipation of a Gabor stimulus and required to perform an accuracy task. This evidence indicates that the C1 component is modulated by top-down factors such as spatial attention.

The P1 is the second visual component (but often the first visible in the average ERP waveform) and typically manifests its peak at 100-130ms after stimulus onset. Both stimulus properties and participants' age can affect the latency to peak of this component (i.e. longer latency to peak of the P1 is reported in infants relative to older children or adults; Lee, Birtles, Wattam-Bell, Atkinson, & Braddick, 2012; McCulloch & Skarf, 1991). The extra-striate cortex is thought to generate the P1 component and source localisation studies have provided some evidence in support of this notion in both adult and developing populations (Di Russo et al., 2002; Richards, 2005; Xie & Richards, 2017). Consistent evidence indicates that the P1 is sensitive to top-down influences in both adults and developing populations. Such influences include the effect of attention (Gazzaley

& Nobre, 2012; Lunghi, Piccardi, Richards, & Simion, 2019; Lunghi, Di Giorgio, Benavides-Varela, & Simion, 2020; Richards, 2000), arousal (Hillyard, Vogel, & Luck, 1998) and memory (Gazzaley & Nobre, 2012; Zanto, Rubens, Thangavel, & Gazzaley, 2011). For example, validly cued stimuli in both simple and choice reaction times tasks elicit amplitude enhancements of the P1 (Hillyard et al., 1998). Similar effects are reported in tasks with infants coupling measurements of the P1 amplitude and saccadic reaction times (i.e. traditional Posner cueing tasks whereby the shorter the saccadic reaction times to the validly cued target, the higher the amplitude of the P1 time-locked to the onset of the target) (Lunghi et al., 2019). The P1 component will be the focus of the analyses reported in Chapters 4 and 5. The reason underlying this choice is twofold: 1) the P1 is often the first sensory-evoked component visible in the average ERP waveform (particularly in tasks presenting stimuli along the horizontal midline, such as those reported in Chapters 4 and 5); 2) the P1 is assumed to maximally capture feedforward visual processing; 3) considerable evidence indicates that top-down factors can modulate the P1 since early in development. Altogether, these properties make the P1 optimal to investigate how feedback signals modulate the feedforward processing of incoming visual stimulation in infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the conditions.

The N1 component is visible in the ERP average waveform after the P1. The N1 peaks around 150-200ms after stimulus onset. The parietal and the lateral occipital cortex are considered the main neural generators of the N1 and source

localisation studies support this notion in both adult and developing populations (Di Russo et al., 2002; Xie & Richards, 2017). Similar to the P1, the N1 is also a sensory-evoked component and evidence from tasks linking modulation of this component to psychobehavioural factors suggest that it is sensitive to top-down influences, particularly the effect of selective and task-directed attention in discrimination tasks (Hillyard et al., 1998; Hopf, Voge, Woodman, Heinze, & Luck, 2002; Vogel & Luck, 2000). For example, Vogel and Luck (2000) reported the amplitude of the N1 to be maximally enhanced in validly-cued trials in a choice reaction times task relative to a simple reaction times task, thus suggesting that this component reflects a discrimination process occurring within the focus of attention.

Finally, the P2 component is visible in the ERP average waveform after the N1. The P2 peaks around 200-300ms after stimulus onset. Parieto-occipital regions are considered responsible for the generation of the P2 (Freunberger, Klimesch, Doppelmayr, & Höller, 2007). Evidence suggests that this ERP component maximally captures feedback processing and it is sensitive to the influences of attention and memory in both adults and developing populations (Freunberger et al., 2007; Kotsoni, Csibra, Mareschal, & Johnson, 2007; Luck & Hillyard, 1994; Taylor & Khan, 2000). For example, common-onset visual masking tasks, whereby a target stimulus and a mask come to view simultaneously indicate that higher amplitude of the P2 component to the target predicts higher behavioural response accuracy (Kotsoni et al., 2007).

2.3.3.2. Time domain analyses – statistical analysis of ERPs

ERPs can be statistically analysed by selecting components of interest and extracting amplitude and/or latency measures. The choice of relevant components is driven by prior literature and by visual inspection of the average waveform for each participant. Given the reliance on prior literature for selecting components, ERP researchers typically employ replicated experimental paradigms using basic sensory stimuli (e.g. black-and-white checkerboards). Further, given the dependence of ERPs on the physical properties of the stimuli, it is essential that researchers compare components elicited by the same physical stimuli rather than stimuli with different properties (Hoehl & Wahl, 2012; Luck, 2014).

Most ERP studies focus on statistically assessing the amplitude and/or latency of components. Peak amplitude approaches require estimating the local peak within a selected time window and pool of electrodes, whereby a local peak is defined as the point manifesting greater voltage than the average three to five points on either sides (Luck, 2014). Data should be filtered to eliminate any source of high frequency noise before extracting a local peak. Since automatic quantification of local peaks may lead to spurious results, researchers should plot the average waveform for each participant rather than rely on automatic tools. This recommendation is crucial when analysing infant ERPs since the time windows where local peaks occur manifest high inter and intra-individual variability. Local peaks should be quantified from baseline for early components such as the C1 or the P1. If the P1 is preceded by a visible C1 (i.e. in tasks presenting stimuli in the

upper or lower part of the visual field), then a peak-to-peak approach is recommended. Similarly, a peak-to-peak approach is almost always better when estimating later components such as the N1 or the P2, given that earlier components may distort the amplitude of later components (Luck, 2014). However, when adopting a peak-to-peak approach, researchers must evaluate the degree to which the adjacent peak or trough remains stable across conditions, ensuring it represents a reliable comparison landmark (Handy, 2005). An alternative approach to estimate the amplitude of relevant components is by extracting the mean amplitude. This approach is used when researchers can specify time windows of interest a priori. Mean amplitude measures are less sensitive to high frequency noise than peak amplitude measures, thus making automatic extraction feasible with adult and infant data. However, the presence of overlapping components can bias mean amplitude measures and lead to unreliable results if the latency of a component varies across conditions (Luck, 2014). Furthermore, mean amplitude measures can underestimate differences between groups and/or experimental conditions (Hoehl & Wahl, 2012). Since specifying a-priori time windows for statistical analyses can lead to spurious results with infant data (i.e. due to the high inter and intra-individual variability), the analyses reported in Chapters 4 and 5 will be based on peak amplitude measures.

Alongside assessing amplitude measures, researchers may want to assess latency measures. This assessment can be performed by extracting either the peak latency or the fractional area latency. The peak latency corresponds to the time of

occurrence of the local peak amplitude from the onset time and analyses on this measure are reported in Chapter 4. In order to compute the fractional area latency, the researcher must first compute the area under the ERP waveform over a given latency and then find the time point that divides the area into a specified fraction (i.e. commonly 50% area latency) (Hansen & Hillyard, 1980; Luck, 2014).

Following the extraction of such measures, researchers may wish to further assess the data for statistical differences between experimental conditions and/or participant groups. Traditional linear modelling techniques usually suffice. However, in certain cases, researchers must deal with correlated observations and/or missing data. Thus, hierarchical modelling techniques and/or generalised estimated equation (GEE) approaches may be employed (Zeger & Liang, 1986; Ziegler, Kastner, & Blettner, 1998). These approaches provide a method of inference for a variety of models, including linear, logistic and Poisson regression as well as proportional odds, when responses are correlated. In the context of ERP research, it may sometime be of interest to evaluate within-participant profiles of change of the amplitude of a certain ERP component. Since amplitude measures extracted for successive time bins are correlated within participants, adopting an approach that accounts for correlations between responses is necessary. An in-depth description of GEE approaches and two exemplative applications can be found in Chapters 4 and 5.

2.3.3.3. Application of time domain analyses in developmental research

ERP research has been widely used to investigate the neural mechanisms underlying cognitive phenomena in infant populations. Studies adopting ERPs have been conducted to assess basic visual perception, face processing and discrimination, auditory processing and stimulus categorization at various points in development (Hoehl & Wahl, 2012). In some studies, ERPs and behavioural data have proven complementary, with the former shedding light on the neural mechanisms underlying certain behavioural manifestations during early development (Grossmann, Striano, & Friederici, 2007; Lunghi et al., 2019; Peltola, Leppänen, Mäki, & Hietanen, 2009). In other studies, ERPs have provided a more sensitive measure of infants' cognitive abilities than behavioural investigations (de Haan & Nelson, 1997; Hoehl, Reid, Mooney, & Striano, 2008; Nelson & Collins, 1992). This notion is critical for researchers interested in investigating the early markers of neurodevelopmental disorders, given that many of these conditions do not immediately manifest in overt behaviour but, rather, have roots in atypical neural structure and function that can be traced back to prenatal and early postnatal development. Indeed, developmental research with ERPs has been conducted to assess putative early-emerging atypicalities in the timing and sequence of stimulus processing in neurodevelopmental disorders such as ASD and ADHD, highlighting the potential of this technique for early detection and prediction of later traits and symptoms (Bowman & Varcin, 2018; Finlay-Jones et al., 2019; Jeste, Frohlich, & Loo, 2015; Jeste & Nelson, 2009; Nelson & McCleery, 2008).

Despite the suitability of ERPs for investigating perceptual and cognitive phenomena in developing populations, researchers wishing to conduct this research should be aware of some methodological challenges. First, collecting a high number of artifact-free trials in early development may be difficult given that infants rarely maintain their attention to a stimulus for a long period of time (Hoehl & Wahl, 2012). Attention getters (e.g. visual, auditory or cross-modal stimuli) may be used in developmental research to re-direct infants' attention to the screen and maximise the number of usable trials (Farroni, Csibra, Simion, & Johnson, 2002; Lunghi et al., 2019). An experimenter may also be present inside the testing room and re-direct the infant's attention to the screen through pointing or gentle speech. The minimum number of artifact-free trials to include an infant in the final participant sample varies between studies, ranging from 7 to 40 trials (Hoehl & Wahl, 2012). However, the majority of ERP studies conform to an inclusion criterion of at least 10 artifact-free segments. I therefore adopt the same inclusion criterion for the ERP analyses reported in Chapters 4 and 5. Secondly, infant ERP data is characterised by high inter and intra-individual variability which may be driven by both developmental factors and movement-related artifacts. This variability makes it difficult to specify a priori time windows for the automatic extraction of mean amplitude and/or fractional area latency measures. Local peak amplitude and latency measures are more commonly used in infant ERP research and can be extracted by plotting the average ERP waveform for each participant. These measures provide reliable estimates when the ERP components are clearly defined,

thus highlighting the importance of using basic sensory stimuli that produce reliable and replicated waveforms for statistical analyses (Hoehl & Wahl, 2012). An example of the procedures adopted in developmental research to extract peak amplitude and latency measures from the average ERP waveform of an infant participant is presented in Figure 2.5. I adopt this approach for extracting the ERP measures reported in Chapters 4 and 5.

In summary, researchers interested in assessing the neural mechanisms underlying perceptual and cognitive processes in infant populations may use ERPs. Some methodological considerations inherent to the properties of this technique and its application to infant populations should be considered. Despite these considerations, ERPs represent a crucial source of information about the timing of neural dynamics mediating perceptual and cognitive functions in the developing brain.

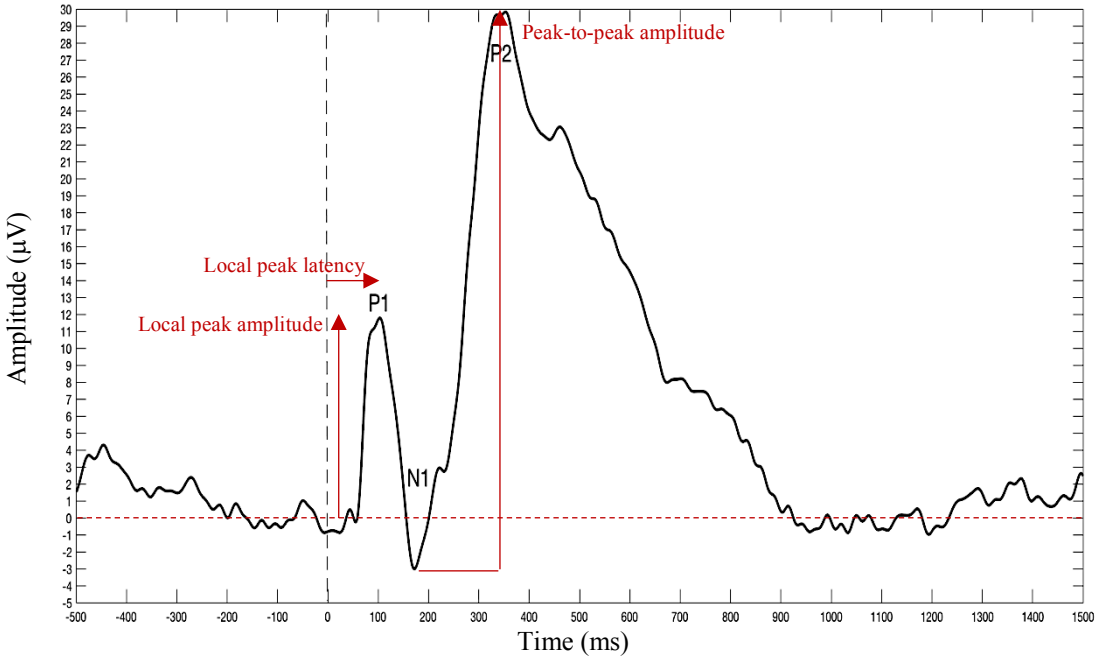

Figure 2.5. Extraction of peak amplitude and latency measures from a 10-month-old infant's ERP average waveform

Schematic representation of the procedures for extracting peak amplitude and latency measures for the P1 and P2 components. The local peak amplitude for the P1 is estimated from baseline. The peak latency corresponds to the time of occurrence of the local peak from the onset time. A peak-to-peak approach should be employed to quantify the amplitude of the P2 component. Plotting the individual average ERP waveform is necessary for accurately quantifying amplitude and latency measures with infant data.

2.3.3.4. Frequency domain analyses – Fourier transform

EEG researchers are frequently interested in analysing the EEG signal in the frequency domain. A time domain signal can be transformed into a frequency

domain signal through the Fourier transform. The Fourier transform is a fundamental signal processing technique and it underlies many EEG approaches (Cohen, 2014). A frequency domain signal contains information about frequency, power and phase. Frequency refers to the number of cycles within 1 second and it is expressed in Hertz (Hz): for example, 4Hz refers to a signal with 4 cycles/second. Complex signals may contain multiple frequency contents, see Figure 2.6. Power is the amplitude squared of a signal. Phase is the timing of the sine wave measured in radians or degrees. It follows that the Fourier transform provides a three-dimensional (3D) representation of a time domain signal. Frequently, the phase information is ignored when plotting results of a Fourier transform, leaving only frequency and power. However, frequency, power and phase are computed as part of the transformation and they are all necessary to fully reconstruct a time domain signal from a frequency domain signal (Cohen, 2014). Researchers typically convert time domain signals into their frequency domain representations using the fast Fourier transform. This approach is quicker, more efficient and elegant when dealing with a high number of data points (e.g. in EEG data analysis) (Cohen, 2014).

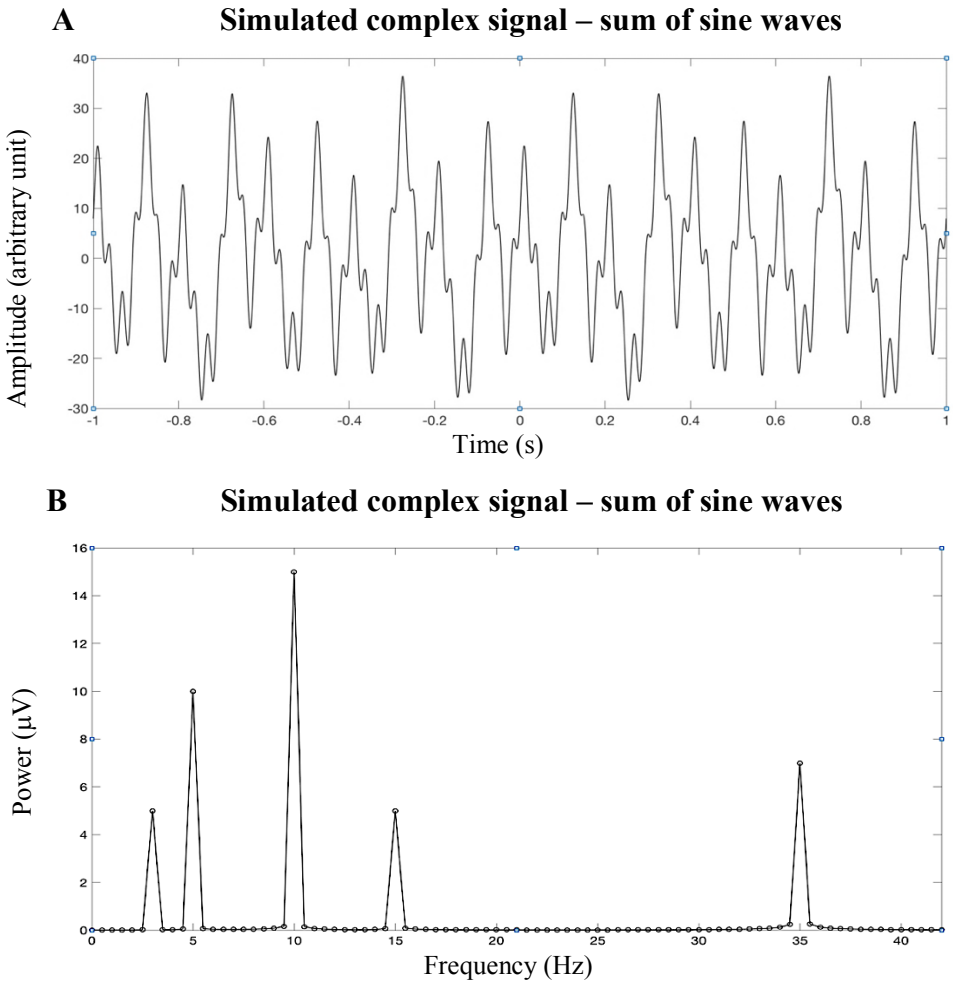

Figure 2.6. Representation of a complex signal as a sum of sine waves in the time and frequency domain

A) Simulation of a complex signal as a sum of sine waves; the signal is plotted in the time domain, making it hard to detect the underlying frequency components; B) Simulation of the same signal as a sum of sine waves; the signal is plotted in the frequency domain, thus highlighting the underlying frequency components.

The mathematical implementation of the Fourier transform is the algebraic operation called *dot product*. The dot product takes two vectors *a* and *b* of equal

length *n* and returns a single number by multiplying each element of the first vector (*a*) by each element of the second vector (*b*) and summing these points together. An EEG signal can be conceptualised as a high dimensional vector whose Fourier transformation from the time domain to the frequency domain occurs by computing the dot product between this vector (i.e. the signal) and sine waves of different frequencies (i.e. the kernels). This operation is described as convolution and can isolate the frequency content of a signal, see Figure 2.7. Convolution requires full temporal overlap between the signal and the kernel. Therefore, zero-padding (i.e. adding zeros to end of a time-domain signal to increase its length) can be performed at the beginning and at the end of the signal to ensure complete convolution. Importantly, the Fourier transform cannot highlight changes in frequency content over time. This is due to the fact that convolution in a Fourier transform is performed using a sine wave kernel that continuously fluctuates over its time series. To overcome this limitation, convolution can be performed using a sine wave windowed with a Gaussian. This approach is called Morlet wavelet analysis and it will be discussed in section 2.3.3.5, given that it provides the base for the analyses reported in Chapters 3, 4 and 5.

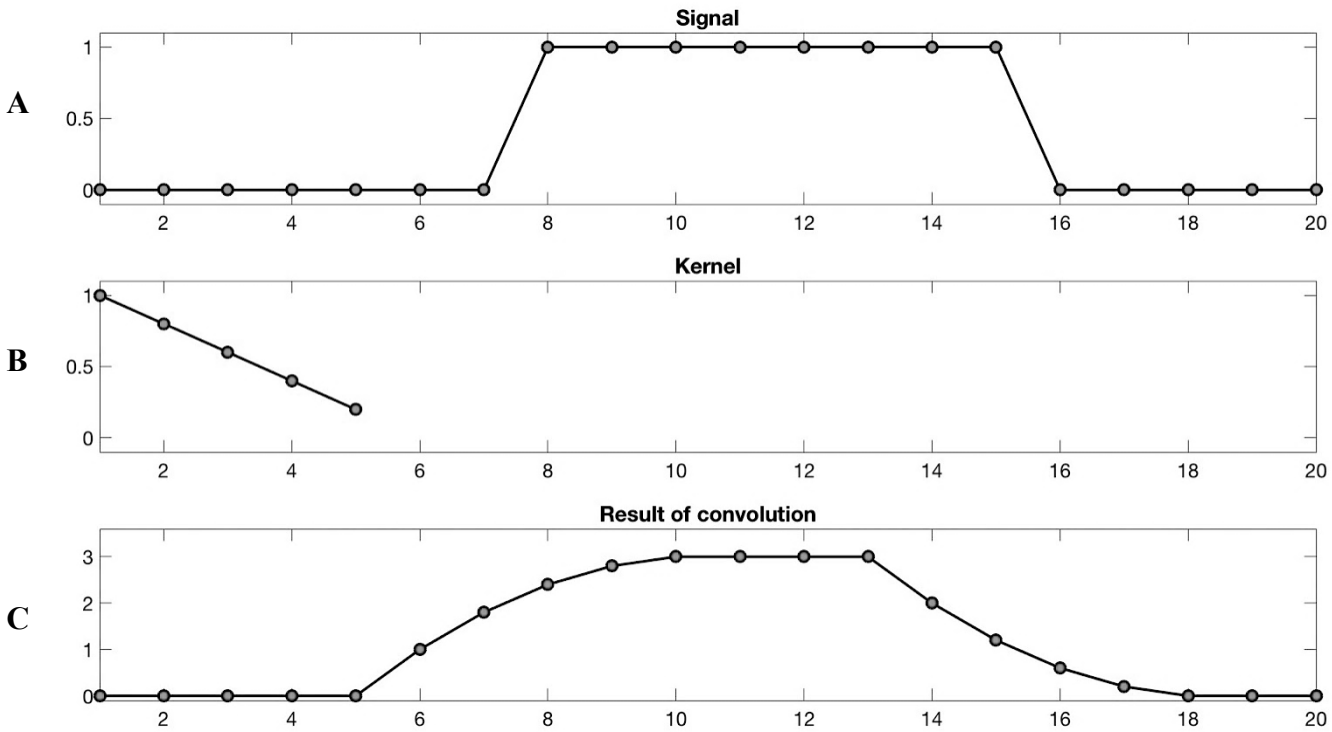

Figure 2.7. Schematic representation of convolution between two vectors

Convolution between two vectors, the signal (A) and the kernel (B). The output of convolution is a new vector (C) that contains information about both the signal and the kernel (note: a sine wave kernel is used in the context of the Fourier transform).

2.3.3.5. Time-frequency domain analyses – Morlet and Complex Morlet wavelets

As mentioned in section 2.3.3.4, the Fourier transform enables extracting frequency domain content from a time domain signal. However, the Fourier transform has two limitations. First, the kernel used in a Fourier transform is a sine wave which constantly fluctuates over its time series. This makes it impossible to visualize time information in the context of a Fourier transform. Secondly, a core assumption of the Fourier transform is signal stationarity. This means that the signal should manifest periodicity and the mean, variance and frequency structure of the signal should remain constant over time. EEG signals are non-stationary, thus violating the core assumption of the Fourier transform. Time-frequency analyses provide a strategy to overcome these limitations (Cohen, 2019; 2014).

A common approach to perform time-frequency analysis of EEG data is through the application of Morlet wavelets. A Morlet wavelet is a kernel composed by a sine wave tapered by a Gaussian, see Figure 2.8. Gaussian windows have no sharp edges, thus enabling temporal weighting of the signal without introducing artifacts. In contrast to the Fourier transform, Morlet wavelets do not assume complete signal stationarity since the power spectrum of the signal is computed over short (sliding) time windows. Morlet wavelets assume signal stationarity only during the time periods in which the wavelet appears like a sine wave (Cohen, 2019; 2014). EEG signals do not violate this assumption since they remain stationary for hundreds of milliseconds (Cohen, 2014; Florian & Pfurtscheller, 1995).

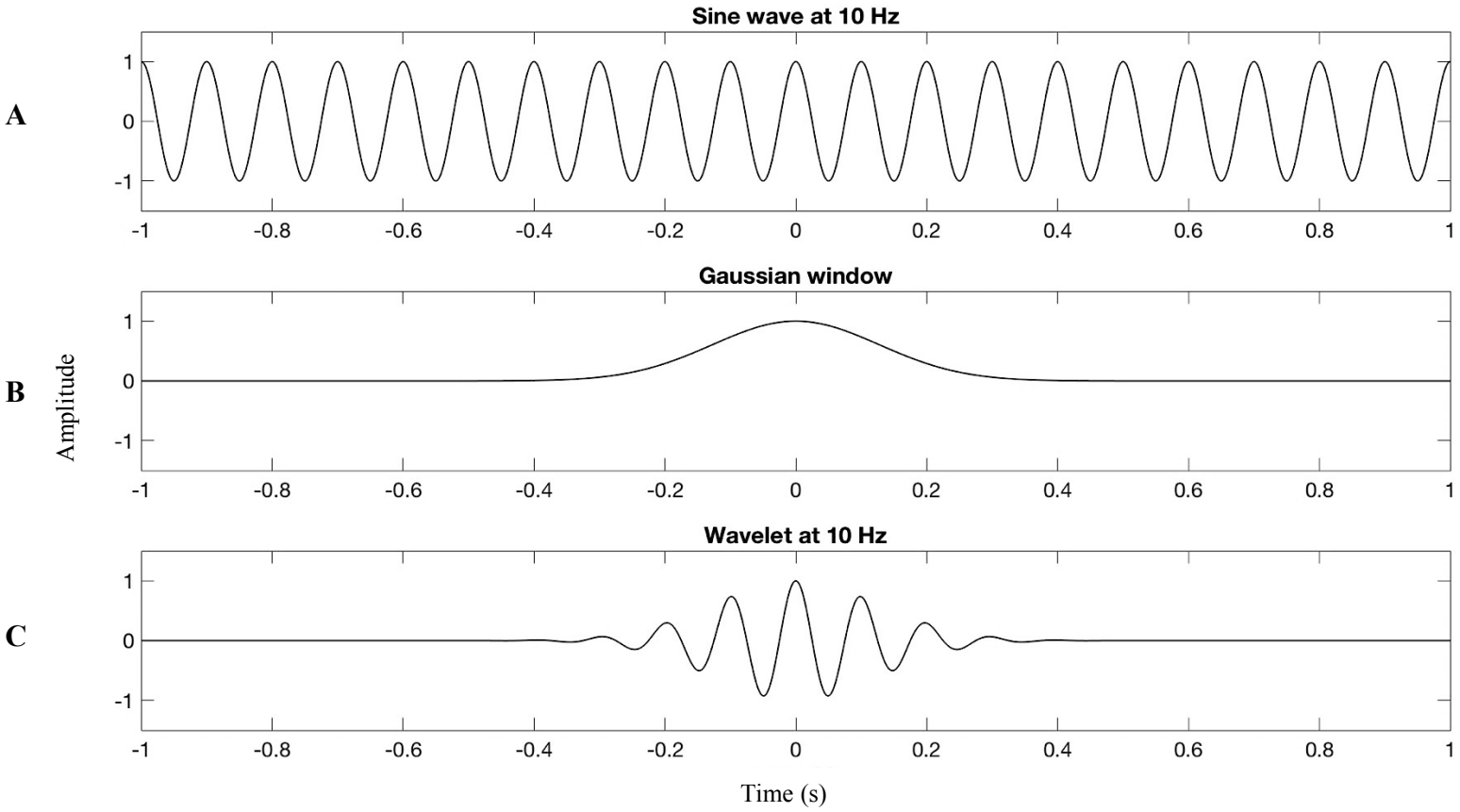

Figure 2.8. Schematic representation of a Morlet wavelet

A Morlet wavelet (C) is created by tapering a sine wave (A - here represented at 10Hz) by a Gaussian (B).

As Figure 2.8. (C) illustrates, a Morlet wavelet provides frequency information at each time point by computing a weighted sum of the frequency information of the surrounding time points. Thus, researchers should consider that time-frequency analyses can only provide an estimate of the instantaneous activity at a certain time point (Cohen, 2019; 2014). Two main limitations underlie Morlet wavelets. Firstly, since Morlet wavelets utilise a real-valued sine wave, they do not convey information about power and phase (i.e. they act as a bandpass filter; Cohen, 2014). Secondly, the output of convolution between the signal and the Morlet wavelet is a function of the relative phase lags. This prevents from quantifying the relationship between the signal and the kernel when the phase lag differs from 0°. Using Complex Morlet wavelets provides a way to overcome these limitations.

A Complex Morlet wavelet is a kernel obtained by tapering a complex-valued sine wave with a real-valued Gaussian. This wavelet occupies a 3D space, with the x-axis representing the real component, the y-axis representing the imaginary component and the z-axis representing time, see Figure 2.9. A Complex Morlet wavelet can be convolved with a time domain signal to obtain information about the instantaneous amplitude (or power, i.e. amplitude squared) and phase of the signal. One crucial parameter influencing the result of convolution between a Complex Morlet wavelet and a time domain signal is the width of the real-valued Gaussian. This parameter is specified as follows:

$$\sigma = \frac{n}{2\pi f}$$

where *n* represents the number of cycles per time unit and defines the time-frequency precision trade-off. The choice of *n* depends on the characteristics of the signal. It is common with EEG data to use values of *n* ranging from 2 to 15 over frequencies ranging from 2Hz to 80Hz (Cohen, 2019). Generally, a noisy but roughly stationary signal is better estimated with a high number of cycles, whereas a signal characterised by transient changes is better estimated with a small number of cycles (Cohen, 2019; 2014). The Complex Morlet wavelet approach used in Chapters 3, 4 and 5 adopts a real-valued Gaussian with $n = 3.5$ cycles per time unit.

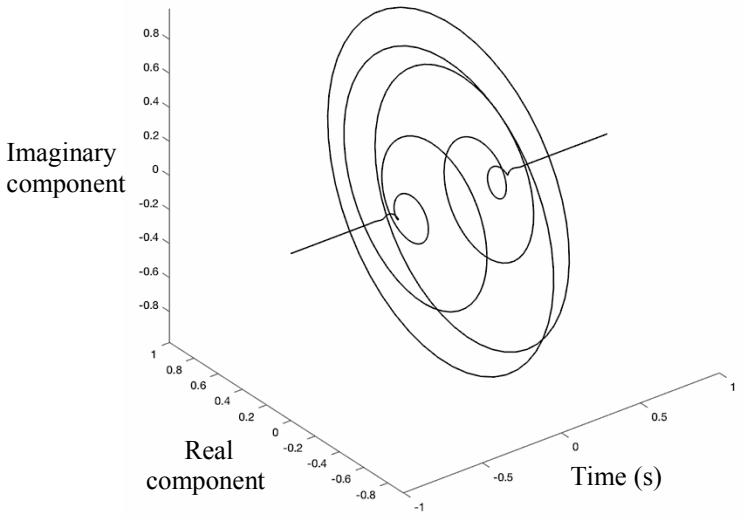

Figure 2.9. Representation of a Complex Morlet wavelet in a three-dimensional space

A Complex Morlet wavelet can be plotted in a three-dimensional space with the x-axis representing the real component, the y-axis representing the imaginary component and the z-axis representing time.

2.3.3.6. Time-frequency domain analyses – statistical analysis of Complex Morlet wavelets outputs

The result of convolution between a Complex Morlet wavelet and a time domain signal is a 3D complex-valued signal from which the instantaneous amplitude (or power) and phase can be estimated. This complex-valued signal has both a real and an imaginary component. Thus, in order to extract these parameters for later statistical analyses, understanding the notion of complex numbers is essential.

A complex number can be expressed in the form $a+ib$, where a is a real component, b is the imaginary component and i is the imaginary operator. This operator corresponds to the square root of -1 (i.e. a number that multiplied by itself gives -1). Complex numbers can be represented in a Cartesian or polar notation, see Figure 2.10. A Cartesian notation consists of the x-axis and the y-axis, whereby x illustrates the real component and y illustrates the imaginary component of the complex number. A polar notation consists of magnitude M and angle θ. Following convolution between a Complex Morlet wavelet and a time domain signal, M corresponds to the amplitude of the complex-valued signal, M^2 corresponds to the power of the signal and θ corresponds to the phase of the angle estimated with respect to the positive real axis and at the peak frequency of the wavelet. These parameters can be extracted over multiple frequency bands to generate a time-frequency plot that illustrates the results of the analysis.

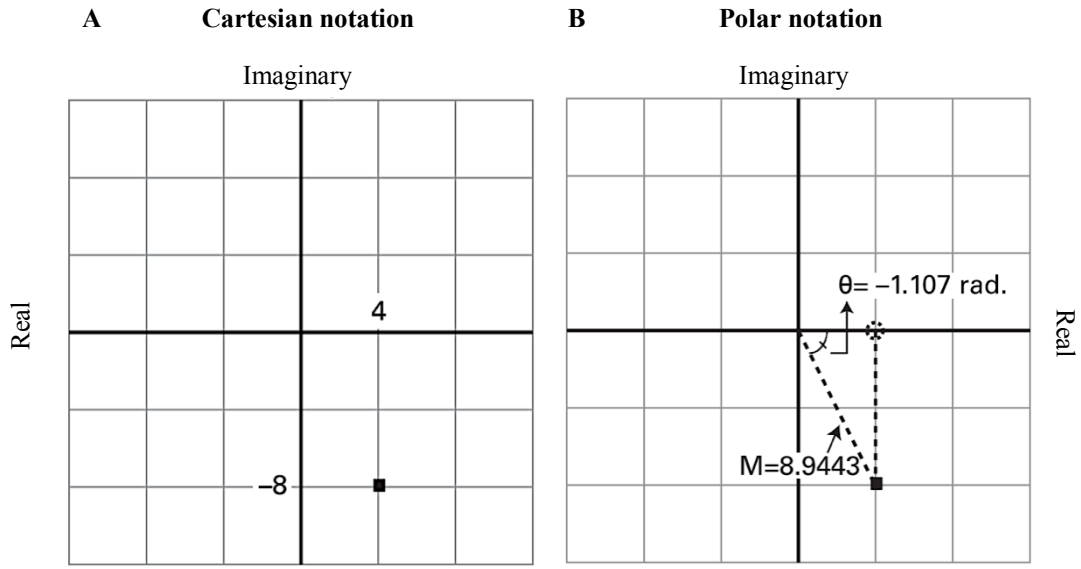

Figure 2.10. Cartesian and polar representation of a complex number

The same complex number (4-8i) can be plotted in a Cartesian notation (A) or in a polar notation (B). From Cohen (2014).

The selection of time windows of interest for performing statistical analysis is commonly done through visual inspection of the time-frequency plots. To quantify event-related activity, researchers may apply baseline correction to the data. Baseline correction enables visualizing activity fluctuations (i.e. power or amplitude) that are linked to relevant events, disentangling background from task-related neural manifestations. Further, baseline correction may improve the distribution of frequencies. Baseline correction can be performed with respect to a pre-trial baseline period (e.g. 100ms before stimulus onset). Various approaches to baseline correction exist including linear baseline subtraction, baseline division and

percentage change (Cohen, 2014). Although these approaches may yield comparable results, evidence indicates that linear baseline subtraction and baseline division may be preferable to percentage change (Cohen, 2014; Hu, Xiao, Zhang, Mouraux, & Iannetti, 2014). Linear baseline subtraction is an unbiased approach which subtracts the mean of the baseline period from each sample along the trial. This approach does not introduce bias but it can be problematic if researchers are interested in assessing amplitude (or power) changes at high EEG frequencies (Ciuparu & Mureşan, 2016). As illustrated in Figure 2.11, a typical EEG frequency spectrum has a 1/f distribution, whereby high frequencies have smaller amplitude (or power) than low frequencies (Nunez & Srinivasan, 2005). It follows that performing baseline subtraction can mask amplitude (or power) changes occurring at high frequencies. However, this may not be an issue if researchers are solely interested in assessing changes occurring at low frequencies. Baseline division enables overcoming this issue by quantifying the relative change in amplitude (or power) at each frequency. However, baseline division can introduce a positive bias to the data, leading the distribution of amplitude (or power) values in the target interval to become spuriously positive following the normalization. This issue must be corrected by applying positive bias correction procedures (Ciuparu & Mureşan, 2016). Given that I assess in the following chapters changes in the amplitude of low frequencies (Chapter 3 = [α = 6-10Hz]; Chapters 4 and 5 = [θ = 3-6Hz]), I adopt a baseline subtraction approach.

Finally, the statistical analysis of time-frequency measures can be conducted using traditional linear modelling techniques. As it was the case for ERPs, also for time-frequency measures, researchers may be sometimes deal with correlated observations and/or missing data. I direct the reader to section 2.3.3.2 for an introduction to approaches applicable in this scenario (Zeger & Liang, 1986; Ziegler et al., 1998), and to Chapters 4 and 5 for a discussion and applications of these approaches.

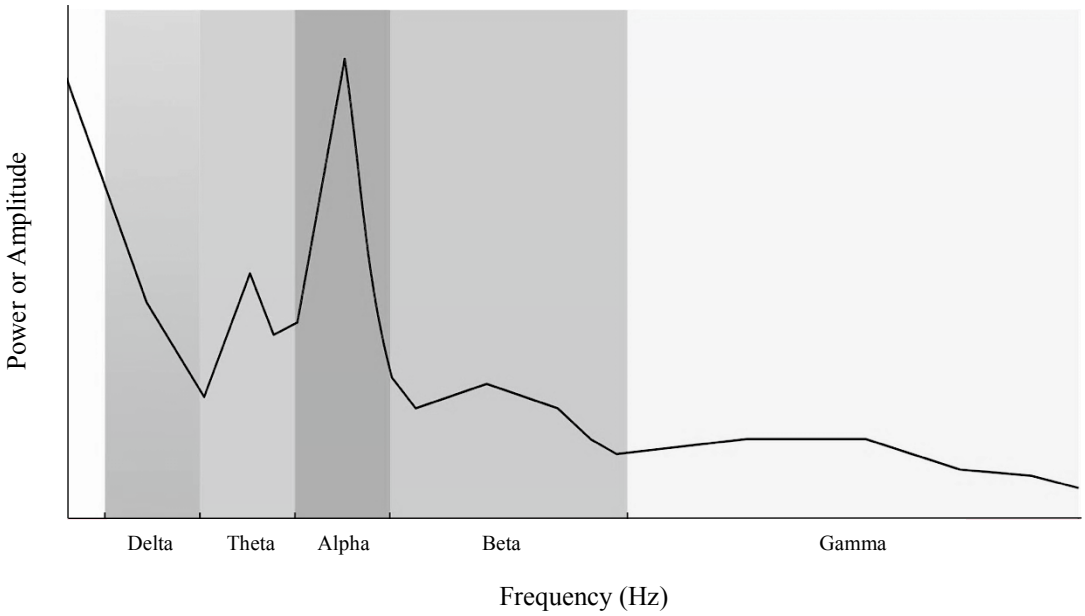

Figure 2.11. Typical EEG frequency spectrum

Schematic representation of a typical EEG frequency spectrum. Lower frequencies manifest higher amplitude or power. The boundaries for each frequency band may differ between studies and/or participants, and are generally lower in early development.

2.3.3.7. Application of frequency and time-frequency analyses in infant research

Analytical approaches relying on the Fourier transform or Complex Morlet wavelets have been employed to investigate the frequency content of EEG signals underlying perceptual and cognitive phenomena in infants. This research has revealed the link existing between specific frequency bands and perceptual or cognitive functions (Saby & Marshall, 2012). Furthermore, this research has highlighted the transition manifesting in the EEG spectra over development (Maguire & Abel, 2013; Saby & Marshall, 2012).

As reviewed in sections 2.3.3.4 and 2.3.3.5, frequency and time-frequency analyses can be applied to a time domain signal to reveal its spectra at specific frequencies. A typical EEG frequency spectrum manifests an inverse relationship between amplitude or power and the frequency content. This inverse relationship is reported since early in development and may be explained by two factors. First, higher frequencies are more attenuated over long distances than lower frequencies (Buzsáki & Watson, 2012). Secondly, phase alignment is higher for lower than higher frequencies (Cohen, 2014). A typical EEG power spectrum manifests a peak in the theta and alpha frequency bands, whereas more attenuated activity can be observed for the beta and gamma bands. The range for specific frequency bands is conventionally defined. Inconsistency in the specification of frequency bands exists in the literature and the range may differ between studies and participants. Common frequency bands identified in adults include delta (δ = 1-3Hz), theta (θ = 4-7Hz),

alpha (α = 8-12Hz), beta (β = 13-30Hz) and gamma (γ = 30-100Hz). Similar frequency bands are present in infancy, although developmental research suggests that the boundaries for specific frequencies are generally lower in early development (Saby & Marshall, 2012).

Growing developmental research has linked oscillatory activity within certain frequency bands to specific psychobehavioural functions. For example, delta oscillations in infancy (δ = 1-3Hz) have been reported during sleep (Schechtman, Harper, & Harper, 1994). Slow δ waves with superimposed fast activity (i.e. delta brushes) have been described in early prematurity during sleep and wakefulness; further, variability in the frequency, amplitude and topography of delta brushes has been linked to both infants' age and vigilance (Whitehead, Pressler, & Fabrizi, 2016).

Beta oscillations in infancy (β = 10-25Hz) have been observed in cortical somatosensory regions in relation to muscular activity and motor experience (van Elk, van Schie, Hunnius, Vesper, & Bekkering, 2008). Specifically, changes in the β band have been linked to movement preparation and execution: voluntary movement causes a decrease in β amplitude/power, whereas inhibition of the motor system associates with an increase in β amplitude/power (Pavlidou et al., 2014).

Gamma oscillations (γ = 20-60Hz) have also been studied in infancy and linked to higher level cognitive functions, including perceptual binding (Csibra, Davis, Spratling, & Johnson, 2000), perceptual learning (Snyder & Keil, 2008a), memory (Leung et al., 2016) and top-down contributions of semantic knowledge

on object perception (Gliga, Volein, & Csibra, 2010). For example, Snyder and Keil (2008) investigated changes in γ activity in 6-month-old infants during the repeated presentations of a stimulus and examined whether such changes predicted behavioural responses to novelty at test. Results indicated that induced γ activity decreased over occipital scale sites with stimulus repetition and greater decrease in γ activity predicted behavioural orienting to a novel stimulus at test.

Much developmental research has been devoted to characterising the functional properties of oscillatory activity in the theta (θ = 3-6Hz) and alpha (α = 6-10Hz) frequency bands. I review below key evidence emerged from this research since the θ and α frequency bands will be the focus of the analyses reported in Chapters 3, 4 and 5 (further, Chapters 3 and 4 provide a more in-depth examination of these frequency bands).

Accumulating evidence from developmental research assessing the functional role of θ oscillations has revealed their role in mediating the top-down control of attention (Bazhenova, Stroganova, Doussard-Roosevelt, Posikera, & Porges, 2007; Meyer, Endedijk, van Ede, & Hunnius, 2019; Orekhova, Stroganova, & Posikera, 1999; Stroganova, Orekhova, & Posikera, 1998; Wass et al., 2018), in mediating information encoding (Begus, Gliga, & Southgate, 2016; Begus, Southgate, & Gliga, 2015; Orekhova, Stroganova, Posikera, & Elam, 2006) and in supporting learning and memory (Begus et al., 2015; Köster, Langeloh, & Hoehl, 2019) since infancy. Orekhova and colleagues (1999) were the first to systematically investigate the role of θ oscillations in mediating sustained attention

in infancy. In this study, the authors recorded EEG activity in infants aged 8-11 months under three experimental conditions (externally-controlled attention, internally-controlled attention and a baseline condition). Results indicated that frontal θ oscillations were enhanced in the internally-controlled condition relative to the other conditions. Further, this θ enhancement correlated with infants' ability to maintain internally-controlled attention, as indicated by behavioural assessment. This predictive relationship between frontal θ oscillations and sustained attention was recently replicated by Wass and collaborators (2018). The authors reported θ power preceding infants' visual fixations during free play with objects to predict total fixation duration. Further, a predictive relationship between θ oscillations and infants' learning was documented by Begus and collaborators (2015), who reported modulations of this specific frequency band during infants' exploration of objects to predict later recognition of these objects.

Similarly, α oscillations have been shown to mediate cortical inhibition and the top-down selection of incoming sensory input since infancy (Saby & Marshall, 2012). Synchronization of the α rhythm at posterior locations was reported during infancy in the absence of visual stimulation (Stroganova, Orekhova, & Posikera, 1999), suggesting that increased α oscillations may reflect an "idling" state (Pfurtscheller, Stancak, & Neuper, 1996). Conversely, desynchronization of the α rhythm at posterior locations was documented in the presence of visual stimulation (Stroganova et al., 1999). Concurrent synchronized and desynchronized α activity was also reported in different cortical regions, leading to the hypothesis

that α oscillations may mediate the inhibition of task-irrelevant networks to optimise stimulus processing in task-relevant networks (Wolfgang Klimesch, Sauseng, & Hanslmayr, 2007). Synchronization and desynchronization of the α rhythm have also been documented at somatosensory locations, suggesting that this rhythm may support tactile sensory processing and the emergence of motor control over development (De Klerk, Johnson, & Southgate, 2015; Hagne, Persson, Magnusson, & Petersen, 1973; Marshall & Meltzoff, 2011; Southgate, Johnson, Osborne, & Csibra, 2009). Further, the somatosensory α rhythm has been associated with GABAergic inhibitory modulation in animals (Lörincz, Crunelli, & Hughes, 2008) and humans (Ahveninen et al., 2007; Schreckenberger et al., 2004).

Importantly, developmental research adopting frequency and time-frequency analyses has also been conducted to assess putative early-emerging atypicalities in brain oscillatory activity in neurodevelopmental disorders such as ASD and ADHD. As reviewed in Chapter 1, this research suggests that the early development of ASD and ADHD is characterised by the presence of alterations in various EEG frequency bands, including the theta, alpha and gamma bands (Bowman & Varcin, 2018; Finlay-Jones et al., 2019; Jeste et al., 2015). It follows that EEG may serve as an ideal methodology for the investigation of putative early markers informing diagnosis and predicting later traits or symptoms in neurodevelopmental disorders such as ASD and ADHD.

Infant research adopting frequency or time-frequency approaches shares methodological challenges with infant ERP research. These include the difficulty

of collecting a high number of artifact-free trials, the need to use attention getters to re-direct infants' attention to the screen, the presence of an experimenter inside the testing room to facilitate infants' engagement with the task through pointing or gentle speech and the overall elevated intra and inter-participant variability that may limit the application of automatic processing pipelines. Furthermore, researchers conducting frequency or time-frequency analyses during development should be aware that the specific boundaries for relevant frequencies will change over time. This aspect has been taken into consideration throughout Chapters 3, 4 and 5, whereby age-appropriate frequency ranges have been selected for time-frequency analyses.

2.3.4. The methodology of EEG - interim summary

EEG measures the electrical potentials generated by ensembles of pyramidal neurons across the scalp with high temporal resolution (i.e. millisecond time-scale). EEG recordings can be collected during development over multiple assessments, making this methodology ideal for supporting longitudinal research with infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the conditions. Several theoretical and practical considerations support the use of EEG to study the early development of sensory perception in infants with later typical or atypical neurodevelopment, including 1) the capability of the technique to capture changes in neural oscillatory and evoked activity, whose role in mediating sensory perception has been demonstrated in research with animals and humans and which

represent the physiological underpinnings of psychological constructs such as "attention", "prediction" and "expectation" and 2) the capability of EEG to offer an accurate time window into the dynamic interplay between top-down and bottom-up contributions to sensory perception from infancy.

2.4. Investigating the early development of sensory perception through parental reports

While EEG research may shed light on the neural mechanisms underlying early-emerging sensory atypicalities in ASD and ADHD, parental reports offer the opportunity to characterize the manifestations of atypical sensory perception on infants' everyday behaviour. The assumption underlying parental reports is that the information held by parents about their infant's sensory behaviours can be disclosed through interrogative methods (Hagekull, Bohlin, & Lindhagen, 1984). Parental reports have both advantages and disadvantages. Among the advantages, parental reports enable characterizing the manifestation of sensory atypicalities on children's everyday behaviour. Further, parental reports enable quick data collection and allow accessing behaviours that may be infrequent or occur only in certain contexts. Despite these advantages, parental reports also have some limitations. These include the inability to uncover putative mechanisms underlying the observed sensory atypicalities, limited reliability due to recollection bias and limited validity (particularly, convergent and discriminative validity). These limitations may, however, be overcome by adopting an integrated, multi-method

approach that combines parental reports with experimental and clinical methods. Further, an integrated approach to the investigation of the early development of sensory perception may clarify issues related to the convergent and discriminant validity of parental reports in early development.

In light of my interest in assessing the early development of sensory perception in infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the conditions, I present in the following sections key properties of the most frequently used parent-reported measure of sensory processing in infancy, the *Infant-Toddler Sensory Profile* (Dunn, 2002). I review information concerning the instrument content, reliability and validity. Furthermore, I critically discuss a construct of this instrument (i.e. sensory seeking) that is central to the analyses reported in Chapters 3, 4 and 6. The ITSP construct of sensory seeking maximally captures infants' active engagement with their surrounding environment. I focus on this construct since I am particularly interested in understanding how early-emerging sensory atypicalities may impact infants' active engagement with their environment. Further, I am interested in assessing the extent to which sensory seeking may mediate or moderate the potential relationship between early-emerging sensory atypicalities and ASD and/or ADHD traits in toddlerhood.

2.4.1. Infant-Toddler Sensory Profile (ITSP) – instrument content

The *Infant-Toddler Sensory Profile* (ITSP) is the most common parent-reported measure of infants' sensory processing (Dunn, 2002). Two age-appropriate versions of this instrument are available for researchers and practitioners: the 0-6 months version and the 7-36 months version. I focus here on the 7-36 months version of the ITSP since data from this instrument will contribute to the following chapters.

The 7-36 months version of the ITSP is a 48-item questionnaire that provides a measure of infants' sensory processing manifestations in four quadrants (i.e. sensory seeking, low registration, sensory avoiding and sensory sensitivity) for each sensory domain (i.e. visual, auditory, tactile and vestibular). Parents are asked to rate the frequency of occurrence of their infant's sensory behaviours on a 5-point scale (i.e. 1=almost always; 5=almost never). Lower scores indicate a higher frequency of behaviours, whereas higher scores indicate a lower frequency of behaviours. The classification system used in clinical practice for the 7-36 months version of the ITSP is based on cut-off scores determining "typical performance", "probable performance" and "definite performance", see Figure 2.12. This classification helps professionals to determine whether a child's performance on the ITSP is of concern. In research, investigators may adopt the same classification system (Ben-Sasson et al., 2008; Beranova et al., 2017) or they may compare average scores between participant groups (Germani et al., 2014). I adopt the second approach in Chapters 3 and 4, given that a sample of infants at typical

likelihood of ASD and/or ADHD was recruited for the studies, alongside infants at elevated likelihood of the conditions.

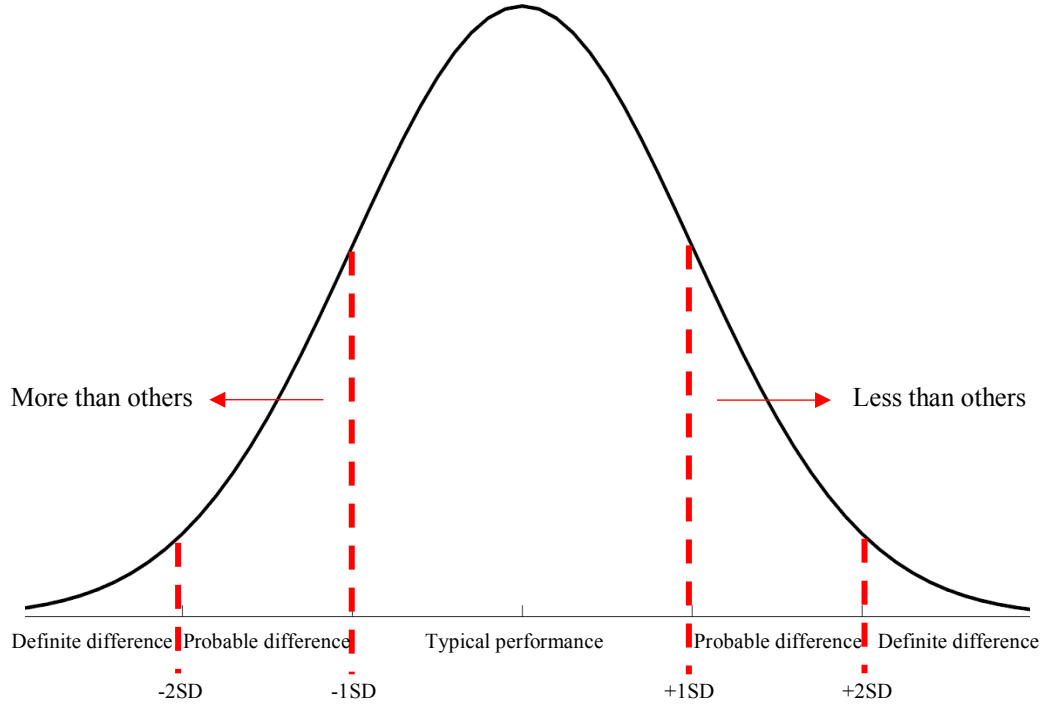

Figure 2.12. The normal curve and the ITSP classification system for children aged 7-36 months

The ITSP classification system for the 7-36 months version of the ITSP is based on cut off scores and norm values. This classification is used for clinical and screening purposes. Research using this version of the instrument may adopt the same classification system or compare scores between participant groups.

The goal of the ITSP is to capture salient information about infants and toddlers' sensory processing abilities. Thus, the ITSP links sensory processing to the child's daily living performance. The theoretical foundation of the instrument

is Dunn's model of sensory processing (Dunn, 1997). This model explains sensory processing as resulting from an interaction between two continua: 1) neurological thresholds, 2) behavioural responses, see Figure 2.13. The individual's neurological threshold refers to the amount of stimulation necessary for neural ensembles to discharge and depends on the balance between cortical excitation and inhibition. Atypical balance between excitation and inhibition is assumed to cause atypical neurological thresholds and affect the brain capacity to modulate its response to incoming sensory stimulation. This atypicality may, in turn, lead to atypical behavioural responses. A behavioural response is the action performed in response to a current neurological threshold. This response manifests along a continuum that includes active and passive strategies. While passive strategies do not contrast the current neurological threshold, active strategies contrast the current neurological threshold to preserve the homeostasis (i.e. active strategies are compensatory). Passive strategies include low registration and sensory sensitivity, whereas active strategies include sensory seeking and sensory avoiding.

Behaviours consistent with low registration are passive strategies in response to a high neurological threshold. Children adopting low registration strategies may appear uninterested, apathetic, self-absorbed and have low energy levels. Conversely, behaviours consistent with sensory sensitivity are passive strategies in response to a low neurological threshold. Children manifesting sensory sensitivity may appear distractible and respond more frequently to incoming sensory input. On the opposite side of the behavioural continuum, behaviours

consistent with sensory seeking are active strategies in response to a high neurological threshold. Children manifesting sensory seeking appear engaged with the surrounding environment and they may generate sensory stimulation by, for example, making noise with objects and/or manipulating objects with their hands and/or mouth. Finally, behaviours consistent with sensory avoiding are active strategies in response to a low neurological threshold. Children displaying sensory avoiding behaviours may withdraw from sensory and/or social contexts and create rituals for their daily activities (i.e. creating rituals may be a strategy to experience only the familiar sensory input; Dunn, 2002). Finally, Dunn's model of sensory processing also proposes that behaviours consistent with sensory sensitivity and sensory avoiding may be combined to obtain an index of children's low threshold manifestations. Children displaying low threshold behaviours may use both active and passive strategies in response to their low neurological thresholds. Therefore, these children may appear fussy or inconsistent in their behaviour and they may be over-vigilant and rigid.

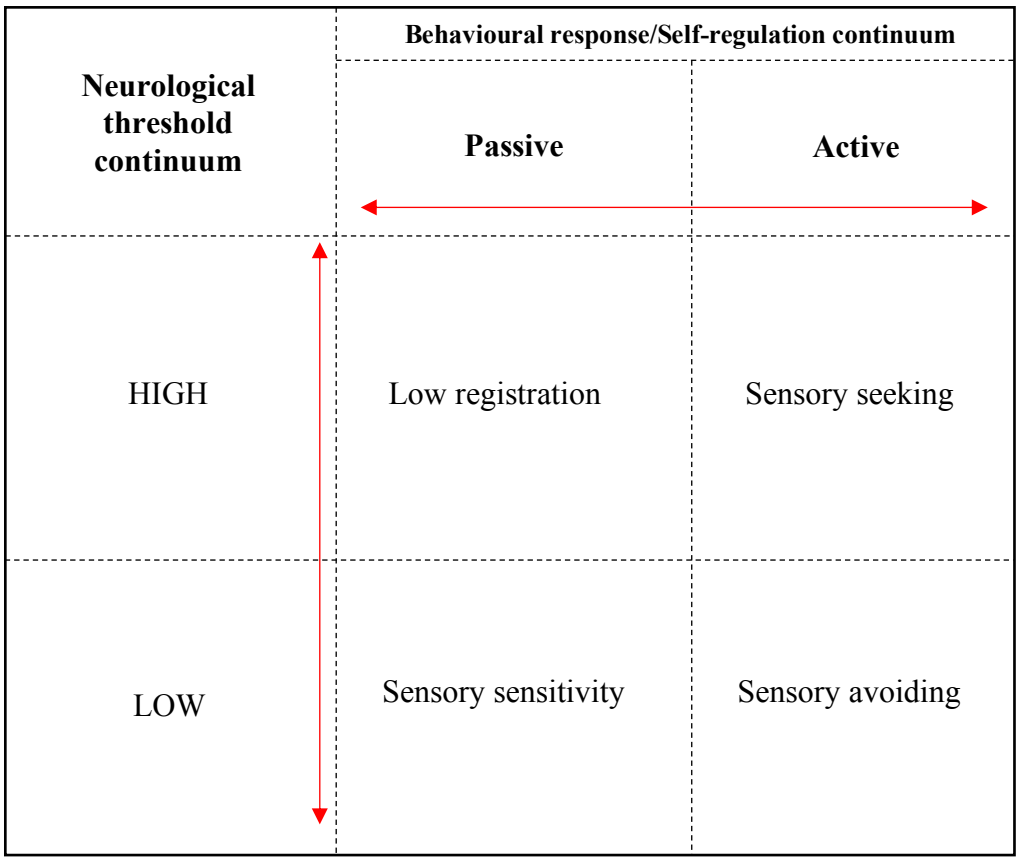

Figure 2.13. Relationship between neurological thresholds and behavioural responses according to Dunn's model of sensory processing (Dunn, 1997)

The neurological thresholds/behavioural response continua provide a basis for understanding individual difference in children's performance. Red arrows indicate these continua. Adapted from Dunn (1997).

2.4.2. Infant-Toddler Sensory Profile (ITSP) – instrument reliability and validity

A common limitation of parental reports, including the ITSP, is limited reliability and/or validity. In particular, extensive research indicates that parental judgement

of infants' behaviour is dependent on the child's developmental stage and this dependence impacts parental perception of infants' sensory processing capacities in early development (Dunn, 2002; Stone & Hogan, 1993).

Reliability refers to the consistency of scores obtained from the same participants through repeated testing under identical conditions. Two types of reliability exist: 1) test-retest reliability and 2) internal consistency. Test-retest reliability can be computed by administering the same questionnaire at two time points. Internal consistency can be computed by investigating the correlations between items within a scale. The test-retest reliability for the domains and quadrants' scores of the 7-36 months version of the ITSP in a normative sample ranges between 0.74 and 0.86. The internal consistency of the domains and quadrants' scores in the same version of the instrument ranges between 0.69 and 0.85 (Dunn, 2002; Eeles et al., 2013). Thus, the 7-36 months version of the ITSP has adequate reliability for assessing sensory processing in infancy and toddlerhood.

Validity refers to the ability of a parent-reported measure to 1) measure what it is supposed to measure and 2) correlate with other measures of the same construct to the degree expected by the theory and related empirical research. The ITSP is reported to have adequate content relevance and coverage, thus highlighting its appropriateness for investigating the construct of sensory processing. In contrast, limited investigation of the convergent and discriminant validity of the ITSP has been conducted. In the original validation of the instrument, Dunn (2002) compared

the ITSP to another parental report of infant sensory processing, the *Infant-Toddler Symptom Checklist* (ITSC; DeGangi, 1995) and reported supporting evidence for 28 out of a total of 231 correlations at or above 0.40. No significant association emerged between the sensory seeking quadrant of the ITSP and the total score on the ITSC – a result that was interpreted as suggesting that sensory seeking may represent a concept unique to the ITSP (see section 2.4.3. for a critical examination of this notion). Currently, only one published report assessed the convergent and discriminant validity of the ITSP in relation to an experimental measure of sensory processing. Woodard and collaborators (2012) investigated the associations between scores on the ITSP and an experimental measure of autonomic arousal (i.e. heart rate) in response to sensory stimuli presented across sensory modalities in 2-3 years old children with and without ASD. While the study was significantly under-powered with a sample size of only 16 participants, the authors only reported a trend towards a significant negative association between scores on the ITSP low registration quadrant and heart rate in children with ASD. Taken together, these results prompt further investigation into the potential associations between the ITSP and experimental measures of sensory perception in infants with later typical and/or atypical developmental outcomes.

Clinical validity refers to the ability of an instrument to detect differences between children known to have alternative profiles of the examined construct (e.g. infants with and without sensory processing difficulties). Generally, the ITSP has proven useful for differentiating children with typical relative to atypical sensory

functioning (Ben-Sasson et al., 2009; Dunn, 2002; Germani et al., 2014; Kolesnik et al., 2019; Mulligan & White, 2012). However, researchers wishing to use the ITSP for clinical purposes and evaluate the child's performance based on published norms should consider that a developmental trend manifests in the instrument scores between 7 and 36 months of age. Specifically, in the normative sample, scores in the domains of tactile and oral sensory processing and in the sensory seeking quadrant increase as the child grows older (i.e. the child responds less frequently as she/he grows older). Thus, using growth charts is recommended for practitioners interested in a clinical application of the instrument (Dunn, 2002).

2.4.3. Infant-Toddler Sensory Profile (ITSP) – the construct of sensory seeking

As stated in section 2.4, one of the goals of my PhD project is to understand how early-emerging sensory atypicalities may impact infants' active engagement with their surrounding environment. I am furthermore interested in examining the extent to which individual differences in infants' active engagement with their environment may mediate or moderate the impact of early atypicalities in sensory perception on ASD and/or ADHD traits emerging in toddlerhood. Towards this goal, I utilise in my research the ITSP sensory seeking quadrant.

As presented in section 2.4.1, sensory seeking is a quadrant of the ITSP measuring behaviours consistent with active self-regulation strategies in response to a high neurological threshold. Children manifesting sensory seeking behaviours would add sensory input to their daily experiences and manifest active engagement

with their surrounding environment (Dunn, 2002). According to the instrument, high sensory seeking behaviours could lead to suboptimal functioning by enhancing distractibility and interfering with ongoing performance. In the original validation of the ITSP, Dunn (2002) presents sensory seeking as a construct unique to the instrument and thus contributing to its discriminant validity. Furthermore, the author alludes to a developmental transition in sensory seeking manifestations from infancy to later toddlerhood and childhood (with older children engaging in less sensory seeking behaviours than younger children). However, further elaboration of the meaning and implications of this transition is not provided, making it difficult to understand 1) the putative mechanism driving this developmental shift and 2) whether the ITSP sensory seeking quadrant measures the same construct over development. For example, the 7-36 months version of the ITSP measures sensory seeking in the visual modality by asking parents whether the child enjoys looking at moving or spinning objects (item 14); enjoys looking at shiny objects (item 15); enjoys looking at own reflection in the mirror (item 19); prefers fast-paced, brightly coloured TV shows (item 20). It is possible that these items capture different constructs during early infancy compared to later toddlerhood and childhood.

Support for the notion that the ITSP sensory seeking quadrant may capture different constructs over development comes from the literature assessing sensory seeking manifestations in ASD. Specifically, parental reports of sensory processing document *elevated sensory seeking* in children diagnosed with ASD relative to age-matched control children (Ben-Sasson et al., 2009; Lane, Young, Baker, & Angley,

2010; Liss, Saulnier, Fein, & Kinsbourne, 2006; Simpson, Adams, Alston-Knox, Heussler, & Keen, 2019; Tomchek, Little, Myers, & Dunn, 2018). Elevated sensory seeking in children with ASD commonly manifests as repetitive/prolonged engagement with a particular type of stimulus. These manifestations may interfere with learning by limiting opportunities for exploration. However, research on early development indicates that *reduced sensory seeking* manifests in infants at elevated likelihood of ASD (Ben-Sasson et al., 2007; Mulligan & White, 2012). In a meta-analysis of 14 studies, Ben-Sasson et al., (2009) observed that infants and toddlers younger than 3 years of age, but not older children with ASD, were more frequently displaying reduced sensory seeking; chronological age was the only factor explaining variability in seeking profiles. This evidence suggests that a developmental transition in the manifestation of sensory seeking occurs in ASD populations. This transition may reflect learning that another strategy to limit incoming novel/diversive stimulation (i.e. which children with ASD may experience as distressing, Mulligan & White, 2012) is to seek restricted, repetitive and often self-produced sensory stimulation. Indeed, several reports suggest that the prevalence and severity of repetitive and restricted behaviours in ASD increases during childhood (Harrop et al., 2014; Richler, Huerta, Bishop, & Lord, 2010).

Taken together, findings from the ASD literature suggest that the same parental report may capture different constructs during early infancy compared to later toddlerhood and childhood. In particular, the ITSP sensory seeking items appear to capture a construct of sensory seeking that may be better operationalised

as *seeking of novel/diversive sensory stimulation* in early development. Altogether, Chapters 3, 4 and 6 demonstrate that this conceptualisation can clarify the mechanisms underlying the developmental shift in sensory seeking manifestations, it can inform the nature of individual differences in infants and children's sensory seeking as well as illuminate the potential long-term effects of sensory seeking manifestations on children's social and cognitive development.

2.5. Clinical assessment measures

Alongside EEG methods and parental reports, clinical assessment measures are a fundamental component of research aimed at assessing the early development of infants at elevated likelihood of ASD and/or ADHD. Since reliable phenotyping can only occur through appropriate psychodiagnostic tools, leading research centres in Europe, the US and Canada have adopted common screening protocols incorporating gold-standard diagnostic measures (e.g. EU-AIMS project: www.eu-aims.eu and www.eurosibs.eu; Baby Siblings Research Consortium, BSRC: www.babysiblingsresearchconsortium.org). I review in the following sections the most common diagnostic instruments used in prospective longitudinal studies of infants at elevated likelihood of ASD and/or ADHD (some of which are disorder specific, whereas others are non-disorder specific). I further highlight which of these measures will contribute data to the following experimental chapters.

2.5.1. ASD-specific scales

The gold-standard clinical assessment instrument for ASD is the *Autism Diagnostic Observation Schedule* (second edition) (ADOS-2) (Lord et al., 2012), a play and interview-based observation scale administered by experienced clinicians. The ADOS-2 empirically operationalises criteria central to the DSM-IV and DSM-5. However, the instrument is by itself insufficient for a diagnosis of ASD. The instrument consists of five modules that can be applied to participants of different ages and expressive language levels: 1) the Toddler Module for children aged 12-30 months without phase speech; 2) Module 1 for children aged >31 months with or without phrase speech; 3) Module 2 for children with phrase speech who are not yet verbally fluent; 4) Module 3 for children or young youths with fluent language and 5) Module 4 for older adolescents and adults with fluent language. The Toddler Module and Module 1 are used in research on the early manifestations of ASD. Calibrated severity scores (CSS) can be computed to estimate the level of ASD traits independently of participant's age, intellectual and language abilities (Gotham, Pickles, & Lord, 2009). Overall stability in CSS is reported between the ages of 2 and 15 years (Gotham, Pickles, & Lord, 2012b). Thus, ADOS-2 CSS are used in Chapters 3 and 4 to measure ASD traits in a cohort of participants at elevated likelihood of ASD and/or ADHD prospectively assessed at 24 months.

The *Quantitative Checklist for Autism in Toddlers* (Q-CHAT) and the *Modified Checklist for Autism in Toddlers-Revised* (M-CHAT) are parental reports of ASD traits that can be used with children aged 16-18 months to 24-30 months.

The Q-CHAT is frequently incorporated in research protocols since it is supposed to produce normally distribute scores (Allison et al., 2008). Recent examinations of the instrument indicate that the Q-CHAT has acceptable sensitivity in early development (i.e. at 18 and 24 months) but low specificity (Raza et al., 2019). To assess concordance between a clinician-based measure (ADOS-2) and parental judgement of ASD traits at 24 months, the Q-CHAT is used in Chapters 3 and 4. Further, since the Q-CHAT is described as a normally distributed measure of ASD traits, I employ it in Chapter 6 to assess early-emerging ASD traits in an independent cohort of participants at typical likelihood of ASD and/or ADHD prospectively assessed at 16 months.

The *Social Communication Questionnaire* (SCQ) is a parent-reported clinical ASD measure derived from the ADI-R (Rutter, Bailey, & Lord, 2003).The SCQ consists of two versions: the "current" version and the "lifetime" version. The measure is appropriate for children aged 4 years or older, with a mental age of at least 2 years.

The *Social Social Responsiveness Scale* (SRS) is a parent or teacher-report measure of ASD traits that can be employed for children aged 4-18 years (Constantino, 2002). The revised version of the instrument (SRS-2) can be used with children aged 2 years and 6 months or older (Constantino & Gruber, 2012).

The *Development and Well-Being Assessment* (DAWBA) is a collection of interviews, questionnaires and rating scales enabling ICD-10/DSM-IV or DSM-5 diagnoses in children aged 5-17 years (Goodman, Ford, Richards, Gatward, &

Meltzer, 2000). This instrument is designed to diagnose several potential disorders, including emotional, behavioural and hyperactivity disorders. These diagnoses are later reviewed by a clinician.

As reported in section 2.8.2, the screening process used for the clinical characterisation of ASD in first degree relatives of infants contributing data to Chapters 3 and 4 relies on a number of measures, including the SCQ, the SRS and the DAWBA.

2.5.2. ADHD-specific scales

The gold-standard clinical assessment instrument for ADHD is represented by the *Conners scales*. Several versions of the Conners exist and they can be used for assessing ADHD traits in individuals of different ages. The Conners Early Childhood (EC; Conners & Goldstein, 2009) can be used with children aged 2-6 years. The instrument is available for use by both parents and teachers/childcare providers. The Conners 3 and the shortened version of the Conners 3 can be used with children between 6 and 18 years of age (Conners, 2009). A self-report form of the Conners 3 is also available and can be completed by individuals aged 8-18 years. Thresholds for suspected ADHD include the presence of six ADHD symptoms on either the hyperactive/impulsive or inattention scale, and a positive score on the impairment scale. The Conners Adult ADHD Rating Scale (CAARS) is also available to use with adults. The CAARS provide multiple-informant assessment through self-report (CAARS-S) and observer ratings (CAARS-O) (Conners,

Erhardt, & Sparrow, 1999). Thresholds for suspected ADHD in adults are the presence of five ADHD symptoms on either the hyperactivity/impulsivity or inattention scale. As reported in section 2.8.2, the screening process used for the clinical characterisation of ADHD in first degree relatives of infants contributing data to Chapters 3 and 4 relies on the Conners scales (i.e. Conners EC and CAARS).

The *Child Behaviour Checklist* (CBCL) is a parent or teacher-rated checklist for assessing a range of emotional and behavioural difficulties manifesting during childhood. It can be used with children aged 6-18 years. Eight syndrome subscales constitute the CBCL. The attention problem subscale is commonly used to detect ADHD in children.

2.5.3. Non ASD/ADHD-specific scales

The most commonly used non ASD/ADHD-specific instrument is the *Mullen Scales of Early Learning* (MSEL; Mullen, 1995). The MSEL can be administered to children from birth to 68 months of age by a clinician. These scales assess general development and learning through measures of gross and fine motor skills, visual reception, expressive language and receptive language. These scales are used in Chapters 3 and 4 to quantify general development and learning in infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the disorders at 10 and 24 months of age.

The *Infant Behaviour Questionnaire-Revised* (IBQ-R) is a parent-reported measure of infant temperament (Gartstein & Rothbart, 2003). It can be completed

by parents of infants aged 3-12 months and it is formed by 14 subscales assessing manifestations including, but not limited to, activity level, distress to limitations, approach, fear and cuddliness. The IBQ is available in a short and very short format. The *Early Childhood Behaviour Questionnaire* (ECBQ) is also a parent-reported measure and it serves the same purpose as the IBQ-R. The instrument is appropriate to use with children aged 18-36 months. The ECBQ is formed by 18 subscales and it measures temperamental manifestations known to emerge later in development including, but not limited to, inhibitory control, attentional focusing and attentional shifting. There is evidence that high activity and low inhibitory control measured through the ECBQ at 24 months are predictive of more severe inattention and hyperactivity/impulsivity symptoms during mid-childhood (Shephard et al., 2018). Therefore, I use the ECBQ activity and inhibitory control subscales to quantify ADHD traits in toddlers aged 24 months in Chapters 3 and 4. Further, in Chapter 6, I use the ECBQ to assess early-emerging ADHD traits in an independent sample of participants at typical likelihood of ASD and/or ADHD prospectively assessed at 16 months.

2.6. An integrated approach to the investigation of the early development of sensory perception in ASD and ADHD

EEG measures could be combined with parental reports and clinical assessment instruments to shed light on the early development of sensory perception in neurodevelopmental disorders such as ASD and ADHD. Combining these measures

would enable researchers to overcome the limitations intrinsic to each approach and provide unique datasets for assessing the putative developmental pathways to later traits and symptoms. In particular, a multi-method, integrated approach to the investigation of sensory perception in ASD and ADHD may illuminate the complex relations between early emerging sensory vulnerabilities linked to genetic factors and manifesting at the level of the brain and compensatory behaviours that may impact children's interaction with the environment.

Growing evidence indicates that core diagnostic features of ASD and ADHD do not manifest until 2-3 years of age (for ADHD, core diagnostic features may emerge even later in development) (Bowman & Varcin, 2017; Finlay-Jones et al., 2019; Johnson, Gliga, et al., 2015; Varcin & Jeste, 2017). Conversely, atypical functional characteristics of sensory cortical networks are the first manifestations of the disorders. EEG is optimally suited for assessing these manifestations from infancy, enabling researchers to uncover the early neural markers of the conditions prior to the onset of behavioural signs. At the same time, evidence suggests that the first behavioural signs of ASD and ADHD affect children's interaction with the environment and may serve a compensatory function (Johnson, Charman, Pickles, Jones, in press; Johnson, 2017; Johnson et al., 2015). These signs may initially be subtle and may, therefore, be more easily noticeable by parents who witness their child's daily life experience. Applied to prospective longitudinal studies of infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the conditions, a multi-method approach integrating experimental and parent-reported

measures may clarify both the early neural markers of atypical sensory perception and the behavioural manifestations of atypical sensory perception impacting on children's interaction with the surrounding environment. Further integration of clinical methods may illuminate how both brain and behaviour converge into shaping the final observable phenotypes through mediated or moderated pathways.

In summary, a multi-method, integrated approach to the investigation of the early development of sensory perception in ASD and ADHD may invaluably enhance our understanding of the disorders, contemporarily informing optimal routes for early interventions.

2.7. Description of datasets and statement of contribution

The current PhD thesis utilises datasets from two main studies, the Predictive Learning study and the BASIS study. The Predictive Learning study is an ongoing longitudinal study on the early development of infants at typical likelihood of ASD and/or ADHD. I have been responsible for designing this study and personally collected, processed and analysed the data. The BASIS study is an ongoing longitudinal study on the early development of infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the disorders. Three cohorts of data contribute to the BASIS study: Phase 1, 2 and 3, see Figure 2.14. Data collection for the first two cohorts is complete, whereas data collection for the third cohort is ongoing. I have not been responsible for collecting this data; rather, data collection for the BASIS study was conducted by a group of research assistants (i.e.

the BASIS team). This thesis utilizes data collected as part of the Phase 3 cohort up to a common data freeze. A characterisation of the sample constituting the Phase 3 cohort is provided in section 2.8. Further, I report in Table 3a an overview of the data used in each experimental chapter of the current thesis and in Table 3b an overview of the paradigms employed in each chapter, including experimental aim and study design.

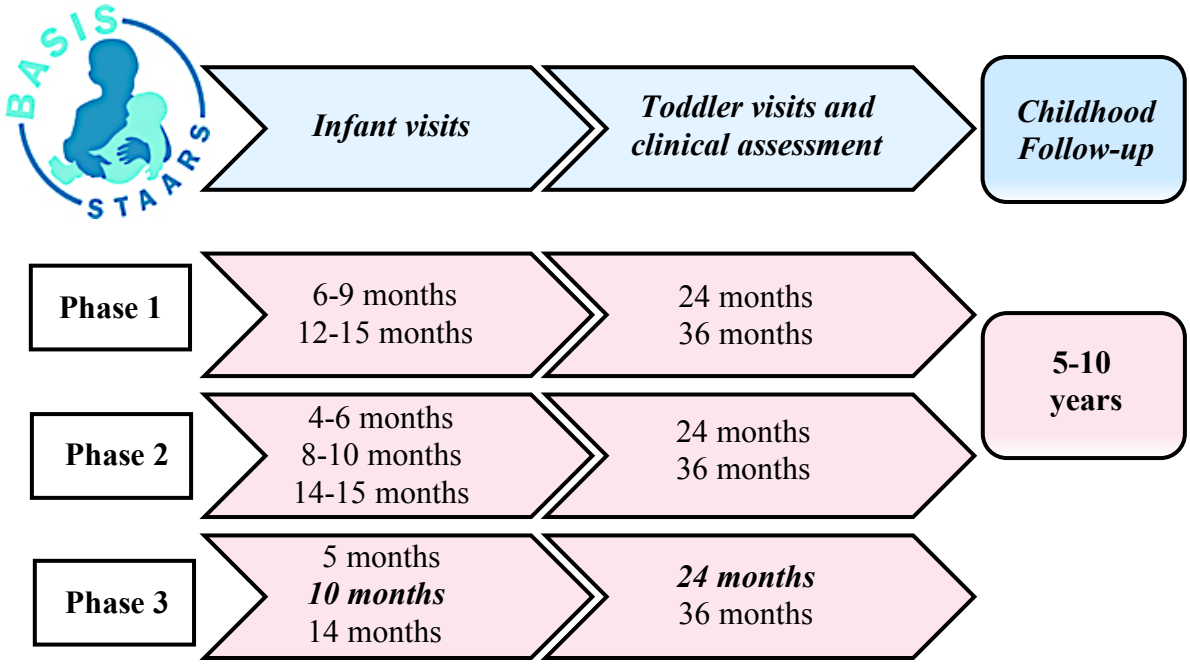

Figure 2.14. The BASIS study

The BASIS study consists of three cohorts named, respectively, Phase 1, 2 and 3. A battery of neural and behavioural assessments is administered at multiple points in development and clinical assessment is performed at 24 and 36 months. Additional follow-up data is collected during childhood. The experimental chapters of this

thesis utilise data from two time points of the Phase 3 cohort (10 and 24 months – highlighted in bold).

***Table 3a**. Summary of data contributing to each experimental chapter of the present thesis, including sample size (N), participants' age and data source*

Chapter	*Paradigm*	*N*	*Age*	*Data source*
3	**Tactile repetition suppression**	91	10 months 24 months	Phase 3 (BASIS)
4	**Visual sensory processing**	94	10 months 24 months	Phase 3 (BASIS)
5	**Visual repetition (group-level investigation)**	48	10 months	Predictive Learning
6	**Visual repetition (individual differences investigation)**	34	10 months 16 months	Predictive Learning

***Table 3b**. Summary of paradigms contributing to each experimental chapter of the present thesis, including experimental aim and study design*

Chapter	*Paradigm*	*Experimental Aim*	*Study Design*
3	**Tactile repetition suppression**	Determine if behavioural/EEG markers of tactile sensory processing differentiate EL-ASD, EL-ADHD and TL participants at 10 months and/or predict ASD/ADHD traits at 24 months.	Prospective longitudinal study of infant siblings (between-subjects design)
4	**Visual sensory processing**	Determine if EEG markers of visual sensory processing differentiate EL-ASD, EL-ADHD and TL participants at 10 months and 24 months and/or predict ASD/ADHD traits at 24 months.	Prospective longitudinal study of infant siblings (between-subjects design)
5	**Visual repetition (group-level investigation)**	Determine the mechanisms underlying hypersensitivity to visual stimulation by investigating the balance between feedback and feedforward processing	Experimental within-subjects design
6	**Visual repetition (individual differences investigation)**	Explain individual differences in infants' visual sensory seeking, ASD and ADHD traits	Prospective longitudinal study of typically developing infants (correlational study design)

Chapter 3 includes EEG and parent-reported data from 10-month-old infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the disorders collected as part of the BASIS Phase 3 cohort. Further, this chapter includes clinical assessments from the same participants prospectively re-assessed at 24 months. In regard to the EEG data, I video coded participants' facial and bodily behaviours. The data was also video coded by a research student for the purpose of inter-coders reliability. Video coding of infants' behaviours was performed with the software EGI Movie Player. Further, I processed, cleaned and analysed the EEG data. I conducted the initial data processing and cleaning in Net Station since this software was used for data acquisition. I used the collection of MATLAB scripts *WTools* for spectral decomposition and time-frequency analysis (see Parise & Csibra, 2013). In regard to parental reports and clinical assessments, I collated and quality checked the phenotypic data in conjunction with members of the BASIS team. Finally, I statistically analysed the data using the software SPSS (IBM SPSS Statistics for Macintosh, Version 23.0).

Chapter 4 includes EEG, parental reports and clinical assessment data from the same 10 and 24-month-old participants at elevated likelihood of ASD and/or ADHD and participants at typical likelihood of the conditions collected as part of the BASIS Phase 3 cohort. In regard to the EEG data, I video coded participants' looking behaviour for the purpose of data cleaning. Video coding was also performed by a research student to establish inter-coders reliability. EGI Movie Player was employed for video coding. I further processed, cleaned and analysed

the EEG data. I conducted the initial data processing steps in Net Station since this software was employed for data acquisition and extracted ERP components' values in MATLAB. Additionally, I employed the collection of MATLAB scripts *WTools* for spectral decomposition and time frequency analysis (Parise & Csibra, 2013). In regard to parental reports and clinical assessments, I collated and quality checked the phenotypic data in conjunction with members of the BASIS team. Finally, I statistically analysed the data using the software SPSS (IBM SPSS Statistics for Macintosh, Version 23.0).

Chapter 5 includes EEG data from an independent cohort of 10-month-old infants at typical likelihood of ASD and/or ADHD tested as part of the Predictive Learning study. I have been responsible for designing the study, programming the experiment and collecting the data with the assistance of two research students. I performed video coding of infants' looking behaviour for the purpose of data cleaning. To ensure inter-coders reliability, video coding was also performed by a research student. The software EGI Movie Player and Mangold Interact were used for the purpose of video coding. Furthermore, I processed, cleaned and analysed the EEG data. I performed the initial processing steps in Net Station since this software was used for data acquisition and extracted ERP components' values in MATLAB. I further employed the collection of scripts *WTools* for spectral decomposition and time frequency analysis (Parise & Csibra, 2013). Finally, I statistically analysed the data using the software SPSS (IBM SPSS Statistics for Macintosh, Version 23.0) and R (Team, 2017).

Chapter 6 utilizes the EEG data presented in chapter 5, alongside parental reports collected from the same participants prospectively re-assessed at 16 months. I collected and managed the follow-up data through the online platform Redcap (Research Electronic Data Capture; Harris et al., 2019, 2009). Within this platform I personally designed the project content and related data dictionaries. I have been further responsible for processing and analysing the data. I conducted statistical analyses with the software SPSS (IBM SPSS Statistics for Macintosh, Version 23.0).

2.8. Characterisation of participants' sample from the BASIS Phase 3 cohort

2.8.1. Recruitment strategy

Participants contributing to the BASIS Phase 3 cohort were recruited for a longitudinal study running from 2013 to 2020. Infants could be enrolled in the study if they either had a first degree relative with ASD, a first degree relative with diagnosed or probable ADHD, or no first degree relative with either diagnosis. The presence of ASD was defined as a clinical diagnosis of ASD from a licensed clinician. The presence of ADHD was defined as a community clinical diagnosis of ADHD or a probable research diagnosis of ADHD. For those who reported concerns of ADHD symptoms in the family where the parent or older sibling did not have a community clinical diagnosis of ADHD, screening questionnaires were used to examine the probable existence of ADHD (see section 2.8.2). This was

implemented because co-occurring conditions are often under-diagnosed in children with ASD (Musser et al., 2014; Visser, Rommelse, Greven, & Buitelaar, 2016), primarily because previously DSM-IV and ICD-10 did not allow a dual diagnosis of ASD and ADHD. Had a clinical diagnosis be required for an infant to be coded as "elevated likelihood of ADHD", under-identification would have been risked in those families with a proband with an ASD diagnosis, significantly compromising the familial diagnosis elevated likelihood design adopted for sampling. Further, it was important not to apply different criteria to those families with and without an older sibling with ASD. Thus, an additional screening process for ADHD in first degree relatives was employed. For siblings (aged less than 6 years), a shortened version of the Conners Early Childhood (EC; Conners & Goldstein, 2009) form was used. For siblings (6 years or older), a shortened version of the Conners 3 was used (Conners, 2009). Thresholds for inclusion in the ADHD category were the presence of six ADHD symptoms on either the hyperactivity/impulsivity or inattention scale, and a positive score on the impairment scale. For parents, a shortened version of the Conners Adults ADHD Rating Scale (CAARS) was used (Conners, Erhardt, & Sparrow, 1999). Thresholds for inclusion were the presence of five ADHD symptoms on either the hyperactivity/impulsivity or inattention scale as per updated DSM-5 guidelines.

In terms of use of the impairment scores, a reduced version of the Conners EC and Conners 3 were adopted for individuals under 18 and the CAARS was employed for individuals aged >18 years. The Conners EC and Conners 3 included

questions regarding impairment, as such these questions were also included in the screening forms. In comparison, the CAARS (adult questionnaire) did not include questions regarding impairment. In order to maintain consistency of measure, the instrument was not adapted to include impairment questions. Of note, at initial contact with participants, parents were asked if there were any diagnoses of ADHD in the immediate family or if they had any concerns about ADHD. It is only if parents reported concerns that the screening process took place. This categorisation protocol is the same adopted by Begum et al., (2020) and resembles that adopted by other research groups using the prospective longitudinal study model in infants at elevated familial likelihood of ADHD (Miller et al., 2020).

Each infant in the study was assigned a rating for elevated likelihood of ASD and ADHD. A rating of 1 for ASD indicated the presence of ASD in a parent or older sibling; a rating of 1 for ADHD indicated that presence of ADHD in a parent or older sibling; and a rating of 0 for either category indicated no confirmed presence of the relevant condition. Thus, infants at elevated likelihood of ASD (EL-ASD), infants at elevated likelihood of ADHD (EL-ADHD), infants at elevated likelihood of ASD and ADHD (EL-ASD+ADHD) and infants at typical likelihood of the conditions (TL) were enrolled in the BASIS Phase 3 study. TL infants had at least one older sibling with typical development and no first degree relative with a diagnosis of ASD or ADHD. These infants were recruited from a participants' database at the Babylab, Centre for Brain and Cognitive Development (Birkbeck, University of London).

2.8.2. Clinical assessment

Information about diagnostic status for participants enrolled in the BASIS Phase 3 study was ascertained through a number of methods. Before families enrolled in the study, a telephone screening form was used to determine the presence of ASD and ADHD in family members. During their infant's visit to the lab, the parent/caregiver also completed a "Medical and Psychiatric History Interview" (Appendix A) with the researcher. The telephone screening form and this formal interview at study visit were the primary sources of information about diagnostic status. In addition, medical updates at each study visit were collected and the "Medical and Psychiatric History Interview" was re-administered at the 3-year timepoint. Diagnostic letters were further requested and parents were asked to complete the DAWBA (ASD and ADHD sections) (Goodman et al., 2000) and these were reviewed by the senior clinician (Prof. Tony Charman). In addition, parents completed the Conners (Conners et al., 1999; for ADHD) and the SCQ (Rutter et al., 2003) and SRS (Constantino, 2002; for ASD) on the family member with a diagnosis and, where possible, all other family members. This information was used to characterise the sample rather than for exclusionary purposes since, in the UK, NHS clinical diagnoses follow a gold-standard procedure including collation of information from parents, teachers and from in-person assessment that is beyond the scope of the BASIS Phase 3 study and more accurate than questionnaire measures.

Up to 30% of children with ASD meet criteria for ADHD when prospectively assessed (Simonoff et al., 2008). In clinical practice, the prevalence of dual diagnosis is lower (Russell, Rodgers, Ukoumunne, & Ford, 2014). Given the nature of the co-occurrence between ASD and ADHD and the current longitudinal study, sometimes family members would have a suspected diagnosis of ADHD at study entry that would be confirmed later in the study. On other occasions, a family would enrol on the basis of an ASD diagnosis in an older sibling but by the end of the study, they would report that the same sibling was now undergoing assessment for suspected additional ADHD. Where possible, families who reported suspected ADHD at study entry were screened using a shortened version of the Conners 3 (Conners, 2009). Families who were screened positive on this instrument were then included as a confirmed case. However, it remains likely that within families with ASD, rates of actual ADHD are higher than those captured by the current 1/0 diagnostically-based rating system. Families where there was significant diagnostic uncertainty about the presence of either ASD or ADHD were removed in a sensitivity analysis to check whether results differed substantially. Information about sensitivity analyses for Chapters 3 and 4 is reported in the Appendix.

2.9. Summary of Chapter 2

EEG is a methodology optimally suited for investigating the neural oscillatory dynamics underlying perceptual and cognitive functions with high temporal

resolution. EEG recordings can be collected during development over multiple time points, making this methodology ideal for investigating the early neural markers of sensory perception in prospective longitudinal studies of infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the conditions. While EEG may reveal objective neural markers of atypical sensory processing, this methodology cannot shed light on the impact that these atypicalities have on infants' early interactions with the surrounding environment. Parental reports offer a route towards overcoming this limitation by enabling researchers to capture infants' behavioural responses manifested during the natural course of daily life. It follows that adopting a multi-method, integrated approach to the investigation of the early development of sensory perception has the potential of advancing our understanding of both the neural markers linked to underlying genetic vulnerabilities and the behavioural manifestations impacting on children's interaction with their environment. Further incorporating clinical methods may clarify how both brain and behaviour converge in shaping the observable phenotypes through mediated or moderated pathways. This multi-method, integrated approach will be used throughout the experimental chapters of this thesis. In this light, Chapter 3 will present results from a longitudinal study investigating behavioural and neural markers of tactile sensory processing in infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the conditions.

Chapter 3: Behavioural and neural markers of tactile sensory processing in the early development of ASD and/or ADHD

3.1. Introduction

As reviewed in Chapter 1, evidence from prospective studies of infants at elevated likelihood of ASD or ADHD highlights similarities and differences in early markers of the two conditions. In particular, commonalities are seen in early sensory vulnerabilities (Johnson, Gliga, et al., 2015; Little, Dean, Tomchek, & Dunn, 2018). For example, impairments in the habituation of EEG responses to repeated auditory tones in infancy associate with later ADHD (Hutchison et al., 2013) and ASD traits (Kolesnik et al., 2019). Further, atypicalities in tactile processing (i.e. tactile hyper/hyposensitivity and atypical tactile seeking) are documented by parental reports in both conditions (Baranek, Foster, & Berkson, 1997; Ghanizadeh, 2008, 2011; Tomchek & Dunn, 2007). Motor atypicalities reported in the early development of ASD and ADHD (Begum Ali, Charman, Johnson, & Jones, 2020; Flanagan et al., 2012; Gurevitz et al., 2014; Iverson et al., 2019) may be a consequence of common sensory vulnerabilities, given the tight link existing between the sensory and motor domains (Ting, 2013; Whyatt & Craig, 2013). Despite accumulating evidence that sensory-motor vulnerabilities manifest in the early development of ASD and ADHD, no study has yet investigated the same sensory-motor markers as early predictors of later ASD and/or ADHD traits. Investigating the specificity of early infant markers is essential to distinguish shared or distinct causal pathways and to understand the nature of the co-occurrence and the aetiology of these disorders.

Much research on early sensory perception within the neurodevelopmental disorder literature has focused on the visual or auditory modalities (Baum, Stevenson, & Wallace, 2015; Marco, Hinkley, Hill, & Nagarajan, 2011), with no study yet assessing the potential mechanisms underlying early tactile atypicalities through controlled experimental designs or direct assessments of brain function. Filling this gap in knowledge is essential, given that 1) touch is the first sense to develop and the mean through which infants learn about the environment and themselves (Bremner & Spence, 2017); 2) touch is the primary modality through which infants and caregivers communicate and interact (Cascio, 2010; Ferber, Feldman, & Makhoul, 2008; Mammen et al., 2016); 3) difficulties in tactile processing dominate first-hand accounts from individuals with ASD (Baranek et al., 1997; Grandin, 1995); 4) many animal models of sensory atypicality in ASD focus on the tactile modality (Chelini et al., 2019; Gibson, Bartley, Hays, & Huber, 2008; He et al., 2017; Orefice et al., 2019).

3.1.1. Tactile sensory processing in ASD and ADHD

Behavioural markers. Different average responses to tactile stimulation are reported in young populations with ASD or ADHD relative to control participants (Ghanizadeh, 2011; Hilton et al., 2010; Mikkelsen, Wodka, Mostofsky, & Puts, 2017), and patterns of behavioural hyper/hyposensitivity to tactile stimulation are documented in the literature (Cascio, 2011; Thye et al., 2018). Parent-reported (e.g. Infant-Toddler Sensory Profile, *ITSP*; Dunn, 2002; Sensory Profile; Dunn, 1999),

examiner-reported or self-reported measures (e.g. Sensory Processing Scale, *SPS*; Schoen, Miller, & Sullivan, 2014) indicate that behavioural hypersensitivity to tactile stimulation exists in children with ASD and persist through adulthood (Baranek et al., 1997; Cascio, Lorenzi, & Baranek, 2016; Tavassoli et al., 2014; Tomchek & Dunn, 2007). Cascio and collaborators (2016) documented a pattern of behavioural hypersensitivity to tactile stimulation and lower self-reported judgement of tactile pleasantness in children with ASD, which associated with elevated severity of social symptoms. Further, in a retrospective study of children with ASD relying on parent-reported measures, Silva and Schalock (2013) observed signs of allodynia (i.e. painful response to touch) in the entire sample. Limited research investigated the early behavioural markers of tactile perception in infants at elevated likelihood of ASD, reporting tactile hypersensitivity from 3 months of age (Van Etten et al., 2017) and reduced orienting to caregiver touch from 12 months of age (Kadlaskar et al., 2019).

Research into tactile sensory processing in ADHD is limited. Clinical investigations using self-reported, examiner-reported and parent-reported measures indicate that behavioural hyper/hyposensitivity to tactile stimulation co-exist in individuals with ADHD and they may relate to different co-occurring symptoms. For example, Ghanizadeh (2008, 2011) reported that hypersensitivity associated with defiant oppositional symptoms, and hyposensitivity with separation anxiety symptoms in children with ADHD. Reduced discrimination of tactile input (e.g., temperature and pinprick discrimination) was documented in children with ADHD

and their unaffected siblings, thus suggesting that hyposensitivity to tactile stimulation may be linked to familial liability for the disorder (Scherder et al., 2008). On the other hand, no study has yet assessed the early behavioural markers of tactile sensory processing in infants at elevated likelihood of ADHD.

In summary, behavioural evidence suggests that tactile hypersensitivity mainly occurs in individuals with ASD. Tactile sensory processing in ADHD remains understudied but the current evidence points to co-occurring hyper/hyposensitivity.

Neural markers. Neurophysiological studies on tactile sensory processing in ASD have mainly investigated stimulus repetition effects through repetition suppression paradigms (Auksztulewicz & Friston, 2016; Nordt, Hoehl, & Weigelt, 2016). As reviewed in Chapter 1, these paradigms have been conceptualised in the context of Predictive coding theories, which describe the brain as an active inference organ constantly trying to predict the sensory input it receives to infer the most plausible representation of the world (Friston & Kiebel, 2009; Kok & De Lange, 2015). Repetition suppression paradigms enable quantification of two measures: 1) the effect of individual tactile stimulation on initial brain responses, henceforth *neural sensitivity*; 2) the effect of repeating tactile stimulation, often manifested as a decrease in the response to the second stimulus with respect to the first stimulus, henceforth *neural repetition suppression*. Studies have generally documented reduced repetition suppression to tactile stimulation in ASD. Reduced neural

repetition suppression to sequences of vibrotactile stimuli in the absence of stimulus-locked neural hypersensitivity was documented in a Fmr1 knock-out mouse model of ASD (He et al., 2017). Increased BOLD activation in the somatosensory cortex and amygdala was reported in response to mildly aversive tactile stimulation in young participants with ASD and attributed to reduced habituation of brain responses (Green et al., 2015). Controlled psychophysical studies have also suggested that reduced repetition suppression underlies the tactile performance of adults with ASD. For example, Puts and collaborators (2014) reported no effect of an adapting (i.e. repeated) stimulus on tactile discrimination thresholds in children with ASD. The effect was replicated in a follow-up study and linked to reduced levels of the neurotransmitter GABA in the somatosensory cortex (Puts et al., 2017).

Neurophysiological studies investigating tactile sensory processing in ADHD are limited and document reduced neural repetition suppression of tactile stimulation and neural hyposensitivity. Neural hyposensitivity to non-painful current pulses, indexed by reduced somatosensory EEG alpha desynchronization, was reported in adults with ADHD (Dockstader et al., 2008). Increased perfusion in the post-central gyrus was observed in adults with ADHD and linked to inability to suppress incoming tactile input (Kim et al., 2002). Controlled psychophysical studies reported higher detection thresholds and reduced repetition suppression in children with ADHD (Puts et al., 2017). Reduced levels of the neurotransmitter

GABA were also reported in the somatosensory cortex of adults with ADHD (Edden et al., 2012).

Overall, the reviewed evidence suggests that different neural responses to tactile stimulation occur in individuals with ASD or ADHD relative to control participants and these differences may result from atypical inhibitory function in GABA-mediated circuits. However, it remains unknown if these differences exist early in development and, if so, whether they associate with traits of ASD or ADHD emerging in childhood.

3.1.2. The role of tactile sensory seeking

Atypical responses to sensory stimulation are documented in the early development of ASD or ADHD but putative mechanisms linking these atypicalities to later traits remain unknown. In the tactile domain, early atypical responsiveness has been proposed to exacerbate later ASD symptomatology by triggering compensatory strategies aimed at minimizing tactile input (Mikkelsen et al., 2017).

As reviewed in Chapter 2, decreased sensory seeking is often reported in infants with later ASD (Ben-Sasson et al., 2009; Mulligan & White, 2012; Thye et al., 2018) and some have proposed that it may mediate the impact of early sensory atypicality on later ASD traits (Thye et al., 2018; Zentall & Zentall, 1983). In the tactile domain, decreased seeking could represent a strategy to minimize tactile input (which may be experienced as distressing in the presence of elevated sensory responsiveness, Johnson et al., 2015; Mulligan & White, 2012). However, reduced

sensory seeking has not always been found to associate with elevated sensory responsiveness (Ben-Sasson et al., 2009). Thus, rather than a mediator, sensory seeking could represent an independent but compounding factor in ASD. For example, it has been proposed that reduced sensory seeking in infants with later ASD reflects reduced capacity or motivation to explore, rather than a consequence of atypical sensory responsiveness (Mulligan & White, 2012). Under this scenario, lower sensory seeking may increase the impact of sensory atypicalities by further limiting early opportunities to develop social skills and share communication.

3.2. The current study

3.2.1. Main analytical pipeline

The goal of the current study was to investigate behavioural and neural markers of tactile sensory processing in 10-month-old infants at elevated likelihood of ASD or ADHD (i.e. by virtue of having a first degree relative with a clinical diagnosis of ASD or ADHD) and infants at typical likelihood of the disorders. A tactile repetition suppression paradigm administering repeated pairs of vibrotactile stimuli (S1-S2) was used and coupled with the recording of EEG. I quantified behavioural markers by coding looking and moving behaviours before and after receiving the pair of tactile stimuli. I quantified neural markers by extracting the amplitude of EEG oscillations in the alpha range (α = 6-10Hz). The choice of analysing the alpha rhythm (i.e. oscillations in the range of 8-12Hz in adults and 6-10Hz in infants) in the present study was motivated by three reasons. First, as reviewed in Chapter 2,

the EEG alpha rhythm has been specifically associated with GABAergic inhibitory modulation in the somatosensory cortex in animals (Lőrincz et al., 2009) and humans (Schreckenberger et al., 2004; Ahveninen et al., 2007). Thus, early differences in GABA-mediated inhibitory modulation in somatosensory regions should be reflected by differences in alpha amplitude desynchronization (i.e. alpha amplitude during the task as compared to alpha amplitude at baseline) over the somatosensory cortex. Secondly, while GABAergic inhibition has also been associated with other EEG frequency bands (e.g. gamma rhythm), these associations are not specific to somatosensory regions (and have mostly been reported in other sensory modalities, e.g. auditory modality; Kolesnik et al., 2019). Thirdly, while event-related potentials (ERPs) have most commonly been employed to quantify repetition suppression, mainly in the auditory modality (Orekhova et al., 2008), the literature on tactile ERPs in early development is scanty and no study has so far assessed ERPs in a tactile repetition suppression paradigm in infancy, thus limiting the ability to specify a-priori testable predictions (e.g. in regard to the choice of ERP components to subject to statistical analysis). Furthermore, ERPs contain little information about the underlying EEG dynamics and task-related information can be lost in the process of ERP averaging (see Cohen, 2014, who provides an excellent demonstration that non-phase-locked dynamics are task-modulated but not observable in the ERPs).

Based on previous work on tactile processing in ASD and ADHD, I predicted observing an effect of the ASD likelihood status on behavioural

sensitivity, manifesting as elevated moving and reduced screen-directed looking (behavioural hypersensitivity) after receiving the tactile stimulation. Since atypical neural repetition suppression has been documented in ASD and ADHD, I predicted observing an effect of the ASD and ADHD likelihood on neural response to repeated tactile input, manifesting as reduced suppression of alpha desynchronization to repeated tactile stimulation. I further predicted observing an effect of the ADHD likelihood status on neural sensitivity, manifesting as reduced alpha desynchronization (neural hyposensitivity) to the first vibrotactile stimulus.

I assessed the longitudinal associations between early neural and behavioural markers of tactile processing and later ASD traits (i.e. quantified through the ADOS-2 CSS at 24 months; Lord et al., 2012) or ADHD traits (i.e. quantified through the ECBQ activity and inhibitory control sub-scales at 24 months; Putnam et al., 2006). As reviewed in Chapter 2, previous research indicates that these measures act as early predictors of later symptoms of ASD and ADHD, respectively. Shephard and collaborators (2018) reported that higher 24-month ECBQ activity levels and inhibitory control predict higher mid-childhood hyperactivity/impulsivity and inattention but not ASD symptoms. Overall stability in ADOS CSS was also reported between the ages of 2 and 15 years (Gotham et al., 2012b). Therefore, I designated ADOS-2 CSS and ECBQ activity and inhibitory control as 24-month outcome measures in the current study. I hypothesized reduced neural repetition suppression to longitudinally predict both ASD and ADHD traits. I further predicted reduced alpha desynchronization to the first vibrotactile stimulus

(neural hyposensitivity) at 10 months to associate with higher activity level and lower inhibitory control at 24 months.

Further, I assessed the role of tactile sensory seeking (i.e. quantified through the parent-reported ITSP at 10 months; Dunn, 2002) as a potential mediator or moderator of the association between early tactile atypicality and later ASD traits.

Finally, previous studies suggested that neural repetition suppression underlies efficient learning during experimental testing (León-Carrión et al., 2010). However, no prior research explored the long-term effects of neural repetition suppression through longitudinal designs. Thus, I planned to investigate the concurrent (10 months) and longitudinal (24 months) associations between behavioural and neural markers emerged from the tactile repetition suppression paradigm and learning (i.e. quantified through the Mullen Scales of Early Learning; Mullen, 1995).

3.2.2. Follow-up and secondary analyses

In addition to the core analyses, I planned to conduct a series of follow-up analyses. Firstly, to exclude any inference of movement on neural markers of tactile sensory processing, I assessed if any associations existed between body movement (as quantified through behavioural coding) and both neural sensitivity to and suppression of repeated tactile stimulation.

Secondly, as reviewed in Chapter 2, limited research has investigated the convergence between experimental and parent-reported measures of sensory perception in early development. Thus, I planned to investigate whether converging results emerged from the analysis of behavioural sensitivity to tactile stimulation quantified in the current experiment and parental reports of infants' behavioural sensitivity to tactile stimulation (i.e. quantified through the ITSP at 10 months; Dunn, 2002).

Thirdly, mixed results have emerged from studies examining the concordance between parent report and clinician observation of ASD or ADHD traits in early development (Evers, Debbaut, Maljaars, Steyaert, & Noens, 2020; Macari et al., 2018; Nobel, Brunnekreef, Schachar, van den Hoofdakker, & Hoekstra, 2019). Thus, I planned to ascertain significant associations between neural and/or behavioural markers of tactile sensory processing and ASD traits quantified through clinician observation (i.e. ADOS-2 CSS at 24 months; Lord et al., 2012) by assessing the potential associations between the same experimental measures and a parental report of ASD traits (i.e. Q-CHAT at 24 months; Allison et al., 2008).

Finally, while I assessed the mediating or moderating role of tactile sensory seeking in the main analyses, I further planned to investigate whether tactile sensory avoiding (i.e. quantified through the ITSP at 10 months; Dunn, 2002), which could be conceived as opposite to tactile sensory seeking and could better capture compensatory manifestations in infancy, would act as a factor mediating or

moderating the potential association between early tactile atypicality and later ASD traits.

3.3. Methods

3.3.1. Recruitment approach

I direct the reader to Chapter 2, sections 2.8.1 ("Recruitment strategy") and 2.8.2 ("Clinical assessment") for a description of the recruitment approach adopted and the clinical assessment procedures used to designate the diagnostic status of each participant involved in the study. All infants recruited for the research were born full-term (gestational age 38-42 weeks). At the time of enrolment, none of the infants had a known medical or developmental condition. Informed written consent was provided by the parent(s) prior to the commencement of the study. Infants were tested if awake and in an alert state. The experimental protocol was approved by the National Research Ethics Service, the Research Ethics Committee of the Department of Psychological Sciences, Birkbeck University of London, and the Research Ethics Committee of the Institute of Psychiatry, Psychology and Neuroscience, King's College London. Families were reimbursed expenses for travel, subsistence and overnight stay if required. Families were given a certificate and t-shirt after each visit.

3.3.2. Participants

One hundred and fifty-two 10-month-old infants participated in the study: 79 EL-ASD infants, 27 EL-ADHD infants, 21 EL-ASD+ADHD infants and 25 TL infants, with no family history of the disorders. Of these, 61 infants were tested but not included in the final sample because of low tolerance of the EEG net (n=8), fussiness/excessive movement artefacts (n=38) and equipment failure (n=15). One infant contributed EEG data but was not included in the behavioural analyses due to missing video recording. Accordingly, EEG data was contributed by 91 infants (90 infants contributed behavioural data): 44 EL-ASD infants, 20 EL-ADHD infants, 9 EL-ASD+ADHD infants and 18 TL infants. Descriptive statistics for the sample are reported in Table 4. There was no significant effect of likelihood status on participants' attrition rate, $\chi^2(3) = 6.9, p = .075$. The minimum number of required participants was determined by a power analysis (conducted with the software *Gpower;* Erdfelder, Faul, Buchner, & Lang, 2009). According to Cohen (1988) and Sawilowsky (2009) a medium effect size in psychological studies is $f^2 = 0.15$ and, considering an estimate power of 0.80, a total sample size of 90 participants was estimated to detect main effects of ASD and/or ADHD at an alpha-level of 0.05; a total sample of 43 participants was estimated to detect hierarchical linear regression effects at an alpha-level of 0.05

3.3.3. Stimuli

Vibrotactile stimuli were delivered by two custom-built voice coil tactors driven by a 220Hz sine wave and controlled by a custom MATLAB script. The choice of a 220Hz sine wave as a tactile stimulus was based on prior literature investigating tactile perception in early typical development (Begum Ali, Spence, & Bremner, 2015). The tactors were placed in direct contact with the bare soles of the infant's feet, securing them with cohesive bandage. A repetition suppression paradigm was used: pairs of 200 ms stimuli (S1-S2) were simultaneously delivered to both feet, with 700 ms ISI (constant) within the pair and 8-12 seconds ISI (random) between the pairs (Figure 3.1A). Thirty-eight pairs of vibrotactile stimuli were administered during two blocks lasting four minutes each, while infants underwent EEG. A two-minute interval corresponded to the end of the first block and beginning of the second block. An animated cartoon with no language component was presented throughout the session (*Fantasia* by Walt Disney) and served two functions: to distract infants' attention away from the tactile stimulation and to mask the sound produced by the tactors themselves. Total experiment duration was 10 minutes but the experimenter could interrupt the session earlier in case of infant's fussiness or if requested by the parent.

3.3.4. Apparatus and procedure

Testing took place in a dimly illuminated room. Infants were seated on a parent's lap, 60cm from a screen (27 inches; width: 59.77cm, height: 33.62cm) and were

allowed to use a pacifier. The sequence and timing of stimulus presentation was controlled using MATLAB. High-density EEG was collected using 124 channels of a 128-channel HydroCel Geodesic Sensor Net connected to a NetAmps 400 amplifier (Electrical Geodesic, Eugene, OR) and referenced on-line to the vertex (Cz). Signals were sampled at 500 Hz. A video camera situated below the screen used for stimulus presentation recorded the infants' bodily and facial behaviour (Figure 3.1B). This information was used for online monitoring of infants' performance and offline behavioural coding.

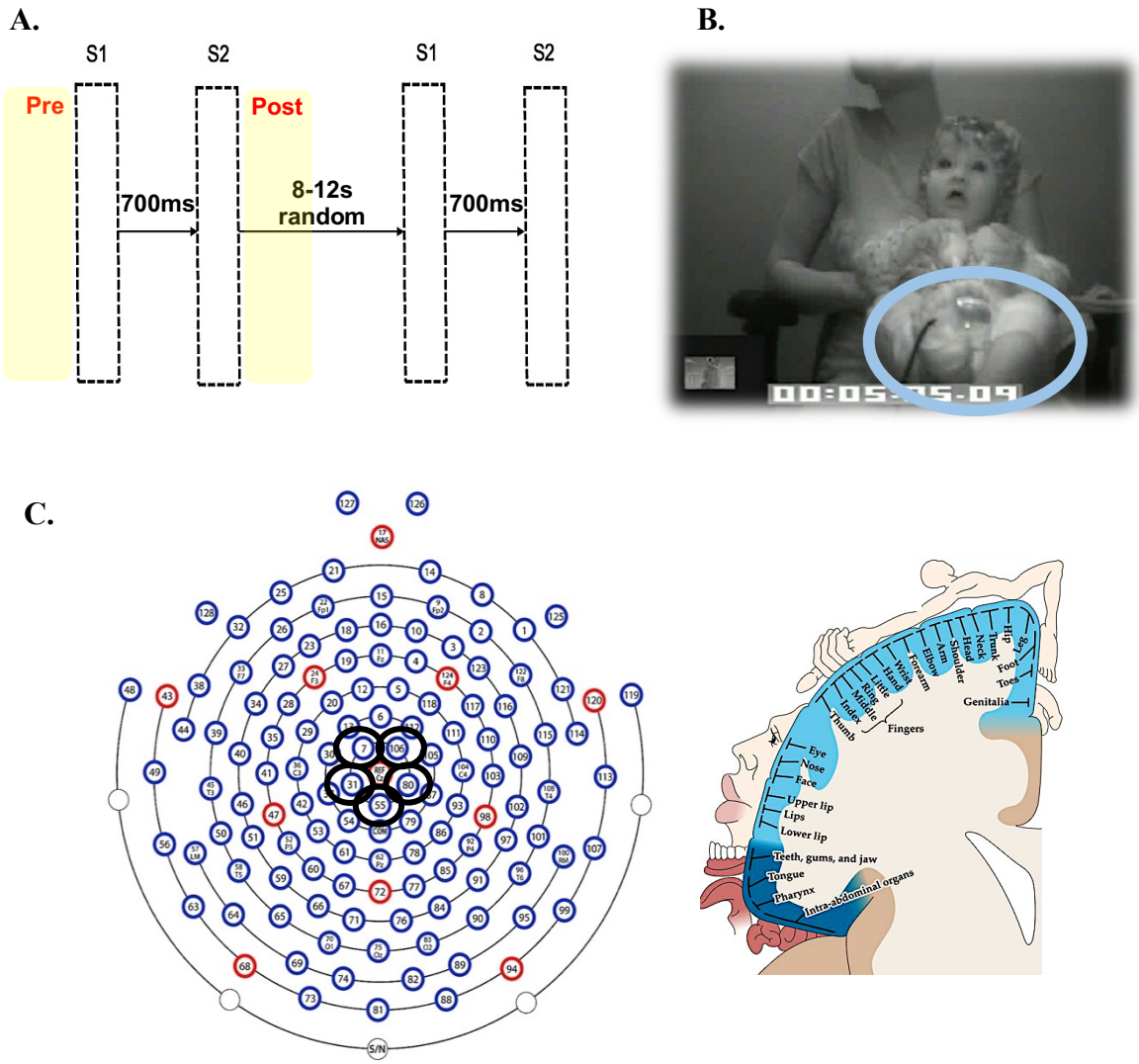

Figure 3.1. Schematic representation of the experimental stimuli, apparatus and procedure

A) Representation of the sequence of events in the tactile repetition suppression paradigm. Pairs of 200ms-long vibrotactile stimuli were delivered to the infants' feet with a 700ms ISI within the pair and 8-12s ISI between the pairs. Pre-stimulus and post-stimulus phases (4s each) are highlighted in yellow. B) High-density EEG was recorded whilst vibrotactile stimuli were delivered to the infants' feet through

custom-made tactors (the light blue circle indicates the location of one tactor). C) Hydrocel-Geodesic Sensor Net montage displaying the central somatosensory pool of electrodes (black circle) used for quantifying alpha desynchronization (α = 6-10Hz) to vibrotactile stimulation. The pool corresponded spatially to the somatotopic representation of the human feet.

3.3.5. Behavioural assessment scales

The Mullen Scales of Early Learning (Mullen, 1995) were administered at the 10 and 24-month visits in the standardised format. 10-month Mullen data was collected for 90 out of 91 infants contributing to the EEG analyses. 10-month ITSP was returned for 78 out 91 participants contributing to the EEG analyses. At 24 months, 12 participants dropped-out from the longitudinal study. Thus, at this visit, Mullen data was collected for 77 participants and ADOS-2 assessment was performed for 79 out of 91 infants contributing to the EEG analyses. 24-month Q-CHAT was returned for 74 participants. 24-month ECBQ was returned for 71 participants. Detailed characterisation of each measure for participants contributing to the EEG analyses is reported in Table 4. Full characterisation is reported in Appendix to Chapter 3, Table 5A. Comparison on each phenotypic measure between participants included in the EEG analyses and those excluded due to fussiness/excessive movement artifacts is also reported in Appendix to Chapter 3, Table 5B.

***Table 4**. Detailed characterisation of behavioural measures at the 10 and 24-month assessments for EL-ASD, EL-ADHD, EL-ASD+ADHD and TL participants who contributed to the EEG analyses.*

	EL-ASD	EL-ADHD	EL-ASD+ADHD	TL	*p values*
10-month visit					
Age in days	318.65 (13.42)	326.55 (29.76)	316.56 (14.05)	323.22 (16.77)	.378 (ns)
MSEL ELC	86.47 (14.39)	86.05 (17.09)	80.78 (15.82)	91.11 (9.65)	.359 (ns)
MSEL GM	37.67 (8.51)	39.75 (9.92)	33.56 (9.81)	33.11 (9.87)	.102 (ns)
MSEL FM	50.14 (11.22)	53.65 (15.26)	46.55 (13.65)	50.78 (8.09)	.499 (ns)
MSEL VR	48.56 (9.09)	47.10 (10.46)	48.00 (8.29)	50.61 (5.75)	.669 (ns)
MSEL RL	36.30 (10.03)	34.65 (10.37)	34.11 (10.87)	41.05 (8.05)	.174 (ns)
MSEL EL	36.35 (13.05)	34.95 (13.22)	30.22 (12.97)	39.11 (9.86)	.367 (ns)
N (% boys)	43 (43.2)	20 (60)	9 (55.6)	18 (50)	
ITSP Tactile Seeking	2.40 (0.99)$_a$	1.90 (0.54)	2.33 (0.97)	1.81 (0.39)	.003*
	EL-ASD	EL-ADHD	EL-ASD+ADHD	TL	*p values*
24-month visit					
Age in days	777.00 (19.66)	771.12 (40.38)	755.57 (19.66)	764.40 (43.63)	.610 (ns)
MSEL ELC	101.87 (20.87)$_a$	104.76 (21.61)	92.86 (18.08)$_a$	120.00 (15.53)	.011*
MSEL GM	N/A	N/A	N/A	N/A	
MSEL FM	50.95 (10.39)$_a$	50.82 (11.90)	49.43 (12.15)	61.20 (10.72)	.015 *
MSEL VR	50.20 (13.27)$_a$	55.53 (11.86)	43.86 (8.80)$_a$	63.67 (8.37)	.001**
MSEL RL	51.41 (14.11)	50.34 (13.44)	47.43 (9.13)	57.87 (7.43)	.217 (ns)
MSEL EL	49.47 (15.72)	52.23 (15.21)	44.28 (11.46)	58.00 (12.79)	.159 (ns)
N (% boys)	38 (42.1)	17 (58.8)	7 (57.1)	15 (40)	
ADOS-2 CSS	2.97 (2.26)$_a$	2.65 (1.97)	3.14 (2.03)$_a$	1.40 (0.63)	.040*
ECBQ Inhibitory Control	3.74 (1.29)	3.84 (0.97)	3.22 (1.61)	4.31 (0.92)	.250 (ns)
ECBQ Activity	4.54 (0.84)	4.88 (1.04)	5.11 (0.74)	4.62 (0.72)	.325 (ns)
Q-CHAT	24.37 (12.17)	28.00 (10.96)	31.08 (15.19)	21.05 (3.82)	.202 (ns)

* $p < .05$; ** $p \leq .001$; $_a$ indicates significant differences with the TL group

M (*SD*) reported for: Age in days; MSEL ELC = Mullen Scales for Early Learning Early Composite Score; MSEL GM = Mullen Scales for Early Learning Gross Motor Score; MSEL FM = Mullen Scales for Early Learning Fine Motor Score; MSEL VR = Mullen Scales for Early Learning Visual reception Score; MSEL RL = Mullen Scales for Early Learning Receptive Language Score; MSEL EL = Mullen Scales for Early Learning Expressive Language; ITSP Tactile Seeking = Tactile sensory seeking average score of the Infant-Toddler Sensory Profile; ADOS-2 CSS = ADOS-2 Calibrated Severity Scores; ECBQ Inhibitory Control = Inhibitory Control subscale of the Early Childhood Behaviour Questionnaire; ECBQ Activity = Activity subscale of the Early Childhood Behaviour Questionnaire; Q-CHAT = Quantitative Checklist for Autism in Toddlers.

3.3.6. Infants' behaviour coding

Infants' bodily and facial behaviour was scored with a computerized frame-by-frame coding system (25 frames/second – EGI Movie Player, Electrical Geodesic). The category of body movement included any head, upper and lower limbs or feet movements. The category of facial behaviour included only screen-directed looking. Looking and movement were scored using a binary coding procedure (i.e. looking=1; not looking=0; moving=1; not moving=0) during the "pre-stimulus phase" (4 seconds before S1) and the "post-stimulus phase" (4 seconds after S2) (Figure 3.1A). The binary codes of looking vs. not looking, and moving vs. not moving were calculated based on whether looking or movement occurred/did not occur during the pre-stimulus and post-stimulus phases. No coding was performed during the 700ms ISI because the interval was too short to observe changes in infants' looking or body movement. A second observer independently coded a random 40% of video files (i.e. 36 infants). Both coders were blind to infants' likelihood status. Conversely, coders were not blind to trial period (i.e. "pre-stimulus phase" and "post-stimulus phase"). An interrater reliability analysis using intraclass correlation (ICC: absolute agreement type, average measures) indicated high agreement for looking behaviours during the pre-stimulus phase, ICC = .996, 95% CI, [.992, .998], $p < .001$; for looking behaviours during the post-stimulus phase; ICC = .998, 95% CI, [.996, .998], $p < .001$; for body movement behaviours during the pre-stimulus phase, ICC = .994, 95% CI, [.989, .997], $p < .001$; for body

movement behaviours during the post-stimulus phase, ICC =.997, 95% CI, [.994, .998], $p < .001$.

3.3.7. EEG recording and analysis

The EEG data was pre-processed offline using Net Station (Electrical Geodesic) following the processing pipeline reported in Chapter 2. Specifically, the continuous EEG was filtered using a 0.3–40 Hz band-pass filter. The EEG signal was segmented from 200ms prior to S1 onset through 1800ms after S1 onset. Automated artifact detection was applied to the segmented data to detect individual epochs that showed >200μV voltage changes within the segment period. EEG recordings were visually inspected and individual channels within segments were eliminated from the analysis if artifacts occurred. Segments in which >15% of the channels (18 channels) were marked as bad were excluded from the analysis. For the remaining trials, spherical spline interpolation was conducted to replace data for bad channels using the five closest electrodes. Infants were excluded from the analysis if they had less than 10 artifact-free segments (see Table 6).

Table 6. *Number of EL-ASD, EL-ADHD, EL-ASD+ADHD and TL infants included and excluded from the 10-month EEG analyses (i.e. due to contributing less than 10 artifact free trials) and number of trials presented and retained for included participants for each group.*

Participants (n)	EL-ASD	EL-ADHD	EL-ASD+ADHD	TL	*p value*
Included	44	20	9	18	.075 (ns)
Excluded	19	4	7	7	.318 (ns)
Trials (n)	EL-ASD	EL-ADHD	EL-ASD+ADHD	TL	*p value*
Presented	35	36	37	35	.570 (ns)
Retained	17	16	18	16	.865 (ns)

3.3.8. Time-frequency analysis of EEG

Time-frequency decomposition was used to quantify oscillatory alpha desynchronization (α = 6-10Hz; alpha amplitude during the task as compared to alpha amplitude at baseline) to tactile stimulation. Artifact-free segments were imported into MATLAB using EEGLAB (v. 13.4.3b) and re-referenced to the average reference. The collection of scripts *WTools* (see Parise & Csibra, 2013; available upon request) was used for spectral decomposition, employing Complex Morlet wavelets for the frequencies 3-20Hz (1Hz resolution; real-valued Gaussian with n = 3.5 cycles per time unit). A continuous wavelet transformation of all segments by means of convolution with each wavelet was performed and the absolute value of the results was extracted. 100ms of data was removed at segment end to remove the distortion due to convolution. The amplitude of the 100ms pre-stimulus window was used as a baseline and subtracted from the whole epoch at

each frequency. Individual epochs were averaged for each participant. Inspection of the time-frequency plots revealed that 6-10Hz alpha desynchronization occurred at S1 and S2 offset over the central scalp site (see Figure A3.2.2 in Appendix to Chapter 3). Based on previous literature (De Klerk et al., 2015) and on visual inspection of both the grand-averaged and individual time-frequency plots, channels (CH) 7, 31, 55, 80, 106 (Figure 3.1C) were selected and the average 6-10Hz alpha desynchronization oscillatory amplitude extracted for two 500ms long time windows time-locked to S1 and S2 offset, respectively (Figure 3.2). Two alpha desynchronization measures were computed: S1 alpha desynchronization (indexing neural sensitivity to the first vibrotactile stimulus) and S2-S1 alpha desynchronization or tactile suppression index, TSI (indexing neural repetition suppression of tactile stimulation).

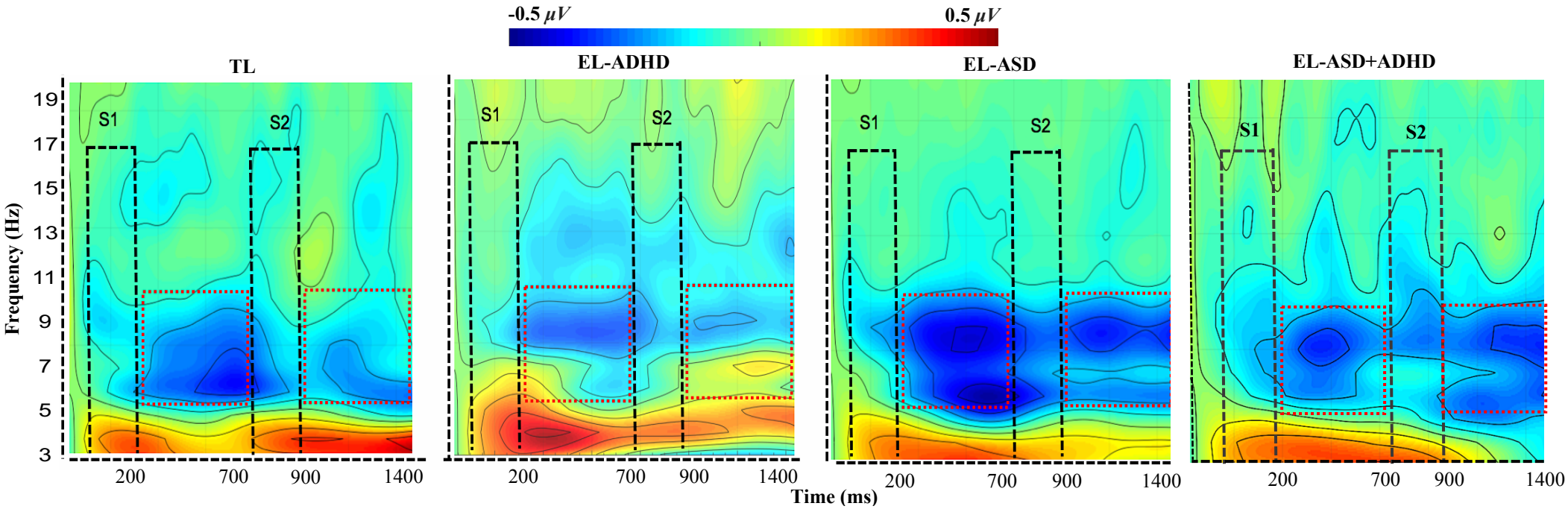

Figure 3.2. ***Time-frequency plots illustrating the amplitude of alpha (α = 6-10Hz) oscillations time-locked to S1 and S2 offset***

(TL=infants at typical likelihood of ASD or ADHD; EL-ADHD=infants at elevated likelihood of ADHD; EL-ASD=infants at elevated likelihood of ASD; EL-ASD+ADHD=infants at elevated likelihood of ASD and ADHD). Black dotted rectangles indicate the first and second vibrotactile stimulations. Red dotted squares indicate the 500ms long time-windows post-stimulus offset selected for statistical analysis. Amplitude scale is -0.5, 0.5μV.

3.3.9. Analytical strategy

Statistical analyses were conducted with SPSS v23 (IBM Corp 2015). Likelihood status was dummy coded and a factorial approach was used to test for the main effect of ASD, ADHD and the interaction between these factors on behavioural and EEG markers of tactile processing. The likelihood factor was computed as follows: EL-ASD infants were assigned a '1' for ASD likelihood and a '0' for ADHD likelihood (1 0), EL-ADHD infants were assigned a '0' for ASD likelihood and a '1' for ADHD likelihood (0 1), EL-ASD+ADHD infants were assigned a '1' for ASD likelihood and a '1' for ADHD likelihood (1 1), and TL infants were assigned a '0' for ASD likelihood and a '0' for ADHD likelihood (0 0). This dummy coding approach was chosen because ought to be more faithful to the elevated likelihood design adopted for the sampling. As discussed in Chapter 2, infants were not recruited as part of four different groups. Rather information about infants' diagnostic status was collected through a number of methods determining the presence of ASD and/or ADHD in family members. Further, this approach was taken to examine any additive/protective effects of having an elevated likelihood of both conditions. The dummy coding approach is preferred over a traditional group approach when one wishes to examine differences between several "treatment groups" and a "control group" (Cohen & Cohen, 2013). In this scenario the "control group" is represented by TL infants and serves as the reference group. An effect of ASD and ADHD likelihood indexes an effect of elevated likelihood in general; as such, this approach enables quantifying the effect of infants' likelihood status while

mitigating the loss of statistical power consequent to splitting participants into four groups. Only for tables and figures, infants were split into four groups: EL-ASD, EL-ADHD, EL-ASD+ADHD and TL.

Given the familial diagnosis elevated likelihood design adopted for sampling, the likelihood factor was included in all the statistical analyses (despite availability of 24-month outcome measures) to examine any changes in infants' developmental trajectory driven by intervening moderating factors (e.g. protective factors mitigating later outcomes in the presence of early liability; for instance, an interaction with the ADHD likelihood status would indicate that additional factors may be moderating the pathway to later outcomes in infants with a family history of this condition).

As described in Chapter 2, it remains likely that within families with ASD, rates of actual ADHD were higher than those captured by the current 1/0 diagnostically-based rating system. Families where there was significant diagnostic uncertainty about the presence of either ASD or ADHD were removed in a sensitivity analysis to check whether results differed substantially. Results of this sensitivity analysis are reported in the Appendix (and replicated those reported in the current chapter).

Prior to performing any inferential statistical analyses, I assessed the variables for normality. Where significant violations of normality existed, I normally transformed the data (i.e. I report details on normality violations and transformations in the results section).

First, I assessed the effect of likelihood status on behavioural markers of tactile sensory processing. I ran separate repeated measures ANOVAs with stimulation (two levels: pre-stimulus and post-stimulus) as within-subject factor and screen-directed looking or body movement occurring during each phase as dependent variables, respectively.

Secondly, I assessed the effect of likelihood status on neural markers of tactile sensory processing. I ran separate univariate ANOVAs with sensitivity to tactile stimulation (i.e. alpha desynchronization to the first vibrotactile stimulus, S1) and neural repetition suppression (i.e. TSI, S2-S1) as dependent variables, respectively.

Thirdly, I examined the longitudinal associations between neural markers/behavioural markers and later ASD or ADHD traits with a set of hierarchical linear regressions for normally distributed outcome measures or Spearman correlations for non-normally distributed outcome measures. When significant associations between predictor and one outcome variable existed, I further investigated the potential moderating effect of the likelihood factors on these associations.

Fourthly, I investigated the role of tactile sensory seeking as a mediator or moderator of the association between early tactile atypicality and later ASD traits. I conducted the mediation and moderation analyses using PROCESS macro in SPSS (Hayes, 2017). I further explored significant moderation effects through spotlight and floodlight analyses (Spiller, Fitzsimons, Lynch Jr, & McClelland,

2013). A simple slop plot for illustrating results of the spotlight analysis and a Johnson-Neyman plot for illustrating results of the floodlight analysis were generated with the workbook CAHOST (Carden, Holtzman, & Strube, 2017).

Finally, I investigated the concurrent and longitudinal associations between behavioural/neural markers of tactile sensory processing and both concurrent and longitudinal learning scores on the Mullen though a set of Pearson correlations.

3.4. Results

3.4.1. Behavioural markers

Screen-directed looking. A main effect of stimulation (pre *vs*. post-stimulus phase) emerged, $F(1,86) = 16.54$, $p < .001$, $\eta^2 = .161$, indicating looking away from the screen after receiving the tactile stimulation. There was no significant interaction between stimulation and ASD likelihood status, $F(1,86) = 0.82$, $p = .776$, $\eta^2 = .001$, or between stimulation and ADHD likelihood status, $F(1,86) = 1.97$, $p = .164$, $\eta^2 = .022$. There was also no significant three-way interaction between stimulation, ASD and ADHD likelihood status, $F(1,86) = 1.006$, $p = .319$, $\eta^2 = .012$. See Figure 3.3A.

Body movement. A main effect of stimulation (pre *vs*. post-stimulus phase) emerged, $F(1,86) = 29.87$, $p < .001$, $\eta^2 = .258$, indicating increased movement after receiving the tactile stimulation. There was, however, no significant interaction between stimulation and ASD likelihood status, $F(1,86) = .001$, $p = .995$, $\eta^2 = .000$,

or between stimulation and ADHD likelihood status, $F(1,86) = 3.35$, $p = .071$, $\eta^2 = .037$. There was also no significant three-way interaction between stimulation, ASD and ADHD likelihood status, $F(1,86) = .081$, $p = .776$, $\eta^2 = .001$. See Figure 3.3B.

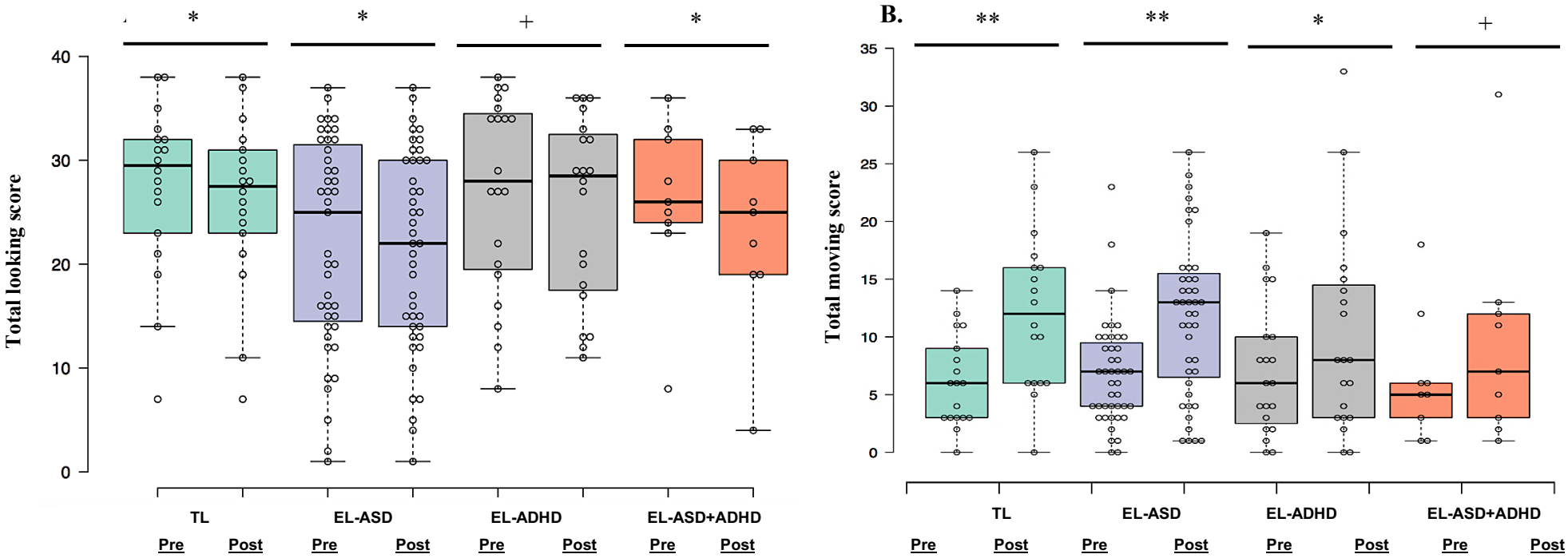

Figure 3.3. Boxplots illustrating A. Total looking score and B. Total moving score during the pre-stimulus phase (Pre) and the post-stimulus phase (Post) for each group

(Green=infants at typical likelihood of ASD or ADHD; Violet=infants at elevated likelihood of ASD; Grey=infants at elevated likelihood of ADHD; Orange=infants at elevated likelihood of ASD and ADHD). $*p<.05$, $**p<.001$, $+p$=trending to significance

3.4.2. Neural markers

Neural sensitivity (S1). There was no significant main effect of ASD likelihood status, $F(1,87) = .803$, $p = .373$, $\eta^2 = .009$, or ADHD likelihood status, $F(1,87) = 1.267$, $p = .263$, $\eta^2 = .014$, and no significant interaction between ASD and ADHD likelihood status, $F(1,87) = .034$, $p = .854$, $\eta^2 = .000$. See Figure 3.4.

Neural repetition suppression (TSI: S2-S1). Infants with an elevated ASD likelihood manifested reduced neural repetition suppression to tactile stimulation $F(1,87) = 6.089$, $p = .016$, $\eta^2 = .065$. There was no significant main effect of ADHD likelihood status, $F(1,87) = .366$, $p = .547$, $\eta^2 = .004$. Further, there was no significant interaction between ASD and ADHD likelihood status, $F(1,87) = .229$, $p = .634$, $\eta^2 = .003$. See Figure 3.4 and 3.5.

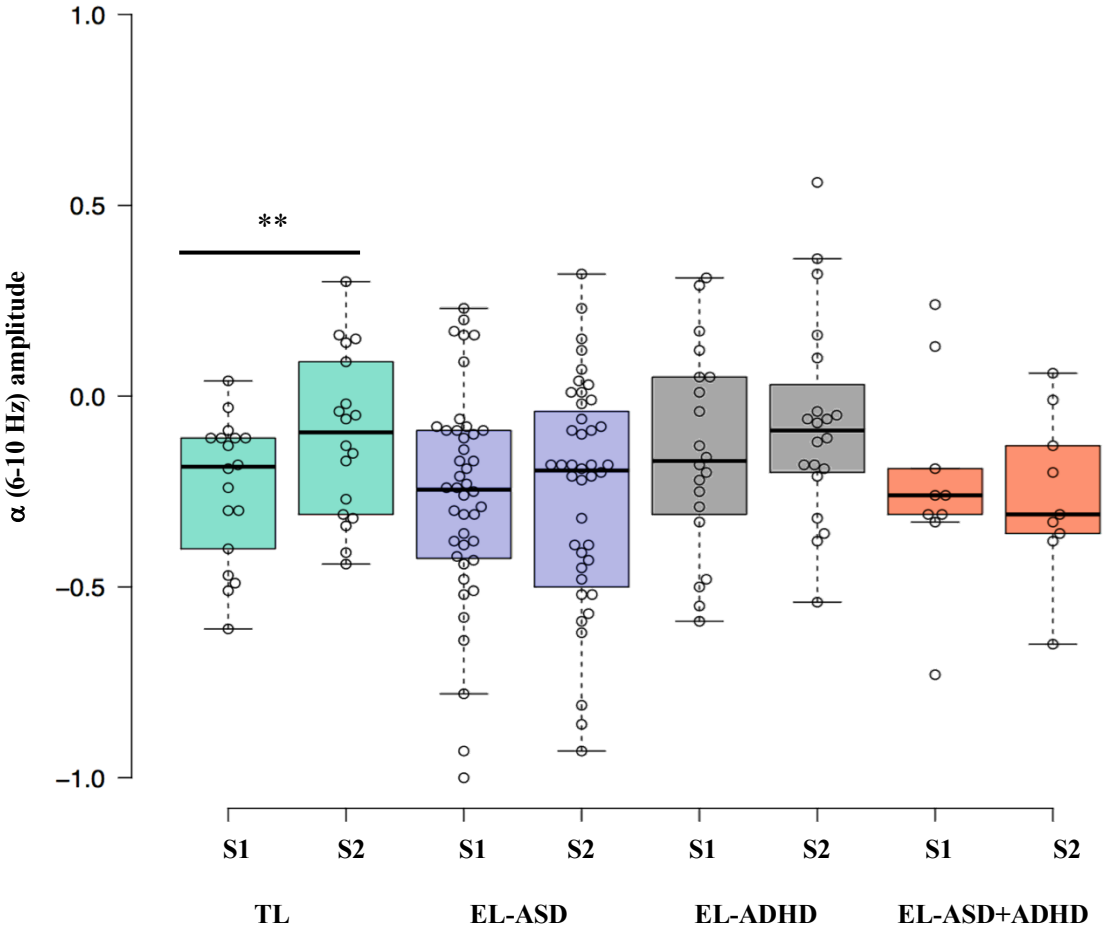

Figure 3.4. Boxplots illustrating the amplitude of α (6-10Hz) oscillations time-locked to S1 and S2 offset for each participant group

(Green=infants at typical likelihood of ASD or ADHD; Violet=infants at elevated likelihood of ASD; Grey=infants at elevated likelihood of ADHD; Orange=infants at elevated likelihood of ASD and ADHD). A significant reduction in α desynchronization with repeated tactile stimulation occurred only in TL infants.

*** p < .001*

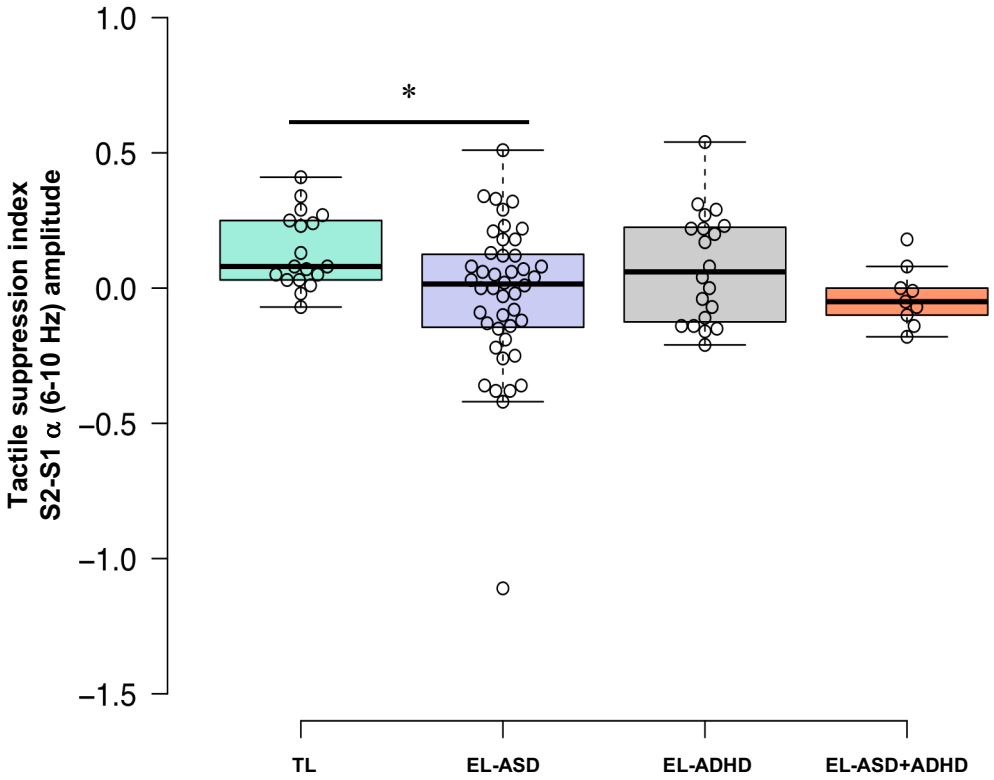

Figure 3.5. Boxplot illustrating the tactile suppression index, α (6-10Hz) for each participant group

(Green=infants at typical likelihood of ASD or ADHD; Violet=infants at elevated likelihood of ASD; Grey=infants at elevated likelihood of ADHD; Orange=infants at elevated likelihood of ASD and ADHD). * $p < .05$*

3.4.3. Associations between behavioural markers and later ASD and/or ADHD traits

Associations with ASD traits at 24 months. ADOS-2 CSS significantly violated normality assumptions (Shapiro-Wilk, $p < .001$; Skewness = 1.471, SE = .218; Kurtosis = 1.571, SE = .433) and were log-transformed prior to the analyses. The hierarchical linear regression with differential looking score (post S2 - pre S1) as

predictor and ADOS-2 CSS (log) as outcome was not statistically significant, $F(1,76) = .013$, $p = .909$, $R^2_{adj} = .000$. The result did not change when ECBQ activity was partialled out, $F(2,65) = .154$, $p = .857$, $R^2_{adj} = .000$, 95% CI for B, [-.139, .244]; when ECBQ inhibitory control was partialled out, $F(2,64) = 2.216$, $p = .117$, $R^2_{adj} = .036$, 95% CI for B, [-.283, -.007].

The hierarchical linear regression with differential moving score (post S2 - pre S1) as predictor and ADOS-2 CSS (log) as outcome was not statistically significant, $F(1,76) = 2.628$, $p = .109$, $R^2_{adj} = .021$. The result trended towards significance when ECBQ activity was partialled out, $F(2,65) = 3.112$, $p = .051$, $R^2_{adj} = .059$, 95% CI for B, [-.192, .186]; reached statistical significance when ECBQ inhibitory control was partialled out, $F(2,64) = 4.883$, $p = .011$, $R^2_{adj} = .105$, 95% CI for B, [-.256, .012].

Associations with ADHD traits at 24 months. The hierarchical linear regression with differential looking score (post S2 - pre S1) as predictor and ECBQ activity as outcome was not statistically significant, $F(1,68) = .016$, $p = .900$, $R^2_{adj} = .000$; and ECBQ inhibitory control as outcome was also not statistically significant, $F(1,67) = .358$, $p = .552$, $R^2_{adj} = .000$. Both results did not change when ADOS-2 CSS (log) was partialled out: for ECBQ activity, $F(2,65) = .155$, $p = .856$, $R^2_{adj} = .000$, 95% CI for B, [-.231, .407]; for ECBQ inhibitory control, $F(2,64) = 2.425$, $p = .097$, $R^2_{adj} = .041$, 95% CI for B, [-.870, -.022].

The hierarchical linear regression with differential moving score (pre S2 – pre S1) as predictor and ECBQ activity as outcome trended towards statistical significance, $F(1,68) = 3.908$, $p = .052$, $R^2_{adj} = .040$; with ECBQ inhibitory control as outcome was not statistically significant, $F(1,67) = 1.347$, $p = .250$, $R^2_{adj} = .005$. Both results did not change when ADOS-2 CSS (log) was partialled out: for ECBQ activity, $F(2,65) = 2.004$, $p = .143$, $R^2_{adj} = .029$, 95% CI for B, [-.329, .320]; for ECBQ inhibitory control, $F(2,64) = 2.446$, $p = .095$, $R^2_{adj} = .042$, 95% CI for B, [-.847, .039].

3.4.4. Associations between neural markers and later ASD and/or ADHD traits

Associations with ASD traits at 24 months. The hierarchical linear regression with S1 alpha desynchronization as predictor and ADOS-2 CSS (log) as outcome was not statistically significant, $F(1,77) = .317$, $p = .575$, $R^2_{adj} = .004$. The result did not change when ECBQ activity was partialled out, $F(2,66) = .245$, $p = .783$, $R^2_{adj} = .000$, 95% CI for B, [-.147, .235]; when ECBQ inhibitory control was partialled out, $F(2,65) = 1.382$, $p = .258$, $R^2_{adj} = .011$, 95% CI for B, [-.249, .030].

The hierarchical linear regression with TSI as predictor and ADOS-S CSS (log) as outcome was statistically significant, $F(1,77) = 15.795$, $p < .001$, $R^2_{adj} = .159$, indicating that infants with lower neural repetition suppression of tactile stimulation at 10 months exhibited higher ASD traits at 24 months. In step 2, the likelihood factors and the interaction terms were entered as predictors (ASD-L, ADHD-L, interaction between ASD-L and TSI, interaction between ADHD-L and

TSI). The model remained statistically significant, F(5,73) = 4.13, p = .002, R^2_{adj} = .167, but did not account for a significantly higher proportion of variance relative to a model with only TSI as predictor, F change (4,73) = 1.17, p = .329. There was no evidence of moderation by either ASD likelihood (β = .059, p = .852) or ADHD likelihood (β = .003, p = .987). The results from step 2 did not change when ECBQ activity was partialled out, F(6,62) = 4.087, p = . 002, R^2_{adj} = .214, 95% CI for B, [-.170, .163]; when ECBQ inhibitory control was partialled out, F(6,61) = 4.226, p = . 001, R^2_{adj} = .294, 95% CI for B, [-.189, .071]. See Figure 3.6A and Table 7.

Associations with ADHD traits at 24 months. The hierarchical linear regression with S1 alpha desynchronization as predictor and ECBQ activity as outcome was not statistically significant, F(1,69) = .797, p = .375, R^2_{adj} = .011; with ECBQ inhibitory control as outcome was also not statistically significant, F(1,68) = .920, p = .341, R^2_{adj} = .013. Both results did not change when ADOS-2 CSS were partialled out: for ECBQ activity, F(2,66) = .497, p = .611, R^2_{adj} = .000, 95% CI for B, [-.225, .371]; for ECBQ inhibitory control, F(2,65) = 1.716, p = .188, R^2_{adj} = .021, 95% CI for B, [-.742, .071].

The hierarchical linear regression with TSI as predictor and ECBQ activity as outcome and was not statistically significant, F(1,69) = 1.92, p = .170, R^2_{adj} = .013; with ECBQ inhibitory control as outcome was also not statistically significant, F(1,68) = .838, p = .363, R^2_{adj} = .012. Both results did not change when ADOS-2 CSS were partialled out: for ECBQ activity, F(2,66) = .947, p = .393, R^2_{adj}

= .000, 95% CI for B, [-.358, .297]; for ECBQ inhibitory control, F(2,65) = 1.329, p = .272, R^2_{adj} = .010, 95% CI for B, [-.754, .174]. See Figure 3.6B, 3.6C and Table 7.

Table 7*. Correlation coefficients (Pearson r) for associations between 10-month neural measures (S1 α desynchronization and S2-S1 α desynchronization) and 24-month measures of ASD or ADHD traits (ADOS-2 CSS log, ECBQ Activity, ECBQ Inhibitory Control) in entire sample*

Entire sample	ADOS-2 CSS (log)	ECBQ Activity	ECBQ Inhibitory Control
α S1	-.064	-.107	.116
α S2-S1	-.413**	-.165	.110

**p < .001

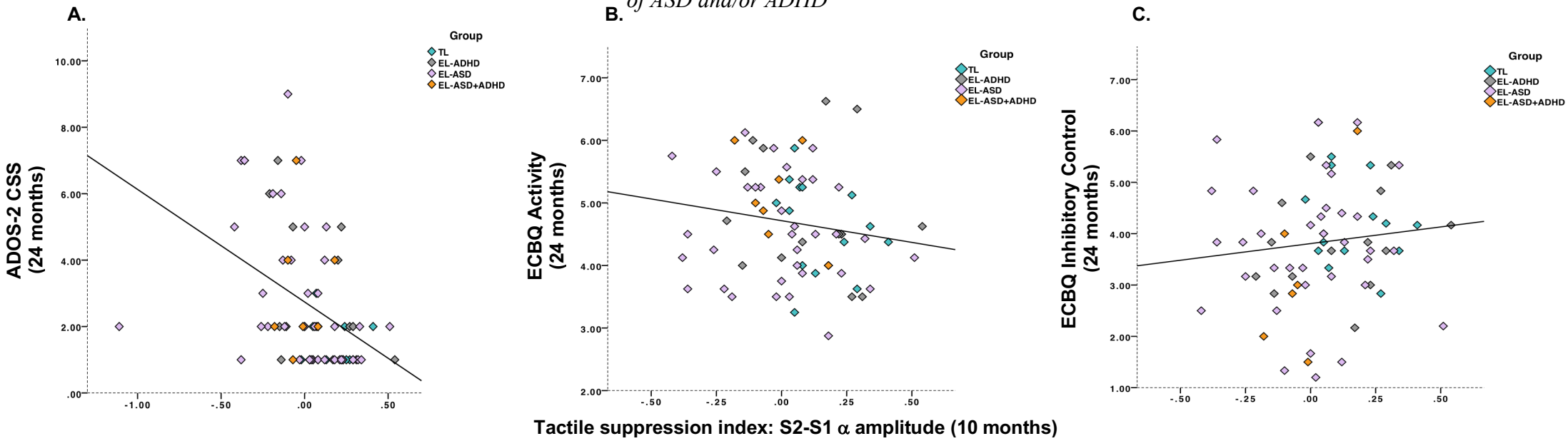

Figure 3.6. Scatterplots illustrating the associations between tactile suppression index (S2-S1 α amplitude) at 10 months and measures of ASD or ADHD traits at 24 months

A. ADOS-2 CSS at 24 months (p <.001); *B. ECBQ Activity at 24 months* (p = ns); C. *ECBQ Inhibitory Control at 24 months* (p = ns). *Groups are illustrated with different colours (green=infants at typical likelihood of ASD or ADHD; violet=infants at elevated likelihood of ASD; grey=infants at elevated likelihood of ADHD; orange=infants at elevated likelihood of ASD and*

ADHD). Note: 1] The fit lines are presented for an average of all infants; 2] The participant with a TSI<-1 in Figure A does not appear in Figures B and C since this infant did not contribute ECBQ data.

3.4.5. Mediating/moderating effect of tactile sensory seeking

Results from previous analyses indicated that reduced neural repetition suppression of tactile stimulation (TSI) is a marker significantly capturing the effect of the ASD likelihood status at 10 months and predicting ASD traits at 24 months.

In light of my interest in investigating the potential impact of early sensory atypicality on infants' engagement with their surrounding environment, I proceeded with assessing whether tactile sensory seeking significantly mediated or moderated the relationship between TSI and later ASD traits, see Figure 3.7. As detailed in Chapter 2, sensory seeking is a construct of the ITSP that maximally captures infants' active engagement with their surrounding environment and reduced sensory seeking is reported in the early development of ASD. Tactile sensory seeking captures infants' engagement with the environment in the tactile modality (see Appendix for a discussion of the contributing items and for assessment of the sub-scale internal consistency; further, see Appendix for analyses that replicate, in the current sample, the profile of reduced tactile sensory seeking in the early development of ASD). To conclude that tactile sensory seeking mediates the relationship between early neural repetition suppression of tactile stimulation and later ASD traits, a significant *indirect effect* of neural repetition suppression on ASD traits, through tactile sensory seeking, should be observed. Two pathways comprise the indirect effect: 1) "a path" represents the relation between neural repetition suppression and tactile sensory seeking; 2) "b path" represents the relation between neural repetition suppression and ASD traits, controlling for tactile

sensory seeking. An indirect effect is statistically significant when the confidence interval for the product of the unstandardized coefficients for these two paths does not include zero.

To conclude that tactile sensory seeking moderates the relationship between early neural repetition suppression of tactile stimulation and later ASD traits, a significant *interaction effect* between neural repetition suppression and tactile sensory seeking on ASD traits should be observed.

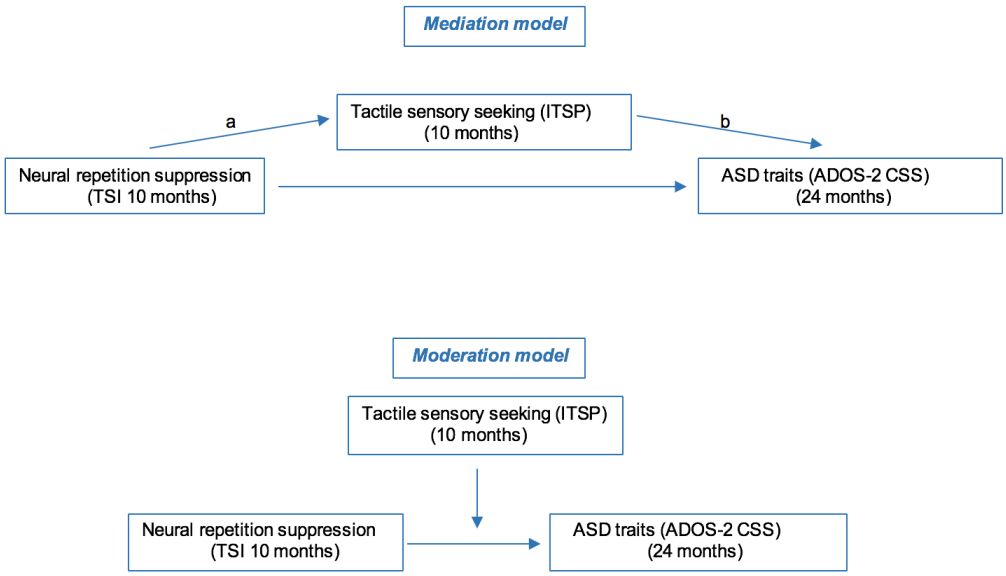

Figure 3.7. Mediation and moderation models illustrating the possible relationships between tactile neural repetition suppression at 10 months, parent-reported tactile sensory seeking at 10 months and ASD traits at 24 months.

The mediation model implies a causal relationship, whereby reduced neural repetition suppression leads to concurrent reduced tactile sensory seeking, which causes later elevated ASD traits. The moderation model implies an interaction effect whereby, at the same level of early neural repetition suppression of tactile

stimulation, infants scoring high in concurrent tactile sensory seeking develop less severe ASD traits at 24 months.

In the following mediation and moderation analyses, bias-corrected confidence intervals for effects of interest were generated using 5000 bootstrap samples with the confidence level set at 95%.

Mediation model. The direct effect of TSI on ADOS-2 CSS (log) was statistically significant at 95% CI, [-1.759, -.537]. The direct effect of tactile sensory seeking on ADOS-2 CSS (log) was also statistically significant at 95% CI, [.091, .547]. No evidence for an indirect effect of TSI on ADOS-2 CSS (log) through tactile sensory seeking emerged: 1] "a path" from tactile sensory seeking to TSI was not statistically significant at 95% CI, [-1.066, .226]; 2] "b path" from TSI to ADOS-2 CSS (log) controlling for tactile sensory seeking was not statistically significant at 95% CI, [-.408, .001].

Moderation model. The interaction effect between TSI and tactile sensory seeking on ADOS-2 CSS (log) was statistically significant at 95% CI, [-2.919, -.154], indicating a moderation role of tactile sensory seeking. Analysis of the conditional effects (i.e. spotlight analysis) indicated that TSI significantly predicted ADOS-2 CSS when tactile sensory seeking was low (95% CI, [-3.340, -1.086], $p < .001$) or average (95% CI, [-1.807, -.614], $p < .001$) but not high (95% CI, [-1.241, .825], p

= .688). Johnson-Neyman analysis (i.e. floodlight analysis) indicated that the association between tactile suppression index and ADOS-2 CSS (log) was not significant for values of tactile sensory seeking ≤ 2.13 (i.e. high tactile seeking). See Figure 3.8 and Table 8.

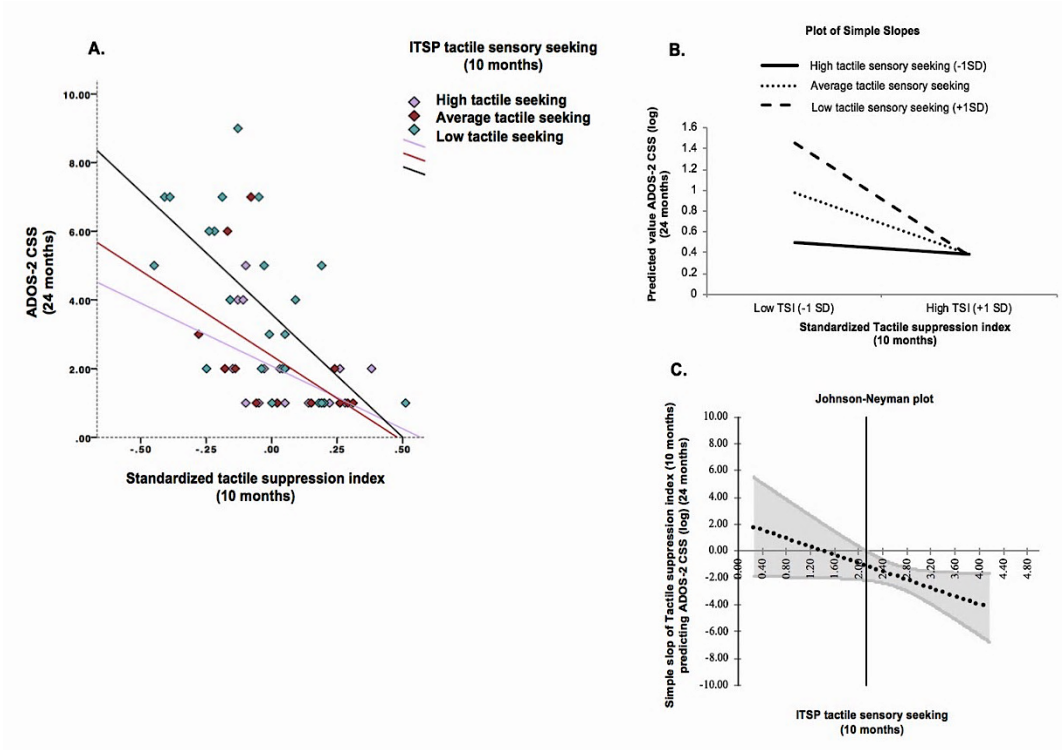

***Figure 3.8*. Scatterplot, plot of simple slopes and Johnson-Neyman plot illustrating the moderating effect of tactile sensory seeking**

A. Scatterplot illustrating the moderating effect of tactile sensory seeking (10 months) on the association between tactile suppression index (S2-S1 α amplitude) at 10 months and ADOS-2 CSS at 24 months. B. Plot of simple slopes illustrating the interaction effect of tactile sensory seeking: the association between tactile suppression index and ADOS-2 CSS (log) is significant for average and low tactile

sensory seeking (p < .001) but not significant for high tactile sensory seeking (p = .688). C. Johnson-Neyman plot illustrating the region of significance of the moderator: the association between tactile suppression index and ADOS-2 CSS (log) is not significant for values of tactile sensory seeking ≤ 2.13 (i.e. high tactile seeking).

***Table 8**. Conditional effects of tactile suppression index (10 months) on ADOS-2 CSS (24 months) depending on ITSP tactile sensory seeking (10 months)*

ITSP tactile sensory seeking	B	*p*	*95% CI*	
Mean +1SD (low seeking)	-2.213**	< .001	-3.340	-1.086
At the mean (average seeking)	-1.210**	< .001	-1.807	-.614
Mean -1SD (high seeking)	-0.208	.688	-1.241	.825

**$p < .001$

3.4.6. Associations between behavioural/neural markers and learning

Associations with behavioural markers. A significant positive association emerged in the whole sample between differential moving score (post S2 – pre S1) at 10 months and concurrent Mullen scores, R (87) = .238, $p = .012$, $R^2 = .057$. The association with later Mullen (24 months) trended towards significance, R (74) = .185, $p = .055$, $R^2 = .034$. These results indicate that infants manifesting more

movement after receiving the tactile stimulation at 10 months also exhibited higher scores on the Mullen Scales at 10 and 24 months.

The association between differential looking score (post S2 – pre S1) and 10-month Mullen was not statistically significant, R (87) = -.065, p = .271, R^2 =.004; and 24-month Mullen was also not statistically significant, R (74) = .005, p = .483, R^2 =.000.

Associations with neural markers. There was no significant association between S1 alpha desynchronization and 10-month Mullen, R (88) = -.015, p = .443, R^2=.000; and 24-month Mullen, R (88) = .023, p = .420, R^2 =.000. The association between TSI and 10-month Mullen was statistically significant, R (88) = .177, p = .047, R^2 = .031; and 24-month Mullen was also statistically significant, R (88) = .210, p = .033, R^2 =.044. Thus, infants manifesting enhanced neural repetition suppression of tactile stimulation at 10 months also exhibited higher scores on the Mullen Scales at 10 and 24 months**.** See Figure 3.9A and 3.9B.

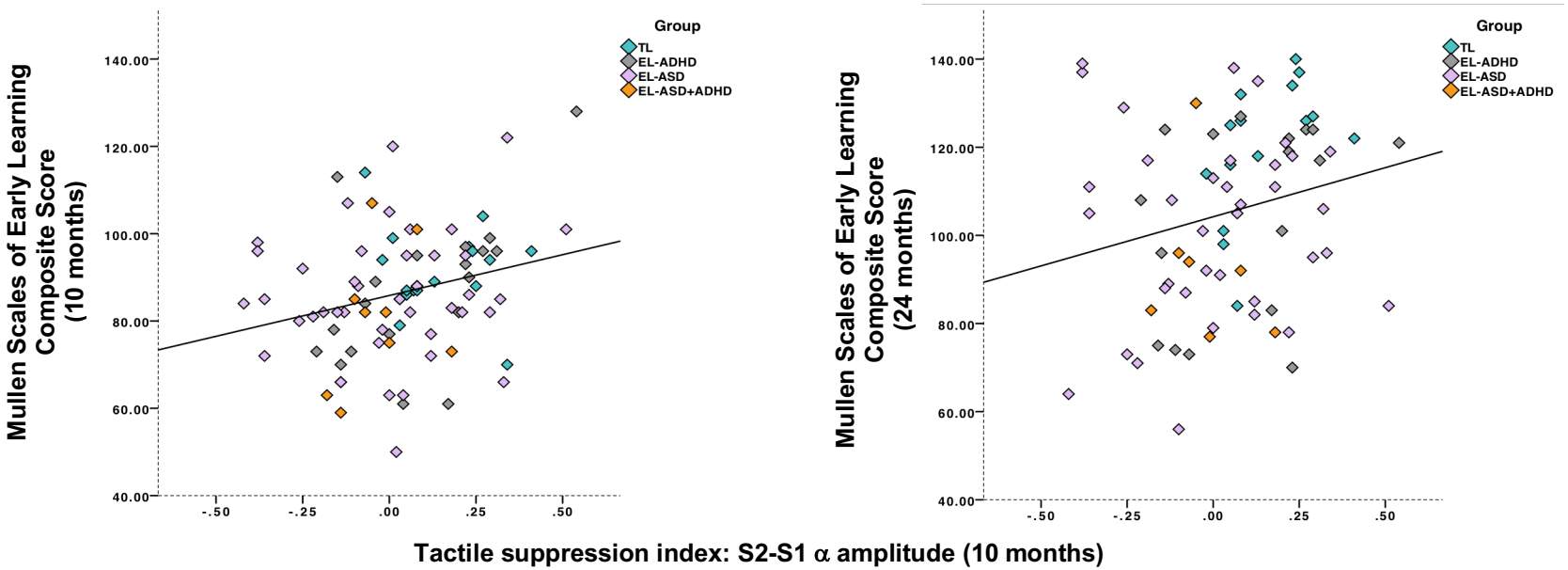

Figure 3.9. Scatterplots illustrating the associations between tactile suppression index (S2-S1 α amplitude) at 10 months and scores on the Mullen at 10 and 24 months

A. Mullen Scales of Early Learning at 10 months ($p < .05$); B. Mullen Scales of Early Learning at 24 months ($p < .05$). Groups are illustrated with different colours (green=infants at typical likelihood of ASD or ADHD; violet=infants at elevated likelihood of ASD; grey=infants at elevated likelihood of ADHD; orange=infants at elevated likelihood of ASD and ADHD). Note: The fit lines are presented for an average of all infants

3.4.7. Main analytical pipeline – Interim summary

Results of the analyses conducted so far indicated that all infants, independent of their likelihood status, manifested a significant decrease in screen-directed looking and an increase in body movement from the pre to the post-stimulus phase. This evidence disconfirms my prediction that the ASD likelihood status would have impacted on behavioural markers, leading to elevated moving and reduced screen-directed looking (behavioural hypersensitivity) after receiving the tactile stimulation.

Results from the investigation of neural markers of tactile sensory processing similarly indicated that neither the ASD likelihood, nor the ADHD likelihood impacted as factors on neural sensitivity to the first vibrotactile stimulus. This evidence disconfirms my prediction that the ADHD likelihood status would have impacted as a factor on neural sensitivity, leading to reduced alpha desynchronization to the first vibrotactile stimulus. Conversely, in line with my prediction, I observed a significant effect of the ASD likelihood status on neural repetition suppression, manifesting as limited reduction in alpha desynchronization with repeated tactile input. This result was reinforced by the finding of a specific association between neural repetition suppression of tactile stimulation at 10 months and ASD traits at 24 months in the entire sample, with infants manifesting reduced neural repetition suppression of tactile input at 10 months reporting higher ASD traits at 24 months.

Fourthly, results from the mediation and moderation analyses disconfirmed the notion that tactile sensory seeking may act as a compensatory factor in early development. Conversely, evidence pointed to a compounding (i.e. protective) role of tactile sensory seeking, with high seeking mitigating the association between early reduced neural repetition suppression and later ASD traits.

Finally, driven by previous studies suggesting that neural repetition suppression underlies efficient learning during experimental testing (León-Carrión et al., 2010), I assessed the associations between neural repetition suppression at 10 months and general development/learning. Results confirmed that infants manifesting enhanced neural repetition suppression also exhibited higher learning scores during the standardized administration of the Mullen both concurrently and longitudinally. It is possible that enhanced neural repetition suppression supports learning by speeding up priors updating (Pellicano & Burr, 2012). While in the current study, neural repetition suppression was measured in the tactile modality, I expect the link documented to manifest across sensory modalities.

I further discuss these results in section 3.5. Additionally, in light of the evidence emerged from these analyses, I proceeded with performing the follow-up analyses introduced in section 3.2.2. These analyses clarify and/or expand on results emerged from the main analytical pipeline.

3.4.8. Associations between body movement and neural markers

To exclude the influence of infants' movement on neural markers of tactile sensory processing, I assessed whether any associations existed between body movement (as emerged from behavioural coding) and both neural sensitivity to and suppression of repeated tactile stimulation.

The Pearson correlation between neural sensitivity (S1) and body movement during the pre-stimulus phase was not statistically significant, R (88) = .032, p = .762; with body movement during the post-stimulus phase was also not statistically significant, R (88) = .057, p = .596.

Similarly, the Pearson correlation between neural repetition suppression (TSI: S2-S1) and body movement during the pre-stimulus phase was not statistically significant, R (88) = .018, p = .868; with body movement during the post-stimulus phase was also not statistically significant, R (88) = -.059, p = .579.

3.4.9. Parental reports of infants' behavioural sensitivity to tactile stimulation

Given the non-significant results emerged from the assessment of the effect of infants' likelihood status on behavioural markers of sensitivity to tactile stimulation, I conducted a set of analyses investigating if infants' likelihood status differentiated parental reports of behavioural sensitivity to tactile stimulation.

ITSP sensory sensitivity and low registration scores for the tactile modality were computed for each 10-month-old infants. The tactile low registration variable significantly violated normality assumptions (Shapiro-Wilk, $p < .001$; Skewness =

-.720, SE = .274; Kurtosis = .257, SE = .541) and was log transformed prior to the analyses. The univariate ANOVA on tactile sensory sensitivity indicated no significant main effect of ASD, F(1,71) = .742, p = .392, η^2 = .010, or ADHD, F(1,71) = .061, p = .805, η^2 = .001. Further, no significant interaction between ASD and ADHD likelihood status emerged, F(1,71) = .267, p = .607, η^2 = .004. The univariate ANOVA on tactile low registration (log) indicated no significant main effect of ASD, F(1,71) = .087, p = .769, η^2 = .001. The main effect of ADHD failed to reach statistical significance, F(1,71) = 3.77, p = .056, η^2 = .050. No significant interaction between ASD and ADHD emerged, F(1,71) = 0.64, p = .800, η^2 = .001.

3.4.10. Associations between neural markers and parent-reported ASD traits

Associations with ASD traits at 24 months. Q-CHAT scores significantly violated normality assumptions (Shapiro-Wilk, p < .001; Skewness = .943, SE = .226; Kurtosis = 1.164, SE = .447). Log transformation did not improve the data distribution (Shapiro-Wilk, p = .001; Skewness = -.778, SE = .226; Kurtosis = 2.485, SE = .447). Thus, Spearman correlations were run to assess the associations between neural markers and this outcome measure.

The Spearman correlation between Q-CHAT and S1 alpha desynchronization was not statistically significant, Rho (72) = -.054, p = .322; and TSI was also not statistically significant, Rho (72) = -.115, p = .165. Given that TSI at 10 months significantly predicted ADOS-2 CSS at 24 months, I also assessed the

concordance between Q-CHAT and ADOS-2 CSS. There was low concordance between the measures, Rho (70) = .244, p = .039.

3.4.11. Mediating/moderating effect of tactile sensory avoiding

ITSP sensory avoiding scores for the tactile modality were computed for each 10-month-old infants. First, descriptive investigation of the variable distribution indicated that 83.2% of the data fell within an interval ranging from 3.5 to 5 (i.e. indexing low tactile sensory avoiding on the ITSP), thus suggesting that infants as young as 10 months may not yet possess a sufficient skills repertoire to display active avoidance behaviours.

Since tactile sensory avoiding could be opposite to tactile sensory seeking, I assessed the relationship between the two ITSP measures. The Pearson correlation between the measures was not statistically significant, R (73) = .014, p = .905, disconfirming the potential link between the two quadrants within the tactile domain of the ITSP. I subsequently assessed the explanatory power of tactile sensory avoiding as a mediator or moderator of the relationship between 10-month neural repetition suppression of tactile stimulation and 24-month ASD traits.

Mediation model. The direct effect of TSI on ADOS-2 CSS (log) was statistically significant at 95% CI, [-1.759, -.537]. The direct effect of tactile sensory avoiding on ADOS-2 CSS (log) was not statistically significant at 95% CI, [-.260, .276]. No evidence for an indirect effect of TSI on ADOS-2 CSS (log) through tactile sensory

avoiding emerged: 1] "a path" from tactile sensory avoiding to TSI was not statistically significant at 95% CI, [-.912, .444]; 2] "b path" from TSI to ADOS-2 CSS (log) controlling for tactile sensory seeking was not statistically significant at 95% CI, [-.112, .087].

Moderation model. The interaction effect between TSI and tactile sensory avoiding on ADOS-2 CSS (log) was not statistically significant at 95% CI, [-2.968, .004], disconfirming the moderation role of tactile sensory avoiding.

3.4.12. Follow-up analyses – Interim summary

I performed a set of follow-up analyses with the goal of clarifying and/or expanding on results emerged from the core analyses.

First, to exclude the influence of infants' movement on neural markers of tactile sensory processing, I investigated the associations between body movement (as emerged from behavioural coding) and both neural sensitivity to and suppression of repeated tactile stimulation. Results indicated that there were no significant associations between these measures, thus excluding the possible influence of movement on both neural indices.

Secondly, given the non-significant results emerged from the investigation of the effect of infants' likelihood status on behavioural markers of sensitivity to tactile stimulation during the experiment (i.e. looking and moving before and after receiving the tactile stimulus), I assessed whether infants' likelihood status

differentiated parental reports of behavioural sensitivity to tactile stimulation. Results indicated that likelihood status did not differentiate parental reports of behavioural sensitivity to tactile stimulation. Thus, this evidence confirms results emerged from the main analyses, suggesting that the absence of behavioural differences at 10 months may not be a consequence of the coding approach used.

Secondly, given the significant association emerged between reduced neural repetition suppression of tactile stimulation at 10 months and higher ASD traits quantified through the ADOS-2 CSS at 24 months, I ascertained whether a comparable association existed with the parent-reported Q-CHAT. Results indicated that parent-reported ASD traits in toddlerhood did not associate with neural sensitivity to and suppression of repeated tactile stimulation in infancy. Further, in the current study, concordance was low between ADOS-2 CSS and scores on the Q-CHAT. Low concordance between standardized clinical assessments and parental reports of ASD or ADHD traits and symptoms during childhood has been previously reported (Evers et al., 2020; Nobel et al., 2019). In younger toddlers, concordance between parental reports and standardised clinical assessments of ASD or ADHD traits may be even lower since atypical manifestations are less prominent. Thus, both the significant associations between neural markers of tactile sensory processing and later ASD traits (quantified through clinician observation) and the non-significant associations between the same neural markers and later ADHD traits (quantified through parental report) in

the present chapter must be followed-up through assessment of clinical outcomes at 3 years.

Finally, while I explored the mediating or moderating role of tactile sensory seeking in the main analyses, I further explored the potential impact of tactile sensory avoiding, which represents an active behavioural strategy to limit engagement with the surrounding sensory environment in the ITSP. Results disconfirmed the existence of a link between parental reports of tactile sensory seeking and avoiding behaviours at 10 months. Further, no evidence of tactile sensory avoiding mediating or moderating the association between neural repetition suppression of tactile stimulation at 10 months and ASD traits at 24 months emerged. Since in the current analysis 83.2% of infants were rated by their parents as never or almost never exhibiting tactile sensory avoiding behaviours, it is possible that 10-month-old infants may not yet possess the ability to display active avoidance strategies. Seeking (as opposed to avoiding) may represent the preferred strategy of information prioritization in early development. Indeed, formal assessment of the ITSP internal consistency indicates that the avoiding quadrant has low internal consistency during the first two years of life (Cronbach $\sigma = 0.56$). Conversely, the seeking quadrant is reported to have adequate internal consistency (Cronbach $\sigma = 0.79$). Sensory avoiding behaviours may increase in frequency and improve in reliability over development, as children gain copying skills and active control over their sensory environment.

3.5. Discussion

3.5.1. General points

The goal of the present study was to investigate behavioural and neural markers of tactile sensory processing in 10-month-old infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the disorders. To this goal, a tactile repetition suppression paradigm administering repeated pairs of vibrotactile stimuli (S1-S2) was used and coupled with the recording of EEG. First, I quantified infants' behavioural responses to repeated tactile stimulation, as objective assessment of infants' behavioural sensitivity. I observed that all infants, independent of their likelihood status, exhibited a significant decrease in screen-directed looking and an increase in body movement from the pre to the post-stimulus phase. Previous reports of behavioural sensitivity used parental reports (Baranek et al., 1997; Ghanizadeh, 2011; Tomchek & Dunn, 2007). Other laboratory-based experimental and observational measures failed to report differences in behavioural sensitivity. For example, behavioural sensitivity measured during a structured observational task comprising self-directed and examiner-directed tactile stimulation (i.e. Tactile Defensiveness and Discrimination Test Revised, *TDDT-R*; Baranek, 1998) did not associate with ASD core symptoms, as measured by the ADOS and ADI-R (Foss-Feig, Heacock, & Cascio, 2012). Further, there is evidence that parental reports do not always correlate with clinical or experimental observations (Foss-Feig et al., 2012; McCormick et al., 2014). In the present study, a parent-reported measure (i.e.

behavioural sensitivity to tactile stimulation quantified through the sensory sensitivity and low registration quadrants of the ITSP; Dunn, 2002) was also unaffected by likelihood status (see section 3.4.9). Thus, this evidence suggests that the absence of behavioural differences at 10 months may not be a consequence of the coding approach used. Nonetheless, it is important to note that the coding approach adopted was not designed to detect fine-grained differences in behavioural sensitivity. Thus, I cannot rule out the possibility that subtle differences in behavioural manifestations existed between the groups. Alternatively, it is also possible that stronger or more aversive stimulation may be needed to observe an effect of likelihood status on behavioural sensitivity to tactile input. Further research is needed to characterize behavioural markers of tactile processing in the early development of ASD and ADHD.

In contrast to my hypothesis, response strength to the first stimulus in the pair did not associate with participants' likelihood status. Based on previous studies, I predicted neural hyposensitivity to S1 to associate with an ADHD likelihood status and to predict later ADHD traits (Dockstader et al., 2008; Kim et al., 2002; Puts et al., 2017). Neither neural sensitivity to S1 differentiated infants with an ADHD likelihood status, nor did it predict later activity or inhibitory control traits measured with the parent-reported ECBQ. The lack of association between neural sensitivity to S1 and the ADHD likelihood status or later ADHD traits is surprising, given that theoretical accounts often assume the hyperactivity and reduced inhibitory control characteristic of ADHD to compensate for sensory

hyposensitivity (e.g. Zentall & Zentall, 1983). Experimental evidence in support of this hypothesis remains scarce. For example, Bijlenga et al., (2017) failed to document hyposensitive-related behaviours in adults with ADHD. I need to note that, in the current study, I used the parental report ECBQ to quantify ADHD traits in 24-month-old toddlers. Although ECBQ activity and inhibitory control at 24 months associate with ADHD symptoms at 7 years (Shephard et al., 2018), these measures may not capture the whole spectrum of later ADHD manifestations.

Neural sensitivity to S1 also did not associate with the ASD likelihood status or predict later ASD traits, quantified through ADOS-2 CSS. Although one report documented a significant positive association between neural sensitivity to S1 and ASD traits in 8-18 years old participant with ASD (Khan et al., 2016), the majority of animal and human research converges in suggesting that reduced neural repetition suppression of tactile stimulation characterises this condition (He et al., 2017; Green et al., 2015; Puts et al., 2014, 2017). In other sensory modalities (i.e. auditory), reduced neural repetition suppression in the absence of neural hypersensitivity in ASD has also been documented (Millin et al., 2018). Reduced neural repetition suppression, rather than increased response to a single stimulus, may account for the behavioural profile of sensory hypersensitivity documented in children with ASD (Baranek et al., 1997; Tomchek & Dunn 2007; Cascio et al., 2016).

In addition to assessing infants' neural sensitivity to S1, the current task was designed to measure neural repetition suppression of tactile stimulation (S2-

S1). Atypicalities in neural repetition suppression have been documented in populations with ASD and ADHD, with accumulating evidence coming from the auditory modality (Millin et al., 2018; Nordt, Hoehl, & Weigelt, 2016; Sinha et al., 2014), including in populations of infants at elevated likelihood of ASD (Guiraud, Kushnerenko, Tomalski, Davies, Ribeiro, & Johnson, 2011; Kolesnik et al., 2019; Seery et al., 2014). Hence, I predicted to observe significant effects of ASD and ADHD likelihood status on neural repetition suppression. While significant reduction in alpha desynchronization to repeated tactile stimulation only occurred in infants at typical likelihood of the conditions, only the ASD likelihood status statistically impacted as a factor on this measure. This result was reinforced by the finding of a specific association between neural repetition suppression of tactile stimulation at 10 months and ASD traits at 24 months, across the entire sample. This association was not moderated by likelihood status, suggesting that the pathway identified is independent of familial contributions. Previous work questioned whether ASD manifests the same phenotype when accompanied by ADHD (Shephard et al., 2018; Tye et al., 2014). The current results suggest that a common pathway to later ASD traits exists in infants at elevated likelihood of ASD or ADHD. However, as discussed in Chapter 1 (section entitled "Clinical assessment"), it remains likely that within families with ASD, rates of actual ADHD were higher than those captured by the adopted 1/0 diagnostically-based rating system. Therefore, it is possible that some infants were mischaracterized into the EL-ASD group when they should have been in the EL-ASD+ADHD group. In turn,

this mischaracterization may have driven the lack of a moderating effect of likelihood status on the association between neural repetition suppression of tactile stimulation at 10 months and ASD traits at 24 months.

Alteration in the excitation/inhibition balance of neural connectivity has been proposed as a mechanism underlying many of the manifestations occurring in ASD and ADHD, including atypical repetition suppression (Kelsom & Lu, 2013; Leonard et al., 2002; Richter, Ehlis, Jacob, & Fallgatter, 2007). Since repetition suppression partly reflects GABAergic inhibition of glutaminergic pyramidal cells in the interneuronal network (Kuravi & Vogels, 2018; Leonard et al., 2002), reduced inhibition in the somatosensory cortex could underlie the impairments in repetition suppression documented in the current study. Additional perceptual phenomena that have been linked to alteration in the excitation/inhibition balance include binocular rivalry, spatial suppression/gain control and orientation discrimination (for reviews see, Dickinson, Jones, & Milne, 2016; Robertson & Baron-Cohen, 2017). Thus, extending to the tactile modality evidence of atypical neural repetition suppression, the current findings suggest that such atypicality may be domain-general rather than tied to a specific sensory modality. Gathering evidence of atypical neural repetition suppression in the tactile modality is essential, given that touch is the first sense to develop and the mean through which infants learn about the environment and themselves (Bremner & Spence, 2017). Further, touch contributes to the development of early social bonds (Cascio, 2010; Ferber et al., 2008; Mammen et al., 2015). Indeed, it has been proposed that early tactile

dysfunction may exacerbate later ASD symptomatology by triggering compensatory strategies aimed at minimizing tactile input (Mikkelsen et al., 2017). Thus, as a final step of the core analytical pipeline, I sought to explore the effect of tactile sensory seeking as a potential mediator or moderator of the relationship between early atypical neural response and later ASD traits. Decreased sensory seeking is often reported in infants later developing ASD (Ben-Sasson et al., 2009; Mulligan & White, 2012; Thye et al., 2018) and may represent a compensatory strategy adopted by infants to minimize sensory input (Johnson, Gliga, et al., 2015; Mulligan & White, 2012). However, reduced sensory seeking could also limit infants' opportunities for learning and socialization, thus exacerbating later ASD traits. Contrary to this hypothesis, I found no evidence of a mediating role of tactile sensory seeking at 10 months. In contrast, I found that tactile sensory seeking significantly moderated the association between 10-month tactile neural repetition suppression and 24-month ADOS-2 CSS. This moderation effect was specific to seeking and did not extend to other sensory behaviours like avoiding. Thus, at the same level of neural repetition suppression of tactile stimulation, infants reported by parents as concurrently seeking more tactile input developed lower ASD traits at 24 months. Thus, tactile sensory seeking could represent an independent compounding factor, moderating the association between early reduced neural repetition suppression and later ASD traits. Indeed, previous research suggests that tactile sensory seeking does not always associate with elevated sensory responsiveness (Ben-Sasson et al., 2009). In line with Predictive coding theories, I

speculate that reduced neural repetition suppression may interfere with learning by slowing prior updating (Pellicano & Burr, 2012) – a notion consistent with the evidence of a link existing between enhanced neural repetition suppression at 10 months and both concurrent and longitudinal higher learning scores assessed though the Mullen. From this perspective, increase tactile sensory seeking may have a protective role during development by widening opportunities for learning and socialization.

3.5.2. How do these results inform our understanding of the mechanisms underlying the early development of sensory perception in ASD and ADHD?

Results from the current study indicate that atypicalities in sensory perception, manifesting as reduced neural suppression of repeated tactile stimulation, exist in the early development of ASD and predict emerging traits of the disorder during toddlerhood. These results align to Predictive coding theories of sensory perception, which hypothesize atypical sensory processing in individuals with ASD to result from reduced integration between feedforward and feedback signals (i.e. active inference), limiting refinement of sensory predictions over time (Lawson, Rees, & Friston, 2014; Pellicano & Burr, 2012). Since reduced reliance on priors could limit the ability to predict forthcoming events, it is possible that infants manifesting limited neural repetition suppression of tactile stimulation had difficulties in predicting the incoming stimulus, thus limiting the progressive refinement of

predictions and the suppression of expected sensory input over time (Auksztulewicz & Friston, 2016; Kok & De Lange, 2015).

Predictive coding theories further postulate active inference as the mechanism underlying efficient learning (Lawson et al., 2014; Pellicano & Burr, 2012). Thus, if reduced active inference capacity is indeed the mechanism underlying limited neural repetition suppression, then a link between this measure and learning outcomes should exist. The current research confirms this prediction by indicating that infants manifesting enhanced neural repetition suppression at 10 months, also displayed higher scores on the Mullen both concurrently (10 months) and longitudinally (24 months). Previous studies reported a link between enhanced neural repetition suppression and better learning during experimental testing (León-Carrión et al., 2010). However, the current study is the first to document this link in a prospective longitudinal assessment of infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the conditions.

Conversely, the current study does not support the notion that reduced active inference may characterize the early development of sensory perception in infants at elevated likelihood of ADHD. While in the present study only infants at typical likelihood of ASD and/or ADHD manifested significant reduction in alpha desynchronization with repeated tactile stimulation, only the ASD (but not the ADHD) likelihood statistically impacted as a factor on this measure. Further, there was no evidence of an association between neural repetition suppression at 10 months and later parental reports of ADHD traits. It is possible that an association

may manifest with 3-year clinical outcomes, although at present data to confirm or disprove this prediction is unavailable (see section 3.7).

Altogether, the present research demonstrates that atypicalities in sensory perception are detectable in infants with later higher ASD traits from early in development. I propose that reduced active inference capacity may be the mechanism behind these early-emerging sensory atypicalities across sensory modalities. I explore this possibility in Chapter 4, whereby I investigate the neural markers of visual sensory processing in the same participant groups.

3.6. Conclusion

Overall, the current study presents the first evidence of atypical neural repetition suppression of tactile stimulation in infants at elevated likelihood of ASD. I demonstrate that reduced tactile neural repetition suppression is an early marker of later ASD traits in both infants at elevated likelihood of ASD or ADHD, suggesting that a common pathway to later ASD exists across these different familial backgrounds. Further, I establish tactile sensory seeking as a moderator of the association between early reduced neural repetition suppression and later ASD traits (i.e. high tactile seeking mitigates the association between early reduced neural repetition suppression and later ASD traits). Thus, I identify a pathway to the emergence of ASD traits, and emphasize the need to discover additional factors for the development of ADHD traits. Future research should assess whether

continuity exists between the marker identified in the current study and later manifestations of sensory hypersensitivity.

3.7. Limitations

The study described in the present chapter has a few limitations. First, as indicated by behavioural coding, infants manifested reduced screen-directed looking and elevated movement following the tactile stimulation. This response manifested in the entire sample, independently of infants' likelihood status. However, the coding system I adopted was not designed to detect fine-grained changes in the quality of infants' manifestations. Therefore, I cannot exclude that subtle differences in the quality, rather than quantity, of body movement existed between the groups.

Secondly, in the current study the parent-reported ECBQ activity and inhibitory control sub-scales were used to quantify ADHD traits at 24 months. While previous research indicates that higher 24-month ECBQ activity levels and inhibitory control predict higher mid-childhood hyperactivity/impulsivity and inattention (Shephard et al., 2018), it is possible that this parental report failed to capture ADHD manifestations in toddlerhood. This possibility should be acknowledged given that neural repetition suppression associated with ASD traits quantified through clinical observation (ADOS-2 CSS) but it did not associate with the parent-reported Q-CHAT. Thus, the specificity of the association between early neural repetition suppression and later ASD traits documented in the current study must be confirmed by assessing the relationships with later clinical outcomes

(which will be possible when data collection for the 3-year follow-up visits for the BASIS Phase 3 study is completed).

3.8. Summary of Chapter 3

Atypicalities in tactile sensory processing are reported in ASD and ADHD but it remains unknown if they precede and associate with traits of these disorders emerging in childhood. Chapter 3 was set out to investigate behavioural and neural markers of tactile sensory processing in infants at elevated likelihood of ASD and/or ADHD compared to infants at typical likelihood of the disorders. Further, the chapter assessed the specificity of associations between infant markers and later ASD or ADHD traits.

To this goal, behavioural and EEG responses to pairs of tactile stimuli were experimentally recorded and concurrent parental reports of tactile responsiveness were collected. ASD and ADHD traits were measured at 24 months through standardised assessment (ADOS-2) and parental report (ECBQ), respectively. Results indicated that there was no effect of infants' likelihood status on behavioural markers of tactile sensory processing. Conversely, increased ASD likelihood associated with reduced neural repetition suppression of tactile input. Reduced neural repetition suppression at 10 months significantly predicted ASD (but not ADHD) traits at 24 months across the entire sample. Elevated tactile sensory seeking at 10 months moderated the relationship between early reduced neural repetition suppression and later ASD traits.

Altogether, these results indicate that reduced tactile neural repetition suppression is an early marker of later ASD traits in both infants at elevated likelihood of ASD or ADHD, suggesting that a common pathway to later ASD traits exists despite different familial backgrounds. Reduced neural repetition suppression in early development may result from limited active inference capacity and detrimentally impact learning by slowing prior update (Lawson et al., 2014; Pellicano & Burr, 2012). I propose that reduced active inference capacity may be the mechanism behind early-emerging sensory atypicalities across sensory modalities. I explore this possibility in Chapter 4, whereby I investigate the neural markers of visual sensory processing in the same participant groups.

Chapter 4: Neural markers of visual sensory processing in the early development of ASD and/or ADHD

4.1. Introduction

As reviewed in Chapter 1 and further discussed in Chapter 3, prospective longitudinal studies of infants at elevated likelihood of ASD or ADHD report similarities and differences in early markers of the two conditions (Gliga et al., 2014; Johnson et al., 2015; Jones et al., 2014; Thye et al., 2018). Commonalities between the disorders in early sensory vulnerabilities are documented in various modalities (Johnson, Gliga, et al., 2015; Little et al., 2018), although research on the early development of sensory perception in ASD and ADHD conducted within a trans-diagnostic framework is still in its infancy. In the visual modality, observational research concurs in suggesting that hypersensitivity to visual stimulation and reduced seeking of visual input manifest in the early development of ASD and/or ADHD (Ben-Sasson et al., 2009; Coulter, 2009; Ghanizadeh, 2011; Milne & Griffiths, 2007). Experimental evidence from prospective longitudinal studies of infants at elevated likelihood of ASD further suggests that early-emerging atypicalities in visual perception are predictive of later ASD traits and/or categorical diagnoses (Cheung et al., 2016; Gliga et al., 2015; Nyström et al., 2018). In contrast, no experimental investigation has so far been conducted to assess the early development of visual perception in infants with an elevated ADHD likelihood. In particular, despite accumulating evidence that sensory vulnerabilities manifest in the early development of ASD and ADHD, no prior research has examined the same sensory markers as potential infant predictors of ASD and/or ADHD in toddlerhood. Investigating the specificity of early infant markers is

essential to distinguish shared or distinct causal pathways and to understand the nature of the co-occurrence and the aetiology of these conditions.

Much research on visual perception within the neurodevelopmental disorder literature has been conducted through observational and behavioural approaches. Conversely, there is a paucity of research evaluating the mechanisms underlying visual perception in infants at elevated likelihood of ASD and/or ADHD through direct assessment of brain function. Filling this gap in knowledge is essential given that: 1) vision is the least functionally mature sensory system at birth, it undergoes significant post-natal development and it is highly influenced by the nature of the early environment (Huttenlocher, 2009); 2) vision is a vehicle through which infants learn about the world and themselves (Johnson, 2010); 3) early perturbations in visual processing may have cascading effects on later socio-cognitive development (Thye et al., 2018); 4) visual atypicalities dominate first-hand accounts from individuals with ASD (Grandin, 1995, 2009); 5) extensive research has studied the functional properties of the visual pathways in animals and humans (Heeger, Behrmann, & Dinstein, 2017), offering background literature for characterizing the nature of early-onset atypicalities in these disorders.

4.1.1. Visual sensory processing in ASD and ADHD

Behavioural markers. Different average responses to visual stimulation are reported in young populations with ASD or ADHD relative to control participants and patterns of visual hypersensitivity co-occurring with atypical seeking of visual

input are documented in the literature (Coulter, 2009; Ghanizadeh, 2011a; Milne & Griffiths, 2007). Research using parent-reported (e.g. Infant-Toddler Sensory Profile, ITSP; Dunn, 2002), examiner-reported or self-reported measures (e.g. Sensory Processing Scale, *SPS*; Schoen, Miller, & Sullivan, 2014) indicate that visual hypersensitivity exists in children with ASD and may persist through adulthood (Coulter, 2009; Milne & Griffiths, 2007). Consistent with this notion are reports suggesting that children with ASD display enhanced light sensitivity (Coulter, 2009; Milne & Griffiths, 2007), enhanced colour sensitivity (Coulter, 2009; Grandgeorge & Masataka, 2016) and severe sensitivity to fluorescent or flickering lights (Coulter, 2009; Milne & Griffiths, 2007). In an early report, Colman and collaborators (1976) further documented that children with ASD displaying enhanced sensitivity to fluorescent flickering lights also manifested elevated restricted and repetitive behaviours, thus suggesting that atypicalities in visual perception may be linked to core diagnostic ASD symptoms. Additional evidence in support of this notion comes from prospective longitudinal studies of infants at elevated likelihood of ASD. Mostly conducted with eye-tracking methods, this research has documented enhanced visual search performance in 9 and 15-month-old infants (but not 24-month-old toddlers) with later ASD (Cheung et al., 2016; Gliga et al., 2015). Further, 9-month-old infants later diagnosed with ASD present a hypersensitive pupillary light reflex (Nyström et al., 2018). Visual fixations and atypical visual engagement with objects (i.e. driven towards the peripheral visual field) have also been reported in infants with later ASD at 6 and

12 months of age (Kaur et al., 2015; Ozonoff, Macari, et al., 2008). Some authors have theorized these features to represent a regulatory mechanism compensating for difficulties with modulating responsiveness to incoming visual input (Tomchek & Dunn, 2007; Zentall & Zentall, 1983).

Research into visual perception in ADHD is limited. Clinical investigations using self-reported, examiner-reported and parent-reported measures mostly document hypersensitivity to visual stimulation in individuals with ADHD. Consistent with this notion are studies suggesting that children and adults with ADHD display enhanced light sensitivity and photophobia (Ghanizadeh, 2008, 2011a; Kooij & Bijlenga, 2014), enhanced colour sensitivity (Banaschewski et al., 2006) and hypersensitivity to flickering lights (Ghanizadeh, 2011a; Reynolds & Lane, 2009). Despite this evidence, the extent to which atypical visual perception may contribute to core ADHD manifestations remains unexplored. Similarly, no experimental assessment has yet been conducted to evaluate the early development of visual perception in infants with an elevated ADHD likelihood.

In summary, behavioural evidence suggests that visual hypersensitivity may be a shared atypicality in ASD and ADHD. However, the mechanisms underlying this atypicality and the extent to which visual hypersensitivity may be shared in the early development of these disorders remain unexplored.

Neural markers. Neurophysiological studies on visual sensory processing in individuals with ASD have mainly assessed EEG responses to the presentation of

threshold or supra-threshold visual stimuli (i.e. visual evoked potentials, VEPs, time-locked to the appearance of achromatic sinewave gratings or black-and-white checkerboards). Conceptualised in the context of excitation/inhibition (E/I) balance theories, these paradigms have mostly tested the hypothesis that visual hypersensitivity in individuals with ASD may result from cortical hyper-excitability (Lee, Lee, & Kim, 2017; Nelson & Valakh, 2015; Rubenstein & Merzenich, 2003). Consistent with this notion, Takarae and collaborators (2016) reported elevated increase in steady-state VEPs occurring as a function of stimulus contrast in adolescents with ASD relative to control participants. Furthermore, the authors reported the above atypicality to positively associate with a self-reported measure of sensory sensitivity in the visual modality (i.e. Adolescent/Adult Sensory Profile; Brown & Dunn, 2002). Elevated P1 mean amplitude in response to high-contrast Gabor stimuli was documented in children with ASD relative to control children and further predicted higher scores on the hyper-responsiveness items on a parental report (i.e. Sensory Experiences Questionnaire, SEQ; Baranek, David, Poe, Stone, & Watson, 2006)(Shuffrey et al., 2018). Research conducted with fMRI reported increased BOLD activation in the visual cortex in response to supra-threshold stimuli (e.g. continually rotating colour wheels) in adolescents with ASD relative to control participants. This atypicality further predicted the severity of sensory over-responsivity on a parental report (i.e. Sensory Over-Responsivity Inventory, SensOR; Schoen, Miller, & Green, 2008) (Green et al., 2013). Additional fMRI studies reported elevated BOLD activation in the visual cortex

during passive viewing of dynamic visual stimuli in adults with ASD and linked this atypicality to reduced GABA concentrations in the same cortical region (Takarae, Luna, Minshew, & Sweeney, 2014). Importantly, this evidence aligns to research conducted with magnetic resonance spectroscopy (MRS) in neurotypical adults, whereby a negative association between local GABA concentrations and the amplitude of BOLD responses in the visual cortex is documented (Donahue, Near, Blicher, & Jezzard, 2010; Muthukumaraswamy, Evans, Edden, Wise, & Singh, 2012). A vast amount of literature further documented enhanced BOLD activation in the visual cortex to co-occur with reduced activation of the prefrontal cortex in individuals with ASD (for a review see, Samson, Mottron, Soulières, & Zeffiro, 2012), suggesting that atypical integration between feedback signals from prefrontal regions and feedforward signals from visual areas may be the mechanism underlying the profile of visual hypersensitivity documented in ASD. As reviewed in Chapter 1, this proposal aligns to Predictive coding theories and it represents the theoretical framework that will guide my investigation in the current chapter.

Neurophysiological studies investigating visual sensory processing in ADHD are limited and mostly document enhanced sensitivity to visual stimulation and reduced or less efficient top-down regulation of visual processing. Neural hypersensitivity to flashed light-emitting diodes, indexed by elevated P1 peak amplitude, was reported in adults with ADHD relative to control participants (and relative to participants with Bipolar Mood Disorder – a condition frequently co-occurring with ADHD) (Nazhvani, Boostani, Afrasiabi, & Sadatnezhad, 2013).

Enhanced P1 peak amplitude was reported in response to patterned onset-offset blue-yellow gratings in adolescents with ADHD relative to control participants and linked to a hypo-dopaminergic tone of the central nervous system (Kim, Banaschewski, & Tannock, 2015). Dopamine is known to regulate the glutamatergic pathway; thus, reduced dopamine neurotransmission in ADHD could lead to overproduction of glutamate and consequent E/I imbalances (Naaijen et al., 2017; Purkayastha et al., 2015). Furthermore, in this study, a significant positive association emerged between P1 peak amplitude and a parental report of inattention (i.e. Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour Scale, SWAN; Swanson et al., 2012), suggesting that neural hypersensitivity to visual stimulation may be linked to core ADHD symptoms. fMRI studies concur in suggesting that elevated activation of the visual cortex characterises adults and children with ADHD (for a review see, Cortese et al., 2012) and this atypicality may be linked to reduced levels of the neurotransmitter GABA in the same cortical region (Edden et al., 2012). Finally, atypical visual network asymmetry (i.e. elevated rightward bias) during visual processing was reported in children with ADHD and further associated with reduced default mode network (DMN) activation. These results were interpreted as suggestive of enhanced perceptual processing of task-extraneous content and reduced top-down regulation over visual processing in ADHD (Hale et al., 2014).

Overall, the reviewed evidence suggests that different neural responses to visual stimulation occur in individuals with ASD or ADHD relative to control

participants and these differences may result from atypical inhibitory function in GABA-mediated circuits. However, it remains unknown if these differences exist in early development and, if so, whether they associate with traits of ASD or ADHD emerging in childhood. Investigating the neural markers of visual sensory processing in ASD and/or ADHD through a developmental lens is essential to tease apart core atypicalities from later compensatory or compounding manifestations that may result from atypical interaction with the environment.

4.1.2. The role of attention and regulation

Visual hypersensitivity is commonly reported in individuals with ASD and/or ADHD. However, as reviewed in Chapter 1, cortical responses to visual input are not simply driven by feedforward signals. Indeed, typical visual perception results from the integration between feedforward and feedback signals (Felleman & Van Essen, 1991; Gilbert & Li, 2013; Shipp, 2016; Shipp et al., 2013; Spratling & Johnson, 2004). It follows that characterising the mechanisms underlying visual hypersensitivity in individuals with ASD and/or ADHD requires assessing the contribution of attention and regulation (i.e. top-down modulatory capacity) on the processing of incoming visual stimulation.

Evidence from research with neurotypical populations indicates that top-down contributions can bias the processing of incoming visual stimulation from 3 months of age through adulthood (Gazzaley & Nobre, 2012; Gilbert & Li, 2013; Lunghi, Piccardi, Richards, & Simion, 2019; Lunghi, Di Giorgio, Benavides-

Varela, & Simion, 2020; Rauss, Schwartz, & Pourtois, 2011; Richards, 2000). At the same time, growing evidence from studies with ASD and/or ADHD individuals indicates that atypicalities in attention and regulation are widespread in these conditions and their contribution to atypical sensory perception is crucial (Green & Wood, 2019). For example, Green and collaborators (2015) demonstrated that typical responsiveness to incoming sensory stimulation manifests in a sub-group of adolescents with ASD concurrently displaying enhanced functional connectivity from the prefrontal cortex to sensory regions. This evidence suggests that the capacity to modulate responsiveness to incoming sensory stimulation can exercise a protective function and mitigate the otherwise observed sensory hypersensitivity in individuals with ASD. Rather than being a characteristic present only in adults with ASD, it is possible that a similar protective function of regulation may exist early in development. In this light, the current chapter will not solely focus on assessing potential atypicalities in sensitivity to feedforward visual input in infants at elevated likelihood of ASD and/or ADHD relative to infants at typical likelihood of the disorders but will also assess potential alterations in the contribution that feedback signals have on the processing of incoming visual stimulation.

4.1.3. The role of visual sensory seeking

Atypical responses to sensory stimulation are documented in the early development of ASD or ADHD but putative mechanisms linking these atypicalities to later traits remain explored. In the visual modality, early atypical responsiveness has been

proposed to exacerbate later ASD symptomatology by triggering compensatory strategies aimed at minimising or overly selecting visual input (Gliga et al., 2014; Thye et al., 2018).

As reviewed in Chapter 2, decreased sensory seeking is often reported in infants with later ASD (Ben-Sasson et al., 2009; Mulligan & White, 2012; Thye et al., 2018) and some have proposed that it may mediate the impact of early sensory atypicality on later ASD traits (Thye et al., 2018; Zentall & Zentall, 1983). Decreased visual sensory seeking could represent a strategy to minimize visual input (which may be experienced as distressing in the presence of visual hypersensitivity; Johnson et al., 2015; Mulligan & White, 2012). However, reduced sensory seeking has not always been found to associate with elevated sensory responsiveness (Ben-Sasson et al., 2009). Thus, rather than a mediator, sensory seeking could represent an independent but compounding factor in ASD (Mulligan & White, 2012). In line with this prediction, evidence from Chapter 3 demonstrated a moderating role of sensory seeking in the tactile modality, with elevated tactile sensory seeking mitigating the association between early elevated sensory responsiveness and later ASD traits. It is possible that also in the visual modality sensory seeking may act as a compounding factor, moderating the potential association between early atypical visual responsiveness and later ASD traits. Under this scenario, elevated visual sensory seeking may exercise a protective function during development by offering opportunities to develop social skills and share communication.

4.2. The current study

4.2.1. Main analytical pipeline

The goal of the current study was to investigate neural markers of visual sensory processing in 10-month-old infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the disorders, prospectively re-assessed at 24 months. A visual task presenting a continuous video clip intermixed with black-and-white static checkerboards flashed on top was used and coupled with the recording of EEG. At both 10 and 24 months, I quantified neural markers of sensitivity to incoming visual stimulation by extracting the peak amplitude and latency of the P1 component time-locked to the onset of the checkerboard. I quantified neural markers of engagement with the ongoing video clip by extracting the amplitude of EEG oscillations in the theta range (4-6Hz). As reviewed in Chapter 2, the frontal theta rhythm is believed to reflect prefrontal-hippocampal information processing loops and it is involved in mediating the executive (top-down) control of attention (Bazhenova, Stroganova, Doussard-Roosevelt, Posikera, & Porges, 2007; Meyer, Endedijk, van Ede, & Hunnius, 2019; Orekhova, Stroganova, & Posikera, 1999; Stroganova, Orekhova, & Posikera, 1998), in mediating information encoding (Begus, Gliga, & Southgate, 2016; Begus, Southgate, & Gliga, 2015; Orekhova, Stroganova, Posikera, & Elam, 2006) and in supporting learning and memory (Begus et al., 2015; Köster et al., 2019) from infancy. Thus, early differences in the top-down control of attention and in

participants' engagement with the ongoing video stimulation should be reflected by differences in theta synchronization over the frontal cortex.

Based on previous work on visual processing in ASD and ADHD, I predicted observing an effect of the ASD and ADHD likelihood status on neural markers of sensitivity to incoming visual stimulation, manifesting as elevated P1 peak amplitude time-locked to checkerboard onset. I further predicted observing an effect of the ASD and ADHD likelihood status on neural markers of engagement with the ongoing video stimulus, manifesting as reduced theta amplitude during video viewing. In line with Predictive Coding theories reviewed in Chapter 1, which explain sensory atypicalities in ASD and ADHD as resulting from limited integration between feedforward and feedback signals, I also predicted elevated P1 peak amplitude in the early development of ASD and ADHD to result from reduced modulation of responsiveness to incoming visual stimulation as a function of engagement with the ongoing video stimulus.

I assessed the longitudinal associations between early neural markers of visual sensory processing and later ASD traits (i.e. quantified through the ADOS-2 CSS at 24 months; Lord et al., 2012) or ADHD traits (i.e. quantified through the ECBQ activity and inhibitory control sub-scales at 24 months; Putnam et al., 2006). As reviewed in Chapter 2, previous research indicates that these measures act as early predictors of later symptoms of ASD and ADHD, respectively (Gotham et al., 2012b; Shephard et al., 2018). Therefore, I designated ADOS-2 CSS and ECBQ activity and inhibitory control as 24-month outcome measures in the current study.

I hypothesized that reduced ability to modulate responsiveness to incoming visual stimulation at 10 months would predict both ASD and ADHD traits in toddlerhood.

Further, I assessed the role of visual sensory seeking (i.e. quantified through the parent-reported ITSP at 10 months; Dunn, 2002) as a potential mediator or moderator of the association between early visual atypicality and later ASD traits.

Finally, drawing on Predictive coding theories, which assume the integration between feedback and feedforward signals to underlie efficient learning, I further planned to assess whether infants manifesting lower capacity to modulate their responsiveness to incoming visual stimulation based on engagement with ongoing information in the EEG task also displayed lower concurrent and/or longitudinal learning scores (i.e. quantified through the Mullen Scales of Early Learning; Mullen, 1995).

4.2.2. Follow-up and secondary analyses

In addition to the core analyses, I planned to conduct a series of follow-up and secondary analyses. Firstly, there is currently no research assessing the longitudinal stability of neural markers of visual sensory processing in the early development of ASD and/or ADHD. Therefore, I planned to assess the longitudinal associations between the same neural markers quantified at 10 and 24 months.

Secondly, mixed results have emerged from studies examining the concordance between parent report and clinician observation of ASD or ADHD

traits in early development (Evers et al., 2020; Macari et al., 2018; Nobel et al., 2019). Further, I have documented low concordance between Q-CHAT and ADOS-2 in Chapter 3. Thus, also in the current chapter, I planned to ascertain significant associations between neural markers of visual sensory processing and ASD traits quantified through clinician observation (i.e. ADOS-2 CSS at 24 months; Lord et al., 2012) by assessing the potential associations between the same experimental measures and a parental report of ASD traits (i.e. Q-CHAT at 24 months; Allison et al., 2008).

Fourthly, while I explored the mediating or moderating role of visual sensory seeking in the main analyses, I further planned to investigate whether visual sensory avoiding (i.e. quantified through the parent-reported ITSP at 10 months; Dunn, 2002), which could be conceived as opposite to visual sensory seeking and could better capture compensatory manifestations in infancy, would act as a factor mediating or moderating the potential association between early visual atypicality and later ASD traits.

Finally, while I assessed the mediating or moderating role of visual sensory seeking in the main analyses, I also planned to ascertain whether any concurrent and/or longitudinal associations manifested between neural markers of visual sensory processing at 10 months and parent-reported visual sensory seeking at 10 and 24 months.

4.3. Methods

4.3.1. Recruitment approach

I direct the reader to Chapter 2, sections 2.8.1 ("Recruitment strategy") and 2.8.2 ("Clinical assessment") for a description of the recruitment approach adopted and the clinical assessment procedures used to designate the diagnostic status of each participant involved in the study. All infants recruited for the research were born full-term (gestational age 38-42 weeks). At the time of enrolment, none of the infants had a known medical or developmental condition. Informed written consent was provided by the parent(s) prior to the commencement of the study. Infants were tested if awake and in an alert state. The experimental protocol was approved by the National Research Ethics Service, the Research Ethics Committee of the Department of Psychological Sciences, Birkbeck University of London, and the Research Ethics Committee of the Institute of Psychiatry, Psychology and Neuroscience, King's College London. Families were reimbursed expenses for travel, subsistence and overnight stay if required. Families were given a certificate and t-shirt after each visit.

4.3.2. Participants

One hundred and fifty-two 10-month-old infants participated in the study: 79 EL-ASD infants, 27 EL-ADHD infants, 21 EL-ASD+ADHD infants and 25 TL infants, with no family history of the disorders. Of these, 58 infants were tested but not included in the final sample because of low tolerance of the EEG net (n=8),

fussiness/excessive movement artefacts (n=34) and equipment failure (n=16). Accordingly, EEG data was contributed by 94 infants: 46 EL-ASD infants, 20 EL-ADHD infants, 9 EL-ASD+ADHD infants and 19 TL infants. Descriptive statistics for the sample are reported in Table 9. There was no significant effect of likelihood status on participants' attrition rate, $\chi^2(3) = 4.06$, $p = .255$.

Participants were contacted to participate to the follow-up visit at 24 months. One hundred and thirty 24-month-old toddlers participated to the study: 66 EL-ASD toddlers, 22 EL-ADHD toddlers, 17 EL-ASD+ADHD toddlers and 25 TL toddlers. 48 toddlers were tested but not included in the final sample because of low tolerance of the EEG net (n=20), fussiness/excessive movement artifacts (n=17) and equipment failure (n=11). Accordingly, data was contributed by 82 toddlers: 42 EL-ASD toddlers, 12 EL-ADHD toddlers, 9 EL-ASD+ADHD toddlers and 19 TL toddlers. Descriptive statistics for the sample are reported in Table 9. There was no significant effect of likelihood status on participants' attrition rate, $\chi^2(3) = 2.71$, $p = .438$.

At both visits, the minimum number of required participants was determined by a power analysis (conducted with the software *Gpower;* Erdfelder, Faul, Buchner, & Lang, 2009). According to Cohen (1988) and Sawilowsky (2009) a medium effect size in psychological studies is $f^2 = 0.15$ and, considering an estimate power of 0.80, a total sample size of 90 participants was estimated to detect main effects of ASD and/or ADHD at an alpha-level of 0.05; a total sample of 43

participants was estimated to detect hierarchical linear regression effects at an alpha-level of 0.05.

4.3.3. Stimuli

Experimental stimuli consisted of a background dynamic video clip selected from the animated cartoon *Fantasia* by Walt Disney and a black-and-white static checkerboard. The clip was presented in the centre of the screen (covering a 22.5 cm wide x 12.5 cm vertical area, subtending a visual angle of 21^o x 12^o) and depicted dynamic, continuous, goal-directed actions, accompanied by music. The black-and-white static checkerboard was presented for 100ms, in the centre of the screen (covering a 30 cm wide x 30 cm vertical area, subtending a visual angle of 28^o x 28^o). The average luminance of the checkerboard was 1.56 cd/m^2 for the black patch and 228 cd/m^2 for the white patch. The checkerboard replaced the video clip which resumed following disappearance of the checkerboard from the interruption point.

As shown in Figure 4.1A, each trial began with the presentation of the video clip accompanied by music. Music was used throughout the task to promote participants' engagement with the visual scene. Further, visual and auditory stimuli remained synchronous throughout the task. The continuous clip was intermixed with presentation of black-and-white static checkerboards flashed on top (10-month assessment: 128 checkerboards; 24-month assessment: 152 checkerboards; ISI=2-4s, random). The time-points (within the background video) when this stimulus was presented were the same for all infants and were not predictable for any individual

infant. A photodiode connected to an oscilloscope was used to measure the onset of checkerboards. Music was not paused during checkerboard presentation since this stimulus lasted only 100ms. The maximum experimental session duration was 8 minutes for the 10-month assessment and 10 minutes for the 24-month assessment but the experimenter could interrupt the session earlier, in case of participants' fussiness, prolonged inattention or if requested by the parent.

4.3.4. Apparatus and procedure

Testing took place in a dimly illuminated room. Infants were seated on a parent's lap, 60cm from a screen (27 inches; width: 59.77cm, height: 33.62cm) and were allowed to use a pacifier. The sequence and timing of stimulus presentation was controlled using MATLAB. High-density EEG was collected using 124 channels of a 128-channel HydroCel Geodesic Sensor Net connected to a NetAmps 400 amplifier (Electrical Geodesic, Eugene, OR) and referenced on-line to the vertex (Cz). Signals were sampled at 500 Hz. A video camera situated below the screen used for stimulus presentation recorded the infants' bodily and facial behaviour. This information was used for online monitoring of infants' performance and offline behavioural coding.

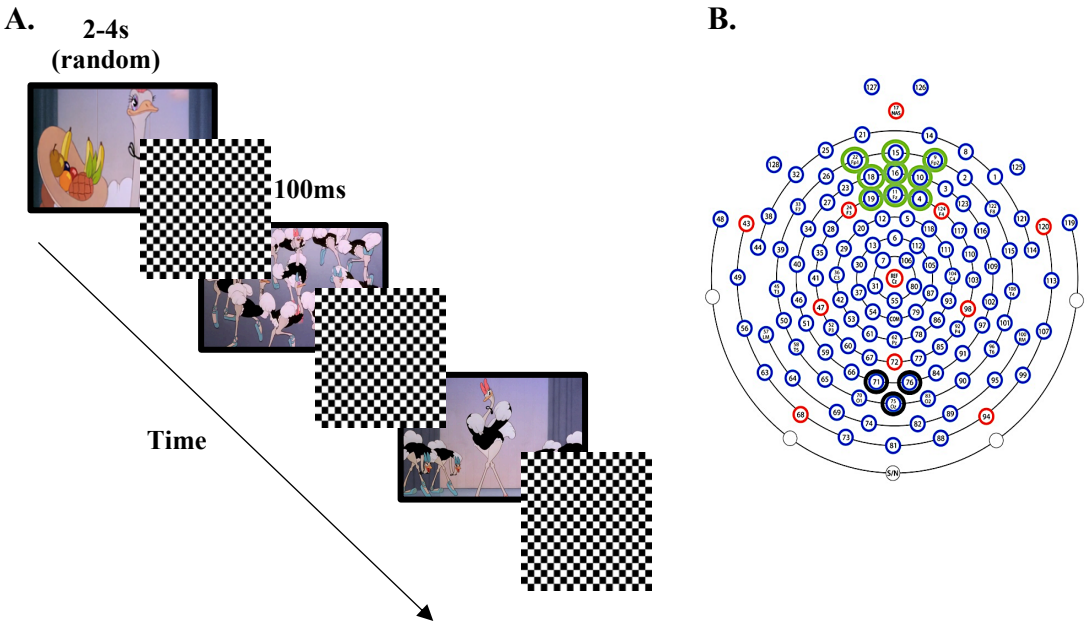

Figure 4.1. Schematic representation of the experimental stimuli, apparatus and procedure

A. Representation of the sequence of events in the experimental paradigm. A continuous video clip from the animated cartoon "Fantasia" was presented accompanied by music and randomly interrupted by the appearance of black-and-white static checkerboards (100ms) flashed on top (ISI = 2-4s, random). B. Hydrocel-Geodesic Sensor Net montage displaying the occipital (black circle) and frontal (green circle) pool of electrodes used for quantifying, respectively, visual evoked potentials (VEPs) time-locked to checkerboard onset and theta amplitude synchronization (θ = 4-6Hz) during video presentation.

4.3.5. Behavioural assessment scales

The Mullen Scales of Early Learning (Mullen, 1995) were administered at the 10 and 24-month visits in the standardised format. 10-month Mullen data was collected for 93 out of 94 infants contributing to the EEG analyses. 10-month ITSP was returned for 82 out 94 participants contributing to the EEG analyses. At 24 months, 12 participants dropped-out from the longitudinal study. Thus, at this visit, Mullen and ADOS-2 assessments were performed for 81 participants. 24-month Q-CHAT was returned for 76 participants contributing EEG data at 10 months and 73 participants contributing EEG data at 24 months. 24-month ECBQ was returned for 75 participants contributing EEG data at 10 months and 72 participants contributing EEG data at 24 months. Detailed characterisation of each measure for participants contributing to the EEG analyses at 10 and 24 months is reported in Table 9. Full characterisation is reported in Table 10A (see Appendix to Chapter 4).

Table 9. *Detailed characterisation of behavioural measures at the 10 and 24-month assessments for EL-ASD, EL-ADHD, EL-ASD+ADHD and TL participants who contributed to the EEG analyses.*

	EL-ASD	EL-ADHD	EL-ASD+ADHD	TL	*p values*
10-month visit					
Age in days	316.42 (14.47)	327.40 (30.30)	320.67 (18.40)	320.89 (17.90)	.240 (ns)
MSEL ELC	88.27 (15.04)	85.04 (15.61)	85.50 (16.95)	88.89 (12.19)	.685 (ns)
MSEL GM	38.45 (9.59)	39.00 (10.22)	35.75 (10.18)	34.89 (11.77)	.166 (ns)
MSEL FM	50.61 (11.31)	51.92 (13.96)	49.60 (12.42)	51.63 (12.89)	.865 (ns)
MSEL VR	49.91 (9.42)	47.04 (9.80)	48.25 (7.73)	48.85 (7.99)	.403 (ns)
MSEL RL	38.03 (10.59)	35.04 (10.22)	35.35 (10.92)	39.26 (8.96)	.362 (ns)
MSEL EL	36.67 (12.84)	34.38 (12.10)	36.05 (15.33)	38.85 (9.89)	.675 (ns)
N (% boys)	46 (52.2)	20 (45)	9 (55.6)	19 (47.4)	
ITSP Visual Seeking	2.58 (0.80)$_a$	1.92 (0.50)	2.28 (0.91)	1.96 (0.50)	.003*
	EL-ASD	EL-ADHD	EL-ASD+ADHD	TL	*p values*
24-month visit					
Age in days	771.65 (45.45)	761.17 (28.33)	750.22 (10.81)	759.21 (31.58)	.370 (ns)
MSEL ELC	101.70 (20.26)	119.08 (16.69)	103.44 (19.44)	112.74 (19.16)	.028*
MSEL GM	N/A	N/A	N/A	N/A	
MSEL FM	50.78 (9.73)	56.92 (11.07)	53.33 (12.92)	53.42 (12.53)	.375 (ns)
MSEL VR	49.05 (13.34)$_a$	63.83 (9.99)	53.55 (10.34)	60.10 (11.64)	.001**
MSEL RL	50.65 (14.97)	59.08 (13.57)	53.33 (9.15)	57.47 (9.03)	.130 (ns)
MSEL EL	51.63 (15.33)	58.50 (8.83)	46.89 (13.95)	54.74 (13.24)	.242 (ns)
N (% boys)	42 (45)	12 (50)	9 (66.7)	19 (57.9)	
ADOS-2 CSS	3.09 (2.38)	2.45 (1.86)	4.00 (2.74)	1.73 (0.73)	.034*
Q-CHAT	23.29 (10.76)	25.79 (7.43)	28.51 (16.96)	21.16 (3.75)	.177 (ns)
ECBQ Inhibitory Control	3.70 (1.25)	3.92 (0.85)	2.97 (1.32)	4.24 (0.89)	.105 (ns)
ECBQ Activity	4.66 (0.83)	4.92 (1.06)	5.28 (1.11)	4.80 (0.76)	.304 (ns)
ITSP Visual Seeking	3.07(0.83)	2.72 (0.68)	2.78 (0.70)	2.95 (0.88)	.551 (ns)

* $p < .05$; ** $p \leq .001$; $_a$ indicates significant differences with the TL group

M (*SD*) reported for: Age in days; MSEL ELC = Mullen Scales for Early Learning Early Composite Score; MSEL GM = Mullen Scales for Early Learning Gross Motor Score; MSEL FM = Mullen Scales for Early Learning Fine Motor Score; MSEL VR = Mullen Scales for Early Learning Visual reception Score; MSEL RL = Mullen Scales for Early Learning Receptive Language Score; MSEL EL = Mullen Scales for Early Learning Expressive Language; ADOS-2 CSS = ADOS-2 Calibrated Severity Scores; Q-CHAT = Quantitative Checklist for Autism in Toddlers; ECBQ Inhibitory Control = Inhibitory Control subscale of the Early Childhood

Behaviour Questionnaire. ECBQ Activity = Activity subscale of the Early Childhood Behaviour Questionnaire; ITSP Visual Seeking = Visual sensory seeking average score of the Infant-Toddler Sensory Profile.

4.3.6. Infants' gaze behaviour coding

Infants and toddlers' gaze behaviour was coded offline with a computerized frame-by-frame observational coding system (25 frames/second – EGI Movie Player, Electrical Geodesic), enabling two independent coders to identify screen-directed looking (coded as 1) and looking away (coded as 0). In accordance with the processing pipeline reported in Chapter 2, offline coding was used for the purpose of EEG data processing and analysis. Trials in which the participant did not look at the screen from 1s before checkerboard onset until 1s after checkerboard offset were excluded from the analysis. To ascertain reliability, the second observer independently coded a random 30% of video files (i.e., 28 infants for the 10-month visit; 25 toddlers for the 24-month visit). An interrater reliability analysis using Cohen's Kappa was performed on the coded individual trials to determine consistency among observers. This analysis indicated that there was high agreement among the observers for the 10-month visit, κ=.991, (95% CI, .986 to .996), $p <$ .001; for the 24-month visit, κ=.990, (95% CI, .985 to .995), $p <$ .001.

4.3.7. EEG recording and analysis

The EEG data was processed offline using Net Station (Electrical Geodesic) following the processing pipeline reported in Chapter 2. Specifically, the continuous EEG was filtered using a 0.3–40 Hz band-pass filter. The EEG signal

was segmented from 500ms prior to checkerboard onset through 1500ms after checkerboard onset. Automated artifact detection was applied to the segmented data to detect individual epochs that showed >200μV voltage changes within the segment period. EEG recordings were visually inspected and individual channels within segments were eliminated from the analysis if artifacts occurred. Segments whereby infants did not look at the screen as indicated by behavioural coding were further excluded from analysis. Segments in which >15% of the channels (18 channels) were marked as bad were excluded from the analysis. For the remaining trials, spherical spline interpolation was conducted to replace data for bad channels using the five closest electrodes. Infants were excluded from the analysis if they had less than 10 artifact-free segments (see Table 11).

Table 11. *Number of EL-ASD, EL-ADHD, EL-ASD+ADHD and TL participants included and excluded from the EEG analyses at 10 and 24 months (i.e. due to contributing less than 10 artifact free trials) and number of trials presented and retained for included participants for each group at both visits.*

10-month visit					
Participants (n)	EL-ASD	EL-ADHD	EL-ASD+ADHD	TL	*p value*
Included	46	20	9	19	.058 (ns)
Excluded	20	4	6	4	.255 (ns)
Trials (n)					
Presented	77	85	84	84	.735 (ns)
Retained	38	35	35	43	.703 (ns)
24-month visit					
Participants (n)	EL-ASD	EL-ADHD	EL-ASD+ADHD	TL	*p value*
Included	42	12	9	19	.356 (ns)
Excluded	8	5	2	2	.438 (ns)
Trials (n)					
Presented	141	146	127	146	.347 (ns)
Retained	96	119	91	104	.293 (ns)

4.3.8. Quantification of visual evoked potentials (VEPs)

To quantify VEPs time-locked to checkerboard onset at 10 and 24 months, averaged waveforms were generated for each participant, re-referenced to average reference and baseline corrected by subtracting the average of the 100 ms pre-stimulus period. Inspection of the grand-averaged waveform indicated that the P1 component was reliably elicited at checkerboard onset over the occipital scalp site (see Figure A4.2.2 in Appendix to Chapter 4). Based on previous literature (Lunghi et al., 2019; Richards, 2000) and on visual inspection of both the grand-averaged and individual waveforms, channels (CH) 71, 75 and 76 (see Figure 4.1B) were clustered and the average activity over these channels was computed for each participant. Based on

the individual and grand-averaged data, as well as on previous literature (Lunghi et al., 2019; Richards, 2000), the peak amplitude and latency of the P1 were extracted following the procedures described in Chapter 2 within a time window of 50-250ms after the onset of the checkerboard (see Figures 4.2A and 4.2B).

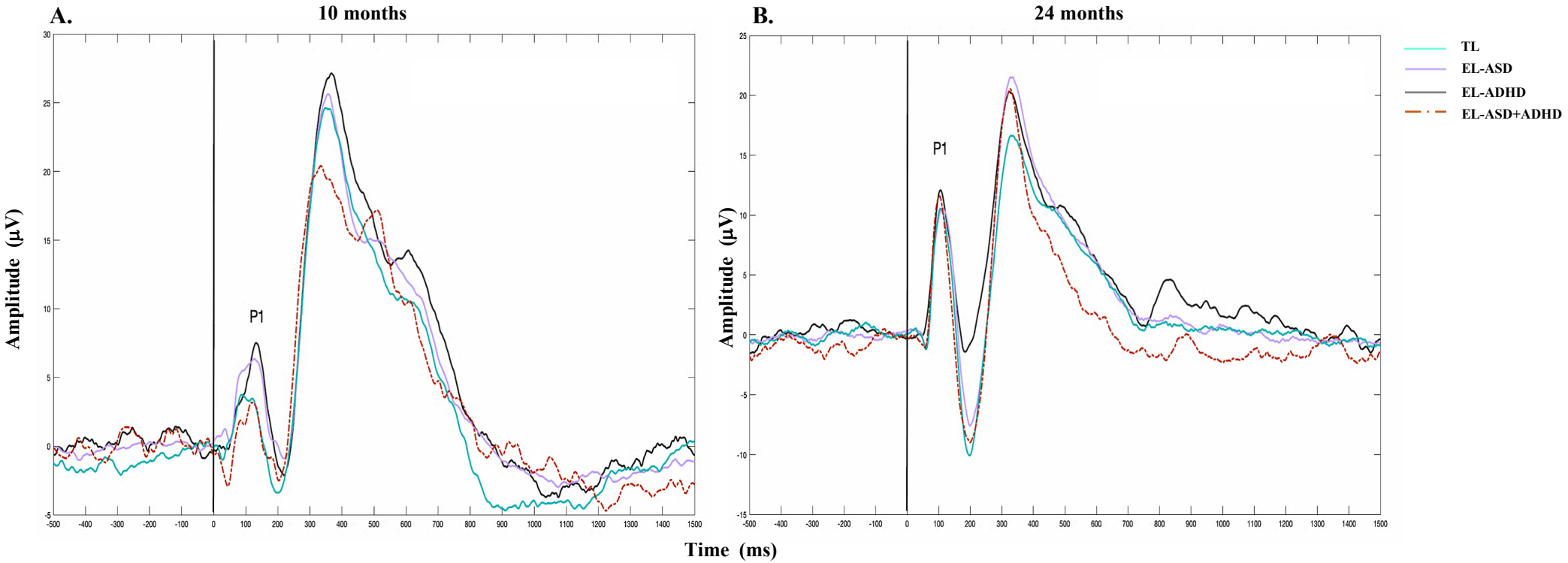

Figure 4.2. Grand-averaged visual evoked potentials (VEPs) time-locked to checkerboard onset for each participant group

A. VEPs at 10 months; B. VEPs at 24 months; *(Green =participants at typical likelihood of ASD or ADHD; Violet=participants at elevated likelihood of ASD; Grey=participants at elevated likelihood of ADHD; Orange= participants at elevated likelihood of ASD and ADHD).*

4.3.9. Time-frequency analysis of EEG

Time-frequency decomposition was used to quantify oscillatory theta synchronization (4-6Hz) during video clip presentation. Artifact-free segments were imported into MATLAB using EEGLAB (v. 13.4.3b) and re-referenced to the average reference. The collection of scripts *WTools* (see Parise & Csibra, 2013; available upon request) was used for spectral decomposition, employing Complex Morlet wavelets for the frequencies 3-20Hz (1Hz resolution; real-valued Gaussian with n = 3.5 cycles per time unit). A continuous wavelet transformation of all segments by means of convolution with each wavelet was performed and the absolute value of the results was extracted. To remove the distortion introduced by convolution at segment ends, 1000ms zero-padding was performed. The amplitude of the 100ms interval prior to the window of interest was used as a baseline and subtracted from the whole epoch at each frequency. Segments were chopped to obtain epochs indexing the activity occurring during a 400ms-long period of video clip presentation before checkerboard onset. Individual epochs were averaged for each participant. Inspection of the time-frequency plots revealed that 4-6Hz frontal theta synchronization was reliably elicited in response to the video clip over the frontal scalp site. As reviewed in Chapter 2, substantial evidence indicates that phases of information encoding are accompanied by a sharp increase in 4-6Hz frontal theta in developing populations (Begus et al., 2015; Orekhova et al., 2006). Based on previous literature and on visual inspection of both the grand-averaged and individual time-frequency plots, channels (CH) 4, 9, 10, 11, 15, 16, 18, 19, 22

(see Figure 4.1B) were clustered and the average 4-6Hz amplitude was extracted during the 400ms of video clip presentation occurring before the onset of the checkerboard for each participant, see Figures 4.3A and 4.3B.

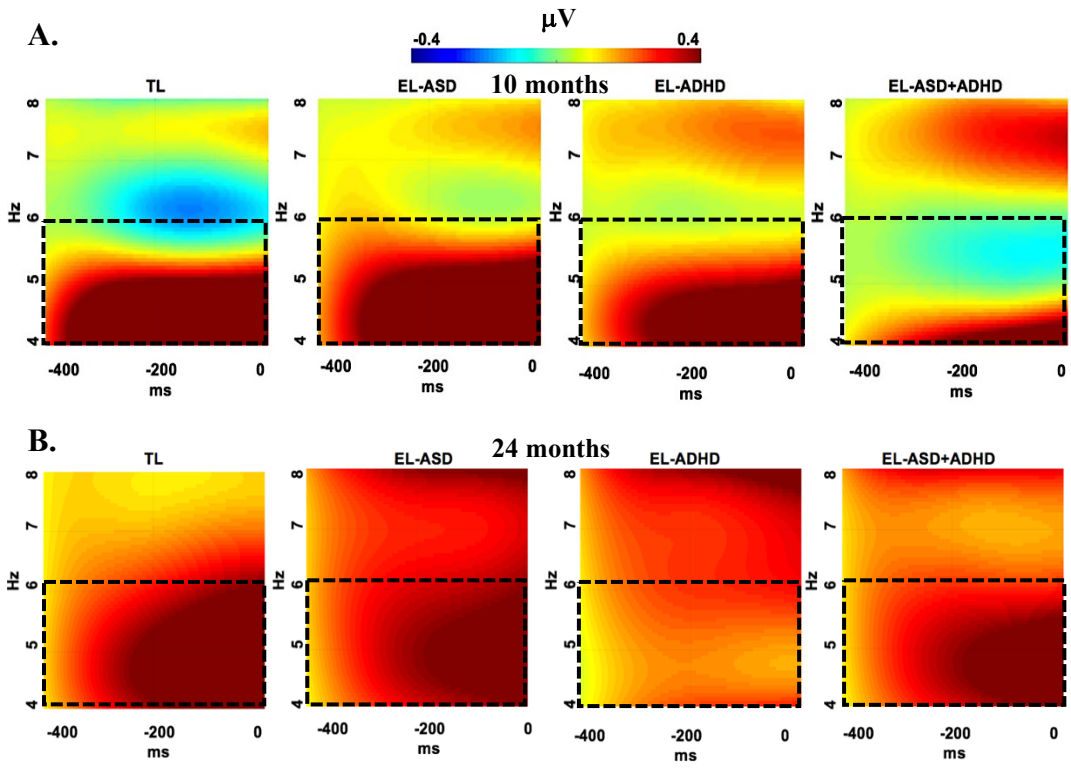

Figure 4.3. Time-frequency plots illustrating the amplitude of theta (θ = 4-6Hz) oscillations during video clip presentation

A. Time-frequency plots at 10 months; B. Time-frequency plots at 24 months. (TL=participants at typical likelihood of ASD or ADHD; EL-ASD=participants at elevated likelihood of ASD; EL-ADHD=participants at elevated likelihood of ADHD; EL-ASD+ADHD=participants at elevated likelihood of ASD and ADHD). Black dotted rectangles indicate the 400ms long time-windows during video clip presentation selected for statistical analysis. Amplitude scale is -0.4, 0.4μV.

4.3.10. Analytical strategy

Statistical analyses were conducted with SPSS v23 (IBM Corp 2015). Likelihood status was dummy coded and a factorial approach was used to test for the main effect of ASD, ADHD and the interaction between these factors on EEG markers of visual processing. The likelihood factor was computed as follows: EL-ASD infants were assigned a '1' for ASD likelihood and a '0' for ADHD likelihood (1 0), EL-ADHD infants were assigned a '0' for ASD likelihood and a '1' for ADHD likelihood (0 1), EL-ASD+ADHD infants were assigned a '1' for ASD likelihood and a '1' for ADHD likelihood (1 1), and TL infants were assigned a '0' for ASD likelihood and a '0' for ADHD likelihood (0 0). An explanation of the rationale behind the choice of this statistical approach and the inclusion of the likelihood factor in all the statistical analyses is provided in Chapter 3 (section 3.3.9). For tables and figures, infants were split into four groups: EL-ASD, EL-ADHD, EL-ASD+ADHD and TL.

As described in Chapter 2 and 3, it remains likely that within families with ASD, rates of actual ADHD were higher than those captured by the current 1/0 diagnostically-based rating system. Thus, families where there was significant diagnostic uncertainty about the presence of either ASD or ADHD were removed in a sensitivity analysis to check whether results differed substantially. Results of this sensitivity analysis are reported in the Appendix (and replicated those reported in the present chapter).

Prior to performing any inferential statistical analyses, I assessed the variables for normality. Where significant violations of normality existed, I normally transformed the data (i.e. details on normality violations and transformations are reported in the results section).

First, I assessed the effect of likelihood status on neural markers of visual sensory processing at 10 and 24 months. I ran separate univariate ANOVAs with P1 peak amplitude, P1 peak latency and frontal theta oscillatory amplitude as dependent variables, respectively.

In light of the results emerged from the above analyses, I proceeded with investigating the moderating effect of likelihood status on the intra-participant modulation of the P1 peak amplitude by ongoing theta amplitude at 10 months. First, to estimate a measure of intra-participant modulation of the P1 peak amplitude by ongoing theta amplitude, I binned the artifact-free data into three groups based on theta amplitude tertiles (i.e. high, average and low theta amplitude). Thus, the P1 peak amplitude was averaged across trials corresponding to the high, average and low theta amplitude bins. I adopted a Generalized Estimated Equation (GEE) approach assuming a Gaussian distribution and identity link with binned P1 peak amplitude (continuous) as dependent variable and tertile bin (categorical: bin 1=high theta; bin 2=average theta; bin 3=low theta) as a factor, alongside the likelihood factors. This approach was chosen to account for within-subject correlations (i.e. correlations across tertile bins in the P1 peak amplitude

within each infant). I computed Wald tests to determine the significance of the effects.

To characterise the continuous dependence between theta and P1 and further quantify differences in infants' ability to modulate responsiveness to incoming visual stimulation as a function of engagement with the ongoing continuous video clip, the scaled difference in frontal theta amplitude and in the peak amplitude of the P1, respectively, were computed between bin 1 (high theta amplitude tertile) and bin 3 (low theta amplitude tertile) for each 10-month-old infant (i.e. theta modulation index: [theta bin 1 – theta bin 3] / [theta bin 1 + theta bin 3]; P1 modulation index: [P1 bin 1 – P1 bin 3] / [P1 bin 1 + P1 bin 3]). I then assessed the moderating effect of the likelihood factors on the association between P1 modulation index and theta modulation index with a hierarchical linear regression.

Thirdly, I examined the longitudinal and concurrent associations between neural markers of visual sensory processing at 10 and 24 months and ASD or ADHD traits at 24 months with a set of hierarchical linear regressions for normally distributed outcome variables; with a set of Spearman correlations for non-normally distributed outcome variables. In the presence of significant associations between predictor and one outcome variable, I further assessed the potential moderating effect of the likelihood factors on these associations.

Fourthly, I planned to investigate the role of visual sensory seeking as a mediator or moderator of the potential association between neural makers of visual

atypicality and ASD traits. I conducted the mediation and moderation analyses using PROCESS macro in SPSS (Hayes, 2017).

Finally, I investigated the concurrent and longitudinal associations between infants' ability to modulate responsiveness to incoming visual stimulation during the EEG task (as indexed by the P1 modulation index) and both concurrent or longitudinal learning scores on the Mullen though a set of Pearson correlations.

4.4. Results

4.4.1. Neural markers

P1 peak amplitude. At 10 months, the P1 peak amplitude significantly violated normality assumption (Shapiro-Wilk, $p < .001$; Skewness = 1.289, SE = .249; Kurtosis = 1.350, SE = .493) and was normally transformed with the Two-Step approach (Templeton, 2011; see Appendix for details on this approach). There was a significant main effect of ASD likelihood status, $F(1,90) = 4.19$, $p = .044$, $\eta^2 = .044$, and ADHD likelihood status, $F(1,90) = 5.18$, $p = .025$, $\eta^2 = .054$, indicating enhanced P1 peak amplitude in response to incoming visual stimulation in infants with an elevated likelihood of ASD or ADHD relative to infants at typical likelihood of the conditions. There was no significant interaction between ASD and ADHD likelihood status, $F(1,90) = 2.19$, $p = .142$, $\eta^2 = .024$. See Figure 4.4A and Table 12.

At 24 months, there was no significant main effect of ASD likelihood status, $F(1,78) = .190$, $p = .664$, $\eta^2 = .002$, or ADHD likelihood status, $F(1,78) =$

.319, $p = .574$, $\eta^2 = .004$. Further, there was no significant interaction between ASD and ADHD likelihood status, $F(1,78) = 1.219$, $p = .273$, $\eta^2 = .015$. See Figure 4.4B. and Table 12.

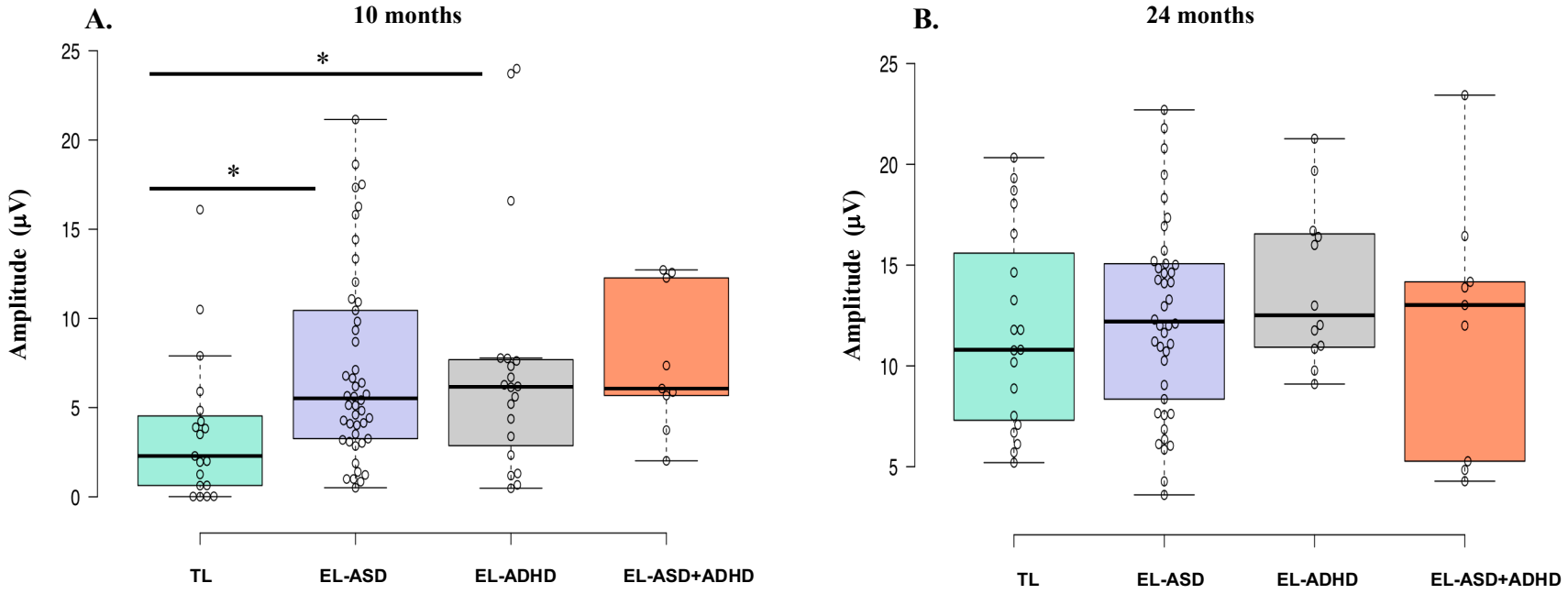

Figure 4.4. Boxplots illustrating the P1 peak amplitude for each participant group at 10 months (A) and 24 months (B)

*(Green=participants at typical likelihood of ASD or ADHD; Violet=participants at elevated likelihood of ASD; Grey=participants at elevated likelihood of ADHD; Orange=participants at elevated likelihood of ASD and ADHD). The P1 peak amplitude in response to the black-and-white checkerboard was enhanced in 10-month-old infants at elevated likelihood of ASD or ADHD relative to infants at typical likelihood of the disorders. * $p < .05$.*

P1 peak latency. At 10 months, the P1 peak latency significantly violated normality assumption (Shapiro-Wilk, p = .001; Skewness = .774, SE = .249; Kurtosis = .711, SE = .493) and was normally transformed with the Two-Step approach**.** There was no significant main effect of ASD likelihood status F(1,90) = .042, p = .837, η^2 = .000, or ADHD likelihood status, F(1,90) = 1.871, p = .175, η^2 = .020. Conversely, there was a significant interaction between ASD and ADHD likelihood, F(1,90) = 6.526, p = .012, η^2 = .068. Post-hoc pairwise comparisons with Bonferroni correction applied indicated that that the P1 peak latency was delayed in infants with an ADHD likelihood status relative to infants at typical likelihood of the conditions. See Figure 4.5A and Table 12.

At 24 months, the P1 peak latency significantly violated normality assumptions (Shapiro-Wilk, p < .001; Skewness = 1.024, SE = .266; Kurtosis = .070, SE = .526) and was normally transformed with the Two-Step approach. There was no significant main effect of ASD, F(1,78) =.007, p = .933, η^2 = .000, or ADHD likelihood status, F(1,78) =2.32, p = .132, η^2 = .029. Further, there was no significant interaction between ASD and ADHD likelihood, F(1,78) =.554, p = .459, η^2 = .007. See Figure 4.5B and Table 12.

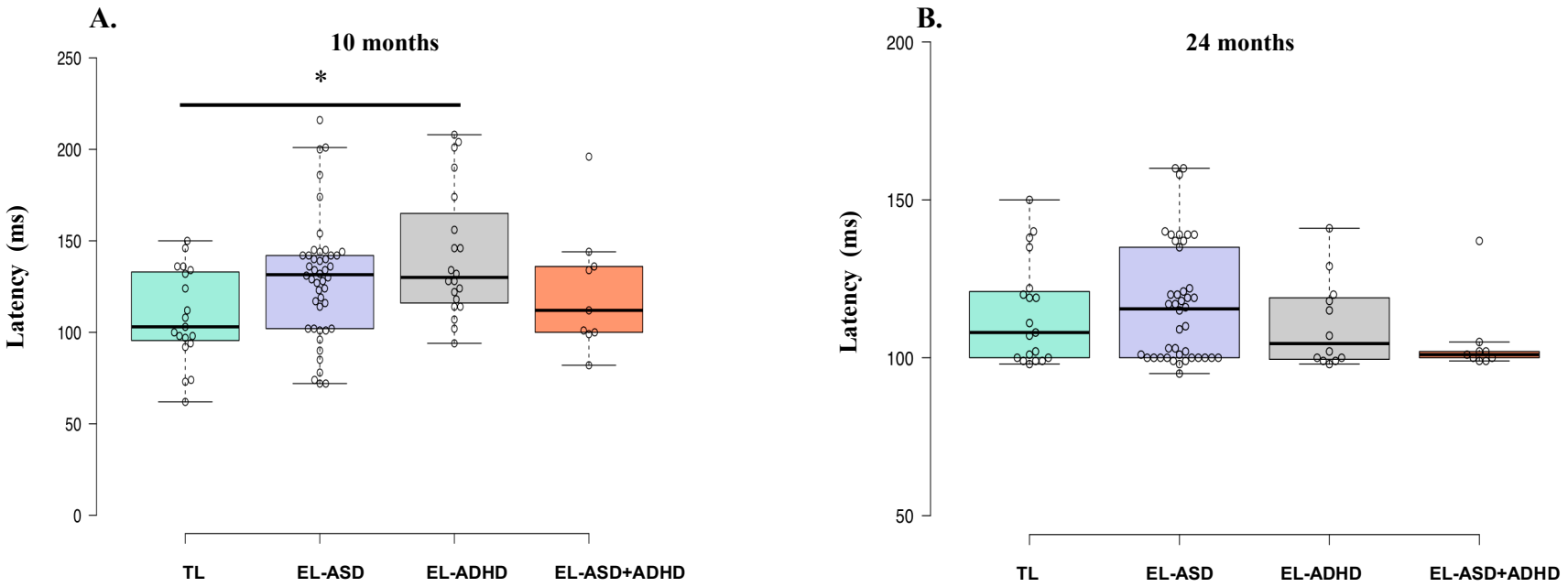

Figure 4.5. Boxplots illustrating the P1 peak latency for each participant group at 10 months (A) and 24 months (B)

*(Green=participants at typical likelihood of ASD or ADHD; Violet=participants at elevated likelihood of ASD; Grey=participants at elevated likelihood of ADHD; Orange=participants at elevated likelihood of ASD and ADHD). The P1 peak latency in response to the black-and-white checkerboard was delayed in 10-month-old infants at elevated likelihood of ADHD relative to infants at typical likelihood of the disorders. * $p < .05$.*

Theta (θ = 4-6Hz) amplitude. At 10 months, theta amplitude significantly violated normality assumptions (Shapiro-Wilk, $p < .001$; Skewness = 1.553, SE = .249; Kurtosis = 3.38, SE = .493) and was normally transformed with the Two-Step approach. The main effect of ADHD likelihood status was statistically significant, $F(1,90) = 12.25$, $p = .001$, $\eta^2 = .120$, suggesting that infants with an elevated likelihood of ADHD manifested reduced theta amplitude during video viewing, see Figure 4.6A. The main effect of ASD likelihood status failed under statistical significance, $F(1,90) = 3.80$, $p = .054$, $\eta^2 = .040$. There was no significant interaction between ASD and ADHD likelihood status, $F(1,90) = .196$, $p = .659$, $\eta^2 = .002$.

At 24 months, theta amplitude significantly violated normality assumptions (Shapiro-Wilk, $p < .001$; Skewness = 2.576, SE = .266; Kurtosis = 8.796, SE = .526) and was normally transformed with the Two-Step approach. There was no significant main effect of ASD likelihood status, $F(1,78) = .012$, $p = .911$, $\eta^2 = .000$, or ADHD likelihood status, $F(1,78) = 1.307$, $p = .256$, $\eta^2 = .016$. Further, there was no significant interaction between ASD and ADHD likelihood status, $F(1,78) = 1.018$, $p = .316$, $\eta^2 = .013$. See Figure 4.6B and Table 12.

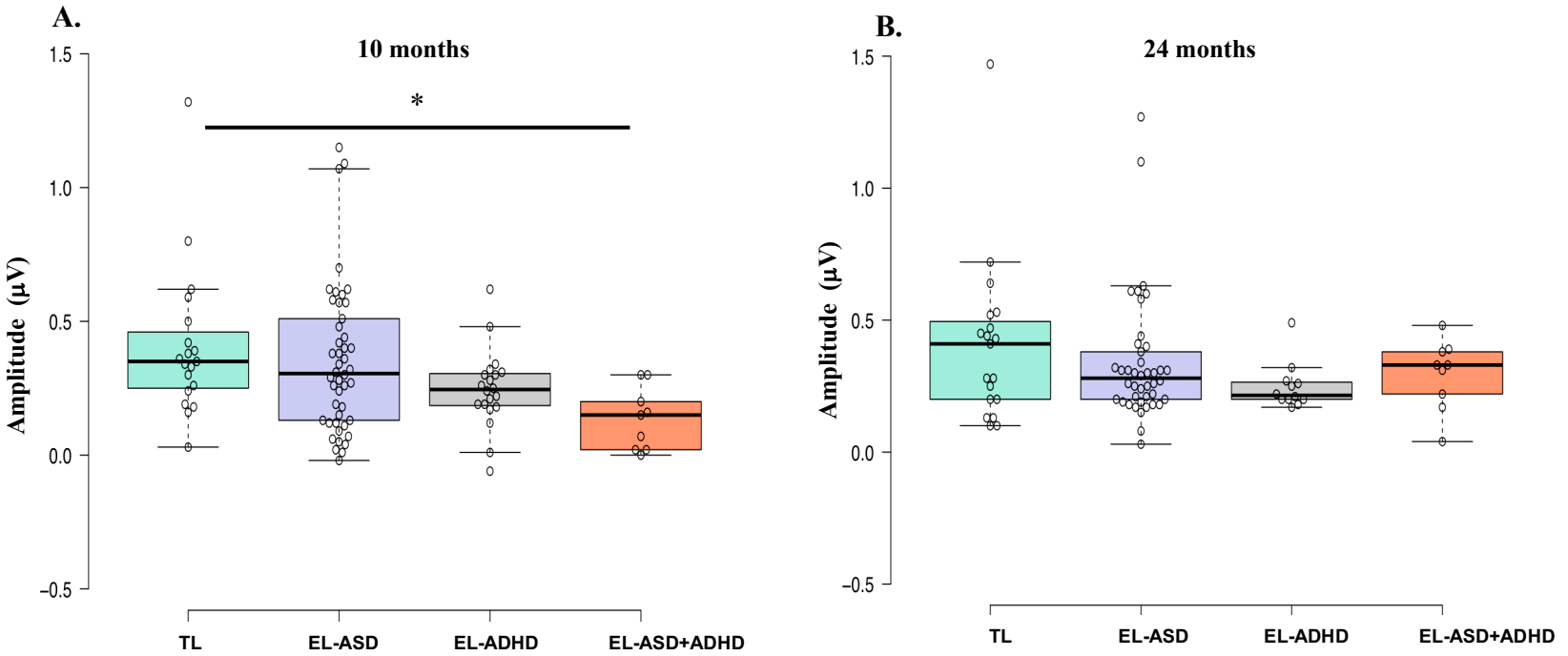

Figure 4.6. Boxplots illustrating theta amplitude (θ = 4-6Hz) for each participant group at 10 months (A) and 24 months (B) *(Green=participants at typical likelihood of ASD or ADHD; Violet=participants at elevated likelihood of ASD; Grey=participants at elevated likelihood of ADHD; Orange=participants at elevated likelihood of ASD and ADHD). At 10 months, theta amplitude during video viewing was significantly lower in infants at elevated likelihood of both ASD and ADHD relative to infants at typical likelihood of the disorders. * $p < .05$.*

Table 12. *Mean and standard error for each neural marker (P1 peak amplitude and latency time-locked to checkerboard onset and 4-6Hz theta amplitude during video viewing). Descriptive statistics are reported separately for each participant group at the 10 and 24-month visits (TL=participants at typical likelihood of ASD or ADHD; EL-ADHD=participants at elevated likelihood of ADHD; EL-ASD=participants at elevated likelihood of ASD; EL-ASD+ADHD=participants at elevated likelihood of ASD and ADHD).*

10-month visit Mean (SE)	TL	EL-ADHD	EL-ASD	EL-ASD+ADHD
P1 peak amplitude	3.66 (.95)	7.23 (1.50)	7.17 (.79)	7.58 (1.33)
P1 peak latency	108.89 (5.83)	142.10 (7.91)	131.24 (5.30)	122.67 (11.46)
Theta amplitude	0.40 (.065)	0.25 (.032)	0.35 (.041)	0.14 (.039)
24-month visit Mean (SE)	TL	EL-ADHD	EL-ASD	EL-ASD+ADHD
P1 peak amplitude	11.76 (1.14)	13.96 (1.14)	12.64 (.79)	11.93 (2.09)
P1 peak latency	114.05 (3.77)	110.66 (4.05)	116.83 (2.89)	105.00 (4.05)
Theta amplitude	0.40 (.072)	0.25 (.025)	0.34 (.037)	0.29 (.026)

4.4.2. Intra-participant modulation of the P1 peak amplitude by ongoing theta amplitude at 10 months

Results reported in section 4.4.1 indicated that, at 10 months, infants at elevated likelihood of ASD or ADHD manifested enhanced P1 peak amplitude to visual input relative to infants at typical likelihood of the conditions. To characterise the source of this difference, I investigated the effect of likelihood status on the intra-participant modulation of the P1 peak amplitude by ongoing theta amplitude with a GEE approach. I followed up this analysis by investigating the effect of the ASD and/or ADHD likelihood on the continuous association between P1 modulation index and theta modulation index computed as detailed in section 4.3.10.

P1 peak amplitude modulation as a function of theta amplitude tertiles (high, average and low theta amplitude bins). A GEE analysis revealed statistically significant interactions between tertile bin and ASD likelihood status, Waldχ^2 (2) = 9.89, p = .007; and ADHD likelihood status, Waldχ^2 (2) = 12.56, p = .002; and both ASD and ADHD likelihood, Waldχ^2(2) = 7.35, p = .025. Post-hoc within-group tests of main effects indicated that only infants at typical likelihood of the conditions manifested a significant modulation of the P1 peak amplitude by ongoing theta amplitude, Waldχ^2 (2) = 17.81, p < .001, see Figure 4.7A and 4.7B. [2]

[2] The validity of the binning strategy was also ascertained statistically by conducting a GEE analysis with tertile bin (categorical) as factor, alongside the likelihood factors, and theta amplitude (continuous) as dependent variable. This analysis confirmed that only a main effect of bin was present, Waldχ^2 (2) = 206.69, p < .001, (see Figure 4.7B)

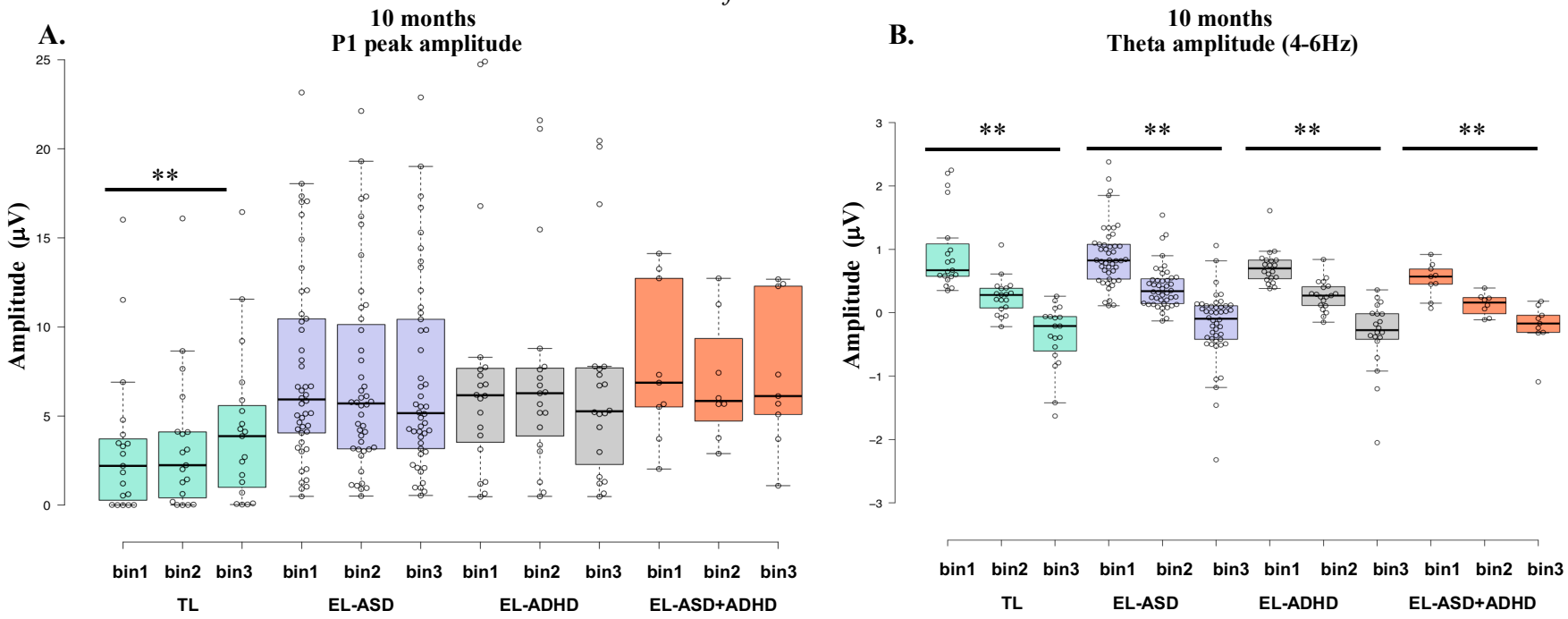

Figure 4.7. Boxplots illustrating the P1 peak amplitude modulation (A) based on theta amplitude tertiles (B) at 10 months *(Green=infants at typical likelihood of ASD or ADHD; Violet=infants at elevated likelihood of ASD; Grey=infants at elevated likelihood of ADHD; Orange=infants at elevated likelihood of ASD and ADHD). Only infants at typical likelihood of the disorders manifested a significant increase in the P1 peak amplitude to the checkerboard as a function of decreasing theta amplitude to the video clip (bin 1=High theta tertile; bin 2=Average theta tertile; bin 3= Low theta tertile). ** p<.001.*

4.4.3. Effect of likelihood status on the continuous association between theta modulation index and P1 modulation index

Theta modulation index. The theta modulation index significantly violated normality assumption (Shapiro-Wilk, $p < .001$; Skewness = -.823, SE = .250; Kurtosis = 4.33, SE = .495) and was normally transformed with the Two-Step approach. There was no significant main effect of ASD likelihood status, $F(1,90) = 2.09$, $p = .151$, $\eta^2 = .023$, or ADHD likelihood status, $F(1,90) = .482$, $p = .489$, $\eta^2 = .005$. Further, there was no significant interaction between ASD and ADHD likelihood status, $F(1,90) = .001$, $p = .974$, $\eta^2 = .000$.

These results further confirmed the validity of the binning strategy adopted, indicating that infants with an elevated likelihood of ASD and/or ADHD manifested a theta modulation index comparable to that of infants at typical likelihood of the condition. Thus, differences in the modulation of the P1 peak amplitude (detailed in section 4.4.2) cannot be imputed to differences in theta amplitude modulation between infants with different likelihood status.

Association between theta modulation index and P1 modulation index. The P1 modulation index significantly violated normality assumption (Shapiro-Wilk, $p < .001$; Skewness = -2.571, SE = .249; Kurtosis = 4.953, SE = .493) and was normally transformed with the Two-Step approach. The hierarchical linear regression with P1 modulation index as outcome and theta modulation index as predictor was not statistically significant, $F(1,91) = .622$, $p = .432$, $R^2_{adj} = .007$. In step 2, the

likelihood factors and the interaction terms were entered as predictors (ASD-L, ADHD-L, interaction between ASD-L and theta modulation index, interaction between ADHD-L and theta modulation index). The model with the added predictors was statistically significant, $F(5,87) = 6.82$, $p < .001$, $R^2_{adj} = .240$, accounting for a significantly higher proportion of variance relative to a model with the only theta modulation index as predictor, F change $(5,87) = 8.32$, $p < .001$. There was significant evidence of moderation by ASD likelihood ($\beta = .551$, $p < .001$) and ADHD likelihood ($\beta = .320$, $p = .002$). See Figure 4.8.

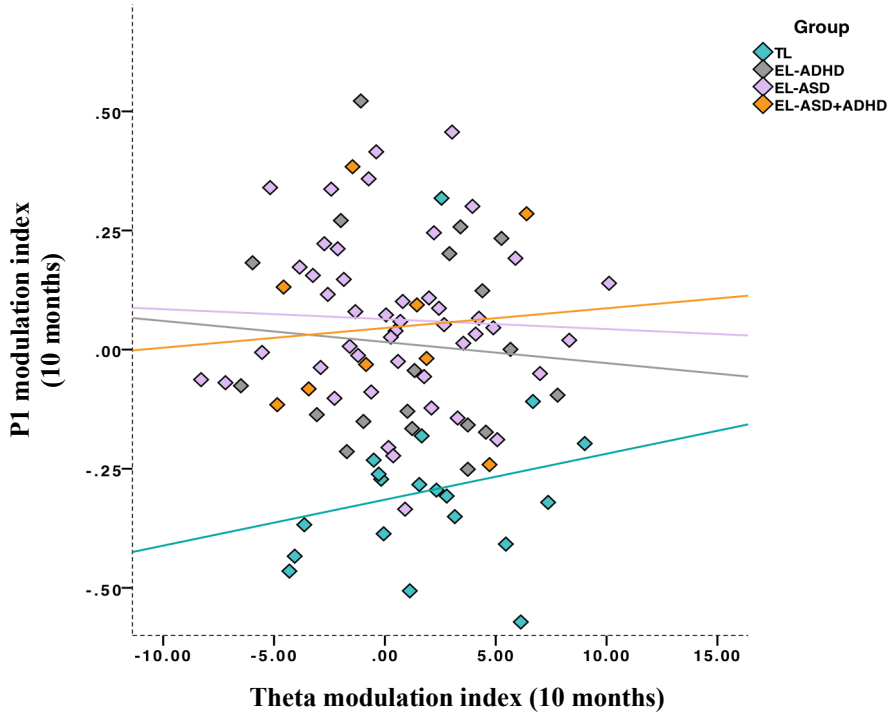

Figure 4.8. Scatterplot illustrating the association between P1 modulation index and theta modulation index for each participant group

(Green=infants at typical likelihood of ASD or ADHD; Violet=infants at elevated likelihood of ASD; Grey=infants at elevated likelihood of ADHD; Orange=infants at elevated likelihood of ASD and ADHD). Only infants at typical likelihood of ASD or ADHD displayed a positive association between P1 modulation index and theta modulation index (i.e. the higher the modulation of engagement with the ongoing video clip, the higher the modulation of responsiveness to the incoming checkerboard). Note: fit lines are presented separately for each group of infants to illustrate the moderating effect of the ASD and/or ADHD likelihood status.

4.4.4. Associations between neural markers at 10 months and later ASD and/or ADHD traits

Associations with ASD traits at 24 months. ADOS-2 CSS significantly violated normality assumptions (Shapiro-Wilk, $p < .001$; Skewness = 1.471, SE = .218; Kurtosis = 1.571, SE = .433) and were log-transformed prior to the analyses.

The hierarchical linear regression with ADOS-2 CSS (log) as outcome and P1 peak amplitude as predictor was not statistically significant, $F(1,79) = 1.312$, $p = .255$, $R^2_{adj} = .016$; with P1 peak latency as predictor was also not statistically significant, $F(1,79) = 2.082$, $p = .153$, $R^2_{adj} = .026$. Further, the hierarchical linear regression with theta amplitude as predictor was not statistically significant, $F(1,79) = 3.143$, $p = .080$, $R^2_{adj} = .026$. The results did not change when ECBQ activity was partialled out: for P1 peak amplitude, $F(2,70) = .849$, $p = .432$, $R^2_{adj} = .000$, 95% CI for B, [-.108, .272]; for P1 peak latency, $F(2,70) = 1.96$, $p = .148$, $R^2_{adj} = .026$, 95% CI for B, [-.08, .301]; for theta amplitude, $F(2,70) = .329$, $p = .721$, $R^2_{adj} = .000$, 95% CI for B, [-.191, .408]. The results reached statistical significance when ECBQ inhibitory control was partialled out, highlighting the significant negative association existing between ADOS-2 CSS and ECBQ inhibitory control at 24 months for participants contributing neural data at 10 months: for P1 peak amplitude, $F(2,69) = 3.655$, $p = .031$, $R^2_{adj} = .070$, 95% CI for B, [-.310, -.035]; for P1 peak latency, $F(2,69) = 5.037$, $p = .009$, $R^2_{adj} = .102$, 95% CI for B, [-.317, -.047]; for theta amplitude, $F(2,69) = 4.938$, $p = .010$, $R^2_{adj} = .100$, 95% CI for B, [-.308, -.038].

In contrast, the hierarchical linear regression with P1 modulation index as predictor and ADOS-S CSS (log) as outcome was statistically significant, F(1,79) = 3.394, p = . 034, R^2_{adj} = .041, indicating that infants manifesting lower modulation of the P1 peak amplitude by ongoing theta amplitude at 10 months exhibited higher ASD traits at 24 months. In step 2, the likelihood factors and the interaction terms were entered as predictors (ASD-L, ADHD-L, interaction between ASD-L and P1 modulation index, interaction between ADHD-L and P1 modulation index). The model remained statistically significant, F(5,75) = 2.45, p = .021, R^2_{adj} = .083, but did not account for a significantly higher proportion of variance relative to a model with only the P1 modulation index as predictor, F change (4,75) = 2.16, p = . 082. There was no evidence of moderation by either ASD likelihood (β = -.064, p = .693) or ADHD likelihood (β = -.072, p = .597). The results from step 2 did not change when ECBQ activity was partialled out, F(6,66) = 2.075, p = . 043, R^2_{adj} = .082, 95% CI for B, [-.124, .144]; when ECBQ inhibitory control was partialled out, F(6,65) = 2.628, p = . 012, R^2_{adj} = .121, 95% CI for B, [-.262, .016]. See Figure 4.9 and Table 13. In step 3, the theta modulation index was entered to the model as predictor. The model became statistically insignificant, F(6,74) = 2.02, p = .073, R^2_{adj} = .071, thus confirming that change in P1 (rather than change in theta) held predictive power in relation to ASD traits emerging in toddlerhood.

Associations with ADHD traits at 24 months. The hierarchical linear regression with ECBQ activity as outcome and P1 peak amplitude as predictor was not

statistically significant, F(1,73) = .246, p = .621, R^2_{adj} = .000; with P1 peak latency as predictor was not statistically significant, F(1,73) = 2.984, p = .088, R^2_{adj} = .026; with P1 modulation index as predictor was also not statistically significant, F(1,73) = .776, p = .381, R^2_{adj} = .000. Further, the hierarchical linear regression with theta amplitude as predictor was not statistically significant, F(1,73) = .022, p = .883, R^2_{adj} = .000. Results did not change when ADOS-2 CSS (log) was partialled out: for P1 peak amplitude, F(2,70) = .462, p = .632, R^2_{adj} = .000, 95% CI for B, [-.168, .424]; for P1 peak latency, F(2,70) = 2.074, p = .133, R^2_{adj} = .029, 95% CI for B, [-.123, .463]; for P1 modulation index, F(2,70) = .913, p = .406, R^2_{adj} = .000, 95% CI for B, [-.175, .432]; for theta amplitude, F(2,70) = .329, p = .721, R^2_{adj} = .000, 95% CI for B, [-.191, .408].

Similarly, the hierarchical linear regression with ECBQ inhibitory control as outcome and P1 peak amplitude as predictor was not statistically significant, F(1,72) = .478, p = .492, R^2_{adj} = .000; with P1 peak latency as predictor was not statistically significant, F(1,72) = .166, p = .685, R^2_{adj} = .000; with P1 modulation index as predictor was also not statistically significant, F(1,72) = .194, p = .167, R^2_{adj} = .026. Further, the hierarchical linear regression with theta amplitude as predictor was not statistically significant, F(1,72) =.041, p = .840, R^2_{adj} = .000. Consequently to the significant negative association existing between ADOS-2 CSS and ECBQ inhibitory control at 24 months, the above results reached statistical significance when the latter variable was partialled out: for P1 peak amplitude, F(2,69) = 3.455, p = .037, R^2_{adj} = .065, 95% CI for B, [-.868, -.099]; for P1 peak

latency, F(2,69) = 3.695, p = .030, R^2_{adj} = .071, 95% CI for B, [-.912, -.137]; for P1 modulation index, F(2,69) = 3.970, p = .023, R^2_{adj} = .077, 95% CI for B, [-.847, -.063]; for theta amplitude, F(2,69) = 3.34, p = .041, R^2_{adj} = .062, 95% CI for B, [-.870, -.060]. See Table 13.

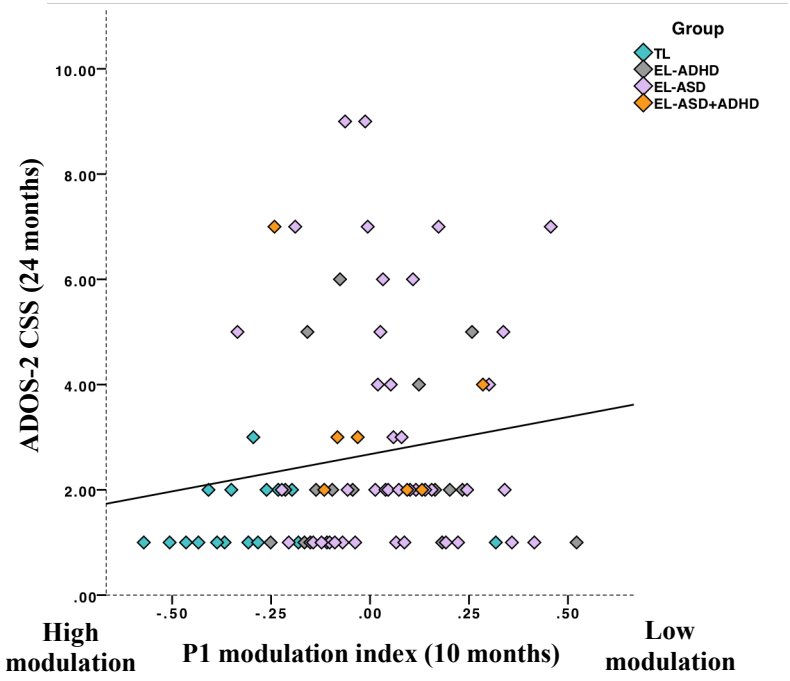

Figure 4.9. Scatterplot illustrating the association between P1 modulation index at 10 months and ADOS-2 CSS at 24 months

(Green=infants at typical likelihood of ASD or ADHD; Violet=infants at elevated likelihood of ASD; Grey=infants at elevated likelihood of ADHD; Orange=infants at elevated likelihood of ASD and ADHD). Infants manifesting lower modulation of the P1 peak amplitude by ongoing theta amplitude at 10 months displayed higher

ASD traits on the ADOS-2 at 24 months (p< .05). Note: fit line is presented for an average of all infants.

***Table 13**. Correlation coefficients (Pearson R) for associations between neural measures at 10 months (P1 peak amplitude and latency to the checkerboard, theta amplitude during video viewing and modulation of the P1 peak amplitude by ongoing theta amplitude) and measures of ASD or ADHD traits at 24 months (ADOS-2 CSS log, ECBQ Activity, ECBQ Inhibitory Control) in entire sample.*

Entire sample (10 months)	ADOS-2 CSS (log)	ECBQ Activity	ECBQ Inhibitory Control
P1 peak amplitude	.128	-.058	-.081
P1 peak latency	.135	-.210	.066
Theta amplitude	-.196	-.017	.024
P1 modulation index	.240*	-.009	-.162

** $p < .05$*

4.4.5. Associations between neural markers at 24 months and concurrent ASD and/or ADHD traits

Associations with ASD traits at 24 months. The hierarchical linear regression with ADOS-2 CSS (log) as outcome and P1 peak amplitude as predictor was not statistically significant, $F(1,79) = .941$, $p = .335$, $R^2_{adj} = .000$; with P1 peak latency as predictor was also not statistically significant, $F(1,79) = 1.127$, $p = .292$, $R^2_{adj} = .014$. Further, the hierarchical linear regression with theta amplitude as predictor

was not statistically significant, F(1,79) = 1.336, p = .251, R^2_{adj} = .004. The results did not change when ECBQ activity was partialled out: for P1 peak amplitude, F(2,69) = 1.518, p = .226, R^2_{adj} = .014, 95% CI for B, [-.023, .329]; for P1 peak latency, F(2,69) = 2.585, p = .083, R^2_{adj} = .043, 95% CI for B, [-.025, .322]; for theta amplitude, F(2,69) = 1.996, p = .144, R^2_{adj} = .027, 95% CI for B, [-.043, .314]. The results reached statistical significance when ECBQ inhibitory control was partialled out, thus confirming the presence of a significant negative association between ADOS-2 CSS and ECBQ inhibitory control in participants who contributed neural data at 24 months: for P1 peak amplitude, F(2,69) = 3.655, p = .031, R^2_{adj} = .070, 95% CI for B, [-.310, -.035]; for P1 peak latency, F(2,69) = 4.848, p = .011, R^2_{adj} = .098, 95% CI for B, [-.328, -.049]; for theta amplitude, F(2,69) = 4.141, p = .020, R^2_{adj} = .081, 95% CI for B, [-.324, -.039]. See Table 14.

Associations with ADHD traits at 24 months. The hierarchical linear regression with ECBQ activity as outcome and P1 peak amplitude as predictor was not statistically significant, F(1,70) = .004, p = .940, R^2_{adj} = .000; with P1 peak latency as predictor was also not statistically significant, F(1,70) = .104, p = .748, R^2_{adj} = .000. Further, the hierarchical linear regression with theta amplitude as predictor was not statistically significant, F(1,70) = 3.00, p = .088, R^2_{adj} = .027. Results did not change when ADOS-2 CSS (log) was partialled out: for P1 peak amplitude F(2,69) = 1.510, p = .228, R^2_{adj} = .014, 95% CI for B, [-.041, .588]; for P1 peak latency, F(2,69) = 1.511, p = .229, R^2_{adj} = .014, 95% CI for B, [-.046, .592]; for theta amplitude, F(2,69) = 2.679, p = .076, R^2_{adj} = .045, 95% CI for B, [-.083, .537].

The hierarchical linear regression with ECBQ inhibitory control as outcome and P1 peak amplitude as predictor was not statistically significant, $F(1,70) = .072$, $p = .789$, $R^2_{adj} = .000$; with P1 peak latency as predictor was also not statistically significant, $F(1,70) = .122$, $p = .728$, $R^2_{adj} = .000$. Further, the hierarchical linear regression with theta amplitude as predictor was not statistically significant, $F(1,70) = 2.113$, $p = .151$, $R^2_{adj} = .015$. Significant results emerged when ADOS-2 CSS was partialled out: for P1 peak amplitude, $F(2,69) = 3.769$, $p = .028$, $R^2_{adj} = .072$, 95% CI for B, [-.874, -.136]; for P1 peak latency, $F(2,69) = 3.717$, $p = .029$, $R^2_{adj} = .071$, 95% CI for B, [-.882, -.133]; for theta amplitude, $F(2,69) = 4.385$, $p = .016$, $R^2_{adj} = .087$, 95% CI for B, [-.822, -.081]. See Table 14.

Table 14. *Correlation coefficients (Pearson R) for associations between neural measures at 24 months (P1 peak amplitude and latency to the checkerboard, and theta amplitude during video viewing) and measures of ASD or ADHD traits at 24 months (ADOS-2 CSS log, ECBQ Activity, ECBQ Inhibitory Control) in entire sample.*

Entire sample (24 months)	ADOS-2 CSS (log)	ECBQ Activity	ECBQ Inhibitory Control
P1 peak amplitude	.108	.008	.032
P1 peak latency	-.119	-.039	.042
Theta amplitude	.129	.203	-.171

4.4.6. Mediating/moderating effect of visual sensory seeking

Results from previous analyses indicated that neither neural markers of sensitivity to visual stimulation, nor neural markers of engagement with the ongoing video clip during infancy or toddlerhood significantly predicted ASD traits at 24 months. Conversely, evidence suggested that the ability to modulate responsiveness to incoming visual stimulation as a function of engagement with the ongoing video clip is a marker significantly capturing the effect of the ASD and ADHD likelihood status at 10 months and predicting ASD traits at 24 months.

In light of my interest in characterising the potential impact of early sensory atypicality on infants' engagement with their surrounding environment, I proceeded with investigating whether visual sensory seeking significantly mediated or moderated the relationship between P1 modulation index at 10 months and ASD traits at 24 months, see Figure 4.10. As reviewed in Chapter 2, sensory seeking is a construct of the ITSP that maximally captures infants' engagement with their surrounding environment and reduced sensory seeking is reported in the early development of ASD. Visual sensory seeking captures infants' engagement with the environment in the visual modality (see Appendix for a discussion of the contributing items and for assessment of the sub-scale internal consistency; further, see Appendix for analyses that replicate, in the current sample, the profile of reduced visual sensory seeking in the early development of ASD). To conclude that visual sensory seeking mediates the relationship between early neural modulation of incoming visual stimulation and later ASD traits, a significant *indirect effect* of

P1 modulation index on ASD traits, through visual sensory seeking, should be observed. Two pathways comprise the indirect effect: 1) “a path” represents the relation between P1 modulation index and visual sensory seeking; 2) “b path” represents the relation between P1 modulation index and ASD traits, controlling for visual sensory seeking. An indirect effect is statistically significant when the confidence interval for the product of the unstandardized coefficients for these two paths does not include zero.

To conclude that visual sensory seeking moderates the relationship between early neural modulation of incoming visual stimulation and later ASD traits, a significant *interaction effect* between P1 modulation index and visual sensory seeking on ASD traits should be observed.

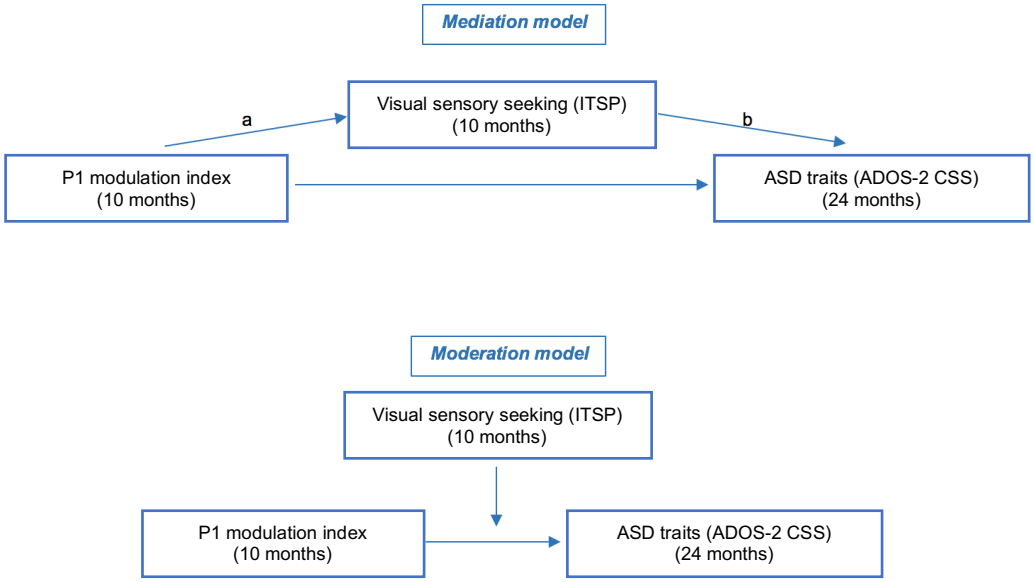

Figure 4.10. Mediation and moderation models illustrating the possible relationships between P1 modulation index at 10 months, parent-reported visual sensory seeking at 10 months and ASD traits at 24 months

The mediation model implies a causal relationship, whereby reduced ability to modulate responsiveness to incoming visual stimulation leads to concurrent reduced visual sensory seeking, which causes later elevated ASD traits. The moderation model implies an interaction effect whereby, at the same level of modulation of responsiveness to incoming visual stimulation, infants scoring high in concurrent visual sensory seeking develop less severe ASD traits at 24 months.

In the following mediation and moderation analyses, bias-corrected confidence intervals for effects of interest were generated using 5000 bootstrap samples with the confidence level set at 95%.

Mediation model. The direct effect of P1 modulation index on ADOS-2 CSS (log) was statistically significant at 95% CI, [.206, 1.01]. The direct effect of visual sensory seeking on ADOS-2 CSS (log) was not statistically significant at 95% CI, [-.102, .243]. No evidence for an indirect effect of P1 modulation index on ADOS-2 CSS through visual sensory seeking emerged: 1] "a path" from visual sensory seeking to P1 modulation index was statistically significant at 95% CI, [.010, .117]; however, 2] "b path" from P1 modulation index to ADOS-2 CSS (log) controlling for visual sensory seeking was not statistically significant at 95% CI, [-.135, .177].

Moderation model. The interaction effect between P1 modulation index and visual sensory seeking on ADOS-2 CSS (log) was not statistically significant at 95% CI, [-1.061, 1.519], disconfirming the moderation role of visual sensory seeking.

4.4.7. Associations between neural markers and learning

Drawing on Predictive coding theories, which assume the integration between feedback and feedforward signals to underlie efficient learning, I proceeded with probing whether any associations existed between the P1 modulation index (which captured infants' ability to modulate responsiveness to incoming visual stimulation based on engagement with ongoing information) at 10 months and learning scores on the Mullen at 10 and 24 months.

The concurrent association between P1 modulation index and scores on the Mullen at 10 months approached statistical significance, R (91) = -.162, p = .061, R^2 = .026 A significant negative association manifested between P1 modulation index and scores on the Mullen at 24 months, R (77) = -.329, p = .002, R^2 = .108. See Figure 4.11A and 4.11B.

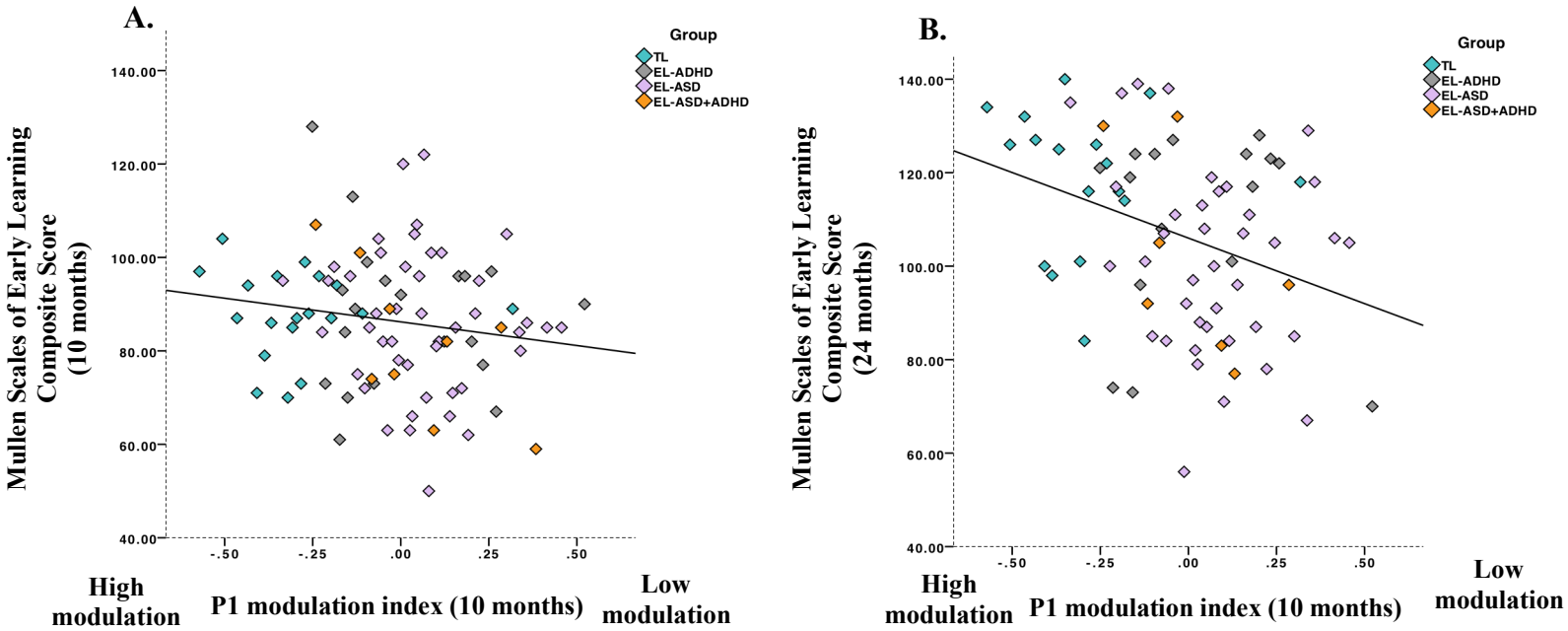

Figure 4.11. Scatterplots illustrating the associations between P1 modulation index at 10 months and scores on the Mullen

A. Mullen Scales of Early Learning at 10 months ($p = .061$); B. Mullen Scales of Early Learning at 24 months ($p < .05$). (Green=infants at typical likelihood of ASD or ADHD; Violet=infants at elevated likelihood of ASD; Grey=infants at elevated likelihood of ADHD; Orange=infants at elevated likelihood of ASD and ADHD). Infants manifesting enhanced ability to modulate responsiveness to incoming visual stimulation at 10 months displayed higher learning scores on the Mullen at 24 months. Note: fit lines are presented for an average of all infants.

4.4.8. Main analytical pipeline – Interim summary

Results of the analyses conducted so far indicated that infants (but not toddlers) with an elevated ASD or ADHD likelihood status manifested enhanced sensitivity to visual stimulation, as indexed by elevated P1 peak amplitude time-locked to checkerboard onset. This evidence confirms my prediction that both the ASD and ADHD likelihood status would have impacted as factors on this neural marker of sensitivity to visual input. Furthermore, results suggested that infants with an elevated ADHD likelihood manifested delayed P1 peak latency to the checkerboard relative to infants at typical likelihood of the disorders. While I did not specify a directional hypothesis for this neural marker, it is possible that reduced P1 peak latency in infants with an elevated ADHD likelihood status may signal slower conduction velocity in the visual pathways. Investigation of infants' engagement with the ongoing video clip indicated that infants with an elevated ADHD likelihood manifested reduced theta oscillatory amplitude during video viewing relative to infants at typical likelihood of the disorders (whereas only a trend towards statistical significance emerged for infants with an ASD likelihood). This result partly confirms my prediction that the ASD and ADHD likelihood factors would have impacted on this neural marker of engagement with ongoing information.

To probe the potential mechanism underlying the enhancement of the P1 peak amplitude in infants with an elevated likelihood of ASD or ADHD, I assessed the intra-participant modulation of this component by ongoing theta amplitude.

Results indicated that only infants at typical likelihood of the disorders exhibited a significant increase in the P1 peak amplitude to the checkerboard as a function of decreasing theta amplitude to the video (i.e. P1 modulation index). This result confirms my prediction that visual hypersensitivity in the early development of ASD and ADHD may result from limited integration between feedforward and feedback signals. While the P1 modulation index was significantly reduced in infants at elevated likelihood of ASD and/or ADHD relative to infants at typical likelihood of the conditions, this neural marker selectively associated with ASD (but not ADHD) traits at 24 months.

Replicating evidence discussed in Chapter 2, infants with an ASD likelihood status manifested lower parent-reported sensory seeking in the visual modality (see Appendix for this analysis). However, results from the mediation and moderation analyses did not allow to conclude that visual sensory seeking acted as a factor mediating or moderating the association between early reduced ability to modulate responsiveness to incoming visual stimulation and later ASD traits in the current sample.

Finally, results from the analyses investigating the link between P1 modulation index and learning scores on the Mullen at 10 and 24 months indicated that infants manifesting higher modulation of responsiveness to incoming visual stimulation at 10 months also displayed higher learning scores at 10 and 24 months.

I further discuss these results in section 4.5. Additionally, in light of the emerged evidence, I proceeded with performing the follow-up analyses introduced

in section 4.2.2. These analyses clarify and/or expand on results emerged from the main analytical pipeline.

4.4.9. Longitudinal stability of neural markers

P1 peak amplitude. There was a significant positive association between P1 peak amplitude at 10 and 24 months in the entire sample, R (53) = .355, p = .004, R^2 = .091, indicating moderate longitudinal stability in participants' sensitivity to visual stimulation. See Figure 4.11A.

P1 peak latency. There was no significant association between P1 peak latency at 10 and 24 months in the entire sample, R (53) = -.128, p = .350, R^2 = .002, disconfirming the longitudinal stability of this neural marker and raising concerns about the reliability of this measure. See Figure 4.12B.

Theta (θ = 4-6Hz) amplitude. There was a significant positive association between theta amplitude at 10 and 24 months in the entire sample, R (53) = .345, p = .01, R^2 = .119, indicating moderate longitudinal stability in participants' engagement with the ongoing video stimulus. See Figure 4.12C.

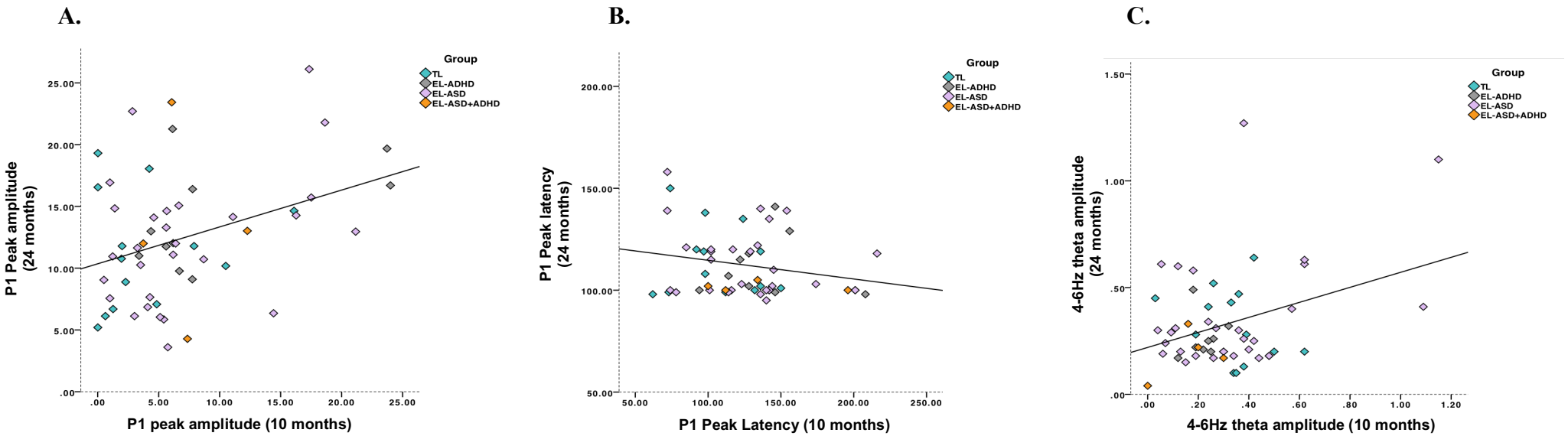

Figure 4.12. Scatterplots illustrating the longitudinal associations between neural markers of visual sensory processing at 10 and 24 months

(Green=infants at typical likelihood of ASD or ADHD; Violet=infants at elevated likelihood of ASD; Grey=infants at elevated likelihood of ADHD; Orange=infants at elevated likelihood of ASD and ADHD). A. P1 peak amplitude (p<.05); B. P1 peak latency to the checkerboard (p=ns); C. Theta amplitude during video viewing (p<.05). Note: fit lines are presented for an average of all infants.

4.4.10. Associations between neural markers and parent-reported ASD traits

Associations with ASD traits at 24 months. Q-CHAT scores significantly violated normality assumptions (Shapiro-Wilk, $p < .001$; Skewness = .943, SE = .226; Kurtosis = 1.164, SE = .447). Log transformation did not improve the data distribution (Shapiro-Wilk, $p = .001$; Skewness = -.778, SE = .226; Kurtosis = 2.485, SE = .447). Thus, a Spearman correlation was run to assess the association between P1 modulation index and this outcome measure.

The Spearman correlation between Q-CHAT and P1 modulation index was not statistically significant, Rho (74) = .041, $p = .362$. Given that the P1 modulation index at 10 months significantly predicted ADOS-2 CSS at 24 months, I also assessed the concordance between Q-CHAT and ADOS-2 CSS. There was low concordance between the measures, Rho (72) = .247, $p = .034$.

4.4.11. Mediating/moderating effect of visual sensory avoiding

ITSP sensory avoiding scores for the visual modality were computed for each 10-month-old infants. First, descriptive investigation of the variable distribution indicated that 85% of the data fell within an interval ranging from 4 to 5 (i.e. indicating low visual sensory avoiding on the ITSP), thus aligning to evidence reported in Chapter 3 and further confirming the notion that 10-month-old infants may not yet possess a sufficient skills repertoire to display active avoidance behaviours.

Since visual sensory avoiding could be opposite to visual sensory seeking, I assessed the relationship between the two ITSP measures. The Pearson correlation between the measures was not statistically significant, R (71) = -.136, p = .251, disconfirming the link between the two quadrants within the visual domain of the ITSP. I subsequently assessed the explanatory power of visual sensory avoiding as a mediator or moderator of the relationship between P1 modulation index at 10 months and ASD traits at 24 months.

Mediation model. The direct effect of P1 modulation index on ADOS-2 CSS (log) was statistically significant at 95% CI, [.206, 1.01]. The direct effect of visual sensory avoiding on ADOS-2 CSS (log) was not statistically significant at 95% CI, [-.315, .101]. No evidence for an indirect effect of P1 modulation index on ADOS-2 CSS (log) through visual sensory avoiding emerged: 1] "a path" from visual sensory avoiding to P1 modulation index was not statistically significant at 95% CI, [-.866, .761]; 2] "b path" from P1 modulation index to ADOS-2 CSS (log) controlling for visual sensory avoiding was not statistically significant at 95% CI, [-.156, .150].

Moderation model. The interaction effect between P1 modulation index and visual sensory avoiding on ADOS-2 CSS (log) was not statistically significant at 95% CI, [-1.153, .562], disconfirming the moderation role of visual sensory avoiding.

4.4.12. Concurrent and longitudinal associations with visual sensory seeking

Results from the core analyses (section 4.4.6) suggested that visual sensory seeking at 10 months did not act as a significant mediator or moderator of the association between infants' ability to modulate responsiveness to incoming visual input and ASD traits in toddlerhood. Thus, I proceeded with probing the concurrent and longitudinal associations between neural markers of visual sensory processing at 10 and 24 months and parental reports of visual sensory seeking.

Concurrent associations. At 10 months, significant concurrent association emerged between ITSP visual sensory seeking and P1 peak amplitude, R (80) = .268, p =.015, R^2 =.072, and P1 modulation index, R (80) = .197, p =.038, R^2 =.039, indicating that infants manifesting enhanced P1 peak amplitude and reduced modulatory capacity were reported by parents to seek significantly less visual stimulation, see Figure 4.13A and 4.13B[3]. Conversely, at the same age point, there was no significant association with P1 peak latency, R (80) = .047, p = .672, R^2 =.002, or theta amplitude during video viewing, R (80) = .109, p = .328, R^2 =.012, or theta modulation index, R (80) = -.018, p = .874, R^2 =.000.

At 24 months, there was no significant concurrent association between ITSP visual sensory seeking and P1 peak amplitude, R (72) = .097, p = .411, R^2

[3] Note that the significant association between P1 modulation index at 10 months and parent-reported visual sensory seeking replicates results emerged from the mediation analysis reported in section 4.4.6.

=.009; and P1 peak latency, R (72) = -.016, p = .893, R^2 =.000; and theta amplitude during video viewing, R (72) = .212, p = .069, R^2 =.062; and theta modulation index, R (72) = .007, p = .949, R^2 =.000.

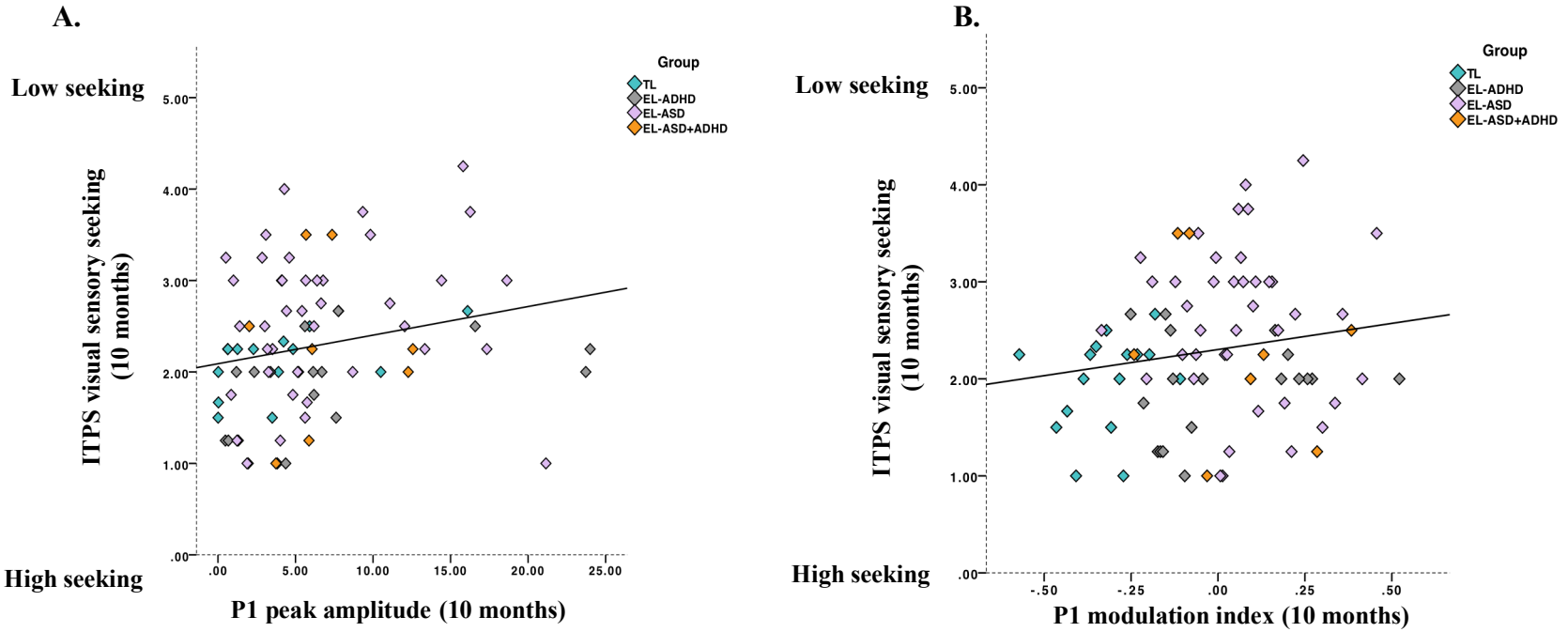

Figure 4.13. Scatterplots illustrating the concurrent associations between ITSP visual sensory seeking at 10 months and A. P1 peak amplitude; B. P1 modulation index

(Green=infants at typical likelihood of ASD or ADHD; Violet=infants at elevated likelihood of ASD; Grey=infants at elevated likelihood of ADHD; Orange=infants at elevated likelihood of ASD and ADHD). Infants manifesting enhanced P1 peak amplitude and reduced ability to modulate responsiveness to incoming visual stimulation at 10 months were concurrently rated by parents

as seeking less visual stimulation ($p < .05$). Notes: 1] fit lines are presented for an average of all infants; 2] the range plotted for the y axes starts at zero for ease of visualization; 3] High scores for the P1 modulation index indicate low modulatory capacity, whereas low scores for the P1 modulation index indicate high modulatory capacity.

Longitudinal associations. None of the longitudinal associations between neural markers of visual processing at 10 months and ITSP visual sensory seeking at 24 months reached statistical significance, for P1 peak amplitude, R (75) = .012, p = .915, R^2 =.000; for P1 peak latency, R (75) = -.032, p = .784, R^2 =.001; for theta amplitude during video viewing, R (75) = .117, p = .309, R^2 =.014.

4.4.13. Follow-up analyses – Interim summary

I performed a set of follow-up analyses with the goal of clarifying and/or expanding on results emerged from the core analyses.

First, no prior research assessed the longitudinal stability of neural markers of visual sensory processing in the early development of ASD and/or ADHD. Thus, I investigated whether longitudinal continuity manifested in the neural markers quantified in this study at 10 and 24 months. Results revealed moderate longitudinal stability for the P1 peak amplitude time-locked to checkerboard onset and theta amplitude during video viewing (but not for the P1 peak latency). This evidence suggests that both P1 peak amplitude and theta amplitude represent reliable neural measures in early development. Contrarily, the lack of longitudinal stability emerged for the P1 peak latency questions the reliability of this measure in early development.

Secondly, given the significant association emerged between reduced modulation of responsiveness to incoming visual stimulation at 10 months and higher ASD traits quantified through the ADOS-2 CSS at 24 months, I ascertained

whether a similar association manifested with the parent-reported Q-CHAT. Results indicated that parent-reported ASD traits in toddlerhood did not associate with the P1 modulation index in infancy. Furthermore, low concordance emerged between ADOS-2 CSS and scores on the Q-CHAT for participants contributing to the study. Low-to-moderate correlation between observational and parent report measures is commonly reported in older samples of children with ASD (e.g. Charman et al., 2007; Evers et al., 2020; Lord et al., 2006) and between clinician ratings and parent ratings of ADHD (Nobel et al., 2019), which is why best practice in diagnostic clinical assessments is to use both methods (Lord et al., 2020). In younger toddlers, concordance between parental reports and standardised clinical assessments of ASD or ADHD traits may be even lower since atypical manifestations are less prominent. Another possibility is that Q-CHAT and the neural measure quantified in the present study captured different constructs. Thus, both the significant association between P1 modulation index and later ASD traits (quantified through clinician observation) and the non-significant associations between the same neural marker and later ADHD traits (quantified through parental report) must be followed-up using both observational and parent report assessments of ASD and ADHD traits at 3 years.

Thirdly, results from the main analyses disconfirmed the role of visual sensory seeking as a factor mediating or moderating the association between early reduced modulation of responsiveness to incoming visual stimulation and later ASD traits. Thus, I proceeded with investigating the concurrent and longitudinal

associations between neural markers of visual sensory processing and parent-reported visual sensory seeking at both 10 and 24 months. Results indicated that lower parent-reported visual sensory seeking manifested in 10-month-old infants concurrently exhibiting enhanced sensitivity to visual stimulation (P1 peak amplitude) and reduced ability to modulate responsiveness to visual input as a function of engagement with the ongoing video (P1 modulation index). Importantly, only the concurrent associations between these neural markers and visual sensory seeking at 10 months (but not the longitudinal associations with visual sensory seeking at 24 months) reached statistical significance, suggesting that lower visual sensory seeking may represent the preferred strategy of information prioritization in the presence of visual hypersensitivity in infancy but not in toddlerhood.

Relatedly, while I assessed the mediating/moderating role of visual sensory seeking in the main analyses, I further probed the potential impact of visual sensory avoiding, which represents an active behavioural strategy to limit engagement with the surrounding sensory environment in the ITSP. Replicating evidence reported in Chapter 3, results disconfirmed the existence of a link between parental reports of visual sensory seeking and avoiding behaviours at 10 months. Further, no evidence of visual sensory avoiding mediating or moderating the association between infants' modulation of responsiveness to incoming visual stimulation at 10 months and ASD traits at 24 months emerged. In the present study, 85% of infants were rated by their parents as never or almost never exhibiting visual

sensory avoiding behaviours. Thus, these results support the notion that 10-month-old infants may not yet possess the ability to display active avoidance strategies. Seeking (as opposed to avoiding) may represent the preferred strategy of information prioritization in early development.

4.5. Discussion

4.5.1. General points

The goal of the current study was to investigate neural markers of visual sensory processing in 10-month-old infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the disorders, prospectively re-assessed at 24 months. A visual task involving a continuous video clip intermixed with black-and-white static checkerboards flashed on top was used and coupled with the recording of EEG. First, at both 10 and 24 months, I quantified neural markers of visual sensitivity by extracting the P1 peak amplitude and latency time-locked to the onset of the checkerboard. I observed that infants (but not toddlers) with an elevated likelihood of ASD or ADHD manifested enhanced P1 peak amplitude to an unexpected incoming visual stimulus relative to infants at typical likelihood of the conditions. Previous reports documenting elevated visual sensitivity in the early development of ASD and/or ADHD employed parental reports (Baranek et al., 1997; Ghanizadeh, 2011; Tomchek & Dunn, 2007). Eye-tracking studies reported infants with later ASD to manifest superior visual search abilities at 9 and 15 months (but not 24 months) (Cheung et al., 2016; Gliga et al., 2015) and a

hypersensitive pupillary light reflex at 9 months (Nyström et al., 2018). However, none of these studies probed the putative mechanism underlying superior visual perception in the early development of ASD. Evidence from this study supports and extends previous research by indicating that enhanced visual processing, as indexed by elevated sensitivity to incoming visual stimulation at 10 months, is a marker shared by infants with an ASD and ADHD likelihood status. By quantifying the trade-off between infants' engagement with the ongoing video (indexed by theta oscillatory amplitude during video viewing) and bias towards incoming stimulation (indexed by P1 peak amplitude modulation), the present study further revealed that reduced modulatory capacity may be the mechanism behind enhanced visual perception in infants with an ASD and/or ADHD likelihood status. Further, in the present study, reduced modulatory capacity at 10 months selectively associated with ASD (but not ADHD) traits at 24 months. Thus, it is possible that this neural marker may be capturing early-emerging comorbid ASD manifestations in ADHD. Relatedly, the association between reduced modulatory capacity at 10 months and elevated ASD traits at 24 months manifested across the entire sample and was not moderated by likelihood status, suggesting that the pathway identified is independent of familial contributions. Previous work questioned whether ASD manifests the same phenotype when accompanied by ADHD (Shephard et al., 2018; Tye et al., 2014). Aligning to evidence discussed in Chapter 3, the present results suggest that a common pathway to later ASD traits may exist in infants with an elevated likelihood of ASD and/or ADHD.

Alteration in the E/I balance of neural connectivity has been proposed as a mechanism underlying many of the manifestations occurring in ASD and ADHD. In the visual modality, these manifestations include atypical visual repetition suppression, atypical binocular rivalry, atypical spatial suppression/gain control and orientation discrimination (for reviews see Chapter 1 and Dickinson, Jones, & Milne, 2016; Robertson & Baron-Cohen, 2017). Reduced ability to modulate responsiveness to incoming visual stimulation may equally be driven by atypical E/I balance in visual cortical regions. Support for this notion comes from research with animals and neurotypical adults, which concurs in suggesting that the gain of neural responses manifesting during the initial stages of visual processing depends on feedback excitatory and inhibitory signals converging on V1 from higher cortical regions (Kok, Bains, Van Mourik, Norris, & De Lange, 2016; Olsen, Bortone, Adesnik, & Scanziani, 2012). The prefrontal cortex may be particularly involved in the generation of descending feedback signals modulating visual processing during the early stages of information selection and encoding (Gazzaley & Nobre, 2012; Zanto et al., 2011). Thus, atypical prefrontal cortical functioning may underlie the reduced modulatory capacity documented in the current study in infants with an ASD and/or ADHD likelihood status. This proposal aligns to previous evidence (Green et al., 2015; Samson et al., 2012) and it is further consistent with results from molecular genetics studies, which suggest that many ASD and ADHD brain-specific genes exhibit the most significant co-expression

during the midfetal period in the prefrontal cortex (Krishnan et al., 2016; Parikshak et al., 2013; Willsey et al., 2013).

Delayed P1 peak latency also manifested in the present study in 10-month-old infants with an elevated ADHD likelihood relative to infants at typical likelihood of ASD and/or ADHD. Delayed P1 peak latency in infants with an elevated ADHD likelihood may signal slower conduction velocity in the visual pathways and be linked to slower cortical maturation during the early stages of development of the condition (Shaw et al., 2007; 2011). However, delayed P1 peak latency at 10 months did not predict ADHD activity or inhibitory control traits in toddlerhood. These results, alongside evidence indicating that the P1 peak latency did not manifest longitudinal continuity between 10 and 24 months, converge in suggesting that delayed P1 peak latency in the early development of ADHD may not be a marker with predictive validity in relation to disorder-specific traits and/or categorical diagnosis. Further, the lack of longitudinal stability for the P1 peak latency from 10 to 24 months questions the reliability of this neural measure in early development. However, it must be noted that in the present research ADHD traits at 24 months were quantified using the parent-reported ECBQ. While previous research indicates that higher 24-month ECBQ activity and inhibitory control predict higher mid-childhood hyperactivity/impulsivity and inattention (Shephard et al., 2018), it is possible that this parental report failed to capture ADHD traits in toddlerhood. Thus, these results must be followed up by assessing the potential associations with clinical diagnoses at 3-years.

Several theoretical proposals have suggested that atypical visual perception in the early development of ASD may exacerbate later traits by triggering compensatory strategies to minimise or overly select visual input (Gliga et al., 2014; Thye et al., 2018). Decreased visual sensory seeking is frequently reported in infants with later ASD (Ben-Sasson et al., 2009; Mulligan & White, 2012; Thye et al., 2018) and it may represent the strategy infants adopt in early development to limit incoming visual input (Johnson et al., 2015; Mulligan & White, 2012). However, reduced visual sensory seeking could also limit infants' opportunities for learning and socialization, thus exacerbating later ASD traits. Thus, as a final step of the core analytical pipeline, I sought to investigate the role of visual sensory seeking as a potential mediator or moderator of the association between early atypical modulatory capacity and later ASD traits. 10-month-old infants manifesting enhanced visual sensitivity and reduced modulatory capacity in the EEG task were concurrently reported by parents as seeking less visual input. However, visual sensory seeking at 10 months did not significantly mediate or moderate the association between P1 modulation index at 10 months and ADOS-2 CSS at 24 months. Thus, reduced visual sensory seeking may be the preferred strategy of information prioritization in the presence of early atypical visual responsiveness; however, this strategy may not be sufficient to explain the link between early atypical visual perception and later ASD traits. Given that reduced sensory seeking in the tactile modality was found to act as a significant moderator in Chapter 3, this evidence also raises the possibility that this strategy of

information prioritization may act differently in different sensory modalities (see Chapter 7 for further elaboration on this notion). This possibility should be acknowledged given that vision, differently from touch, is the last sensory system to develop and it is highly influenced by the nature of the early environment. Future research should assess the possibility that visual sensory seeking may exercise its moderating function in combination with additional compounding factors.

Altogether, this study provides the first demonstration that enhanced visual perception manifests in infants at elevated likelihood of ASD or ADHD. Reduced capacity to modulate responsiveness to unexpected incoming visual stimulation during engagement with ongoing information underlies enhanced visual perception in infants at elevated likelihood of ASD and/or ADHD and further predicts ASD traits in toddlerhood. In line with Predictive coding theories, I speculate that reduced capacity to modulate responsiveness to incoming visual stimulation may interfere with learning by slowing prior updating (Pellicano & Burr, 2012) – a notion consistent with evidence of a link between reduced modulatory capacity at 10 months and lower scores on the Mullen at 10 and 24 months.

4.5.2. How do these results inform our understanding of the mechanisms underlying the early development of sensory perception in ASD and ADHD?

Results from this study indicate that atypicalities in sensory perception, manifesting as reduced modulation of responsiveness to incoming visual stimulation, exist in infants at elevated likelihood of ASD and/or ADHD and predict emerging ASD

traits in toddlerhood. Reduced modulatory capacity in infants at elevated likelihood of the disorders may be a marker capturing early-emerging comorbid ASD manifestations in ADHD. These results align to evidence reported in Chapter 3 and further extend to the visual modality the notion advanced by Predictive coding theories that atypical sensory perception in individuals with ASD may result from reduced integration between feedforward and feedback signals (i.e. active inference), limiting refinement of sensory predictions over time (Lawson, Rees, & Friston, 2014; Pellicano & Burr, 2012). Predictive coding theories further postulate the integration between feedforward and feedback signals to be the mechanism underlying efficient learning (Lawson et al., 2014; Pellicano & Burr, 2012). Consistent with this proposal, infants manifesting higher modulation of responsiveness to unexpected incoming visual stimulation during engagement with the ongoing video displayed higher learning scores on the Mullen concurrently (10 months) and longitudinally (24 months). Thus, these results replicate evidence reported in Chapter 3 and extend to the visual modality the link between active inference capacity and learning in a prospective longitudinal sample of infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the conditions.

Conversely, evidence from this study does not support the notion that reduced integration between feedforward and feedback signals may be a marker of later ADHD traits. While both infants at elevated likelihood of ASD and ADHD manifested reduced modulatory capacity at 10 months, this neural marker

selectively associated with later ASD (but not ADHD) traits. It is possible that an association may manifest with 3-year clinical outcomes, although currently data to confirm or disprove this prediction is unavailable (see section 4.7).

Altogether, these results demonstrate that atypicalities in sensory perception are detectable in infants with later higher ASD traits from early in development. I propose that reduced active inference may be the mechanism underlying early-emerging sensory atypicalities across sensory modalities. I further explore this notion in Chapter 5, whereby I lay out a demonstration that variation in infants' responsiveness to incoming stimulation (reflecting feedforward processing) is driven by variation in engagement with ongoing information (reflecting feedback processing).

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4.6. Conclusion

Overall, the current study presents the first evidence that enhanced visual perception, as indexed by elevated P1 peak amplitude to incoming visual stimulation, manifests in infants at elevated likelihood of ASD or ADHD. Results indicate that enhanced visual perception in infants with an ASD or ADHD likelihood status is consequent to reduced modulatory capacity. Results further indicate that reduced modulatory capacity in infancy is an early marker of later ASD traits in both infants at elevated likelihood of ASD or ADHD, suggesting that a common pathway to later ASD traits may exist across these different familial backgrounds. Results do not allow to establish visual sensory seeking as a factor

mediating or moderating the association between early reduced modulatory capacity and later ASD traits. However, evidence suggests that reduced seeking of visual input may be the preferred strategy in the face of early reduced modulatory capacity. The extent to which visual sensory seeking may moderate the pathway from early visual atypicality to later ASD traits in combination with additional compounding factors remains to be established.

4.7. Limitations

The study described in the present chapter has a few limitations. First, there is evidence that ophthalmological pathologies exist in children with ASD and ADHD, although the exact age of onset of these atypicalities is unclear (Decarlo et al., 2014, 2016; Little, 2018). Although infants and toddlers involved in the study were reported by their parents to have normal vision at the time of the assessment, direct screening for potential ophthalmological pathologies was not performed. Thus, I cannot exclude the possibility that pre-existent ophthalmological atypicalities may partly contributed the reported results (e.g. lack of significant group differences in the 24 months sample).

Secondly, as it was the case for Chapter 3, also in the present study I used the parent-reported ECBQ activity and inhibitory control sub-scales to quantify ADHD traits at 24 months. It is possible that this parental report failed to capture ADHD traits in toddlerhood. This possibility should be acknowledged given that infants' modulatory capacity associated with ASD traits quantified through clinical observation (ADOS-2 CSS) but it did not associate with the parent-reported Q-

CHAT. Thus, the specificity of the association between P1 modulation index at 10 months and later ASD traits must be confirmed by assessing the relationships with later clinical outcomes (which will be possible when data collection for the 3-year follow-up visits for the BASIS Phase 3 study is completed).

4.8. Summary of Chapter 4

Atypicalities in visual sensory processing are reported in ASD and ADHD but it remains unknown if they precede and associate with traits of these disorders emerging in childhood. Chapter 4 set out to investigate neural markers of visual sensory processing in 10-month-old infants at elevated likelihood of ASD and/or ADHD relative to infants at typical likelihood of the disorders, prospectively re-assessed at 24 months. Further, the chapter assessed the specificity of associations between infant markers and later ASD or ADHD traits.

To this goal, EEG responses to black-and-white checkerboards briefly flashed on top of a continuous video clip were experimentally recorded. At both ages, parental reports of visual sensory seeking were collected. Further, ASD and ADHD traits were measured at 24 months through standardised assessment (ADOS-2) and parental report (ECBQ), respectively. Results indicated that infants with at elevated likelihood of ASD or ADHD manifested enhanced visual perception, as indexed by elevated P1 peak amplitude time-locked to checkerboard onset. Furthermore, infants at elevated likelihood of ASD or ADHD manifested reduced capacity to modulate responsiveness to incoming visual stimulation as a function of engagement with the ongoing video. Reduced modulatory capacity at

10 months significantly predicted higher ASD (but not ADHD) traits at 24 months across the entire sample. Enhanced visual perception and reduced modulatory capacity at 10 months further associated with concurrent parental reports of reduced visual sensory seeking.

Altogether, these results suggest that reduced capacity to modulate responsiveness to incoming visual stimulation is an early marker of later ASD traits in both infants at elevated likelihood of ASD or ADHD, indicating that a common pathway to later ASD may exist despite different familial backgrounds. Reduced modulatory capacity in early development may result from limited integration between feedforward and feedback signals (i.e. active inference) and detrimentally impact learning by slowing prior update (Lawson et al., 2014; Pellicano & Burr, 2012). I propose that reduced active inference capacity may be the mechanism underlying early-emerging sensory atypicalities across sensory modalities and further probe this notion in Chapter 5.

Chapter 5: Mechanisms of visual sensory processing in early typical development – a *proof-of-concept* study

5.1. Introduction

As reviewed in Chapter 1 and further discussed in Chapter 4, prospective longitudinal studies of infants at elevated likelihood of ASD and/or ADHD report commonalities between the disorders in early sensory vulnerabilities (Johnson, Gliga, et al., 2015; Little et al., 2018). In the visual modality, hypersensitivity to visual stimulation is documented as common evidence of unusual sensory profiles (Coulter, 2009; Ghanizadeh, 2011; Milne & Griffiths, 2007). In line with this evidence, results from Chapter 4 demonstrated that enhanced visual perception, indexed by elevated P1 peak amplitude to incoming visual stimulation, manifests in 10-month-old infants at elevated likelihood of ASD or ADHD. Further, results pointed to reduced modulatory capacity as a potential mechanism underlying the reported profile of hypersensitivity to visual input.

Evidence detailed in Chapter 4 aligns to Predictive coding theories, which postulate atypical visual perception to result from limited integration between feedforward and feedback signals (i.e. reduced active inference). However, the analysis conducted in Chapter 4 to assess the relationship between infants' engagement with the ongoing video clip and responsiveness to the incoming checkerboard stimulus was implemented post-hoc. Establishing a relationship between infants' engagement with the ongoing video clip (indexed by theta amplitude during video viewing) and responsiveness to the incoming checkerboard stimulus (indexed by P1 peak amplitude time-locked to the onset of the checkerboard) would require an independent study designed to experimentally

manipulate infants' engagement with the ongoing information. This study could provide further support for the notion that feedback signals (indexed by theta amplitude during video viewing) may modulate feedforward signals (indexed by P1 peak amplitude time-locked to checkerboard presentation). By uncovering the link between variation in responsiveness to incoming visual stimulation and variation in engagement with ongoing information, this study could shed light on the mechanisms underlying visual hypersensitivity in infants at elevated likelihood of ASD or ADHD, contemporarily fostering advancements in our understanding of the mechanisms underlying visual perception in early typical development. Chapter 5 details evidence from this *proof-of-concept* study.

5.1.1. Mechanisms of visual sensory processing in early typical development

Behavioural evidence. A widely used approach in developmental research to manipulate infants' engagement with ongoing information is through visual habituation procedures. Visual habituation paradigms have been extensively used in research with infants to assess the dynamics of visual perception through stimulus repetition (Nordt et al., 2016). In particular, these paradigms have been used to characterise infants' attention shifting from familiar (ongoing) to unfamiliar (incoming) information. In behavioural habituation studies, infants are repeatedly presented with a stimulus, such as a repeated image, either on its own, or paired with a stimulus that changes from trial to trial (for a review see, Colombo & Mitchell, 2009). A pattern of sustained, followed by decreasing, look durations to

a central stimulus is believed to reflect initial encoding of stimulus properties and subsequent depletion of information, once encoded (Hunter & Ames, 1988). When familiar and unfamiliar stimuli are presented side by side (i.e. paired-comparison procedure), an initial preference for the repeated but incompletely encoded stimulus is followed by a shift of looking to the changing stimulus (Fantz, 1964; Roder, Bushnell, & Sasseville, 2000; Rose & Feldman, 1987). Thus, in behavioural habituation paradigms, attention acts as a determinant of the observed effects. If exposure is too short for infants to build a complete representation of the repeated stimulus, infants will continue attending at the repeated rather than novel stimulus, thus manifesting a familiarity preference. Conversely, a novelty preference at test is suggestive of complete encoding of the repeated stimulus, rather than decrease in looking caused by general fatigue.

Overall, behavioural habituation paradigms have been fruitful for characterising the dynamics of infants' attention shifting from familiar (ongoing) to unfamiliar (incoming) information. In particular, these paradigms have enabled researchers to experimentally manipulate engagement with ongoing information through stimulus repetition and obtain a measure of infants' active processing of visual stimulation over time.

Neural evidence. In contrast to the abundant literature exploring the dynamics of infant visual perception through behavioural habituation paradigms, limited research has been conducted to evaluate the neural mechanisms underlying infants'

attention shifting from familiar (ongoing) to unfamiliar (incoming) information. Using a paired-comparison procedure, Snyder and Keil (2008) reported greater decreases in gamma power over occipital scalp sites during the repeated presentation of a face stimulus to predict enhanced behavioural orienting (i.e. looking) to a novel face stimulus in 6-month-old infants. Similarly, decreases in the amplitude of the ERP slow wave at right anterior temporal regions with repetition were documented during the encoding of a novel object in 6-month-old infants and predicted better memory performance at test (Snyder, 2010).

Thus, despite limited, the current evidence suggests that neural signatures signalling information processing progress can be detected in the developing brain and further predict infants' behavioural performance (as assessed by looking time measures) on stimulus selection tasks (e.g. novelty preference at test and recognition memory).

5.2. The current study

The current study was set up with the goal of assessing the hypothesis that variation in the P1 peak amplitude to incoming visual stimulation reflects variation in infants' engagement with ongoing information. To this goal, a modified version of the task described in Chapter 4 was developed to induce variation in engagement with ongoing information by means of stimulus repetition and an independent sample of 10-month-old infants at typical likelihood of ASD or ADHD was tested. Building on evidence from behavioural habituation paradigms, the task was designed to

manipulate information prioritization demands, thus enabling the quantification of separate indices of information processing progress and stimulus selection. A repeated video clip was presented intermixed with black-and-white static checkerboards flashed on top and coupled with the recording of EEG. Infants' information processing progress was quantified by assessing the modulation of frontal theta oscillatory amplitude (4-6Hz) during the repeated presentation of the video clip. Infants' stimulus selection was quantified by assessing the modulation of the P1 peak amplitude time-locked to checkerboard onset during the task.

As reviewed in Chapter 2 and further detailed in Chapter 4, modulations of the frontal theta rhythm have been shown to index information encoding in both adults (Klimesch, 1999) and infants (Begus et al., 2016, 2015; Orekhova et al., 2006). For example, oscillations in the frontal theta band during object manipulation predicted infants' subsequent object memory (Begus et al., 2015). Sustained frontal theta power was linked to the initial phase of learning and declined, as adult participants improved performance (Clarke, Roberts, & Ranganath, 2018). Based on this evidence and further informed by evidence from traditional habituation studies, I predicted observing a profile of initial sustained theta amplitude, followed by a later decrease in amplitude occurring as a function of video clip repetition. This non-linear modulation would reflect the progressive encoding and depletion of information (Clarke et al., 2018; Nordt, Hoehl, & Weigelt, 2016). Further, I predicted observing a reverse profile of modulation of

the P1 peak amplitude time-locked to checkerboard onset, which would inversely relate to theta amplitude.

This design resembles traditional habituation paradigms, in that repetition of the same video clip occurred throughout the task. However, in the present study, no behavioural criterion of cognitive habituation was employed (e.g. looking time). Rather EEG activity (i.e. frontal theta oscillatory amplitude) provided a measure of infants' progressive engagement and disengagement with the ongoing repeated video clip (Xie, Mallin, & Richards, 2018). Further, this design resembles the "interrupted stimulus paradigm", where a brief, peripheral stimulus is presented while the infant is engaged with another stimulus, typically a video (Richards & Turner, 2001). In contrast to the "interrupted stimulus paradigm", in the present study the infant did not have to make a gaze shift towards this stimulus; however, in both paradigms, the response evoked by the sudden-onset checkerboard captures a trade-off in infants' attention distribution between the incoming stimulus and the ongoing video.

5.3. Methods

5.3.1. Recruitment approach

All infants recruited for the research were born full-term (gestational age 38-42 weeks), weighed > 2,500g at birth and had no history of pre or perinatal medical complications. Further, all infants included in the study were typically developing, therefore had no known developmental atypicality, based on parental reports at

recruitment. Participants were recruited from a volunteer database at the Babylab, Centre for Brain and Cognitive Development. Informed written consent was provided by the parent(s) prior to the commencement of the study. Infants were tested if awake and in an alert state. The experimental protocol was approved by the Research Ethics Committee of the Department of Psychological Sciences, Birkbeck University of London (Protocol no. 171805). Families were reimbursed expenses for travel, subsistence and overnight stay if required. Further, families were given a certificate and t-shirt after their visit.

5.3.2. Participants

Forty-eight 10-month-old infants (24 females, mean age = 10 months and 4 days, SD = 14 days) participated in the study. Five infants were tested, but not included in the final sample of participants because of low tolerance of the EEG net, fussiness or excessive movement artifacts. Accordingly, n = 43 infants (22 females, mean age = 10 months and 4 days, SD = 14 days) were included in the final sample of participants and contributed to the analyses. The minimum number of required participants was determined by an a priori power analysis (conducted with the software *Gpower;* Erdfelder, Faul, Buchner, & Lang, 2009). According to Cohen (1988) and Sawilowsky (2009) a medium effect size in psychological studies is *R* = 0.50 and, considering an estimate power of 0.80, a minimum sample size of 24 infants was estimated to detect within-group repeated measure effects at an alpha-level of 0.05.

5.3.3. Stimuli

A modified version of the experiment described in Chapter 4 was employed for this study. Experimental stimuli consisted of a background dynamic video clip selected from the animated cartoon *Fantasia* by Walt Disney and a black-and-white static checkerboard. The clip was 40s long, it was repeated 10 times during the session and it was presented in the centre of the screen (covering a 22.5 cm wide x 12.5 cm vertical area, subtending a visual angle of 21^{o} x 12^{o}). The clip depicted dynamic, continuous, goal-directed actions, accompanied by music. The black-and-white static checkerboard was presented for 100ms, in the centre of the screen (covering a 30 cm wide x 30 cm vertical area, subtending a visual angle of 28^{o} x 28^{o}). The average luminance of the checkerboard was 1.56 cd/m^2 for the black patch and 228 cd/m^2 for the white patch. The checkerboard replaced the video clip which resumed following disappearance of the checkerboard from the interruption point.

As shown in Figure 5.1A, each trial began with the presentation of the video clip accompanied by music. Music was used throughout the task to promote infants' engagement with the visual scene. Further, visual and auditory stimuli remained synchronous throughout the task. The repeated clip was intermixed with presentation of black-and-white static checkerboards flashed on top (128 checkerboards; ISI=2-4s, random). The time-points (within the background video) when this stimulus was presented were the same for all infants and were not predictable for any individual infant. A photodiode connected to an oscilloscope was used to measure the onset of checkerboards. Music was not paused during

checkerboard presentation since this stimulus lasted only 100ms. The total experimental session duration was 8 minutes but the experimenter could interrupt the session earlier, in case of participants' fussiness, prolonged inattention or if requested by the parent.

5.3.4. Apparatus and procedure

Testing took place in a dimly illuminated room. Infants were seated on a parent's lap, 60cm from a screen (27 inches; width: 59.77cm, height: 33.62cm) and were allowed to use a pacifier. The sequence and timing of stimulus presentation was controlled using MATLAB. High-density EEG was collected using 124 channels of a 128-channel HydroCel Geodesic Sensor Net connected to a NetAmps 400 amplifier (Electrical Geodesic, Eugene, OR) and referenced on-line to the vertex (Cz). Signals were sampled at 500 Hz. A video camera situated below the screen used for stimulus presentation recorded the infants' bodily and facial behaviour. This information was used for online monitoring of infants' performance and offline behavioural coding.

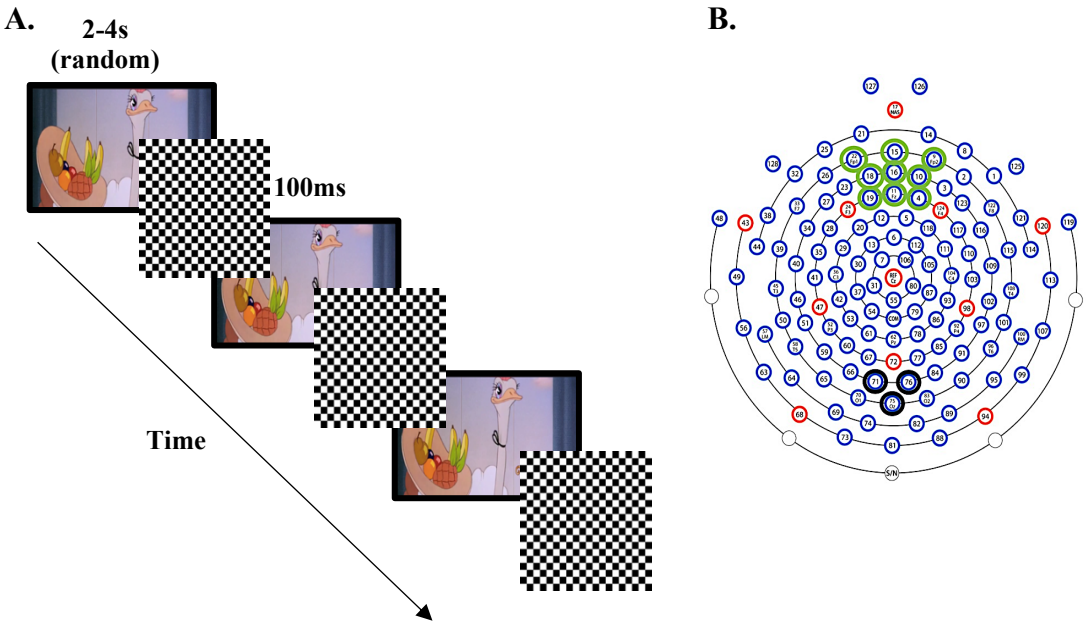

Figure 5.1. Schematic representation of the experimental stimuli, apparatus and procedure

A. Representation of the sequence of events in the experimental paradigm. A 40s long video clip from the animated cartoon "Fantasia" was repeatedly presented accompanied by music and randomly interrupted by the appearance of black-and-white static checkerboards (100ms) flashed on top (ISI = 2-4s, random). B. Hydrocel-Geodesic Sensor Net montage displaying the occipital (black circle) and frontal (green circle) pool of electrodes used for quantifying, respectively, visual evoked potentials (VEPs) time-locked to checkerboard onset and theta amplitude synchronization (θ = 4-6Hz) during video presentation.

5.3.5. Infants' gaze behaviour coding

Infants' gaze behaviour was coded offline with a computerized frame-by-frame observational coding system (25 frames/second – EGI Movie Player, Electrical Geodesic and Mangold Interact), enabling two independent coders to identify screen-directed looking (coded as 1) and looking away (coded as 0). In accordance with the processing pipeline reported in Chapter 2, offline coding was used for the purpose of EEG data processing and analysis. Trials in which the participant did not look at the screen from 1s before checkerboard onset until 1s after checkerboard offset were excluded from the analysis. To ascertain reliability, the second observer independently coded a random 30% of video files (i.e., 13 participants). An interrater reliability analysis using Cohen's Kappa was performed on the coded individual trials to determine consistency among observers. This analysis indicated that there was high agreement among the observers, κ=.992, (95% CI, .983 to .997), $p < .001$.

5.3.6. EEG recording and analysis

The EEG data was processed offline using Net Station (Electrical Geodesic) following the processing pipeline reported in Chapter 2. Specifically, the continuous EEG was filtered using a 0.3–40 Hz band-pass filter. The EEG signal was segmented from 500ms prior to checkerboard onset through 1500ms after checkerboard onset. Automated artifact detection was applied to the segmented data to detect individual epochs that showed >200μV voltage changes within the

segment period. EEG recordings were visually inspected and individual channels within segments were eliminated from the analysis if artifacts occurred. Segments whereby infants did not look at the screen as indicated by behavioural coding were further excluded from analysis. Segments in which >15% of the channels (18 channels) were marked as bad were excluded from the analysis. For the remaining trials, spherical spline interpolation was conducted to replace data for bad channels using the five closest electrodes. Infants were excluded from the analysis if they had less than 10 artifact-free segments (see Table 15).

Artifact-free data was binned into four consecutive time intervals, each consisting of maximum 32 segments. Binning of artifact-free data was implemented to estimate a measure of intra-participant modulation of VEPs time-locked to checkerboard presentation and EEG frontal theta amplitude during video viewing. The choice of 4 time bins was made to achieve optimal balance between 1) having enough trials per time bin to maximise the signal-to-noise ratio and 2) having enough time bins to estimate non-linear modulatory effects in the extracted EEG/VEP measures. On average, the mean number of segments by which infants contributed to the analysis of VEPs time-locked to checkerboard presentation and EEG frontal theta amplitude during video viewing was M = 30.74, SD=4.12 for bin 1, M=29.13, SD=6.54 for bin 2, M=25.69, SD=8.29 for bin 3 and M=22.46, SD=8.23 for bin 4. Results of statistical analyses are reported below with and without inclusion of number of valid trials as covariate.

Table 15. *Number of 10-month-old infants included and excluded from the EEG analyses (i.e. due to contributing less than 10 artifact free trials) and number of trials presented and retained.*

Participants	**n**
Included	43
Excluded	5
Trials	**n**
Presented	101
Retained	81

5.3.7. Quantification of visual evoked potentials (VEPs)

To quantify VEPs time-locked to checkerboard onset, averaged waveforms were generated for each participant, re-referenced to average reference and baseline corrected by subtracting the average of the 100 ms pre-stimulus period. Inspection of the grand-averaged waveform indicated that the P1 component was reliably elicited at checkerboard onset over the occipital scalp site (see Figure A5.2.2 in Appendix to Chapter 5). Based on previous literature (Lunghi et al., 2019; Richards, 2000) and on visual inspection of both the grand-averaged and individual waveforms, channels (CH) 71, 75 and 76 (see Figure 5.1B) were clustered and the average activity over these channels was computed for each participant. Based on the individual and grand-averaged data, as well as on previous literature (Lunghi et al., 2019; Richards, 2000), the peak amplitude of the P1 was extracted following the procedures described in Chapter 2 within a time window of 100-150ms after the onset of the checkerboard (see Figures 5.2).

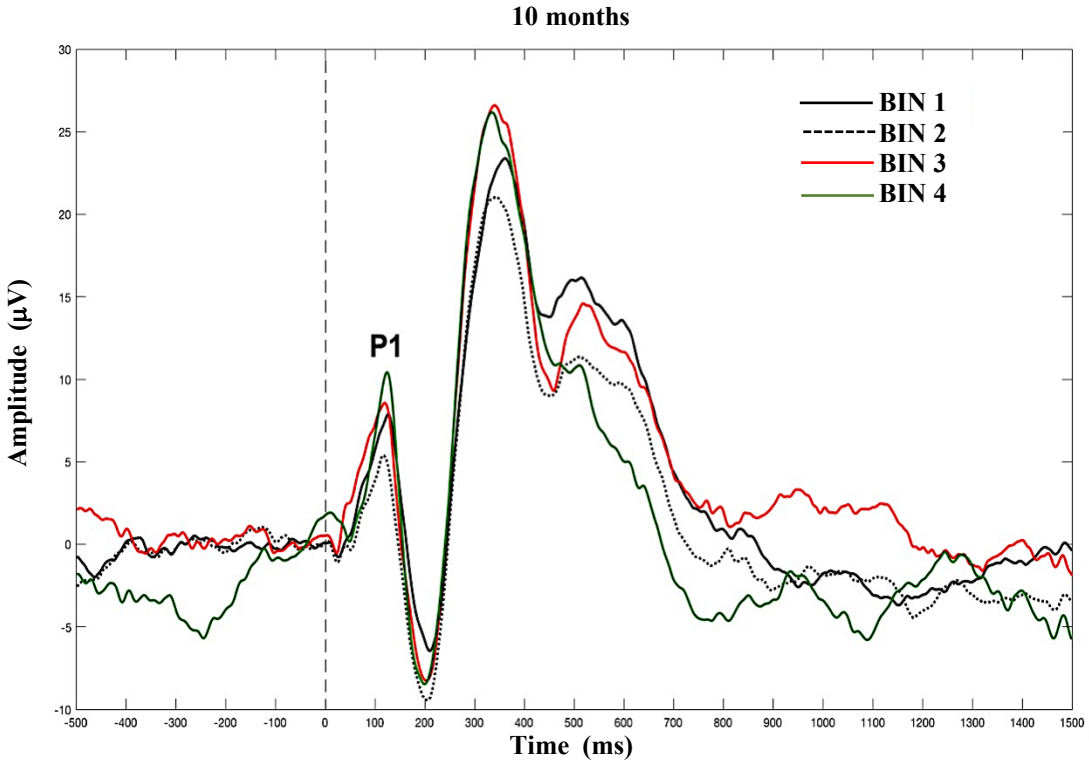

Figure 5.2. Grand-averaged visual evoked potentials (VEPs) time-locked to checkerboard onset for each time bin

Grand-averaged VEPs at 10 months; (Black=VEPs for bin 1; Dotted black= VEPs for bin 2; Red=VEPs for bin 3; Green= VEPs for bin 4).

5.3.8. Time-frequency analysis of EEG

Time-frequency decomposition was used to quantify oscillatory theta synchronization (4-6Hz) during video clip presentation. Artifact-free segments were imported into MATLAB using EEGLAB (v. 13.4.3b) and re-referenced to the average reference. The collection of scripts *WTools* (see Parise & Csibra, 2013; available upon request) was used for spectral decomposition, employing Complex Morlet wavelets for the frequencies 3-20Hz (1Hz resolution; real-valued Gaussian with n = 3.5 cycles per time unit). A continuous wavelet transformation of all segments by means of convolution with each wavelet was performed and the absolute value of the results was extracted. To remove the distortion introduced by convolution at segment ends, 1000ms zero-padding was performed. The amplitude of the 100ms interval prior to the window of interest was used as a baseline and subtracted from the whole epoch at each frequency. Segments were chopped to obtain epochs indexing the activity occurring during a 400ms-long period of video clip presentation before checkerboard onset. Individual epochs were averaged for each time bin. Inspection of the time-frequency plots revealed that 4-6Hz frontal theta synchronization was reliably elicited in response to the video clip over the frontal scalp site. As reviewed in Chapter 2 and further discussed in Chapter 4, substantial evidence indicates that phases of information encoding are accompanied by a sharp increase in 4-6Hz frontal theta during infancy and toddlerhood (Begus et al., 2015; Orekhova et al., 2006). Based on previous literature and on visual inspection of both the grand-averaged and individual time-frequency plots,

channels (CH) 4, 9, 10, 11, 15, 16, 18, 19, 22 (see Figure 5.1B) were clustered and the average 4-6Hz amplitude was extracted during the 400ms of video clip presentation occurring before the onset of the checkerboard for each time bin, see Figures 5.3.

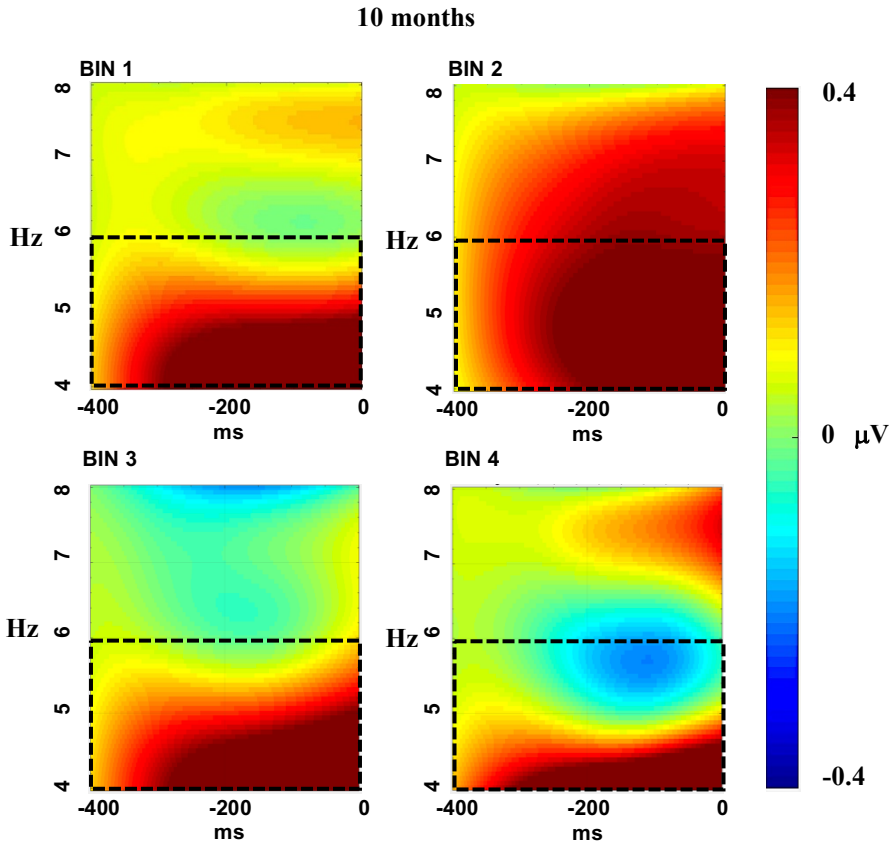

Figure 5.3. Time-frequency plots illustrating the amplitude of theta (θ = 4-6Hz) oscillations during video clip presentation

Grand-averaged time-frequency plots at 10 months; Black dotted rectangles indicate the 400ms long time-windows during video clip presentation selected for statistical analysis. Amplitude scale is -0.4, 0.4µV.

5.3.9. Analytical strategy

Statistical analyses were conducted with SPSS v23 (IBM Corp 2015) and R (Team, 2017). Prior to performing any inferential statistical analyses, I assessed the variables for normality. No significant violations of normality emerged, therefore no transformations were applied to the data.

I first investigated the change in frontal theta oscillatory amplitude during video viewing and P1 peak amplitude time-locked to checkerboard onset as a function of time (bin). I adopted a Generalized Estimated Equation (GEE) approach assuming a Gaussian distribution and identity link with time (categorical: bin 1, bin 2, bin 3 and bin 4) as factor and P1 peak amplitude (continuous) or theta amplitude (continuous) as dependent variables, respectively. This approach was chosen to account for within-subject correlations and to handle missing data consequent to not all infants completing the experimental session. Wald tests were computed to determine the significance of the effects in both cases.

Secondly, I performed a repeated measure correlation analysis assessing the association between P1 peak amplitude time-locked to checkerboard onset and theta amplitude during video viewing for the four time bins. This statistical approach was chosen to account for the non-independence of observations and preserve the individual variation present in the data. The package "*rmcorr*" was used for the analysis (R Core Team, 2017; Bakdash & Marusich, 2017).

Finally, to further characterize the dependency between the neural measures, I computed the scaled difference in frontal theta amplitude and in the

peak amplitude of the P1, respectively, between bin 3 and bin 2 for each infant (i.e. theta modulation index: [theta bin 3 – theta bin 2] / [theta bin 3 + theta bin 2]; P1 modulation index: [P1 bin 3 – P1 bin 2] / [P1 bin 3 + P1 bin 2]). These time bins were chosen for three reasons: 1) they suffered less form data loss than bin 4 did (29 participants with 3 bins, 13 with 4 bins), 2) the change between bins 2 and 3 was on average larger than between bins 1 and 2, thus providing more variance for the analysis and 3) conceptually, the decrease in theta amplitude (rather than the increase occurring from bin 1 to 2) was closer to a measure of information depletion (Clarke et al., 2018). A follow-up analysis on earlier time bins (i.e. bin 1 and bin 2) was also conducted to corroborate results emerged from the analysis of later time bins.

5.4. Results

5.4.1. Task-dependent modulation of neural measures

Theta (θ = 4-6Hz) amplitude. A significant main effect of time bin was observed, (Waldχ^2 (3) =23.22, $p < .001$). This result did not change when the number of valid trials for the four time bins was added as a covariate (Waldχ^2 (3) =21.94, $p < .001$). Bonferroni corrected pairwise comparisons indicated that frontal theta amplitude significantly increased from bin 1 to bin 2 ($p < .001$), significantly decreased from bin 2 to bin 3 ($p < .001$) and did not change from bin 3 to bin 4 ($p = .128$). See Figure 5.4A and Table 16.

P1 peak amplitude. A significant main effect of bin was observed (Waldχ^2 (3) =53.69, $p < .001$). This result did not change when number of valid trials for the four time bins was added as a covariate (Waldχ^2 (3) =55.21, $p < .001$). Bonferroni corrected pairwise comparisons indicated that the peak amplitude of the P1 significantly decreased from bin 1 to bin 2 ($p < .001$) and significantly increased from bin 2 to bin 3 ($p < .001$). No change was observed from bin 3 to bin 4 ($p = .115$). See Figure 5.4B and Table 16.

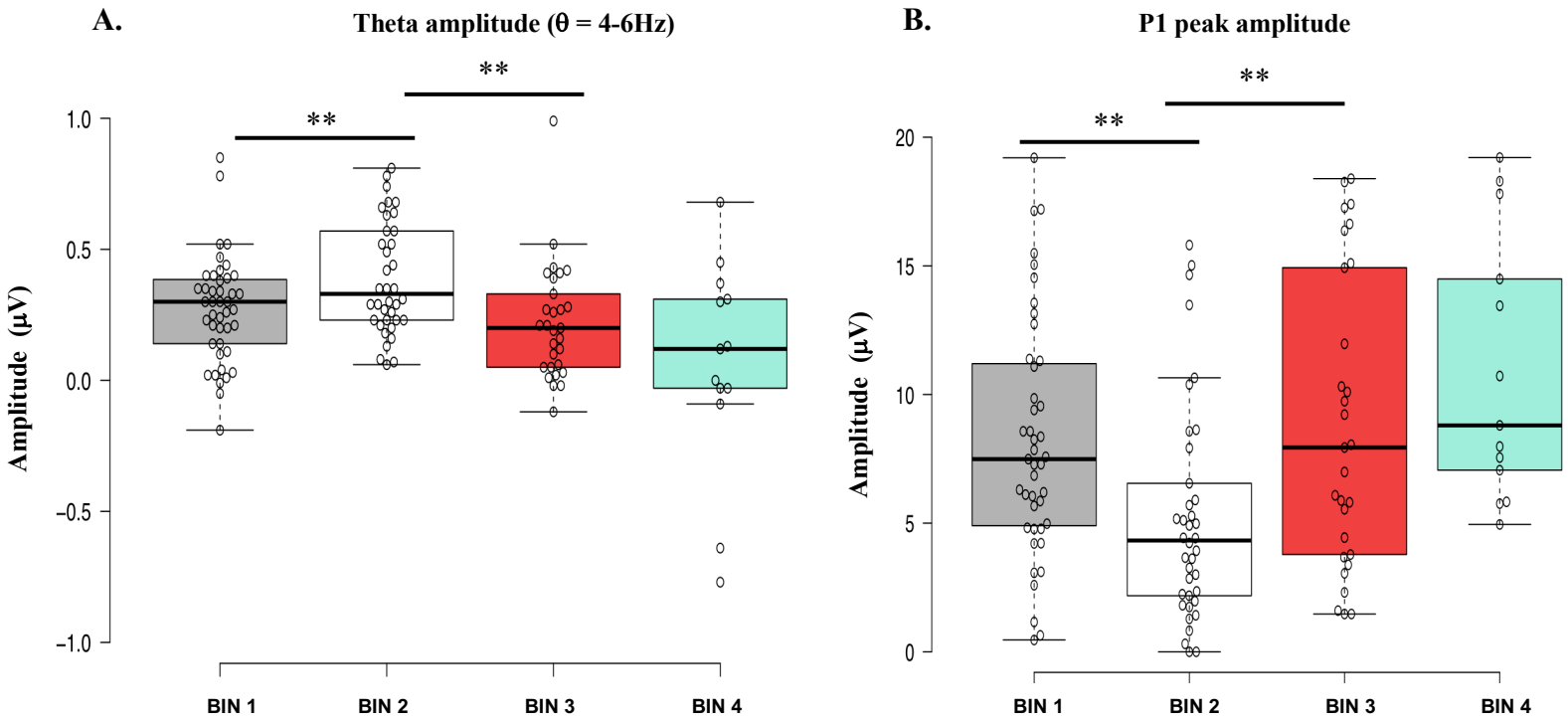

Figure 5.4. Boxplots illustrating theta amplitude and P1 peak amplitude for each time bin

A. *Theta amplitude modulation; B. P1 peak amplitude modulation; (Grey= bin 1; White= bin 2; Red= bin 3; Green= bin 4). A significant change in theta amplitude and in the P1 peak amplitude manifested from bin 1 to bin 2 and from bin 2 to bin 3.*

*** p < .001.*

Table 16. *Mean and standard error for each neural measure (P1 peak amplitude time-locked to checkerboard onset and 4-6Hz theta amplitude during video viewing). Descriptive statistics are reported separately for each time bin.*

Mean (SE)	BIN 1	BIN2	BIN3	BIN 4
P1 peak amplitude	8.22 (.694)	5.21 (.679)	8.86 (1.04)	10.91 (1.36)
Theta amplitude	.270 (.030)	.404 (.039)	.219 (.040)	.062 (.108)

5.4.2. Intra-participant modulation of the P1 peak amplitude by ongoing theta amplitude

Association between theta amplitude and P1 peak amplitude. The repeated measure correlation between the measures was statistically significant, (R_{rm} (79) = -0.250, p = .025, 95% CI [−0.45, −0.029]), indicating that the higher the engagement with the video stimulus, as indexed by frontal theta oscillatory amplitude, the lower the responsiveness to the checkerboard, as indexed by the peak amplitude of the P1. Additionally, the negative association between P1 peak amplitude and frontal theta amplitude held within each time bin. See Table 17.

Association between theta modulation index and P1 modulation index. The Pearson correlation between the measures was statistically significant, R (27) = -.386 p = .021, R^2 = .149, indicating that the stronger the modulation of frontal theta

amplitude, the stronger the modulation of the P1 peak amplitude. See Figure 5.5 and Table 17.

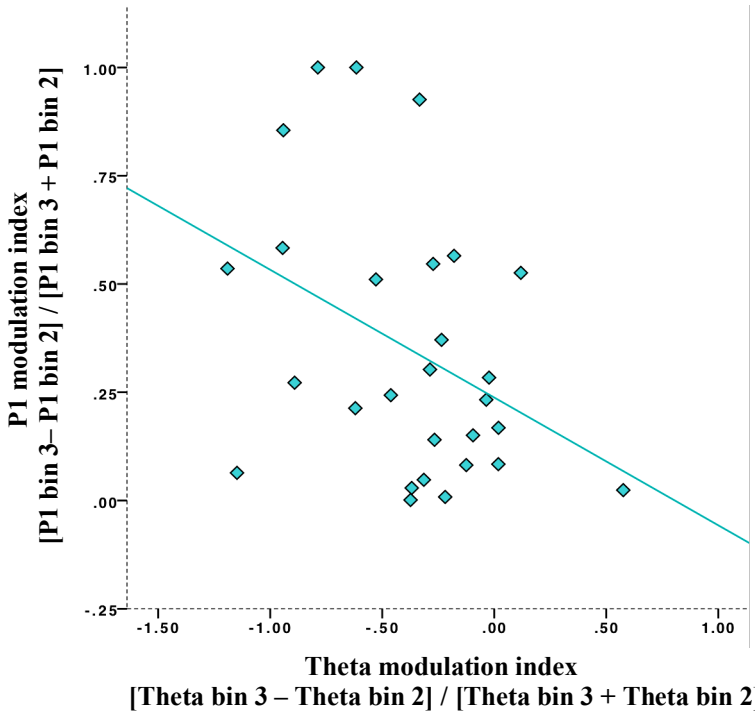

Figure 5.5. ***Scatterplot illustrating the association between theta modulation index and P1 modulation index for bin 2 and 3***

The stronger the modulation of frontal theta amplitude to the video, the stronger the modulation of the P1 peak amplitude to the checkerboard (p< .05). Individual variation manifested in the association between theta modulation index and P1 modulation index: above the fit line are infants whose P1 change is larger than expected from theta change, below the fit line are infants whose P1 change is smaller than expected from theta change. Note: the direction of the association is

negative since theta amplitude decreased and P1 peak amplitude increased from bin 2 to bin 3.

***Table 17**. Correlation coefficients (Pearson R) for associations between neural measures (P1 peak amplitude to the checkerboard and theta amplitude during video viewing estimated with a repeated measure approach; P1 modulation index and theta modulation index estimated with a traditional approach).*

Repeated measure correlation	P1 peak amplitude
Theta amplitude	-.250*
Pearson correlation	P1 modulation index
Theta modulation index	-.386*

* $p < .05$

5.4.3. Main analytical pipeline – Interim summary

Results of the analyses conducted to this point confirmed the capability of the experimental paradigm to capture a trade-off in infants' attention distribution to the ongoing repeated video clip and incoming checkerboard stimulus. In particular, results from the investigation of theta oscillatory amplitude during video viewing indicated that this neural measure manifested an initial increase, followed by a later decrease. This evidence confirmed my prediction that theta amplitude during the repeated presentation of the video clip would have exhibited a non-linear modulatory profile, reflecting the progressive encoding and depletion of information. Similarly, as predicted, results from the investigation of the P1 peak

amplitude time-locked to checkerboard onset indicated that this neural measure was non-linearly modulated and exhibited a profile that was inversely related to theta oscillatory amplitude (i.e. initial decrease, followed by a later increase). Importantly, results from the analyses investigating the association between P1 modulation index and theta modulation index disclosed individual variation in infants' information prioritization, with some infants prioritizing the processing of the incoming checkerboard stimulus, and other infants prioritizing engagement with the ongoing video clip (see caption to Figure 5.5) – a notion that I will further explore in Chapter 6.

5.4.4. Analysis on bin 1 and bin 2

To further support results of the analyses run on bin 2 and bin 3, the same analytical pipeline was conducted on bin 1 and bin 2. First, a theta modulation index and a P1 modulation index were quantified for bin 1 and bin 2 using the procedure described in section 5.3.9. Normality assumptions for the two indexes were assessed and no violations detected.

Association between theta modulation index and P1 modulation index. The Pearson correlation between the theta modulation index and the P1 modulation index estimated for bin 1 and 2 was statistically significant, R (36) = .288, p = .040, R^2 = .083, indicating that the stronger the modulation of theta amplitude, the stronger the modulation of the P1 peak amplitude. See Figure 5.6.

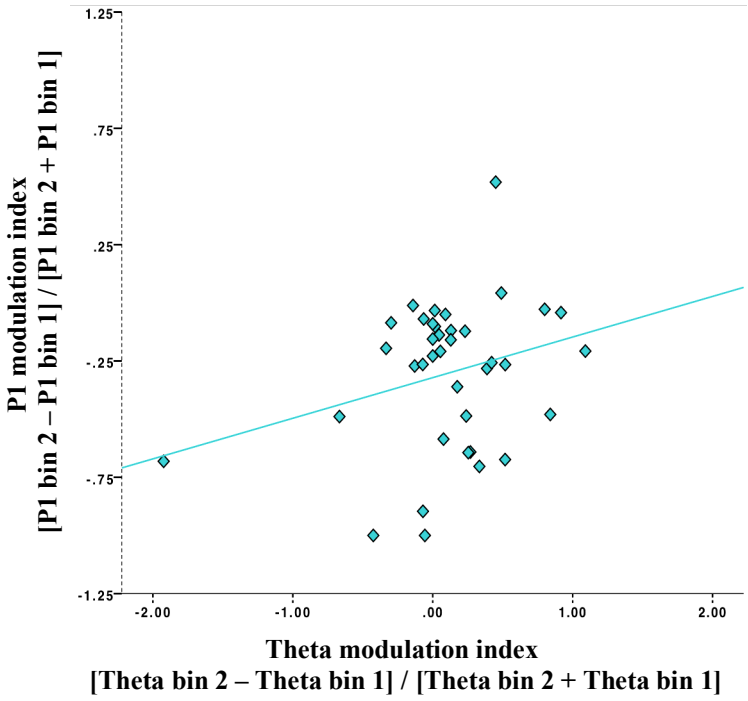

Figure 5.6. ***Scatterplot illustrating the association between theta modulation index and P1 modulation index for bin 1 and bin 2***

The stronger the modulation of frontal theta amplitude to the video, the stronger the modulation of the P1 peak amplitude to the checkerboard (p< .05). Note that the direction of the association is positive since theta amplitude increased and P1 peak amplitude decreased from bin 1 to bin 2.

5.4.5. Follow-up analysis – Interim summary

I performed a follow-up analysis with the goal of corroborating results emerged from the core analyses. Results from the analysis of theta amplitude and P1 peak amplitude modulation occurring during earlier time bins (bin 1 and 2) confirmed the dependency between the neural measures. In particular, results confirmed that

also for earlier time bins, stronger modulation of theta amplitude (i.e. increase manifested from bin 1 to bin 2) associated with stronger modulation of the P1 peak amplitude (i.e. decrease manifested from bin 1 to bin 2).

5.5. Discussion

5.5.1. General points

The goal of the current study was to assess the hypothesis that variation in responsiveness to incoming visual stimulation reflects variation in engagement with ongoing information. To this goal, a modified version of the task described in Chapter 4 was developed and an independent sample of 10-month-old infants at typical likelihood of ASD or ADHD was tested. Building on evidence from traditional habituation paradigms, whereby the repeated presentation of a stimulus is known to induce a pattern of sustained, followed by decreased look durations reflecting the initial encoding of stimulus properties and subsequent depletion of information (Fantz, 1964; Hunter & Ames, 1988; Roder et al., 2000; Rose & Feldman, 1987), the current paradigm was designed to experimentally manipulate information prioritization demands. 10-month-old infants were repeatedly presented a video clip briefly interrupted by black-and-white static checkerboards overlaid on top. EEG/VEP responses were recorded. This paradigm enabled quantification of separate indices of information processing progress (i.e. modulations of frontal theta oscillatory amplitude to the ongoing video) and

stimulus selection (i.e. modulations of the P1 peak amplitude time-locked to the incoming checkerboard stimulus).

Results demonstrated the capability of the paradigm to capture a trade-off in infants' attention distribution to the ongoing video and flashed checkerboard stimuli. Frontal theta oscillatory amplitude to the repeated presentation of the video clip manifested a non-linear modulatory profile, which reflected the progressive encoding and depletion of information (Clarke et al., 2018; Nordt, Hoehl, & Weigelt, 2016). Although I hypothesised theta oscillatory amplitude to manifest a profile of initial sustained activation, followed by a later decrease, I actually observed an increase from bin 1 to bin 2. Other studies have characterised an initial phase of increased engagement with information in the visual modality. For example, infants become less distractible as a look towards a video stimulus progresses (Richards & Turner, 2001). The mechanism involved remains unknown but some have observed changes in scanning from shorter to longer fixations made to adjacent regions of the scene, as adult participants viewed video material (Fischera, Graupnera, Velichkovsky, & Pannasch, 2013; Pannasch, Helmert, Roth, & Walter, 2008). While this explanation remains speculative, it is possible that, when presented with new information (i.e. the unfamiliar video clip), infants initially explored the scene before fully engaging with its contents to extract information about particular aspects of the video.

More importantly for the hypothesis under examination, the peak amplitude of the P1 to sudden-onset checkerboards was non-linearly modulated and

exhibited a profile that was inversely related to theta amplitude. Specifically, an increase in the P1 peak amplitude to the checkerboard manifested as a function of decreased theta amplitude to the repeated video clip.

Altogether, these results confirm the hypothesis that variation in the P1 peak amplitude to the checkerboard reflects variation in theta amplitude to the ongoing video clip. By establishing a link between infants' engagement with the ongoing video clip and responsiveness to the incoming checkerboard stimulus, the present study corroborates the notion that limited integration between feedback and feedforward signals may be the mechanism underlying the profile of hypersensitivity to incoming visual stimulation documented in infants at elevated likelihood of ASD or ADHD in Chapter 4.

5.5.2. How do these results inform our understanding of the mechanisms underlying the early development of sensory perception in in ASD, ADHD and typical development?

Altogether, results from the current study foster progress in our understanding of the mechanisms of visual sensory processing in early typical and atypical development. First, aligning to Predictive coding theories, the present results indicate that the integration between feedforward and feedback signals lies at the core of typical visual perception since early in development. Relatedly, by supporting the hypothesis that variation in the P1 peak amplitude to the incoming stimulus reflects variation in theta amplitude to the ongoing video clip, the current

results corroborate the notion that reduced integration between feedforward and feedback signals may underlie the profile of enhanced visual sensory processing documented in infants at elevated likelihood of ASD or ADHD in Chapter 4. Further, the current results reduce the likelihood of enhanced perceptual functioning (conceptualised as a purely bottom-up or feedforward-oriented processing style) as an alternative explanation for the profile of hypersensitivity to visual input manifested in infants at elevated likelihood of ASD or ADHD.

The trade-off between information processing progress (indexed by frontal theta oscillatory amplitude modulation) and bias towards incoming stimulation (indexed by P1 peak amplitude modulation) highlighted by this research also provides support for developmental theories portraying optimal learning as evidenced by a shift from exploitation of the resource at hand to exploration of incoming sensory input (Cohen, McClure, & Yu, 2007; Mather, 2013; Twomey & Westermann, 2018). The specificity of the current paradigm lies in its ability to characterise these interacting mechanisms at a neural level. By disclosing individual differences in the prioritisation of incoming stimulation relative to ongoing information, the current research leads to the hypothesis that variation in information prioritization may manifest early in development and potentially canalise trajectories towards later atypical development. I further explore this notion in Chapter 6, whereby I investigate the extent to which individual differences in the prioritization of incoming relative to ongoing stimulation may explain parent-reported sensory profile differences, ASD and ADHD traits emerging in

toddlerhood. I speculate that preserving individual variation in how we assign relative value to ongoing relative to incoming stimulation and in how we are differentially drawn to seek sensory input carries an evolutionary advantage, in that it promotes discovery, at a population level, contemporarily fostering learning and consolidation of the acquired knowledge.

5.6. Conclusion

Overall, the current study suggests that the integration between feedforward and feedback signals lies at the core of typical visual perception since infancy. Relatedly, by highlighting a link between modulation of the P1 peak amplitude to incoming visual stimulation and theta amplitude during video viewing, the present results support the notion that the weaker association between the measures in infants at elevated likelihood of ASD or ADHD may reflect reduced feedback modulation of feedforward visual processing.

5.7. Summary of Chapter 5

Informed by evidence emerged in Chapter 4, Chapter 5 set out to test the hypothesis that variation in the P1 peak amplitude time-locked to checkerboard onset reflects variation in theta amplitude during video viewing. To this goal, a modified version of the experiment used in Chapter 4 was designed to manipulate engagement with the ongoing video clip by means of stimulus repetition and an independent sample of 10-month-old infants was tested. Results confirmed that variation in the P1 peak

amplitude to the incoming stimulus is linked to variation in theta amplitude during video viewing. Altogether, this proof-of-concept study confirms the hypothesis that the integration between feedforward and feedback signals lies at the core of typical visual perception since early in development and provides evidence in favour of the idea that reduced feedback modulation of feedforward visual processing may be the most likely mechanism underlying the profile of enhanced visual sensory processing in infants at elevated likelihood of ASD or ADHD.

Chapter 6: An *individual differences* approach to the investigation of sensory seeking, ASD and ADHD traits in early development

6.1. Introduction

Chapter 4 reported evidence of hypersensitivity to visual stimulation in 10-month-old infants at elevated likelihood of ASD or ADHD and pointed to reduced modulatory capacity (i.e. the ability to modulate responsiveness to incoming visual stimulation based on engagement with ongoing information) as a likely mechanism underlying the observed profile of enhanced visual perception. Evidence also indicated that early reduced modulatory capacity is a marker predicting later ASD (but not ADHD) traits in toddlerhood. While results did not enable establishing visual sensory seeking as a factor mediating or moderating the association between early reduced modulatory capacity and later ASD traits, they nonetheless suggested that reduced seeking of visual input may be the preferred strategy of information prioritization in the face of early reduced modulatory capacity.

Chapter 5 extended evidence from Chapter 4 by indicating that variation in responsiveness to incoming visual stimulation reflects variation in engagement with ongoing information, thus establishing reduced feedback modulation of feedforward visual processing as a mechanism underlying the profile of hypersensitivity to visual stimulation in infants at elevated likelihood of ASD or ADHD. Importantly, results from Chapter 5 also disclosed individual variation in infants' information prioritization, with some infants prioritizing the processing of incoming checkerboard stimuli, and other infants prioritizing engagement with the ongoing, repeated video clip. In light of these results, the dataset described in Chapter 5 appears suitable to investigate whether, also in an independent cohort of

infants at typical likelihood of ASD or ADHD, an association may exist between modulatory capacity and parental report of visual sensory seeking. Furthermore, given the controlled nature of the experiment reported in Chapter 5, whereby variation in infants' responsiveness to incoming visual stimulation was elicited through manipulation of engagement with the ongoing, repeated video clip, the dataset contributing to Chapter 5 may prove useful to clarify the nature of visual sensory seeking manifestations in infancy.

The current chapter aims at achieving both goals, that is 1) replicating the evidence reported in Chapter 4 in an independent cohort of infants at typical likelihood of ASD or ADHD and 2) characterising of the nature of sensory seeking behaviours in early typical development, with important implications for our understanding of sensory seeking in early atypical development. To these goals, an *individual differences* approach will be employed and data from the same cohort of 10-month-old infants that contributed EEG data in Chapter 5 will be re-analysed in conjunction with concurrent and longitudinal parental reports of sensory seeking, ASD and ADHD traits emerging in toddlerhood.

6.1.1. Explaining individual differences in infant visual sensory seeking

As reviewed in Chapters 1 and 2, manifestations consistent with reduced seeking of sensory input are often reported in the early development of ASD (Ben-Sasson et al., 2009; Beranova et al., 2017; Damiano-Goodwin et al., 2018; Mulligan & White, 2012; Tomchek & Dunn, 2007). This evidence was further replicated in

Chapters 3 and 4, whereby infants at elevated likelihood of ASD manifested reduced sensory seeking (in the tactile and visual modality, respectively). Importantly, evidence from Chapter 3 further indicated that elevated sensory seeking in infancy may act as a protective factor and mitigate later-emerging ASD traits. Two questions arise from this evidence: *1) what may be the consequences of reduced sensory seeking for the early development of ASD?* and *2) why would elevated sensory seeking in infancy have a beneficial effect over development?* Adopting an individual differences approach towards explaining sensory seeking behaviours in infancy may help answering these questions.

Individual differences in infants' engagement with their environment are reported from early in development. For example, observational studies, in which infants' exploration of their environment is recorded, describe variation in how many of the objects in their proximity or how many different aspects of a complex object infants engage with (Bornstein, Hahn, & Suwalsky, 2013; Muentener, Herrig, & Schulz, 2018). As reviewed in Chapter 2, studies using parent-reported questionnaires, such as the ITSP (Dunn, 2002), capture differences in the extent to which infants are driven towards novel stimulation, for example by asking how much the child enjoys looking at shiny or moving objects or at fast-paced TV shows. Different theoretical proposals have been put forward to explain individual differences in seeking sensory stimulation. According to one theoretical view, individuals' active engagement with their environment strives to achieve an optimal level of stimulation (Zentall & Zentall, 1983). For example, it was suggested that

decreased seeking of stimulation develops as a strategy to protect an organism that is either exposed to intense stimulation or that responds too strongly to sensory input. This proposal draws heavily on studies of sensory processing in atypical populations. As discussed throughout the chapters of this thesis, sensory atypicalities, manifested as increased or decreased sensitivity or as atypical seeking of sensory stimulation, are documented in populations with ASD (Ben-Sasson et al., 2009; Damiano-Goodwin et al., 2018; Mulligan & White, 2012) or ADHD (Bijlenga, Tjon-Ka-Jie, Schuijers, & Kooij, 2017; Dunn & Bennett, 2002; Ghanizadeh, 2011; Yochman, Parush, & Ornoy, 2004). During early childhood, ASD has often been associated with increased behavioural (Baranek, Foster, & Berkson, 1997; Baranek et al., 2007) and neural response to sensory input (Kolesnik et al., 2019; Miyazaki, Fujii, Saijo, Mori, & Kagami, 2007), and decreased seeking of sensory stimulation (Ben-Sasson et al., 2009; Beranova et al., 2017; Damiano-Goodwin et al., 2018; Mulligan & White, 2012; Tomchek & Dunn, 2007). Conversely, during late childhood and adulthood, ASD has been linked to both increased and decreased behavioural (Ausderau et al., 2014; Rogers & Ozonoff, 2005) and neural response to sensory input (Cascio, Gu, Schauder, Key, & Yoder, 2015; Marco et al., 2011), and elevated seeking of restricted, repetitive and often self-produced sensory stimulation (Ben-Sasson et al., 2009; Lane, Young, Baker, & Angley, 2010; Liss, Saulnier, Fein, & Kinsbourne, 2006; Simpson, Adams, Alston-Knox, Heussler, & Keen, 2019; Tomchek, Little, Myers, & Dunn, 2018). Increased or decreased sensitivity and atypical seeking of sensory stimulation have

mostly been investigated separately in individuals with atypical development, but Donkers et al., (2015) reported that enhanced amplitude of evoked potentials to auditory input associated with decreased sensory seeking in 4-12 years old children with ASD – a result aligning to the optimal stimulation hypothesis. Further, I documented in Chapter 4 that 10-month-old infants at elevated likelihood of ASD and/or ADHD displaying hypersensitivity to visual input and reduced ability to modulate responsiveness to incoming visual stimulation based on engagement with ongoing information manifested reduced visual sensory seeking, as quantified through the parent-reported ITSP. Despite this evidence, no research has yet assessed the validity of the optimal stimulation hypothesis in infants at typical likelihood of ASD or ADHD.

Others have proposed that individual differences in seeking stimulation may reflect differences in information processing abilities. Models of attention concur in suggesting that information is foraged for in a similar way as other resources (e.g. food), where a current source of information is sampled (exploited) until the effort needed to extract additional information outweighs the effort needed to seek information (explore) elsewhere, at which point a shift in the direction of attention occurs (Calhoun & Hayden, 2015; Hills et al., 2015). It follows that the faster individuals process information, the more different sources of information they may be able to seek, and process. From a developmental perspective, information processing speed was proposed as a factor underlying cognitive continuity from infancy to childhood (Colombo, 1993). Indeed, early observational

measures of object exploration (e.g. the number of objects infants touched and the duration of object manipulation), which can be conceived as an index of seeking perceptual novelty, associate with childhood measures of IQ (Banerjee & Tamis-LeMonda, 2007; Bornstein et al., 2013). Despite this evidence, it remains a question for debate whether cognitive ability drives the seeking of novel sensory input (Powell & Nettelbeck, 2014; Von Stumm, Hell, & Chamorro-Premuzic, 2011).

Finally, a third theoretical proposal suggests that, rather than reflecting differences in information processing, differences in seeking novel stimulation are a marker of individual variation in the prioritisation of incoming relative to ongoing information processing (Desimone & Duncan, 1995). While a shift between exploitation and exploration is expected as a current source of information is depleted (i.e. the information is learned) (Cohen, McClure, & Yu, 2007), exactly how much learning is considered sufficient to disengage with a current stimulus, when the opportunity to engage with novel stimulation appears, is subject to individual variation. Infants' approach of novel objects is under the influence of dopamine receptor polymorphisms (Lakatos et al., 2003), thus suggesting that prioritization of novel stimulation may be done by assigning it a reward value (Snyder, Blank, & Marsolek, 2008).

In summary, three theoretical proposals have been advanced in the literature to explain individual differences in infant visual sensory seeking: 1) the *optimal stimulation* hypothesis; 2) the *processing speed* hypothesis and 3) the *information prioritization* hypothesis. As detailed in section 6.1, Chapter 5 reported

evidence from an EEG/VEP task performed with 10-month-old infants at typical likelihood of ASD or ADHD which proved suitable for the quantification of separate indices of infants' information processing progress and stimulus selection. These measures, in turn, may be useful for probing which of the above hypotheses may best explain individual differences in parent-reported visual sensory seeking in infants with later typical development, with important implications for our understanding of sensory seeking manifestations in the early development of ASD.

6.2. The current study

6.2.1. Core analytical pipeline

In line with the three hypotheses present in literature to explain individual differences in seeking sensory stimulation in early development, I first tested whether visual sensory seeking differences reflect striving for *optimal stimulation*: in this case I predicted that lower visual seeking would associate with stronger VEPs (P1 peak amplitude) in response to the checkerboard (i.e. a measure of the strength of bottom-up responsiveness to sensory input). I tested the *processing speed* hypothesis by investigating the association between visual sensory seeking and the degree of change in frontal theta oscillatory amplitude with video repetition. In particular, I analysed the decrease in theta amplitude observed after repeatedly seeing the video and indexing the depletion of information. I predicted that stronger decrease in theta amplitude, indexing faster processing of ongoing information, would associate with increased visual seeking. Finally, I tested whether seeking

relates to *information prioritization* – under this hypothesis, I expected higher visual seeking in those infants whose modulation of VEP responses (change in P1 peak amplitude) was stronger than expected based on their change in theta amplitude. As indicated in Chapter 5, while the P1 and theta measures remained inversely related throughout the task, individual variations occurred in infants' information prioritization, with some infants prioritizing the processing of incoming stimulation and other infants prioritizing the processing of the ongoing repeated video clip. Thus, I expected infants to depart from this regression line, with some exhibiting larger P1 changes than those expected from the decrease in theta amplitude and other participants manifesting smaller changes. A larger than expected change would capture stronger bias attributed to incoming over ongoing information processing.

As in previous chapters, also in the current chapter I quantified visual sensory seeking through the parent-reported ITSP (Dunn, 2002). Given the goal of replicating in an independent cohort of infants at typical likelihood of ASD or ADHD the evidence emerged from Chapter 4 (whereby 10-month-old infants were tested) also in the current study data was contributed by infants aged 10 months (and results replicated at a later time point, i.e. 16 months). The second reason behind the choice of this age range lies in the qualitative shift in the nature of visual attention that occurs during the first year of life (Colombo, 2001; Johnson & De Haan, 2015). While infants aged 0-6 months tend to prioritise exogenously salient but simple visual stimuli, from 6 months infants' attention begins to be drawn to

more complex and naturalistic visual input (Reynolds & Romano, 2016). This is accompanied by a refinement of infants' capacity to sustain attention to complex scenes, an ability that reaches functional maturity between 9 and 11 months (Colombo, 2001; Colombo & Cheatham, 2006). Therefore, I expected the 10-month age to be optimal to characterize the nature of individual differences in visual sensory seeking through combination of parent-reported and experimental measures.

In addition to assessing the concurrent and longitudinal associations between the EEG/VEP measures and parental reports of visual sensory seeking (quantified through the ITSP at 10 and 16 months; Dunn, 2002), I assessed the domain-specificity of these associations by investigating the link between the same neural measures and parent-reported sensory seeking across sensory modalities (quantified through the ITSP at both ages; Dunn, 2002). Further, in an attempt to replicate the evidence from Chapter 4, I investigated whether an association existed between infants' modulatory capacity (i.e. infants' ability to modulate responsiveness to incoming visual stimulation based on engagement with ongoing information) and later parental reports of ASD traits (quantified through the Q-CHAT at 16 months; Allison et al., 2008) or ADHD traits (quantified through the ECBQ activity and inhibitory control sub-scales at 16 months; Putnam et al., 2006).

6.2.2. Follow-up analyses

I planned to conduct a follow-up analysis to expand on results emerged from the main analysis. Specifically, the main analyses were conducted on EEG/VEP measures estimated on later time bins (i.e. bin 2 and bin 3; see Chapter 5 for further details). These time bins were chosen since the decrease in theta occurring from bin 2 to bin 3, rather than the increase manifesting from bin 1 to bin 2, was closer to a measure of information depletion (Clarke et al., 2018). However, it could be argued that similar results (albeit opposite in direction) should manifest by conducting the same analytical pipeline on earlier time bins, given that also for the latter, stronger modulation of theta amplitude (i.e. increase manifested from bin 1 to bin 2) associated with stronger modulation of the P1 peak amplitude (i.e. decrease manifested from bin 1 to bin 2). Thus, I probed this notion in a follow-up analysis.

6.3. Methods

6.3.1. Recruitment approach

All infants recruited for the research were born full-term (gestational age 38-42 weeks), weighed > 2,500g at birth and had no history of pre or perinatal medical complications. Further, all infants included in the study were typically developing, therefore had no known developmental atypicality, based on parental reports at recruitment. Participants were recruited from a volunteer database at the Babylab, Centre for Brain and Cognitive Development to take part to the assessment at 10 months. Informed written consent was provided by the parent(s) prior to the

commencement of the study. Infants were tested if awake and in an alert state. Families were re-contacted 6 months after the infants participated to the study to take part to the follow-up online assessment. Informed written consent was provided by the parent(s) prior to the study. The experimental protocol (including both the laboratory-based and online assessments) were approved by the Research Ethics Committee of the Department of Psychological Sciences, Birkbeck University of London (Protocol no. 171805). Families were reimbursed expenses for travel, subsistence and overnight stay if required. Further, families were given a certificate and t-shirt after their visit.

6.3.2. Participants

I direct the reader to section 5.3.2 (Chapter 5) for a description of the sample of 48 infants that participated in the study. Forty-three infants provided usable data at 10 months (22 females, mean age = 10 months and 4 days, SD=14 days) and were included in the EEG and VEPs analyses. Parents were re-contacted six months after their infant participated to the study to fill in a set of questionnaires online. Thirty-nine families participated to the follow-up study at 16 months (34 out of 43 participants contributing EEG data at 10 months; 18 females, mean age = 16 months and 18 days, SD=37 days), whereas n=9 participants dropped out from the longitudinal study at 16 months. The minimum number of required participants was determined by an a priori power analysis (conducted with the software *Gpower;* Erdfelder, Faul, Buchner, & Lang, 2009). According to Cohen (1988) and

Sawilowsky (2009) a medium effect size in psychological studies is $R = 0.50$ and, considering an estimate power of 0.80, a minimum sample size of 23 participants was estimated to detect one-tailed correlational effects at an alpha-level of 0.05.

6.3.3. Stimuli, apparatus and procedure

I direct the reader to section 5.3.3 (Chapter 5) for a description of the experiment, apparatus and procedure used for the EEG assessment at 10 months.

6.3.4. Behavioural assessment scales

At completion of the EEG assessment at 10 months, caregivers were asked to fill in the parent-reported ITSP (Dunn, 2002). 10-month ITSP data was collected for all infants contributing to the EEG analyses (n = 43). Further, parents were re-contacted six months after their infant participated to the study to fill in a set of questionnaires online (administered through the platform Redcap; Harris et al., 2019, 2009). This set of questionnaires included the ITSP (Dunn, 2002), the ECBQ (Putnam et al., 2006) and the Q-CHAT (Allison et al., 2008). 16-month ITSP, ECBQ and Q-CHAT data was returned for 34 out of 43 participants contributing EEG data at 10 months. Detailed characterisation of each measure at 10 and 16 months for participants contributing EEG data is reported in Table 18 (for comparison purposes, scores on the same phenotypic measures are also reported for the cohort of infants at elevated likelihood of ASD or ADHD contributing data to Chapter 4).

Table 18. *Detailed characterisation of behavioural measures at 10 and 16 months for participants who contributed to the EEG analyses at 10 months. For comparison purposes, scores on the same phenotypic measures are also reported for the cohort of participants at elevated likelihood of ASD and/or ADHD contributing data to Chapter 4 (assessed at 10 and 24 months).*

	Current cohort		**Chapter 4 cohort**		
10-month visit	**TL**	**10-month visit**	**EL-ASD**	**EL-ADHD**	**EL-ASD+ADHD**
Age in days	308.17 (14.0)		316.42 (14.47)	327.40 (30.30)	320.67 (18.40)
ITSP Visual Seeking	1.91 (0.627)		2.58 (0.80)	1.92 (0.50)	2.28 (0.91)
ITSP Sensory Seeking	1.65 (0.39)		2.22 (0.50)	1.67 (0.21)	2.04 (0.72)
16-month visit	**TL**	**24-month visit**	**EL-ASD**	**EL-ADHD**	**EL-ASD+ADHD**
Age in days	505 (37.51)		771.65 (45.45)	761.17 (28.33)	750.22 (10.81)
ITSP Visual Seeking	2.48 (0.61)		3.07(0.83)	2.72 (0.68)	2.78 (0.70)
ITSP Sensory Seeking	2.01 (0.36)		2.89 (0.63)	2.57 (0.62)	2.74 (0.69)
ECBQ Activity	5.18 (0.79)		4.66 (0.83)	4.92 (1.06)	5.28 (1.11)
ECBQ Inhibitory Control	3.48 (0.84)		3.70 (1.25)	3.92 (0.85)	2.97 (1.32)
Q-CHAT	30.50 (6.89)		23.29 (10.76)	25.79 (7.43)	28.51 (16.96)

M (*SD*) reported for: Age in days; ITSP Visual Seeking = Visual sensory seeking average score of the Infant-Toddler Sensory Profile; ITSP Sensory Seeking = Sensory seeking average score of the Infant-Toddler Sensory Profile; ECBQ Activity = Activity average score of the Early Childhood Behaviour Questionnaire; ECBQ Inhibitory Control = Inhibitory control average score of the Early Childhood Behaviour Questionnaire; Q-CHAT = Quantitative Checklist for Autism in Toddlers.

6.3.5. EEG/VEP processing pipeline

The present chapter utilises EEG/VEP measures from the same participant sample that contributed data at 10 months in Chapter 5. Therefore, I direct the reader to Chapter 5 for a presentation of the processing steps undertaken to quantify the EEG/VEP measures used in the following analyses (i.e. P1 peak amplitude time-locked to checkerboard onset, theta modulation index, P1 modulation index).

6.3.6. Analytical strategy

Statistical analyses were conducted with SPSS v23 (IBM Corp 2015). Prior to performing any inferential statistical analyses, I assessed the variables for normality (i.e. details on normality violations are reported in the results section; the choice of using Pearson vs. Spearman correlation models was driven by results of normality assessments).

I first investigated the source of individual differences in parent-reported visual sensory seeking at 10 months by analysing the concurrent associations between the EEG/VEP measures and the ITSP sensory seeking quadrant in the visual modality through sets of Spearman correlations. Under the *optimal stimulation hypothesis*, I predicted infants with lower overall P1 peak amplitude time-locked to checkerboard onset to be rated as "high visual seekers"; conversely, I predicted infants with higher overall P1 peak amplitude time-locked to checkerboard onset to be rated as "low visual seekers". Under the *processing speed hypothesis*, I predicted infants manifesting faster decline in frontal theta amplitude

after repeatedly seeing the video to afford seeking more information, thus being rated as "high visual seekers"; conversely, infants manifesting slower decline in frontal theta amplitude should afford less, thus being rated as "low visual seekers". Finally, under the *information prioritization hypothesis*, I expected infants exhibiting a modulation of the P1 peak amplitude stronger than expected based on the change in theta amplitude (i.e. more weight allocated to incoming over ongoing information processing) to be rated as "high visual seekers"; conversely, I predicted infants exhibiting a modulation of the P1 peak amplitude weaker than expected based on their change in theta amplitude (i.e. less weight allocated to ongoing over incoming information processing) to be rated as "low visual seekers".

Secondly, informed by results from previous analyses and to further characterise the source of individual variation in visual sensory seeking profiles, I proceeded with extracting residuals from a linear regression with theta modulation index as predictor and P1 modulation index as outcome. I reasoned that, in a linear regression, the residual represents the difference between the observed value and the predicted value of the outcome variable for each data point. Thus, an increase in the P1 peak amplitude greater than that predicted by change in frontal theta amplitude would be indexed by a larger residual. Conversely, an increase in the P1 peak amplitude smaller than that predicted by change in frontal theta amplitude would be indexed by a smaller residual. I then conducted a Spearman correlation between the infants' visual sensory seeking scores and the regression residuals.

Thirdly, I assessed the relative explanatory power of the three hypotheses through a hierarchical linear regression with 10-month visual sensory seeking as outcome and each of the predictors (i.e. P1 peak amplitude time-locked to checkerboard onset, theta modulation index and P1 modulation index) entered to the model at separate steps. This analysis was driven by consideration that any non-significant results emerged from the set of Spearman correlations would solely suggest absence of evidence, thus preventing to conclude that either of the hypotheses carried no explanatory power for the current dataset.

Fourthly, I assessed the domain specificity of the documented associations by investigating through sets of Pearson correlations the link between the same EEG/VEP measures and parent-reported sensory seeking scores across sensory modalities. Relatedly, I ascertained the stability of the associations reported at 10 months by replicating significant results at a later time-point (i.e. 16 months).

Finally, I investigated the potential link between variation in information prioritization, and parent-reported ASD and ADHD traits at 16 months through sets of Pearson correlations. Informed by results from Chapter 4, whereby reduced modulation of the P1 peak amplitude by ongoing theta amplitude at 10 months predicted ASD traits at 24 months, I hypothesized infants manifesting lower P1 modulation index and lower regression residuals in the EEG task to exhibit higher ASD traits at 16 months.

6.4. Results

6.4.1. Concurrent associations with visual sensory seeking

In order to investigate the source of individual differences in parent-reported visual sensory seeking, infants' average scores for the sensory seeking quadrant in the visual domain were first computed (see Appendix for a discussion of the contributing items and for assessment of the sub-scale internal consistency). I investigated the associations between this measure and (1) the overall P1 peak amplitude (taken as a measure of the strength of bottom-up responsiveness to sensory input), (2) the change in frontal theta oscillatory amplitude from bin 2 to 3 (indexing the speed of information processing) and (3) the degree of modulation of the P1 peak amplitude by ongoing theta amplitude (taken as a measure of how successful incoming sensory input was in capturing infants' attention away from the ongoing video infants were engaged with).

Since the distribution of the visual sensory seeking variable violated normality assumptions (Shapiro-Wilk test, p = .034; Skewness = .167, SE = .354; Kurtosis = -.485, SE = .695), a Spearman correlation was conducted to assess the relationship between this measure and the overall P1 peak amplitude. This test was not statistically significant, Rho (41) = -.065, p =.681. Infants visual seeking scores were similarly not related to modulation of ongoing theta (i.e. theta modulation index), Rho (27) = -.067, p = .728. Rather, they significantly associated with the degree of peak amplitude modulation of the P1 component (i.e. P1 modulation index), Rho (27) = -.359, p = .028. See Figure 6.1A, B and C. The ITSP item most

strongly correlating with the P1 modulation index was item 20, which asks whether the child prefers fast-paced, brightly coloured TV shows (see Table 19).

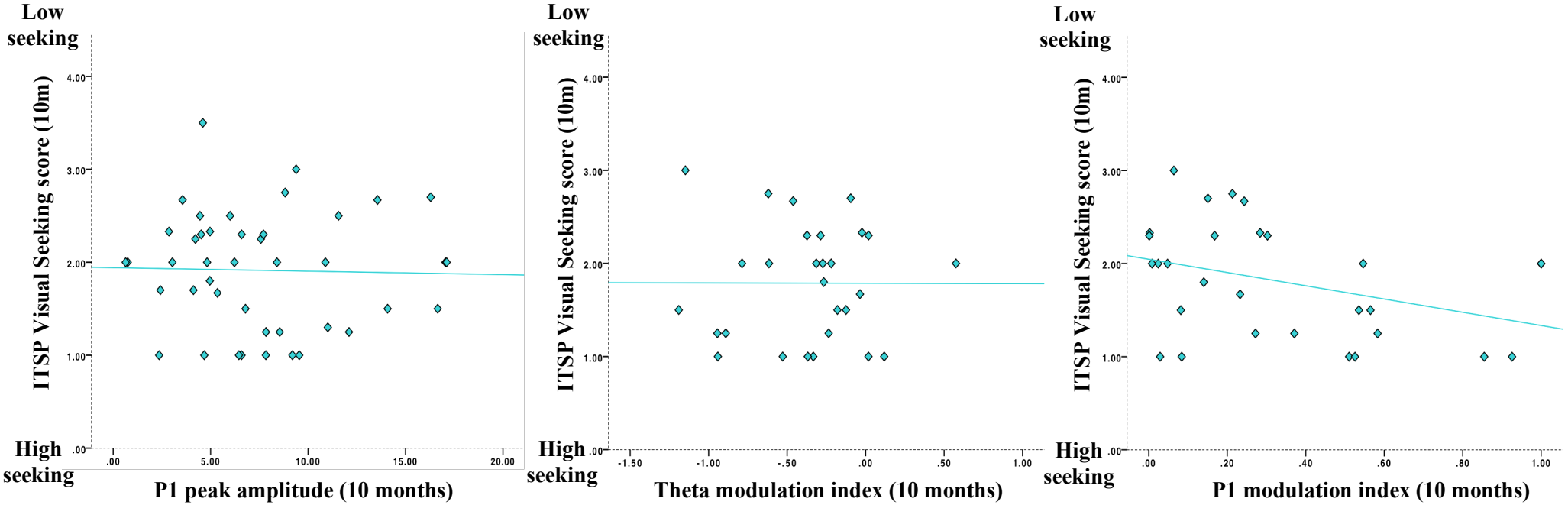

Figure 6.1. Scatterplots illustrating the concurrent associations between ITSP visual sensory seeking at 10 months and A. P1 peak amplitude; B. Theta amplitude; C. P1 modulation index

Parental reports of infants' visual sensory seeking at 10 months (ITSP) were not significantly related to the overall P1 peak amplitude or the theta modulation index. Contrarily, they were significantly related to the P1 modulation index ($p<.05$). Note: the range plotted for the y axes starts at zero for ease of visualization.

6.4.2. Association with regression residuals

The contrasting results emerged from the analyses reported in section 6.4.1 indicated that there was individual variation in the degree to which theta changes modulated change in the P1 peak amplitude. In order to directly assess whether this source of variation explained individual differences in visual sensory seeking profiles, I extracted residuals from a linear regression having the theta modulation index as predictor and the P1 modulation index as outcome. A Spearman correlation between the infants' visual sensory seeking scores and the regression residuals was computed. This test was statistically significant, Rho (27) = -.373, p = .023. The negative direction of this association indicated that those infants who exhibited a modulation of the P1 peak amplitude greater than that predicted by change in frontal theta amplitude, i.e. a stronger increase in P1 peak amplitude, were rated by parents as "high visual seekers". Conversely, infants who exhibited a reduced modulation of the P1 peak amplitude than that predicted by change in frontal theta amplitude were rated by parents as "low visual seekers" . See Figure 6.2. The ITSP item most strongly correlating with the regression residuals was item 20, see Table 19.

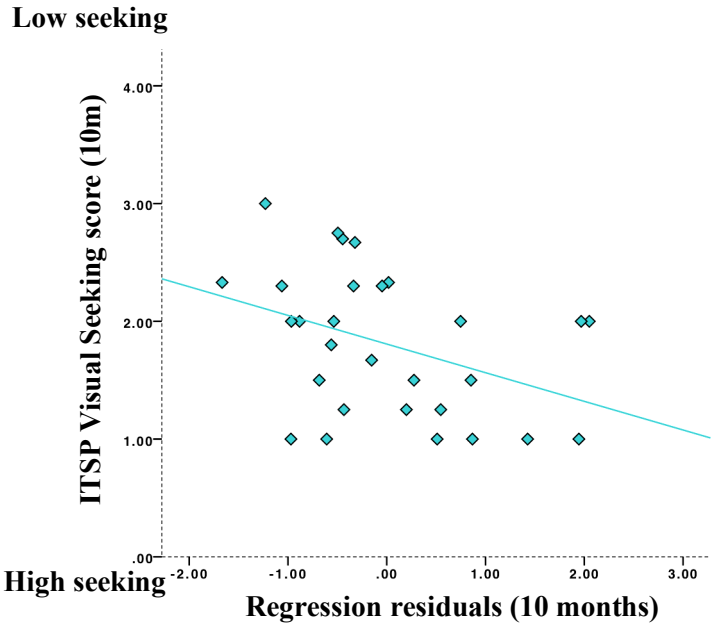

Figure 6.2. Scatterplot illustrating the concurrent association between ITSP visual sensory seeking at 10 months and regression residuals

A significant negative association manifested between ITSP visual sensory seeking at 10 months and the residuals of a regression with theta modulation index as predictor and P1 modulation index as outcome ($p<.05$). Infants whose P1 modulation index was higher than predicted by theta amplitude change were rated as "high visual seekers". Infants whose P1 modulation index was lower than expected by theta amplitude change were rated as "low visual seekers". Note: the range for the y axis starts at zero for ease of visualization.

6.4.3. Relative explanatory power of the three hypotheses

Results from previous analyses did not support either the optimal stimulation hypothesis or the processing speed hypothesis as potential explanations for

individual differences in visual sensory seeking in early typical development. However, absence of evidence does not allow to conclude that these hypotheses carry no explanatory power for the current dataset. Thus, a hierarchical linear regression with 10-month visual sensory seeking as outcome and each of the predictors entered to the model at separate steps was performed.

First, the P1 modulation index was entered to the model as predictor. The model was statistically significant, $F(1,27) = 4.068$, $p = .027$, $R^2_{adj} = .131$, confirming the explanatory power of the information prioritization hypothesis. In step 2, the theta modulation index was entered to the model as a predictor. The model was no longer statistically significant, $F(2,25) = 1.976$, $p = .160$, $R^2_{adj} = .067$, and did not account for a higher proportion of variance relative to a model with the only P1 modulation index as predictor, F change $(1,25) = .609$, $p = .442$. In step 3, the overall P1 peak amplitude was added to the model as predictor. The model was not statistically significant, $F(3,24) = 1.976$, $p = 1.354$, $R^2_{adj} = .038$, and did not account for a significantly higher proportion of variance relative to a model with the only P1 modulation index as predictor, F change $(1,24) = .231$, $p = .635$. These results indicated that neither the processing speed hypothesis, nor the optimal stimulation hypothesis added explanatory power for the current dataset.

6.4.4. Association with visual sensory seeking at follow-up

To further support results of the associations with the ITSP visual sensory seeking scores at 10 months, an additional set of analyses was conducted with data from the

follow-up ITSP that parents completed online six months after their infant participated in the EEG study. Replication at a later time point would increase confidence in the results, given that parents' ability to report on their infant's sensory behaviour is dependent on the child's developmental stage (Stone & Hogan, 1993; Baranek, 1999). Similarly, some of the psychometric properties of the ITSP improve with the infant's developmental stage (Eeles et al., 2013).

Following the same analytical pipeline conducted at 10 months, I first replicated the significant association between the P1 modulation index and the visual sensory seeking scores at 16 months, Rho (22) = -.415, p = .022. Secondly, I replicated the significant association between the residuals of a regression with the theta modulation index as predictor and the P1 modulation index as outcome and the visual sensory seeking scores at 16 months, Rho (22) = -.388, p = .031, see Figure 6.3. Similar to the 10-month results, also at 16 months, the item most strongly correlating with the EEG measures was item 20, see Table 19.

I also ascertained this association in a sub-group of n = 15 infants whose parents did not report TV exposure at 10 months (i.e. did not answer ITSP item 20; see Table 19). In this sub-group, significant associations emerged between ITSP visual sensory seeking at 16 months and P1 modulation index, Rho (9) = -.553, p = .039; and regression residuals, Rho (9) = -.659, p = .014. In both cases, the item most strongly correlating with these measures was item 20: for P1 modulation index, Rho (9) = -.465, p = .075; for regression residuals, Rho (9) = -.600, p = .025. This analysis rules out the possibility of reverse causation for the present dataset,

i.e. that TV exposure at 10 months may drive information processing biases and reinforces the hypothesis that it is infants' information processing bias that explains concurrent and later individual differences in visual sensory seeking.

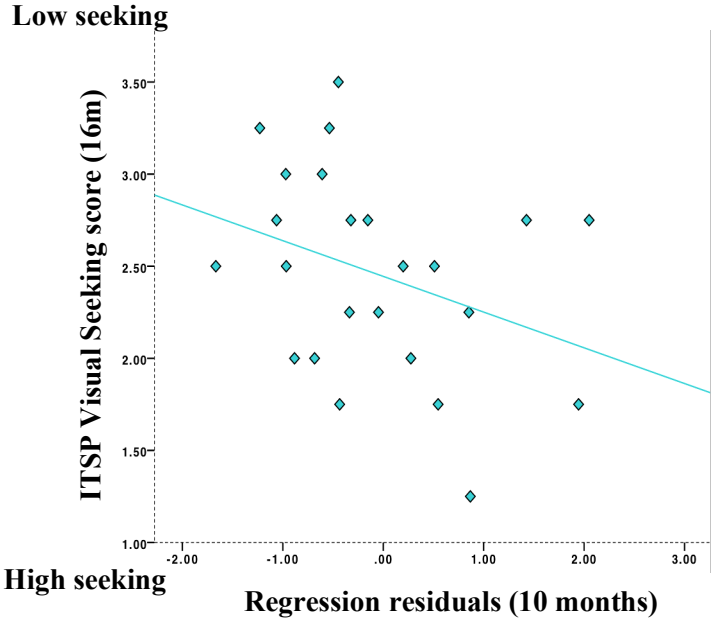

Figure 6.3. Scatterplot illustrating the longitudinal association between ITSP visual sensory seeking at 16 months and regression residuals at 10 months

A significant negative association manifested between ITSP visual sensory seeking at 16 months and the residuals of a regression with theta modulation index as predictor and P1 modulation index as outcome. Thus, the association between the measures was replicated at a later time point ($p < .05$).

Table 19. *Cross-correlation table between the ITSP items contributing to the visual sensory seeking score at 10 and 16 months and the EEG measures (Spearman Rho, *p < .05).*

ITSP 10m	Item 14 (N=29)	Item 15 (N=29)	Item 19 (N=29)	Item 20 (N=14)
P1 modulation index	.118	.085	-.074	-.191
Regression residuals	.045	-.032	-.054	-.267
ITSP 16m	**Item 14 (N=24)**	**Item 15 (N=24)**	**Item 19 (N=24)**	**Item 20 (N=24)**
P1 modulation index	-.211	-.211	-.133	-.369*
Regression residuals	-.119	-.204	-.117	-.381*

6.4.5. Association with overall sensory seeking scores

I assessed the domain specificity of the reported associations by quantifying an overall sensory seeking score from the ITSP (i.e. sensory seeking across modalities; see Appendix for assessment of the scale internal consistency). I investigated the associations between this measure and (1) the overall P1 peak amplitude, (2) the change in theta amplitude and (3) the degree of modulation of the P1 component

by ongoing theta amplitude. Normality assumptions were assessed and no violation was detected. A bivariate Pearson correlation between the P1 peak amplitude and the overall sensory seeking scores at 10 months yielded an insignificant association between the measures, R (41) = -.019, p = .904, R^2 = .0003. Infants sensory seeking scores were similarly not related to modulation of ongoing theta amplitude (i.e., theta modulation index), R (27) = -.229, p = .240, R^2 = .053 or to the degree of peak amplitude modulation of the P1 component by ongoing theta amplitude (i.e., P1 modulation index), R (27) = -.032, p = .872, R^2 = .001. Following the same analytical pipeline reported in section 6.4.2, I extracted residuals of a regression with the theta modulation index as predictor and P1 modulation index as outcome. The Pearson correlation between the regression residuals and the overall sensory seeking scores was not statistically significant, R (27) = -.088, p = .649, R^2 = .008. Overall, this analysis confirmed the modality specificity of the reported effects.

6.4.6. Associations between information prioritization at 10 months and later ASD and/or ADHD traits

Associations with ASD traits at 16 months. Q-CHAT scores were assessed for normality and no significant violations emerged (see Figure 6.4 for boxplot illustrating the variable distribution). The Pearson correlation between Q-CHAT and P1 modulation index was not statistically significant, R (22) = -.182, p = .395, R^2 = .063; and regression residuals was also not statistically significant, R (22) = -.102, p = .637, R^2 = .010, thus suggesting that infants' information prioritization

during the EEG task at 10 months did not associate with parental reports of ASD traits at 16 months.

Associations with ADHD traits at 16 months. ECBQ activity and inhibitory control sub-scales were assessed for normality and no significant violations detected (see Figure 6.4 for boxplot illustrating the variables distribution). There was no significant association between ECBQ activity and P1 modulation index, R (22) = -.246, p = .247, R^2 = .061; and regression residuals, R (22) = -.106, p = .622, R^2 = .011. Similarly, there was no significant association between ECBQ inhibitory control and P1 modulation index, R (22) = .322, p = .125, R^2 = .104; and regression residuals, R (22) = .339, p = .105, R^2 = .114. These results suggested that infants' information prioritization during the EEG task at 10 months did not associate with parental reports of ADHD traits at 16 months.

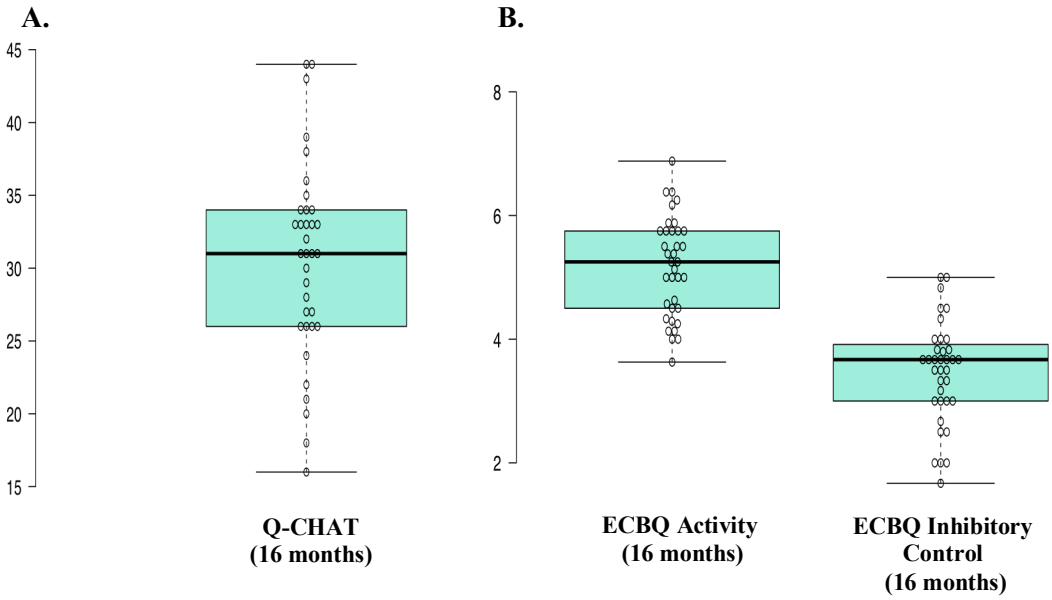

Figure 6.4. Boxplots illustrating the distribution Q-CHAT, ECBQ Activity and ECBQ Inhibitory Control at 16 months

Variability manifested in the distribution of A) Q-CHAT; B) ECBQ Activity and Inhibitory Control sub-scales at 16 months.

6.4.7. Follow-up analyses

6.4.7.1. Concurrent associations with visual sensory seeking

To further support results of the analyses run on bin 2 and bin 3, the same analytical pipeline was conducted on bin 1 and bin 2. A Spearman correlation was run to assess the association between the visual seeking scores at 10 months and the theta modulation index computed on earlier time bins. The result was not statistically significant, Rho (36) = -.013, p = .940. The association between the P1 modulation index computed on earlier time bins and the visual seeking scores was also

insignificant, Rho (36) = .080, p = .316, but the direction of this relationship aligned to that reported for bin 2 and bin 3 and reported in the main analyses. I extracted residuals of a regression having the theta modulation index as predictor and the P1 modulation index as outcome. A Spearman correlation between the infants' visual sensory seeking scores at 10 months and the regression residuals was computed. This test was not statistically significant, Rho (36) = .105, p = .265. Despite lacking statistical significance, the direction of this association confirmed results reported for earlier time bins. Since a moderate change in engagement with the video stimulus occurred during the first two bins (theta modulation index SD=.34) relative to later bins (theta modulation index SD=.42), the lack of statistical significance is not surprising. During the earlier time bins, infants were still engaged with the video and not ready to orient away from ongoing to incoming stimulation.

6.5. Discussion

6.5.1. General points

The current study adopted a principled approach to 1) replicate in an independent cohort of infants at typical likelihood of ASD or ADHD evidence emerged from Chapter 4 and 2) characterise the nature of sensory seeking manifestations in early typical development, thus informing our understanding of these manifestations in early atypical development. To this goal, an individual differences approach was employed and EEG/VEP data from the same cohort of participants who contributed to Chapter 5 was re-analysed in conjunction with concurrent parental reports of

sensory seeking (10 months), as well as longitudinal parent-reported measures of sensory seeking, ASD and ADHD traits emerging in toddlerhood (16 months).

I characterised the nature of individual differences in infants' visual sensory seeking by testing three hypotheses existing in the literature. First, I tested the *optimal stimulation hypothesis*, according to which individuals' active engagement with their environment strives to achieve an optimal level of stimulation (Zentall & Zentall, 1983). According to this hypothesis, individuals seek stimulation if they are under-responsive to current sensory input. Under this hypothesis, I predicted that higher parent-reported visual seeking would associate with weaker VEPs (i.e. overall P1 peak amplitude) in response to incoming stimulation (i.e. checkerboards). I found no evidence in support of this hypothesis. Infants rated by parents as high visual seekers did not exhibit reduced P1 peak amplitude in the task. The *optimal stimulation hypothesis* draws heavily on research with atypical populations and evidence supporting this account is scarce in neurotypical individuals (Carrol, Zuckerman, & Vogel, 1982). It is possible that only under conditions of extreme sensory input (e.g. sensory overload or deprivation), would typically developing individuals make use of compensatory strategies resembling those observed in atypical populations. Evidence for the optimal stimulation hypothesis exists in children with ASD (Donkers et al., 2013). Further, I documented evidence aligning to the optimal stimulation hypothesis in Chapter 4, given that infants at elevated likelihood of ASD and/or ADHD manifesting enhanced visual perception (indexed by elevated P1 peak amplitude

time-locked to checkerboard onset) also manifested lower parent-reported visual sensory seeking. However, the present study is the first to test the validity of optimal stimulation hypothesis in an independent sample of infants at typical likelihood of ASD or ADHD.

Second, I tested the *processing speed hypothesis*, according to which individual differences in seeking novel stimulation reflect differences in information processing abilities (Colombo et al., 1991). Under this hypothesis, I predicted that higher visual seeking would associate with more rapid information processing, as indexed by a stronger decrease in frontal theta amplitude with repetition of the video in the EEG task. Results did not support this hypothesis either. Infants' modulation of EEG frontal theta to the video was not related to parent-reported visual seeking profiles. Information processing progress was proposed as a potential driver of attention and sensory seeking (Gottlieb et al., 2013), however these findings suggest that infants speed of processing information is insufficient to account for individual differences in visual sensory seeking profiles.

From early in development, infants are equipped with the ability to actively acquire information and modulate their learning on the basis of their own exploratory drives (Begus, Gliga, & Southgate, 2014; Begus & Southgate, 2018). Thus, individual biases in *information prioritization* might associate with alternative seeking profiles. Under this hypothesis, I predicted higher visual seeking in those infants whose modulation of VEP responses (i.e. change in P1 peak

amplitude) was stronger than expected based on their change in theta amplitude, thus attributing stronger weight to incoming relative to ongoing information processing. Evidence from this study confirmed this hypothesis. Infants rated as "high visual seekers" exhibited an increase in P1 peak amplitude from bin 2 to 3 greater than that predicted by the concurrent decrease in frontal theta oscillatory amplitude (with the opposite occurring in infants rated as "low visual seekers"). This result suggests that a bias towards incoming stimulation characterized the sensory behaviour of high seeking infants. At the same degree of information uptake, high seeking infants (but not low seeking infants) were more readily disengaging from ongoing stimulation to orient to incoming input. Importantly, this result replicates evidence emerged in Chapter 4, whereby 10-month-old infants manifesting higher modulatory capacity concurrently displayed higher parent-reported visual sensory seeking (with the opposite occurring in infants manifesting lower modulatory capacity).

The current study made use of the ITSP to capture parent-reported visual sensory seeking profiles at 10 and 16 months. Interestingly, among the four items contributing to the ITSP visual sensory seeking score, the item that at both time points explained the highest proportion of variance in the EEG measures was item 20, which asks if the child prefers fast-paced, brightly coloured TV shows. This item maximally captures infants seeking of novel visual stimulation. Further, the strength of the association between item 20 and the EEG measures increased from 10 to 16 months – a result which may be consequent to the larger sample size (i.e.

fewer parents rated this question as non-applicable and thus the sample answering this question was larger at 16 months). Having replicated the associations with the ITSP at 16 months also increases confidence that the captured trait is stable and reliable.

The associations between task performance and infants' seeking found in the current study were specific to the visual modality. Individual differences in disengaging from ongoing stimulation to orient to incoming input did not associate with infants' seeking scores averaged across modalities. One reason behind this result might be the poor reliability of the seeking quadrant observed for some of the ITSP sensory modalities (i.e. Cronbach's α at 10 months [auditory] = 0.231; [tactile] = 0.439; [vestibular] = 0.450; at 16 months [auditory] = 0.465; [tactile] = 0.680; [vestibular] = 0.587). Further, the present paradigm was designed to capture a trade-off in the allocation of attentional resources in the visual modality. Therefore, it comes to no surprise that task-related differences were only explaining alternative visual seeking profiles. However, I expect similar principles to apply to other sensory modalities (Frost et al., 2016). Future studies should capitalize on the current task and apply adapted versions to the investigation of the auditory or tactile modalities.

Although I assessed the extent to which data supported three hypotheses, I do not conceptualize these hypotheses as being mutually exclusive. For example, evidence from Chapter 4 indicated that infants at elevated likelihood of ASD or ADHD manifesting elevated P1 peak amplitude to the checkerboard and reduced

modulatory capacity also manifested reduced visual sensory seeking, as quantified through the parent-reported ITSP. This evidence suggests that while in infants at typical likelihood of ASD or ADHD the information prioritization hypothesis may best account for individual differences in visual sensory seeking profiles, a combination of both the optimal stimulation hypothesis and the information prioritization hypothesis may best explain visual sensory seeking manifestations in infants at elevated likelihood of ASD and/or ADHD.

Visual orienting to incoming sensory events is known to enhance neural responses in primary visual areas (Ranganath & Rainer, 2003) and this orienting response is influenced by dopamine receptor polymorphisms (Lakatos et al., 2003). Influences of these polymorphisms have been reported on neonatal and infant temperament (Ebstein et al., 1998; Lakatos et al., 2003), as well as adult personality traits (Benjamin et al., 1996; Ebstein et al., 1996). For example, the dopamine-transporter gene DRD4 exists in two common forms, the 4-repeat variety and the 7-repeat form. The 7-repeat variety of DRD4 is less sensitive to dopaminergic influences than the 4-repeat form and infants as young as 12 months with this transporter gene are reported to be less anxious and driven towards novelty than those with the shorter version. Further, the DRD4 7-repeat form has been associated with conditions characterized by extreme sensory seeking behaviours such as ADHD (Comings et al., 1999; Swanson et al., 1998). While evidence from the current study did not allow me to establish infants' information prioritization (as indexed by the P1 modulation index and regression residuals) as an early marker

capturing later ASD or ADHD traits in infants at typical likelihood of the conditions, the evidence suggest that individual differences in information prioritization can explain alternative visual sensory seeking profiles in infancy. Thus, the present paradigm and analytical pipeline may offer an intermediate phenotype between genes and behaviour that could help better characterising typical and atypical sensory seeking manifestations.

An additional question is to what extent the drive towards novel stimulation which is captured with the current measures maps onto higher levels of information seeking manifested later in development through pointing (Begus & Southgate, 2012) or questioning (Kurkul & Corriveau, 2018). Indeed, a distinction is made in adult self-report questionnaires between seeking perceptual as opposed to epistemic novelty. The former construct inquires about the need to take a closer look at something perceived in the distance, whereas the latter construct covers manifestations like the need to solve problems or the enjoyment of learning something new (Litman & Spielberger, 2003; Piotrowski, Litman, & Valkenburg, 2014). This is an important question awaiting future empirical investigation. I speculate that the current measure of prioritization of information will capture stable individual differences with variable behavioral manifestations as children discover new means to actively seek or elicit new information.

6.5.2. How do these results inform our understanding of the mechanisms underlying the early development of sensory perception in in ASD, ADHD and typical development?

The present study offers an objective marker of individual differences in visual sensory seeking in early typical development, with important implications for our understanding of sensory seeking manifestations in early atypical development. Results indicate that individual differences in the prioritization of incoming stimulation relative to ongoing information can explain concurrent and longitudinal parental reports of visual sensory seeking. By indicating that visual sensory seeking in early development is explained by infants' drive towards novelty, the present results validate the proposal that reduced sensory seeking in infants at elevated likelihood of ASD reflects a lower drive towards novel and diversive sensory input. Thus, elevated sensory seeking in early development may exercise a protective function by promoting exposure to novel contexts and/or situations, thus broadening learning opportunities. Altogether, this study offers an intermediate phenotype between brain and behaviour that may help better characterising typical and atypical sensory seeking manifestations from infancy.

6.6. Conclusion

Overall, findings from this research provide the first demonstration that visual sensory seeking in early typical development is explained by a bias towards incoming stimulation, thus supporting the information prioritization hypothesis.

This study offers an objective marker of individual differences in visual sensory seeking in early typical development, which may further inform research aimed at characterising atypical sensory seeking manifestations in infants at elevated likelihood of adverse neurodevelopmental outcomes (including ASD and ADHD). Additionally, this study may inform future research interested in probing the longitudinal continuity between early drives towards novelty and later manifestations of information seeking. I predict that the measure of information prioritization used in the current study may capture stable individual differences with variable behavioural traits as children discover new means of actively seeking or eliciting new information.

6.7. Limitations

The present study made use of Q-CHAT and ECBQ to quantify, respectively, ASD and ADHD traits in 16-month-old toddlers at typical likelihood of the conditions. While variability was observed for both measures (see Figure 6.4 for boxplots illustrating the distributions of these variables), it is possible that these parental reports failed to capture early-emerging ASD and ADHD traits in this sample of participants at typical likelihood of the conditions. This possibility should be acknowledged given that, also in previous chapters (Chapters 3 and 4), significant associations emerged between neural measures and a clinician observation of ASD traits (i.e. ADOS-2) but not with the parent-reported Q-CHAT or ECBQ at 24 months.

6.8. Summary of Chapter 6

Chapter 6 set out to adopt a principled approach and 1) replicate in an independent cohort of infants at typical likelihood of ASD or ADHD the evidence emerged from Chapter 4 and 2) characterise the nature of sensory seeking manifestations in early typical development, with implications for our understanding of these manifestations in early atypical development. EEG/VEP data from the same cohort of participants who contributed to Chapter 5 was re-analysed in conjunction with concurrent parental-reports of sensory seeking, as well as longitudinal parental reports of sensory seeking, ASD and ADHD traits emerging in toddlerhood. Results did not allow to establish a link between variation in information prioritization (quantified during the EEG task at 10 months) and later parental reports of ASD or ADHD traits (quantified, respectively, with the Q-CHAT and ECBQ activity and inhibitory control sub-scales at 16 months). However, results replicated evidence of an association between infants' modulatory capacity and parental reports of visual sensory seeking (with infants manifesting higher modulatory capacity exhibiting concurrent and longitudinal higher visual sensory seeking scores on the ITSP). Thus, results from this research demonstrate that variation in information prioritization at 10 months can explain differences in seeking novel visual stimulation at 10 and 16 months. Altogether, these findings clarify the nature of sensory seeking manifestations in early typical development, with important implications for research aimed at assessing sensory seeking manifestations in early atypical development.

Chapter 7: General Discussion

7.1. Summary of the current PhD thesis and key findings

ASD and ADHD are heritable neurodevelopmental disorders emerging early in life. These disorders co-occur more often than expected based on their individual incidence (Antshel & Russo, 2019; Joshi et al., 2017) and later-born siblings of children with ASD or ADHD appear to be at elevated likelihood to develop both conditions (Miller et al., 2019). Thus, some common developmental mechanisms are proposed to underlie the emergence of ASD and ADHD, yet specific pathways have not been identified (Johnson, Gliga, Jones, & Charman, 2015; Jones, Gliga, Bedford, Charman, & Johnson, 2014). Genetic and neurobiological research implicates structural atypicalities manifesting during prenatal and early postnatal stages of brain development as early risk factors for both conditions (Courchesne et al., 2019; Kasah et al., 2018; Krishnan et al., 2016). Consequent to, or interacting with brain structural atypicalities are functional perturbations, including E/I imbalances in putative cortical regions (Lee, Lee, & Kim, 2017; Nelson & Valakh, 2015; Rubenstein & Merzenich, 2003). Some have proposed that, over development, these early risk factors may impact several common areas of phenotypic functioning, including sensory perception, motor functioning and sleep (Krishnan et al., 2016; Johnson et al., 2015; Johnson, Charman, Pickles, Jones, 2020). Aligning to this proposal is evidence emerged from prospective longitudinal studies of infants at elevated likelihood of ASD and/or ADHD, which suggests that some common sensory vulnerabilities manifest in the early development of these conditions (Johnson, Gliga, et al., 2015; Little et al., 2018). Despite this evidence,

no prior research examined the same sensory markers as potential infant predictors of later ASD and/or ADHD traits in toddlerhood within a trans-diagnostic framework.

The current PhD thesis set out to fill this gap in our knowledge of the disorders and investigate the early development of sensory perception in infants at elevated likelihood of ASD and/or ADHD relative to infants at typical likelihood of the conditions. Towards this goal, an integrated approach to sensory perception that draws on Predictive coding theories was applied within a developmental framework. Underlying this research was the notion that mapping the longitudinal associations between early infant markers of sensory perception and later ASD and/or ADHD traits in toddlerhood would help distinguishing shared and distinct causal pathways, contemporarily highlighting risk and protective factors and promoting advancements in our understanding of the nature of the co-occurrence and aetiology of these conditions.

Altogether, results from this PhD investigation demonstrate that atypicalities in sensory perception manifest early in development in infants with later higher ASD traits (Chapters 3 and 4). Furthermore, results reveal that such sensory atypicalities are not tied to one sensory system, but rather impact multiple systems, including touch and vision (Chapters 3 and 4). Results from this PhD research further highlight the benefit of an approach to the investigation of sensory perception that characterises the relative contribution of feedback and feedforward processing. By applying this approach within a developmental framework, the

current research indicates that reduced feedback modulation of feedforward processing is a likely mechanism underlying early-emerging sensory atypicalities in infants with later higher ASD traits (Chapters 3, 4 and 5). Results from this PhD research also shed some light on the debate concerning the nature of co-occurring manifestations in ASD and ADHD. Specifically, evidence suggests that early sensory manifestations may hold predictive power in relation to later ASD (but not ADHD) traits in toddlerhood and indicate that a common pathway to later ASD traits may exist across these different familial backgrounds (Chapters 3 and 4). Relatedly, by demonstrating that, as early as 10 months of age, infants may adopt strategies compensating or compounding concurrent sensory manifestations, the current work offers evidence that may inform clinical research on early interventions (Chapters 3, 4 and 6).

Altogether, results of the studies reported in this PhD thesis contribute to previous research in several ways and carry implications for our understanding of 1) *methodological approaches* to the investigation of the early development of sensory perception in ASD and ADHD, 2) *mechanisms* underlying the early development of sensory perception in ASD and ADHD, 3) *theories of comorbidity* in ASD and ADHD, 4) potential routes for designing *early interventions* in ASD and ADHD. The following sections of this chapter elaborate on these themes, highlighting the contribution of this research and discussing limitations. Chapter 7 concludes by considering implications for future research aimed at investigating the early development of sensory perception in ASD and ADHD.

7.2. Methodological approaches to the investigation of the early development of sensory perception in ASD and ADHD

Sensory atypicalities, manifested as increased or decreased sensitivity or as atypical seeking of sensory input, are reported in 90% of children with ASD (Jasmin et al., 2009; Leekam et al., 2007) and 50% of children with ADHD (Yochman et al., 2004). Currently, most work on sensory manifestations in the early development of ASD and/or ADHD relies on caregiver reports. While caregiver reports are fundamental to characterise the influence of sensory atypicalities on everyday activities, these measures lack specificity: when observed, a child's behavioural response to a sensory stimulus only represents the final manifestation of a chain of processes starting from the brain. Thus, objective assessments of sensory perception are necessary to complement existing phenomenological descriptions with mechanistic explanations shedding light on the nature and characteristics of sensory atypicalities in these conditions from early in development. Particularly, objective assessments of sensory perception in prospective longitudinal studies of infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the conditions may enable researchers to 1) distinguish core atypicalities linked to genetic factors from later compensatory or compounding manifestations triggered by atypical interaction with the environment, 2) evaluate the specificity of early manifestations as potential infant predictors of later traits and/or categorical diagnoses, 3) inform early detection, contemporarily laying the translational foundations for early intervention protocols.

The studies reported in this PhD thesis provide the first comprehensive assessment of the early development of sensory perception in infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the conditions combining controlled experimental designs and direct assessment of brain function with parental reports. Results from this research indicate that atypicalities in sensory perception not yet manifested at the level of behaviour can be detected in infants with later higher ASD traits through direct assessment of brain function. In particular, results from Chapter 3 indicate that reduced neural repetition suppression of tactile stimulation manifests in 10-month-old infants at elevated likelihood of ASD (and further predicts higher ASD traits at 24 months) in the absence of detectable differences in behavioural sensitivity to tactile stimulation quantified through parental report (ITSP) or laboratory-based observation. What may be the reason behind this discrepancy?

Evidence from prospective longitudinal studies of infants at elevated likelihood of ASD concurs in suggesting that core behavioural signs of the disorder do not appear until the second year of life (i.e. between 12 and 24 months). Indeed, few behavioural predictors of later ASD traits have been identified within the first year of life (Johnson, Gliga, et al., 2015; Varcin & Jeste, 2017). Several theoretical proposals have been advanced to explain this phenomenon. Some authors proposed that ASD may result from a typical developmental trajectory that is derailed over later infancy and toddlerhood (Ozonoff et al., 2010). Molecular genetics and neurobiological research contrasts this notion by implicating structural atypicalities

occurring during prenatal and early postnatal developmental stages as early risk factors for the condition (Courchesne et al., 2019; Kasah et al., 2018; Krishnan et al., 2016). Other authors proposed that atypical behaviours in the first year of life may be subtle and/or transient (possibly due to infants' limited skills repertoire), and generally lie outside the core dimension of diagnostic ASD manifestations (Flanagan et al., 2012; Varcin & Jeste, 2017). Support for this proposal is offered by evidence that behavioural manifestations displaying phenotypic continuity and specificity with respect to a later ASD diagnosis emerge only from the second year of life (Gammer et al., 2015). A third, non-exclusive possibility is that the lack of behavioural signs identified within the first year of life reflects limitations intrinsic to the instruments and experimental approaches used to quantify these markers (Varcin & Jeste, 2017). This possibility should be acknowledged given that, during the first year of life, infants possess a restricted skills repertoire which could constrain the sensitivity of the adopted measures. In line with this proposal, evidence suggests that parents' ability to detect and report on their infants' behaviours improves with the child's developmental stage (Stone & Hogan, 1993; Baranek, 1999). Further, some of the psychometric properties of parental reports used during infancy, including the ITSP, improve with the child's developmental stage (Eeles et al., 2013). It is likely that the absence of significant differences documented in Chapter 3 for observational behavioural markers and parental reports of sensitivity to tactile stimulation reflects both the subtle and/or transient nature of these manifestations in early development as well as the limitations of the

employed measures, which may be constrained by the restricted skills repertoire of 10-month-old infants. Given that behavioural manifestations consistent with hypersensitivity to sensory stimulation (across sensory modalities) increase with age in children with ASD, reaching their peak between 6-9 years of age (Ben-Sasson et al., 2009; Talay-Ongan & Wood, 2000), it is likely that these manifestations may be hard to detect through laboratory-based observation or parental reports during infancy. In line with this proposal, Ben-Sasson and collaborators (2010) indicated that parental reports of behavioural hypersensitivity (across sensory modalities) are relatively unstable during the first year of life in typically developing infants and only reach stability from 2 years of age. It is possible that developmental transitions, including the onset of walking, may expose infants to a wider range of activities or actions promoting the expression of behaviours signalling hypersensitivity to sensory stimulation during the second year of life (Ben-Sasson et al., 2010; Kraemer, 2001). This proposal would explain why parent-reported measures, such as the ITSP, may be limited in capturing behavioural manifestations of sensory hypersensitivity during the first year of life. Indeed, a few sensory sensitivity items of the 7-36 months version of the ITSP imply children to possess a sophisticated repertoire of skills, including the ability to crawl and walk (for instance, by asking parents to rate the extent to which the child becomes anxious or agitated when walking or crawling on certain surfaces). It is also possible that the refinement in verbal and non-verbal communicative skills during the second year of life may help children to more clearly express the sources

of their distress (Ben-Sasson et al., 2010). This would explain why, in Chapters 3 and 4, 83-85% of 10-month-old infants were reported by their parents as never or almost never exhibiting sensory avoiding behaviours. Indeed, several sensory avoiding items of the 7-36 months version of the ITSP assume children to possess a certain level of control over their sensory experiences (for instance, by asking parents to rate the extent to which the child withdraws from social situations or avoids playing with others).

In summary, it is likely that both laboratory-based observation and parental reports may be limited in capturing behavioural manifestations of sensory hypersensitivity in early development due to infants' restricted skills repertoire. These manifestations may become easier to detect during the second year of life due to developmental transitions, including the onset of walking and the refinement in communication skills, which may 1) enable children to have more control over their sensory experiences and more clearly express their reactions in response to those experiences, 2) enhance parents' ability to detect and report on their children's sensory behaviours, linking negative emotional reactions to specific sensory experiences. Our understanding of the nature and characteristics of manifestations consistent with behavioural sensitivity to sensory stimulation in ASD and/or ADHD would benefit from further research assessing the developmental trajectory of these features in cohorts at typical likelihood of the conditions. This research would clarify the extent to which behavioural manifestations of sensory sensitivity may be stable over time or undergo developmental transitions (i.e. normative increases or

decreases). Further, this research would shed light on the potential mediating or moderating role of skills that are acquired and progressively refined over development. By clarifying the typical developmental trajectory of behavioural manifestations of sensory sensitivity, this research could advance our understanding of atypical manifestations and elucidate the effect that these manifestations may have on children's interaction with and exploration of their surrounding environment.

While revealing the limitations of laboratory-based observation and parental reports for quantifying behavioural manifestations of sensory sensitivity in early development, results from this research also demonstrated the capability of EEG to identify signatures of sensory sensitivity holding predictive power in relation to ASD traits emerging in toddlerhood. The novelty of the EEG paradigms employed in this PhD thesis is twofold. First, relatively simple sensory stimuli were used across all the EEG paradigms, maximising the replicability of results, supporting usage in various cohorts and promoting translability across cultures and species. Secondly, the paradigms were designed to enable quantification of the relative contribution of feedback and feedforward processing to sensory perception, thus offering a route towards clarifying the mechanism underlying early-emerging sensory atypicalities in infants with later higher ASD traits. Further, integrating the evidence emerged from these EEG paradigms with parental reports of infants' active seeking of sensory stimulation demonstrated crucial to disclose a potential protective factor that, in early development, may mitigate the otherwise observed

association between early sensory atypicality and later ASD traits. I further discuss this issue in section 7.5.

In summary, the work presented in this PhD thesis informs methodological approaches to the investigation of the early development of sensory perception in ASD and ADHD by 1) drawing attention to the importance of an integrated approach, whereby experimental (neural and behavioural) and parent-reported measures are adopted within a single, comprehensive framework, 2) emphasizing the need for further longitudinal research investigating the developmental trajectory of behavioural manifestations of sensory sensitivity in infants at typical likelihood of ASD or ADHD. This approach towards careful phenotyping of sensory processing holds potential for advancing our mechanistic understating of these disorders and for differentiating primary features of the conditions from later-emerging manifestations.

7.3. Mechanisms underlying the early development of sensory perception in ASD and ADHD

As discussed in Chapter 1, progress in our understanding of the mechanisms underlying ASD and ADHD aetiologies has occurred over the last two decades. These advances clarified some factors underlying the emergence of these conditions, contemporarily prompting the formulation of several theoretical frameworks attempting to integrate the heterogeneous spectrum of ASD and ADHD manifestations into a single explanatory phenotype. Results from this PhD research

inform the debate regarding the aetiology of ASD and ADHD across multiple areas. Firstly, the current results inform cognitive theories attempting to channel the wide spectrum of ASD and ADHD traits into a single explanatory phenotype. Secondly, results from this research inform neurobiological accounts linking neural vulnerabilities to disorder-specific traits in ASD and ADHD. Finally, results from this research inform theoretical approaches drawing on neurobiological, cognitive and behavioural research with the goal of integrating sensory and social features in ASD within a unitary framework.

7.3.1. Cognitive theories of ASD

As reviewed in Chapter 1, multiple cognitive theories attempting to canalize the heterogeneous spectrum of ASD manifestations into one explanatory phenotype have been elaborated over the years. While theoretical explanations were initially formulated to capture social atypicalities in ASD, progress in this field promoted a gradual shift from "social-first" accounts to "sensory-first" accounts, whereby sensory manifestations are considered responsible for higher-level social and cognitive atypicalities (Gliga et al., 2014). Results from this PhD research support this theoretical transition by demonstrating that neural signatures signalling sensory atypicalities can be detected as early as 10 months of age in infants with later higher ASD traits. In particular, results from Chapter 3 demonstrate that 10-month-old infants at elevated likelihood of ASD manifest reduced neural repetition suppression of tactile stimulation, which further predicts higher ASD traits at 24

months. Similarly, results from Chapter 4 indicate that 10-month-old infants at elevated likelihood of ASD display neural hypersensitivity to visual stimulation and reduced feedback modulation of feedforward visual processing (as indexed by reduced modulation of the P1 peak amplitude by ongoing theta amplitude), with the latter predicting higher ASD traits at 24 months. Combined with prior evidence from prospective longitudinal studies of infants at elevated likelihood of ASD, whereby atypicalities in social functioning are not documented until after 12 months of age (Gliga et al., 2014; Johnson, 2014), results from this research challenge the notion that ASD may originate from reduced social motivation and consequent reduced social orienting early in development (Johnson, 2014). Results from this research suggest instead that early-emerging vulnerabilities in ASD may appear in the sensory domain and potentially cascade into later social and cognitive manifestations.

Results from this PhD investigation also shed light on theoretical accounts proposed to explain sensory atypicalities in ASD. As reviewed in Chapter 1, the *Enhanced Perceptual Functioning theory* was first proposed to explain sensory manifestations in individuals with ASD (Mottron et al., 2006). According to this theory, a bottom-up processing style underlies the strength or preference for local information in individuals with ASD. Therefore, global processing may be intact in these individuals and it could be recruited when necessary. However, the local perceptual bias would improve their performance across tasks assessing sensory sensitivity, perceptual discrimination and processing of first-order static

information (Mottron et al., 2006). Results from Chapters 3 and 4 contrast this notion. In particular, evidence from Chapter 3 indicates that 10-month-old infants with later higher ASD traits manifest reduced neural repetition suppression of tactile stimulation in the absence of neural hypersensitivity to the first vibrotactile stimulus. Accumulating evidence from animal and human research indicates that repetition suppression does not represent a neural adaptation (or fatigue) effect (Grill-Spector et al., 2006; Heilbron & Chait, 2018). In fact, multiple studies indicate that feedback modulation through signals descending the cortical hierarchy via backward connections underlies repetition suppression (Rubin et al., 2016; Rummell et al., 2016; Ulanovsky et al., 2004). Thus, the profile of reduced neural repetition suppression of tactile stimulation reported in infants with later higher ASD traits in Chapter 3 could be explained as resulting from reduced feedback modulation of feedforward processing. While this evidence does not enable ruling out the possibility that individuals with higher ASD traits may possess higher discrimination ability (e.g. due to narrower receptive fields), it nonetheless contradicts Mottron and collaborators' proposal of typical top-down processing in ASD.

Chapters 4 and 5 provide additional evidence in support of the notion that early atypicalities in sensory perception in ASD may result from limited feedback modulation of feedforward processing. Specifically, results from Chapter 4 indicate that infants with later higher ASD traits manifest reduced modulation of the P1 peak amplitude time-locked to checkerboard onset by ongoing theta amplitude during

video viewing. Chapter 5 extends on evidence reported in Chapter 4 by demonstrating that variation in responsiveness to incoming visual stimulation also reflects variation in engagement with ongoing information in an independent cohort of infants at typical likelihood of ASD or ADHD. Altogether, evidence from Chapters 3-5 suggests that the integration between feedback and feedforward signals underlies typical sensory perception from an early age and further supports the notion that reduced feedback modulation of feedforward processing is a likely mechanism underlying early-emerging sensory atypicalities in infants with later higher ASD traits.

Results from this PhD investigation appear more consistent with the *Weak Central Coherence theory* and *Predictive coding theories* of ASD. Both accounts hypothesize atypicalities in sensory perception in individuals with ASD to result from atypical integration between feedback and feedforward processing. However, while the Weak Central Coherence theory is confined to a descriptive level of analysis, Predictive coding theories offer a mechanistic, biologically plausible explanation of the context-sensitive atypicalities reported in individuals with ASD. Drawing on evidence from neurobiology and neuroanatomy, Predictive coding theories hypothesize the brain to be an "active inference" organ, constantly trying to predict the sensory input it receives (Friston, 2005; Rao & Ballard, 1999). This function is assumed to rely on descending feedback signals modulating the feedforward processing of sensory input over time. Thus, in the context of Predictive coding theories, feedback signals operate in a hierarchical manner

leading, though learning, to the generation of priors modulating the processing of incoming sensory information. Several variants of Predictive coding theories exist in the literature, with some models hypothesizing sensory atypicalities in ASD to result from limited feedback modulation of feedforward processing (Pellicano & Burr, 2012) and others attributing these manifestations to inflexible precision of prediction errors, leading to overfitted priors (Van de Cruys et al., 2013, 2014, 2017). Results from this PhD investigation do not enable refuting either theoretical explanation. However, the discussed evidence appears more consistent with Pellicano and colleagues' account (2012), rather than Van de Cruys and collaborators' account (2017). Specifically, one could speculate that infants manifesting reduced neural suppression of repeated tactile stimulation (Chapter 3) experienced difficulties predicting the forthcoming event due to reduced feedback modulation of feedforward processing, impeding learning of the task structure. This hypothesis is consistent with previous research indicating that typical neural repetition suppression underlies efficient learning during experimental testing (León-Carrión et al., 2010). In line with this proposal, results from Chapter 3 also indicated that infants manifesting higher neural repetition suppression of tactile stimulation at 10 months display concurrent and longitudinal higher learning scores on the Mullen. Thus, this evidence supports the notion that enhanced neural repetition suppression may foster learning by speeding up priors updating (Pellicano & Burr, 2012).

Results from Chapters 4 and 5 also support Predictive coding of sensory perception (specifically Pellicano and colleagues' account). In particular, Chapter 4 indicates that neither infants' responsiveness to incoming stimulation (indexed by P1 peak amplitude time-locked to checkerboard onset), nor infants' engagement with the ongoing information (indexed by theta amplitude during video viewing) associate with higher ASD traits at 24 months. Conversely, it is infants' ability to modulate responsiveness to incoming visual stimulation based on engagement with ongoing information that predicts ASD traits in toddlerhood. This evidence supports the notion that studying feedback or feedforward processing in isolation may not advance our understanding of the early development of sensory perception in ASD. Conversely, an integrated approach to the investigation of sensory perception that draws on Predictive coding theories may help clarifying the mechanisms underlying early-emerging sensory atypicalities in this condition. Further evidence in support of this notion is presented in Chapter 5 which offers further demonstration that variation in responsiveness to incoming visual stimulation reflects variation in engagement with and learning of ongoing information in infants at typical likelihood of ASD or ADHD.

Taken together, evidence from Chapters 3-5 support Predictive coding theories of ASD by indicating that 1) the integration between feedforward and feedback signals lies at the core of typical sensory perception from an early age and 2) reduced feedback modulation of feedforward processing is a likely mechanism underlying early-emerging sensory atypicalities in ASD.

7.3.2. Cognitive theories of ADHD

As reviewed in Chapter 1, several cognitive theories have been advanced to channel the heterogeneous spectrum of ADHD manifestations into one explanatory phenotype. Most of these theories have been elaborated based on research with older children and/or adults with ADHD, rather than on prospective longitudinal studies of infants at elevated likelihood of ADHD. Indeed, research on the infant predictors of later ADHD traits remains scanty.

Overall, results from this PhD investigation provide limited evidence to confirm or refute existing cognitive theories of ADHD. In particular, neither results emerged from Chapter 3, nor results documented in Chapter 4 disclose a link between early-emerging sensory vulnerabilities and later ADHD traits. It is possible that the sensory manifestations reported in older children and adults with ADHD may not represent core features of the condition but, rather, be secondary compensatory or compounded manifestations triggered by atypical interaction with the environment. However, evidence from this research does not fully support this notion, given that already at 10 months of age, infants at elevated likelihood of ADHD displayed sensory manifestations, including neural hypersensitivity to visual stimulation and reduced capacity to modulate responsiveness to incoming visual stimulation based on engagement with ongoing information (Chapter 4).

A second possibility is that sensory atypicalities reported in children with ADHD reflect co-occurring traits, rather than core features of the disorder. Results from this PhD thesis provide some evidence in support of this notion, given that

neither in Chapter 3, nor in Chapter 4 infants' likelihood status significantly moderated the longitudinal association between early-emerging sensory vulnerabilities and later ASD traits. The lack of a moderating effect of infants' likelihood status is suggestive of a common pathway to later ASD traits existing in infants at elevated likelihood of ASD and/or ADHD. However, it is also possible that the lack of a moderating effect of likelihood status reflects mischaracterization of a proportion of participants into the group of infants at elevated likelihood of ASD. As discussed in Chapter 1, the screening method used in this PhD project was designed to reduce group mischaracterization (given that screening occurred for those families who reported ADHD concerns). However, it remains likely that within families with ASD, rates of actual ADHD were higher than those captured by the employed 1/0 diagnostically-based rating system, reflecting the fact that in the UK clinically diagnosed prevalence rates of ADHD are lower than population prevalence estimates (which is not the case for ASD; see Russell, Rodgers, Ukoumunne, & Ford, 2014).

The lack of a significant effect of the ADHD likelihood status on neural markers of tactile and visual sensory processing at 10 months was also substantiated by evidence that neither of these markers significantly predicted ADHD traits in toddlerhood (as quantified by the parent-reported ECBQ). The parent-reported ECBQ provides a measure of infants' temperament across various dimensions. It is possible that the activity and inhibitory control subscales of the ECBQ used in Chapters 3 and 4 failed to capture ADHD traits emerging in toddlerhood. In the

current research, the choice of designating ECBQ activity and inhibitory control subscales as ADHD outcome measures was driven by prior literature. In particular, Shephard et al., (2018) reported higher ECBQ activity and lower inhibitory control at 24 months to predict higher mid-childhood hyperactivity/impulsivity and inattention symptoms. However, since ADHD manifestations are less prominent in toddlerhood compared to later childhood, the possibility that this parental-report failed in capturing ADHD traits cannot be ruled out. This possibility should be acknowledged given that, also for ASD traits, significant associations emerged between neural markers of sensory atypicality and the researcher-rated ADOS-2 CSS but not the parent-reported Q-CHAT at 24 months. Low-to-moderate correlations are documented in the literature between clinician ratings and parent ratings of ADHD traits (particularly for children manifesting fewer ADHD traits – as it is the case in toddlerhood) (Nobel et al., 2019), which is why best practice in diagnostic clinical assessment is to use both methods. Evidence from a recent meta-analysis investigating the predictive power of parental reports of infants and toddlers' temperament (i.e. activity and inhibitory control) in relation to ADHD traits emerging in childhood further indicates that these measures yield small effects sizes, accounting for only 7% to 19% of variance in later traits (Kostyrka-Allchorne et al., 2020). These modest effect sizes suggest that other factors likely modulate the link between early temperament and later ADHD traits. Given that temperamental stability increases after 24 months of age (Lemery, Goldsmith, Klinnert, & Mrazek, 1999), it is possible that the predictive power of parent-

reported measures of temperament may also improve during childhood. Thus, the non-significant associations between neural markers quantified in the tactile and visual modalities at 10 months and ADHD traits at 24 months (quantified through parental report) must be followed-up using both observational and parent-report assessment of ADHD traits at 3 years.

Taken together, results from this PhD investigation provide insufficient evidence to confirm or falsify existing cognitive theories of ADHD. While disappointing, these results are consistent with a more general limited attempts of success to identify infants' markers of later ADHD traits (Kostyrka-Allchorne & al., 2020). Mapping the longitudinal associations between sensory manifestations that appear shared in the early development of ASD and/or ADHD and ADHD traits emerging in later childhood could help clarifying the extent to which these manifestations may be core features of ADHD or index co-occurring ASD features in the early development of ADHD.

7.3.3. Neurobiological explanations of ASD

As reviewed in Chapter 1, driven by cognitive theories of ASD, several neurobiological explanations have been proposed to illuminate the mechanisms underlying ASD manifestations. Results from this PhD research align to neurobiological evidence and suggest that atypical neural responses to sensory stimulation can be detected in infants with later higher ASD traits as early as 10 months of age. This evidence corroborates the notion that atypicalities in brain

function may appear before behavioural manifestations in populations with later higher ASD traits (Varcin & Jeste, 2017). Results from this PhD research provide particular support for neurobiological accounts hypothesizing ASD manifestations to result from *atypical E/I balance* in putative cortical areas (Lee, Lee, & Kim, 2017; Nelson & Valakh, 2015; Rubenstein & Merzenich, 2003). Prior studies suggested that E/I imbalances may contribute to sensory and social atypicalities in ASD (Kolesnik et al., 2019; Puts et al., 2017; Robertson et al., 2013, 2016; Rojas et al., 2014). However, with the exception of Kolesnik and collaborators (2019), who investigated mechanisms of auditory repetition suppression in a prospective longitudinal sample of infants at elevated likelihood of ASD, prior research mostly assessed the validity of E/I theories in older children and adults with the disorder.

Aligning to results from Kolesnik and colleagues (2019), evidence emerged in Chapter 3 indicates that 10-month-old infants with later higher ASD traits manifest reduced neural suppression of repeated tactile input (as indexed by limited reduction in alpha desynchronization with repeated tactile stimulation). Since the alpha rhythm (i.e. oscillations in the range of 8-12Hz in adults and 6-10Hz in infants) has been linked to GABAergic inhibitory modulation in the somatosensory cortex in animals (Lőrincz et al., 2009) and humans (Schreckenberger et al., 2004; Ahveninen et al., 2007), this evidence supports the notion that E/I imbalances in putative cortical regions may characterise the early development of ASD and impact sensory perception from infancy.

Results from Chapters 4 and 5 provide further support for E/I theories of ASD. Much research indicates that typical visual perception relies on the delicate balance between feedback signals descending the cortical hierarchy from higher cortical regions and feedforward signals ascending the cortical hierarchy from lower cortical regions (Spratling & Johnson, 2004). Research with animals and adults further suggests that the gain in neural responses manifested during the initial stages of visual processing depends on feedback excitatory and inhibitory signals converging on V1 from higher cortical layers (Kok et al., 2016; Olsen et al., 2012). Thus, reduced modulation of responsiveness to incoming visual stimulation based on engagement with ongoing information in infants with later higher ASD traits could be consequent to reduced feedback excitatory and inhibitory signals descending from higher to lower cortical regions. This proposal is further consistent with evidence that E/I imbalances in visual cortical areas underlie manifestations such as atypical visual repetition suppression, atypical binocular rivalry, atypical spatial suppression/gain control and orientation discrimination (for reviews see, Dickinson, Jones, & Milne, 2016; Robertson & Baron-Cohen, 2017). Atypical feedback signals sent from layers 5/6 (which, in turn, receive input from higher cortical regions) to lower-order layers may contribute to the generation of these imbalances (Kok et al., 2016; Olsen et al., 2012; Zolnik et al., 2020).

Taken together, results from this PhD research provide support for E/I theories of ASD and suggest that E/I imbalances of neural connectivity may underlie many sensory atypicalities documented in infants with later higher ASD

traits. By linking E/I theories of ASD to Predictive coding theories of ASD, the current research offers a comprehensive framework towards careful sensory phenotyping which could advance our understanding of this condition from infancy.

7.3.4. Neurobiological explanations of ADHD

As reviewed in Chapter 1, several neurobiological explanations have been advanced to characterise the mechanisms behind ADHD traits, including E/I theories and theories implicating atypicalities in prefrontal cortical functioning. Results from this PhD research provide preliminary evidence in support of *E/I theories* of ADHD. In particular, results from Chapter 4 indicate that infants at elevated likelihood of ADHD share neural atypicalities in visual sensory processing with infants at elevated likelihood of ASD (including enhanced P1 peak amplitude time-locked to checkerboard onset and reduced modulation of the P1 peak amplitude by ongoing theta amplitude). As discussed in section 7.3.4, these vulnerabilities may reflect E/I imbalances of neural connectivity in visual cortical networks. However, results from Chapter 4 also suggest that neither of the identified neural markers of visual sensory processing at 10 months holds predictive power in relation to ADHD traits at 24 months. Thus, it is possible that E/I imbalances affecting sensory functions in the early development of ADHD may not be a primary characteristic of the condition but, rather, secondary features of comorbid ASD. Indeed, the prediction that ADHD may be underlined by E/I

imbalances in putative cortical regions originated from the observation that such atypicalities exist in several neurodevelopmental disorders comorbid with ADHD (Naaijen et al., 2017). Further research is needed to establish the extent to which E/I imbalances affecting sensory systems may be a primary feature of ADHD or a secondary manifestation linked to co-occurring conditions.

Results from this PhD research provide also preliminary and indirect evidence that *atypical prefrontal cortical functioning* may manifest in infants at elevated likelihood of ADHD. In particular, results from Chapter 4 indicate that infants at elevated likelihood of ADHD manifest reduced modulation of the P1 peak amplitude to incoming visual stimulation based on engagement with ongoing information. Prior research indicates that the prefrontal cortex is involved in generating descending feedback signals modulating visual processing during the early stages of information selection and encoding (Gazzaley & Nobre, 2012; Zanto et al., 2011). Thus, atypical prefrontal cortical functioning may underlie the reduced modulatory capacity documented in infants at elevated likelihood of ADHD. However, results from Chapter 4 also indicate that this atypicality occurs in infants at elevated likelihood of ASD, thus questioning its specificity to ADHD. Altogether, this evidence provides preliminary supports for the theoretical proposal that atypical prefrontal cortical functioning in early development may be a risk factor shared across conditions and potentially limit the capacity for compensation in the face of pre-existing vulnerabilities (Johnson, 2012).

Taken together, results from this PhD research provide indirect support for theories postulating E/I imbalances and atypical prefrontal cortical functioning as postnatal risk factors for the development of ADHD. At the same time, results cast doubt on the specificity of these risk factors for the development of ADHD and emphasize the need for further research aimed at clarifying the link between early-emerging sensory vulnerabilities and ADHD traits emerging later in development.

7.3.5. An integrative framework towards unifying sensory and social features in ASD

For a long time, researchers focused on characterising sensory and social manifestations separately in individuals with ASD. Recently, efforts have been made to integrate these manifestations into a unitary framework, leading to the proposal that sensory atypicalities in ASD may precede and possibly cascade into later social manifestations (Gliga et al., 2014; Thye et al., 2018). Evidence from empirical investigations concurs in suggesting that atypical sensory functioning (manifesting as sensory hyper/hyposensitivity and/or atypical seeking of sensory stimulation) in early childhood predicts later joint attention and language development (Baranek et al., 2013), social play development (Kuhaneck & Britner, 2013) and withdrawal from social contexts (Brock et al., 2012). Some have proposed that, over development, sensory atypicalities could trigger in some infants behaviours minimizing exposure to social situations (which could be experienced as distressing in the presence of sensory difficulties; Mulligan & White, 2012). In

turn, limited exposure to social contexts could exacerbate later ASD traits (Thye et al., 2018). On the other hand, one could speculate that those infants manifesting active seeking of situations maximising social exposure (despite co-occurring sensory atypicalities) may experience broader opportunities for learning and socialization. Thus, active seeking could represent a protective factor in early development and mitigate the otherwise observed association between sensory atypicality and later ASD traits.

Results from this PhD investigation inform theoretical accounts aimed at unifying sensory and social features in ASD. First, aligning to previous literature, results from Chapters 3 and 4 document reduced seeking of sensory stimulation (in the tactile and visual modalities, respectively) in infants at elevated likelihood of ASD relative to infants at elevated likelihood of ADHD or infants at typical likelihood of the conditions. Given that several items of the 7-36 months version of the ITSP imply a certain degree of social participation (for instance, by asking parents to rate the extent to which their child enjoys being held up in the air, or splashing during bath time), this evidence supports the proposal that reduced sensory seeking in early development may limit social opportunities. Secondly, results from Chapter 3 indicate that enhanced tactile sensory seeking at 10 months moderates the association between early reduced neural suppression of repeated tactile stimulation and later ASD traits. Thus, at the same level of neural suppression of repeated tactile stimulation, infants reported by their parents to concurrently seek more tactile stimulation manifest lower ASD traits in

toddlerhood. Taken together, this evidence suggests that active seeking of tactile stimulation in early development may act as a protective factor. The protective function of elevated tactile seeking in infancy could be exercised by widening opportunities to develop social skills and share communication. This function could be especially important in the tactile modality since touch is the first sense to develop and the mean through which infants learn about the environment and themselves (Bremner & Spence, 2017). Furthermore, since touch is the primary modality through which infants and caregivers communicate and interact (Cascio, 2010; Ferber, Feldman, & Makhoul, 2008; Mammen et al., 2016), active seeking behaviours may be easier for parents to observe in the tactile modality, compared to other sensory modalities (e.g. vision).

Results from Chapter 4 do not replicate the moderating effect of parent-reported sensory seeking in the visual modality. It is possible that elevated visual seeking may exercise a protective function during infancy in combination with additional compounding factors (i.e. multiplicative effects in a multiple moderator model). Despite not replicating the moderating effect of sensory seeking in the visual modality, results from Chapter 4 concur in suggesting that sensory seeking represents the preferred strategy of information prioritization in the presence of atypical visual perception during infancy (i.e. with infants manifesting visual hypersensitivity and reduced modulatory capacity concurrently displaying reduced parent-reported visual sensory seeking). Further support for the notion that seeking represents the preferred strategy of information prioritization in early development

is presented in Chapter 6, whereby results are replicated and extended in an independent cohort of infants at typical likelihood of ASD or ADHD.

In summary, evidence from this PhD investigation informs theoretical accounts aimed at integrating sensory and social features in ASD by disclosing a strategy that infants may adopt to restrict or broaden the range of available learning opportunities, ultimately impacting their developmental trajectories. I speculate that reduced sensory seeking may represent a strategy adopted by infants at elevated likelihood of ASD to construct an environment optimally suiting their neural processing styles (Johnson, Jones, & Gliga, 2015). This strategy may be advantageous in the short-term to limit exposure to distressing sensory environments. However, reduced sensory seeking may likewise carry detrimental long-term effects by limiting opportunities for sharing communication and refining social interaction. Under this scenario, elevated sensory seeking could exercise a protective function during development by widening opportunities to develop social skills and share communication.

7.4. Theories of comorbidity in ASD and ADHD

ASD and ADHD are neurodevelopmental disorders manifesting substantial overlap in traits and symptoms (Leitner, 2014; Rommelse et al., 2010). Despite consistent co-occurrences, distinct features are also reported in ASD and ADHD; as such, the two disorders appear readily and reliably distinguished in clinical assessment (Mayes, Calhoun, Mayes, & Molitoris, 2012). Genetic research suggests that the

overlap in traits and symptoms between ASD and ADHD may result from the common presence of genes with copy number variations or single nucleotide polymorphism. At the same time, genetic research indicates that many of the identified common genes in ASD and ADHD are pleiotropic and expressed in early prenatal development, thus affecting multiple functions over neurodevelopment (Courchesne et al., 2020, 2019; Dark et al., 2018). This property would explain why common genetic contributions in ASD and ADHD may lead to shared and distinct manifestations. Despite this evidence, studies have often focused on assessing ASD or ADHD manifestations separately. Particularly, research on the infant markers of later ASD and/or ADHD traits conducted within a trans-diagnostic framework remains scanty.

The current PhD investigation represents the first comprehensive assessment of the early development of sensory perception in infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the disorders conducted within a trans-diagnostic framework. As such, results from this investigation can inform existing theoretical models of comorbidity in ASD and ADHD.

Several theories of comorbidity in ASD and ADHD were reviewed in Chapter 1. Close examination of the evidence for/against each of these theoretical accounts suggested that ASD and ADHD should neither be considered independent disorders, nor alternate forms of a common liability dimension. Conversely, evidence indicated that the overlap in traits and symptoms between ASD and

ADHD may result from some overlapping liabilities. Results from this PhD investigation shed some light on the debate concerning the nature of co-occurring features in ASD and ADHD. By embracing a developmental perspective towards mapping the specificity of early markers as potential infant predictors of ASD and/or ADHD traits emerging in toddlerhood, the current research indicates that a common pathway to later ASD traits may exist across these different familial backgrounds. The absence of a moderating effect of infants' likelihood status on the association between neural markers of sensory atypicality (in the tactile and visual modalities) at 10 months and ASD traits at 24 months contrasts the notion that ASD and ADHD may represent independent disorders or arise from random multiformity (i.e. the two disorders have different dimensions of liability but one disorder increases the chance of developing the other disorder). Conversely, the most plausible explanation for the current set of results is that ASD and ADHD may present partial overlapping liabilities. The presence of some overlapping liabilities would explain the existence of common and distinct neural markers of sensory vulnerability in infants at elevated likelihood of ASD and/or ADHD (Johnson, Gliga, et al., 2015). Further, the presence of partial overlapping liabilities would explain the existence of some shared sensory atypicalities holding predictive power in relation to ASD (but not ADHD) traits emerging in toddlerhood. Thus, it is likely that the shared profile of neural hypersensitivity to visual stimulation and reduced modulatory capacity reported at 10 months in infants at elevated likelihood of ASD and/or ADHD (and predicting ASD traits at 24 months) may reflect co-occurring

ASD features in the early development of ADHD. An alternative explanation for such co-occurring ASD manifestations in the early development of ADHD is (cross) assortative mating. According to this theoretical account, ASD and ADHD would not share common aetiological factors. However, non-random mating between individuals with ASD or ADHD would cause heritability, leading to co-occurring features between the disorders. Currently, limited research has been conducted to assess the explanatory power of this theoretical account in relation to ASD and ADHD (van Steijn et al., 2012). As such, evidence from this PhD investigation prompts further research in the area.

Taken together, the current PhD investigation informs our understanding of the potential mechanisms underlying comorbid manifestations in the early development of ASD and ADHD by suggesting that a common pathway to later ASD traits may exist despite different familial backgrounds. However, at this stage, this proposal should be considered preliminary. Replicating the association between neural markers of sensory atypicality reported in this research and ASD traits at a later time point (i.e. early and/or mid-childhood) is essential to confirm of refute this proposal.

7.5. Implications for research on early interventions

As discussed in section 7.2, ample evidence emerged from prospective longitudinal studies of infants at elevated likelihood of ASD indicates that core behavioural manifestations holding predictive power in relation to later traits and/or diagnostic

outcome do not appear until the second year of life (i.e. between 12 and 24 months). In line with this evidence, researchers have proposed that the earliest features of ASD may lie outside the core dimension of diagnostic manifestations (Flanagan et al., 2012; Varcin & Jeste, 2017) – a proposal that comes to no surprise if one considers the *developmental nature* of disorders such as ASD (and ADHD). Development is a nonlinear process (Karmiloff-Smith, 1998) and phenotypic outcomes in neurodevelopmental conditions result from complex nonlinear interactions between early-emerging vulnerabilities and later compensatory and/or compounding factors triggered by atypical interaction with the environment (Elsabbagh, 2020; Johnson, Jones, et al., 2015; Thomas, 2016). Characterizing the nature of compensatory and/or compounding factors mediating or moderating the association between infant markers of atypicality and later ASD and/or ADHD traits is fundamental to reveal systems that could promote resilience in the face of existing neural vulnerability (Johnson, Charman, Pickles & Jones, in press). In turn, this research may provide clinical insight to lay the translational foundations for the development of effective early intervention protocols.

A common theme emerged throughout the chapters of this PhD thesis relates to the role of sensory seeking as a strategy of information prioritization in early development. First, replicating previous research, evidence from Chapters 3 and 4 converged in suggesting that infants at elevated likelihood of ASD manifest, as a group, reduced seeking of sensory stimulation (in the tactile and visual modalities, respectively). Results from Chapter 3 further indicated that sensory

seeking in the tactile modality is a significant moderator of the association between reduced neural repetition suppression of tactile stimulation at 10 months and ASD traits at 24 months.

In light of these results, one could wonder if and to what extent elevated sensory seeking in infancy may promote resilience in the face of existing neural vulnerability. To answer this question, re-examining the properties of the sensory seeking construct, as captured by parental reports of sensory processing (i.e. ITSP and related age-dependent sensory questionnaires) is important. As discussed in Chapter 2, the sensory seeking construct in early development captures infants' active engagement in activities or actions providing exposure to novel/diversive sensory stimulation. Evidence from the ASD literature indicates that reduced sensory seeking manifests in infants at elevated likelihood of the condition (Ben-Sasson et al., 2009) – a notion replicated in the current cohort of 10-month-old infants at elevated likelihood of ASD in the tactile and visual modalities. Reduced sensory seeking in the early development of ASD may represent a strategy that infants adopt to limit incoming sensory input (which could be experienced as distressing in the presence of sensory difficulties; Mulligan & White, 2012). While advantageous in the short-term, this strategy could carry long-term detrimental consequences for children's development, restricting opportunities for learning and socializations. It follows that infants manifesting elevated sensory seeking despite concurrent difficulties in sensory processing may experience more opportunities to develop social skills and share communication which could, in turn, promote

further learning. From a clinical perspective, one could hypothesize that providing infants with experiences or contexts fostering their active engagement with and seeking of novel/diversive sensory stimulation may have a positive effect on their long-term developmental outcomes. As such, strategies supporting infants' learning of active seeking behaviours could be incorporated into parent and clinician mediated interventions. By promoting learning, these strategies could support the development of new skills and/or generalization of pre-existing skills with potential cascading effects over development. This proposal is consistent with prior research suggesting that infants and toddlers at elevated likelihood of ASD may benefit from interventions supporting learning through self-generated experiences, rather than observation and/or passive experiences (Landa, 2018). Self-generated experiences hold potential for early interventions due to their capacity to harness neuroplasticity (i.e. the brain capacity to reorganize), thus supporting the encoding of new experiences and the development of adaptive behaviours (Kleim & Jones, 2008).

7.6. Implications for future research

Results from this PhD investigation inform our understanding of the early development of sensory perception in ASD and/or ADHD, contemporarily opening new exciting avenues of investigation. I discuss themes for future research in the following sections.

7.6.1. *Investigating if continuity exists between infant markers of sensory atypicality and the heterogeneous spectrum of sensory manifestations emerging later in development*

Results from this PhD investigation provide evidence of sensory hypersensitivity in the tactile and visual modalities in 10-month-old infants with later higher ASD traits. This evidence supports previous research on the early development of sensory perception in ASD, whereby hypersensitivity to sensory stimulation is reported. In contrast to this evidence, sensory manifestations in older children and adults with ASD appear highly heterogeneous: while some individuals display manifestations consistent with hypersensitivity to sensory stimulation, others display manifestations signalling hyposensitivity to sensory input (Tillmann et al., 2020). Co-occurring hyper/hyposensitivity may also exist in different sensory modalities in the same individual. Given this evidence, investigating whether continuity exists between the neural markers of sensory atypicality identified in the present research and the heterogeneous spectrum of sensory manifestations appearing later in development in children with ASD is important. This could be done by probing the longitudinal associations between neural markers of sensory atypicality and parental reports of sensory processing collected from the same sample of participants over childhood (i.e., SP or SSP; Dunn, 1999). Further, research programs administering the same EEG paradigms at multiple points over development would tremendously advance our understanding of the mechanisms underlying the early development of sensory perception in ASD and/or ADHD by

either disclosing longitudinal continuity or transitions. When conducted in cohorts with large sample sizes, this research could capture meaningful individual variation, fostering our understanding of the heterogeneity of sensory features in these disorders and potentially supporting precision-based therapeutics through the identification of sensory-based subgroups (Marco, Hinkley, Hill, & Nagarajan, 2011; Schauder & Bennetto, 2016).

7.6.2. *Characterising the factors promoting resilience in the face of early sensory vulnerability*

Results from this PhD research demonstrate that individual differences in seeking sensory stimulation manifest early in development and further suggest that elevated sensory seeking in the tactile modality may act as a protective factor, mitigating the association between early tactile atypicality and later ASD traits. However, it is likely that additional factors underlie infants' propensity towards seeking tactile input in early development. Given that touch is the primary modality through which infants and caregivers communicate and interact, one could hypothesize that synchrony in parent-child interaction mediated by positive/supportive touch may promote infants' learning of tactile sensory seeking strategies, generating a reinforcement loop that could exercise a protective function over development. This prediction could be experimentally assessed by evaluating the quantity of positive/supportive touches occurring during parent-child interaction assessments and by relating this measure to concurrent and/or later parental reports of tactile

sensory seeking. Further, while results from this PhD research highlighted the protective function of elevated tactile sensory seeking, it is likely that many other factors (intrinsic and environmental) are involved in promoting resilience in the face of existing sensory atypicality. While some factors may protect against specific risks (e.g. elevated tactile sensory seeking mitigating later ASD traits), other factors may exercise a broader protective function (e.g. good executive functioning yielding better cognitive and social outcomes later in development). Future research should focus on characterising protective factors promoting resilience in the face of existing sensory vulnerability. This research would considerably advance our understanding of the early development of sensory perception in ASD and/or ADHD, contemporarily laying the translational foundations for the development of early intervention protocols.

7.6.3. *Investigating sensory contributions to anxiety in the early development of ASD and/or ADHD*

High levels of anxiety are reported in children with ASD or ADHD (van Steensel & Heeman, 2017; Reynolds & Lane, 2009). Prior research indicates that hypersensitivity to sensory stimulation may contribute to co-occurring anxiety in both conditions (Mazurek et al., 2013; Reynolds & Lane, 2009). Despite this evidence, no research has so far investigated the contribution of early-emerging sensory features to concurrent and later anxiety manifestations in prospective longitudinal cohorts of infants at elevated likelihood of ASD and/or ADHD.

Investigating the contribution of early sensory features to concurrent and later anxiety manifestations could clarify the mechanisms underlying these common co-occurrences in ASD and ADHD. Practically, this research could be conducted in cohorts of infants at elevated likelihood of ASD and/or ADHD by probing the associations between early markers of sensory atypicality (quantified through objective experimental assessments, including EEG paradigms, and parental reports of sensory processing, e.g. ITSP), concurrent predictors of later anxiety (quantified by objective experimental assessments, including measures of physiological arousal, and parental reports of fearfulness and shyness, e.g. ECBQ) and mid-childhood anxiety symptoms (quantified through parental reports, e.g. Spence Children's Anxiety Scale, SCAS; Spence, 1998).

7.7. Reproducibility and replicability

Reproducibility and replicability are core principles of scientific research. *Reproducibility* means obtaining the same set of results when identical input data, computational approaches and conditions of analysis are employed. *Replicability* means obtaining consistent results across studies aimed at answering the same scientific question, each of which has obtained its own data. While the present PhD thesis did not set out to examine issues of reproducibility and replicability per se', efforts were made to minimise variation and maximise scientific rigor.

In regard to research reproducibility, clarity, accuracy, specificity, and completeness in the description of study methods all contribute to this aspect

(National Academies of Sciences, Engineering, and Medicine, 2019). In the current PhD thesis, effort was taken to transparently document details about the research, including details about the study design, the acquisition of data, the curation of data, the operationalization of variables and the computational approaches used for data analysis. Importantly, in all the experimental chapters of this thesis, primary analyses were distinguished from secondary or follow-up analyses and the level of uncertainty intrinsic to the results was carefully communicated to the reader (i.e. through quantification of *p* values, confidence intervals, measures of effect size and generation of plots illustrating the distribution of the individual data points).

The transparency of data, study design and computational approaches used for the analysis are also central components of research replicability, alongside issues of statistical power and the "researcher's degrees of freedom" (National Academies of Sciences, Engineering, and Medicine, 2019; Davis-Kean & Ellis, 2019). Across all the experimental chapters of this thesis, effort was taken to maximise statistical power and minimise the "researcher's degrees of freedom", that is the researcher's flexibility in applying changes to the experimental protocol or making decisions not amenable to objective assessment (Wicherts et al., 2016).

First, the data contributing to Chapters 3 and 4 was collected as part of the BASIS study, a large multisite project involving collaborations across several institutions. In both chapters, data from a subset of participants up to a common data freeze, was included and analysed. In particular, the study reported in Chapter 3 was sufficiently powered to detect effects of interest, as assessed through a power

analysis. The study reported in Chapter 4 was slightly underpowered at the 24-month time point (but not at the 10-month time point), thus highlighting the importance of confirming the lack of significant effects in a larger participant sample. Of note, the Phase 3 stage of the BASIS study is still ongoing: as such, further data collection will enable increasing the sample size, enhancing statistical power and replicating the documented results in a larger cohort of participants. Given the multisite nature of the BASIS study, analysing pooled data sets at project completion, sharing data curation protocols and computational pipelines will also support more robust and replicable research.

The data contributing to Chapters 5 and 6 was collected as part of the Predictive Learning study, which I personally designed and programmed. This study was sufficiently powered to detect effects of interest. Further, attention was taken to minimise variability during the stages preliminary to collecting the data. Specifically, to test my prediction, I developed a modified version of the experiment reported in Chapter 3, whereby only exposure to the background scene of Fantasia was experimentally manipulated, maintaining the other properties of the task unchanged. Data collection for the Predictive Learning study was conducted in the same setting and adhering the same testing protocols utilized for the BASIS study, hence limiting the variability linked to data acquisition.

While effort was taken to adhere to standardized data acquisition protocols, subtle adjustments to the testing environment revealed to be necessary given the age of the participants tested (i.e. 10 months). For example, in the study

reported in Chapter 5, a second experimenter remained inside the testing room for the whole duration of the assessment and intervened, when necessary, to re-direct the infants' attention to the screen and/or facilitate infants' engagement with the ongoing stimulation through pointing or gentle speech. Similarly, in the study reported in Chapter 3, infants experienced a "multisensory environment" during the assessment, given the concurrent presentation of a video with auditory component (i.e. scene from Fantasia) and the presence of a caregiver inside the testing room for the whole duration of the study. Similar adjustments are common in research with developing populations. However, when systematically occurring, these adjustments may introduce spurious confounds (i.e. non-random errors) and limit results replicability. An attempt to control for such non-random errors was made in the context of both the BASIS study (Chapter 3 and 4) and the Predictive Learning study (Chapter 5) by videotaping all the testing sessions, thus providing documentation that could be examined to identify potential differences in results and/or characterise further the rationale behind the inclusion/exclusion of particular sets of data.

In conclusion, multiple efforts were taken in this PhD project to maximise the reproducibility and replicability of the research findings. Yet, it is possible that these efforts may not have removed all the possible sources of bias. This could either be seen as a limitation or as a challenge for future research: indeed, if findings are replicated despite wide variation in experimental details, that suggests that the

phenomenon is generalizable and robust, rather than circumscribed to a narrow set of conditions.

7.8. Concluding remarks

The overall aim of this PhD thesis was to investigate the early development of sensory perception in infants at elevated likelihood of ASD and/or ADHD and infants at typical likelihood of the conditions. Towards this goal an integrated approach that draws on Predictive coding theories was applied within a developmental framework. Results demonstrated that neural markers signalling atypicalities in sensory perception and holding predictive power in relation to ASD traits emerging in toddlerhood can be detected at early as 10 months of age. Further, by disclosing factors that could compound early-emerging sensory vulnerabilities, results highlighted the complexity of the pathway linking sensory features to ASD traits emerging in toddlerhood.

The current results carry implications for our understanding of *methodological approaches* to the investigation of the early development of sensory perception in ASD and/or ADHD, *mechanisms* underlying the early development of sensory perception in ASD and/or ADHD, *theories of comorbidity* in ASD and ADHD and research aimed at laying the translational foundations for the development of *early intervention* protocols.

Future directions for research include characterising the potential links between early-emerging sensory features and the heterogeneous spectrum of

sensory manifestations emerging later in development (including hyper/hyposensitivity and atypical sensory seeking), investigating the factors promoting resilience in the face of early sensory vulnerability and mapping the contribution of sensory features to concurrent and later anxiety traits in the early development of ASD and/or ADHD. This research would tremendously advance our understanding of the mechanisms underlying the early development of sensory perception in ASD and ADHD, contemporarily informing clinical research on early interventions.

It is my hope that this PhD thesis highlighted the importance of studying sensory perception in ASD and ADHD within a developmental framework, thus providing a foundation that could guide research in this area moving forward.

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Equations : An Annotated Bibliography Key words : Correlated data analysis ; Generalised linear model ; Longitudinal data analysis ; Marginal model; Pseudo maximum likelihood. *Biometrical Journal*, *40*, 115–140.

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Appendix

Appendix to Chapter 1

A.1.1. Look-up table detailing EEG and psychobehavioural evidence emerged from research conducted in the context of Predictive coding theories

Experimental studies	Participant sample	EEG evidence	Psychobehavioural evidence	Interpretation
Garrido et al., (2008)	Neurotypical adults	MMN in auditory oddball paradigm	N/A	MMN reflects learning (i.e. progressive refinement of sensory predictions)
Haenschel et al., (2005)	Neurotypical adults	MMN in auditory oddball paradigm	N/A	MMN reflects learning (i.e. formation of "sensory memory")
Tremblay et al., (1998)	Neurotypical adults	MMN in auditory oddball paradigm	MMN precedes behavioural improvements in speech discrimination (i.e. accuracy)	MMN is a correlate of perceptual learning
Kujala et al., (2001)	Neurotypical adults	MMN in auditory oddball paradigm	MMN predicts gains in auditory discrimination (i.e. accuracy and RTs)	MMN is a correlate of perceptual learning
Costa-Faidella et al., (2011)	Neurotypical adults	MMN in roving paradigm	N/A	MMN reflects perceptual learning and is modulated by stimulus predictability
Lieder et al., (2013)	No human participants (i.e. computational modelling study)	MMN in roving paradigm	N/A	MMN reflects learning (not adaptation)

Hughes et al., (2001)	Epileptic patients	ERPs in an auditory stimulus-omission paradigm	N/A	Stimulus-omission potentials reflect the comparison between the content of short-term memory and the (lack of) incoming sensory stimulus
Raij et al., (1998)	Neurotypical adults	ERPs in an auditory stimulus-omission paradigm	Stimulus-omission potentials are enhanced in the presence of task-directed attention (i.e. silently counting omissions)	Stimulus-omission potentials reflect the comparison between a pre-existing expectation and the (lack of) incoming sensory stimulus
Yabe et al., (1997)	Neurotypical adults	ERPs in a visual stimulus-omission paradigm and visual oddball paradigm	Self-reports rating the stimulus-omission task as more demanding than the visual oddball paradigm	Stimulus-omission potentials reflect top-down volitional engagement of cognitive processing
Chennu et al., (2016)	Neurotypical adults	ERPs in an auditory stimulus-omission paradigm	Stimulus-omission potentials are enhanced in the presence of task-directed attention (i.e. counting the omissions silently)	Stimulus-omission potentials reflect the comparison between a pre-existing expectation and the (lack of) incoming sensory stimulus
Bendixen et al., (2009)	Neurotypical adults	ERPs in an auditory stimulus-omission paradigm (with predictability manipulation)	N/A	Stimulus-omission potentials are present when sequences are prospectively predictable and reflect the comparison between a pre-existing expectation and the (lack of) incoming sensory stimulus
Janata et al., (2001)	Neurotypical adults	ERPs in an auditory stimulus-omission paradigm (with mental imagery manipulation)	Active mental imagery	Stimulus-omission potentials depends on mental imagery and reflect the comparison between a pre-existing expectation and the (lack of) incoming sensory stimulus

Appendix to Chapter 2

A.2.1. EU AIMS Medical and Psychiatric History Interview

EU AIMS Medical and Psychiatric History v3 17.9.2013

Site _____ ID_____Date: _____/_____/__ __ __ __Interviewer_____

Relationship of responder to child to be seen in study (circle one):

biological mother stepmother adoptive mother

biological father stepfather adoptive father Other (please explain)_____

3. The items below ask about the medical history of the child participating in the research project (and that of the child's *blood* relatives). In the first column, please indicate anyone in the family has the given disorder or problem listed (No, Yes, or Not Sure). If you select Yes or Not Sure, write Y (yes) or NS (not sure) under the person/persons wit that disorder/problem. All family relationships refer to the child participating in the research project (e.g. Siblings = Siblings of child participating in research project).

	(circle one for each item)			*Only complete detail information if child or child's blood relative has disorder or problem*														
Disorder or Problem	***Child/blood relative has disorder***			***IF Y or NS***	***Child***	***Parents of Child***		***Siblings***	***½ Siblings***		***First Cousins***		***Aunts & Uncles***		***Grand-parents***		***Other***
	NO	***YES***	***NOT SURE***	→		*Mom*	*Dad*	*N/A*	*Mat*	*Pat*	*Mat*	*Pat*	*Mat*	*Pat*	*Mat*	*Pat*	*Specify Relationship*
a. Autism Spectrum Disorder	N	Y	NS														
b. Fragile X	N	Y	NS														
c. Tuberous Sclerosis	N	Y	NS														
d. Neurofibromatosis	N	Y	NS														
e. Rett Syndrome	N	Y	NS														
f. Childhood Disintegration Disorder	N	Y	NS														
g. Prader Willi Syndrome	N	Y	NS														
h. Angelman Syndrome	N	Y	NS														
i. Other chromosomal abnormality, disorder or syndrome _____ *(please specify)*	N	Y	NS														
j. Congenital rubella	N	Y	NS														
k. PKU	N	Y	NS														
l. Hydrocephalus (water on the brain)	N N	Y Y	NS NS														
m. Cerebral Palsy	N	Y	NS														
n. Intellectual Disability	N	Y	NS														
o. Seizures	N	Y	NS														
p. Speech delay requiring therapy	N	Y	NS														
q. Attention Deficit Disorder (ADHD)	N	Y	NS														
r. Panic or anxiety disorder	N	Y	NS														
s. Depression	N	Y	NS														
t. Manic depression/Bipolar	N	Y	NS														
u. Schizophrenia	N	Y	NS														
v. Been admitted to a hospital for psychiatric illness	N	Y	NS														
w. Birth defects (e.g., cleft lip or palate, open spine)	N	Y	NS														
y. Norrie Syndrome……	N	Y	NS														

Appendix to Chapter 3

A.3.1. ITSP list of items and reliability assessment

Four items contributed to the ITSP tactile sensory seeking score. These items ask parents to rate on a 5-point scale (1 = almost always; 5 = almost never) if the child enjoys playing with food (item 31); if the child seeks opportunities to feel vibrations (for example, stereo speakers, washer, dryer) (item 32); if the child enjoys splashing during bath time (item 34); if the child uses hands to explore food and other textures (item 35). I investigated reliability of the ITSP sensory seeking items in the tactile modality for participants contributing to the EEG analyses by extracting Cronbach's α and composite reliability (CR). CR was extracted since Cronbach's α depends on the number of items and tends to underestimate internal consistency with fewer items (Tavakol & Dennick, 2011). At 10 months, Cronbach's α = 0.527 and CR = 0.758, indicating satisfactory internal consistency.

A.3.2. Effect of likelihood status on tactile sensory seeking

As reviewed in Chapter 2, lower sensory seeking is reported in the early development of ASD. Thus, I investigated the effect of likelihood status on the ITSP tactile sensory seeking scores measured at 10 months for infants contributing to the EEG analysis. A univariate ANOVA with tactile sensory seeking as dependent variable, ASD and ADHD likelihood status (dummy coded) as factors was run. The analysis revealed a significant main effect of ASD, $F(1,75) = 10.53$, $p = .002$, $\eta^2 = .123$. No significant main effect of ADHD was observed, $F(1,75) = .002$, $p = .964$,

η^2 = .000. Further, there was no significant interaction between ASD and ADHD, F(1,75) = .292, p = .590, η^2 = .004. See Figure A3.2.1.

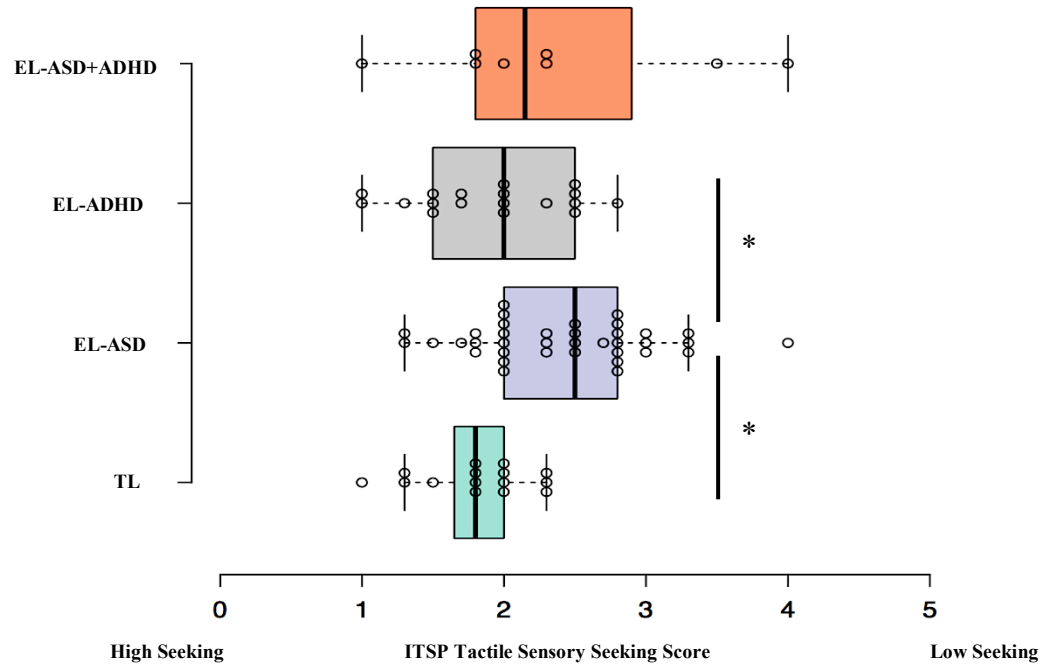


Figure A3.2.1. Boxplots illustrating the ITSP tactile sensory seeking score at 10 months for each group

*(Green=infants at typical likelihood of ASD or ADHD; Violet=infants at elevated likelihood of ASD; Grey=infants at elevated likelihood of ADHD; Orange=infants at elevated likelihood of ASD and ADHD). 10-month-old infants at elevated likelihood of ASD were reported by parents to seek tactile stimulation significantly less that infants at elevated likelihood of ADHD or infants at typical likelihood of the conditions. * $p < .05$*

A.3.3. Sensitivity analysis

All the analyses reported in Chapter 3 were re-run after removing n=2 cases contributing behavioural and EEG data for whom significant diagnostic uncertainty existed.

Behavioral results (i.e. looking and body movement to tactile stimulation) did not differ from those reported in Chapter 3. Neural results were also replicated following removal of the uncertain cases. Precisely, the significant effect of the ASD likelihood status on TSI was replicated, $F(1,85) = 5.30$, $p = .024$, $\eta^2 = .059$. The non-significant results from the investigation of infants' neural sensitivity (S1) and neural repetition suppression of tactile stimulation (TSI) were replicated. The longitudinal associations between EEG measures at 10 months and ASD or ADHD traits at 24 months remained unchanged since none of the removed cases contributed outcome data. For the same reason, results from the analyses investigating the potential mediating/moderating effect of tactile sensory seeking remained unaltered.

A.3.3. Table list

Table 5A. *Detailed characterisation of behavioural measures at the 10 and 24-month assessments for EL-ASD, EL-ADHD, EL-ASD+ADHD and TL participants who participated in the study.*

	EL-ASD	EL-ADHD	EL-ASD+ADHD	TL	*p values*
10-month visit					
Age in days	319.23 (14.68)	324.12 (27.75)	319.70 (14.66)	321.24 (17.17)	.684 (ns)
MSEL ELC	88.26 (15.04)	85.04 (15.61)	85.50 (3.79)	88.60 (12.62)	.713 (ns)
MSEL GM	38.45 (9.59)	39.00 (10.22)	35.75 (10.17)	35.32 (12.00)	.409 (ns)
MSEL FM	50.61 (11.31)	51.92 (13.96)	49.60 (12.41)	50.64 (12.67)	.934 (ns)
MSEL VR	49.91 (9.42)	47.04 (9.80)	48.25 (7.73)	48.92 (8.19)	.554 (ns)
MSEL RL	37.92 (10.55)	35.04 (10.22)	35.35 (10.92)	40.00 (8.90)	.271 (ns)
MSEL EL	36.67 (12.84)	34.38 (12.10)	36.05 (15.33)	36.40 (10.13)	.887 (ns)
N (% boys)	79 (51.9)	27 (55.6)	21 (57.1)	25 (56)	
ITSP Tactile Seeking	2.38 (0.62)$_a$	1.90 (0.54)	2.33 (0.97)	1.81 (0.39)	.005*

	EL-ASD	EL-ADHD	EL-ASD+ADHD	TL	*p values*
24-month visit					
Age in days	774.90 (48.00)	766.43 (37.65)	756.56 (22.65)	762.25 (36.07)	.343 (ns)
MSEL ELC	101.40 (20.01)$_a$	107.00 (21.72)	96.94 (17.12)$_a$	114.25 (17.90)	.020*
MSEL GM	N/A	N/A	N/A	N/A	
MSEL FM	50.34 (11.14)	52.19 (11.90)	51.75 (10.93)	56.00 (12.98)	.253 (ns)
MSEL VR	49.34 (12.79)$_a$	56.71 (12.04)	47.94 (10.28)$_a$	56.62 (10.66)	.001**
MSEL RL	51.46 (13.55)	52.24 (14.12)	49.00 (10.39)	57.67 (8.73)	.128 (ns)
MSEL EL	50.16 (14.70)	52.52 (14.07)	44.94 (11.07)	55.42 (12.30)	.114 (ns)
N (% boys)	62 (50)	21 (44.4)	16 (52.4)	24 (48.1)	
ADOS-2 CSS	2.83 (2.17)$_a$	2.75 (2.09)	3.69 (0.57)$_a$	1.55 (0.67)	.004*
ECBQ Inhibitory Control	3.67 (1.19)	3.80 (0.88)	3.61 (1.28)	4.095 (0.96)	.632 (ns)
ECBQ Activity	4.69 (0.86)	5.06 (1.04)	5.19 (0.94)	4.76 (0.74)	.159 (ns)
Q-CHAT	24.41 (11.61)	28.47 (10.63)	28.51 (12.63)	20.68 (5.48)	.120 (ns)

* $p < .05$; ** $p \leq .001$; $_a$ indicates significant differences with the TL group

M (*SD*) reported for: Age in days; MSEL ELC = Mullen Scales for Early Learning Early Composite Score; MSEL GM = Mullen Scales for Early Learning Gross Motor Score; MSEL FM = Mullen Scales for Early Learning Fine Motor Score; MSEL VR = Mullen Scales for Early Learning Visual reception Score; MSEL RL = Mullen Scales for Early Learning Receptive Language Score; MSEL EL = Mullen Scales for Early Learning Expressive Language; ADOS-2 CSS = ADOS-2 Calibrated Severity Scores; ITSP Tactile Seeking = Tactile sensory seeking average score of the Infant-Toddler Sensory Profile; ECBQ Inhibitory Control = Inhibitory

Control subscale of the Early Childhood Behaviour Questionnaire; ECBQ Activity = Activity subscale of the Early Childhood Behaviour Questionnaire; Q-CHAT = Quantitative Checklist for Autism in Toddlers.

Table 5B. *Detailed comparison of participants included and excluded from the EEG analyses due to fussiness/excessive movement artifacts on behavioural assessment scales at 10 and 24 months*

	Excluded	Included	*p values*
10-month visit			
Age in days	322.06 (15.97)	321.11 (18.92)	.796 (ns)
MSEL ELC	85.91 (13.36)	86.73 (14.41)	.773 (ns)
MSEL GM	35.47 (9.66)	36.81 (9.41)	.484 (ns)
MSEL FM	48.73 (12.11)	50.69 (11.92)	.419 (ns)
MSEL VR	47.44 (8.74)	48.59 (8.73)	.515 (ns)
MSEL RL	38.00 (10.19)	36.68 (9.95)	.510 (ns)
MSEL EL	36.02 (11.76)	35.97 (12.53)	.983 (ns)
N (% boys)	34 (56)	91 (49.5)	
ITSP Tactile Seeking	4.38 (0.80)	4.38 (0.64)	.979 (ns)

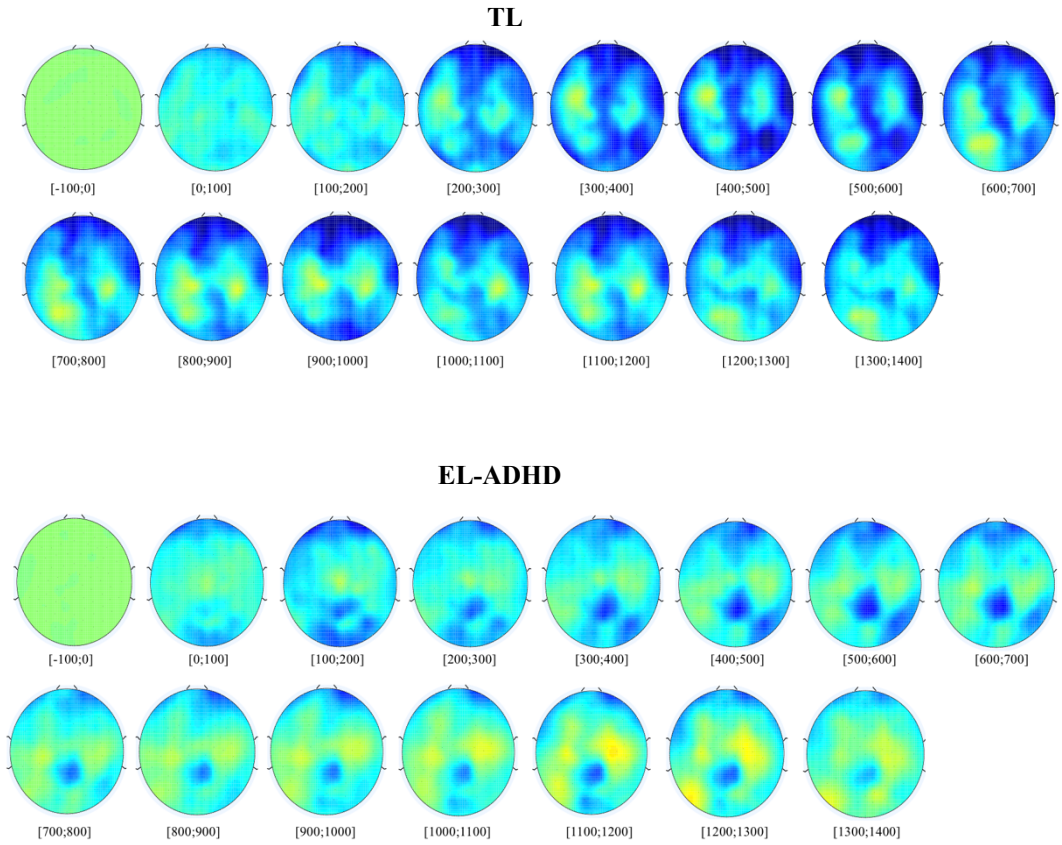
	Excluded	Included	*p values*
24-month visit			
Age in days	766.74 (44.31)	771.30 (44.48)	.648 (ns)
MSEL ELC	103.48 (18.39)	105.22 (21.06)	.704 (ns)
MSEL GM	N/A	N/A	N/A
MSEL FM	51.63 (11.94)	52.75 (11.51)	.665 (ns)
MSEL VR	51.74 (12.82)	53.34 (13.04)	.581 (ns)
MSEL RL	53.92 (11.86)	52.06 (12.72)	.506 (ns)
MSEL EL	49.67 (10.40)	51.23 (15.01)	.618 (ns)
N (% boys)	27 (53)	77 (40)	
ADOS-2 CSS	2.69 (2.20)	2.62 (2.03)	.878 (ns)
ECBQ Inhibitory Control	3.54 (0.94)	3.83 (1.20)	.278 (ns)
ECBQ Activity	5.02 (0.99)	4.68 (0.85)	.110 (ns)
Q-CHAT	23.59 (9.13)	25.02 (11.27)	.583 (ns)

M (*SD*) reported for: Age in days; MSEL ELC = Mullen Scales for Early Learning Early Composite Score; MSEL GM = Mullen Scales for Early Learning Gross Motor Score; MSEL FM = Mullen Scales for Early Learning Fine Motor Score; MSEL VR = Mullen Scales for Early Learning Visual reception Score; MSEL RL = Mullen Scales for Early Learning Receptive Language Score; MSEL EL = Mullen Scales for Early Learning Expressive Language; ADOS-2 CSS = ADOS-2 Calibrated Severity Scores; ITSP Tactile Seeking = Tactile

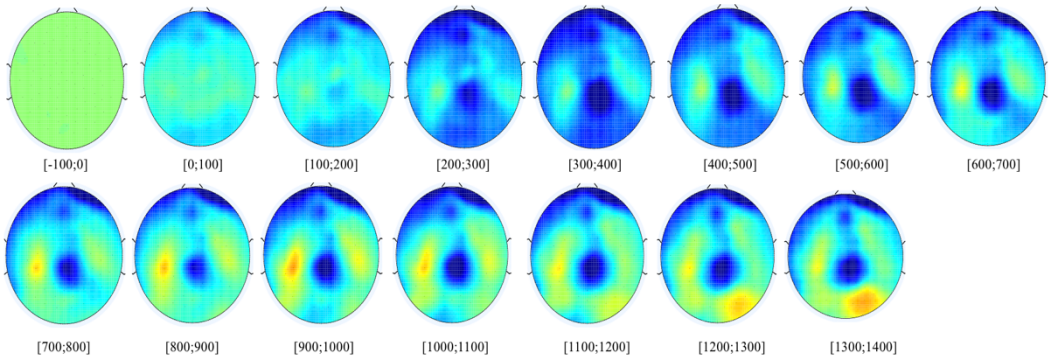
sensory seeking average score of the Infant-Toddler Sensory Profile; ECBQ Inhibitory Control = Inhibitory Control subscale of the Early Childhood Behaviour Questionnaire; ECBQ Activity = Activity subscale of the Early Childhood Behaviour Questionnaire; Q-CHAT = Quantitative Checklist for Autism in Toddlers.

A.3.4. Distribution of α desynchronization (6-10Hz) across the entire scalp

Topomaps illustrating the distribution of α desynchronization (6-10Hz) in the tactile repetition suppression paradigm for each participant groups were extracted and visually inspected prior to conducting the channel-based analysis.



EL-ASD



EL-ASD+ADHD

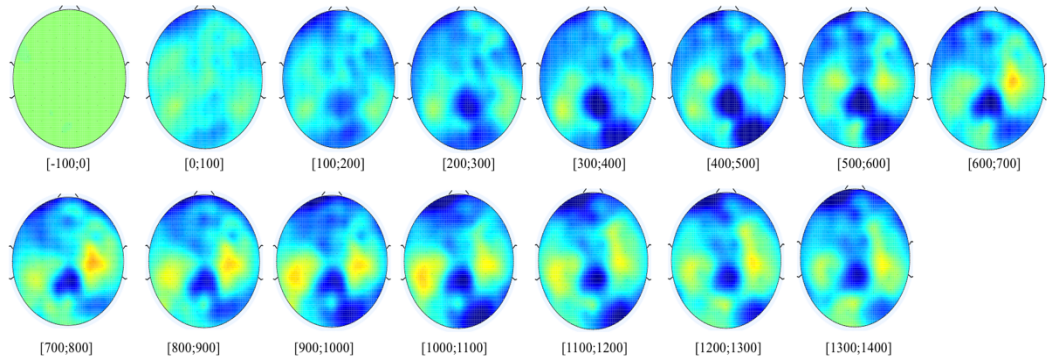


Figure A3.2.2. Topomaps illustrating the scalp distribution of α desynchronization (6-10Hz) for each participant groups

(TL = infants at typical likelihood of the conditions; EL-ADHD = infants at elevated likelihood of ADHD; EL-ASD = infants at elevated likelihood of ASD; EL-ASD+ADHD = infants at elevated likelihood of ASD and ADHD). α *desynchronization activity (nose up) is plotted in the topomaps for the entire segment; the amplitude scale ranges from -0.5μV to 0.5μV.*

Appendix to Chapter 4

A.4.1. ITSP list of items and reliability assessment

Four items contributed to the ITSP visual sensory seeking score. These items ask parents to rate on a 5-point scale (1 = almost always; 5 = almost never) if the child enjoys looking at moving or spinning objects (for example ceiling fans, toys with wheels, floor fans) (item 14); enjoys looking at shiny objects (item 15); enjoys looking at own reflection in the mirror (item 19); prefers fast-paced, brightly coloured TV shows (item 20). I investigated reliability of the ITSP sensory seeking items in the visual modality for participants contributing to the EEG analyses at both age points by extracting Cronbach's α and composite reliability (CR). CR was extracted since Cronbach's α depends on the number of items and tends to underestimate internal consistency with fewer items (Tavakol & Dennick, 2011). At 10 months, Cronbach's α = 0.679 and CR = 0.804, indicating good internal consistency. At 24 months, Cronbach's α = 0.733 and CR = 0.833, equally indicating good internal consistency.

A.4.2. Effect of likelihood status on visual sensory seeking

As reviewed in Chapter 2 and further documented in Appendix to Chapter 3, lower sensory seeking is reported in the early development of ASD. Thus, I assessed the effect of likelihood status on the ITSP visual sensory seeking scores measured at 10 months for participants contributing to the EEG analyses. A univariate ANOVA with visual sensory seeking as dependent variable, ASD and ADHD likelihood

status (dummy coded) as factors was run. At 10 months, there was a significant main effect of ASD likelihood, F(1,78) = 7.169, p = .009, η^2 = .084. No significant main effect of ADHD likelihood was observed, F(1,78) = .899, p = .346, η^2 = .011. Further, there was no significant interaction between ASD and ADHD, F(1,78) = .516, p = .475, η^2 = .007. See Figure A4.2.1.

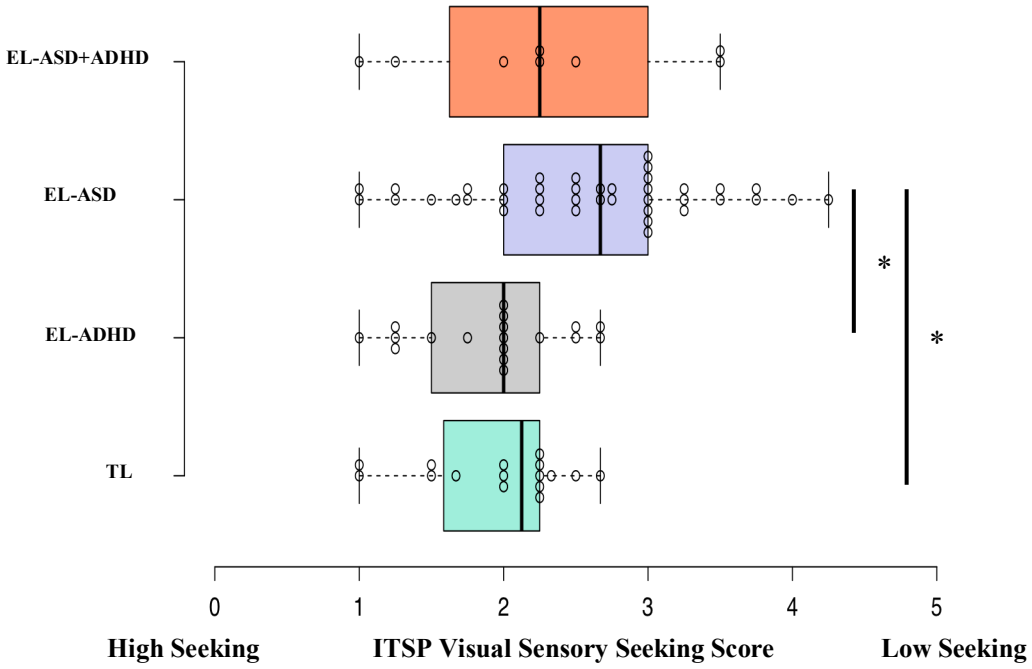


Figure A4.2.1. Boxplots illustrating the ITSP visual sensory seeking score at 10 months for each group

(Green=infants at typical likelihood of ASD or ADHD; Violet=infants at elevated likelihood of ASD; Grey=infants at elevated likelihood of ADHD; Orange=infants at elevated likelihood of ASD and ADHD). 10-month-old infants at elevated likelihood of ASD were reported by parents to seek visual stimulation significantly

*less that infants at elevated likelihood of ADHD or infants at typical likelihood of the conditions. * $p < .05$*

A.4.3. Sensitivity analysis

All the analyses reported in Chapter 4 were re-run after removing n=3 cases contributing EEG data at 10 months and 24 months for whom significant diagnostic uncertainty existed.

Neural results were replicated at 10 months and 24 months following removal of the uncertain cases. At 10 months, for the P1 peak amplitude, the main effect of ASD likelihood status was replicated, $F(1,87) = 4.95$, $p = .029$, $\eta^2 = .054$, alongside the main effect of ADHD likelihood status, $F(1,87) = 6.08$, $p = .016$, $\eta^2 = .065$. For P1 peak latency, the significant interaction between ASD and ADHD likelihood was replicated, $F(1,87) = 6.714$, $p = .011$, $\eta^2 = .072$. For theta amplitude during video viewing, the main effect of ADHD likelihood status was replicated, $F(1,87) = 12.53$, $p = .001$, $\eta^2 = .126$. Further, for P1 modulation index, the main effect of ASD likelihood status was replicated, $F(1,87) = 12.90$, $p = .001$, $\eta^2 = .129$, alongside the main effect of ADHD likelihood status, $F(1,87) = 7.99$, $p = .006$, $\eta^2 = .084$, and the significant interaction between ASD and ADHD likelihood status, $F(1,87) = 16.98$, $p < .001$, $\eta^2 = .163$.

Since none of the uncertain cases contributed data at 24 months, neural results at that age point remained unchanged. For the same reason, results of the

longitudinal associations between neural markers of visual sensory processing at 10 months and ASD or ADHD traits at 24 months remained unchanged.

Since none of the uncertain cases contributed ITSP data at 10 months, results of the concurrent associations between P1 peak amplitude or P1 modulation index and parental reports of visual sensory seeking remained unchanged. Finally, results of the concurrent and longitudinal associations between P1 modulation index at 10 months and concurrent or longitudinal scores on the Mullen were replicated (for 10-month Mullen: R (88) = -.129, p = .098, R^2 = .017 ; for 24-month Mullen: R (77) = -.329, p = .002, R^2 = .108).

A.4.4. Details on the Two-Step approach

The Two-Step approach is a method to transform non-normally distributed continuous variables towards statistical normality (Templeton, 2011). Statistical normality is achieved via two steps: 1) the original variable is transformed towards statistical uniformity by calculating the percentile (fractional) rank of each score; 2) the inverse normal transformation is applied (this takes as input the calculated fractional rank as well as the mean and standard deviation of the treated variable). The Two-Step approach does not change the order of values in the original variable, as such statistical inferences made with the normally transformed variable remain valid. Evidence indicates that the Two-Step approach for achieving normality significantly improves power in statistical estimates (Templeton, 2011; Templeton & Watson, 2010) and previous studies have employed this approach in

neuroscience research (Panier et al., 2020; Trevisan, Bowering, & Birmingham, 2016; Wallmark, Deblieck, & Iacoboni, 2018).

A.4.4. Table list

Table 10A. *Detailed characterisation of behavioural measures at the 10 and 24-month assessments for EL-ASD, EL-ADHD, EL-ASD+ADHD and TL participants who took part in the study.*

	EL-ASD	EL-ADHD	EL-ASD+ADHD	TL	*p values*
10-month visit					
Age in days	319.23 (14.68)	324.12 (27.75)	319.70 (14.66)	321.93 (16.69)	.684 (ns)
MSEL ELC	88.26 (15.04)	85.04 (15.61)	85.50 (3.79)	88.60 (12.62)	.713 (ns)
MSEL GM	38.45 (9.59)	39.00 (10.22)	35.75 (10.17)	35.32 (12.00)	.409 (ns)
MSEL FM	50.61 (11.31)	51.92 (13.96)	49.60 (12.41)	50.64 (12.67)	.934 (ns)
MSEL VR	49.91 (9.42)	47.04 (9.80)	48.25 (7.73)	48.92 (8.19)	.554 (ns)
MSEL RL	37.92 (10.55)	35.04 (10.22)	35.35 (10.92)	40.00 (8.90)	.271 (ns)
MSEL EL	36.67 (12.84)	34.38 (12.10)	36.05 (15.33)	36.40 (10.13)	.887 (ns)
N (% boys)	79 (51.9)	27 (55.6)	21 (57.1)	25 (56)	
ITSP Visual Seeking	2.49 (0.75)	1.93 (0.55)	2.34 (0.83)	2.06 (0.49)	.003*
	EL-ASD	EL-ADHD	EL-ASD+ADHD	TL	*p values*
24-month visit					
Age in days	774.90 (48.00)	766.43 (37.65)	756.56 (22.65)	762.25 (36.07)	.343 (ns)
MSEL ELC	101.40 (20.01)$_a$	107.00 (21.72)	96.94 (17.12)$_a$	114.25 (17.90)	.020*
MSEL GM	N/A	N/A	N/A	N/A	
MSEL FM	50.34 (11.14)	52.19 (11.90)	51.75 (10.93)	56.00 (12.98)	.253 (ns)
MSEL VR	49.34 (12.79)$_a$	56.71 (12.04)	47.94 (10.28)$_a$	56.62 (10.66)	.001**
MSEL RL	51.46 (13.55)	52.24 (14.12)	49.00 (10.39)	57.67 (8.73)	.128 (ns)
MSEL EL	50.16 (14.70)	52.52 (14.07)	44.94 (11.07)	55.42 (12.30)	.114 (ns)
N (% boys)	62 (50)	21 (44.4)	16 (52.4)	24 (48.1)	
ADOS-2 CSS	2.83 (2.17)$_a$	2.75 (2.09)	3.69 (0.57)$_a$	1.55 (0.67)	.004*
Q-CHAT	24.41 (11.61)	28.63 (10.23)	28.51 (12.63)	20.24 (5.73)	.061(ns)
ECBQ Inhibitory Control	3.67 (1.19)	3.80 (0.95)	3.61 (1.28)	4.07 (0.98)	.504 (ns)
ECBQ Activity	4.69 (0.86)	5.06 (1.04)	5.19 (0.94)	4.76 (0.74)	.159 (ns)
ITSP Visual Seeking	3.11 (0.80)	2.61 (0.57)	2.70 (0.79)	2.89 (0.85)	.033*

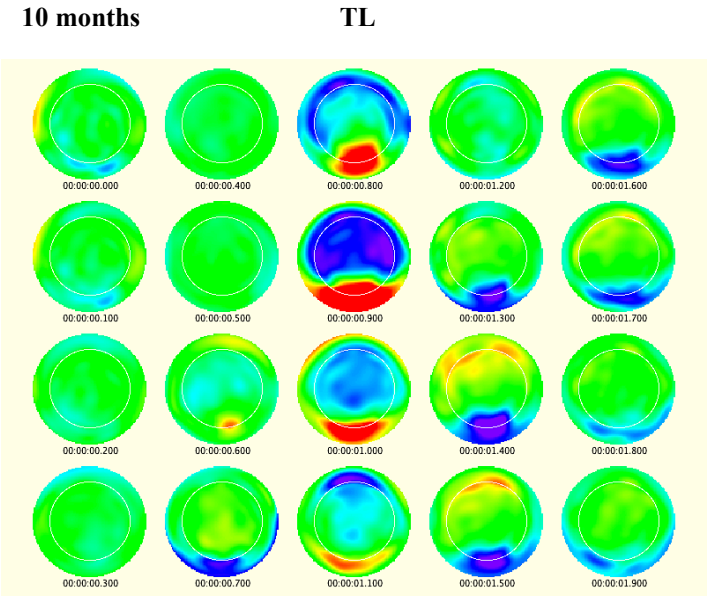
* $p < .05$; ** $p \leq .001$; $_a$ indicates significant differences with the TL group

M (*SD*) reported for: Age in days; MSEL ELC = Mullen Scales for Early Learning Early Composite Score; MSEL GM = Mullen Scales for Early Learning Gross Motor Score; MSEL FM = Mullen Scales for Early Learning Fine Motor Score; MSEL VR = Mullen Scales for Early Learning Visual reception Score; MSEL RL = Mullen Scales for Early Learning Receptive Language Score; MSEL EL = Mullen Scales for Early Learning

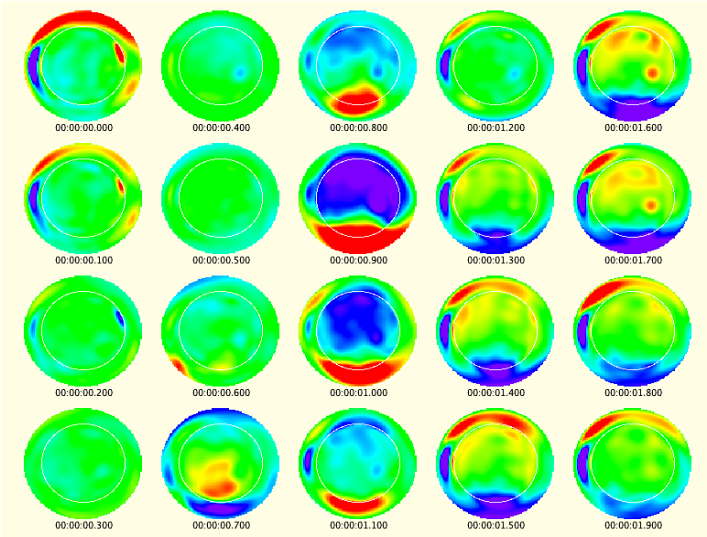
Expressive Language; ADOS-2 CSS = ADOS-2 Calibrated Severity Scores; Q-CHAT = Quantitative Checklist for Autism in Toddlers; ECBQ Inhibitory Control = Inhibitory Control subscale of the Early Childhood Behaviour Questionnaire; ECBQ Activity = Activity subscale of the Early Childhood Behaviour Questionnaire; ITSP Visual Seeking = Visual sensory seeking average score of the Infant-Toddler Sensory Profile.

A.4.5. Distribution of EEG potentials across the entire scalp at 10 and 24 months

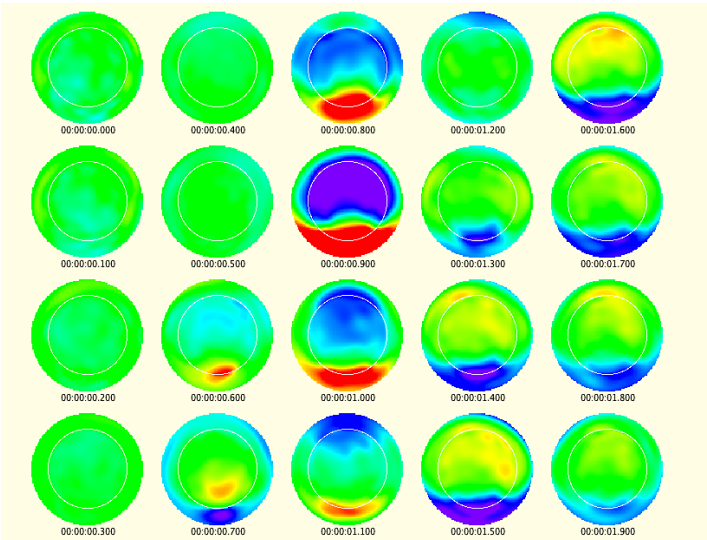
Topomaps illustrating the distribution of EEG scalp potentials for each participant groups in the visual paradigm at 10 and 24 months were extracted and visually inspected prior to conducting the channel-based analyses.



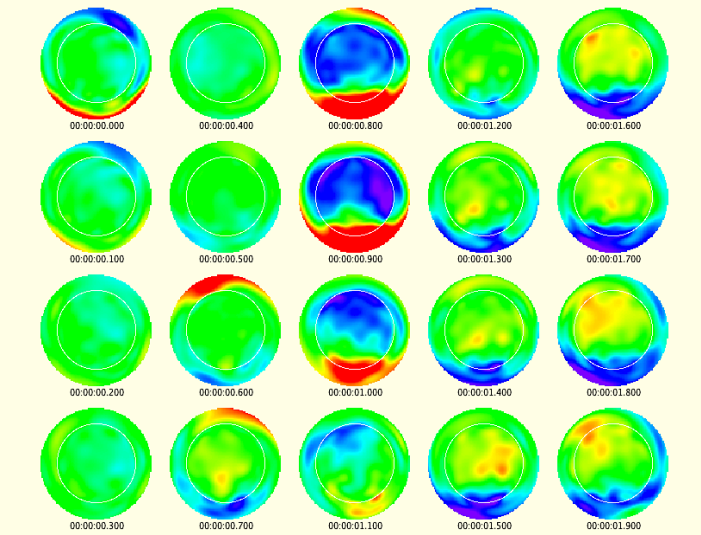
10 months **EL-ADHD**



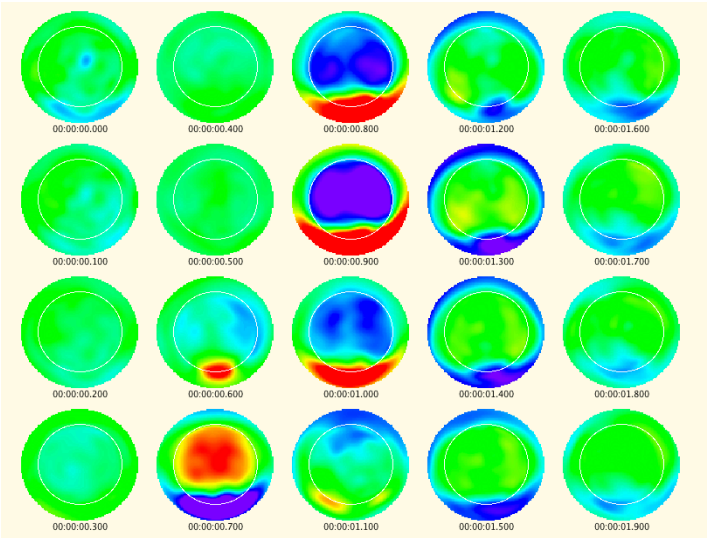
10 months **EL-ASD**



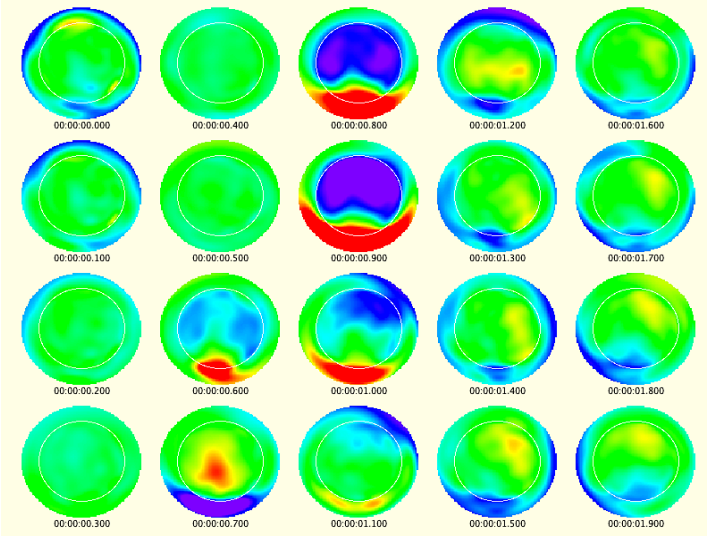
10 months **EL-ASD+ADHD**



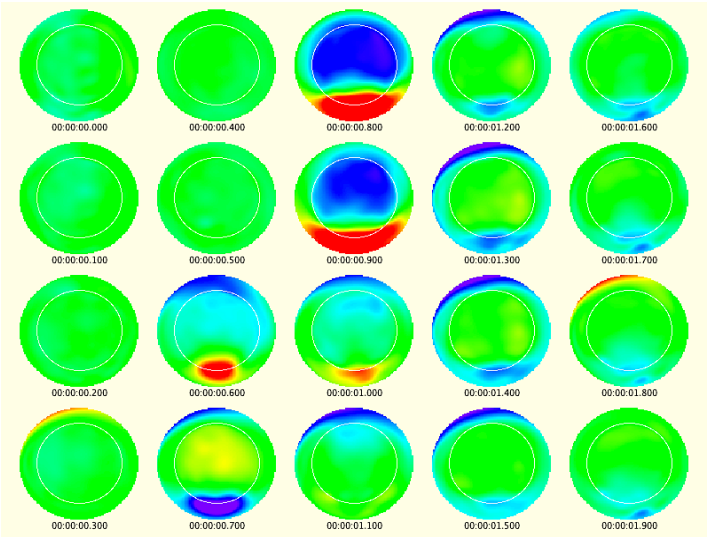
24 months **TL**



24 months **EL-ADHD**



24 months **EL-ASD**



24 months **EL-ASD+ADHD**

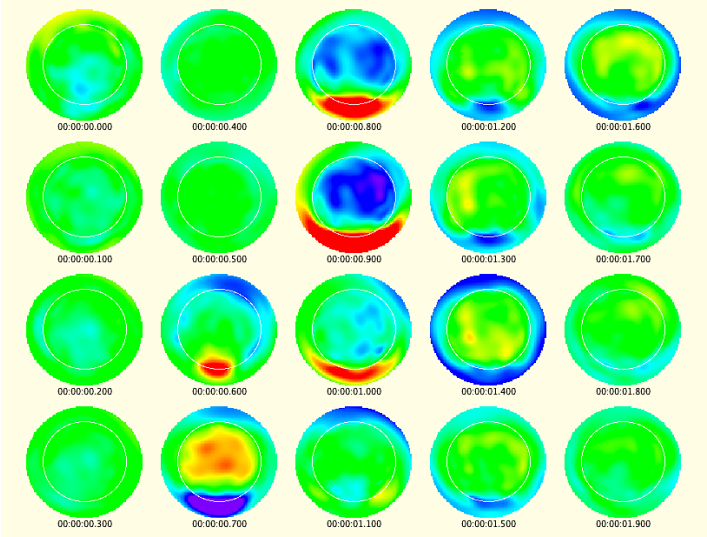


Figure A4.2.2. Topomaps illustrating the scalp distribution of EEG potentials for each participant groups at 10 months and 24 months

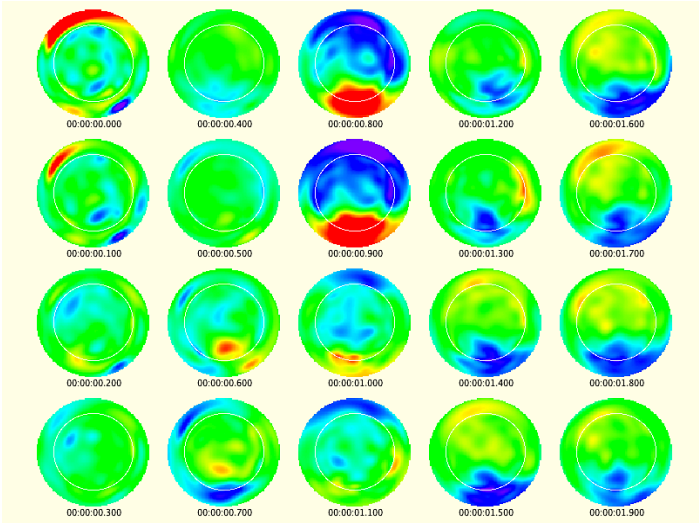
(TL = infants at typical likelihood of the conditions; EL-ADHD = infants at elevated likelihood of ADHD; EL-ASD = infants at elevated likelihood of ASD; EL-ASD+ADHD = infants at elevated likelihood of ASD and ADHD). Full potentials projection (nose up) is plotted in the topomaps for the entire segment; the amplitude scale ranges from -7μV to 7μV.

Appendix to Chapter 5

A.5.1. Distribution of EEG potentials across the entire scalp

Topomaps illustrating the distribution of EEG scalp potentials for each time bins in the visual repetition paradigm were extracted and visually inspected prior to conducting the channel-based analyses.

BIN 1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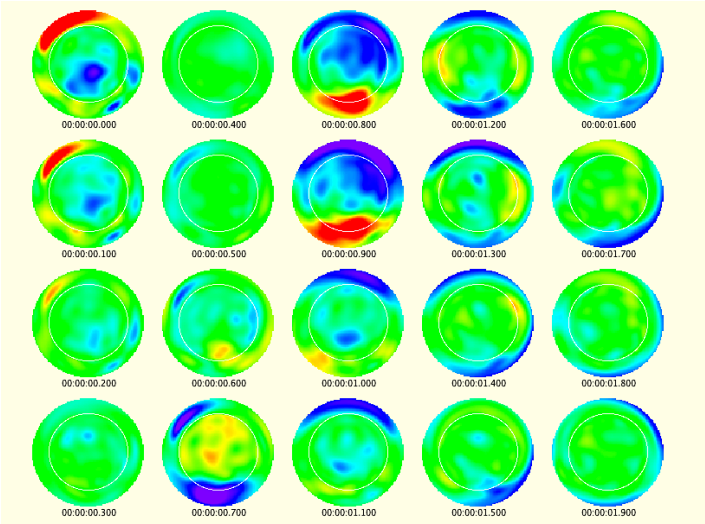
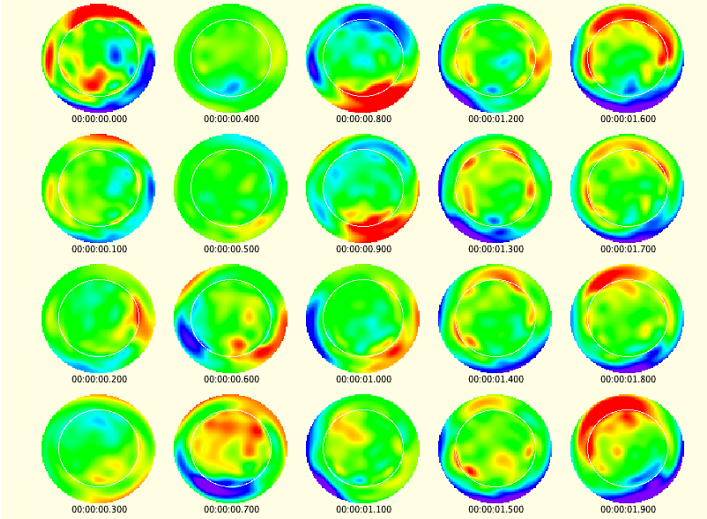
00:00:00.400
00:00:00.800
00:00:01.200
00:00:01.600
00:00:00.100
00:00:00.500
00:00:00.900
00:00:01.300
00:00:01.700
00:00:00.200
00:00:00.600
00:00:01.000
00:00:01.400
00:00:01.800
00:00:00.300
00:00:00.700
00:00:01.100
00:00:01.500
00:00:01.900

BIN 2


00:00:00.000
00:00:00.400
00:00:00.800
00:00:01.200
00:00:01.600
00:00:00.100
00:00:00.500
00:00:00.900
00:00:01.300
00:00:01.700
00:00:00.200
00:00:00.600
00:00:01.000
00:00:01.400
00:00:01.800
00:00:00.300
00:00:00.700
00:00:01.100
00:00:01.500
00:00:01.900

BIN 3



BIN 4

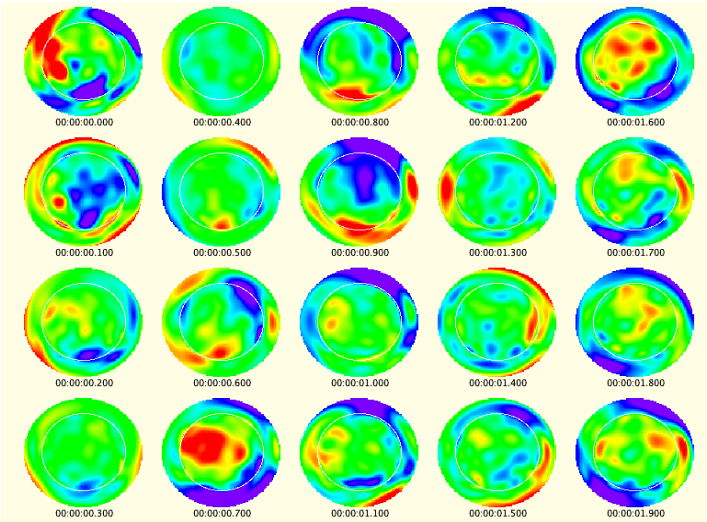


Figure A5.2.2 Topomaps illustrating the scalp distribution of EEG potentials for each time bins

Full potentials projection (nose up) is plotted in the topomaps for the entire segment; the amplitude scale ranges from -7μV to 7μV.

Appendix to Chapter 6

A.6.1. ITSP list of items and reliability assessment

Four items contributed to the ITSP visual sensory seeking score. These items ask parents to rate on a 5-point scale (1 = almost always; 5 = almost never) if the child enjoys looking at moving or spinning objects (for example ceiling fans, toys with wheels, floor fans) (item 14); enjoys looking at shiny objects (item 15); enjoys looking at own reflection in the mirror (item 19); prefers fast-paced, brightly coloured TV shows (item 20). First, I investigated reliability of the ITSP sensory seeking quadrant at 10 and 16 months by extracting Cronbach's α. At 10 months, Cronbach's α = 0.811; at 16 months, Cronbach's α = 0.774, thus indicating satisfactory internal consistency. Second, I assessed reliability of the ITSP sensory seeking items in the visual modality at both age points. Since Cronbach's α depends on the number of items and tends to underestimate internal consistency with fewer items (Tavakol & Dennick, 2011), I also extracted composite reliability at both age points. At 10 months, Cronbach's α = 0.561 and CR = 0.751, indicating satisfactory internal consistency. At 16 months, Cronbach's α = 0.521 and CR = 0.663, confirming acceptable internal consistency.