Relationship between atypical sensory processing and development of autism-like symptoms

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Abstract

Individuals with Autism Spectrum Disorder (ASD) display deficits in social communication and repetitive and stereotyped behaviours, including atypical sensory behaviours. ASD cannot be diagnosed before 3 years old. However, earliest interventions are believed to provide the best outcomes. It is therefore necessary to evidence early markers of ASD. Many theorists argue that hypersensitivity to environmental stimulation leads to the development of ASD. The aim of the study was thus to investigate the relationship between early hypersensitivity and development of ASD-like symptoms. Auditory processing was assessed in 49 nine months old babies at low and high risk of developing ASD using electroencephalography. Two types of hypersensitivity were measured: the ability to discriminate subtle changes in sounds and responses to noise. Assessed ASD-like symptoms were atypical verbal and non-verbal communication skills and repetitive behaviours at 24 months old. Babies at high risk who developed typical language skills had increased ability to discriminate sounds, compared to babies at high risk with poor language skills and babies at low risk (i.e., with typical language skills). Hypersensitive sound discrimination might therefore help babies at high risk develop good language skills. The better the ability of babies at high risk was to discriminate sounds, the better their non-verbal communication skills at a later age. This relationship was not significantly different in babies at low risk, suggesting that the ability to discriminate sounds might be helpful in typical and atypical development of non-verbal communication skills. Babies at high risk who had enhanced responses to noise went on to develop repetitive behaviours.

Repetitive behaviours might therefore help over-aroused babies to self soothe. The current study did not show a causal relationship between early hypersensitivity and development of ASD. Nevertheless, early markers of hypersensitivity could be used to index development of some ASD symptoms.

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Chapter 1: Introduction

In this chapter, Autism Spectrum Disorder (ASD) will first be defined. Atypical sensory behaviours and conflicting theories stating that atypical sensory behaviours are either playing a role in the development of ASD or developing as a consequence of other factors will then be described. This will be followed by a presentation of the treatments used to alleviate ASD symptoms, including sensory interventions. Finally, the literature highlighting a possible role of atypical sensory processing in the development of ASD symptoms will be reviewed.

1. Autism Spectrum Disorder (ASD)

Autism is a disorder presenting with a spectrum of symptoms. The presence and severity of these symptoms is variable across individuals. The definition of autism has thus evolved much over time. First, diagnosis criteria most recently accepted by the clinical community will be presented in this section. The onset and evolution of autistic symptoms also are highly variable. The various patterns of autism development will thus be described next. The heterogeneity of the condition has led to question whether autism is due to a spectrum of pathologies or a single common pathology. Hence, several aetiologies have been proposed to explain autism. The possible causes of autism will be presented last.

1.1. Definition.

Leo Kanner first described autism as being a disorder including insistence on sameness, language impairment and social isolation (Kanner, 1943). Recently, the term ‘autistic disorder’ (as well as other terms associated with autism, such as ‘Asperger disorder’, ‘childhood disintegrative

disorder' and 'pervasive developmental disorder not otherwise specified') were merged into one category 'Autism Spectrum Disorder' (ASD). In the most recent version of the Diagnostic Statistical Manual (DSM-5; APA, 2013), ASD is described as being a neurodevelopmental disorder present from infancy or early childhood, including impairments in social verbal and non-verbal communication and interaction as well as restricted and repetitive patterns of behaviour, interests or activities.

Deficits in social communication and interaction must not be accounted for by general developmental delays. For instance, delays in expressive language are no longer described as an ASD symptom because they are not specific to individuals with ASD. Deficits in social communication and interaction manifest by the following:

- Deficits in social-emotional reciprocity; including abnormal social approach (e.g., licking of others) and failure of normal conversation (e.g., failure to respond when name is called) through reduced sharing of interests (e.g., lack of showing), reduced emotions and affect (e.g., failure to share achievement with others) and reduced response to social interaction to total absence of initiating social interaction (e.g., initiation only to get help).
- Deficits in nonverbal communicative behaviours; including poorly integrated verbal and nonverbal communication, atypical eye contact and body-language (e.g. facing away from a listener), deficits in understanding and use of nonverbal communication (e.g., abnormal prosody or volume in speech) and lack of facial expression or gestures (e.g., lack of joyful expressions directed at others).

- Deficits in developing and keeping relationships; including difficulties adjusting behaviour to suit different social contexts (e.g., not noticing another's disinterest in an activity), difficulties in sharing imaginative play (e.g., lack of imaginative play with peers) and in developing friendships and an apparent lack of interest in people (e.g., not responding to the social approaches of other children, preferring solitary activities).

Restricted, repetitive patterns of behaviours, interests or activities include at least two of the following:

- Stereotyped or repetitive speech (e.g., child speaking like an adult or "little professor", referring to self by own name, immediate or delayed echolalia, repetitive humming), motor movements (e.g., flapping hands, foot to foot rocking) or use of objects (e.g., lining up of toys, repetitively turning lights on and off).

- Ritualized patterns of (non) verbal behaviour (e.g., requiring others to say things in a specific way, insisting on turning in a circle twice before entering a room), excessive adherence to routines or excessive resistance to change (e.g., overreacting to walking on a different sidewalk).

- Restricted interests that are atypical in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, such as a piece of string) or excessively circumscribed or perseverative interests (e.g., in time tables or historical events).

- Hypo- or hyper-reactivity to sensory stimulation or unusual interest in sensory aspects of environment, such as lack of reaction to heat, cold and pain (e.g., poking own eyes), adverse response to specific sounds or textures

(e.g., disliking contact with some textures), unusual sensory exploration with objects (e.g., licking or sniffing objects), fascination with lights or spinning objects and unusual visual exploration and activity (e.g., looking at objects or people out of corner of eye). Sensory symptoms were recently added to the list of ASD symptoms, which is one of the major changes from DSM-4-TR (APA, 2000) (Guthrie, Swineford, Wetherby, & Lord, 2013; Lauritsen, 2013).

ASD symptoms are seen on a continuum ranging from mild to severe expression. To be diagnosed with ASD, symptoms must limit and impair everyday functioning. They must also be present in early childhood. They may however only become observable when social demands increase with age, and ASD is often as a result diagnosed around three years old and later. ASD affects one in 100 children (Baird et al., 2006), and more often boys than girls with rates of ASD in boys being three to four times higher than in girls (Lord, Leventhal, & Cook, 2001).

1.2. Development of ASD. Young children with ASD generally exhibit marked impairment before three years old (Rapin, 1997). Parents typically report that they became concerned about their child's development around 16-18 months old (Coonrod & Stone, 2004). Their most frequent initial concern is about their child's verbal and non-verbal communication (De Giacomo & Fombonne, 1998). Most toddlers with ASD have delays in acquiring language and significantly decreased vocal output compared with developmentally delayed (DD) or typically developing (TD) children (e.g., Luyster et al., 2005). They are also less likely to use eye contact and conventional gestures (e.g., pointing) and more likely to use unconventional

gestures like manipulating their parent's hand to obtain objects (Stone, Ousley, Yoder, Hogan, & Hepburn, 1997). Parents also often report that their infant is "too good" or highly irritable (for review, see Mitchell, Cardy, & Zwaigenbaum, 2011). A study on temperament by Clifford, Hudry, Elsabbagh, Charman, and Johnson (2013) showed that babies later diagnosed with ASD have increased 'Negative Affect' (e.g., they are more difficult to soothe and they get frustrated and angry more often) and reduced 'Cuddliness' (i.e., they appear to have less desire for warmth and closeness with others and enjoyment in and moulding of the body to caregiver) in their second year of life. These early symptoms may change over time (Kanner, 1968; Lord, 1995). For instance, children later diagnosed with ASD are more adaptable and more likely to approach others than TD infants at 6 and 12 months of age, but less so at 24 and 36 months (Del Rosario, Gillespie-Lynch, Johnson, Sigman, & Hutman, 2014).

Historically, ASD was thought to have two types of onset and development. Some children experience an early onset of ASD symptoms development (in the first year of life or so) with lack of typical communication and social development (for review, see Ozonoff, Heung, Byrd, Hansen, & Hertz-Picciotto, 2008). Other children seem to develop typically for the first year or two and lose or fail to progress the language and/or social skills that they had previously acquired. In this regressive pattern, ASD symptoms often appear in the second year of life (for review, see Barger, Campbell, & McDonough, 2013). In some rare cases (previously described as 'childhood disintegrative disorder'), however, the child develops normal language and cognitive abilities until three or four years old, and then loses these skills and

exhibits ASD symptoms (Volkmar & Rutter, 1995). The reasons why children exhibit different patterns of symptom development are unknown. It was suggested that genetic differences (Gregg et al., 2008; Molloy, Keddache, & Martin, 2005) and increased rates of head growth (Webb et al., 2007) may play a role in regression. A recent study by Ozonoff et al. (2010) suggested that there may be a third type of development of ASD, by which cognitive and language skills increase in toddlerhood, but at a significantly slower growth than in developing children. A review by Rogers (2009), however, showed that there is a great variability in the timing of onset and rate of ASD development preventing the categorization of ASD development types.

1.3. Aetiology. The exact causes of ASD are unknown. The heterogeneity of the condition has led to question whether ASD is due to a spectrum of pathologies or a single common pathology. It is usually accepted however that ASD is a highly heritable complex genetic disorder. The chance that the identical twin of a child with ASD also has ASD is around 70 percent (Wong et al., 2014). Diversity in clinical presentation of ASD might result from the large number of risk genes involved (at least 200) (Sanders et al., 2011) and the numerous environmental and epigenetic factors that may modulate their expression (Abrahams & Geschwind, 2009). Specifically, it was found that children with ASD have an increased number of copies of DNA segments (Levy et al., 2011). However, a recent study of twins proposed that environmental influences during early development are more important than genetics. Hallmayer and his colleagues (2011) estimated that 38 percent of ASD are caused by genetic factors and 58 percent by unspecified

environmental factors. Examples of environmental factors found to increase the risk of pregnant women of having a child with ASD are use of certain antidepressants (Croen, Grether, Yoshida, Odouli, & Hendrick, 2011) and maternal infection during pregnancy (Brown et al., 2004).

It is likely that genetic and environmental influences lead to atypical development of the nervous system. Individuals with ASD were found to have increased white/grey matter ratio and overall brain volume (Casanova et al., 2006; Mostofsky, Burgess, & Gidley Larson, 2007) and low serotonin levels and high testosterone levels (for review, see Hughes, 2008). Specific ASD traits were found to be associated with abnormalities in specific brain areas. Neural overconnectivity in sensory parts of the cerebral cortex and atypical neural processing (e.g., density or sensitivity of sensory receptors, inhibitory and exhibitory neurotransmitter imbalance or speed of neural processing) were described at a peripheral sensory level (Mottron & Burack, 2001). They were proposed to explain hypersensitivity to environmental stimuli (Belmonte et al., 2004; Murias, Webb, Greenson, & Dawson, 2007). Atypical nervous system was also suggested to explain the difficulty some individuals with ASD may have to understand others' mental states, i.e. their poor theory of mind (Simon Baron-Cohen, 1988). Hughes and Ensor (2007) suggested that neural underconnectivity in a variety of brain regions, including the prefrontal, temporal, brainstem and cerebellar regions of the central nervous system, which are involved in processing others' mental states (Buckner & Carroll, 2007) led to abnormal theory of mind. Korkmaz (2011) proposed that mirror neurons, which are normally active when a person moves and on observation of movement of another person thus helping understand others' intentions

(Altschuler, 2008), are dysfunctional in people with ASD. Repetitive behaviour and narrow interests, which might result from deficient executive functioning as it is involved in flexible switching of attention and planning, and when impaired may lead to perseveration, could result from abnormal activity in the prefrontal cortex (Russell, 1997). Dysfunctional prefrontal cortex could also explain deficit in language, social cognition and regulation of emotional behaviour (Struss & Knight, 2002). Some studies showed that the activity in the prefrontal cortex of individuals with ASD is diminished (e.g., Ring et al., 1999; Castelli, Frith, Happé, & Frith, 2002), while other studies showed that it is increased (e.g., Belmonte, Gomot, & Baron-Cohen, 2010). These various findings suggest that ASD is due to a spectrum of neuropathologies.

1.4. Conclusion. ASD is a heterogeneous condition in terms of presence, severity, onset, development and most likely also aetiology of symptoms. Interestingly, sensory symptoms are now recognized as a criterion to diagnose ASD. However, it is unclear why they have been classified as restricted, repetitive patterns of behaviours, interests or activities in DSM-5. For instance, apparent indifference to heat, cold and pain and adverse response to specific sounds or textures do not seem to fit in this category. On the other hand, apparent indifference to name calling, which has a very strong sensory component was listed in the social communication deficit category. The next section describes the various types of sensory atypicalities in ASD and their relationship to other ASD symptoms.

2. Atypical sensory behaviours in ASD

Abnormal sensory behaviours are typical of ASD. Atypical sensory behaviours were added to the revised DSM-V (APA, 2013) because they are found in over 90 percent of children with ASD (e.g., Tomchek & Dunn, 2007). This section describes the various types of sensory behaviours in ASD. Given that ASD consists in a set of several symptoms, atypical sensory behaviours co-exist with other symptoms in individuals with ASD. The relationship between sensory behaviours and other symptoms in ASD is also described in this section.

2.1. Description. Atypical perception is described both as a source of distress and anxiety, and a source of fascination and interest for individuals with ASD (Jones, Quigney, & Huws, 2003). Children can be hyporesponsive, hyperresponsive or seek sensations (for review, see Suarez, 2012). Hyporesponsiveness is defined as a lack of the expected response to stimulation, a response with a delay or a response requiring higher intensity stimulation. For instance, children may not startle when a door is banged and not respond to sensations that others find deeply unpleasant, such as extreme heat. Hyporesponsiveness is displayed in response to both social and non-social stimuli, with the patterns being more pronounced with social stimuli in 5 years old children (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998). Hyperresponsiveness is defined as an increased response, aversive reaction or attempt to avoid a sensory stimulus. Some children with sensory hyperresponsiveness cover their ears when their environment is noisy and seem excessively cautious. Children who seek sensations display behaviours

that lengthen or increase a sensory experience. For instance, they would stare intensely at the spinning wheel of a toy car or sniff a person.

Children with ASD display more hyporesponsive behaviours than children with other DD (Baranek, David, Poe, Stone, & Watson, 2006; Miller, Reisman, McIntosh, & Simon, 2001; Rogers & Ozonoff, 2005). They are also less reactive to sensory stimuli than typically developing peers (Schoen, Miller, Brett-Green, & Nielsen, 2009; Baker, Lane, Angley, & Young, 2008). Children with ASD do not usually demonstrate more hyperresponsive behaviours than children with DD (Baranek et al., 2006; also see review by Rogers & Ozonoff, 2005), but they are more likely to display both hypo- and hyper-responsiveness than children with DD (Baranek et al., 2006). No study seems to have compared levels of hyperresponsiveness between children with ASD and TD, and levels of sensory seeking across populations.

Atypical sensory behaviours are displayed by children as young as 6 months old (Clifford & Dissanayake, 2008). The frequency of hyperresponsiveness and sensory seeking increases up to age 6–9 years and decreases thereafter, while hyporesponsiveness does not have a consistent course (for review, see Ben-Sasson et al., 2009). A recent study, however, showed that patterns of atypical sensory behaviours are relatively stable over time for hyporesponsiveness, but less so for hyperresponsiveness and sensory seeking (Freuler, Baranek, Watson, Boyd, & Bulluck, 2012). A child may display these three types of sensory behaviours across senses (Liss, Saulnier, Fein, & Kinsbourne, 2006). Hyporesponsiveness is most evident in infants who later develop ASD, while infants with DD have few sensory precursors (Freuler et al., 2012). The presentation of these symptoms is

heterogeneous in older children with ASD, with highest incidence of sensory hyporesponsiveness followed by hyperresponsiveness and sensory seeking (Suarez, 2012).

2.2. Relationship between atypical sensory behaviours and other ASD symptoms.

First-hand accounts of individuals with ASD suggest that sensory difficulties significantly influence the social difficulties they experience (e.g., Grandin, 1992), but studies on the relationship between sensory symptoms and impairment in social communication and interaction have yielded contradictory results.

2.2.1. Relationship with deficits in social communication and interaction.

Cross-sectional studies showed an association between atypical perception and social communication symptoms. Lane, Young, Baker, and Angley (2010) found that children with the most impairment in taste and smell sensitivity (e.g., avoiding certain tastes or food smells that are typically part of children's diets) have the most difficulties in the communication domain (e.g., cannot say correct age when asked, cannot move easily from one topic to another). Liss et al. (2006) found that adults with ASD with high levels of hyporesponsiveness and sensory seeking behaviours also have poor communication. These relationships are likely to exist in toddlers with ASD too. Sensory seeking was found to correlate to failure to orient to social stimuli at 18 months old (Damiano, Churches, Ring, & Baron-Cohen, 2011). Similarly, longitudinal studies looking at sensory patterns in 28 to 42 months old toddlers with ASD predicted later language and communicative development. Watson et al. (2011) showed that hyporesponsive and sensory

seeking behaviours, but not hyperresponsive behaviours, were negatively correlated with language skills and positively correlated with social-communication symptoms of ASD. Nonverbal children with ASD were found to be more likely to demonstrate higher hyporesponsiveness and sensory seeking behaviours than verbal children with ASD (Patten, Ausderau, Watson, & Baranek, 2013). Anomalous speech perception and processing is thus likely to contribute to abnormalities of pre-speech vocalisation and language delay (Oller et al., 2010; Watson et al., 2011).

Cross-sectional studies also showed a relationship between atypical sensory behaviours and social development of children with ASD. Lane et al. (2010) showed that children who had taste and smell difficulties, as well as impairment in the auditory filtering domain (e.g., are distracted or have trouble functioning if there is a lot of noise around) and movement sensitivity domain reflecting difficulties in proprioception (e.g., fear falling or heights) had more maladaptive behaviours (e.g., cry or laugh too easily, say embarrassing things). Similarly, Hilton et al. (2010) showed that impairment in multisensory responsiveness and responsiveness to taste, smell and touch are the strongest predictors of greater social impairment.

Sensory seeking, hyporesponsiveness and hyperresponsiveness were found to relate to severity of communication symptoms and social impairment in children with ASD older than four years old, and not in children with DD suggesting that this relationship is unique to ASD (Watson et al., 2011). However, other studies found no relationship between severity of sensory behaviours and impairment in social communication and interaction in toddlers (Wiggins, Robins, Bakeman, & Adamson, 2009) and older children

(Rogers et al., 2003; Foss-Feig, Heacock, & Cascio, 2012). These discrepancies may result from the studies using different populations to assess behaviours (i.e., parents or professionals) or operationalising behaviours differently with different questionnaires and including children of different ages.

2.2.2. Relationship with restricted and repetitive behaviours and interests. There might be a relationship between atypical sensory behaviours and restricted and repetitive behaviours and interests (Gerrard & Rugg, 2009). For instance, clinicians and parents describe children with ASD who only eat foods of a particular texture or flavour (for a review, see Suarez, 2012). Studies showed a relationship between severity of sensory symptoms and repetitive behaviours in 17–45 month-old toddlers (Wiggins et al., 2009) and children older than four years old (e.g., Gabriels et al., 2008; Gal, Dyck, & Passmore, 2010). For instance, Wiggins et al. (2009) found that toddlers whose parents rated their sensory behaviours across all modalities as being the most impaired had the most severe scores in the Stereotyped Behaviors and Restricted Interests domain (e.g., mannerisms, unusual repetitive interests) of the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989).

The relationship between severity of sensory symptoms and repetitive behaviours is especially strong for sensory hyperresponsiveness across modalities in children with ASD (Chen, Rodgers, & McConachie, 2009; Boyd et al., 2010). Specifically, Boyd et al. (2011) found that high levels of hyperresponsive behaviours predicted high levels of repetitive behaviours,

and that sensory seeking was specifically associated with ritualistic behaviours (i.e., child performs activities of daily living in a similar manner) and sameness behaviours (i.e., child resists to change, insists that things stay the same). However, they found non-significant associations between hyporesponsiveness and repetitive behaviours across modalities. Nevertheless, another study conducted by Foss-Feig et al. (2012) in the tactile modality only showed that severity of repetitive behaviours correlated with severity of hyposensitivity and sensory seeking, but not hypersensitivity in 5-8 years old children. These conflicting findings might result from the fact that repetitive behaviours were assessed with parental questionnaires in Chen and Boyd and colleagues' studies and with the ADOS, a test administered by expert examiners over a couple of hours in the study by Foss-Feig and colleagues. It is unlikely that parents would identify repetitive behaviours the same way as professionals. Professionals may also have a limited opportunity to observe the children during the experiment, while parents can give an overview of the child's every day behaviour. In addition, different modalities were looked at in the different studies, while it is possible that sensory behaviours vary across modalities.

Repetitive behaviours have been suggested to represent an effort to relieve stress produced by difficulty in processing sensory information (Joosten & Bundy, 2010). High levels of anxiety were found to accompany over-responsivity (Lane, Reynolds, & Dumenci, 2012). It is thus likely that a child who is rocking upon hearing a police siren is trying to soothe herself. A child who has hyporesponsive and sensory seeking behaviours might on the other hand be under-responsive to environmental stimuli and develop

repetitive behaviours to increase sensory input and compensate for under-stimulation (Lovaas, Newsom, & Hickman, 1987; Zentall & Zentall, 1983). Repetitive behaviours can thus accompany both hyposensitivity and hypersensitivity.

2.2.3. Relationship with other ASD symptoms. Other difficulties that are commonly associated with ASD were significantly related to the presence of sensory abnormalities. Klintwall et al. (2011) showed that toddlers with ASD who toe-walk and have sleep problems also have severe sensory difficulties. Brock et al. (2012) found a relationship between temperament and sensory features in children with ASD: Sensory hyporesponsiveness was associated with slowness to adapt, low reactivity and low distractibility, and a combination of increased hyporesponsiveness, hyperresponsiveness and sensory seeking was associated with increased withdrawal and more negative mood. In addition, Baranek et al. (2013) found that hyporesponsiveness to social and nonsocial stimuli predicted lower levels of joint attention in children with ASD.

2.2.4. Conclusion. Overall, ASD symptom severity positively correlated with frequency of sensory symptoms (e.g., Ben-Sasson et al., 2008) and number of modalities affected by sensory abnormalities (Klintwall et al., 2011) rather than the type of sensory difficulty (Ben-Sasson et al., 2009). The relationship between sensory symptoms and other ASD symptoms raises the question whether atypical sensory processing plays a role in the development of ASD. Several theories, presented in the next section, have been proposed to explain the development of ASD. They conflict as to whether atypical sensory processing leads to the development of other ASD symptoms.

3. Theories of ASD

There are a large number of theories related to ASD. Because of the heterogeneity of the condition, theories of ASD have focused on the most recurrent symptoms of ASD. The many atypical sensory behaviours exhibited in ASD individuals led several theorists of ASD to propose atypical sensory processing as the root cause of the development of atypical cognition from which other ASD symptoms result. However, other theories propose that higher-level, cognitive (rather than sensory) abnormalities are the root cause of ASD or develop at the same time as atypical sensory processing. Excellent attention to detail being a universal feature of ASD (Shah & Frith, 1993; Jolliffe & Baron-Cohen, 1997; O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001), it was suggested that detail-focused processing is a cognitive atypicality leading to the development of other ASD symptoms. Examples of detail-focused processing are stable memory for exact pitches in the auditory modality (Bonnel et al., 2003) and outstanding speed when picking out hidden figures in the visual modality (Shah & Frith, 1993). Hence, theories of ASD describing atypical sensory processing as causing, resulting from or being concurrent to the development of atypical cognition, such as detail-focused processing from which other ASD symptoms may result will be focused on in this section (see Figure 1). Specifically, the weak central coherence theory, hypersystemization theory and intense world theory will be described.

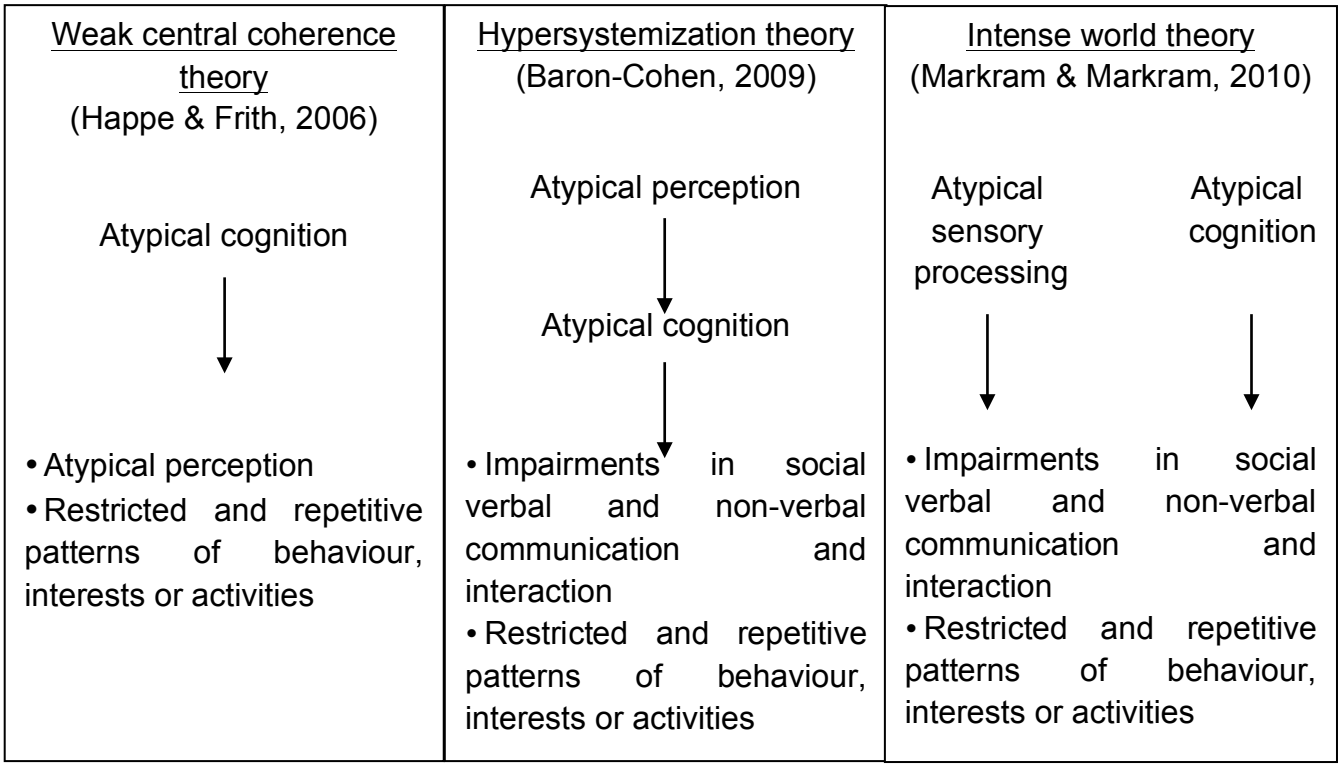

Figure 1. Schema illustrating the relationship between atypical sensory processing and atypical cognition and other ASD symptoms in ASD theories.

3.1. Weak central coherence theory. Frith (1989) defined central coherence as the tendency for typically developing individuals to process information in a global form to extract meaning, often at the expense of attention to or memory for details. Individuals with ASD were hypothesised to show weak central coherence (WCC), a cognitive difficulty in ‘‘seeing the big picture’’ in everyday life that leads to a processing bias for detailed information and therefore to greater perception (Happé & Frith, 2006). They would thus have increased attention to details and remember each situation instead of extracting prototypes (Klinger & Dawson, 2001).

According to Frith (2012), this atypical cognitive processing could lead to development of narrow interests and repetitive behaviours. The WCC theory cannot however explain deficits in social skills development (Happé, 2003). It would therefore need to be completed by another theory. An example of such a theory is the Mindblindness theory (Baron-Cohen, 1988). According to this theory, people with ASD do not have the ability to infer others' mental states because they are not directly observable. This impairment would prevent them from understanding and predicting another person's behaviour and lead to inadequate social development. Another example of a theory developed to explain the social deficits in ASD is the poor social motivation theory (Dawson et al., 2005). This theory states that children with ASD lack psychological dispositions and biological mechanisms biasing TD children to preferentially orient to the social world, seek and take pleasure in social interactions and work to foster and maintain social bonds. Children with ASD would thus be deprived of adequate social learning experiences, which would result in disrupting their social skills and social cognition development.

3.2. Hypersystemization theory. Baron-Cohen (2009) theorized that atypical sensory processing affects information processing at an early stage of development. Hypersensitive perception may overload cognitive processes leading the developing brain to evolve a cognitive style that avoids reliance on high level integrative processing and instead emphasizes low-level features (Belmonte et al., 2004). Children may become attentive to details, and unable to use contextual information. These characteristics may lead them to hypersystemize and rely overly on identifying the rules that govern a system

(e.g., a TV remote or a person) to predict how that system will behave (Baron-Cohen, 2006). Hypersystemization in turn may lead children to repeat their behaviour to check if they get the same outcome every time. They would get pleasure when it does (e.g. when watching washing machines spin round and round) and distress when it does not (e.g., when a person does not complete a sentence the expected way). Children using hypersystemization as a learning style would also be unable to develop their social and communication skills as social interactions often are unpredictable. For instance, inability to use contextual information on complex perceptual and executive tasks may impact on capacity to form a model of another person's mental state, impairing the development of joint attention, necessary to develop communication and social-cognitive skills (Tomasello & Kruger, 1992).

3.3. Intense world theory. According to Markram and Markram (2010), ASD results from an exaggerated response to stimuli at all levels of processing. Both hyper-reactivity and hyper-plasticity at perceptual and cognitive levels could enhance sensitivity and overly consolidate memories of stimuli characteristics, which could lead to attention bias towards and easier processing of the low-level features, difficulty to interrupt processing of these features and avoidance of processing of other features. On the one hand, hyper-preference could generate increased selectivity, sensitivity and specialization of characteristics at a sensory level and thus hyper-perception. On the other hand, hyper-preference could also lead to hyper-attention, hyper-memory and impaired holistic processing at a cognitive level. Impairment of holistic processing would lead to sensory sensitivity and

development of repetitive behaviours. Lack of social interaction may result from compulsively attending to and excessively processing and remembering subsets of social cues. High order functions, such as language, would be difficult to develop when attention is focused on low-level features (e.g., sound pitch).

3.4. Conclusion. The hypersystemization theory and intense world theory were designed following criticism that the weak central coherence theory could not explain the majority of ASD symptoms. Whilst these theories provide an explanation for the development of most ASD symptoms, they have attracted less critical assessment and experimental investigation. All three theories endeavour to explain ASD symptoms by finding out which ASD characteristic(s) could explain the development of most symptoms. No studies have been conducted to investigate whether there is a causal link between these ASD characteristics, and it is therefore unknown whether the assumptions made in each theory are correct. The lack of evidence for these theories has a practical impact. Treatments for ASD either are based on assumptions as to how ASD develops and, as a result try to address several symptoms by alleviating one symptom (e.g., sensory hypersensitivity), or address each symptom individually when they are not based on theory. The current treatments in use are described in the following section.

4. Treatments

As discussed above, the presentation of ASD is heterogeneous and the causes of ASD are unclear; perhaps because of this, it has been hard to find an effective treatment. It is assumed that treatments need to be tailored to each individual's ASD presentation, but the efficiency of treatments for specific presentations is unknown (for review, see Martínez-Pedraza & Carter, 2009). In this section, treatments aimed at improving social skills in children will first be described. This will be followed by a presentation of interventions conducted at an early age to improve various ASD symptoms. Finally, sensory interventions will be described.

4.1. Treatments targeting social skills. Social skills programs for higher-functioning children and adolescents (i.e., with higher intelligence quotient) include the use of social stories (Gray, 2003). For instance, a social story describes how to behave in specific situations (e.g., when a housemate changes the TV channel) to help the individual with ASD have an adapted reaction (e.g., go watch TV in their own bedroom rather than hit their housemate). Modelling is also often used to help high-functioning children develop their social skills. Video modelling, a strategy involving the use of videos to provide modelling of targeted skills (Bellini & Akullian, 2007), is also often used to increase appropriate social interactions, improve conversation skills and improve play skills (Rispoli, Neely, Lang, & Ganz, 2011). For instance, a child could learn to initiate a conversation by watching a video demonstration and then imitating the behaviour of the model. Peer modelling can also be used to teach social skills (Kasari, Rotheram-Fuller,

Locke, & Gulsrud, 2012). For instance, typically developing classmates are taught how to identify isolated children with ASD (e.g., those standing on the side of the yard instead of participating in a game), and given strategies to engage them (e.g., ask them to play in an ongoing game on the playground) and lend social support to them (e.g., via direct instruction, modelling, role-playing and rehearsal). Significant improvement in children's social skills were found with these methods (e.g., Sansosti et al., 2004).

Interventions for children with no or limited language often use the Picture Exchange Communication System (PECS) to help them develop a way of communicating with others. PECS helps children to initiate communication about things that can be presented or symbolized on a card (e.g., a request, a thought). For instance, children would learn to give someone a picture of something they want to obtain it. Benefits in communication and social skills, daily living skills, motor, adaptive behaviour and cognitive ability were reported for these interventions (for a review, see Maglione, Gans, Das, Timbie, & Kasari, 2012).

There are also many other types of treatments, including pharmacotherapy. For instance, Risperidone can be prescribed to reduce aggression or self-injurious behaviours (Jesner, Aref-Adib, & Coren, 2007). Robots have also been used to teach social skills (e.g., Billard, Robins, Nadel, & Dautenhahn, 2007). However, all these other treatments yielded contradictory results (for review, see Fernell, Eriksson, & Gillberg, 2013). Different findings often result from variety of methodologies. For instance, studies evaluating the use of robots to alleviate ASD symptoms differ in terms of number of interaction sessions, the size of the sample, the degree to which

interactions are structured or free form and the way in which data are analyzed (for review, see Scassellati, Admoni, & Matarić, 2012).

4.2. Early interventions. Early intervention is likely to have the greatest positive impact (e.g., Dawson et al., 2010). There are two major early intervention programmes.

Applied behaviour analysis (ABA) is a home-based program, founded on basic principles of learning, motivation and positive reinforcement to increase useful behaviours and reduce those that may cause harm or interfere with learning (Smith & Eikeseth, 2011). For instance, ABA includes breaking down desired skills into manageable steps to be taught from the simplest (e.g., imitating single sounds) to the more complex (e.g., carrying on a conversation).

Treatment and Education of Autistic and related Communication handicapped Children (TEACCH) is a school-based program that emphasizes visual work systems, positive routines and structured teaching (Mesibov & Shea, 2010). TEACCH uses strategies targeting the possible reasons why a child behaves atypically. For instance, children have access to charts showing the sequence of activities that will be conducted throughout the day at school. Understanding what activity will happen after the current one helps reduce challenging behaviour that would result from a difficulty to cope with changing of activity.

Intervention before four years of age was found to improve later communication skills and ability to adapt behaviour to situations (Rogers & Vismara, 2008). Overall, however, the evidence that any of the early

intervention programs are effective in changing the natural long-term outcomes of ASD is limited (Parr, 2010). There have not been large scale studies regarding highly individualized interventions and it is difficult to integrate findings from different studies as they often differ in terms of methods, designs and treatment features (Virués-Ortega, 2010). In addition, randomized controlled trials were conducted at short term only (Fernell, Eriksson, & Gillberg, 2013).

4.3. Sensory interventions. Sensory interventions, including sensory integration therapy, are widely used in older children (Seida et al., 2009). With these approaches, it is assumed that ASD symptoms result from atypical sensory processing. The sensory integration theory proposes that the provision of enhanced sensory inputs in the context of a meaningful activity leads to changes in brain function and behaviour (May-Benson, Barraza, & Flanagan, 2013). For instance, children with ASD often enjoy a sense of firm overall pressure, which can be given by wrapping them up in blankets, being squashed by pillows and firm hugs along with playing and showing affection.

A review by Sinha, Silove, Wheeler, and Williams (2006) showed no significant improvements in core deficits of ASD following sensory integration therapy. However, a subsequent study found improvements in language and social skills and self-care following sensory integration therapy (Schaaf et al., 2013). Contradictory findings yield from the different techniques of sensory integration therapy used in studies. Within a study, it is also possible that therapists did not apply the techniques in the same way. In Schaaf's study, a fidelity measure was used to ensure that each therapist was delivering the

intervention in a manner faithful to its principles. Their finding that sensory integration therapy can improve some ASD symptoms may therefore be genuine.

Other sensory interventions include massages (Silva, Cignolini, Warren, Budden, & Skowron-Gooch, 2007) and music therapy (Kern, Wolery, & Aldridge, 2007; Boso, Emanuele, Minazzi, Abbamonte, & Politi, 2007). They were found to be efficient in improving certain behavioural symptoms (e.g., the ability to regulate behaviour and emotions in response to social cues). Rationales for using many sensory therapies, however, are questionable (Baranek, 2002). This motivates further research into establishing the role of atypical sensory processing in the development of ASD.

5. Does atypical sensory processing play a role in the development of ASD symptoms?

The following sections will examine the literature on the development of atypical symptoms in ASD individuals, paying particular attention to which symptoms are the first to emerge. If abnormalities in sensory behaviours appear first, prior to higher-level cognitive deficits (e.g., in joint attention), then this would favour Hypersystemization theory and argue against WCC and Intense world theories. Findings from behavioural retrospective and prospective studies, as well as imaging studies are presented.

5.1. Retrospective studies. Analyses of videos of first birthday parties of children with ASD revealed that atypical sensory behaviours (assumed to reflect atypical sensory processing) are early symptoms of ASD. Infants had unusual visual inspection of objects and excessive mouthing compared with

infants with DD and TD at 9-12 months old (Baranek, 1999; Osterling, Dawson, & Munson, 2002). However, studies have also shown the existence of other, non-sensory, ASD symptoms in the same age range. Infants were found to have diminished overall social responsiveness. For instance, they had limited eye contact, smiled less frequently and vocalized less compared to infants with TD (Maestro et al., 2002) and DD (Baranek, 1999). They also used joint attention gestures (e.g., showing and giving objects) less often than infants with DD and TD (Watson, Crais, Baranek, Dykstra, & Wilson, 2013) and used less varied social interaction gestures compared to infants with TD (Colgan et al., 2006). They also oriented to their name and looked at faces less (Osterling & Dawson, 1994; Werner, Dawson, Osterling, & Dinno, 2000) than in infants with DD and TD (Osterling et al., 2002), but it is unknown whether these characteristics reflect deficit in processing of sensory or social information. These studies therefore do not enable us to conclude which symptoms appear first and whether atypical sensory processing is likely to cause ASD symptoms. This might be because video analysis is not adapted to determine onset of symptoms. The length and the quality of the footage vary. Parents also often do not film their child when they are behaving in a way they do not want to see again. For instance, taping frequency drops dramatically when a child regresses when parents are likely to be too concerned to film (Palomo et al., 2008). Finally, these videos are not representative of all children with ASD as not all families film the early years of their children.

Parental reports have also been used to determine onset of symptoms. They did not show that infants have sensory symptoms in their first year. They

revealed instead that lack of typical social behaviour was noticed by 12 months old, such as lack of anticipatory postures (e.g., raising arms when adults pick them up), reaching for familiar persons, showing interest in others and engaging in simple social interaction games compared to children with TD (Klin, Volkmar, & Sparrow, 1992), and lack of joint attentional skills compared with children with DD (Wimpory, Hobson, Williams, & Nash, 2000). Whilst retrospective parental reports seem to suggest that sensory difficulties do not emerge first, caution is often recommended when using this method to collect data. Parents may have difficulty recalling specific behaviours and their exact timing (Palomo, Belinchón, & Ozonoff, 2006). They also have been found to report negative, rather than positive, symptoms more accurately (Stone, Hoffman, Lewis, & Ousley, 1994), biased by the knowledge of their child's eventual diagnosis. In addition, there might be cultural differences in the way parents assess typical development (Caron, Schaaf, Benevides, & Gal, 2012).

Studies combining both video analyses and parent reports showed that anomalies in gaze (e.g., abnormal intensity of eye contact, disproportionate fixation of non-social aspects, difficulty disengaging attention) and affect emerged as early as the first 6 months of life, generally becoming more severe just prior to the second birthday (Clifford & Dissanayake, 2008, 2009). Atypical sensory behaviours could therefore be among the first ASD symptoms to appear. Discrepancy with previous findings might result from the different methodologies used (e.g., different parental questionnaires, different ways of coding behaviours in videos) and the difficulty to determine onset of symptoms with retrospective studies. In addition, these studies have not looked at the relationship between early atypical sensory behaviours and

other ASD symptoms at a later age. Therefore, no conclusion can be drawn on the possible role of atypical sensory processing on ASD symptom development based on retrospective studies.

5.2. Prospective studies. Most prospective studies are conducted in baby siblings of children with ASD. Following up their development gives the possibility to investigate early markers of ASD as between 15% and 20% of siblings develop ASD (Rogers, 2009). Another 20% of siblings present with broader autism phenotype (BAP), and exhibit behavioural and brain features of ASD (Pickles et al., 2000). Siblings are more likely to show non-verbal and verbal communication impairments (Lindgren, Folstein, Tomblin, & Tager-Flusberg, 2009; Ruser et al., 2007), atypical theory of mind (Baron-Cohen & Hammer, 1997; Gliga, Senju, Pettinato, Charman, & Johnson, 2014) and atypical face processing (Dawson et al., 2005) compared to children without a sibling with ASD. They also display some patterns of brain structure and function involved in atypical social-communicative behaviours in ASD (e.g., Dawson et al., 2005; Lindgren et al., 2009). Siblings evidence impairments and/or delays by 12 to 18 months of age, including delays in cognitive development and language comprehension and production (Zwaigenbaum, 2010).

Findings on the onset of atypical sensory behaviours in babies at risk of ASD are conflicting. Some studies showed that most babies who were later diagnosed with ASD had atypical sensory behaviours by six and seven months old. A case study of the development of a child with ASD revealed that professionals observed that he exhibited unusual sensory responses

(e.g., he was hypersensitive to touch) during the first six months of his life (Geraldine Dawson, Osterling, Meltzoff, & Kuhl, 2000). However, as this study included one child only, it is not possible to generalize this finding to other infants with future diagnosis of ASD. Studies including groups of children have also been conducted. Parents described their seven month-old baby later diagnosed with ASD as being sensory sensitive (i.e., able to atypically detect slight, low-intensity stimulation from the external environment) (Hudry et al., 2013; Clifford et al., 2013). Zwaigenbaum et al. (2005) also observed that some six month-old infants later diagnosed with ASD did not orient to their name and had atypical sensory-oriented behaviours (e.g., rub their hands repeatedly over tables). These group studies did not make the distinction between atypical responses to social versus non-social sensory stimuli, which prevents from concluding whether one of the early signs of ASD is atypical social rather than sensory processing. Other studies involving non-social stimuli only revealed that sensory atypicalities develop later on. They showed that babies developed difficulty to disengage their attention from visual stimuli by 12-14 months old but not by 6-7 months old (Zwaigenbaum et al., 2005; Elsabbagh et al., 2013). Ozonoff and colleagues (2008) also found that infants later diagnosed with ASD were not different from TD infants in typical uses of objects, such as mouthing, by 6 months old, but by 12 months old, showed significantly more atypical uses, specifically rotating, spinning and unusual visual exploration (e.g., looking at objects from the corner of one's eyes) compared to TD and DD children. Discrepancies in the findings might result from the use of different methods (e.g., experimental tasks were conducted in studies using non-social stimuli only while other studies involved professional

observation and parental reports) and investigation of different social versus non-social behaviours. Whilst studies including non-social visual stimuli only suggested that sensory atypicalities emerge by 12 months old rather than 6 months old, other studies reported presence of atypical non-social sensory behaviours at 6-7 months old in other modalities (e.g., touch). These studies therefore do not enable us to conclude whether there is presence of atypical perception of non-social stimuli across modalities at an early age in children later diagnosed with ASD.

No limitations in social communication development were found in six and seven months old babies who were later diagnosed with ASD. Babies exhibited a clear orienting response to faces (Elsabbagh et al., 2013). They were interested in social interactions, responsive to others and demonstrated sustained eye contact and social smiles (Bryson et al., 2007). They also interacted typically with their mother (Yirmiya et al., 2006; Merin, Young, Ozonoff, & Rogers, 2007). At 12-14 months, however, ASD outcome was predicted by atypical attitude to parent and affect (Wan et al., 2013) and other social behaviours including initiation of joint attention and shared positive affect (Landa, Gross, Stuart, & Faherty, 2013). Difficulties in social communication thus seem to emerge by 12-14 months old. Most babies by then gazed at faces less often (Ozonoff et al., 2010), failed to respond to their name (Nadig et al., 2007; Presmanes, Walden, Stone, & Yoder, 2007), had decreased imitation, social smiling and social interest (Zwaigenbaum et al., 2005; Presmanes et al., 2007) and had reduced eye contact (Presmanes et al., 2007) compared to TD babies. They also showed decreased responding to bids for joint attention (Presmanes et al., 2007) and delayed and decreased

intentional communication using social gestures, such as pointing (Mitchell et al., 2006; Iverson & Wozniak, 2007). In addition, they had delays in the acquisition of babbling (Iverson & Wozniak, 2007), directed vocalizations (Ozonoff et al., 2010), receptive language (Zwaigenbaum et al., 2005; Mitchell et al., 2006; Ozonoff et al., 2010; Hudry et al., 2013) and expressive language (Zwaigenbaum et al., 2005; Iverson & Wozniak, 2007; Ozonoff et al., 2010). A prospective study by Veness and colleagues (2012) in babies from the general population who later received a diagnosis for ASD also showed that children with ASD differed from TD children on most social communicative measures by 12 months of age. They further showed that the only social communication characteristic which could differentiate the children with ASD from children with TD, DD and specific language impairment was severity of impairment in communicative gestures at 12 months old. Atypical social-communication skills seem to emerge by 12 months old. However, as most studies did not include data from an earlier age, it is not possible to exclude that these social difficulties emerged before appearance of sensory atypicalities. In addition, many of the social behaviours looked at in these studies have a strong sensory component (e.g., gazing to faces, responding to name). It is therefore not possible to exclude that these behaviours reflect impairment in sensory processing rather than social processing.

Atypical repetitive behaviours were also observed by 12-14 months old in infants later diagnosed with ASD. A study showed that they displayed more atypical arm waving movements than TD infants (Loh et al., 2007), while another study found that more repetitive arm movements were observed in TD infants (Iverson & Wozniak, 2007). Differences in findings might result

from the researchers coding repetitive behaviours in the laboratory for a set amount of time in the former study and used videos filmed by parents at home in the latter study. Loh et al. (2007), however, also reported that children with ASD and TD have similar repetitive behaviours. TD children might have repetitive behaviours because they contribute to motor development (Thelen, 1979). Fewer repetitive movements in babies at risk could thus explain why some children have delays in motor development at 12 months old (Landa & Garrett-Mayer, 2006) and most children by 14-18 months old (Landa, Holman, & Garrett-Mayer, 2007; Brian et al., 2008). The difficulty to distinguish atypical repetitive behaviours from normal baby movements necessary for their motor development makes it difficult to investigate whether sensory rather than ASD-like motor movements appear first.

Prospective behavioural studies do not enable us to conclude as to whether social communication difficulties and atypical repetitive behaviours or atypical sensory behaviours emerge first. Zwaigenbaum and colleagues (2005) showed that babies later diagnosed with ASD exhibit at least seven atypical behaviours at 12 months old, including atypicalities in eye contact, visual tracking, disengagement of visual attention, orienting to name, imitation, social smiling, reactivity, social interest and affect and sensory-oriented behaviours. The current consensus is thus that atypical sensory behaviours, when accompanied by other atypical social, attentional and motor behaviours at 12 months old are predictive of a diagnosis of ASD at a later age.

5.3. Imaging studies. Any plausible hypothesis about processes underlying the phenotypic expressions of ASD needs to consider a developmental perspective (Bailey, Phillips, & Rutter, 1996). Impairments in one developing system may have secondary consequences for later developing systems. As stated by Frith (2003), “autism affects development, and in turn development affects autism” (p.2). Some social communication and repetitive behaviours displayed at 12 months old may thus be compensatory for early atypical sensory processing. In one study, all the infants displaying early atypical sensory behaviours went on to develop more severe ASD symptoms (Bryson et al., 2007). Reciprocally, atypical processing of social information might lead a child to develop atypical sensory behaviours (e.g., engage in self-stimulation to avoid social interaction). As atypicality is more likely to be seen at a neural level before being expressed in behaviours, it is important to look at findings from imaging studies to understand what neural processes are affected first (Rogers, 2009).

One prospective study found that infants later diagnosed with ASD had atypical visual evoked potentials in response to viewing faces with different eye gaze direction at 6–10 months old (Elsabbagh et al., 2012). Visual evoked potentials are electrical potentials recorded from the nervous system using electroencephalography (EEG) following presentation of a visual stimulus. The authors found that the evoked potentials of infants later diagnosed with ASD did not differ according to whether people look at them or away from them, contrary to typically developing infants. This atypicality might reflect impairment in sensory perception. However, it is possible that rather than reflecting sensory (visual) processing, this measure instead reflects atypical

processing of social information because the authors used faces to stimulate the infants. It is therefore important that studies looking at the neural sensory processes involved in ASD use non-social stimuli.

No prospective imaging study using non-social stimuli was conducted to investigate whether children who develop ASD have atypical sensory processing at an early age. Evoked potential studies using non-social auditory stimuli were conducted in older children with ASD. Whilst they cannot show whether sensory neural atypicalities develop before cognitive ones, they allow us to look at whether older children with ASD have atypical sensory coding of environmental stimuli. One study found that sensory processing did not differ from TD controls in children with ASD (Ceponiene et al., 2003). Other studies showed atypical cognitive processing of auditory stimuli (e.g., Tecchio et al., 2003), including atypical attentional processing (e.g., Lincoln, Courchesne, Harms, & Allen, 1995; Ceponiene et al., 2003). These studies therefore suggested that children with ASD have difficulties to process non-social sounds at a cognitive level rather than at a sensory level. However, it is possible that children with ASD developed cognitive processes helping them to regulate sensory processing that were atypical when they were younger. A longitudinal study using imaging data and non-social stimuli would therefore be needed to look at whether infants later diagnosed with ASD have atypical sensory processing.

Few imaging studies have investigated the relationship between sensory processing of non-social sounds and ASD symptoms. Gomot et al. (2011) found that the brains of children with ASD who are less tolerant to everyday changes process changes in auditory stimuli more quickly than children with

ASD who are more tolerant to everyday changes. Orekhova et al., (2012) showed that young adults with ASD whose brains code sounds atypically (i.e., neural activity was more prominent in the left hemisphere while activity was predominantly in the right hemisphere in TD controls) were reported by their parents as having greater severity of sensory abnormalities (e.g., auditory hypersensitivity) during their first two years of life. A study recently conducted by Donkers et al. (2013) showed both atypical sensory and cognitive differences between children with ASD and TD. They found that the neural activity reflecting perception of and attention to non-social sounds was attenuated in children with ASD and associated with greater sensory seeking behaviours. This finding may confirm the hypothesis that sensory seeking is a compensatory strategy used by an individual with a high threshold for registering sensory stimuli (Kientz & Dunn, 1997). Imaging studies suggest that atypical sensory processing of non-social stimuli are associated with the presence and severity of ASD symptoms. These imaging studies being retrospective and cross-sectional, it is not possible to conclude however whether atypical perception plays a role in the generation of ASD symptoms.

5.4. Conclusion. Studies conducted so far do not enable a conclusion as to whether atypical sensory processing plays a role in the development of ASD. As illustrated by the theories of ASD, it is unclear whether atypical sensory processing leads to atypical development of cognitive processing (and thus ASD symptoms), whether atypical cognitive processing (e.g., cognitive bias towards local rather than global information) leads to atypical development of sensory processing, or whether ASD symptoms result from

general atypical processing. Clarifying this question would not only have theoretical implications but also practical applications in terms of identifying the need to address atypical sensory processing in intervention.

To answer this question, a protocol was designed that takes into account the problems that were highlighted in the studies described above. Thus, a longitudinal imaging study using non-social sensory stimuli in babies at risk of developing ASD was conducted to investigate whether atypical sensory processing at an early age is associated to the development of ASD characteristics at a later age when symptoms become apparent. The current study could not however investigate whether atypical early sensory processing was particular of toddlers with ASD because at the time when the analysis was carried out participants were still younger than 36 months old when symptoms stabilise and a diagnosis can be made (Jones et al., 2013).

The relationship between presence and severity of symptoms in both major categories of ASD symptoms as described in DSM-5 at 24 months old (i.e., impaired communication and presence of repetitive behaviours) and atypical sensory processing at 9 months old was investigated:

- It was expected that impairments in verbal and non-verbal communication would be associated with poor early processing of subtle (language relevant) changes in the acoustic environment. Toddlers and adults with ASD with poor verbal and non-verbal communication skills have high levels of sensory behaviours reflecting hyposensitivity (Liss et al., 2006; Watson et al., 2011). It is indeed necessary for a child to be able to discriminate rapidly changing auditory cues to develop language (Benasich & Tallal, 2002; Kuhl, 2004), and it is likely that children with poor language skills

will develop a ASD-like communication style relying more on gestures. It was therefore expected that toddlers at high risk of developing ASD with poor verbal or non-verbal communication skills compared to toddlers at low risk at 24 months old would have smaller neural responses to acoustic changes reflecting hyposensitivity at nine months old than babies at low and high risk with typical communication skills at a later age.

- It was also expected that presence of restricted and repetitive behaviour would be found in babies with hypo- and hypersensitive reaction to potentially disturbing sounds (noise). Early theoretical accounts considered the use of repetitive behaviours to be a coping mechanism for maintaining a homeostatic state of arousal, with these behaviours helping to increase sensory stimulation when an individual is under-aroused and reduce stimulation or soothe when over-aroused (Kinsbourne, 1980; Ornitz & Ritvo, 1968; Zentall & Zentall, 1983). It was therefore expected that 24 month-old toddlers at high risk of developing ASD with restricted and repetitive behaviours would have either smaller or larger neural responses to noise (respectively reflecting hypo- or hypersensitivity) at 9 months old than babies at low and high risk without restricted and repetitive behaviours at a later age.

The next chapter describes the methods used to test these hypotheses.

Chapter 2: Materials and methods

1. Design

The present study used a quantitative correlational and differential design. It followed up babies at high risk of developing ASD and their controls (i.e., babies at low risk of developing ASD) over time:

- When babies were nine months old, Auditory evoked response potentials (ERPs) were collected to assess auditory perception and the Communicative Development Inventory (CDI) was administered to look at possible early atypical development of language.
- When babies were 14 months old, the CDI was administered to follow up language development.
- When babies were 24 months old, the CDI and Autism Diagnostic Observation Schedule (ADOS) were administered to investigate development of language and ASD-like symptoms respectively.

The ERP and behavioural measures are described in the Method chapter below.

2. Setting

Data were collected and analysed at the Centre for Brain and Cognitive Development (CBCD), Birkbeck College, University of London. This study formed part of an on-going project conducted within the British Autism Study of Infant Siblings (BASIS; www.basisnetwork.org), a collaborative research network for the study of infants at-risk for ASD. This on-going project looks at various aspects of development that might be atypical in babies who will

receive a diagnosis of ASD, including the perception of emotions and faces, integration of audiovisual language information and interaction with parents. Participants attend research sessions at the CBCD at various ages (4, 9, 14, 24, 36 months old and beyond) and undergo a series of imaging recordings (e.g., functional Magnetic Resonance Imaging (fMRI) to see which parts of the brain are activated when they hear emotions in voices) and behavioural tests, including eye-tracking experiments (e.g., to look at whether they are interested in objects rather than people's faces) and clinical testing (e.g., to measure their mental age or assess whether they have ASD). Each test and the number of tests run in each session were adapted to the child's age. For instance, one imaging testing only is conducted per session: the fMRI part of the study is run when participants are 4 months old, and electroencephalographical parts of the study are run at 9 and 14 months old to prevent children from becoming restless. Parents also fill in a series of questionnaires at each session (e.g., to assess the adaptive skills of their child over time). Most participants were not old enough to be tested at their 36 months old session yet at the time when the data for the current study was analysed. The data used for the current study were recorded during the 9, 14 and 24 months old sessions, among the data recorded for other parts of the on-going BASIS project.

3. Participants

We tested 49 infants at high risk of developing ASD from the BASIS, all of whom had an older full sibling with a community clinical diagnosis of ASD. This diagnosis was confirmed by a clinical psychologist based on information

using the Development and Wellbeing Assessment (DAWBA) (Goodman et al., 2000) and/or the Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003). Infants were recruited by advertising the study on the website of charities for children and adults with ASD (e.g., National Autistic Society), in NHS services and schools involved in the care of children with ASD (e.g., The little group nursery) and laboratories involved in ASD research (e.g., Cambridge Autism Research Centre). The poster used to advertise the study is shown in Appendix 1.

We also recruited 27 low-risk infants with no reported family history (first-degree relative) of ASD from a volunteer database at the Birkbeck Centre for Brain and Cognitive Development (CBCD). Parents often join the database because they hear about the CBCD by word of mouth. Studies are also advertised on the CBCD website. All low-risk infants had at least one older full sibling (none of their siblings had a diagnosis of ASD).

Inclusion criteria for both groups were that babies should not have epilepsy as brain measures could be altered by epilepsy related activity, and were born full-term and with a normal birth weight. Their family also needed to speak English at home as this study included language measures in English.

Power analysis based on the analyses central to the study were conducted using G*Power 3 software (Faul, Erdfelder, Lang, & Buchner, 2007) and data from a similar study conducted at the CBCD by Guiraud et al., (2011), which provided a large effect size. Statistical power was calculated with a α value of 0.05. Power analysis showed that the statistical power of 0.8 (as recommended by Cohen, 1988) would be reached with at least 27 participants in each group. Our initial sample size of 49 high risk babies and

27 low risk babies was therefore adequate to show differences between groups. However, full set of data could only be collected for 28 high risk babies and 15 low risk babies for reasons described in the Procedure section below. Whilst there was a risk that the current study would be underpowered, pilot studies conducted at the CBCD showed that group sample sizes of 15 infants were enough to show differences in electroencephalographic data and questionnaires across groups. In addition, analyses included data from babies who did not have full set of data. For instance, nine month-old sensory processing data and 24 month-old language skill data of a baby were used to look at the relationship between these two variables, even if the language skills data at 14 months old or the extent of repetitive behaviours at 24 months old in this child could not be assessed. Post-hoc power analysis showed that statistical power of at least 0.8 was achieved on the main analyses of the current study. Table 1 indicates number of participants from whom each measure could be obtained at each time point.

Characteristics of participants whose ERP data quality allowed them to be included in the study can be seen in Table 1. This table shows the average of the age of babies at both visits (around 9 and 24 months old), the number of females and males and the mean values for each measure conducted at each time point in babies at low and high risk of developing ASD. The data collected from low-risk infants were used to reflect typical development. The table also reports when data from high-risk children significantly differed from the ones of low-risk children. The statistical analyses used to look at differences between the groups are described in the Note below the Table.

Table 1. Characteristics of babies included in the current study

Variable	Babies at low risk (n = 19)		Babies at high risk (n = 34)	
	First visit	Second visit	First visit	Second visit
Age in months (Mean, SD, Range)	9.33, 0.77, 8.27-11.20	25.41, 0.98, 24.47-27.87	9.39, 0.90, 8.07-11.27	25.80, 1.54, 24.47-32.50
Gender: Female, Male	11, 8		11, 23	
Mean ERP amplitude (μV) in response to: -Tone deviants (SD) -Tone standards (SD) -Noise (SD)	 -0.20 (3.73) -0.77 (3.72) 0.22 (4.92)		 1.17 (3.64) -0.75 (3.52) 2.86 (4.51)	
CDI (N, Mean, SD, Range): -At 9 months old -At 14 months old -At 24 months old	 17, 1.12, 0.48, 0-2 17, 38, 49.59, 0-176 17, 388.47, 155.80, 162-656		 29, 0.66, 2.14, 0-11 28, 9.32*, 12.20, 0-50 30, 188.40*, 160.22, 2-555	
ADOS communication at 24 months old (N, Mean, SD, Range)	18,1, 1.08, 0-3		34, 2.23*, 1.83, 0-6	
ADOS stereotyped behaviours and restricted interests at 24 months old (N, Mean, SD, Range): -SBRI scale -Mannerisms subscale -Repetitive and stereotyped subscale	 18, 0.44, 0.78, 0-3 18, 1.17, 0.51, 0-2 18, 0.28, 0.46, 0-1		 34, 1.00*, 1.07, 0-4 34, 0.47, 0.66, 0-2 34, 0.41, 0.56, 0-2	

Note: * indicates when data in the high-risk group of babies significantly differed from data in the low-risk group. Mann-Whitney U-tests were used to compare data across the groups (normality was checked using a Shapiro-Wilk test).

4. Ethical Issues

The study was approved by London National Health Service Research Ethical Committee (reference number: 06/MRE02/73) and the ethics committee at Royal Holloway (University of London). Copies of the ethics approval letters can be found in Appendixes 2 and 3. The study was conducted in accordance with the Declaration of Helsinki (1964) (http://www.wma.net/en/30publications/10policies/b3/). For instance, informed consent was sought (see Procedure below).

Some parents may be worried that the younger sibling of their child with ASD might also develop ASD. They are often aware that their child participating in the current study is at high risk because it is standard practice in clinical settings to inform parents of the risk of ASD to the younger sibling, and because this information is readily available through public channels (e.g., the National Autistic Society). Parental concerns are best addressed by their health care providers, and no validated diagnostic instruments or interventions can currently be used prior to 36 months old in the research setting. Therefore, a letter was sent to the GP of worried parents and the clinician/specialist involved in the care of their older child diagnosed with ASD. This letter explains that the parents have expressed worry about their younger child during the study and gives details on the study (Appendix 4). If the parents did not feel that this was effective in addressing their concerns, they were referred to Dr. Gillian Baird (child psychiatrist at Guy's Hospital) who agreed to be consulted in these situations. Hence, in all cases, the research

team ensured that the parents' concerns were addressed by the appropriate services or individuals.

5. Procedure for the study

Parents interested in the study called the CBCD administrator as requested on the advertising poster. The administrator provided them with information on the purpose of the study and what it would involve. If the parents were still interested to participate and if their infant filled in the inclusion criteria, the administrator sent them an information sheet (Appendix 5) and a map to the CBCD and set an appointment for their first visit.

During their visit to the CBCD, parents and children were received in reception. The reception staff have extensive experience in dealing with both typically and atypically developing children. The decor is child friendly and toys for all age groups are available. At the beginning of the visit the parents were offered a cup of tea or coffee while the baby or child got used to the new environment. Staff then reminded parents of the details of the study and encouraged them to ask any questions they might have had. Once the parent was happy with the information provided he/she was asked to sign a consent form (Appendix 6). When parents felt ready and if the baby seemed happy and alert, we proceeded with the testing.

Parental questionnaires were sent to parents to fill in before the visit. The order of administration of the measures during the visit was adapted to infant needs. Certain tasks were omitted if the infant was fatigued or unhappy. Each part of the study was baby-friendly and usually babies liked to participate in it. Any task or experiment was stopped immediately if the parent wished to

discontinue or if the baby became restless or tired. During a piloting phase, parents could feedback on the pleasantness of the procedure, which was then amended based on their comments. Experimenters also changed the procedure based on babies' reaction during piloting so that they would remain happy and alert during data collection. For instance, imaging data were collected after behavioural data as it was noticed that babies were more restless during behavioural experiments when they followed a period of inactivity during the imaging experiments.

At first visit, ERP data could not be recorded in seven nine month-old babies (four at high risk, three at low risk) who became restless. Out of the 45 high-risk babies and 24 low-risk babies from whom EEG data could be recorded, data from 11 high-risk babies and five low-risk babies could not be used because they were too noisy (usually because the baby was moving too much). Seven CDI questionnaires could not been obtained from parents of the 34 babies at high risk and 19 babies at low risk whose ERP data could be used in the study (five high-risk babies, two low-risk babies). Eight CDI questionnaires were not sent back by parents of 14 months old babies with usable ERP data (six high-risk babies, two low-risk babies). During the 24 months old visit, six CDI questionnaires could not be collected from parents of babies with usable ERP data (four high-risk babies, two low-risk babies), while the ADOS could be conducted in all but one baby (at low risk). The reason why CDI data could not be collected from some parents is that they said they filled in the questionnaires at home, forgot to bring them to the visit and would send them by post. A phone call was given to them to remind them of sending

the questionnaires when they had not done so, but a few parents still forgot to send them.

The study was further discussed with the parents after testing, and any question raised by testing was answered. We also gave the family a certificate for the child's participation (Appendix 7). Before the parents left, we reimbursed their visit-related expenses and thanked them for their participation in the study.

6. Electrophysiological data

6.1. Brief introduction to electroencephalography.

Electroencephalography (EEG) offers a non-invasive way to study cortical activity that provides high temporal resolution (on the order of milliseconds). EEG signals are recorded on the scalp. They consist of synchronized activity in thousands of pyramidal apical dendrites aligned perpendicular to the cortical surface (for a review, see Hansen et al., 2010). EEG is sensitive to both radial and tangential sources (Figure 2), which lie in cortical gyri and sulci, respectively. They therefore reflect activity over large-scale brain areas. A drawback of this technique is that EEG signals are distorted by the skull and scalp, which results in them often providing ambiguous information on the location of their underlying brain sources.

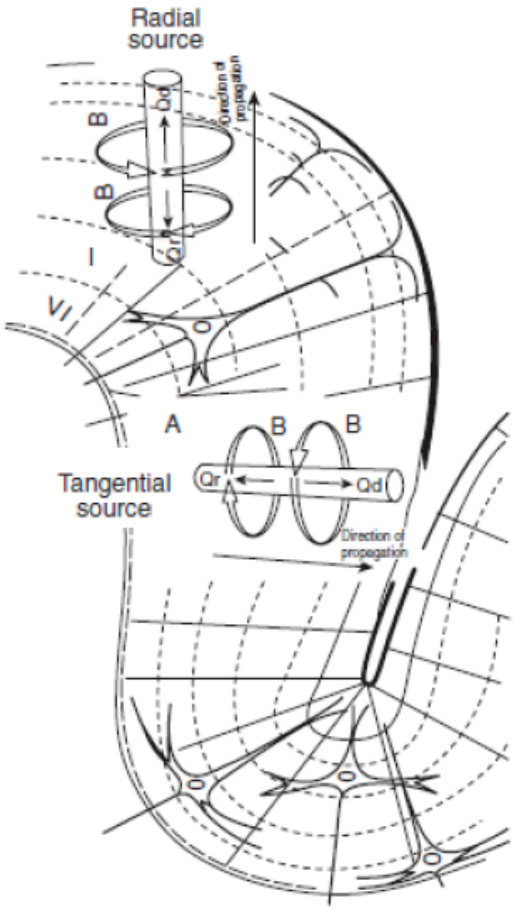

Figure 2. Illustration of radial and tangential sources in the cortex. EEG is sensitive to both radial and tangential sources. Black arrows represent direction of current in each source. Taken from Hansen, Kringelbach, & Salmelin (2010).

The most common way to conduct EEG analysis is to analyse the data across time. Evoked responses are typically obtained that reflect only neural activity strictly phase-locked to stimulus onset (Herrmann, Grigutsch, & Busch, 2005). The ERP curve is composed of peaks and troughs labelled according to their polarity and latency. The main positive peaks in response to auditory stimuli on the anterior part of the skull of babies peak at about 150

and 350 ms after presentation of the sounds (Figure 3). They are called P150 and P350 (P stands for Positive). They offer a unique opportunity to evaluate cortical auditory processes. P150 is often thought to be the precursor for P1 found in adults (Kushnerenko, 2003) and known to reflect activity in the Heschl's gyrus in the auditory cortex (Liégeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994). It is assumed to reflect acoustic processing (Rivera-Gaxiola et al., 2007). P350 is believed to evolve into P2 in adults (Kushnerenko, 2003), which is known to reflect activity in the superior temporal gyri in the auditory cortex (Hari et al., 1987). It is assumed to play a role in sound representation, which occurs after sensory encoding largely independently of conscious perception (attention and cognition) (Kraus & Cheour, 2000) and is a critical process for successful perception (Tremblay, Ross, Inoue, McClannahan, & Collet, 2014). Both P150 and P350 are therefore believed to reflect sensory processing and auditory perception. Figure 4 illustrates the anatomy of the auditory cortex.

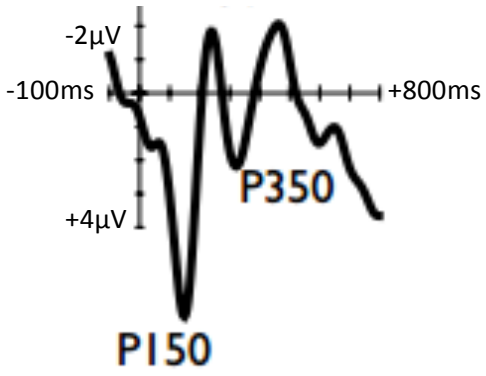

Figure 3. ERPs obtained in response to tones in 9 month-old babies. Taken from Kushnerenko, Ceponiene, Balan, Fellman, & Näätänen (2002).

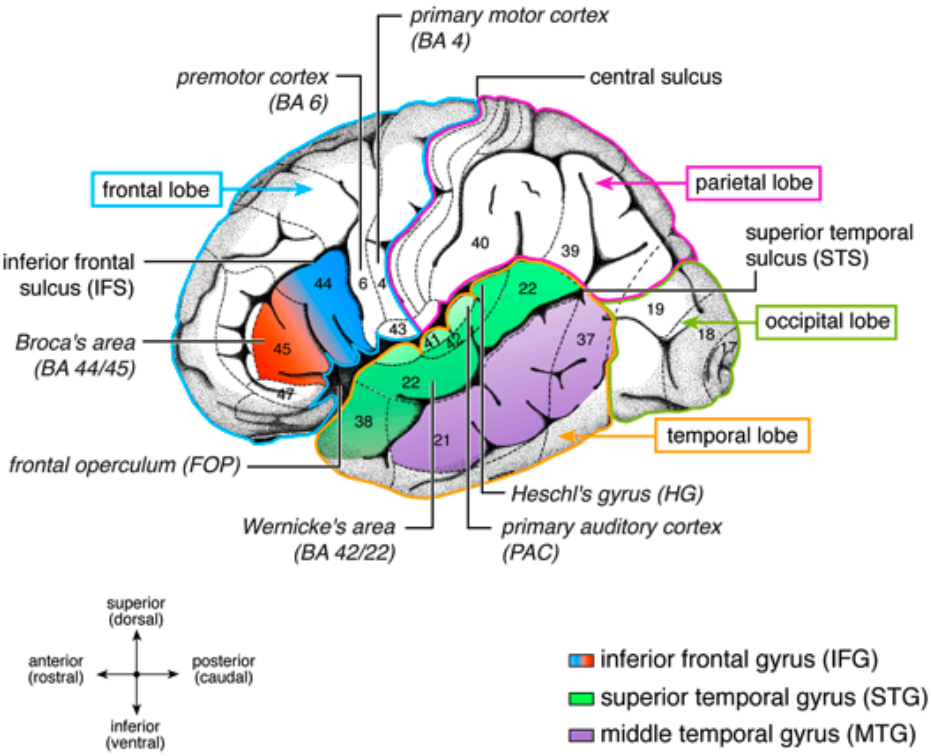

Figure 4. Anatomical details of the left hemisphere illustrating the location of the neural sources assumed to generate P150 (Heschl's gyrus) and P350 (superior temporal gyri) in the auditory cortex. Taken from Friederici (2011).

6.2. Procedure to record ERPs. Infants were seated on their parent's lap within a sound attenuated room. Sounds were presented through two speakers, 1m apart and located 1m in front of the infant. To enable passive processing of sounds, the attention of the infant was directed away from the sounds by a researcher blowing bubbles in front of the infant during the presentation of the sounds (Webb et al., 2010).

Auditory ERPs were recorded after the babies had had time to get used to the testing room and the experimenters. First, the infant's head was measured so that an appropriately sized sensor-net could be selected. The net consists

of 128 electrodes, each imbedded in a soft sponge and sewn together with elastic threads (Photo 1). The ERP net was soaked in warm water that had a small amount of potassium chloride to enable electrical conduction and reduce infection risk, blotted to remove excessive water, and placed on the baby's head. A small chin-strap was secured to keep the nets in place. These types of nets are known to be particularly good to use with young infants because they are comfortable and very quick to put in place.

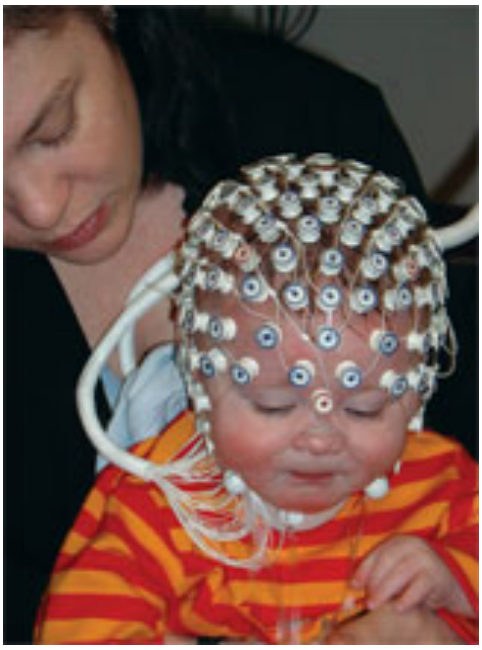

Photo 1. An infant wearing the EEG net (from EGI website: http://www.egi.com/research-division-geodesic-system-components/geodesic-sensor-nets)

6.3. ERP data acquisition.

6.3.1. Acquisition parameters. Brain electrical activity was measured using an EGI 128-electrode Hydrocel Sensor Net. The reference electrode at recording was the vertex (top of the head).

6.3.2. Stimuli. Two types of sensory processing were investigated in this study: 1. the ability to discriminate subtle changes in the acoustic environment, as illustrated by differences in amplitude of potentials evoked by tones of different pitch, and 2. the sensitivity to spectrally rich and thus potentially disturbing sounds (e.g., similarly to a vacuum cleaner sound), as illustrated by the amplitude of potentials evoked by white noise. Sounds were presented in an oddball paradigm adapted from Kushnerenko et al. (2007): two different types of infrequent sounds (deviants) occurred with an 11.5% probability each, at random positions within a sequence of 500-Hz pure tones (standards), with the restriction that these sounds were always followed by at least two standards. One infrequent sound was a pure tone of 650 Hz used to look at whether babies could perceive subtle changes in their auditory environment. Speech perception involves rapid discrimination of tones in on-going speech (Bailey & Snowling, 2002). The ability to process and classify rapidly changing auditory signals presented within a brief time frame is crucial to language development (Benasich & Tallal, 2002). The spectral cues (e.g., tone pitch) are important for discriminating the sounds of a language, and in order for language to develop, a child must be able to discriminate and categorize the sounds of their language (Kuhl, 2004). Thus, ERPs in response to tone deviants were used to look at influence of discrimination of subtle

language relevant changes from tone standards in the auditory environment on the development of language and communication. Amplitude of responses to standards is expected to be smaller than amplitude of responses to deviants as neural responses decrease over time during repeated stimulation with identical stimuli through neural habituation (Thompson & Spencer, 1966). A larger response to tone deviants compared to tone standards was therefore assumed to reflect perception of a difference between the two types of tones.

The other infrequent sound was white noise. White noise is a spectrally rich stimulus. Kushnerenko et al. (2007) showed that this deviant generates a reliable and invariant response in infants. It was used to look at the development of ASD-like repetitive behaviours in babies with atypical (hypo- or hypersensitive) processing of rich and potentially disturbing sounds.

The duration of the sounds was 100 ms, including 5-ms rise and 5-ms fall times. The interval between the sounds was of 700 ms. The intensity of the sounds was 70 dB SPL. We presented the stimuli until the infants became restless, resulting in about 320 events being presented to each baby.

6.4. ERP data processing. Several processing steps were conducted. The signal was digitized at 500-Hz sampling rate and filtered with 0.1–200-Hz bandpass to remove the low and high EEG frequency components outside of the range reflecting auditory activity. Epochs of 800-ms duration, including 100-ms prestimulus interval, were extracted for each stimulus. The baseline (or prestimulus interval) reflects neural activity before stimuli are presented and therefore when auditory neurons are at rest. A duration of 700-ms after stimulation was equivalent to the inter-stimuli interval. This time window was

therefore big enough to enable visualization of ERPs following auditory stimulation.

Epochs were separately averaged for the different conditions of auditory stimulation (standards, tone deviants and noise). ERPs are 'hidden' within continuous EEG stream. Averaging consists of calculating the mean value for each time-point across all epochs. It enabled a cancelling out of the noise that is not phase-locked to stimuli presentation (e.g., due to baby movements) so that the ERPs (which are phase-locked) can become apparent. Figure 5 illustrates the process of epoching and averaging EEG data. ERPs were filtered with a 15-Hz low-pass filter to further smooth the signals by removing the DC components (due to contamination by surrounding electrical devices) of the signals.

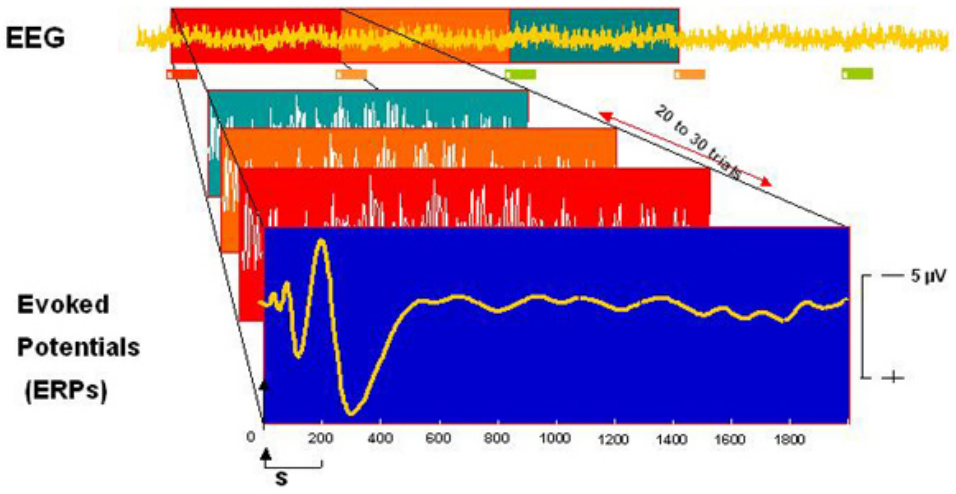

Figure 5. Epoching and averaging method used to extract the ERP from the background EEG. Taken from Magne et al. (2005).

The first three epochs were excluded from averaging as neural responses might be influenced by orientation to new stimuli. Epochs exceeding 150 μV at any electrode were also automatically excluded from averaging as they might reflect artefacts (e.g., blinks and eye movements). Figure 6 illustrates examples of artefact in the EEG signal. The EEG trace was also manually cleaned to eliminate any noise of less than 150 μV. The average amount of trials for each condition after cleaning of the data was 49 events (±12) in the 19 low-risk infants and 37 events (±7) in the 34 high-risk infants with quality of EEG data good enough to be used in the current study.

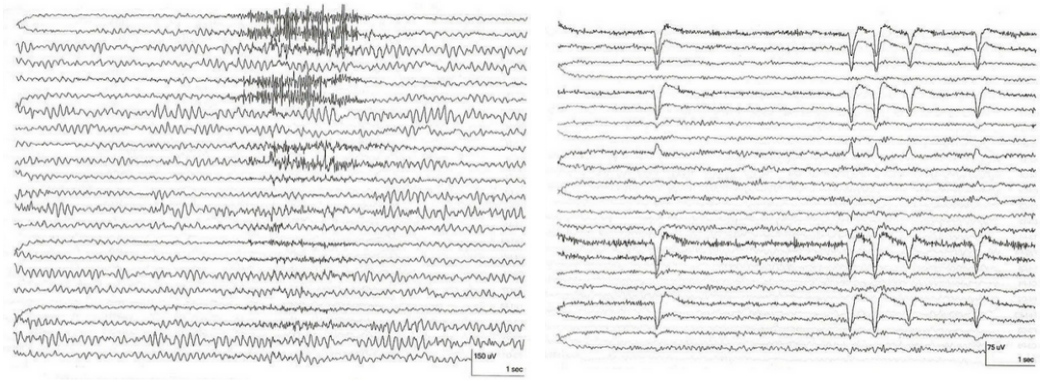

Figure 6. Examples of artefact in the EEG signal on several electrodes: muscle activity (left) and blinks (right).

The data were rereferenced to the average of all data over all the electrodes to estimate a true, non-arbitrary zero value to which to reference the voltage measurements. Finally, the data were baseline corrected using the 100-ms long prestimulus baseline to ensure that the trace was close to zero volt (i.e., close to the average of the neural activity at rest) at the time when stimuli were presented.

6.5. ERP data analysis. During the first year of life, the most salient component in the auditory ERP waveform is P350 (Kushnerenko et al., 2002; Ponton, Eggermont, Kwong, & Don, 2000). P350 was therefore used in this study to reflect sensory processing. P350 in response to tone deviants and standards was used to look at the association between discrimination of subtle (language relevant) changes in the environment and development language and communication skills. However, P350 could not be distinguished from P150 in response to noise (Figure 8), possibly because more neurons are activated in response to more spectrally rich sounds generating more spread activity (Herrmann, Henry, & Obleser, 2013). Amplitude for the P150-P350 complex was therefore used to look at the association between sensory processing of possibly disturbing sounds and development of soothing strategies, like repetitive behaviours. Amplitude of P350 in response to tones and P150-P350 complex in response to noise was calculated as the mean voltage within a latency window of 320-400 ms and 100-450 ms respectively (i.e., from beginning to end of P350 or P150-P350 complex obtained from averaging data across electrodes used in the current study and babies).

Figures 7 and 8 respectively show the responses to tone deviants and standards and noise in babies at low and high risk of developing ASD over all the electrodes. They show that the P150-P350 complex could be seen on most electrodes with a positive polarity frontally and negative polarity in posterior positions reflecting activity in the auditory cortex (i.e., in the temporal lobe located between the frontal lobe and the back of the head). Electrodes in frontal positions were considered as they are typically used in the infant

auditory research literature (e.g., Kushnerenko et al., 2007). Responses recorded over frontal areas are the most likely to represent sound perception. They are believed to reflect activity in the primary auditory cortex where P150 and P350 are generated (Kushnerenko, 2003), whereas responses over lateral areas are likely to be generated in the secondary auditory cortex, which is involved in more cognitive processes (Kurtzberg et al., 1984). The electrodes used for extraction of ERP amplitude are electrodes 10, 11, 15, 16 and 18 in Figures 7 and 8. Table 1 shows the mean amplitude of P350 in response to tone deviants and standards and P150-P350 complex in response to noise over the frontal areas in both baby groups.

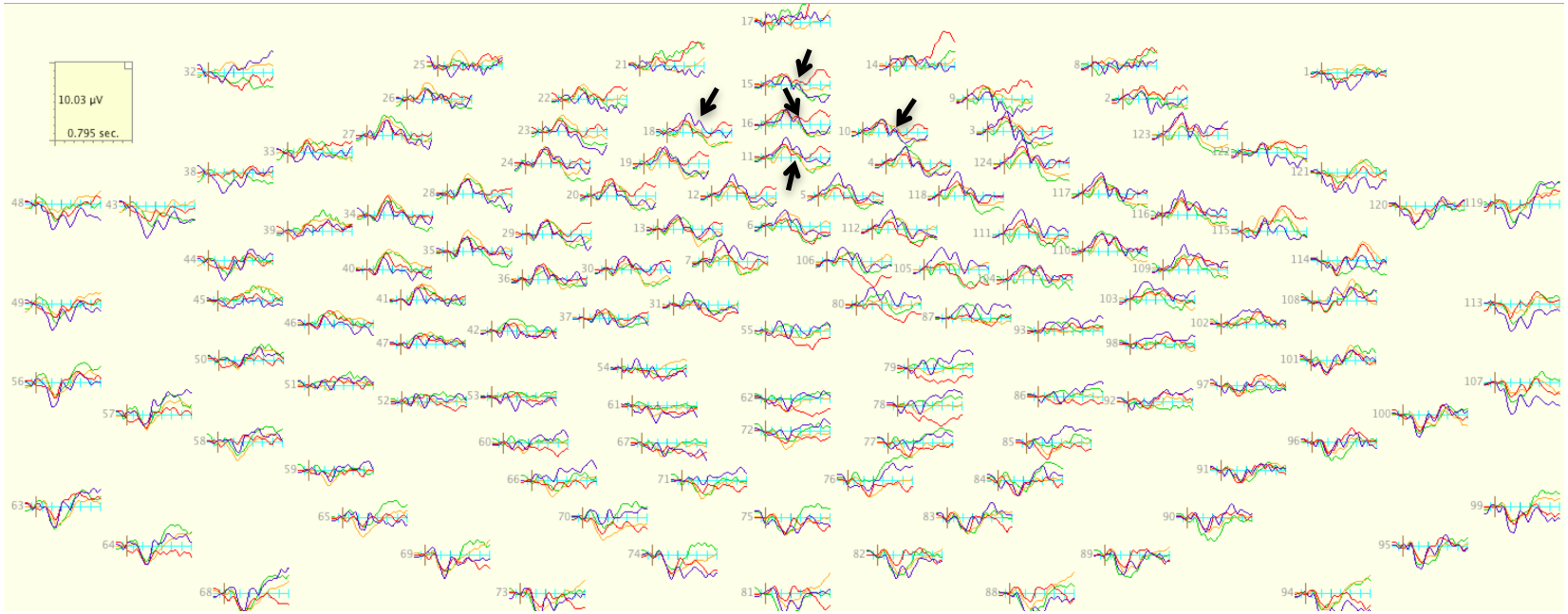

Figure 7. Neural responses to tone deviants and standards on all electrodes in babies at low risk of developing ASD (deviants: blue; standards: green) and babies at high risk of developing ASD (deviants: red; standards: orange). P350 looks larger in response to tone deviants than standards in babies at low risk on some frontal electrodes, possibly reflecting discrimination of subtle changes in the auditory environment. The difference in amplitude across condition was not significant in either group of babies (Repeated ANOVA with baby groups as between subject factor: $F(1,51) = 1.12$, $p = 0.29$; Tone type X Group interaction: $F(1,51) = 0.06$, $p = 0.80$). Arrows indicate P350 chosen for analysis.

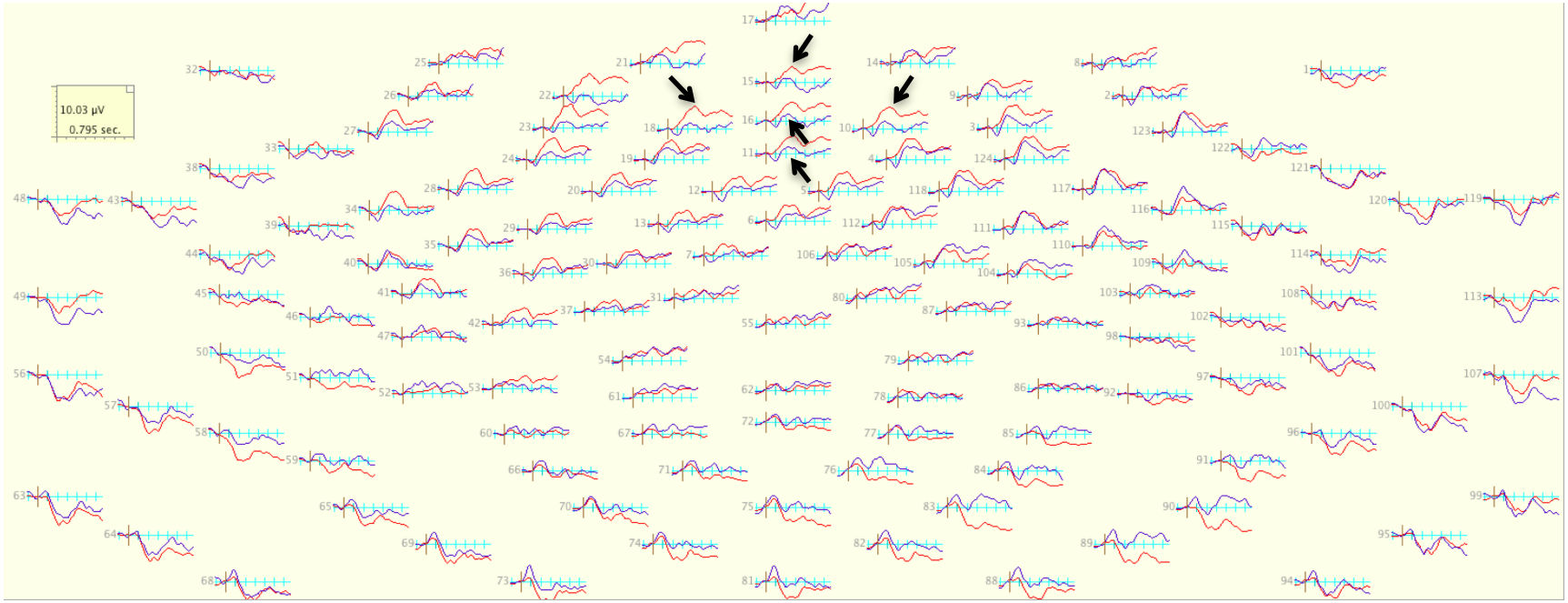

Figure 8. ERPs in response to noise in babies at low risk of developing ASD (blue) and high risk of developing ASD (red) over all the electrodes. P150-P350 complex looked larger in babies at high risk on frontal electrodes, possibly reflecting hypersensitivity to potentially disturbing sounds. Difference between the groups was only marginally significant (Mann-Whitney U test: U = 210, p = 0.065). Arrows indicate P150-P350 complex chosen for analysis.

7. Behavioural data

7.1. Language development at 9, 14 and 24 months old.

The Communicative Development Inventory (CDI; Dale, Bates, Reznick, & Morisset, 1989) was used to assess language development. It was posted to the parent before the visit and the parent was asked to complete it and bring/send it to the CBCD. The CDI (Appendix 8) is a set of inventories about the language and communication abilities of a child. The CDI–Words and Gestures (CDI–WG) is appropriate for children aged between 8 and 16 months. It assesses comprehension and production of vocabulary, communicative gestures, symbolic behaviour and nonverbal imitation. The CDI–Words and Sentences (CDI–WS) evaluates children aged between 16 and 30 months. It assesses productive vocabulary, knowledge of irregular word forms, overgeneralization of word endings to irregular nouns and verbs and syntactic complexity. The number of words understood and spoken at 9, 14 and 24 months old were used in the current study as this measure is likely to reflect best what language skills and vocabulary children have.

The CDI is often used in research to address theoretical issues, such as evaluating the link between early speech perception and later language development (Tsao, Liu, & Kuhl, 2004). The CDI has good reliability (Dale, Bates, Reznick, & Morisset, 1989) and fair to excellent concurrent and predictive validity (e.g., Feldman et al., 2006).

7.2. Development of ASD symptoms at 24 months old. Module 1 of the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1989) was administered at 24 months old to assess ASD-related social and communication behavioural characteristics. The ADOS (Appendix 9) is a semi-structured play assessment that involves social interaction between the examiner and the child. Research-determined cut-offs identify the potential diagnosis of ASD, allowing a standardized assessment of ASD symptoms. This measure has high reliability and validity (Lord et al., 2000). Module 1 is used with children who use little or no phrase speech. Some examples of Module 1 include response to name, social smile and free play. Specifically in the current study, ASD symptoms that could result from atypical perception were looked at, i.e. communication skills and repetitive behaviours. The communication scale, which includes measures of frequency of vocalization directed to others, stereotyped use of words or phrases (including echolalia and consistent intonation patterns), use of other's body to communicate, poor use of socially-directed pointing (e.g., a child with ASD traits would point only when close to or object without coordinated gaze or vocalization) and lack of or inappropriate use of communicative gestures (e.g., facial expression to communicate emotional feeling or hand movement to express desire to be given an object) was used to look at development of ASD-like communication style. Communication skills as assessed by the ADOS communication scale differ from the language skills assessed by the CDI (i.e., number of words produced by children) because the ADOS does not take into account the verbal abilities of the child, but rather assesses non-verbal ways of

communicating that are typical to ASD. The Stereotyped Behaviours and Restricted Interests (SBRI) scale was used to assess presence and severity of ASD-like repetitive behaviours. This scale includes three subscales, which assess unusual sensory interest, mannerisms and unusually repetitive interests or stereotyped behaviours. The mannerisms and unusually repetitive interests or stereotyped behaviours were also specifically looked at, as they were more likely to reflect use of a soothing strategy to cope with hypersensitivity than the SBRI scale (i.e., they assess presence of repetitive motor behaviours with less sensory components than the unusual sensory interest subscale). The ADOS was administered in a large testing room. The children usually enjoyed interacting with the parents and experimenter. The ADOS is of limited value for children with nonverbal mental ages below 16 months (Gotham, Risi, Pickles, & Lord, 2007). The ADOS was therefore not conducted in 9 and 14 months old testing sessions. No early measure of communication and repetitive behaviours could be obtained for the current study as no tools exist that assess these behaviours in young infants in a way similar to the ADOS.

8. Statistical analyses

The association between atypical sensory processing and development of ASD-like symptoms was investigated in two ways:

1. Presence of early atypical auditory processing in babies at high risk who developed ASD-like symptoms at 24 months old was looked at. Early sensory processing in babies at high risk of developing ASD with atypical

language/communication skills or ASD-like repetitive symptoms at 24 months old was deemed to be atypical when their ERP amplitudes at 9 months old differed from either babies at high risk with good language/communication skills or no ASD-like repetitive symptoms, or babies at low risk of developing ASD. Primacy of early atypical sensory processing over development of ASD-like symptoms was further investigated by looking at whether ASD-like symptoms were present at 9 and 14 months old when data was available (i.e., CDI data).

2. Correlation between early sensory processing and behavioural skills at various time points (when data was available and with sufficient variance) was investigated and compared between babies at low and high risk of developing ASD to look at the evolution of strength of the relationship over time, and differentiate typical from atypical relationship between the variables.

We tested the relationship between categories of babies (e.g., who developed language difficulties vs. communication difficulties at 24 months old) to ensure that we were looking at different groups of babies. Normality of the data within each group was assessed with a Shapiro-Wilk test. Parametric tests were used when the data were normally distributed in all groups (i.e., if $p > 0.05$). Otherwise, non-parametric tests were used. Statistical results were corrected accordingly depending on sphericity of the data.

8.1. Presence of atypical sensory processing in babies who developed language difficulties and ASD-like symptoms. A one-way ANOVA was used to look at whether ERP amplitudes of nine month-old babies at high risk who developed language or communication difficulties or repetitive

behaviours at 24 months old differed from the ones of babies at high risk who did not develop ASD-like symptoms and babies at low risk of developing ASD. Where significant differences were obtained, independent t-tests were used to look at which groups significantly differed in amplitude. Where non significant results were obtained, planned comparisons were used as they can be conducted to test specific hypotheses when F is not significant. One-tailed results were reported as specific hypotheses were tested: 1. P350 amplitude in response to tone deviants would be lower in babies at high risk who developed poor language or communication skills, showing that babies with poor language and communication skills at 24 months old had poorer ability to perceive different sounds at 9 months old, and 2. Amplitude of P150-P350 complex would be larger in babies at high risk who developed repetitive behaviours, showing that babies who developed repetitive soothing behaviours at 24 months old were hypersensitive to potentially disturbing sounds at 9 months old (given that visual analysis of ERP amplitude in Figure 8 suggests that babies at high risk are hypersensitive). To ensure that different perceptual mechanisms were investigated, a correlation analysis was conducted to look at relationship between hypersensitivity to subtle changes in the environment and hypersensitivity to disturbing sounds.

For most analyses on discrimination of subtle sounds, the amplitude of ERP in response to tone deviants was contrasted with the one in response of tone standards. Responses to deviants are believed to reflect perception as well as discrimination skills to different sounds, while responses to standards are

believed to reflect perception/habituation to repetitive sounds. The difference between the two response types is therefore more likely to reflect discrimination skills only. However, no difference between the two responses was found between babies at low and high risk of developing ASD. The amplitude of P350 in response to tone deviants was not significantly different to the one of P350 in response to tone standards in babies at low risk (paired t-test: $t(18) = 0.52$, $p = 0.606$). This is likely to reflect typical maturation of the auditory cortex rather than difficulty to discriminate sounds. Responses to tone deviants typically decrease during the second half of the first year of life (Morr et al., 2002), possibly reflecting the development of neural mechanisms inhibiting the processing of contextually less informative stimuli (for review, see: Kushnerenko et al., 2013). As a consequence, some authors have looked at responses to deviants only to reflect discrimination skills (Kushnerenko et al., 2002). In the present study, discrimination skills were compared across groups using the response to deviants only.

Groups of babies at high risk of developing ASD with atypical or typical language and communication skills at 24 months old were determined by splitting high-risk babies into two groups depending on whether their language and communication scores were below or above the median. Babies at high risk of developing ASD who could understand and speak more than 119 words (median value) at 24 months old were defined as having typical language skills. They had similar CDI scores as babies at low risk of developing ASD (Mann-Whitney U test: $U = 90.5$, $p = 0.165$), further suggesting that they had typical language skills.

As girls are known to develop language earlier than boys (e.g., Ramer, 1976), a Chi-square test was conducted to investigate gender differences between groups. It showed that the distribution of gender in the low CDI score group (12 males, 3 females) and high CDI score group (9 males, 6 females) did not differ ($\chi^2(1) = 1.43$, $p = 0.232$). It is therefore unlikely that gender distribution influences differences between the groups. Similarly, babies at high risk of developing ASD were defined as having good communication skills at 24 months old when their ADOS communication scores fell over the median. Their ADOS communication scores were not different to the ones of babies at low risk of developing ASD (Mann-Whitney U test: $U = 104$, $p = 0.274$), suggesting that their communication skills were typical. A Chi-square test showed that the distribution of gender in the low ADOS score group (13 males, 6 females) and high ADOS score group (10 males, 5 females) did not differ ($\chi^2(1) = 0.01$, $p = 0.914$).

As CDI data could be collected at 9 and 14 months old, primacy of early atypical sensory processing over early atypical language skills could be investigated. Timeline of appearance of differences in CDI scores (9 months old vs. 14 months old vs. 24 months old) between baby groups (low risk vs. high risk with good language skills at 24 months old vs. high risk with poor language skills at 24 months) was looked at using a mixed model ANOVA with CDI scores as the dependent variable. If significant interaction was found, post-hoc independent tests compared the CDI scores of babies at each age across groups.

Babies at high risk of developing ASD were also divided into groups based on the repetitive and stereotyped behaviours they developed at 24 months old.

Babies with a score of 0 on the SBRI scale, D2 subscale or D4 subscale had not developed repetitive behaviours, similarly to babies at low risk. Babies with scores above 0 on these scales were described as having developed stereotyped behaviours and restricted interests, mannerisms or unusually repetitive interests and stereotyped behaviours respectively. Roughly half of the babies in the group at high risk fell into one or the other category (i.e., had developed repetitive behaviours or not) on each scale. The gender distribution did not differ between these groups as shown by Chi-square tests ($p > 0.05$).

8.2. Relationship between early sensory processing and development of language difficulties and ASD-like symptoms.

Relationship between early sensory processing and development of language difficulties and ASD-like symptoms was investigated using standard regressions. Assumptions to analyse the data with regressions were checked (i.e., presence of linear relationship between the variables, absence of outliers, homoscedasticity of the data, normal distribution of residuals of the regression line), and corrections were made when needed. To look at whether discrimination of subtle changes in the auditory environment was related to language and communication skills, a standard multiple regression was performed with P350 amplitude in response to tone deviants and standards at 9 months old as the independent variables. Responses to standards were included in these analyses as they were conducted separately in babies at low and high risk, therefore allowing investigation of possibly different developmental mechanisms across groups. CDI scores were used as the dependent variable to look at relationship

between early sensory processing and language skills. Several analyses with CDI scores at 9, 14 and 24 months old were conducted to investigate whether relationship with early sensory processing existed at all age, and compared to see whether the strength of the relationship between early sensory processing and future language skills differ across ages by calculating the z-score of the difference between the correlations. ADOS communication scores at 24 months old were used as the dependent variable to look at relationship between early sensory processing and future communication skills. A Durbin-Watson test was conducted to ensure that the language and communication skill scores were independent and that separate regression analyses could be used to investigate the relationship between early sensory processing and language and communication skills. A simple regression was performed with ADOS SBRI scores at 24 months old in babies at high risk of developing ASD as the dependent variable and P150-P350 amplitude in response to noise at 9 months old as the independent variable to look at whether there was a relationship between development of repetitive behaviours and hypersensitivity. Analyses were conducted in babies at low risk and in babies at high risk. We also looked at whether the relationship between early discrimination of subtle acoustic changes and development of future language difficulties or ASD symptoms skills differed between babies at low and high risk of developing ASD by calculating z-score of the difference between these correlations and the corresponding p-value. These analyses allowed us to determine which relationship reflected typical development and which relationship reflected ASD-like development.

Chapter 3: Results

This study investigated the association between early atypical sensory processing and development of language and ASD-like symptoms in babies at high risk of developing ASD. First, primacy of early atypical ability to discriminate subtle (language relevant) changes in the acoustic environment over appearance of language difficulties was investigated, as well as the relationship between ability to discriminate sounds and severity of language difficulties at various ages. Second, presence of early atypical ability to discriminate subtle (language relevant) changes in the acoustic environment in babies who later developed communication difficulties and relationship between discrimination skills and severity of communication symptoms were investigated. Third, presence of early hypersensitivity to potentially disturbing sounds in babies who later developed repetitive behaviours and relationship between severity of hypersensitivity and repetitive symptoms were investigated. Specificity of these relationships to babies at high risk of developing ASD was also looked at.

A Shapiro-Wilk test (appropriate for small samples) was used to assess whether the data were normally distributed (i.e., when $p > 0.05$). Parametric tests were used where the data were normally distributed. Levene's tests were used to assess homogeneity of variance assumptions and separate variance estimates were used when appropriate.

1. Association between atypical early sensory processing and development of atypical language skills

Neural P350 responses to tone deviants and standards at 9 months old were used to look at the impact of early auditory processing of acoustic changes on the development of language skills. Difficulty in processing and discriminating subtle acoustic differences is likely to lead to the development of language difficulties. The number of words understood and spoken as measured by the Communicative Development Inventory (CDI) was used to assess language development at 9, 14 and 24 months old. First, we looked at whether appearance of atypical sensory processing occurred before emergence of atypical language skills. Second, we determined whether severity of atypical early auditory processing was associated with severity of language difficulties in babies at low and high risk of developing ASD.

1.1. Timeline of emergence of atypical development of auditory processing and language skills.

The amplitude of auditory ERPs in response to tone deviants at 9 months old was compared between babies at high risk of developing ASD with poor language skills at 24 months old (i.e., with CDI scores below the median in that group), babies at high risk with good language skills at 24 months old (i.e., with CDI scores above the median in that group) and babies at low risk of developing ASD whose CDI scores are likely to reflect typical variance in language development (Table 1). Figure 9 shows the ERPs in response to tone deviants over a frontal electrode in all three groups of babies.

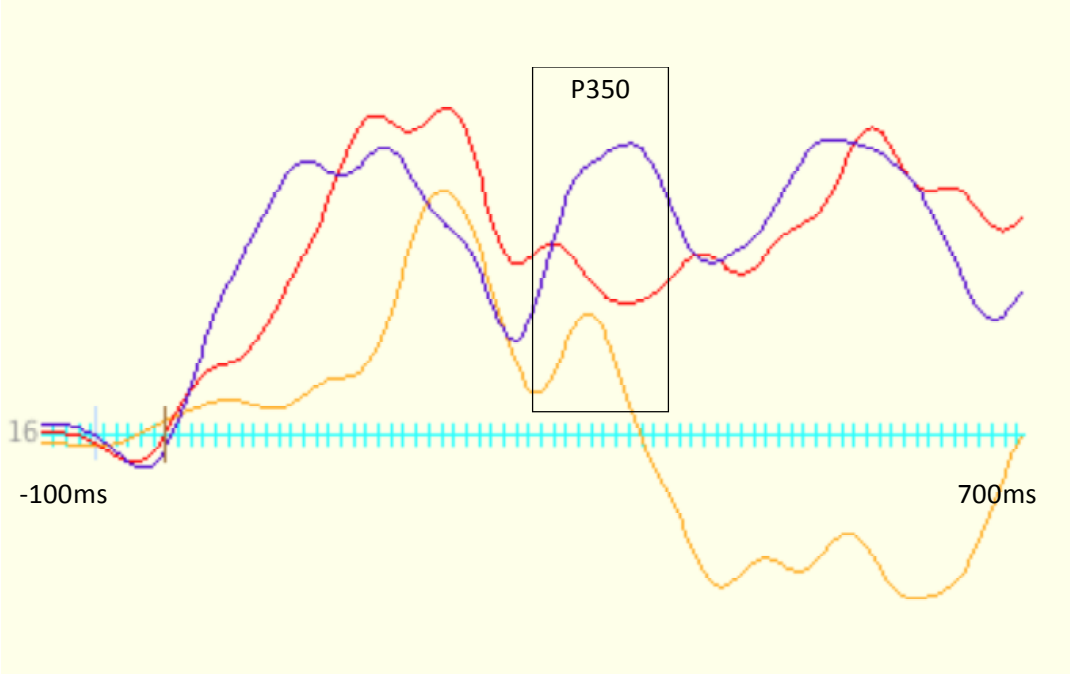

Figure 9. An example of P350 in response to tone deviants over a frontal electrode in 9-month-old babies at low risk of developing ASD (red), and babies at high risk of developing ASD with poor language skills (orange) and good language skills (blue/purple) at 24 months old.

A one-way independent ANOVA showed that P350 amplitude to tone deviants did not differ significantly across all three groups of babies ($F(2,46) = 2.02$, $p = 1.149$). A planned contrast was tested given that a specific hypothesis was defined a priori. As it was expected that P350 amplitude in the group at high risk of developing ASD with poor language skills would be lower than P350 amplitude in the other two groups, one-tailed result is reported. The trend analysis showed that the mean of P350 amplitude in babies at high risk with poor

language skills differed from the means of P350 amplitude in babies at high risk with good language skills and babies at low risk of developing ASD ($F(1,46) = 4.03$, $p = 0.025$). Results for specific one-tailed hypotheses showed that P350 amplitude was significantly reduced in babies at high risk of developing ASD with poor language skills compared to babies at high risk with good language skills ($t(46) = -1.73$, $p = 0.045$), but not compared to babies at low risk of developing ASD ($t(46) = -0.04$, $p = 0.484$). Babies at high risk with poor language skills thus could perceive different sounds less well than babies at high risk with typical language skills, but as well as babies at low risk of developing ASD. Babies at high risk with typical language skills seem therefore to be hypersensitive to subtle changes in the acoustic environment. Pooled variance estimates were used since homogeneity of variance assumptions were met ($p > 0.05$). Figure 10 shows the mean amplitude of P350 in response to tone deviants over 5 frontal electrodes in all three groups.

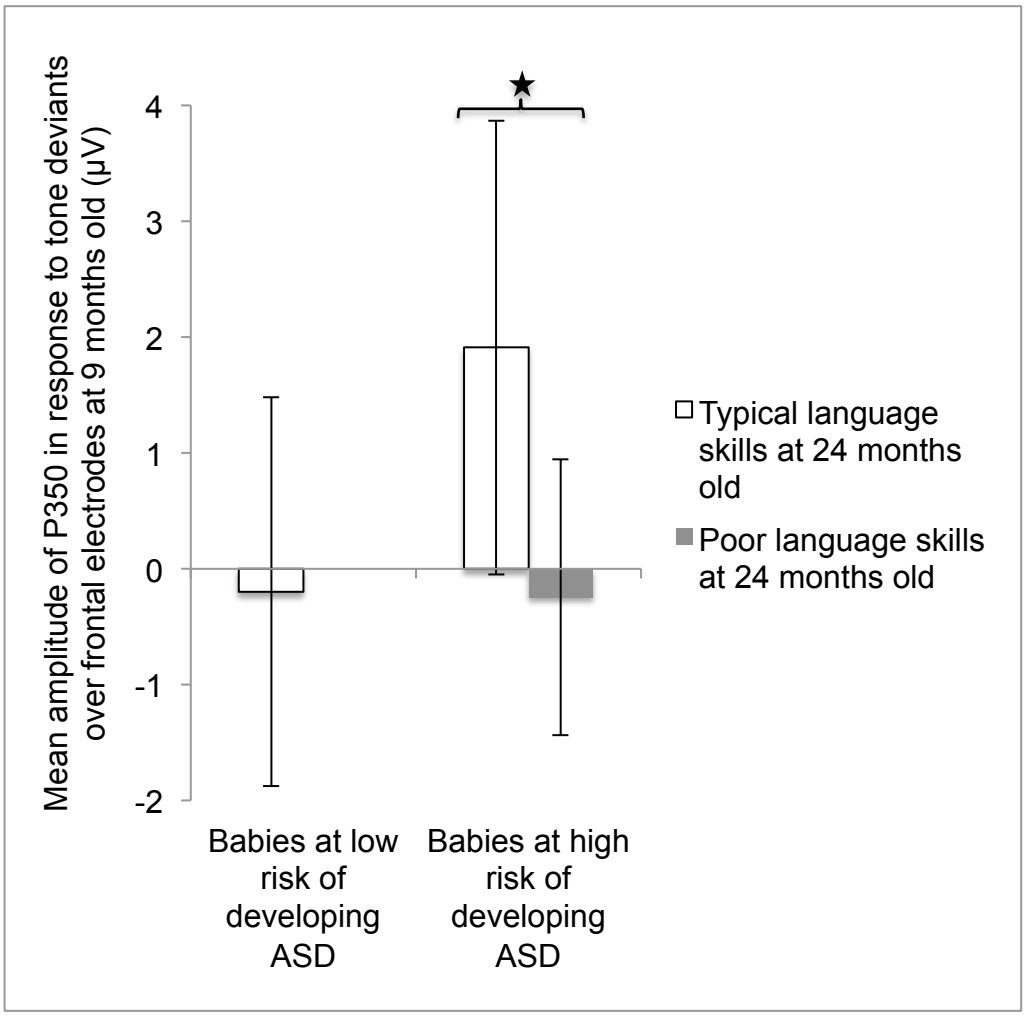

Figure 10. Mean amplitude of P350 in response to tone deviants over 5 frontal electrodes at 9 months old in babies at low risk of developing ASD, and babies at high risk of developing ASD with typical and atypical language skills at 24 months old. * indicates significant differences in amplitude across groups. Error bars show the 95% confidence interval.

We also investigated whether language difficulties in babies at high risk of developing ASD emerged after atypical sound processing was evidenced at 9

months old. An age of babies at testing (9 months old / 14 months old) x baby group (low risk vs. high risk with good language skills at 24 months old vs. high risk with poor language skills at 24 months) mixed model ANOVA with CDI scores as the dependent variable showed a significant interaction of age and baby group ($F(42,42) = 3.32$, $p = 0.046$). Huynh-Feldt correction was applied as Mauchly's test of sphericity showed departure from sphericity assumptions. This indicated that language skills at both ages differed between the groups of babies. Post-hoc Mann Whitney U-tests compared the CDI scores of babies at each age across groups. Babies at high risk with poor language skills at 24 months old had similar language skills as babies in other groups at 9 months old (compared with babies at high risk with good language skills at 24 months old: $U = 70$, $p = 0.134$; compared with babies at low risk: $U = 112$, $p = 0.799$). Very few babies (one baby at low risk and five babies at high risk) could speak at that age so lack of differences in language skills between the groups was not surprising. At 14 months old, babies at high risk of developing ASD with poor language skills at 24 months old had poorer language skills than babies at low risk ($U = 55.5$, $p = 0.010$) and babies at high risk with good language skills at 24 months old ($U = 63$, $p = 0.034$). At 24 months old, babies at high risk with poor language skills had poorer language skills than babies at low risk ($U < 0.001$, $p < 0.001$) and babies at high risk with good language skills at 24 months old ($U < 0.001$, $p < 0.001$). Development of language difficulties seem therefore to occur after nine months old, that is after development of atypical auditory processing. Most effects remained significant after Bonferroni correction for multiple comparisons

(corrected p value = 0.025), with differences in language skills at 14 months old within the group of babies at high risk possibly appearing later than differences between language skills of babies at high risk with poor language skills at 24 months old and babies at low risk. Figure 11 shows the CDI score mean for each baby group at each age.

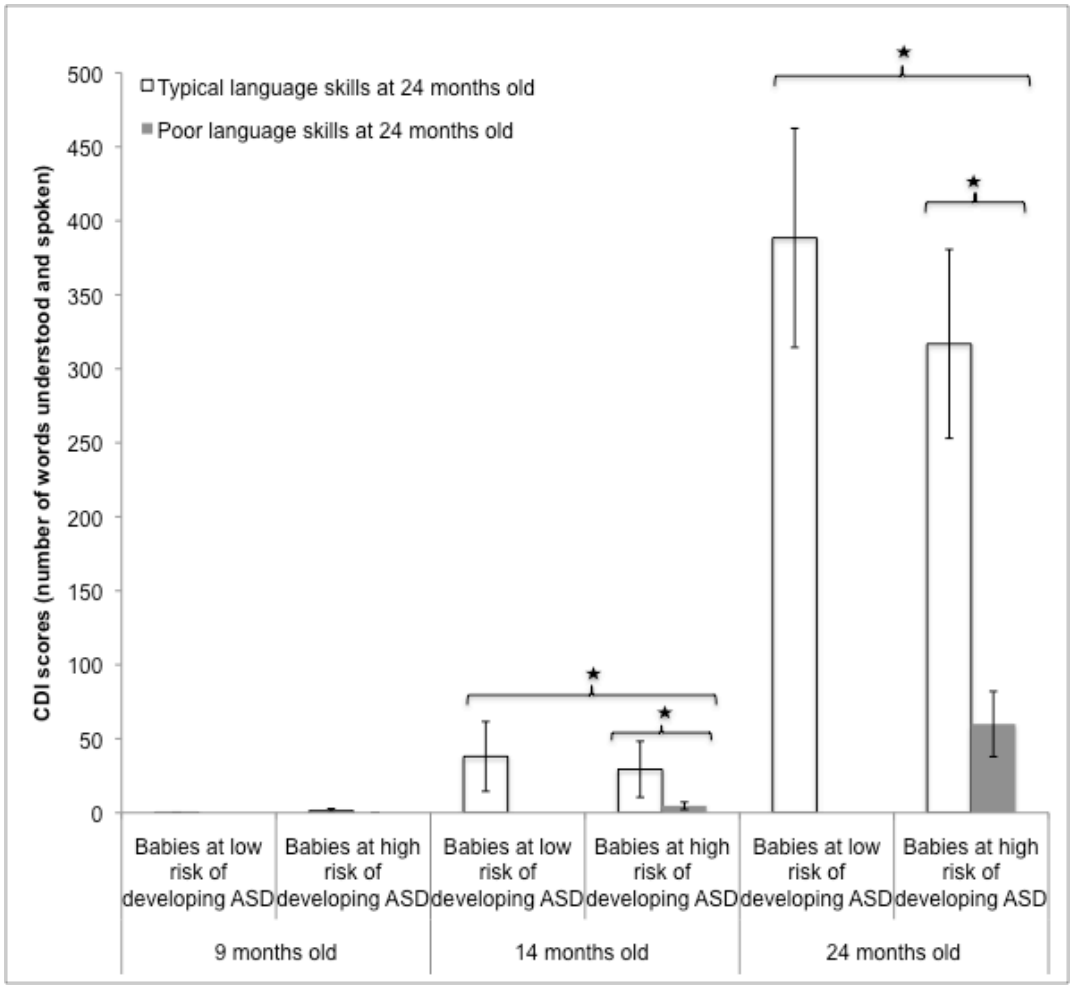

Figure 11. Mean CDI scores at 9, 14 and 24 months old of babies at low risk of developing ASD and babies at high risk of developing ASD with typical and poor language skills at 24 months old. * indicates when values are significantly different across groups. Error bars show the 95% confidence interval.

1.2. Relationship between early sensory discrimination skills and development of language skills. A standard multiple regression was performed with CDI scores in babies at high risk of developing ASD at 24 months old as the dependent variable and P350 amplitude in response to tone deviants and standards at 9 months old as the independent variables to look at whether there is a relationship between future language skills and early ability to discriminate acoustic changes. It showed that P350 amplitude in response to sounds did not account for a significant amount of variance in CDI scores ($F(2,27) = 2.02$, $p = 0.152$). However, the partial regression coefficients showed that amplitude of P350 in response to tone deviants had a marginally significant unique contribution to CDI scores ($B = 17.35$, ß = 0.36, $p = 0.053$). Thus, after controlling for encoding of sounds (i.e., response to standards), P350 amplitude in response to tone deviants (i.e., reflecting discrimination of acoustic changes only) at 9 months old tended to be larger in babies at high risk of developing ASD who went on to develop better language skills. Figure 12 shows the relationship between amplitude of P350 in response to tone deviants at 9 months old and CDI scores at 24 months old in babies at high risk of developing ASD. Amplitude of P350 in response to tone standards was not independently associated with CDI scores ($B = -2.01$, ß = -0.045, $p = 0.806$), further suggesting that ability to discriminate rather than perceive sounds is related to severity of language difficulties.

If the correlation between perception at 9 months old and language development at 24 months old cannot be found with language development at 14

months old, then a causal relationship between early perception and future language skills would be more likely. A standard multiple regression was therefore performed with CDI scores in babies at high risk of developing ASD at 14 months old as the dependent variable and P350 amplitude in response to tone deviants and standards at 9 months old as the independent variables to look at whether the relationship between auditory discrimination and language skills already existed at an earlier age. Two outliers were removed from this analysis as their CDI scores at 14 months old deviated more than three standard deviations from the CDI mean. The analysis showed that P350 amplitude in response to sounds did not account for a significant amount of variance in CDI scores at 14 months ($F(2,25) = 0.83$, $p = 0.447$). Partial regression coefficients further showed that amplitude of P350 in response to neither tone deviants nor tone standards had a unique contribution to CDI scores at 14 months old (tone deviants: B = -0.62, ß = -0.16, p = 0.410; tone standards: B = -0.79, ß = -0.22, p = 0.274). These results suggest that early ability to discriminate sounds tend to be related to language difficulties at 24 months old, but not at 14 months old. However, the relationship between perception of acoustic changes and future language skills at 14 and 24 months old did not significantly differ in babies at high risk of developing ASD. Pearson correlation coefficients reflecting the degree of relationship between the difference between amplitude of P350 in response to tone deviants and standards at 9 months old and the CDI scores were calculated at 14 and 24 months old ($r_{14monthsoldCDI} = 0.04$; $r_{24monthsoldCDI} = 0.29$) and converted to z_r (z_r (14 months old CDI) = 0.04, z_r (24 months old CDI)

= 0.30). A z-score of the difference between these correlations was calculated ($Z_{Difference}$ = -0.97), and the corresponding p-value showed that the relationship between early sensory processing and language skills at 14 months old did not differ from the one with language skills at 24 months old (p = 0.166). The relationship between P350 amplitude and CDI scores at 9 months old could not be investigated as only five babies could speak at this early age.

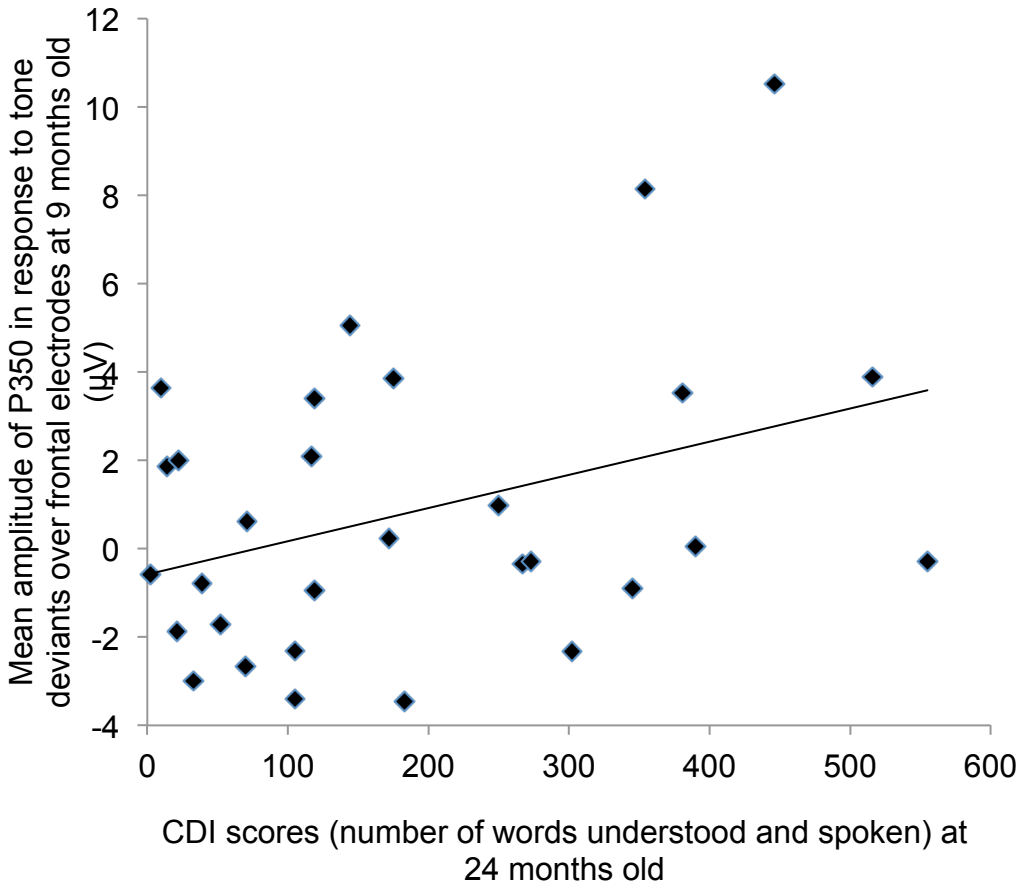

Figure 12. Relationship between amplitude of P350 in response to tone deviants over 5 frontal electrodes at 9 months old and CDI scores at 24 months old in babies at high risk of developing ASD.

We tested whether the trend towards a relationship between early discrimination of sounds and language skills at 24 months old was unique to babies at risk of developing ASD. A standard multiple regression was performed with CDI scores in babies at low risk of developing ASD at 24 months old as the dependent variable and P350 amplitude in response to tone deviants and standards at 9 months old as the independent variables to look at whether there was a relationship between future language skills and discrimination of acoustic changes and/or encoding of sounds in the control group. It showed that P350 amplitude in response to sounds did not account for a significant amount of variance in CDI scores at 24 months ($F(2,14) = 1.52$, $p = 0.252$). Partial regression coefficients further showed that amplitude of P350 in response to neither tone deviants nor tone standards had a unique contribution to CDI scores at 24 months old (tone deviants: B = -17.65, ß = -0.42, $p = 0.105$; tone standards: B = 0.67, ß = 0.01, $p = 0.954$). We also looked at whether the relationship between discrimination of subtle acoustic changes at 9 months old and language skills at 24 months old differed significantly between babies at low and high risk of developing ASD. Pearson correlation coefficients reflecting the degree of relationship between the difference between amplitude of P350 in response to tone deviants and standards at 9 months old and the CDI scores at 24 months old were calculated in each group ($r_{\text{low risk}} = -0.30$; $r_{\text{high risk}} = 0.29$) and converted to z_r (z_r (low risk) = -0.31, z_r (high risk) = 0.30). A z-score of the difference between these correlations and the corresponding one-tailed p-value were then calculated ($Z_{\text{Difference}} = 1.93$, $p = 0.027$). The relationship between perception of

acoustic changes and future language skills differed between babies at low and high risk of developing ASD. This suggests that different mechanisms are involved in language development in both groups, with early ability to discriminate sounds and future language skills tending to be positively related in babies at high risk whilst they tend to be negatively related in babies at low risk.

1.3. Summary. Neural responses to subtle (language-relevant) changes in the auditory environment was lower in babies at high risk of developing ASD who went on to develop poor language skills compared to babies at high risk with typical language skills at 24 months old. The difference in P350 amplitude seemed to emerge at an earlier age than differences in CDI scores. Atypical auditory processing may thus emerge before atypical language skills in babies at high risk of developing ASD. In addition, the amplitude of early auditory responses to tone deviants tended to predict the severity of language difficulties after controlling for responses to tone standards in babies at high risk of developing ASD at 24 months old. It is therefore possible that poor discrimination of auditory changes at 9 months old plays a role in the development of atypical language skills at 24 months old in babies at high risk of developing ASD. Interestingly, babies at high risk with poor language skills had similar amplitude of P350 in response to tone deviants as babies at low risk of developing ASD and no relationship was found between amplitude of P350 in response to tone deviants and CDI scores at 24 months old in babies at low risk of developing ASD. It is therefore possible that large P350 amplitude reflects a process that specifically enabled babies at high risk to develop good language skills.

2. Association between atypical early sensory processing and development of atypical communication skills

P350 in response to tone deviants and standards over frontal electrodes was used to look at the impact of auditory discrimination on development of communication skills. Difficulty in processing and discriminating subtle acoustic differences is likely to lead to the development of ASD-like communication traits (e.g., atypical intonation of speech, less spontaneous expressive language and vocalization) and compensatory strategies (e.g., use of hands) as assessed by the communication scale of the ADOS.

First, we looked at whether 24 month-old babies at high risk of developing ASD with poorer communication skills had atypical sensory processing at 9 months old. As the ADOS cannot be performed before the age of 24 months old, timeline of ASD-like communication symptoms in the babies at high risk could not be investigated. Second, we determined whether severity of atypical early auditory processing was associated with severity of communication difficulties in babies at low and high risk of developing ASD.

2.1. Difference in early auditory processing across groups of babies at low risk of developing ASD and at high risk of developing ASD with typical and atypical communication skills.

Amplitude of auditory ERPs in response to tone deviants at 9 months old was compared between babies at high risk of developing ASD with poor communication skills at 24 months old (i.e., with ADOS scores on the communication scale above the median in that group), babies at high risk with good communication skills at 24 months old (i.e., with

ADOS communication scores below the median) and babies at low risk of developing ASD whose ADOS communication scores are likely to reflect typical variance in communication development (Table 1).

A one-way independent ANOVA showed that P350 amplitude in response to tone deviants did not differ significantly across all three groups of babies ($F(2,50) = 1.423$, $p = 0.251$). Planned comparisons were used as they can be conducted to test specific hypotheses when F is not significant. Two planned comparisons were conducted to specifically look at the group differences of interest: one to test whether the amplitude of the babies at high risk of developing ASD with poor communication skills was reduced compared to the one of babies at high risk with good communication skills, and one to see whether the amplitude of the babies at high risk of developing ASD with poor communication skills was reduced compared to the one of babies at low risk. The trend analysis showed that the means of P350 amplitude did not differ across baby groups ($F(1,50) = 2.59$, $p = 0.114$). The ability to perceive different sounds was thus similar in babies at low risk and babies at high risk of developing ASD with poor and good communication skills at 24 months old. The mean amplitude for P350 was -0.20 μV (±3.73) in babies at low risk of developing ASD, and -0.91 μV (±3.1) and 1.13 μV (±3.90) in babies at high risk of developing ASD with poor and good communication skills respectively.

2.2. Relationship between atypical early sensory processing and development of atypical communication skills. To rule out that communication skills should be looked at in the same regression analysis as

language skills, a Durbin-Watson test was conducted to see whether CDI and ADOS communication scores were independent. The size of the test statistic was 2.40 for babies at high risk and 1.93 for babies at low risk, which is close enough to 2, meaning that the residuals are uncorrelated for the two variables in each group. Communication skills were therefore looked at in regression analyses separate to the ones for language skills.

A standard multiple regression was performed with ADOS communication scores at 24 months old in babies at high risk of developing ASD as the dependent variable and P350 amplitude in response to tone deviants and standards at 9 months old as the independent variables to look at whether there is a relationship between future communication skills and discrimination of acoustic changes. It showed that P350 amplitude in response to sounds accounted for a significant amount of variance in communication scores (R^2 = 1.18, adjusted R^2 = 1.12; F(2,31) = 3.36, p = 0.048). The partial regression coefficients showed that amplitude of P350 in response to tone deviants had a significant unique contribution to communication scores (B = -0.19, ß = -0.38, p = 0.027). Early ability to discriminate subtle changes in sounds therefore predicted future communication skills in babies at high risk. Amplitude of responses to tone standards was not independently associated with communication skills at 24 months old (B = 0.10, ß = 0.20, p = 0.233), further suggesting that future communication skills are related to early ability to discriminate rather than perceiving sounds. Figure 13 shows the relationship between amplitude of P350 in response to tone deviants at 9 months old and ADOS communication scores

at 24 months old in babies at high risk of developing ASD. P350 amplitude in response to tone deviants at 9 months old was smaller for babies at high risk of developing ASD who went on to have higher ADOS communication scores. Thus, the better the ability to discriminate changes in sounds at an early age, the better the communication skills at a later age.

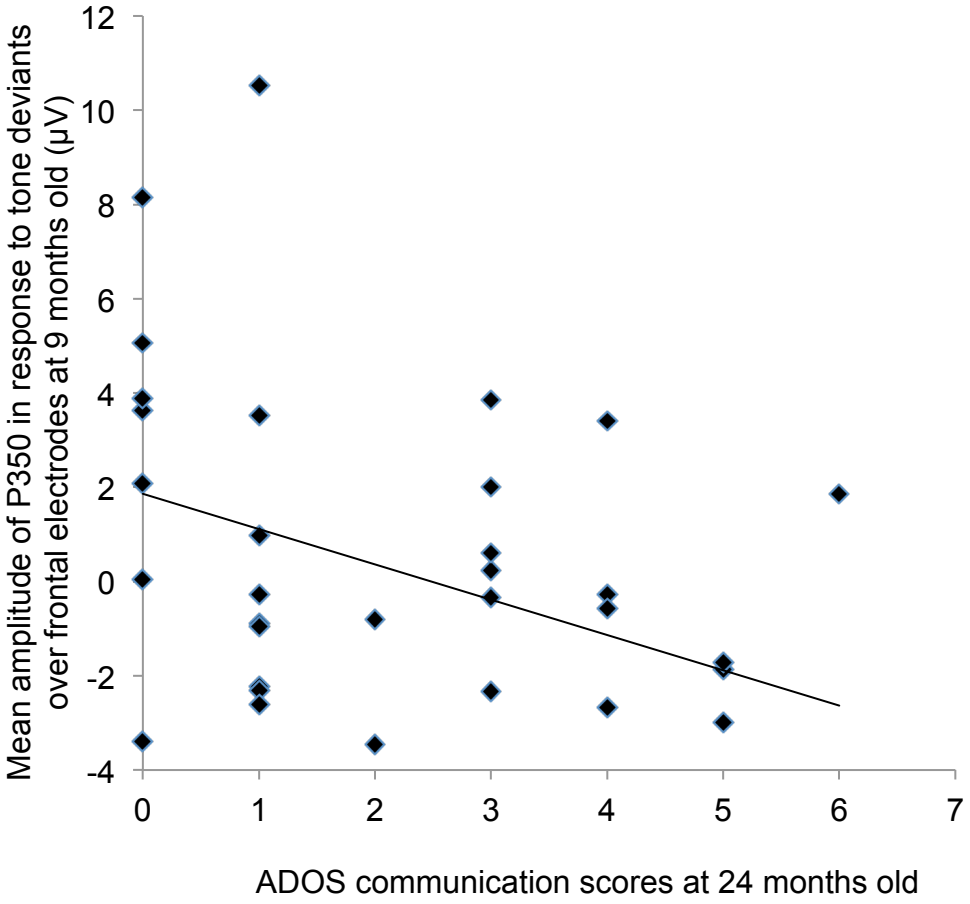

Figure 13. Relationship between P350 amplitude over 5 frontal electrodes at 9 months old and ADOS communication scores at 24 months old in babies at high risk of developing ASD.

We tested whether the relationship between discrimination of sounds and communication skills was unique to babies at risk of developing ASD. A standard multiple regression was performed with ADOS communication scores in babies at low risk of developing ASD at 24 months old as the dependent variable and P350 amplitude in response to tone deviants and standards at 9 months old as the independent variables to look at whether there is a relationship between future communication skills and discrimination of acoustic changes in babies at low risk. It showed that P350 amplitude in response to sounds only marginally accounted for a significant amount of variance in ADOS communication scores at 24 months (R^2 = 0.27, adjusted R^2 = 0.17; F(2,15) = 2.72, p = 0.098). Partial regression coefficients further showed that amplitude of P350 in response to tone deviants tended to have a unique contribution to communication scores at 24 months old (B = -0.12, ß = -0.40, p = 0.097). They showed that amplitude of P350 in response to tone standards did not have a unique contribution to communication scores at 24 months old (B = -0.07, ß = -0.26, p = 0.270). We also looked at whether the relationship between discrimination of subtle acoustic changes at 9 months old and language skills at 24 months old differed significantly between babies at low and high risk of developing ASD. Pearson correlation coefficients reflecting the degree of relationship between the difference between amplitude of P350 in response to tone deviants and standards at 9 months old and the CDI scores at 24 months old were calculated in each group ($r_{\text{low risk}}$ = -0.08; $r_{\text{high risk}}$ = -0.40) and converted to z_r (z_r (low risk) = -

0.08, z_r (high risk) = -0.41). A z-score of the difference between these correlations and the corresponding p-value were then calculated ($Z_{Difference}$ = 1.07, p = 0.142). The relationship between perception of acoustic changes and future communication skills therefore did not differ between babies at low and high risk of developing ASD. The relationship between early ability to discriminate sounds and development of good communication skills seems therefore not to be specific to babies at high risk of developing ASD.

2.3. Overlap between language and communication skills investigated in the current study.

It is likely that different language and communication processes are investigated in the current study. The CDI reports the number of words understood and spoken by participants, while the ADOS communication scale reports non-verbal abilities to communicate (e.g., use of gesture, vocalization directed at others, intonation, use of other's body to communicate). A Chi-square test showed that babies at high risk of developing ASD who developed poor communication skills as assessed by the ADOS communication scale were not likely to also have developed poor language skills as assessed by the CDI at 24 months old ($\chi^2(1) = 2.14$, p = 0.272). Table 2 shows the distribution of babies at high risk of developing ASD with or without language difficulties and/or communication difficulties. Whilst the majority of children with poor language skills also had poor communication skills and the majority of children with good language skills also had good communication skills, a significant proportion of children developed good language skills but an

ASD-like communication style or had poor language skills and good communication skills.

Table 2. Distribution of number of babies at high risk of developing ASD with or without language difficulties and/or communication difficulties at 24 months old.

	High ADOS communication scores	Low ADOS communication scores
Low CDI scores	9	6
High CDI scores	5	10

2.4. Summary. The amplitude of early neural auditory responses in response to acoustic changes predicted the severity of future communication difficulties in babies at high risk of developing ASD. Larger responses to tone deviants were associated with lower ADOS communication scores, after controlling for responses to tone standards. Babies at low risk of developing ASD also tended to show an association between early discrimination of acoustic changes and future communication skills. This relationship was not significantly different in low- and high-risk groups and no difference between neural responses to subtle (language-relevant) changes in the auditory environment at 9

months old were found across groups. It is therefore possible that better discrimination of subtle acoustic changes reflect a strategy enabling development of better communication skills that is not specific to babies at high risk of developing ASD. A significant proportion of babies had poor communication skills but good language skills and vice-versa suggesting that if a causal relationship existed between the variables, ways to use ability to discriminate sounds to develop non-verbal communication skills differed from the strategy used to help development of language skills.

3. Association between atypical early sensory processing and development of ASD-like repetitive symptoms

This study investigated the association between early hypersensitivity to potentially disturbing sounds and development of repetitive behaviours. Babies who are hypersensitive to sounds at 9 months old may develop soothing strategies, such as repeating movements (e.g., rock) and have unusually repetitive interests or stereotyped behaviours (e.g., lining up of toys). Sounds like white noise that are spectrally rich (e.g., sound of a vacuum cleaner) can be disturbing. Hypersensitive babies would have heightened neural responses to noise. A Pearson correlation test showed no significant correlation between amplitude of difference in P350 response to tone deviants and standards (reflecting discrimination) and P150-P350 complex in response to noise (reflecting hypersensitivity to disturbing sounds) in babies at high risk ($r(32) = 0.03$, $p = 0.855$). The type of hypersensitivity investigated in this part of the study

is therefore different to the one investigated in previous sections, which focused on the ability to discriminate subtle differences in sounds rather than encode disturbing sounds.

First, we looked at whether 24 month-old babies at high risk of developing ASD who developed repetitive behaviours were hypersensitive to potentially disturbing sounds at 9 months old. As the ADOS cannot be performed before the age of 24 months old, timeline of ASD-like repetitive symptoms in the babies at high risk could not be investigated. Second, we looked at whether severity of atypical early auditory processing was associated with severity of repetitive behaviours in babies at low and high risk of developing ASD at 24 months old. Analyses were performed using the ADOS SBRI scale. However, this scale includes assessment of sensory seeking behaviours, which a hypersensitive child trying to self soothe would not be likely to have. Therefore, subscales D2 and D4 were also used. D2 specifically looks at potentially soothing motor strategies (mannerisms), while D4 also includes stereotyped behaviours with a sensory component (e.g., ritualized ways of touching objects).

3.1. Association between amplitude of ERP in response to noise and ADOS SBRI scores. The amplitude of P150-P350 complex in response to noise at 9 months old was compared between babies at high risk of developing ASD with stereotyped behaviours and restricted interests at 24 months old (i.e., with ADOS SBRI scores above 0), babies at high risk without stereotyped behaviours and restricted interests at 24 months old (i.e., with ADOS SBRI scores of 0) and babies at low risk of developing ASD whose ADOS SBRI scores are likely to

reflect typical variance in development of stereotyped behaviours and restricted interests (Table 1). Figure 14 shows an example of the ERPs in response to noise over a frontal electrode in all three groups of babies.

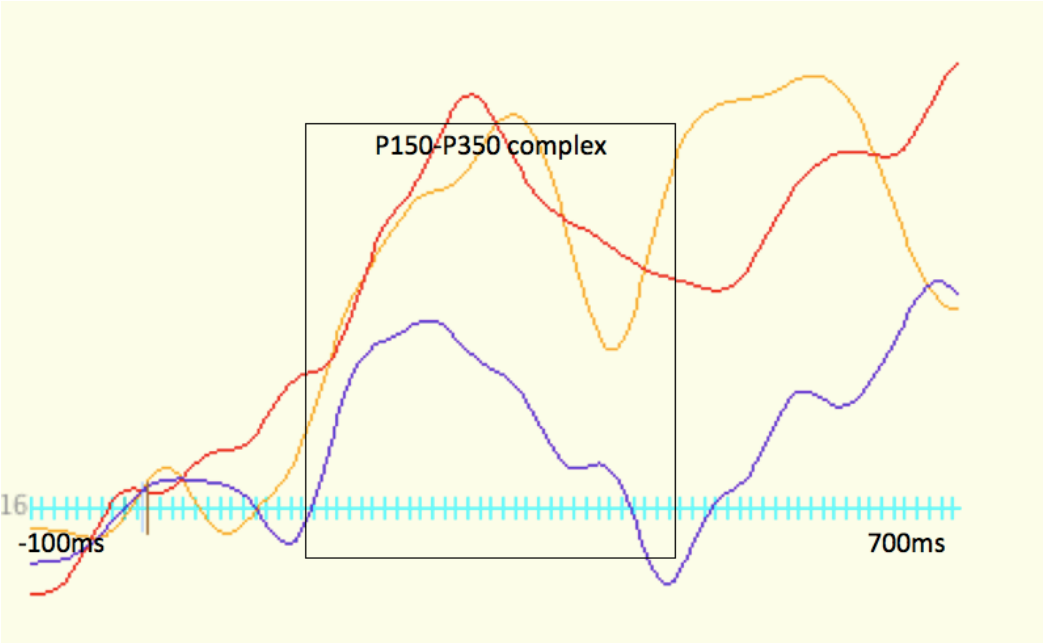

Figure 14. An example of a P150-P350 complex in response to noise over a frontal electrode in 9-month-old babies at low risk of developing ASD (blue/purple), and babies at high risk of developing ASD with stereotyped behaviours and restricted interests (red) and without stereotyped behaviours and restricted interests (orange) at 24 months old.

A one-way independent ANOVA showed that P150-P350 amplitude in response to noise did not differ significantly across babies at low risk of developing ASD and babies at high risk of developing ASD with and without stereotyped behaviours and restricted interests ($F(2,49) = 1.880$, $p = 1.163$). A planned contrast was tested given that a specific hypothesis was defined a priori.

As it was expected that amplitude in the group at high risk of developing ASD with stereotyped behaviours and restricted interests would be higher than amplitude in the other two groups, one-tailed result is reported. The trend analysis showed that the amplitude mean in babies at high risk with stereotyped behaviours and restricted interests did not differ from the amplitude means in babies at high risk without stereotyped behaviours and restricted interests and babies at low risk of developing ASD ($F(1,49) = 1.16$, $p = 0.143$). It is therefore unlikely that 24 month-old babies with a wide range of repetitive behaviours, including sensory seeking behaviours were hypersensitive at 9 months old. The mean amplitude for P150-P350 was 0.22 μV (±4.90) in babies at low risk of developing ASD, and 3.05 μV (±5.12) and 2.73 μV (±4.17) in babies at high risk of developing ASD with and without stereotyped behaviours and restricted interests respectively.

A simple regression was performed with ADOS SBRI scores at 24 months old in babies at high risk of developing ASD as the dependent variable and P150-P350 amplitude in response to noise at 9 months old as the independent variable to look at whether there was a relationship between development of repetitive behaviours and hypersensitivity. It showed that P150-P350 amplitude in response to noise did not account for a significant amount of variance in SBRI scores ($R^2 = 0.01$, adjusted $R^2 = -0.02$; $F(1,32) = 0.37$, $p = 0.547$). No relationship was found in babies at low risk either ($R^2 = 0.03$, adjusted $R^2 = -0.03$; $F(1,16) = 0.57$, $p = 0.459$). Early perception of potentially disturbing sounds

seems therefore to be unrelated to future development of repetitive behaviours, when they include sensory seeking behaviours.

3.2. Association between ERP amplitude and specific ADOS SBRI subscales scores. One-way independent ANOVAs were used to look at whether babies' ERP amplitude differed on subscales of the ADOS SBRI scale that specifically look at potentially soothing behaviours (mannerisms and repetitive behaviours). They showed that P150-P350 amplitude in response to noise did not differ across babies at low risk of developing ASD whose scores on the ADOS D2 subscale are likely to reflect typical variance in mannerism development (two babies in this group received a score above zero) and babies at high risk of developing ASD with or without mannerisms ($F(1,49) = 2.40$, $p = 0.101$). A planned contrast was tested given that a specific hypothesis was defined a priori. As it was expected that P150-P350 amplitude in babies at high risk of developing ASD with mannerisms would be higher than P150-P350 amplitude in the other two groups, one-tailed result is reported. The trend analysis showed that the mean of P150-P350 amplitude in babies at high risk with mannerisms differed from the means of P150-P350 amplitude in babies at high risk without mannerisms and babies at low risk of developing ASD ($F(1,49) = 4.70$, $p = 0.015$). Results for specific one-tailed hypotheses showed that P150-P350 amplitude was significantly increased in babies at high risk of developing ASD with mannerisms compared to babies at low risk ($t(49) = 2.16$, $p = 0.015$), but not compared to babies at high risk of developing ASD without mannerisms ($t(49) = 1.01$, $p = 0.159$). Thus, babies at high risk who developed mannerisms at

24 months old are likely to be hypersensitive to potentially disturbing sounds at 9 months old. Pooled variance estimates were used since homogeneity of variance assumptions were met ($p > 0.05$). Figure 15 shows the mean amplitude of P150-P350 complex in response to noise on 5 frontal electrodes in all three groups.

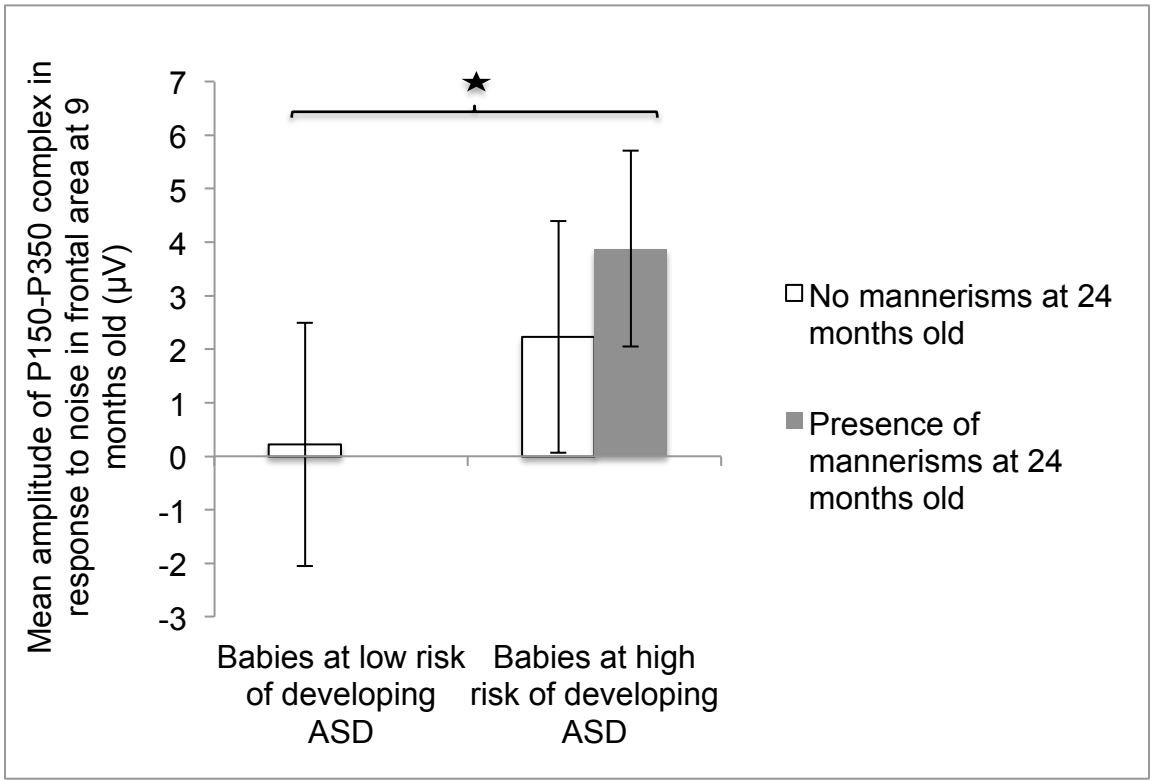

Figure 15. Mean amplitude of P150-P350 complex in response to noise across 5 electrodes in frontal area at 9 months old in babies at low risk of developing ASD, and babies at high risk of developing ASD with and without ASD-like mannerisms at 24 months old. * indicates where amplitude differs across groups. Error bars show the 95% confidence interval.

A one-way independent ANOVA showed that P150-P350 amplitude in response to noise did not differ across babies at low risk of developing ASD

babies whose scores on the ADOS D4 subscale are likely to reflect typical variance in development of repetitive and stereotyped behaviours (five babies in this group received a score of one showing presence of few repetitive behaviours that do not prevent the child from completing other activities) and babies at high risk of developing ASD without or with unusually repetitive interests or stereotyped behaviours (i.e., with scores of zero or above on the ADOS D4 subscale) ($F(2,49) = 2.40$, $p = 0.101$). Planned comparisons were used as they can be conducted to test specific hypotheses when F is not significant. Two planned comparisons were conducted to specifically look at the group differences of interest: one to test whether the amplitude of the babies at high risk of developing ASD with unusually repetitive interests or stereotyped behaviours was increased compared to the one of babies at high risk without unusually repetitive interests or stereotyped behaviours, and one to see whether the amplitude of the babies at high risk of developing ASD with unusually repetitive interests or stereotyped behaviours was increased compared to the one of babies at low risk of developing ASD. The trend analysis showed that the means of P150-P350 amplitude did not differ across baby groups ($F(1,49) = 1.70$, $p = 0.198$). Hypersensitivity is therefore unlikely to be associated to repetitive behaviours that include sensory components (e.g., banging of object in D4 subscale).

The relationship between atypical development of auditory processing and mannerisms and stereotyped behaviours could not be explored because of the lack of variation in severity of ADOS scores at 24 months old in babies at high

risk of developing ASD. Twenty one babies out of 34 babies at high risk of developing ASD received a score of zero (i.e., had no mannerisms), ten babies received a score of one (i.e., had brief instances of mannerisms) and only three babies received a score of two on the D2 subscale of the ADOS (i.e., had severe mannerisms). Twenty one babies out of 34 babies at high risk of developing ASD received a score of zero (i.e., had no repetitive or stereotyped behaviours), twelve babies received a score of one (i.e., had few repetitive or stereotyped behaviours that did not impair with their functioning) and only one baby received a score of two on the D4 subscale of the ADOS (i.e., had severe repetitive or stereotyped behaviours).

3.3. Summary. Babies at high risk of developing ASD who went on to develop ASD-like symptoms including mannerisms at 24 months old had atypical neural responses to spectrally rich and potentially disturbing sounds at 9 months old. Babies with mannerisms had P150-P350 complex in response to noise over frontal electrodes of atypically large amplitude that might reflect hypersensitivity. It is not possible to say whether the more hypersensitive babies developed more mannerisms as the relationship between the variables could not be investigated. No significant results were found when repetitive behaviours were investigated using the SBRI scale and D4 subscale, possibly showing that hypersensitivity is not associated to behaviours including strong sensory components.

4. Overall summary of findings

Enhanced ability to discriminate subtle changes in sounds was found to be associated to development of better language and communication skills. The association between early discrimination skills and future language skills was specific to babies at high risk, while the association between early discrimination and future communication skills was found in babies at low and high risk of developing ASD. Primacy of early auditory atypicalities over appearance of language difficulties suggested that atypical language development might happen consequently to development of high-risk specific discriminatory strategy. A different type of hypersensitivity was also investigated. Perception of potentially disturbing sounds was heightened in babies at high risk of developing ASD who developed mannerisms. The present results thus showed an association between atypical early sensory processing and future language and ASD-like symptoms.

Chapter 4: Discussion

In this chapter, aims of the study are first reviewed. Study findings are then interpreted in relation to previous research. The results on the relationship between ability to discriminate sounds and development of language and communication skills are discussed. This is followed by a discussion on the results on the relationship between hypersensitivity to potentially disturbing sounds and development of repetitive behaviours. The strengths and limitations of the study and ways to improve current limitations in future research are also provided. Finally, the theoretical and clinical implications of the study are discussed.

1. Reviewing the study aims

The current study looked at early differences in perception of sounds in babies at high risk of developing ASD (i.e., with an older sibling with ASD) with or without ASD-like symptoms at a later age and babies at low risk of developing ASD (i.e., with an older sibling without ASD). Neural processing of sounds was investigated at 9 months old using electroencephalography. Behavioural studies showed that children with ASD present with three types of sensory behaviours: hyporesponsiveness (e.g., not reacting to loud sounds), hyperresponsiveness (e.g., blocking sounds by covering their ears) and sensory seeking (e.g., banging an object on a table). It is not known what sensory neural processing these behaviours reflect. They could be generated by atypically low or high neural responses (respectively resulting in hyposensitivity and hypersensitivity) to

different types of auditory stimuli. For instance, hyporesponsiveness could result from a cognitive strategy to block out sensory stimulation in hypersensitive children as well as lack of sensory input in hyposensitive children. Hypo- and hypersensitivity could also result from different types of sensory processing. A child with ASD could have increased neural responses to sounds making them hypersensitive to auditory stimulation, but decreased neural response to differences in sounds making them hyposensitive to acoustic changes in the environment (e.g., a door banging next to them). This distinction between types of sensory processing has received seldom attention in research conducted in ASD (for review, see Keehn, Müller, & Townsend, 2013). It was therefore important to investigate neural sensory processing rather than sensory behaviours and distinguish between the various types of sensory processing to understand the processes involved in ASD-like sensory atypicalities.

Two types of sensory processing were investigated in this study: 1. the ability to discriminate subtle changes in the acoustic environment, as illustrated by differences in amplitude of potentials evoked by tone deviants and standards of different pitch, and 2. the sensitivity to spectrally rich and thus potentially disturbing sounds, as illustrated by the amplitude of potentials evoked by white noise. As data recorded for this study showed that neural activity in response to tone and noise deviants in babies at high risk of developing ASD tended to be larger than in babies at low risk, we looked at how early hypersensitivity (i.e., better discrimination ability and hyperreaction to sounds) related to the presence and severity of future ASD-like symptoms in our participants. The ability to

discriminate subtle changes in the acoustic environment at 9 months old was compared in babies who developed typical and atypical language and communication skills at 24 months old. The presence of hyperreaction to sounds at 9 months old in babies who developed repetitive and stereotyped behaviours at 24 months old was also looked at. When allowed by the quality of the data, association between severity of hypersensitivity and ASD-like symptoms and primacy of sensory differences over appearance of other ASD-like symptoms were also investigated to see whether atypical sensory processing could possibly play a role in the development of ASD symptoms as argued in the hypersystemization and intense world theories.

2. Association between early ability to discriminate subtle acoustic changes and future ASD-like symptoms

2.1. Relationship between hypersensitivity at 9 months old and language skills at 24 months old.

First, findings regarding the relationship between early ability to discriminate sounds and development of language skills will be described and discussed in relation to previous research. The specificity of this relationship to ASD will then be discussed.

2.1.1. Description of findings and discussion in relation to previous research.

The ability to discriminate subtle (language-relevant) changes in the auditory environment at 9 months old was compared across babies at high risk of developing ASD with typical and atypical language skills at 24 months and babies at low risk. Toddlers at high risk of developing ASD with typical language

skills had similar scores on the Communicative Development Inventory (CDI) to toddlers at low risk. They could discriminate sounds better than toddlers at high risk with poorer language skills (i.e. with CDI scores at 24 months old lower than in babies at low risk). The amplitude of their P350 in response to tone deviants was larger. Better language skills in toddlers at high risk also showed a trend to increase with better early ability to discriminate subtle sound differences as illustrated by an association between higher CDI scores at 24 months old and higher amplitude of P350 in response to tone deviants (but not tone standards) at 9 months old.

Albeit only marginally significant, these findings tended to support our hypothesis. We were expecting to find better early ability to discriminate tones in toddlers with better language skills, given that it is necessary for a child to be able to discriminate rapidly changing tone cues to develop language (Benasich & Tallal, 2002; Kuhl, 2004). This necessity is illustrated by the poor tone discrimination skills of typically developing children with language difficulties (Loui, Kroog, Zuk, Winner, & Schlaug, 2011; McArthur & Bishop, 2004). Whilst it is not known whether toddlers in our study will go on to develop ASD, we nevertheless showed that toddlers likely to develop ASD traits who have better language skills at 24 months old had better sound discrimination skills at 9 months old.

Interestingly, the amplitude of P350 in response to tone deviants in toddlers at high risk with atypical language skills was close to baseline. Similarly, children and adults with ASD with language impairment were found to show no difference

in amplitude between responses to tone deviants and standards in cross-sectional studies (Tecchio et al., 2003b; Kujala et al., 2007; Näätänen & Kujala, 2011). Results from the current study thus suggested that toddlers at high risk with poor language skills had poor early auditory discrimination skills. This finding is in line with findings from previous behavioural studies showing that hyporesponsive children with ASD have poorer language skills (Watson et al., 2011; Patten et al., 2013).

Several cross-sectional behavioural studies showed results contradicting our finding that better auditory processing might be related to better language skills in children who are at risk of developing ASD. No association was found between language skills and tone perception (Heaton, Hudry, Ludlow, & Hill, 2008) and discrimination (Eigsti & Fein, 2013) in young adolescents with ASD. It is however possible that discrimination skills are important to acquire language and then become less essential with age. In addition, several studies found results suggesting that better tone discrimination skills could impair language skills. A group of adolescents with ASD made up of a high proportion of participants with language impairment and/or early language delay exhibited superior tone identification (Järvinen-Pasley, Pasley, & Heaton, 2008a) and discrimination (Jones et al., 2009) relative to typically developing controls without language difficulties. Difficulty in learning words at an early age was found to be associated with current ability to better discriminate tones in young adolescents with ASD (Eigsti & Fein, 2013). Adults with ASD with early language delay had better tone discrimination skills than controls without ASD, while adults with ASD with no

early language delay had similar skills to controls (Bonnel et al., 2010). Jones et al. (2009) suggested that enhanced pitch perception may disrupt language processing. Hypersensitivity to certain sounds could lead to sensory overload and thus impair processing of linguistic information. An over-focus on perceptual cues, particularly pitch, during speech may also negatively impact upon linguistic processing and decrease experience with language-related stimuli (Järvinen-Pasley, Pasley, & Heaton, 2008a; Järvinen-Pasley, Wallace, Ramus, Happé, & Heaton, 2008b), which would result in the development of poor language skills. However, these studies present several limitations preventing the authors from concluding that better tone discrimination impairs development of language. It is possible that participants' ability to discriminate sounds as adults does not reflect their auditory skills in early childhood. Most studies being cross-sectional and not manipulating discrimination skills (e.g., with training), they do not allow investigation of a causal relationship. In addition, delay in word acquisition was measured based on retrospective questionnaires filled in by parents whose recall of when their adolescent or adult child developed language may be unreliable or biased. Nevertheless, these studies highlight the need to demonstrate whether a causal relationship exists between auditory discrimination skills and development of language skills and the direction of this relationship.

Several authors suggested that better discrimination of non-speech sounds (e.g., tones) in ASD could result from diminished interest in or attention to language during development (Bonnel et al., 2010; Blackstock, 1978; Dawson et al., 1998; Kuhl, Coffey-Corina, Padden, & Dawson, 2005). Our study showed that

early tone discrimination skills tended to be associated with language skills at 24 months old but not at 14 months old, albeit the strength of the association between early sensory processing and language skills at both ages was found to be similar. This finding nevertheless suggests that it is unlikely that an ASD-like language processing style influences the ability to discriminate non-speech sounds. Our study further showed primacy of atypical sensory processing over appearance of differences in language skills. Nine months old babies in our study did not speak many words, thus preventing from comparing early language skills across groups. However, it is likely that babies at high risk of developing ASD with poor language skills at a later age have similar language skills at 9 months old to babies at high risk who go on to develop good language skills. In other studies, parents reported no difference in CDI scores at 12 months old in high risk siblings with fewer words produced on the CDI at 18 months old (Mitchell et al., 2006; Zwaigenbaum et al., 2005). The presence of atypical sensory processing and typical language skills at 9 months old in babies at high risk of developing ASD who developed language difficulties at a later age may further suggest that it is the ability to discriminate non-speech sounds that plays a role in the development of poor language skills, rather than the opposite. This interpretation would however need to be confirmed by showing that manipulating early discrimination skills impacts on future language skills of babies who go on to develop ASD.

2.1.2. Specificity of the relationship between early hypersensitivity and language development to ASD. The tendency for early auditory discrimination skills to be related to future language skills seems to be specific to babies at high risk of developing ASD. Amplitude of P350 in response to tone deviants at 9 months old did not 'predict' CDI scores at 24 months old in babies at low risk of developing ASD. Furthermore, the relationship between perception of acoustic changes and future language skills significantly differed between babies at low and high risk of developing ASD. The amplitude of P350 in response to tone deviants in babies at low risk of developing ASD was close to the baseline, which might explain this difference in the relationship of P350 amplitude to future CDI scores across groups. It is possible that the quasi-absence of P350 reflects typical maturation of the auditory cortex. A neural network inhibiting the processing of contextually less relevant changes in the acoustic environment might develop by one year old resulting in less sensitivity to tone changes in typically developing babies (for review, see Kushnerenko, Van den Bergh, & Winkler, 2013). The trend towards a negative correlation between ability to discriminate tone pitch at 9 months old and language skills at 24 months old suggests that poorer ability to discriminate changes in a sequence of tones is related to development of better language skills in babies at low risk. Different mechanisms might therefore be involved in the development of good language skills in both populations, as it seems that better early ability to discriminate pitch in a sequence of tones is related to development of better language skills in babies at high risk. Similarly, cross-sectional studies showed that the amplitude

of the difference between neural responses to tone deviants and standards were enhanced in children (Jansson-Verkasalo et al., 2003; Lepistö et al., 2006) and adults (Kujala et al., 2007) with ASD with good language skills. Hypersensitive sound discrimination might therefore predominate the neural basis of auditory perception in individuals with ASD with good language skills. The finding that babies at high risk of developing ASD with poor language skills have quasi-inexistent P350 in response to tone deviants suggested that they are hyposensitive to changes in the environment (rather than a typically maturing auditory system as in babies at low risk with typical language skills). It is therefore possible that the relationship between early auditory processing and future language skill is specific to babies at high risk of developing ASD because early auditory processing skills go from hyposensitive skills to hypersensitive skills, which would be unlikely to be found in children at low risk.

One can only speculate about the specificity of the present findings to ASD. A limitation of the current study is that it is not known which participants will go on to be given a diagnosis of ASD. Some children at high risk of developing ASD with typical language skills at 14 and 24 months old may not develop ASD, while some with poor language skills may develop ASD. Language milestones are strongly related to long-term ASD prognosis (e.g., Stone & Yoder, 2001; Szatmari et al., 2003). In addition, high risk siblings who developed ASD have been found to have poor language production at 12-14 months old (Zwaigenbaum et al., 2005; Landa & Garrett-Mayer, 2006). However, other studies showed that better early language skills in children with ASD are

associated with regression (Luyster et al., 2005; Andrew Pickles et al., 2009), and typical language skills have been observed in 18 and 24 month-old toddlers at high risk who later developed ASD (Hudry et al., 2013; Talbott, Nelson, & Tager-Flusberg, 2013). In addition, some children at high risk who did not develop ASD have been found to have a high rate of language delay (Gamliel, Yirmiya, Jaffe, Manor, & Sigman, 2009). Thus, some children with typical language skills at 14 and 24 months old could develop ASD and some children with atypical language skills at 14 and 24 months old could not develop ASD. One must therefore wait until the diagnosis of the participants is known at a later age to further be able to discuss the issue of the specificity of the relationship between sensitivity to auditory changes and development of language skills to ASD.

2.2. Relationship between hypersensitivity at 9 months old and communication skills at 24 months old.

2.2.1. Description of the results and discussion in relation with previous research. The relationship between ability to discriminate subtle (language relevant) auditory changes at an early age and severity of future communication skills was investigated. Communication skills as assessed by the ADOS communication scale differ from the language skills assessed by the CDI (i.e., number of different words children produce) because they encompass socially-directed vocalization (e.g., to make needs known) without taking into account the number of words produced by the child, ASD-like ways of speaking (e.g.,

consistent intonation patterns) and non-language ways of communicating (e.g., use of other's body to communicate, use of pointing, use of emotional or descriptive gestures to communicate). We expected that poorer early discrimination skills would be associated with the development of ASD-like communication traits. A couple of behavioural studies showed that toddlers and adults with ASD with poor communication skills had high levels of hyporesponsiveness and sensory seeking behaviours (Liss et al., 2006; Watson et al., 2011). In line with our hypothesis, the current study showed a negative relationship between amplitude of P350 in response to acoustic changes at 9 months old and ADOS communication scores at 24 months old, after controlling for amplitude of responses to tone standards. Poorer early auditory discrimination skills are thus likely to be associated with development of poorer communication skills. Hearing impaired individuals, who often have poor tone discrimination skills (for review, see Moore & Carlyon, 2005), also often have flat speech prosody (O'Halpin, 2001) and use sign language. Similarly, children at high risk of developing ASD who cannot discriminate tones might not be able to modulate the intonation of their voice. They might also use gestures to communicate rather than language. It is worth noting that poorer communication skills are unlikely to result from adapting to poorer language skills, as many babies at high risk of developing ASD with poorer communication skills had good language skills. A study involving manipulation of auditory discrimination skills at 9 months old would be needed to confirm that discrimination skills play a role in the development of communication skills.

2.2.2. Specificity of findings to ASD. It is likely that common mechanisms are involved in babies at low and high risk of developing ASD. The relationship between early auditory discrimination abilities and future communication skills was not specific to ASD. Babies at low risk of developing ASD tended to show an association between early discrimination of acoustic changes and future communication skills, which was not significantly different to the one found in babies at high risk. In addition, no difference was found in amplitude of P350 in response to tones deviants between the babies at low risk and high risk of developing ASD who developed atypical and typical communication skills. It is therefore unlikely that babies at high risk of developing ASD who developed better communication skills had atypical discrimination skills (i.e., were hypersensitive) at 9 months. The current finding might therefore highlight that children at high risk of developing ASD rely on typical auditory mechanisms to develop their communication skills. The superior temporal sulcus is activated when discriminating tones (Specht & Reul, 2003) and interpreting the communicative significance of both auditory and visual inputs, such as body movements, eye-gaze, head orientation, lip reading, facial expressions, vocal sounds and speech (Redcay, 2008) in typically developing individuals. Similar anatomical structure might be involved in ASD. Better auditory discrimination skills in babies at high risk would then reflect better functioning of anatomical structures, which being involved in both auditory discrimination and interpretation of communication signals would also enable development of better communication skills. Data should be analysed again once the diagnosis of the

participants is known at 36 months old to decipher whether this relationship is specific to ASD.

2.3. Conclusion. This study showed that early abilities to discriminate subtle changes in the acoustic environment predict future language and communication skills in children at high risk of developing ASD. More research is needed to determine whether better auditory discrimination skills cause the development of better language and communication skills and whether this relationship is specific of ASD. Finding that better auditory discrimination skills could help children at risk of developing ASD develop better language and communication skills is novel and interesting. Studies on the possible impact of hypersensitivity on development of ASD-like symptoms have thus far focused on the impairments likely to be caused by atypical sensory processing. For instance, the relationship between pitch discrimination skills as reflected by enhanced neural responses to tone deviants and need for sameness in ASD was investigated by Gomot et al., 2011). Our finding is in line with the current thinking that atypical sensory skills in ASD might be an asset rather than a deficit, based on the findings that people with ASD can have savant skills in maths, music and drawing thanks to their attention to details (Happé, 1999).

3. Association between early neural reactivity to potentially disturbing sounds and future ASD-like repetitive and stereotyped behaviours.

First, findings on the relationship between early hypersensitivity and development of repetitive behaviours as assessed by different behavioural

measures will be described. Findings supporting our hypothesis that a relationship exists between early hypersensitivity and development of repetitive behaviours will then be discussed in relation to previous research. Finally, several explanations will be proposed to explain why no relationship could be found between hypersensitivity and repetitive behaviours in some circumstances.

3.1. Description of findings. The relationship between sensory processing of noise, a spectrally rich and potentially disturbing sound at 9 months old and ASD-like repetitive and stereotyped behaviours at 24 months old was investigated. Repetitive and stereotyped behaviours were measured in three different ways with the ADOS: 1. scores on the Stereotyped Behaviours and restricted Interests (SBRI) scale, which encompasses the unusual sensory interest subscale, mannerism subscale and unusually repetitive interests or stereotyped behaviours subscale and provides a global measurement of various repetitive behaviours, 2. Scores on the mannerism subscale as it only looks at motor repetitive behaviours that could potentially be used by hypersensitive children to self soothe, and 3. Scores on the unusually repetitive interests or stereotyped behaviours subscale as it includes sensory and motor repetitive behaviours, which could be self-soothing for the hypersensitive child.

An association was found between scores on the mannerism subscale of the ADOS and auditory hypersensitivity. Babies at high risk of developing ASD who developed ASD-like mannerisms at 24 months old had larger amplitude of neural responses to noise at 9 months old. Babies at high risk of developing ASD with higher scores on the ADOS SBRI scale and the subscale looking specifically at

repetitive and stereotyped behaviours (i.e., with ASD-like repetitive behaviours) at 24 months old did not show hypersensitivity to disturbing sounds at 9 months old. The amplitude of their P150-P350 complex in response to noise was not larger than in babies at high risk of developing ASD with typical ADOS scores on the two scales investigated at 24 months old and babies at low risk of developing ASD.

3.2. Discussion of finding that early hypersensitivity is associated to mannerisms in relation to previous research. The association found between early auditory hypersensitivity and scores on the mannerism subscale of the ADOS at 24 months old in the current study supports our hypothesis that repetitive and stereotyped behaviours may regulate a state of over-arousal in individuals with ASD. As suggested by the optimal stimulation theory, response output's function is to homeostatically regulate stimulus input (Zentall & Zentall, 1983). Typically developing individuals often use motor stereotypies such as leg swinging, rocking, repetitive finger movements and nail biting when they are bored or in an understimulating environment to increase stimulation (Mason, 1991) and in demanding situations where they are likely to help block excessive stimulation (Wehmeyer, 1989). The presence of stereotypy found in individuals with ASD with increased basal EEG activity (Hutt, Hutt, Lee, & Ounsted, 1965) further suggests that some repetitive behaviours regulate a state of over-arousal in ASD. First-hand accounts illustrate how mannerisms can help self-soothe. Donna Williams (1992), a woman with ASD, explained that she repetitively blinks her eyes to slow down incoming information: "You got the effect of strobe lights

without the control being taken out of your hands. If anything, my blinking was sometimes a reaction to sound" (p. 45). Hypersensitive children at high risk of developing ASD might therefore develop mannerisms to self soothe.

There might be a need to self soothe because children feel anxious when they are over-aroused. Children with ASD have been found to display mannerisms when anxious (Militerni, Bravaccio, Falco, Fico, & Palermo, 2002). The amygdala, which plays a role in regulating reaction to environmental stimuli that are perceived as fearful or anxiety-provoking, was found to be activated when individuals with ASD are engaged in repetitive behaviours (Dziobek, Fleck, Rogers, Wolf, & Convit, 2006). Anxiety might increase with level of over-arousal. More severe hypersensitivity is associated with presence of more repetitive behaviours in toddlers with ASD (Chen et al., 2009). This relationship could not be investigated in the current study because of the lack of variation in the behavioural data. It is therefore not possible to say whether more hypersensitive babies developed more mannerisms. More babies would need to be tested to increase the variation in the data.

The current study nevertheless provided interesting information on the specificity of the relationship between presence of mannerisms and neural sensory atypicalities. Behavioural studies so far could not help identify the type of sensory atypicalities mannerisms are associated with. Mannerisms have been found to be associated with sensory seeking, hyporesponsiveness and hyperresponsiveness (Wiggins et al., 2009; Boyd et al., 2010), not associated with hyperresponsiveness (Baranek et al., 1997) and only associated with

hyperresponsiveness (Gal et al., 2010). Using EEG data in the current study thus enabled to show that there might be a specific relationship between hypersensitivity and development of mannerisms in children at high risk of developing ASD.

The current study did not allow us to draw any conclusion as to whether there is a causal relationship between presence of mannerisms and hypersensitivity. The impact of manipulating hypersensitivity to sounds on severity of mannerisms would need to be investigated to see whether a causal relationship between these two factors can be inferred. It is also not possible to say whether the relationship found between hypersensitivity and mannerisms in the current study is specific of ASD. These data should be looked at again at a later age when ASD-like symptoms have stabilised and ASD diagnosis in children can be established.

3.3. Possible explanations to the lack of relationship between hypersensitivity and some measures of repetitive behaviours. The lack of relationship found in the current study between hypersensitivity at 9 months old and the SBRI scale and the subscale looking specifically at repetitive and stereotyped behaviours at 24 months old may be explained by several limitations of the study:

- The ADOS might not be appropriate to assess repetitive and stereotyped behaviours. While laboratory observation enables experts to identify repetitive behaviours, which might be difficult for parents to do, ADOS observations occur within a brief time period and may not provide an optimal opportunity for the

assessment of repetitive and stereotyped behaviours. An improvement to the current study could therefore be to add parental questionnaires looking at presence and severity of repetitive behaviours.

- The ADOS does not enable to look at specific types of repetitive and stereotyped behaviours. These behaviours in ASD are manifest in many ways from simple sensory and motor actions to complex circumscribed interests. They have been divided in two categories (Prior & Macmillan, 1973; Turner, 1999): lower level repetitive behaviours, including repetitive motor mannerisms and unusual sensory interests and higher level cognitive behaviours, including preoccupation with restricted interests and need for sameness. These different types of repetitive behaviours involve disruption in activity of different brain structures (for review, see Langen, Durston, Kas, van Engeland, & Staal, 2011), with sensorimotor structures being involved in lower level behaviours and other structures including the prefrontal cortex and limbic system being involved in higher level repetitive behaviours (Haber & Calzavara, 2009). These behaviours are likely to serve different functions. They may either increase or reduce sensory stimulation (Leekam, Prior, & Uljarevic, 2011). Some repetitive behaviours with a strong sensory component (e.g., spinning objects or the self) are assumed to provide sensory feedback (Lovaas, Newsom, & Hickman, 1987), which the child is likely to look for when under-aroused (Kinsbourne, 1980; Ornitz & Ritvo, 1968; Zentall & Zentall, 1983). Other behaviours may not include sensory feedback and are likely to be soothing when a child is overaroused (for review, see Hazen, Stornelli, O'Rourke, Koesterer, & McDougle, 2014). Lydstone

et al. (2014) showed that behaviours reflecting insistence on sameness (e.g. lining up of objects) are linked to arousal by sensory sensitivity and sensation avoiding and may function to narrow sensory input. The ADOS SBRI scale looks at behaviours that could serve the function of reducing and increasing sensory stimulation. Specifically, the unusual sensory interests subscale looks at the child's interest in or unusual response to sensory aspects of toys or surroundings, i.e. sensory seeking behaviours (Ben-Sasson et al., 2007), whilst the mannerism subscale looks at motor stereotypies that do not have a strong sensory component. Similarly, the repetitive interests or stereotyped behaviours subscale encompasses behaviours that could either help increase or decrease sensory input (e.g., banging objects vs. blocking sounds with fingers into ears). It is therefore likely that a possible relationship between hypersensitivity and soothing repetitive behaviours was cancelled out by the sensory increasing behaviours being coded in these (sub)scales. As argued by Cunningham and Schreibman (2008), repetitive behaviours should be classified based on their functions rather than their lower or higher level type.

- No data was available in participants older than 24 months old in the current study. It is likely that the type of repetitive behaviours will change when participants get older. It is possible that participants develop more high level repetitive behaviours with soothing function at an older age. Whilst lower level repetitive behaviours (e.g., mannerisms) are more apparent in younger children with ASD, higher level repetitive behaviours are more often found in older children (e.g., Esbensen, Seltzer, Lam, & Bodfish, 2009; Richler, Huerta, Bishop,

& Lord, 2010). Militerni et al. (2002) further showed that children with ASD start with developing mannerisms and go on to develop higher level behaviours. Repetitive behaviours become more pronounced after three years of age (Lord, 1995; Moore & Goodson, 2003). Similar analyses should therefore be conducted with the ADOS data collected in the participants when they are older.

- The diagnosis of the participants is unknown. Repetitive and stereotyped behaviours are not specific to ASD in the early years of life. Babies at low and high risk of developing ASD who will not go on to develop ASD may have high levels of repetitive behaviours at 24 months old, which would reduce the likelihood of finding group differences in level of hypersensitivity at 9 months old. Repetitive motor behaviours are common in typical development (Thelen, 1979), with rituals, habits and compulsions increasing between age one and two years and decreasing again after age four (Evans et al., 1997). These repetitive behaviours are presumably constructive elements of early development that lead to behavioural precision, efficiency and adaptive outcomes (Wolff, 1967). However, there is increasing evidence that repetitive behaviours manifest before and around two years old in children who develop ASD more than in children with typical or delayed development (e.g., Kim & Lord, 2010; Barber, Wetherby, & Chambers, 2012). Sibling studies have also yielded contradictory results. Wolff et al. (2014) found that high-risk toddlers who have developed ASD had higher rates of repetitive behaviours across subtypes at 12-15 months old than low-risk and high-risk toddlers who did not develop ASD. However, Damiano, Nahmias, Hogan-Brown, and Stone (2013) found no difference between high risk babies

who developed ASD or those who did not. Analysis of the ADOS data when participants are older should therefore shed light on whether current lack of difference in hypersensitivity at 9 months across groups is due to differences in severity of repetitive behaviours not showing at 24 months old yet. We will then also be able to separate the groups depending on whether children have developed ASD, which will provide more information on the specificity of the relationship between hypersensitivity and repetitive behaviours to ASD.

4. Implications of findings

4.1. Theoretical implications. Atypical processing of sensory information has often been proposed to play a major role in the development of ASD symptoms by theorists. Some theorists have argued that atypical perception leads to the development of ASD. Baron-Cohen (2009) proposed in his Hypersystemization theory that early hypersensitivity generates a learning style based on the recognition of repeating patterns or rules leading children to develop repetitive behaviours and not being able to understand social relationships. Some theorists have argued that atypical cognitive processing of sensations leads children to become hypersensitive and develop ASD. Happé and Frith (2006) suggested that children with ASD have Weak Central Coherence (WCC), a cognitive difficulty to ‘‘see the big picture’’ in everyday life that leads to a processing bias for detailed information and therefore to greater perception and development of repetitive behaviours. Finally, other theorists have argued that both perceptual and cognitive processing of sensory

information are altered at the same time and lead to the development of ASD. According to Markram and Markram (2010)'s Intense world theory, ASD results from an exaggerated response to stimuli at all levels of processing. Hence, theories of ASD describe atypical perception as causing, resulting from or being concurrent to the development of atypical cognition from which other ASD symptoms may result. By looking at whether perception is atypical at an early age in babies at high risk of developing ASD who go on to develop ASD traits and see whether hypersensitivity is related to ASD traits, we were hoping to clarify whether theories suggesting that ASD symptoms result from atypical perception can be supported by the data.

The present study provided an interesting insight, showing that enhanced perception of simple sensory information is present at an early stage of development of ASD-like symptoms. By showing that early atypical abilities to discriminate and perceive non-social auditory stimuli are linked to poor language and communication skills and presence of mannerisms at a later age, this study answered several questions raised by previous electrophysiological studies. It showed that sensory processing of non-social rather than social stimuli as suggested by Elsabbagh et al.'s finding (2012) is atypical in babies at high risk who develop ASD-like symptoms, therefore demonstrating that enhanced processing of low level information might be involved at an early stage of ASD development. Given that a relationship between presence of ASD traits and amplitude of sensory ERPs was found, the current study also showed that early atypical processing of non-social stimuli in babies who go on to develop ASD-like

symptoms is sensory rather than cognitive as suggested by studies in older children with ASD (e.g., Ceponiene et al., 2003; Tecchio et al., 2003). The current findings showed that babies who develop ASD-like symptoms have atypical sensory processing of low level information at an early age. Therefore, they tend to support the Hypersystemization theory and the Intense world theory.

It is however not possible to rule out that an atypical cognitive style led to the development of the early sensory atypicalities observed in the current study. The WCC theory would indeed argue that the hypersensitivity highlighted in the current study might result from a cognitive bias towards low levels of sensory information. In older individuals with ASD, the question whether they have difficulty shifting attention from local to more global auditory levels can be investigated behaviourally. Previous studies looked at whether individuals with ASD showed lack of susceptibility to gestalt interference (e.g., presentation of words) during a tone pitch discrimination task in adults (Foxton et al., 2003) and children (Järvinen-Pasley, Pasley, et al., 2008). The ability of individuals with ASD to discriminate pitch was not disturbed by stimuli requesting ‘global’ processing contrary to individuals with typical development. This suggests an over-focus of attention towards simple perceptual information and resilience to the distracting effect of linguistic content. However, such a protocol cannot be conducted in babies, and it is unlikely conclusions can be reached regarding whether babies who develop ASD have difficulties processing global information that leads them to develop hypersensitivity to local sensory information. Whilst the present study could not clarify which of the sensory theories might be correct,

it provided evidence of the likelihood of the involvement of atypical sensory processing in the development of ASD traits.

4.2. Clinical implications. The ERP components identified in the current study as reflecting sensitivity to subtle changes in the acoustic environment and disturbing sounds could be used as early markers for development of ASD-like symptoms in children at high risk of developing ASD. More research needs to be conducted to determine the ERP amplitude range that indicates likelihood of development of future ASD-like symptoms. One day, it might however be possible to predict that a baby at high risk of developing ASD might develop poor language and communication skills because their P350 in response to tone deviants at 9 months old is below a specific amplitude. Similarly, P150-350 complex in response to noise above a specific amplitude could indicate future development of mannerisms in babies at high risk of developing ASD.

Developing a way of predicting possible development of ASD using an imaging technique would present several advantages. It would provide an objective measure of risk and therefore prevent human errors or subjective variation in prognosis. It would also enable assessment of neural functioning directly, thus avoiding any masking of sensory atypicalities by development of compensatory behavioural strategies. Similarly, by providing information on the neural functioning of the infant, this technique enables to explore atypicalities before they manifest behaviourally. It therefore has the potential to flag babies likely to develop ASD traits at a very young age, giving thus to parents the opportunity to provide their child with treatment that is likely to be more effective

when it is delivered earlier (Lord & McGee, 2001). Such early interventions however have yet to be devised, and future research will hopefully be conducted to develop therapies delivered before ASD symptoms become manifest. The efficiency of these therapies on preventing the development or alleviating the severity of ASD symptoms will also have to be investigated. Another purpose for the evoked potentials used in the current study could then be to follow up the progress of the intervention on neural processes before development of ASD-like behaviours. For instance, an efficient intervention would lead to a decrease of neural responses to noise, ideally then indicating that mannerisms will not be developed. The neural markers found in the current study to be indicative of development of future ASD-like traits could thus be clinically used in different ways.

This study did not show a causal relationship between sensory processing and development of ASD-like symptoms. Thus, no theoretical background for currently used sensory programs, such as sensory integration therapy that assume that ASD develops as a consequence of atypical sensory processing could be provided. It is also not possible to conclude whether developing treatments that either increase subtle auditory discrimination to enhance language and communication skills (e.g., tone discrimination training) or diminish hypersensitivity to disruptive sounds to decrease likelihood to develop mannerisms would be helpful. Nevertheless, the current study suggested that treatments should not focus on increasing tolerance of sensory input only, as is often the case in therapies presently used (for review, see Hazen et al., 2014).

Findings suggested that increasing discrimination skills could also be helpful. For instance, early tone discrimination training could be provided. An example of a training task could involve rewarding babies looking longer at (for example) a cartoon duck making a different tone sound to other ducks on an eye tracker by having that duck jumping up and down to encourage the baby to discriminate tones. This training could be combined with physical exercise adapted to babies (e.g., playing in a swimming pool). Physical exercise is known to decrease mannerisms in individuals with ASD (Lang, Regester, Rispoli, Pimentel, & Camargo, 2010), possibly because it helps diminish arousal due to hypersensitivity, thus decreasing the need to engage in stereotypy to modulate one's level of arousal (Boyd, McDonough, & Bodfish, 2012). Understanding the causal developmental pathway towards ASD symptomatology would allow interventions to act on a small number of early factors with wide downstream effects instead of treating each symptom independently. Finally, there is a discrepancy between providing early behavioural markers for ASD and the lack of proven interventions for children under the age of 2 years, combined with the notion that earlier intervention is highly desirable to maximize the chances of a positive outcome. If a causal relationship between sensory processing and ASD development is evidenced, controlled clinical trials of interventions that specifically target sensory atypicalities in babies at risk will be essential to resolve this issue. More research is needed to show a causal relationship between sensory treatment and development/management of ASD-like symptoms.

Even if early therapies have not yet been developed, the current study could have implications in terms of clinical intervention. Being able to say which children are likely to develop ASD-like traits would help support families earlier than presently. Training could be provided to parents before their child develops ASD-like traits to help them learn about ASD and how to manage a child with ASD. They could also be offered early psychological support to help them cope with the fact that their child develops atypically. Supporting parents would have a great impact on the well-being of their child with ASD and their siblings. Family members would feel empowered when they know how to deal with their child or sibling with ASD. Being psychologically supported could help parents avoid being depressed and remain emotionally available to their children and able to deal with daily family activities. Early access to specialised support in school could be facilitated for infants flagged as being likely to develop ASD traits. This would prevent children from being bullied or suffering from isolation, not understanding what they are supposed to do or what is asked from them, being over-stimulated, etc. An often currently distressing phase at school before an ASD diagnosis can be made and support provided could thus be avoided. The current findings therefore have the potential to help support families cope emotionally and manage their child both at home and at school in the early days when ASD symptoms become apparent.

5. Strengths and limitations of the study

5.1. Strengths of the study.

The current study had four major strengths, which have already been mentioned throughout the Introduction and Discussion and will therefore only be summarized in this section:

- This study was prospective, thus preventing parental recall biases. It therefore enabled to avoid possible difficulty to remember specific behaviours and their exact timing (Palomo et al., 2006) and bias towards reporting negative, rather than positive, symptoms more accurately (Stone et al., 1994).
- This study was conducted from an early age, which might have enabled assessment of sensory processing before the development of major compensatory mechanisms.
- This study used imaging data. Atypical functioning of participants could therefore be explored before this might manifest behaviourally, thus providing the possibility to develop earlier prognosis/diagnosis tools than currently in use.
- This study used non-social stimuli to look at neural encoding of sounds, thus enabling to investigate sensory processing without possible bias that participants have difficulty processing social information rather than coding sensory stimuli.

The current study was the first one to combine all these strengths to look at the relationship between atypical sensory processing and other ASD-like symptoms. Given the novelty of the study, current findings are therefore the

most likely to reflect genuine relationships between hypersensitivity and difficulties in (non) verbal communication and presence of mannerisms.

5.2. Limitations of the study and ways to improve them in future research. Several limitations to the study were discussed in the interpretation of the findings given in the earlier sections of this chapter. They included that the causal relationship between atypical sensory processing and development of ASD traits could not be explored and that the specificity of the relationship between sensory atypicalities and ASD traits to a later ASD diagnosis could not be established.

To explore whether sensory atypicalities generate ASD symptoms, perception would need to be manipulated in babies to see whether changes in perception impact on the appearance or severity of ASD symptoms. For instance, babies at high risk of developing ASD could be trained to discriminate tones to see whether they develop better language and communication skills. The number of words they produce and their ability to discriminate tones after training (or at 24 months old) would then be compared to the ones of babies with similar ability to discriminate tones and language skills at 9 months old who did not receive training. If babies in the training group have better tone discrimination skills and language and/or communication skills after training than babies in the control group, then it could be concluded that better discrimination of non-speech sounds leads to the development of better language and or communication skills. Finding ways to manipulate hypersensitivity to sounds in babies might be difficult. At least, it would be worth conducting a functional analysis (Rapp & Vollmer,

2005) of the participants at a later age to look at whether repetitive behaviours in babies at high risk of developing ASD serve the purpose of removing or escaping from an aversive stimulus.

In addition to exploring the specificity of the relationship between sensory atypicalities and ASD-like traits to babies who go on to develop ASD, it would be important to rule out the presence of other pathologies in the participants. This relationship could be found in other clinical populations. For instance, language difficulties in children with specific language impairment could also be associated with difficulty to discriminate sounds (e.g., Loui et al., 2011). Children with obsessive compulsive disorder who use lower level type of repetitive behaviours, such as mannerisms to decrease anxiety (Boyd et al., 2012) could also be hypersensitive (Dar, Kahn, & Carmeli, 2012). Similarly, children with ASD often also have attention deficit/hyperactivity disorder suggesting that the development of the two disorders shares common processes (Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). Concluding that early sensory markers are specific to ASD will therefore require that presence of other pathologies is excluded in participants at a later stage of the study.

Finally, the current study could be improved by recruiting more babies to participate. Lack of variation in the data prevented some analyses from being conducted. It would indeed be interesting to be able to explore the correlation between degree of early hypersensitivity and severity of mannerisms developed at a later age. Some analyses showed marginally significant results or results that were significant when one-tailed probability was taken into account. This

may reflect type 1 errors, where findings were described in the absence of a significant effect. However, rejecting the hypotheses of the current study by imposing more stringent significance levels could have increased the risk of making a type 2 error, where the hypothesis was rejected when it was true, which may have been more detrimental given the novelty of the current study. Increasing the sample size would nevertheless be necessary to confirm the current findings.

6. Overall conclusion

Early ability to discriminate subtle (language relevant) changes in the acoustic environment was found to be associated with language and communication skills in toddlers at high risk of developing ASD. This finding shows that better discrimination of low level sensory information could be an asset in some cases for children at high risk of developing ASD. In addition, early hypersensitivity to disruptive sounds was found to be associated with the development of mannerisms, probably resulting from a need to self soothe in children at high risk of developing ASD. If a causal relationship exists between hypersensitivity and mannerisms, hypersensitivity in some cases could therefore be problematic. This study therefore shows the importance of distinguishing different types of hypersensitivity, thus addressing a gap in the literature (for review, see Keehn et al., 2013). Causal relationship between hypersensitivity and development of good language and communication skills and mannerisms still needs to be evidenced. It cannot thus be concluded which theories stating that

ASD symptoms result from atypical sensory processing are supported by the data. As such, no conclusion can also be drawn as to whether focusing on hypersensitivity in early treatments of ASD could be helpful in preventive or treating therapies. Future research should look at whether manipulating early sensory processing helps prevent development of ASD traits. Nevertheless, perceptual neural sensitivity could serve as a useful biomarker to indicate whether children at high risk of developing ASD might develop poor language and communication skills and mannerisms. Such markers could be helpful to ensure that parents and children get support as soon as possible. The reliability and validity of prognosis assessment using neurophysiological markers should however be tested as rigorously as standardized behavioural assessment, a process that is currently uncommon (for review, see Bishop, 2013). The study also did not address whether the relationship between sensory processing and language/communication skills and presence of mannerisms is specific to individuals with a diagnosis of ASD. Knowing the ASD diagnosis of the participants at a later stage of the study will help determine whether the relationships evidenced in the current study are exclusively found in children who develop ASD. Whilst the current study highlighted the early presence and sometimes the primacy of atypical sensory processing in babies developing ASD-like symptoms, suggesting a possible major role of sensory processing in the development of ASD as suggested by several theories, more research is needed to investigate the causal role of sensory processing in the development of symptoms specific of ASD.

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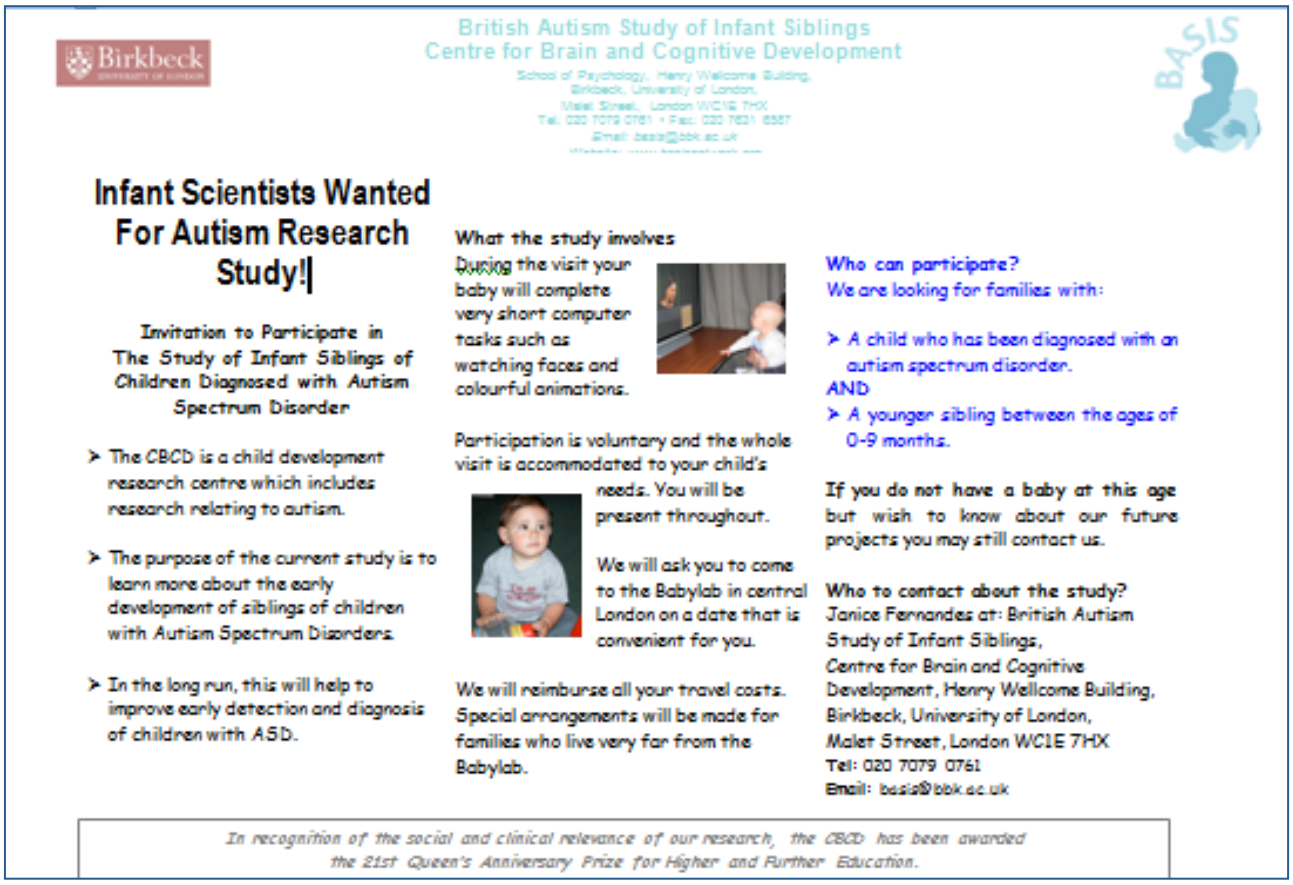
Appendices

Appendix 1. Poster used to advertise the study and recruit infant siblings of children with ASD (i.e. at high risk of developing ASD).



Birkbeck

British Autism Study of Infant Siblings
Centre for Brain and Cognitive Development

School of Psychology, Henry Wellcome Building,
Birkbeck, University of London,
Malet Street, London WC1E 7HX
Tel: 020 7079 0761 • Fax: 020 7631 6587
Email: basis@bbk.ac.uk

BASIS

Infant Scientists Wanted For Autism Research Study!

Invitation to Participate in The Study of Infant Siblings of Children Diagnosed with Autism Spectrum Disorder

- The CBCD is a child development research centre which includes research relating to autism.
- The purpose of the current study is to learn more about the early development of siblings of children with Autism Spectrum Disorders.
- In the long run, this will help to improve early detection and diagnosis of children with ASD.

What the study involves

During the visit your baby will complete very short computer tasks such as watching faces and colourful animations.

Participation is voluntary and the whole visit is accommodated to your child's needs. You will be present throughout.

We will ask you to come to the Babylab in central London on a date that is convenient for you.

We will reimburse all your travel costs. Special arrangements will be made for families who live very far from the Babylab.

Who can participate?
We are looking for families with:

- A child who has been diagnosed with an autism spectrum disorder.

AND

- A younger sibling between the ages of 0-9 months.

If you do not have a baby at this age but wish to know about our future projects you may still contact us.

Who to contact about the study?
Janice Fernandes at: British Autism Study of Infant Siblings,
Centre for Brain and Cognitive Development, Henry Wellcome Building,
Birkbeck, University of London,
Malet Street, London WC1E 7HX
Tel: 020 7079 0761
Email: basis@bbk.ac.uk

In recognition of the social and clinical relevance of our research, the CBCD has been awarded the 21st Queen's Anniversary Prize for Higher and Further Education.

Appendix 2. Copy of letter by the NHS ethics committee approving changes made to the main BASIS project to include the current study

NHS

National Research Ethics Service

London REC

Level 7, Maternity
Northwick Park Hospital
Watford Road
Harrow HA1 3UJ

Tel: 020 8869 2915
Fax: 020 8869 5222

16 November 2009

Dr Jeanne Guiraud
Centre for Brain and Cognitive Development
Birkbeck, University of London
The Henry Wellcome Building
London WC1E 7HX

Dear Jeanne

Study title: **Longitudinal study of infant siblings of children diagnosed with autism**
REC reference: **06/MRE02/73**
Amendment number: **2b, 10 November 2009**

The above amendment was reviewed at the meeting of the Sub-Committee held on 13 November 2009.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
CV for Kim Raff Davies		
CV for Helena Riberio		
Review by Fox et al. (2009)		
Infant scientist leaflet	2, tracked changes	10 November 2009
Protocol summary	4, with tracked changes	10 November 2009
Participant Consent Form	2, tracked changes	10 November 2009
Participant Information Sheet	5a, tracked changes	10 November 2009
Protocol	4a, tracked changes	10 November 2009
Notice of Substantial Amendment (non-CTIMPs)		10 November 2009
Covering Letter		10 November 2009
CV for Sarah Lloyd-Fox		
CV for Jeanne Guiraud		

This Research Ethics Committee is an advisory committee to London Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

06/MRE02/73: **Please quote this number on all correspondence**

Yours sincerely

A Bhayani

Mrs Alka Bhayani
Committee Administrator

E-mail: alka.bhayani@nwlh.nhs.uk / alkabhayani@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to:

Professor Mark Johnson
CBCD Henry Wellcome Building
Malet Street
London WC1E 7HQ

London REC

Attendance at Sub-Committee of the REC meeting on 13 November 2009

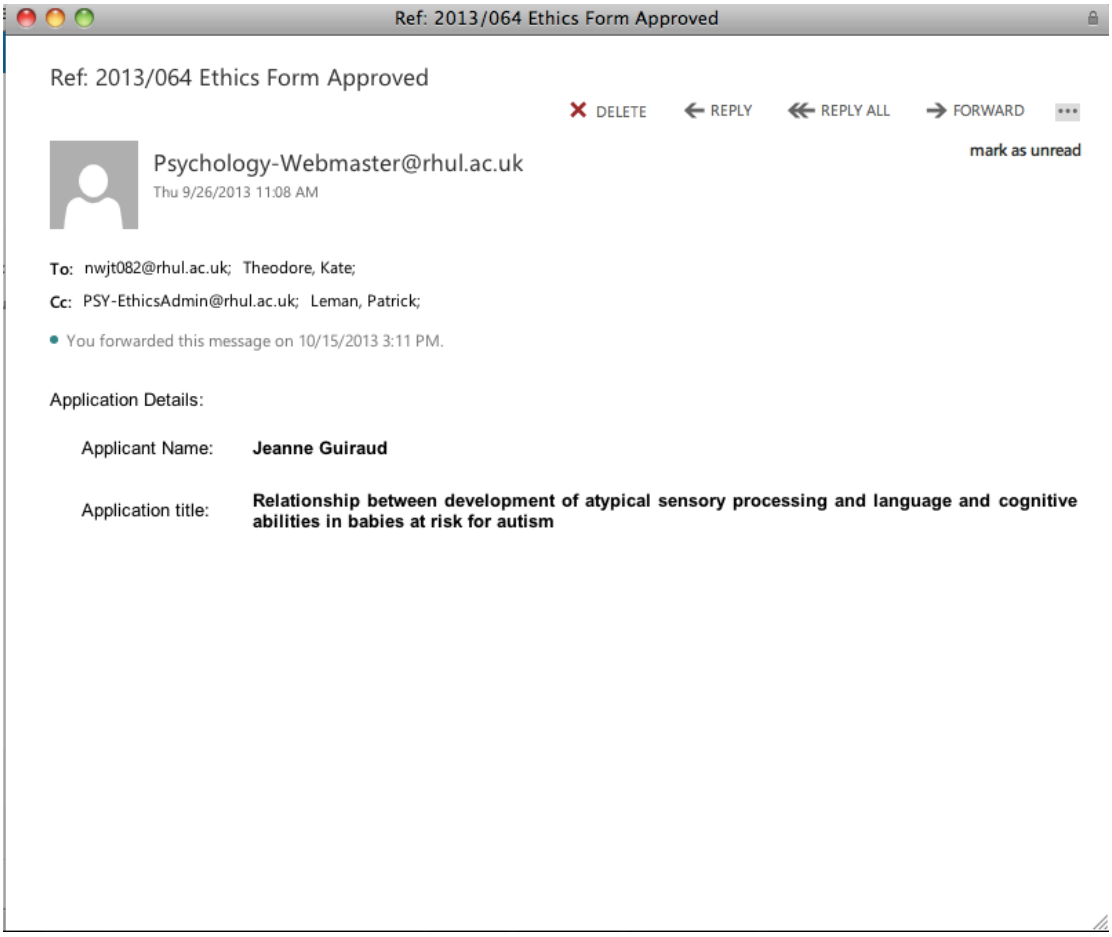
Name	*Profession*	*Capacity*
Dr Peter Brodrick	Consultant Anaesthetist	Expert
Dr John Keen	General Practitioner	Expert

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Alka Bhayani	Ethics Administrator

This Research Ethics Committee is an advisory committee to London Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Appendix 3. Copy of approval letter by Royal Holloway's Ethics Committee



Ref: 2013/064 Ethics Form Approved

Ref: 2013/064 Ethics Form Approved

DELETE REPLY REPLY ALL FORWARD

mark as unread

Psychology-Webmaster@rhul.ac.uk
Thu 9/26/2013 11:08 AM

To: nwjt082@rhul.ac.uk; Theodore, Kate;
Cc: PSY-EthicsAdmin@rhul.ac.uk; Leman, Patrick;

You forwarded this message on 10/15/2013 3:11 PM.

Application Details:

Applicant Name: **Jeanne Guiraud**

Application title: **Relationship between development of atypical sensory processing and language and cognitive abilities in babies at risk for autism**

Appendix 4. Letter sent to the GP of parents worried about their younger child

The Babylab

Centre for Brain and Cognitive Development
School of Psychology, Birkbeck College

32 Torrington Square, London WC1E 7HX, UK

Tel: (+44)020 7631 6258 Fax: (+44)020 7631 6587

Email: babylab@psychology.bbk.ac.uk

Dear (GP or specialist's name)

Regarding (baby sibling's name)

(Parents' titles and names) kindly agreed to take part in our study investigating the cognitive and social development of baby siblings of children diagnosed with Autism Spectrum Disorder (ASD). Their child, (name of the child diagnosed with ASD), has been diagnosed with ASD by (clinician's name). (Parents' names) visited the Centre for Brain and Cognitive Development on (date). During/after this visit the parents expressed worries about the development of their younger child, (baby siblings name), and we agreed to let you know about their concerns. We hope you would be able to offer further help and advice to this family.

Please find attached a copy of the consent form and information sheets for our study. Should you need any further information please do not hesitate to contact us on (please see contact details above).

(Parents' names) have seen this letter and agreed to send it to you. They will contact you shortly for consultation.

Sincerely,

Appendix 5. Information sheet given to parents about the BASIS study

British Autism Study of Infant Siblings
Centre for Brain and Cognitive Development
School of Psychology, Henry Wellcome Building,
Birkbeck, University of London,
Malet Street, London WC1E 7HX

Longitudinal study of infant siblings of children with ASD

Research Participant Information For All Groups Sheet 2

Network Scientific Protocol & Data Repository

Date: **{Insert Date}**

Dear parent,

The **British Autism Study of Infant Siblings** (BASIS) is a collaborative research network for studying the development of brothers and sisters of children diagnosed with Autism Spectrum Disorder (ASD). We would like to invite you and your baby to take part in one of our affiliated projects. Below is a description of the study and an outline of what would be involved should you choose to participate. Further information on the study can be found in the BASIS Frequently Asked Questions Sheet enclosed.

Aim

Our network aims to provide a platform for the study of infants at-risk for autism in the UK. Through affiliating with multiple projects, BASIS scientists will investigate differences during development, between babies who have an older brother or sister diagnosed with ASD and those who do not. It is our hope that

our research will help us gain a better understanding of why some children develop ASD and others do not. Although the tasks we use in our research studies cannot predict or diagnose ASD, we hope to use our findings to develop new tests that may in the long-term, help us to support children with ASD earlier.

What the research involves

If you wish to participate, we will invite you and your child to visit our research centre, the BabyLab at the Centre for Brain and Cognitive Development in London**.** Depending on your willingness and the age of your child when he/she is recruited, we will invite you to participate for a maximum of three visits until your child is 18 months. Later we will invite you for two follow-up visits, at 2 and 3 years of age respectively. Additional home visits can also be arranged at your convenience, but they will not always substitute the visits to the research centre.

Before your visits

Before your visits to the research centre, we will send you a number of questionnaires on your child's behaviour. These will include questions about your child's motor abilities (such as whether they can grasp objects or crawl), vocalizations (for example the sounds your baby makes), as well as their behaviour in everyday settings. This will help us to get information about how babies are in their everyday environment. One of the questionnaires will also ask about your child diagnosed with autism if you have one. This will help us get information about the older sibling with ASD of the babies involved in the project. We will ask you to bring the questionnaires with you when you visit the centre, at which point you can discuss any questions you find difficult to answer. You are welcome to phone the research centre before your visit with any questions you might have.

What will happen during your visits to the research centre

Your child will complete a number of short tasks and games, each examining a different area of development, and varying according to the age of your child. These may include watching animations on a screen or playing with the researcher. These tasks and games are designed to be fun and stimulating for babies. You will be present with your child throughout and are welcome to ask questions at any time. Some sessions will be tape recorded and viewed only by centre staff. You may decline to have your child's videotape retained for viewing by others if you wish. Participation in any part of the study is entirely voluntary, and you may choose to end the session at any time.

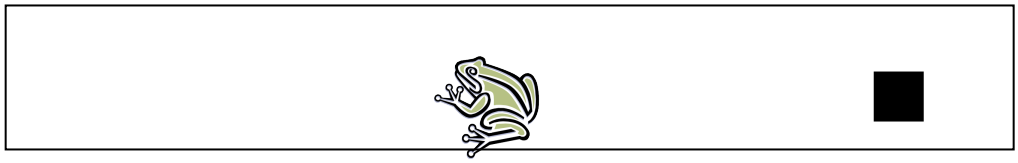
Here are some detailed descriptions of the tasks and games:

Fun and Games: *The researcher will have a short play session with the child. During this session the researcher will try to prompt your child to make eye contact and track moving toys. The games are designed to allow observation of the child's natural behaviour and of his or her responses to everyday play situations. After this task, we will ask you to play with your child for a few minutes the way you normally would. This will tell us how the child's behaviour changes when interacting with someone they are familiar with relative to people he/she is less familiar with.*

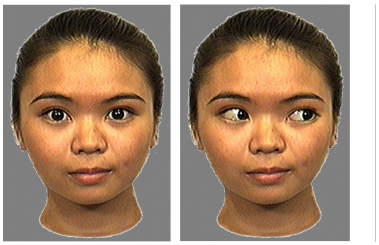
Short Games: *In this task, the researcher will play a series of short games with your child that will examine their cognitive development. Cognitive development means the development of language, thinking and understanding of the world and other people. The games are designed to tap motor abilities (such as grasping objects or crawling), visual, and language skills. During the task, the researcher will also ask you about certain abilities your child displays that would be difficult to observe during this short session. The main purpose of this task is for us to measure the child's developmental level and how it changes over time in the different visits.*

Scanning Faces and Objects: *We will also be looking at how babies scan faces and objects, i.e., how long they look at different regions of the face like the eyes or the mouth. We will do this using an "eye-tracker", which is a small camera that records the babies' eye movements while they look at the screen.*

Computer Animations: *During this task, your child will sit on your lap in front of a monitor showing various cartoons. This task will help us understand the babies' developing ability to pay attention to their environment and to switch their attention among different objects and events. To test this ability, we will show your child a series of fun cartoons designed to interest the child. While these cartoons are on, other animations appear on the screen, either to the left or to the right of the cartoon as illustrated below. We will then measure how long it takes the child to move their attention from the central cartoon and look towards the other animation. This will tell us how flexibly babies can switch their attention.*



Faces, Objects, and Sounds: *During this task your child will sit on your lap in front of a monitor. We will record the naturally occurring activity of your child's brain by placing a non-invasive "hairnet" or headband very gently on your child's head. The "hairnet" and headband have little sensors attached to them that pick up the brain's activity. The "hairnet" and headband are very quick to put on and are comfortable to wear. Once the "hairnet" or headband is in place your child will be presented with pictures on a computer monitor consisting of objects (e.g. toys, cars, etc.), a woman's face as she either looks straight to the front towards your child, or to the side (as shown below), or as she talks or plays 'Peek-a-boo'. Voice sounds like laughter or coughing, and non-voice sounds like toy or water sounds are also presented. The task continues as long as the child shows interest in looking, and listening. This task looks at how babies react to eye contact from human faces in contrast with looking at objects, and to voices versus non-voice sounds.*



The 24-36m follow-up

This visit will take place at one of the three collaborating research centres in London. Prior to the visit, we will send you a few questionnaires to fill in and bring with you to the visit. During the visit the researcher will ask you a number of questions regarding your child's development and they will make observations during a structured play session with the researcher. The structured play session consists of several activities designed to elicit social and communicative behaviours such as eye contact and language.

Please note that we always adapt testing sessions to each child's individual needs. While the tasks we use target the development of specific abilities over time, each session is adapted for each child's specific age and individual needs.

This means that we take as many breaks as the child needs to feed, rest, or play. We will do our best to make your visit as comfortable and enjoyable as possible.

After the session you will be kindly requested to fill in an anonymous feedback form, which will help us to improve our project in the future.

Optional collection of a DNA sample

We would like to ask your permission to obtain DNA samples from your child at each session using a cheek swab. The cheek swab is done by gently wiping a cotton wool bud on the inside of your child's cheek. We can let you do it, while one of us helps if you prefer. The procedure does not take long and does not involve any risks or side effects. It collects a few cheek cells, from which we can then extract DNA that will be analysed to help us find out more about the genetic factors involved in the development of the brain and autism. The DNA samples cannot be used for any other purpose than research within BASIS. Nobody outside of BASIS will ever be able to access these samples. The DNA sampling in this research does not qualify as genetic testing because these samples cannot be used for diagnostic or prognostic purposes. We have enclosed a more detailed FAQ sheet about obtaining DNA samples in this pack.

We should also stress that this aspect of your visit is entirely optional. If you feel that you do not wish to become involved in the cheek swab component of the study, you can still participate in the main study.

How the data will be used

The data collected during the visit will be coded so that all identifying information is removed. The anonymised cheek swabs will be sent securely to the Institute of Psychiatry (IoP), which is one of the centers affiliated with BASIS for analysis. They will be stored at IoP indefinitely for use in future BASIS studies only. We will use your child's anonymised data to publish scientific reports with important discoveries. We will also communicate our findings to the public through our website and other sources. Published reports on the results from BASIS will not mention individuals. The anonymised results of the research will be held in the BASIS Data Repository, which is intended to provide a shared resource for UK scientists and clinicians wishing to study infant siblings to better understand the early onset of autism. BASIS affiliated scientists will have secure access to the data collected.

Please refer to the FAQ sheets for further details

If you have any questions please contact

the BASIS Coordinating Centre:

Ms. Janice Fernandes on 020 7079 0761 or email basis@bbk.ac.uk

BASIS takes the protection of your personal information very seriously.
To find out more about how we do that please see our Privacy Policy.

Thank you

Appendix 6. Consent form signed by parents who agreed that their child participates in the study

Research Participant Consent Form For All Groups

British Autism Study of Infant Siblings

Information sheet 1 ☐

Information sheet 2 ☑

Name of Researchers: Jeanne Guiraud, Kim Davies, Helena Ribeiro, Leslie Tucker, Janice Fernandes, Sarah Fox, Mark Johnson, Mayada Elsabbagh

Please initial box

1. I confirm that I have read and understood the information sheet dated _____ for the above research network and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

3. I agree to take part on behalf of my child in the above research network. ☐

_____ _____ _____

Name of parent Date Signature

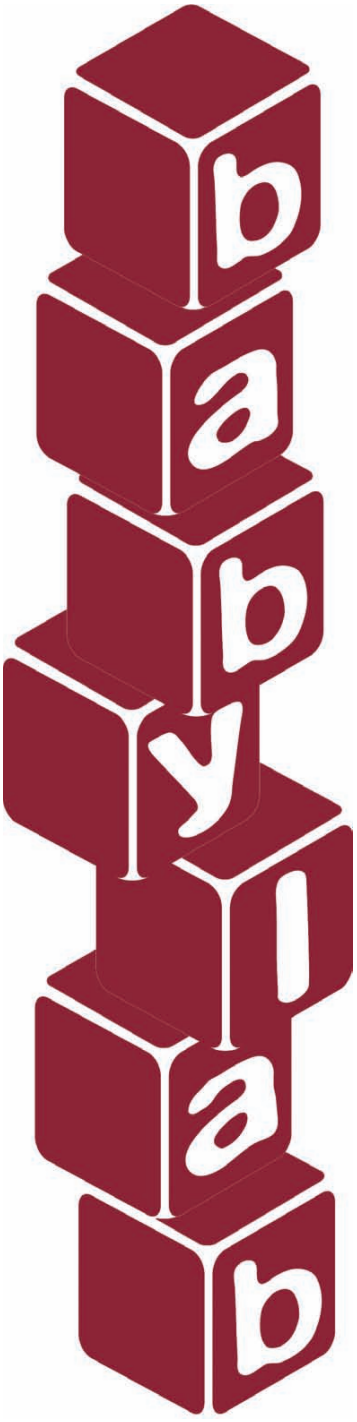
_____

Name of child

_____ _____ _____

Researcher Date Signature

Appendix 7. Certificate given to the child for their participation in the study



Birkbeck
UNIVERSITY OF LONDON

The Babylab

Centre for Brain and Cognitive Development

This infant scientist degree is to acknowledge that

has made an outstanding contribution to developmental psychology by participating in

Babylab Director
Professor Mark Johnson

Researcher

Date

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2006

Supported by the
Medical Research Council

Appendix 8. Communicative Development Inventory (Not included due to copyright restrictions)

Appendix 9. Autism Diagnostic Observation Schedule (Not included due to copyright restrictions)