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An investigation of language and communication, from infancy to middle-childhood, in children at high familial risk for Autism Spectrum Disorder (ASD)

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Volume I

Systematic Review

Empirical Research Project

Service Related Project

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Thesis submitted in partial fulfilment of the degree
of Doctorate in Clinical Psychology

Institute of Psychiatry, Psychology and
Neuroscience

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Contribution

I contributed to the BASIS-7 team by helping to score and code assessments, carry out data management and data entry. With the help of my supervisors, I planned the studies outlined in this thesis and carried out preparatory analyses on previous BASIS datasets, which provided the background for the current project.

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Exploring clinician's views on a lack of treatment response in a sub-group of young people being treated for Obsessive Compulsive Disorders (OCD) at the National Specialist (NS) OCD and Related Disorders Service.

Supervised by Dr Laura Bowyer and Dr Amita Jassi

Systematic Review

A systematic review of early markers of language development in autism spectrum disorder (ASD)

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4 Abstract

Atypical language development has been well documented in autism spectrum disorder (ASD) and may also form part of the broader phenotype. The principle aim of this review is to systematically examine the early predictors of language development in ASD and those at familial risk of developing ASD. In addition, it aims to examine whether early markers of language development are the same or different for those with ASD/familial risk and typically developing controls, and to examine the point in development at which markers emerge. PsychINFO, PsychArticles, Medline, Embase and Web of Science databases were searched systematically in line with PRISMA guidelines. Studies were included if they were a prospective longitudinal design and reported potential predictors of language outcomes in ASD and at risk populations at ≤ 3 years of age. Results from 37 papers, meeting inclusion criteria, were synthesised. Aspects of social attention, attention to and processing of speech, gesture use, responding to and eliciting interaction, motor skills and imitation predicted language outcome. There was no evidence that infant affect predicted language outcomes. Studies did not report the longitudinal association between neurocognitive abilities such as executive function and language outcomes. The results highlighted the need for future studies to examine causal mechanisms in order to uncover the origin of language impairment in ASD and also indicated a number of potential targets for early intervention in those at risk of the disorder. Intervention studies, as well as multi-level and multi-time point techniques, may elucidate causal mechanisms in future work.

5 Background

5.1 Language development in autism spectrum disorder (ASD) and the broader phenotype

Atypical language acquisition has been well documented in autism spectrum disorder (ASD) (Eigsti, de Marchena, Schuh, & Kelley, 2011) and language delay is one of the most common initial parental concerns (De Giacomo & Fombonne, 1998; Herlihy, Knoch, Vibert, & Fein, 2013). Language abilities in individuals with ASD can range from severe language delay with an estimated 10% of people with ASD never developing functional language skills (Hus, Pickles, Cook, Risi, & Lord, 2007), to intact skills on standardised language tests (Kjelgaard & Tager-Flusberg, 2001). However, even those with intact language skills have difficulties with the pragmatic use of language, i.e. the use of language for communicative purposes (Bauminger-Zviely, Karin, Kimhi, & Agam-Ben-Artzi, 2014). Developmental trajectories differ among individuals with ASD. Some show initial impairments, followed by a period of accelerated language development such that they no longer meet diagnostic criteria for language impairment (Szatmari, Bryson, Boyle, Streiner, & Duku, 2003), whilst others show the initial stages of language acquisition followed by developmental regression in the second year (Pickles et al., 2009). Early language ability is a key prognostic indicator for long term outcomes for children and adults with ASD (Anderson, Liang, & Lord, 2014; Lord & Ventner, 1992; Pickles, Anderson, & Lord, 2014; Szatmari et al., 2003), therefore improved understanding of language development in ASD is clinically imperative.

Family members who do not have a diagnosis of ASD, may display subclinical autistic traits known as the “Broad Autism Phenotype (BAP)” (Bolton et al., 1994; Losh, Childress, Lam, & Piven, 2008). The BAP constitutes the behavioural and brain characteristics associated with ASD which are found both in affected individuals and

their relatives (Bolton et al., 1994; Pickles et al., 2000; Piven, Palmer, Jacobi, Childress, & Arndt, 1997). With respect to language differences, several studies have reported that parents of children with ASD show difficulties with pragmatic language (Losh et al., 2008; Losh & Piven, 2007; Piven et al., 1997; Whitehouse, Barry, & Bishop, 2007). Atypical language development has also been reported among infant siblings of children with ASD (Hudry et al., 2014; Mitchell et al., 2006; Paul, Fuerst, Ramsay, Chawarska, & Klin, 2011) with evidence indicating that language deficits may persist to middle childhood (Ben-Yizhak et al., 2011; Gamliel, Yirmiya, Jaffe, Manor, & Sigman, 2009). However, not all studies have reported language difficulties among first degree relatives (Pilowsky, Yirmiya, Shalev, & Gross-Tsur, 2003). Nonetheless the evidence suggests that atypical language profiles may be a feature of the broader phenotype and that problems with language may be a persistent area of difficulty for some family members. As such, it is important to improve understanding of the factors that contribute to language outcomes in ASD and the broader phenotype and how these may differ from those in typical development. This will provide insight into whether or not language development is qualitatively different in ASD and the BAP.

5.2 Language acquisition in typical development

Typically developing (TD) infants show a bias towards listening to speech from birth (Vouloumanos & Werker, 2007) and rapidly learn to understand and produce words, with first word understanding occurring at approximately 9 months and production commencing at approximately 12 months (Fenson et al., 1994). The evidence suggests that this rapid acquisition of language occurs in the context of perceptual, computational, neural and social constraints (Kuhl, 2004, 2010). For example, young infants' sensitivity to the changes that occur at the phonetic boundaries between categories facilitates phonetic learning (Eimas, Siqueland, Jusczyk, & Vigorito, 1971; Werker & Lalonde, 1988), whilst statistical learning

mechanisms are thought to lead to increasing specialisation for phonetic sequences that occur in the infant's native language between 6-12 months of age (Jusczyk & Luce, 1994; Werker & Lalonde, 1988). Similarly, word learning involves the use of the sequential probabilities between adjacent syllables to parse speech into potential words (Saffran, 2002).

Prosodic cues also help infants to identify words. For example, most multisyllabic English words begin with stress in the first syllable, a strong-weak stress pattern, trochaic stress (e.g. pencil), whereas other languages such as Polish have a weak-strong, iambic pattern (e.g. exist) (Cutler & Carter, 1987). By approximately 7-8 months of age infants use this stress information to detect words in continuous speech (Curtin, Mintz, & Christiansen, 2005; Jusczyk, Houston, & Newsome, 1999). The statistical and prosodic information in language input are thought to influence the brain's ability to learn language, 'bootstrapping' native language learning (Morgan & Demuth, 1996).

Social learning theory posits that social interaction plays an important role in language learning (Bruner, 1983). This has been upheld by evidence showing that phonetic learning is enhanced by social interaction and that social feedback plays an important role in word learning (Goldstein, King, & West, 2003; Kuhl, Tsao, & Liu, 2003). The role of social interaction in language learning has traditionally been examined in the context of joint attention (JA) – the ability to coordinate the attention of at least two individuals to an object or event (Bruner, 1983; Carpenter, Nagell, Tomasello, Butterworth, & Moore, 1998; Tomasello & Farrar, 1986). JA is thought to facilitate language learning by creating a shared referential framework within which the child may experientially ground the language used by adults (Carpenter et al., 1998). Numerous longitudinal studies have documented the role of JA in language learning (Carpenter et al., 1998; Morales, Mundy, & Rojas, 1998; Mundy & Gomes, 1998), however the specific mechanisms that underlie this association have not been clearly delineated. More recently – the 'social gating

hypothesis' (Kuhl, 2007) has been proposed, suggesting that social interaction 'gates' computational learning by ensuring that learning focuses on the speech in the child's environment. In addition, early domain-general cognitive skills such as memory and representational competence have been associated with language skills longitudinally (Rose, Feldman, & Jankowski, 2009). However, the specific processes by which language learning mechanisms, social processes and cognitive skills contribute to language acquisition are not fully understood in TD.

5.3 Models of language acquisition in ASD

Theoretical accounts of language development in ASD can be broadly classified into two domains (Yoder, Watson, & Lambert, 2015). Child-focused accounts view variation in language development as secondary to other child factors - pertaining to their social, cognitive, or motor development – whereas transactional models view variation in language as secondary to the bidirectional interchange that takes place between a child and others (Yoder et al., 2015). The current review seeks to examine how child-focused factors map onto language outcomes. As such, child focused theories shall be briefly outlined.

Theories of social attention and interaction propose that an initial impairment in the ability to attend to social and affective cues give rise to deficits in joint attention, which in turn impacts on language development (Dawson et al., 2004). This initial deficit in social orienting may be due to 'social motivation' deficits, i.e. an inability to find social stimuli rewarding (Chevallier, Kohls, Troiani, Brodtkin, & Schultz, 2012; Dawson et al., 2005) or may be a consequence of impairments in processing social information - namely biological motion (Allison et al., 2000; Kaiser, Shiffrar, & Pelphrey, 2012). Specifically, it has been proposed that deficits in gaze perception could give rise to impairments in joint attention (Butterworth & Jarrett, 1991; Elsabbagh et al., 2012), which in turn could impact on language development.

These theories mirror models of ASD, explaining language difficulties as a consequence of social attention and interaction difficulties.

It has also been proposed that early deficits in imitation may be a primary difficulty in ASD, disrupting early social interaction, leading to a cascade of social and communication deficits (Rogers & Pennington, 1991). In line with this theory, the 'Mirror Neuron (MN)' hypothesis proposes that disturbances in the MN system in the frontal cortex, which is active during actions performed by the self and others, gives rise to deficits in imitation in ASD (Dapretto et al., 2006; Williams, Whiten, Suddendorf, & Perrett, 2001). In terms of social development, imitation is thought to help to establish coordinated activities and shared understating with others (Stone, Ousley, & Littleford, 1997). In terms of language development, imitation is thought to be a precursor to symbolic functioning (Piaget, 1966) and may also be an important learning strategy (Meltzoff & Keith, 1983). Therefore, deficits in imitation could give rise to social, communication and language difficulties in ASD.

A number of theories propose that general abilities, for example neurocognitive and motor capacities, underlie both ASD and language difficulties. Neurocognitive theories propose that the core difficulties in ASD arise from deficits in cognitive processes involving executive control, potentially arising from abnormalities in the prefrontal cortex (Kriete & Noelle, 2015; Ozonoff, Pennington, Rogers, & others, 1991). In terms of language development, an impairment in attention shifting could give rise to joint attention difficulties, which requires rapid shifting of attention between objects and people (McEvoy, Rogers, & Pennington, 1993) and this in turn could impact upon language development. Theories of conceptual development propose that diminished top-down influences on information processing lead to diminished influences of categorisation on discrimination (Soulières, Mottron, Saumier, & Larochelle, 2007). In terms of language development, this could give rise to difficulties with the formation and organisation of lexical categories (Dunn, Gomes, & Sebastian, 1996). It has also been suggested that sensory and motor

deficits may underlie social communication difficulties in ASD (Belmonte et al., 2004; Donnellan, Hill, & Leary, 2009; Leary & Hill, 1996). The 'theory of embodied cognition' proposes that cognition emerges as a result of sensorimotor activity as the infant learns through interaction with its environment (Smith & Gasser, 2005). According to this theory, sensorimotor difficulties could reduce the opportunity for learning language in ASD.

5.4 The contribution early screening and high-risk sibling studies

Until the 1990's, ASD was rarely diagnosed before the age of 3-4 years (Charman & Gotham, 2013) and research examining early markers of ASD relied upon retrospective data (Palomo, Belinchón, & Ozonoff, 2006). However, several developments have allowed researchers to begin to identify those at risk of developing ASD and prospectively examine early markers for the disorder. The development of screening instruments such as the CHAT (Baron-Cohen, Allen, & Gillberg, 1992) and M-CHAT (Robins, Fein, Barton, & Green, 2001) facilitated the early detection of those at risk in the population as well as in clinical samples. In addition, one of the 'gold standard' diagnostic tools, the ADOS, was revised to include a toddler module (Luyster et al., 2009) facilitating ASD diagnosis in toddlerhood.

Recently, studies have begun to prospectively study younger siblings of children already diagnosed with ASD. Due to the high heritability of ASD (Tick, Bolton, Happé, Rutter, & Rijdsdijk, 2015), these 'infant siblings' are at high risk of developing ASD, with estimates suggesting that approximately 20% reach a diagnosis of ASD by their third birthday (Ozonoff et al., 2011). A further 10-20% of these infants develop sub-clinical autistic symptoms or other developmental disabilities (Messinger et al., 2013). High-risk sibling designs seek to uncover early markers of ASD as well as the broader phenotype and have the potential to highlight possible compensatory

mechanisms and/or protective factors among those at familial/genetic risk who do not show atypical outcomes (Elsabbagh & Johnson, 2010a).

With specific reference to language acquisition, longitudinal designs in those at risk of developing ASD can improve understanding of the developmental processes that contribute to language outcomes in ASD, as well as those at heightened risk.

Improved understanding of how early developmental markers map onto later functioning can help to inform theoretical accounts of language development in ASD and the broader phenotype. In addition, these studies have the potential to indicate whether mechanisms of language development are the same or different among these groups. Evidence of similar developmental mechanisms would be in keeping with the BAP and the view that that autistic traits are continuous, quantitative traits that vary in the general population (Constantino & Todd, 2005; Hoekstra, Bartels, Verweij, & Boomsma, 2007; Whitehouse, Hickey, & Ronald, 2011). Children with ASD and/or those at heightened risk may employ the same language learning mechanisms but may be less efficient in doing so due to impairments in other supporting mechanisms such as memory and attention (Arunachalam & Luyster, 2015). On the other hand, language development may be qualitatively different in ASD and/or HR siblings and sub-served by different developmental mechanisms. Disruptions in typical language learning mechanisms may lead to the development of alternative routes to language in ASD/HR sibling. These insights can potentially highlight targets for early intervention and hence improve long term outcomes for people with ASD and/or those who are at increased risk.

5.5 Rational and aims

Language and atypical social communication in ASD are typically assumed to be interlinked. However, longitudinal studies of early markers of language development in ASD and the BAP have not been systematically examined. In

addition, the predictors of language development in TD have not been clearly defined. The current review seeks to systematically examine prospective, longitudinal studies of early markers of language development in ASD and high-risk siblings – encompassing social, neurocognitive, sensory and motor skills. The review shall include participants from early screening studies and clinically ascertained samples, as well as high-risk sibling designs.

The principle aim of this review is to identify early markers for language development in ASD and HR siblings. As outlined above, this will inform theoretical accounts of language development ASD and help to identify targets for early intervention. The second aim is to identify similarities and differences between early markers for language development in HR siblings/ASD and LR siblings/typically developing (TD) controls. This may provide insight into whether or not language development is qualitatively the same in ASD and HR siblings. The third aim is to identify the point in development at which early markers have been identified. Atypical developmental trajectories have been reported as early as the first six months of life in ASD (Jones & Klin, 2013) therefore it is important to identify the time point at which markers are identified in order to begin to differentiate mechanisms that may contribute to language outcomes directly, as opposed to those that may be the consequence of brain adjustment to non-optimal early functioning (Johnson, Jones, & Gliga, 2015). Finally, the potential specificity of predictors to aspects of language outcome (i.e. expressive and receptive language, structural language) shall be explored.

6 Method

6.1 Literature search

This review is based on a systematic search of longitudinal peer-reviewed publications published between 1980 and June 2015. The search was carried out in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Moher, Liberati, Tetzlaff, & Altman, 2009) guidelines. A computer search of the online databases Ovid SP (including PsychINFO, PsychArticles, Medline and Embase) and Web of Science (all databases) was carried out on 1st June 2015. Title, Abstracts, Keywords and Author Keywords were searched for the terms “autis*”, “Asperger*” or “pervasive developmental disorder*”. This was combined with the terms “language”, “speech”, “word*”, “verbal*”, “vocab*” or “linguistic” as well as the terms “infant*”, “toddler*”, “pre\$chooler*”, “predict* and child*”, “precurs* and child*”, “longitudinal and child*” or “prospective and child*”. Truncation and wildcard symbols were used as appropriate. The search was limited to English language publications, human studies and studies published after 1980. Reference lists of relevant papers and reviews were screened to identify additional papers, not identified in the online search.

Following the removal of duplicates (see Figure 1), 2511 publications were screened using the following inclusion criteria: i) prospective longitudinal designs; ii) report potential child predictors of language in ASD or at risk populations as the main independent variable (not mediators or moderators of other variables); iii) report potential predictors measured at ≤ 3 years; iv) report standardised/reliable measures of language outcome; v) report outcomes assessed < 18 years of age. Retrospective and qualitative studies, as well as studies where the $N \leq 10$ per group, were excluded. In addition, intervention studies, studies of second language learning, studies of developmental regression or other developmental disabilities

associated with ASD (e.g. genetic syndromes) and studies that examined potential predictors that were not specifically child variables (e.g. environmental, parent-child interaction, maternal synchrony) or measure medical status, physical development, general cognitive ability, severity of autistic symptoms, measures that form part of the diagnostic criteria (e.g. age at first words), or measure early language development were excluded. Finally, book chapters, conference abstracts dissertations and lectures were excluded.

Thirty-seven of the 124 papers screened on the basis of the full-text were included in the review. Twenty were excluded as they did not meet age criteria, 22 were excluded as the predictor did not meet criteria, five were not peer reviewed articles, three did not meet the specified language outcome criteria, 13 did not report a longitudinal association between a marker and outcome, 23 were intervention studies and one had fewer than 10 participants. Twenty-five percent of the included studies were checked against the inclusion/exclusion criteria by an independent researcher and no discrepancies were noted.

6.2 Data extraction

Studies were categorised according to the recruitment method used. These included HR sibling designs, early screening studies, clinically ascertained samples and studies using other or unspecified recruitment methods. The following methodological information was extracted: sample size, percentage male (% male), age of assessments in months (both predictor and outcome), type of predictor(s) and language measure(s) used at outcome. In addition, where one or more publication had overlapping or the same sample this was indicated.

6.3 Data quality assessment

An adapted version of the data quality checklist for observational studies (Downs & Black, 1998) used in a previous systematic review of longitudinal outcomes in ASD

(Tobin, Drager, & Richardson, 2014) was used in the current study. The checklist was modified to include 16 items relevant to the current review and instructions were amended where necessary (see appendix A). Twenty-five percent of the included studies were rated by an independent researcher to calculate inter-rater reliability.

6.4 Data synthesis

Results pertaining to the variables of interest were summarised. Group differences in the independent variables of interest were summarised for case-control designs when these were reported in the original publication. Associations between independent variables relevant to the current review and language outcomes were then reported. The effects of covariates and mediating factors were summarised where these were reported in the original publication. Results are summarised in Tables 1-6 by domain, in order of the age at which the predictor variable was first assessed. The studies were then summarised to illustrate potential causal mechanisms between markers and language outcome (see figure 2). Between group differences in language outcomes for case-control designs and specificity of associations with different aspects of language were also summarised.

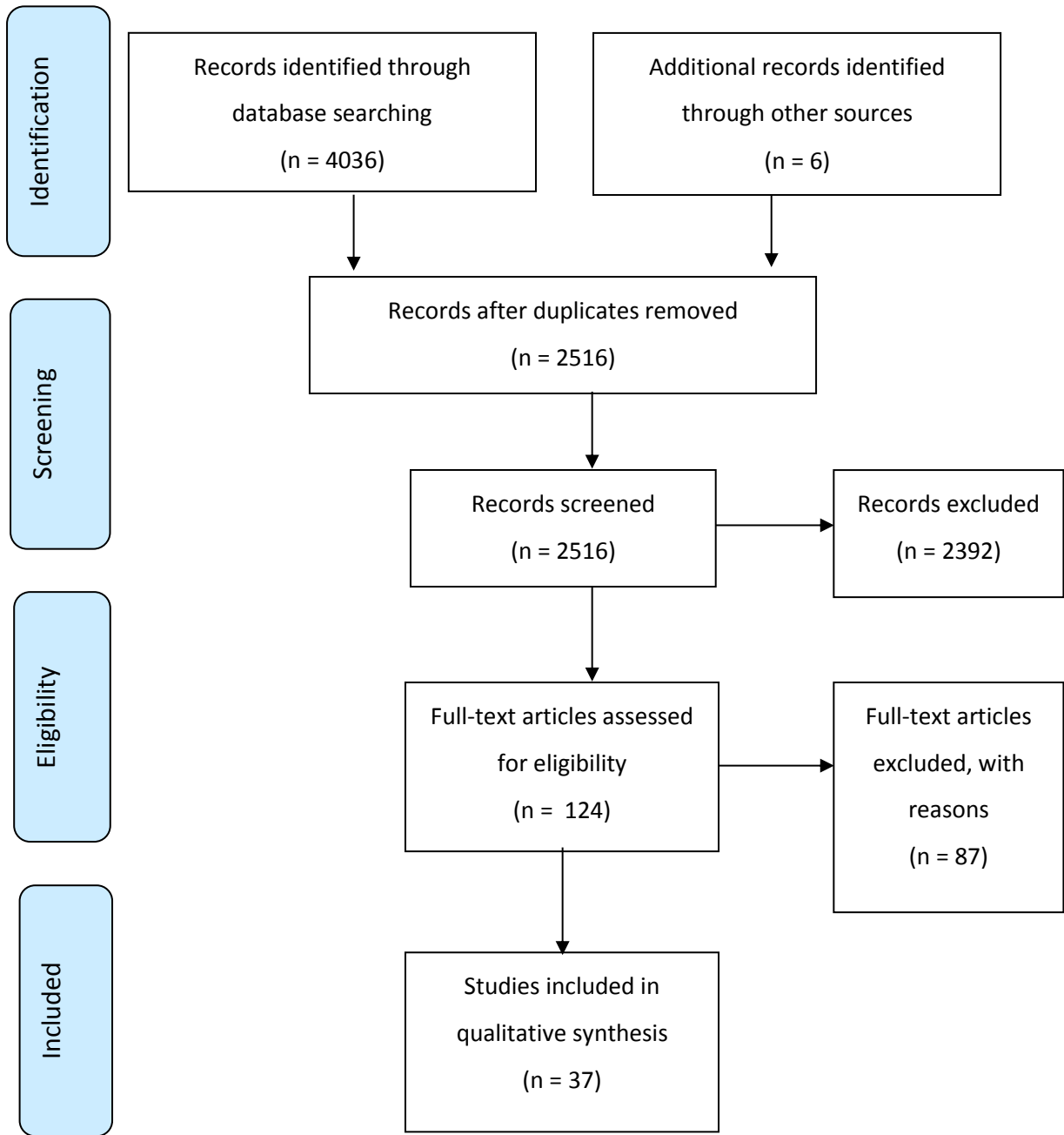


Figure 1: Prisma flow chart of screening and inclusion process

7 Results

7.1 Study design and methods

7.1.1 Design and recruitment

All studies included in the review were longitudinal designs. The majority of the studies were HR infant sibling designs (n=15), followed by clinically ascertained samples (N=7), screening studies (N=6), clinically ascertained/screening study (N=1) other research recruitment (N=5), unspecified recruitment (N=2) and community screening and referral (N=1).

7.1.2 Sample characteristics

The review includes 3186 (65% male) participants. There were 1141 (82% male) ASD, 192 (85% male) referred to a clinic for suspected ASD, 589 (52% male) HR participants, 465 (48% male) LR, 265 (75% male) TD and 534 (67% male) DD. The average age at entry to the study was 19 months with ages ranging from 4 to 35 months.

7.1.3 Predictor variables

The predictor variables examined can be broadly categorised into those examining social attention and affect (table 1; N=5), attention to and processing of speech (table 2; N=8), pre-speech and gesture use (table 3; N=2), responding to and eliciting interaction (table 4; N=13), motor skills (table 5; N=6) and imitation (N=3).

7.1.4 Language outcome measures

Measures used to evaluate language outcomes included the Bayley Scales of Infant Development (BSID) (Bayley, 1993), the MacArthur Communicative Development Inventory (MCDI) (Fenson et al., 1993), the Mullen Scales of Early Learning (MSEL), the Vineland Adaptive Behaviour Scale (VABS) (Sparrow, Cicchetti, & Balla, 2005),

the Clinical Evaluation of Language Fundamentals (CELF) (Semel, Wiig, & Secord, 2003), the Reynell developmental language scales (Reynell, 1985), the Preschool Language Scale (PLS) (Zimmerman, Steiner, & Pond, 2002), the Sequenced Inventory of Communication Development (SCID) (Hendrick, Semel, & Tobin, 1984), the Children's Communication Checklist (CCC) (Bishop, 2003), the Differential Ability Scales (Elliot, 2007), the Wechsler Intelligence Scale (WISC) (Wechsler, 1991), the Peabody Picture Vocabulary Test (PPVT) (Dunn & Dunn, 1997), the Communication and Symbolic Behaviour Scales- Developmental Profile Behaviour Sample (CSBS) (Wetherby & Prizant, 2002) and an Unstructured Communication Sample (UCS), as well as a reliable measure of lexical density (Yoder, 2006). A number of studies used more than one measure and/or used an aggregate measure based on several scales (see tables 1-6).

7.1.5 Quality assessment

Summary results of the quality assessment ratings are provided in table 1 below. Full item scores for each study are presented in appendix A. Quality assessment ratings ranged from a minimum of 10 to a maximum of 16 out of a total of 16. The average rating was 14.1. Twenty-five percent of the studies were rated by an independent researcher and there was 90% agreement between raters. Reliability analysis, calculated using the intraclass correlation coefficient ((ICC; Shrout & Fleiss, 1979) indicated very good inter-rater reliability (ICC = .981; 95% CI = .929 -.995; $p < .0001$).

Table 1 Summary of quality assessment (QA) ratings with studies ranked in terms of QA scores

Study	QA Score	Study	QA Score	Study	QA Score	Study	QA Score
Adamson et al 2009	10	Luyster et al 2007	13	Paul et al 2007	15	Hellendoorn et al	15
Droucker et al 2013	12	Yirmiya et al 2006	13	Young et al 2009	15	Yoder et al 2015	15
Young et al 2011	12	Elsabbagh et al 2014	14	Curtin & Vouloumanos 2013	15	Stone & Yoder 2001	15
Bhat et al 2012	12	Charman et al 2005	14	Gillespie-Lynch et al 2015	15	Weatherby et al 2007	15
Ben-Sasson & Gill et al 2014	12	Thurm et al 2007	14	LeBarton & Iverson 2013	15	Watson et al 2010	16
Plumb & Wetherby 2013	12	Anderson et al 2007	14	Leonard et al 2015	15	Campbell et al 2014	16
Charman 2003 and Charman et al 2003	13	Paul et al 2008	14	Ference & Curtin 2015	15	Malesa et al 2013	16
Talbott et al 2015	13	Bedford 2015	14	McDuffie et al 2005	15	Lombardo et al 2015	16
Stone et al 1997	13	Kuhl et al 2013	15	Seery et al 2014	15	Yoder 2006	16
Ference & Curtin 2013	13						

7.2 Early markers of language outcomes

The results of the studies included in the review are summarised below and in tables 2-7 and figure 2.

7.2.1 Attention and affect during processing of faces and social scenes (table 2)

Attention to faces emerged as one of the earliest predictors of expressive language (EL) in HR siblings. HR and LR infants (between 6-18 months) looked longer at faces than at a non-social stimulus (checkerboard) but the magnitude of this difference was smaller in the HR group than in the LR group (Droucker, Curtin, & Vouloumanos, 2013). When the groups were examined together, there was no significant association between preference for faces and EL. Attention to the checkerboards was negatively associated with EL at 18 months, but this was driven by a significant association in the LR group. When groups were examined separately, preference for faces (over checkerboards) between 6-12 months was positively associated with later EL in HR siblings whereas attention to faces between 6-12 months was negatively associated with EL in controls (Droucker et al., 2013).

Two studies examined attention to the eyes relative to the mouth – eye-mouth index (EMI) in relation to language outcomes among HR siblings. Young et al. (Young, Merin, Rogers, & Ozonoff, 2009) reported that HR and LR siblings did not differ in terms of EMI, when interacting with their mothers. Across both HR and LR groups, greater attention to the eyes relative to the mouth during the still face procedure at 6 months was associated with poorer EL at 18 and 24 months, as well as slower EL growth and poorer RL at 24 months. There were no group differences in the association between EMI and language outcome (Young et al., 2009). Similarly, Elsabbagh et al. (2014) reported that HR and LR siblings did not differ in terms of EMI while viewing simple and complex social scenes. When groups were examined together (controlling for clinical outcome and NVIQ), more looking towards the mouth at 7 months was associated with better EL at 36 months

(Elsabbagh et al., 2014). The association between EMI and EL was significant when controlling for RL, suggesting that there is a specific association between EMI and EL.

A further study examined social attention and EMI in toddlers with ASD. Toddlers who showed limited social attention did not show a significant increase in verbal ability or communication scores (Campbell, Shic, Macari, & Chawarska, 2014). Those who showed greater attention to the mouth relative to the eyes showed an improvement in language outcomes; but had higher verbal ability relative to their communication scores suggesting that they had better formal language relative to their functional language.

Finally, two HR sibling studies examined infant affect during mother-infant interaction. Affect was not associated with language outcomes (Yirmiya, Gamliel, Shaked, & Sigman, 2007; Young et al., 2009) in either study suggesting that affect may not be a predictor of language development.

Table 2 Attention and affect during processing of faces and social scenes

Study		Design and Sample N (%Male) Age (months)	Methods and Results	
1	Yirmiya et al. 2007	High Risk 21 HR (61%); 21 LR (61%) 4 & 14 m	Predictor Gaze and affect during the still face procedure Group differences No difference: gaze to the face, hands/body, averted, to objects, or closed) HR > LR: neutral affect during the still face procedure at 4m.	Outcome BSID-II Group differences The HR group had a significantly lower developmental language age than the LR group at 14 months.
			Affect and language outcomes No significant association between neutral affect and language outcomes in either group. (Associations between gaze and language outcomes not reported).	
2	Droucker et al 2013	High Risk 36 infants: 14 HR and 22 LR infants (gender not reported) 6, 8, 12 & 18m	Predictor Attention to faces and checkerboards, infant directed (ID) and adult directed (AD) speech at 6, 8, 12 & 18m. Group differences No difference: attention to speech Faces v checkerboards: Both groups looked significantly longer at faces than checkerboards but the magnitude of this difference was greater in the LR group. Looking time to faces: no group differences Looking time to checkerboards: HR > LR. Group by age interaction: HR groups' overall looking time greater than the LR group at 8 and 18 months. Speech type by age interaction: infants look more at ID than AD speech at 12 and 18 months.	Outcome MCDI-EL Group difference The LR group scored significantly higher on the MCDI EL scale at 18 but not 12 months.

			Attention to speech and faces and language Both groups: No significant associations between preference for faces (over checkerboards) and MCDI EL. Attention to the checkerboard from 6-12m negatively associated with MCDI EL at 18 months (association driven by TD group). HR group: preference for faces (over checkerboards) between 6-12m positively associated with MCDI EL at 18m. TD only: Negative association between attention to faces at 6-12m and MCDI EL scores at 18 months Both groups: Preference for ID speech (over. AD speech) at 6-12m was positively associated with MCDI EL at 18m , whereas attention to AD speech was negatively associated with language outcome (LR only when groups examined separately).	
3	Young et al 2009	High Risk 33HR sibs (52%) 25 TD sibs (60%) 6,12,18 &24m	Predictor Eye–mouth index (EMI), gaze aversion and affect during the still face procedure Group differences No difference in EMI, gaze aversion or affect at 6m	Outcome MSEL RL & EL, Vineland EL & RL, MCDI EL, Group differences LR>HR: RL but not EL at 24m
			EMI, gaze aversion, affect and language Gaze aversion and affect at 6m not related to language outcomes. Higher EMI (greater fixation on the eyes relative to the mouth) at 6m was associated with decreased MCDI EL at 18 and 24m, and negatively related to MSEL EL at 24 months and Vineland EL at 24m. Higher EMI at 6 months was also associated with slower EL growth. EMI was negatively associated with MSEL RL at 24m. No significant effects of group (or excluding 3 participants with ASD). EMI during interactive and re-engagement phases (but not the unresponsive phase) was negatively associated with EL outcome.	
4	Elsabbagh et al 2014	High Risk 104 infants: 54 HR (39 %) 50 LR (42 %) 7,14,24 & 38m (HR ASD = 17; HR DD =12; HR typical =24).	Predictor EMI in simple and complex social scenes. Group differences No differences: EMI according to risk status or clinical outcome	Outcome MSEL EL &RL
			EMI and language outcomes Both groups: Negative EMI (more looking towards the mouth) at 7m during complex social scenes was associated with better EL but not RL at 36m (controlling for NVIQ and diagnostic status at outcome). EMI at 14 m did not predict EL or RL. The relationship between 7m EMI and 36m EL remained significant even after controlling for EMI during simple social scenes and RL at outcome.	

5	Campbell et al 2014	Clinical ascertainment 65 (80%) toddlers with ASD 21 & 26m (N = 48)	Predictor Visual attention (% time looking at eyes, eyes-to mouth & the scene) during 'dyadic bids' for social engagement with Child Directed Speech (CDS) <i>Subgrouping based on visual attention:</i> Three subgroups were defined: (1) limited attention to the social scene and face; (2) divided attention to eye & mouth equally and (3) focused more on the mouth/lower EMI.	Outcome MSEL VDQ & VABS communication scale
			<i>Social attention and language</i> VQQ and VABS communication increased in all groups but this was not significant in group 1 after correcting for multiple comparisons, whereas group 2 and 3 did show a significant increase on both measures. Group 3 had significantly higher VDQ than VABS communication score indicating that they have better formal language compared to their functional language. Intensity of intervention was included as a covariate in all analyses.	

7.2.2 Attention to and processing of speech (table 3)

Sensitivity to language specific stress patterns was amongst the earliest predictors of language outcomes, though the findings suggest that this may be a more important predictor in TD infants. In a study by Ference and Curtin (2013), LR infants showed greater attention to speech sounds and greater preference for trochaic over iambic stress patterns, as well as better RL at 12 months. Examining, HR and LR groups together, preference for trochaic stress (words with strong-weak stress) over iambic stress (weak-strong stress) at five months was positively associated with later RL, though this was significant in the LR group only when groups were examined separately (Ference & Curtin, 2013). In a second study, the same authors reported that HR siblings had greater difficulty in matching word-object pairings than LR controls. Only the HR group was reassessed at 24 months; the ability to map differentially stressed words to objects at 12 months positively predicted EL in the HR infants (Ference & Curtin, 2015).

A number of studies have used event related potential (ERPs) and functional magnetic resonance imaging (fMRI) to examine attention to and processing of speech in relation to later language outcomes. HR infant siblings showed greater P150 amplitudes to repeated speech sounds, over frontal electrodes at nine months, which is likely to reflect altered attentional processes (Seery, Tager-Flusberg, & Nelson, 2014). There were no associations between ERPs and language outcome in the LR group. In the HR group, P150 amplitudes to speech sounds were positively associated with EL at 18 months, suggesting that altered attentional processing facilitated better language outcomes.

In a further study of toddlers with ASD, Kuhl and colleagues (Kuhl et al., 2013) reported that toddlers with more severe ASD symptoms showed more diffuse right hemisphere activation to known words when compared to those with less severe symptoms and controls. In the ASD group, ERPs during speech processing were associated with RL outcome at four and six years of age, when controlling for initial cognitive ability. The TD group was not re-assessed. Finally, in an fMRI study of 27 month old toddlers with ASD, Lombardo et al (2015) reported that those with ASD

and poorer language outcomes had reduced activation in the left superior temporal cortex during speech processing, when compared with those with ASD and good language outcomes, and control groups. A combination of fMRI (percent signal change during speech processing in the left superior temporal cortex) and clinical measures at baseline outperformed either behavioural measures alone or fMRI alone in classifying 'good' or 'poor' language outcomes at 38 months in ASD participants.

Another set of studies examined early preference for speech over non-speech sounds and preference for infant directed (ID) over adult directed (AD) speech in relation to language outcomes. In a study of HR infant siblings it was reported that LR siblings showed a significant preference for speech whereas the HR siblings did not. When both HR and LR groups were examined together, speech preference at 12 months was associated with EL at 18 months, however there were no significant associations when groups were examined separately (Curtin & Vouloumanos, 2013). This may have been due to differences in the marker (potentially driving the association when groups were examined together) or to power issues when groups were examined separately. Droucker et al (2013) reported that HR and LR groups did not differ in terms of their preference for speech at 6-12 months. When groups were examined together, preference for ID speech (over AD speech) was positively associated with EL at 18 months, whereas attention to AD speech was negatively associated with language outcome. However, when groups were examined separately these associations were only significant in the LR group.

Two further studies examined attention to child directed speech (CDS) speech in young toddlers with ASD. Twenty-six month old toddlers with ASD spent less time listening to CDS than controls. Only the ASD group was re-assessed. The time they spent listening to CDS was positively correlated with RL outcomes approximately 1 year later (Paul, Chawarska, Fowler, Cicchetti, & Volkmar, 2007). Similarly, in a study of toddlers with Autism, attention to CDS speech at 35 months was positively associated with EL and RL 12 months later when measured by looking time and EL when measured by vagal activity (Watson, Baranek, Roberts, David, & Perryman, 2010). However, the association with EL and RL was no longer significant when

controlling for entry level communication ability, whereas the association between vagal activity during CDS and EL accounted for additional variance in EL after controlling for entry level communicative ability.

Table 3 Attention to/processing of speech

	Study	Design and Sample N (%Male) Age (months)	Methods and Results	
6	FERENCE & CURTIN 2013	High Risk* 26H HR (50%); 30 LR (50%) 5 months; 12months	Predictor 'Stress Preference' (preference for trochaic over iambic word stress). Group differences in stress preference LR> HR: attention to speech sounds; preference for words with strong-weak (trochaic) over weak-strong (iambic) word stress.	Outcome MCDI RL & EL Group differences in language outcomes LR >HR: RL 12 months. No difference in EL.
			Relationship between stress preference and language outcome All groups: Preference for trochaic stress over iambic stress was positively associated with MCDI RL but not EL in all infants (significant in the TD only).	
7	Seery et al 2014	High Risk 40 HR (53%); 45 LR (51%) (35 HR & 45 LR included in the final sample after excluding those with autism at 36 months). 9, 12 & 18m	Predictor RPs (P150) to repeated speech sounds. Group differences HR>LR: P105 amplitudes over frontal electrodes at 9m. No group differences in ERP amplitudes to deviant speech sounds.	Outcome MSEL EL and RL Group differences No differences in RL or EL at 6 months. HR < LR: EL at 12 months; RL & EL at 18 months.
			ERP responses and language HR: P150 amplitudes to speech sounds, over frontal and central electrodes, positively associated with EL at 18m. LR: no significant associations.	
8	Curtin & Vouloumanos 2013	High Risk HR N=31 (52%); LR N=31 (46%) 12 & 18m	Predictor Preference for speech over non-speech auditory stimuli Group differences	Outcome MCDI EL, RL Group differences No difference at 12m. LR>HR: EL & RL at 18m.

			No differences: speech preference at 12m. The LR group showed a preference for speech over non-speech but the HR group did not.	
			Speech preference and language Both groups: Speech preference index (speech minus non-speech) associated with MCDI EL (not significant in either group separately). Only marginally significant when controlling for general ability (Mullen ELC).	
9	Ference & Curtin 2015	High Risk* 19 LR (42%) & 19 HR (42%) HR =12 &24m; LR= 12m	Predictor Ability to map differentially stressed labels to objects Group differences There we no group by trial type interactions on the 'switch task' (a measure of the ability to map differentially stressed labels to objects). LR group looked significantly longer at mismatched compared to familiar word object pairing, whereas the HR group did not differ between mismatch and familiar trials, suggesting that they did not match word-object pairings.	Outcome MCDI RL & EL; MSEL EL & RL Group differences LR >HR: RL. No differences in EL.
			Ability to map differentially stressed labels to objects and language outcomes in the HR group HR: Ability to map differentially stressed labels to objects at 12 months positively predicted EL on the MCDI and MSEL at 24m (controlling for 12m general cognition). *Sample same as Ference and Curtin (2013)	
10	Kuhl et al 2013	Research recruitment ASD: 24 (70%); TD: 20 (85%) ASD =25m, 4 & 6 years & 73m; TD = 25m	Predictor ERPs (MMN) during speech processing (known and unknown words) Group differences in ERP amplitudes to speech TD children show a focal response to known words at a single electrode site in the left temporal/parietal region. Children with ASD and less severe symptoms showed a similar pattern of ERP response to TD Children with more severe ASD symptoms and showed significant differences in ERP amplitudes (more diffuse right	Outcome PLS4 RL

			hemisphere activation) to known words when compared with children with less severe symptoms and controls. No differences in ERP amplitudes between the less severe ASD group and the controls.	
			Association between ERP amplitude and language outcomes in ASD Baseline ERP amplitude at P3 was negatively associated with RL at 4 and 6 years. Children showing a strong negative response to known words showed better RL. Baseline ERP continued to account for RL at 4 and 6 years, after controlling for initial cognitive ability (regardless of treatment group).	
11	Lombardo et al 2015	Community referral and screening study. 24 ASD 'poor' language (79%); 36 ASD 'good' language (78%);19 LD/DD (89% m); 24 TD (79%). ASD 'poor' = 27 & 38m; ASD 'good' = 25 & 33m; TD= 27 & 29m; LD/DD = 21 & 31m 'Good' language outcome = MSEL EL or RL 1SD ≥ 40 (mean); 'Poor' language outcome MSEL EL and RL < 40 (mean)	Predictor Percent signal change in the left superior temporal cortex during speech processing. Group differences in neural systems associated with language processing There was a significant main effect of group on the left superior temporal cortex during speech processing. The ASD 'poor' group showed hypoactivation in the left temporal cortex compared to all other groups.	Outcome MSEL EL and RL Group differences TD group had highest EL & RL, followed by ASD Good, LD/DD, and ASD Poor (with exception of similar RL for the LD/DD group and the ASD 'Good' group). Significant age by group interactions for EL and RL, driven by the ASD 'Poor' group who showed a declining developmental trajectory with time (i.e. falling behind age appropriate norms), compared with other groups.
			Predictors of language outcome Multimodal combination of fMRI (percent signal change during speech processing in the left superior temporal cortex) and clinical measures (ADOS, Mullen, Vineland subscales) at baseline outperformed either behavioural measures alone or fMRI alone in classifying 'good' and 'poor' language outcomes in the ASD group	
12	Paul et al 2007	Clinical ascertainment 52 ASD (77%); 32 DD (78%); 44 TD age matched (TDa)	Predictor Time spent listening to child directed speech (CDS). Preference for auditory stimulus patterns:	Outcome MSEL RL

		(70%); 30 TD language matched (TDI) (70%) ASD =26 & 45m (N=23) DD: 24m TDa 26m TDI 14m	Although children with autism showed a preference for CDS, they spent less time listening to CDS compared to age matched TD controls	
			Attention to CDS and language Time spent listening to CDS was positively correlated with RL outcomes approximately 1 year later in the Autism group.	
13	Watson et al 2010	Research recruitment Autism N=19 (100%) 35m (&12m later)	Predictor Attention to non-social and CDS stimuli (behavioural & physiological)	Outcome Composite RL & EL scores using the MCDI-W&G, PLS-4, & MSEL
			Attention to CDS and language Percentage looking during CDS positively associated with EL & RL at follow-up. Percentage looking during CDS did not account for additional variance in language outcomes after controlling for entry level communicative ability. Percentage looking also positively associated with EL in the non-social condition. Vagal activity during CDS was associated with EL at follow-up. There were no significant associations in the non-social condition. Vagal activity during CDS accounted for additional variance in EL after controlling for entry level communicative ability.	

7.2.3 Pre-speech and gesture use (table 4)

Three studies examined gesture use in relation to later language with one of these studies also examining pre-speech in relation to later language. Talbot and colleagues (Talbot, Nelson, & Tager-Flusberg, 2015) examined infant's gesture use at 12 months, during interaction with an examiner and interaction with his/her mother. The HR ASD group showed less gesture use than the HR non-ASD group and LR controls. For all groups, overall infant gesture use and gesture use during interaction with the examiner was positively associated with 18-month language (EL and RL). In the ASD group only, infant gesture use during interaction with his/her mother was positively related to language outcomes. In a second study of 29 month old toddlers with ASD, it was reported that early gestures (e.g. showing, pointing) as well as pre-speech (responding to "no, no" , imitating words) at two years of age were correlated with both EL and RL at age nine but that these correlations were no longer significant when other variables (NVIQ, RL and EL and age at outcome (approximately 9 years)) were modelled (Luyster, Qiu, Lopez, & Lord, 2007). This suggests that initial nonverbal cognitive ability, initial language level and/or age at outcome accounted for the association between gestures/pre-speech and later language ability. However, the number of late gestures (e.g. sweeping) at 2 years predicted age 9 VIQ, communication and EL, controlling for initial NVIQ, RL, EL and age at outcome. Gesture use at age three did not predict later language in this sample. Finally, in a further study of toddlers with ASD, behavioural regulation (including gestures) at 21 months was associated with VDIQ at 38 months, when controlling for age and understanding of single words (Wetherby, Watt, Morgan, & Shumway, 2007). In the same study, inventory of gestures used was also significantly associated with language outcomes, when controlling for age but not understanding of single words.

Table 4 Pre-speech and gesture use

Study		Design and Sample N (%Male) Age (months)	Methods and Results	
14	Talbot et al 2015	High Risk 48 HR (55%); 27 LR (52m) 12 & 18m	Predictor Infant gesture use during interaction with examiner and interaction with mother Group differences Gesture use: HR ASD < HR non-ASD & LR	Outcome MSEL language score (EL & RL) Group differences No differences between HR ASD (n=9), HR non-ASD (n=38) & LR
			Gesture use and language All groups: Overall infant gesture use and gesture use during interaction with examiner positively associated with 18-month MSEL language score. ASD only: Infant gesture use during interaction with mother positively related to language outcomes.	
15	Luyster et al 2007	Clinical ascertainment ASD 62(87%); DD= 19 (42%) ASD = 29, 42 & 124m; DD = 28 & 120m	Predictors Pre-speech (e.g. response to “no, no,” imitate words) and early (showing, pointing) and late gestures (feeding a doll, sweeping).	Outcome CELF-, CELF-P, Reynell, VABS or SCID-R AE scores Group differences in language outcomes ASD < DD: verbal mental age at age 2.
			Pre-speech, gestures and language ASD only: Number of late gestures at 2 but not 3 years predicted age 9 VIQ, VABS & EL, controlling for initial NVIQ, RL & EL and age at outcome. Early gestures at age 2 and pre-speech were correlated with both EL and RL at age 9. Pre-speech/early gestures no longer predicted language outcomes when other variables modelled (NVIQ, RL & EL and age at outcome). The difference scores between 2 & 3 years did not predict outcome for any of the predictor variables. Similar results obtained when including only participants with EL at 2.	

7.2.4 Responding to and eliciting interaction (table 5)

Two high-risk sibling studies and several screening, clinical and other research studies, among toddlers with ASD, have examined joint attention skills in relation to later language. Gillespie-Lynch et al. (2015) examined 'low level' (e.g. gaze alternation) and 'high level' (e.g. gestural indication) initiation of joint attention (IJA), as well as response to joint attention (RJA; e.g. following gaze, or pointing), in HR siblings. There were no group differences in JA measures at 12 months. However, at 18 months, the ASD group had poorer 'high' level IJA and RJA than HR non-ASD group. High level IJA at 18 months was associated with school aged structural language in both ASD and non-ASD groups. In a second study of infant siblings, it was reported that HR siblings had poorer IJA and RJA than LR siblings at 14-16 months (Malesa et al., 2013). For both groups IJA and RJA at baseline was positively related to the later language composite but only IJA remained significant when IJA and RJA combined in single model. These associations did not differ between groups.

Charman and colleagues (Charman et al., 2003; Charman, 2003) examined JA among several other predictor variables (functional and pretend play, JA, goal detection & imitation of action on object) in toddlers with ASD. JA at 21 months was associated with EL and RL at follow-up when controlling for initial NVIQ. In another study of 22 month old toddlers with ASD, who were classified as having 'good' or 'poor' EL at 47 months, it was reported that those with 'good' EL showed more RJA and symbolic play. However, when RJA and play were examined together with other predictor variables (initial stereotype behaviours, Vineland EL & RL, NVIQ) they did not account for additional variance in EL at follow-up. Similarly, Anderson et al. (2007) reported that change in JA between 2 and 3 years positively correlated with verbal outcome at age 9 in participants with ASD. However, change in JA did not explain additional variance in language when change in other variables (NVAE, verbal ability, and symptoms severity) were modelled. When the ASD sample was grouped based on level of improvement in verbal ability over time, JA at age 2 was a significant risk factor for the likelihood to be assigned to the lowest functioning group. Finally, Thurm and colleagues (Thurm, Lord, Lee, & Newschaffer, 2007)

examined IJA and RJA 30 month old toddlers with ASD, in relation to EL and RL status at 5 years and reported that only RJA significantly predicted RL status at age 5 when other factors were modelled (responding to joint attention, initiating joint attention, imitating sounds and imitating simple movements).

Adamson and colleagues distinguished between supported and coordinated joint engagement, where supported engagement refers to a child attending to a shared topic whereas in coordinated engagement the child also explicitly attends to the partner (Adamson, Bakeman, Deckner, & Ronski, 2009). They also distinguished between symbol-infused (the child is actively attending to symbols) and non-symbol infused joint engagement. Children with ASD did not differ from Down's Syndrome (DS) or language matched controls in terms of symbol infused or supported joint engagement at 30 months but they showed reduced coordinated joint engagement compared to the other groups. The DS group had the lowest EL and RL scores, followed by the ASD group and finally the TD group, who had the highest scores. For all three groups, supported symbol-infused JA predicted both RL and EL (controlling for initial EL).

Mc Duffie (McDuffie, Yoder, & Stone, 2005) and colleagues examined the behaviours required for joint attention (attention following, motor imitation, commenting & requesting) in 33 month old toddlers with ASD. Motor imitation of actions without objects and commenting were associated with RL but commenting was the only unique predictor of RL after controlling for cognitive delay. All four triadic attention skills measured were associated with EL. Commenting and motor imitation of actions without objects predicted EL over and above the other triadic attention skills and when initial cognitive delay was controlled.

Wetherby et al. (2007) examined social communicative behaviours in toddlers with ASD who, when compared with TD controls, showed fewer social, speech and symbolic behaviours. Behavioural regulation and consonant inventory were associated with VDI when controlling for age and initial understanding of single words in the ASD group. Plumb and Wetherby (2013) reported that 21 month old toddlers with ASD used fewer vocalisations with speech sounds and fewer

communicative vocalisations than typically developing controls. The frequency of vocalisations with speech sounds and the proportion of vocalisations with speech sounds used communicatively, significantly correlated with VDQ at outcome in the ASD group. Both communicative and non-communicative vocalisations related to VDQ at outcome. However, only communicative vocalisations uniquely predicted VDQ, when non-communicative vocalisation was included in the model. Similarly Charman et al. (2005) reported that the rate of communicative acts at 2 years of age was associated with EL and VABS communication scores at 3 years of age, as well as RL at 7 years in toddlers with ASD.

Yoder (2006) examined attention following, intentional communication, motor imitation and diversity of object play in relation to lexical density growth in 34 month old children with ASD. Only intentional communication and diversity of object play were significant predictors of lexical density growth after controlling for initial EL impairment and initial lexical density but neither were significant predictors of lexical density after controlling for each other. In a further study, Yoder et al. (2015) examined 'value added predictors' of EL and RL growth in 35 month old toddlers with ASD. For both EL and RL growth, RJA and intentional communication were value added predictors of language growth.

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Table5 Responding to and eliciting interaction

	Study	Design and Sample N (%Male) Age (months)	Methods and Results	
16	Gillespie-Lynch et al 2015	High Risk 10 ASD (80%); 31 HR non ASD (42%); 23 LR non- ASD (61%) 6,12,18,24,36 & 89 m	Predictor IJA ('low' level and 'high' level) and RJA Group differences No differences on JA measures at 12 months. ASD<HR non-ASD on 'high' level IJA & RJA at 18 months.	Outcome CELF-4; CCC-2 Group differences ASD<LR pragmatic and structural language on the CCC-2 and structural language on the CELF-4. ASD< HR non-ASD: pragmatic & structural language on the CCC-2
			JA and language ASD: JA at 12m not associated with school aged language (89m). 'High' level IJA (gestural indication) at 18m was associated with language structure on the CELF-4 and the structural composite on the CCC-2. Non-ASD: 'high' level IJA at 18 months was associated with CCC-2 structural language	
17	Malesa et al 2013	High Risk 36 HR sibs; 23 LR sibs (59% overall) HR = 14 & 64m; LR =16 &66m	Predictor IJA & RJA Group differences HR<LR: IJA and RJA at baseline but not at 5 years	Outcome Language aggregate based on CELF-4 & DAS-2 Group differences No difference at 5 years
			JA and language Both groups: IJA and RJA at baseline positively related to the later language composite. Only IJA remained significant when IJA and RJA combined in single model. Growth of JA over time not associated with language.	
18	Plumb & Wetherby 2013	Screening study 50 ASD; 25 DD; 50 TD (gender not reported, ASD & TD group matched on gender) ASD=21 &39m; DD = 21 & 36m); TD =21 &35m)	Predictor Communicative and non-communicative vocalisations Group differences ASD < TD vocalisations with speech sounds; communicative vocalisations. ASD>TD: atypical vocalisations, ASD> TD/DD: distress vocalisations	Outcome MSEL VDQ (EL & RL) Group differences ASD<TD: VDQ

			Vocalisation and language outcomes in the ASD group Frequency of vocalisations with speech sounds & proportion of vocalisations with speech sounds used communicatively, significantly correlated with VDQ at outcome. Both communicative & non-communicative vocalisations related to VDQ at outcome. However, only communicative vocalisations uniquely predicted VDQ at outcome, when non-communicative vocalisation was included in the model. Age was included as a covariate in all analyses.	
19	Charman 2003 and Charman et al 2003*	Screening Study 18 (9 Autism & 9 PDD) (gender not reported). Autism: 21 & 42m; PDD: 20 & 44m	Predictor Functional and pretend play, JA, goal detection & imitation of action on object.	Outcome Reynell
			JA, imitation and language JA (gaze switch) associated with EL and RL and imitation associated with RL (controlling for initial NVIQ). Play and goal detection were not associated with language outcomes. High>Low JA & imitation at 20 m, superior RL at 42m. <i>*Results from these publications are combined as the same sample, predictors and outcome variables were reported.</i>	
20	Wetherby et al 2007	Screening study 50 ASD (86%); 23 DD (83%); 50 TD (86%) ASD = 21 & 38m; DD = 21 & 36m); TD = 21 & 36m	Predictors Social communication behaviours - social, speech & symbolic Group differences ASD <TD: all social, speech and symbolic behaviours. ASD group and DD group matched on the symbolic behaviours only.	Outcome MSEL VDQ (EL & RL) Group differences Autism<TD VDQ at outcome. ASD vs DD no significant difference
			Social communication behaviours and language ASD Understanding of single words was the most strongly associated with VDQ at outcome. Acts (vocal & gestural) for behavioural regulation and consonant inventory were associated with VDQ when controlling for age and understanding. All other behaviours correlated with VDQ when controlling for age only (gaze/point follow, rate of communicating, acts for social interaction and JA, inventory of gestures, inventory of words, inventory of play actions, pretend play actions and stacking blocks) were no longer significant when controlling for understanding	
21	Paul et al 2008	Clinical ascertainment* 37 ASD 22& 47m	Predictor RJA, Symbolic play Group Difference: 'good' vs 'poor' EL The sample was divided into 'good' and 'poor' EL at follow-up. 'Good' > 'poor': play and RJA	Outcome EL based on MSEL EL, VABS EL & ADOS communication scale

			Predictors of EL outcome Play and RJA did not account for additional variance in EL at outcome when other variables (initial stereotype behaviours, Vineland EL & RL, NVIQ) modelled. <i>*Same sample as Paul 2007</i>	
22	Charman et al 2005	Screening Study / Clinical ascertainment 26 ASD(85% m) 25, 37 & 85m	Predictor Non-verbal communication acts to examiner during play interaction.	Outcome MCDI at 2 and 3, Reynell-III at 7; VABS communication Group differences: Autism vs non-autism Autism (12/26) on the ADI-R at 7 years < RL scores than those who did not. No difference in EL.
			Rate of communication and language Rate of communicative acts at 2 years of age was associated with EL and VABS communication scores at 3 years of age, as well as RL at 7 years.	
23	Anderson et al 2007	Clinical ascertainment 192 referred for possible autism (85%); 22 non-autistic DD children (45 %). Sample divided into Autistic (N=84); PDDNOS (N= 46) & non-spectrum (N=42) 29m, aprox. 3,5 & 9 years	Predictor JA	Outcome Verbal ability based on subtests from Mullen, DAS-P, DAS-S or WISC-III, dependent on age/ability. Group differences ASD< other groups from age 2 Group by time interaction significant with the PDDNOS/non-spectrum children improving at a faster rate than the autistic children. Rate of growth slowed in the non-spectrum group at age 9 whereas the ASD groups continued to improve.
			JA and rate of change in verbal ability Initial JA was not significantly associated with change in verbal ability but there was a trend between JA skills and improvement in verbal ability with time. ASD only: change in JA between 2 and 3 years positively correlated with verbal outcome at age 9. Change in JA did not explain additional variance in language when change in other variables (NVAE, verbal ability, and symptoms severity) modelled. When the ASD sample was grouped based on level of improvement in verbal ability over time, JA at age 2 was a significant risk factor for the likelihood to be assigned to the lowest functioning group.	

24	Thurm et al 2007	Clinical ascertainment 59 Autism (88%); 24 PDDNOS (79%); 35 non-spectrum DD (60%) Autism=30 & 57m PDD= 30 & 57m DD= 28 & 54m	Predictors RJA & IJA; oral-motor imitation	Outcome DAS EL & RL; MSEL EL & RL (MSEL used if base scores achieved on DAS) Group difference ASD < PDD-NOS group / non-spectrum: EL and RL at age 5.
			Predictors of EL and RL status at age 5 in the ASD/PDDNOS groups Sample grouped into those who did and did not have EL and RL at age 5. Imitating sounds significantly predicted EL status at age 5 when accounting for IJA, RJA and imitating simple movements. Only RJA significantly predicted RL status at age 5 when other factors were modelled.	
25	Adamson et al 2009	Clinical ascertainment 23 ASD (87%); 29 DS (66% m); 56 TD toddlers from previous study ASD=30m; DS=30m; TD=18 & 30m	Predictors Symbol infused, supported and coordinated joint engagement Group differences No differences in symbol infused or supported joint engagement. ASD < DS group / language matched TD: coordinated joint engagement at 30m	Outcome PPVT-III RL, EVT EL Group Differences Mean scores DS < ASD < TD.
			Joint engagement and language Language outcomes available for 18 ASD, 22 DS, and 53 TD children (n = 93). All groups: Supported symbol-infused JA predicted both RL and EL (controlling for initial MCDI EL). Coordinated symbol infused JA accounted for additional variance on DD EL scores only.	
26	McDuffie et al 2005	Recruitment not specified 29 ASD (93%) 33m; 6m follow up	Predictors Triadic (joint) attention skills: Attention following, motor imitation, commenting & requesting	Outcome MCDI EL & RL

			Triadic attention and language outcomes: Motor imitation of actions without objects and commenting associated with RL. Commenting was the only unique predictor of RL after controlling for cognitive delay. All four triadic attention skills measured were associated with EL. Commenting and motor imitation of actions without objects predicted EL over and above the other triadic attention skills and when initial cognitive delay was controlled.	
27	Yoder 2006	Research recruitment 35 ASD (89%) with little or no EL at entry 34m; 6 & 12m follow up	Predictors Attention following, intentional communication, motor imitation & diversity of object play.	Outcome Growth in lexical density (coding of language samples during structured & unstructured free play).
			Predictors of lexical density growth Only intentional communication (including a measure of IJA) & diversity of object play were significant predictors of lexical density growth after controlling for initial EL impairment and initial lexical density. Neither intentional communication nor diversity of object play were significant predictors of lexical density after controlling for each other.	
28	Yoder et al 2015	Recruitment Not specified 87 ASD (82%) 35m; 5 further time points aprox. every 4 months	Predictors RJA; intentional communication; attention to CDS; Play; Motor imitation;	Outcome Aggregate measures of EL (MCDI, CSBS, UCS) & RL (MCDI, CBCS) growth.
			Value added predictors of EL and RL growth For both EL and RL growth, RJA and intentional communication, (as well as parent linguistic responses) were value added predictors of language growth. Consonant inventory explained additional variance in EL. Parent reported receptive vocabulary and autism severity further explained RL growth. Other included predictors - play, motor imitation and cognitive impairment - were not value added predictors of language growth.	

7.2.5 Motor skills (table 6)

Motor skills emerged as one of the earliest reported predictors of language development. Bhat and colleagues (Bhat, Galloway, & Landa, 2012) reported that HR infants were more likely to show motor delays than LR infants at 4 and 7 months. When the association between motor delay and language delay was examined in the HR group, motor delay at 4 months was associated with language delay at 18 months. In a second study of HR infants, Leonard and colleagues (Leonard, Bedford, Pickles, & Hill, 2015) examined fine and gross motor (FM, GM) skills in relation to rates of EL and RL growth between 7 and 36 months. There was a significant difference in the association between GM skills and EL between HR ASD and LR groups, with only the HR ASD group showing a significant positive relationship between GM skills and EL growth. In a further study of HR infants, it was reported that HR infants had fewer FM skills at 12, 18 and 24 months and were significantly more likely than LR infants to have FM delay at 24 months (LeBarton & Iverson, 2013). FM skills at 12, 18 & 24 months were positively related to EL in the HR group, controlling for NVIQ and ASD at outcome.

Bedford and colleagues (Bedford, Pickles, & Lord, 2015) examined age of walking onset and GM skills in toddlers with ASD, in relation to language development between the ages of two and nine years. GM skills were a significant predictor of both EL and RL when controlling for walking onset, NVIQ and symptom severity. Walking onset was a significant predictor of EL and RL development but these relationships were no longer significant when ASD severity and NVIQ were modelled. In a further study of toddlers with ASD or DD, Hellendoorn et al. (2015) examined FM skills in relation to later language. The ASD group had significantly lower FM skills than the DD group at baseline (27 and 18 months respectively) and significantly lower EL and RL at follow up (46 and 44 months respectively). Higher FM scores at baseline predicted better EL and RL, controlling for age. The relationship between FM skills and RL was not moderated by group. However, for EL the interaction between FM skills and group was significant, with a stronger relationship in the ASD group than in the DD group.

Finally, in a screening study of toddlers at risk for ASD (Ben-Sasson & Gill, 2014), participants were divided into subgroups based on whether they had 'stable,' 'increasing' or 'decreasing' scores on MSEL subtests between 13 and 29 months. 61% of the decreasing GM subgroup increased on at least one language area. In the decreasing FM subgroup, all showed an increase in a language score. The findings of this study run contrary to other findings and suggest that decreases in motor skills can be associated with increases in language scores.

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Table 6 Motor Skills

	Study	Design and Sample N (%Male) Age (months)	Methods and Results	
29	Bhat et al 2012	High Risk 24 HR (50%) & 24 LR (38%) 4 & 7m; Follow up at aprox. 18m for 16 HR and 21 LR	Predictor Motor delay on the Alberta Infant Motor Scale (AIMS). Group differences HR>LR motor delays (defined as $\leq$ 25th percentile) at 4 and 7 months	Outcome Communication delay on the MSEL EL &/or RL
			Motor delay and communication delay in HR infants Motor delay at 4m significantly associated with communication delay (defined as $T \leq 40$, or >1 SD below the mean on RL and/or EL of the MSEL) at 18 months. Trend for significant association between motor delay at 6 months and communication delay at 18 months.	
30	Leonard et al 2015	High Risk 54 HR infants (41%) 17 HR ASD (65%); 36 HR Non-ASD (28%) 48 LR infants (35%); 7, 14, 24 & 36 months	Predictor Fine Motor (FM) & Gross Motor (GM) development (MSEL)	Outcome Rate of EL and RL growth on the VABS-II
			GM Skills and the Rate of EL Development Significant interaction between group and GM score. ASD only: positive relationship between GM score and EL. The relationship between GM skills and EL growth was different between HR ASD and LR groups after controlling for developmental level and 7m EL. No interaction between the HR ASD and HR non-ASD groups FM Skills and Rate of EL Development Significant interaction between group and FM but no significant relationships when each group was examined separately. Positive trend between FM skills and EL in ASD. Motor Skills and Rate of RL Development There were no significant group by GM or FM score interactions for the rate of RL.	
31	LeBarton & Iverson 2013	High Risk 34 HR infants (53%); 25 LR (40%)	Predictor FM skills at 12, 18 & 24 months. Group differences HR < LR: FM skills at 12 & 18m;	Outcome MCDI EL & MSEL EL Language development in HR infants HR ASD & HR non-ASD significantly more likely than chance to show EL

		12, 18, 24 and 36 months	HR>LR: FM delay at 24 m. HR ASD (N= 7) < HR non-ASD (N=27): FM skills at 18m HR ASD> HR non-ASD FM delay at 24 months. Relationship between fine motor skills and language development in HR infants FM skills at 12, 18 & 24 months were positively related to EL on the MSEL and the MCDI. Composite FM scores in the first 24 months were significantly related to composite EL scores at 36 months. This relationship held when controlling for NVIQ & ASD outcome.	delays at 36 months on the MCDI. HR- ASD group alone significantly more delay than would be expected by chance on MSEL EL at 36 month.
32	Ben-Sasson & Gill et al 2014	Screening study 76 toddlers at risk for ASD (55%). 13 & 29m	Predictor MSEL GM, FM & VR Group classification Three groups were defined; (1) those with ‘stable’ scores on the MSEL between T1 and T2 (defined by a difference score -23 to 23); (2) an increasing group (difference scores >23); and (3) a decreasing group (difference scores <23).	Outcome MSEL EL & RL
			Motor and language development 61% of the decreasing GM subgroup increased on at least one language area. In the decreasing FM subgroup, all had an increase in a language score. In the increasing EL group, 26% showed decrease in in at least 1 motor score. In the increasing RL group, 30% decreased in at least 1 motor score.	
33	Bedford et al 2015	Research recruitment 209 ASD (81%) 2,3,5 & 9 years	Predictor Age of walking onset, GM skills	Outcome VABS EL & RL
			Motors skills and language development Walking onset was a significant predictor of EL and RL development but these relationships were no longer significant when autism severity and NVIQ were modelled. GM skills were a significant predictor of both EL and RL when controlling for walking onset, NVIQ and symptom severity.	

34	Hellendoorn et al 2015	Screening study 63 ASD (78%) & 46 (33%) at follow-up; 269 DD (73%) & 121 (79%) at follow-up. ASD = 27 & 46m DD = 18 & 44m	Predictor MSEL FM & VR scales; exploration (object spatial & social orientation). Group differences The ASD group scored significantly lower on measures of exploration, FM & VR scales at baseline.	Outcome MSEL EL and RL Group differences The ASD group had significantly lower EL and RL at follow up.
			Predictors of language outcome Both groups: Higher FM scores at baseline predicted better EL & RL, controlling for age. Relationship between FM skills and RL not moderated by group. For EL the interaction between FM skills and group was significant, with a stronger relationship in the ASD group than in the DD group. Mediator–moderator analyses showed that exploration and VR were mediators of the relationships between FM functioning and language. Some of these relationships were moderated by diagnostic status with stronger relationships between variables in the ASD group compared to the DD group.	

7.2.6 Imitation (table 7)

One study has examined imitation in relation to language functioning in HR infants (Young et al., 2011). The HR ASD group had poorer imitations skills across time points (12, 18, 24 and 36 months) but like other groups, they showed a linear increase in motor skills over time. For all groups (HR ASD, DD, HR TD and LR), growth in imitation between 12 and 24 months was associated with growth in EL, with no group differences in the relationship between imitation and language growth.

In terms of toddlers with ASD, Charman and colleagues (Charman et al., 2003; Charman, 2003) reported that imitation of actions on an object at 20-21 months was associated with superior RL at 42-44 months (controlling for initial NVIQ). In a study of oral-motor imitation, Thurm et al. (2007) reported that imitating sounds significantly predicted EL status at age 5 when accounting for IJA, RJA and imitating simple movements. McDuffie et al. (2005) reported that motor imitation of actions without objects predicted RL over and above the other triadic attention skills and when initial cognitive delay was controlled. Stone et al (Stone et al., 1997) reported that motor imitation did not differ in toddlers with ASD, DD or TD toddlers. Total imitation (body and object) and imitation of body movements (but not object imitation) at 32 months was associated with EL skills at 46 months. Similarly, Stone and Yoder (2001) reported that motor imitation at 31 months predicted EL outcome at age 4 in children with ASD, when controlling for baseline language level.

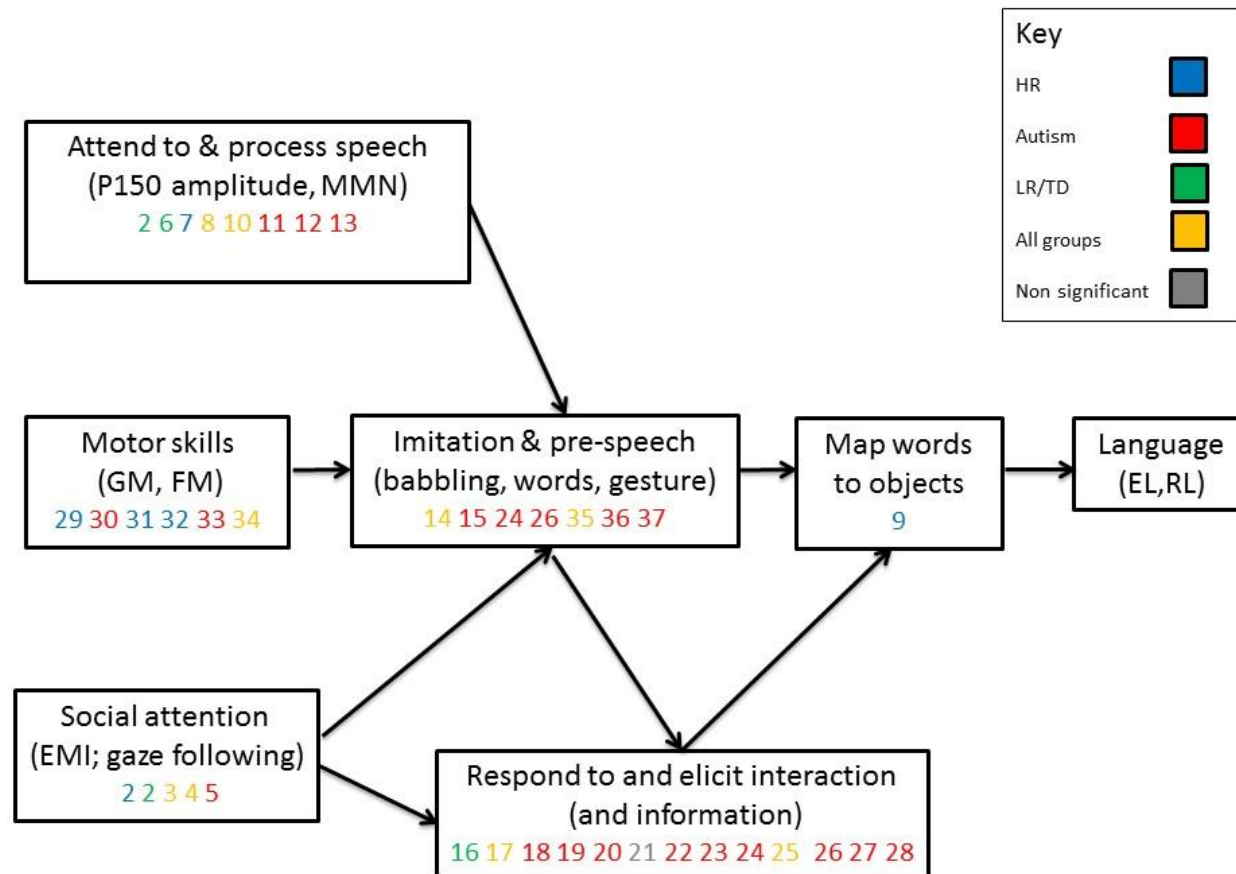
However, non-significant findings have also been reported. There was no association between motor imitation initial lexical density in toddlers with ASD in the study carried out by Yoder (2006). Similarly, motor imitation was not a value added predictor of EL growth in a further study (Yoder et al., 2015) suggesting that other factors may mediate the relationship between imitation and language outcomes.

Table 7 Imitation

	Study	Design and Sample N (% Male) Age (months)	Methods and Results	
35	Young et al 2011	High Risk 24 ASD (88%) 43 DD (60%) 90 HR TD (42%) 75 LR (57%) 12,18,24 & 36months	Predictor Imitation battery Group differences ASD < LR TD imitation skills across time points. Groups showed a similar significant linear increase in imitation between 12 and 24 months.	Outcome MSEL EL; MCDI EL
			Growth of imitation skills and language development All groups: Growth in imitation between 12 and 24 months associated with growth on the MSEL EL & MCDI EL. (No main effect of group; no group by language or time by language interaction effects).	
36	Stone & Yoder 2001	Screening study 35 children with ASD (77%) 31 & 58m	Predictor Motor imitation, IJA & object play	Outcome EL aggregate based on the MCDI, SICD-R & PLS-3
			Predictors of EL Motor imitation (as well as number of hours of SLT) predicted EL outcome at age 4, when controlling for baseline language level. IJA and play significantly correlated with EL (but not when controlling for initial language level).	
37	Stone et al 1997	Research recruitment <i>Study 1:</i> 18 autism (72%); 18 DD (72%); 18 TD (67%) Autism = 31m; DD = 31m; TD 19m <i>Study 2:</i>	Predictor Motor imitation (total, body & object) Differences in imitation All groups: higher object imitation scores than body imitation scores, and higher scores meaningful imitation than non-meaningful imitation. There were no group by imitation interactions. (Autism < DD total MIS) Change in imitation over time	Outcome MCDI EL

		26 autism (81%); 32 & 46m	There was a significant increase in imitation skills between T1 and T2.	
			<i>Imitation and EL skills in Autism</i> Total imitation and imitation of body movements (but not object imitation) at T1 was associated with EL skills at T2.	

Figure 2 Potential causal mechanisms to language development. Studies are summarised according to predictor variables and group in which significant finding were reported.



7.3 Language outcomes

Although the purpose of the current review was not to systematically examine group differences in language outcomes, a summary of outcomes is provided for contextual information. Nineteen of the included studies provided information on group differences in language outcomes. Of these, nine were studies of ASD. Reduced verbal ability (Anderson et al., 2007; Luyster et al., 2007; Plumb & Wetherby, 2013; Wetherby et al., 2007), EL and RL (Adamson et al., 2009; Hellendoorn et al., 2015; Lombardo et al., 2015; Thurm et al., 2007) were reported among ASD participants from two to five years of age, compared to controls, and reduced RL was also reported in autism compared to ASD at seven years of age (Charman et al., 2005). Ten HR studies reported language outcomes. Two of these studies reported no difference in language outcomes at 18 months and five years respectively (Malesa et al., 2013; Talbott et al., 2015). Five reported group differences in EL and/or RL (Curtin & Vouloumanos, 2013; Droucker et al., 2013; Ference & Curtin, 2015; Seery et al., 2014; Young et al., 2009) among HR infants aged between 12 and 24 months – although two of these studies reported that there were differences at 18 but not 12 months (Curtin & Vouloumanos, 2013; Droucker et al., 2013). One study indicated increased risk of EL delay among HR toddlers at 36 months (LeBarton & Iverson, 2013), one study reported lower developmental language level at 14 months (Yirmiya et al., 2007) and one study reported reduced structural and pragmatic language in HR ASD compared to HR non ASD and LR groups at 36 months (Gillespie-Lynch et al., 2015).

In relation to the specificity of language outcomes, the majority of the studies examined early markers in relation to EL and RL. Verbal ability, structural language and composite language outcomes were also reported. In terms of the specificity of outcomes, there was more evidence for an association between social attention and EL than RL (Droucker et al., 2013; Elsabbagh et al., 2014; Young et al., 2009). Social attention was also associated with overall verbal ability (Campbell et al., 2014) and EMI was associated with RL in one study (Young et al., 2009) but this was not replicated in a second study (Elsabbagh et al., 2014). Several studies reported

associations between imitation and EL (Stone et al., 1997; Stone & Yoder, 2001; Young et al., 2011), however when associations with RL were also examined a significant correlation was reported (Charman et al., 2003; McDuffie et al., 2005). There were no other clear patterns of association in terms of the specificity of language outcomes, with associations with both EL and RL reported for all of the other domains (see tables 2-6). Gesture use and frequency of vocalisations were also associated with VDI (Plumb & Wetherby, 2013; Wetherby et al., 2007) and IJA was also associated with structural language (Gillespie-Lynch et al., 2015) and both IJA and RJA associated with composite language scores (Malesa et al., 2013).

8 Discussion

8.1 Early markers of language outcomes

The results of the studies included in this review indicated that aspects of social attention, attention to and processing of speech, gesture use, responding to and eliciting interaction, motor skills and imitation predicted language outcomes in ASD, HR siblings and controls. Infant affect during mother-infant interaction did not predict language outcomes in HR or LR groups. Associations with the domains reported above were not always significant when other factors such as language at baseline and nonverbal ability were modelled (Anderson et al., 2007; Luyster et al., 2007; Paul, Chawarska, Cicchetti, & Volkmar, 2008; Yoder et al., 2015). As such some of these associations may be the consequence of other developmental processes as will be discussed further below. There was some evidence that social attention may be a better predictor of EL than RL (Droucker et al., 2013; Elsabbagh et al., 2014; Young et al., 2009) but there was no other strong evidence for specific associations between predictors and aspects of language development.

8.1.1 Similarities and differences between early markers for language development between groups

As described in the introduction, similarities between ASD, HR, LR and TD groups may highlight qualitatively similar pathways to language, regardless of diagnosis or

risk status, whereas differences may indicate disrupted pathways or potential compensatory mechanisms in ASD and HR siblings. Early screening studies and clinically ascertained ASD samples indicated that social attention and EMI (Campbell et al., 2014) attention to (Kuhl et al., 2013) and processing of speech (Lombardo et al., 2015), attention to CDS (Paul et al., 2007; Watson et al., 2010), pre-speech and gestures (Luyster et al., 2007), communicative vocalisations (Plumb & Wetherby, 2013), acts for behavioural regulation (Wetherby et al., 2007), JA (Adamson et al., 2009; Anderson et al., 2007; Charman et al., 2003; Charman, 2003; Thurm et al., 2007; Yoder et al., 2015), rate of communication (Charman et al., 2005) and intentional communication (Yoder, 2006; Yoder et al., 2015), motor skills (Rachael Bedford et al., 2015; Ben-Sasson & Gill, 2014; Hellendoorn et al., 2015) and imitation (Stone et al., 1997; Stone & Yoder, 2001) were all predictors of language outcomes in ASD. However, the majority of these studies did not have a control groups for comparison (Bedford et al., 2015; Ben-Sasson & Gill, 2014; Campbell et al., 2014; Charman et al., 2003, 2005; Charman, 2003; McDuffie et al., 2005; Stone & Yoder, 2001; Watson et al., 2010; Yoder, 2006) or only assessed language outcome in the ASD group (Anderson et al., 2007; Kuhl et al., 2013; Plumb & Wetherby, 2013; Stone et al., 1997; Thurm et al., 2007; Wetherby et al., 2007), therefore one cannot make inferences about qualitative similarities or differences in language development in ASD from these studies.

Three of these studies provide some insight into commonalities and differences between ASD and TD groups. Adamson et al. (2009) reported that symbol infused JA predicted EL and RL in ASD, DS and TD groups, suggesting that JA predicts language outcomes regardless of group. Pre-speech and gesture use were shown to predict language outcomes in ASD but not DD, though there was no TD group for comparison (Luyster et al., 2007). Finally, FM skills were associated with RL in both ASD and DD; an effect that was not moderated by group. The association between FM and EL was moderated by group with the ASD group showing a stronger association than the DD group (Hellendoorn et al., 2015).

A number of studies indicated that the same markers predicted language outcomes in HR and LR siblings. Greater attention to the mouth relative to the eyes (Elsabbagh

et al., 2014; Young et al., 2009), infant gesture use during interaction with an examiner (Talbot et al., 2015) and IJA (Gillespie-Lynch et al., 2015; Malesa et al., 2013) predicted language outcomes in HR and LR siblings. Growth in imitation skills predicted language outcomes in HR and LR groups as well as those with DD (Young et al., 2011). In addition, the results of these studies suggest that clinical outcome did not significantly impact on the associations reported (Elsabbagh et al., 2014; Malesa et al., 2013; Talbot et al., 2015; Young et al., 2011). This suggests that these markers may be important for language outcome regardless of risk status or clinical outcome.

The result of other studies suggested potential alternative routes to language in HR infants. For example, preference for faces was associated with better EL in HR siblings whereas attention to faces was associated with poorer outcomes in LR siblings (Droucker et al., 2013). The association may follow an inverted U-shape curve whereby greater preference for faces over checkerboards is associated with better language in HR infants but more attention to faces is associated with poorer language in LR infants. The authors suggest that in TD infants, auditory and visual information may compete such that greater attention to faces may detract from speech information, giving rise to poorer language outcomes in the LR group. Similarly, attention to speech as indexed by P150 amplitude was positively associated with later EL in HR but not LR infants (Seery et al., 2014). The HR group showed greater P150 amplitudes to repeated speech sounds over frontal electrodes suggesting that altered attentional processing facilitated better language outcomes in this group. HR infants who had a diagnosis of ASD at 36 months were excluded from the final sample, therefore these results may reflect a compensatory mechanism that is present in HR infants who do not develop ASD. However, the HR infants had poorer language outcomes than LR infants, suggesting that although altered attentional processing led to better language outcomes in this group, the mechanism they employed was less effective than that used by LR infants.

The results of these studies also pointed to markers that predicted language outcomes in HR infants who develop ASD but not in other groups. For example, infant gesture use during interaction with mothers was significantly associated with

language outcomes in HR ASD but not HR non-ASD or LR controls (Talbot et al., 2015). It may be that differences in variability between groups explain the significant association in the ASD group or that these results were confounded by other factors, for example, severity of autistic symptoms. Similarly, only the HR ASD siblings showed a significant positive relationship between GM skills and EL growth (Leonard et al., 2015). There was no significant relationship in the LR group, perhaps due to less variability in motor scores in this group.

Certain markers predicted language outcomes in LR but not HR infants. For example, preference for strong-weak (trochaic) stress over weak-strong (iambic) word stress was a significant positive predictor of language outcomes in LR but not HR infants (Ference & Curtin, 2013). The HR group showed reduced preference for words with trochaic over iambic word stress suggesting that they may not be able to use this information for language learning. Similarly, preference for ID speech (over AD speech) was positively associated with EL, and attention to AD speech was negatively associated with language outcome in LR infants but not HR infants (Droucker et al., 2013). Preference for ID speech emerged later in the HR group in this study and attention to CDS was associated with language outcomes in toddlers with ASD (Paul et al., 2007; Watson et al., 2010) suggesting that developmental differences account for the findings reported by Droucker et al. (2013).

8.1.2 Developmental time course of early markers

Motor skills emerged as the earliest predictor of language outcomes in HR and ASD groups. Bhat et al. (2012) reported that motor delay at four months was significantly associated with communication delay at 18 months in HR siblings. The association between motor skills and language development was not specific to HR and ASD groups with associations also reported in those with DD (Hellendoorn et al., 2015). This suggests that delays in motor development may index general developmental delays and is not a specific marker of language outcomes in ASD/HR siblings. Sensitivity to language specific stress patterns (Ference & Curtin, 2013) and preference for ID speech (Droucker et al., 2013) were the earliest predictors of language outcomes in LR siblings. Attention to faces emerged as one of the earlier

predictors of language outcomes in both HR and LR groups (Droucker et al., 2013). Converging evidence from studies of EMI indicates that social attention is one of the earliest predictors of language outcome in both HR and LR groups (Elsabbagh et al., 2014; Young et al., 2011).

JA emerged later in development, predicting language outcomes in HR and LR infants at 14 month (Malesa et al., 2013) but not 12 months (Gillespie-Lynch et al., 2015). Numerous studies indicated that JA was associated with later language in toddlers with ASD (see table 4). JA is likely to develop from more rudimentary social and attentional processes (Butterworth & Jarrett, 1991; Elsabbagh et al., 2012; McEvoy et al., 1993) therefore the association between JA and language may be the upstream consequence of other impairments, for example social or attentional processes. The results of these studies indicated that the timeline of the predictors of language development reflect the timeline of the pathways to language, with imitation, gesture use, pre-speech and other aspects of communication emerging as later predictors of language outcomes in HR and ASD studies (see figure 2).

8.2 Theoretical implications

Theories of social motivation (Dawson et al., 2004) and biological motion (Kaiser et al., 2012) propose that difficulties in orienting to and processing social cues respectively, give rise to deficits in JA, which in turn impacts on language development. Social attention emerged as an early predictor of language outcomes, whereas JA predicted language outcomes slightly later in development, which is in keeping with these hypotheses. These theories regard language impairment as emerging alongside ASD, with the social impairments that characterise the disorder, leading to language impairments. Interestingly, a number of these markers were significant for LR and TD groups as well as HR and ASD groups. This suggests that social development is important for language acquisition regardless of risk status or clinical outcome and plays a direct role in language learning as proposed by social learning theory, theories of joint attention and the 'social gating' hypothesis (Bruner, 1983; Carpenter et al., 1998; Kuhl, 2007).

The evidence reviewed here also supports the role of imitation in language development in HR, ASD, LR and DD groups. It has been proposed that early deficits in imitation disrupt early social interaction, leading to further social and communication deficits in ASD (Rogers & Pennington, 1991). Imitation could also directly impact on language development through its' role in the development of symbolic functioning (Piaget, 1966) and as learning strategy for language acquisition (Meltzoff & Keith, 1983). Motor skills predicted language outcomes in HR siblings and ASD supporting theories implicating motor abilities in language development in ASD (Belmonte et al., 2004; Donnellan et al., 2009; Leary & Hill, 1996). These theories suggest that impairments in motor development reduce the opportunity for learning giving rise to ASD symptoms and language impairments. Indeed the studies reviewed here suggest that motor development was a more important predictor of language outcomes in HR/ASD groups than LR/TD groups, supporting this view.

8.3 Direction for future research

Language development involves the acquisition of a succession of skills, as illustrated in figure 2. Some of the markers reported in this review may be secondary to other impairments therefore it is important that future studies seek to go back along causal pathways in order to better understand the origin of language difficulties in ASD. In addition the role of other factors involved in language development, that may contribute to language difficulties in ASD, such as difficulties with multisensory integration (Stevenson, Segers, Ferber, Barense, & Wallace, 2014) should be investigated longitudinally. Although theory suggests that neurocognitive skills such as executive functioning and conceptual development (specifically the use of categorisation for discrimination) may be important in predicting language in ASD (Ozonoff et al., 1991; Soulières et al., 2007), the studies reviewed here did not examine these factors in relation to later language. Future studies should also examine differences in the developmental trajectories of early markers of language in HR siblings and ASD, as certain markers may become important for language learning later in development in HR siblings and ASD.

Methodological issues such as the role of potential confounding factors, including gender and non-verbal cognition on language development should also be considered. Previous research suggests that non-verbal IQ is not associated with ASD severity (Gotham, Pickles, & Lord, 2009). Future studies should examine the association between ASD symptoms, non-verbal IQ and language development over time and whether the risk factors for these domains are the same or different. Examining these relationships in greater detail will enable future studies to go beyond identifying risk factors and elucidate the mechanisms by which language develops in ASD and the broader phenotype. The HR studies in this review did not all reported ASD outcome therefore it is difficult to infer whether potential compensatory mechanisms are operating in those who do not develop ASD or whether a marker could potentially lead to better language in the presence of increased ASD symptoms. Reporting of clinical outcomes will also help to clarify the relationship between language and ASD symptoms in HR siblings.

8.4 Limitations

The purpose of this review was to examine child factors associated with language outcomes in HR and LR siblings, as well as ASD and TD controls. The review did not examine the role of general cognition, transactional or environmental factors in language development. These factors are likely to play an important role in language development and their contribution should also be reviewed. The review focused on the markers of language development and did not specifically examine how different markers map onto different aspects of language, for example vocabulary as opposed to language structure. Finally, there is no standard measure for assessing the methodological quality of longitudinal studies, therefore the quality assessment ratings provided in this review should be regarded as a guide to interpreting results rather than an absolute measure of study quality.

8.5 Practical implications

Previous studies suggest that joint attention training improves language outcomes in ASD and that these gains are maintained at five year follow-up (Kasari, Gulsrud,

Freeman, Paparella, & Hellemann, 2012; Kasari, Paparella, Freeman, & Jahromi, 2008; Whalen, Schreibman, & Ingersoll, 2006). In addition, interventions that target social interaction on the one hand, and speech production on the other, have both been associated with language gains in non-verbal children with ASD, with no significant difference between the two types of intervention in terms of language outcomes (Rogers et al., 2006). The results of this review suggest that interventions could target earlier markers of language outcomes including social attention and/or motor development. Intervening earlier has the potential to lead to greater improvements in language outcomes in those at risk of developing ASD. However, evidence from a positive parenting intervention (using video-feedback to promote sensitive responding) in 7-10 month old HR infants showed that early intervention may not impact on language outcomes or may even have a negative effect (Green et al., 2015). It may be that other targets for intervention highlighted in this review could lead to better outcomes and it will be important to examine outcomes of potential interventions longitudinally. This will also allow us to examine whether the correlations reported in the studies included in this review reflect causal relations.

8.6 Summary

Social attention, specifically - greater attention to the mouth relative to the eyes as measured by the eye mouth index (EMI) - emerged as one of the earliest predictors of language outcomes regardless of risk status and non-verbal cognition in a relatively large sample of HR and LR infants (Elsabbagh et al., 2014). Converging results from another HR sibling study and a clinical sample of toddlers with ASD (Campbell et al., 2014; Young et al., 2009) lends further weight to the hypothesis that social attention is an important predictor of language development in ASD, HR and TD groups. Numerous studies indicate that JA predicted language outcomes in ASD, HR and LR groups as well as in DS (e.g. Adamson et al., 2009; Charman et al., 2003; Gillespie-Lynch et al., 2015; Malesa et al., 2013), again suggesting similar routes to language regardless of clinical outcome. The evidence indicates that these associations were mediated by other factors, which is in keeping with the view outlined above that JA emerges from other social and cognitive skills. Taken

together, these results support theories that propose that social attention and interaction play an important role in language development and suggest that the mechanisms sub-serving language development are qualitatively the same across ASD, the BAP and TD.

The evidence indicated that imitation predicted language outcomes in ASD, HR, LR and DD groups (Charman et al., 2003; Charman, 2003; McDuffie et al., 2005; Stone et al., 1997; Stone & Yoder, 2001; Thurm et al., 2007; Young et al., 2011). This included a HR study with a relatively large sample size and several ASD studies. The results also suggested that imitation predicts language outcomes when controlling for other factors such as group membership, nonverbal cognitive ability, intervention and baseline language level – though see (Yoder, 2006; Yoder et al., 2015). Imitation is thought to be amore a basic skill sub-serving JA (A. McDuffie et al., 2005), which may explain why it was no longer significant when examined together with other aspects of JA and communication (Yoder, 2006; Yoder et al., 2015). Overall, findings are in keeping with theories of imitation and mirror neuron (MN) dysfunction in ASD, but suggest that imitation plays a role in language development regardless of clinical status, again supporting the view that qualitatively similar mechanisms underlying language development in ASD and other groups.

Convergence between ASD and HR studies – some of which had relatively large sample sizes - also indicated that motor skills predicted language outcomes in these groups (Rachael Bedford et al., 2015; Ben-Sasson & Gill, 2014; Bhat et al., 2012; Hellendoorn et al., 2015; LeBarton & Iverson, 2013; Leonard et al., 2015). Unlike the results from studies of social attention, joint attention and imitation, these studies suggested that motor skills are more important in predicting language outcomes in ASD and HR groups than in TD controls. There was also evidence that motor skills are associated with language outcomes in DD, though associations were stronger in ASD. The evidence also indicated that motor skills predicted language outcomes when controlling for other factors such as initial language ability, nonverbal cognition and ASD severity (Bedford et al., 2015; LeBarton & Iverson, 2013;. Leonard et al., 2015). Evidence from one study (Bhat et al., 2012) suggests that

motor skills may be one of the earliest predictors of language outcomes, though methodological issues limit the conclusions that can be drawn from this study. Nonetheless, there is strong evidence that poor motor skills impact on later language development in ASD and HR groups supporting theories implicating motor difficulties in language acquisition in ASD.

There was some evidence of alternative routes to language in ASD and HR siblings from studies of face processing, gesture use and speech processing (Droucker et al., 2013; Seery et al., 2014; Talbott et al., 2015). However, methodological issues as well as the need for further replication limit conclusions that can be drawn from these studies. Nonetheless, they point to potential qualitative differences in language development in ASD and the BAP.

8.7 Conclusions

Language development draws on a variety of developmental processes and the results of the studies included in this review suggest that several early prerequisites to language predict language development in ASD, HR siblings and TD controls. However, the weight of the evidence supports theories of social attention, imitation and interaction, in predicting language outcomes regardless of clinical status, suggesting qualitatively similar routes to language in ASD, the BAP and TD. There was also substantial evidence that disruptions in early motor development impact on later language outcomes in ASD. As illustrated in figure 2, disruptions at any point along the causal pathway may lead to language outcomes in ASD and the BAP. The results of this review highlighted the need for future studies to go back along the causal pathway in order to better understand the origin of language difficulties in ASD and those at heightened familial risk.

9 References

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10 Appendix A: Quality assessment checklist

Questions Q1, Q2, Q3, Q4, Q5, Q6, Q7, Q10, Q16, Q18, Q19, Q20, Q25, Q28, Q30 & Q31 from the quality assessment checklist for observational studies used by Tobin et al. (2014) was used. Additional specifications used to evaluate study quality in this review are italicised. Items were scored on a yes (1), no (0), don't know (0) basis.

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes (*language*) to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the participants included in the study clearly described, including background information (*age, gender, ASD diagnosis (participant and /or proband for HR)*)?
4. Are the study methods clearly described?
5. Are the distributions of principal confounders (*NVIQ/VR, gender, age, SES*) in each group of participants to be compared clearly described? (*Describe >3*)
6. Are the main findings of the study clearly described? (*e.g. group differences on main outcome measures*).
7. Does the study provide estimates of the random variability in the data for the main outcomes? (*mean and SD/SE/CI*)
8. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?"
9. If any of the results of the study were based on "data dredging" was this made clear?
10. Were the statistical tests used to assess the main outcomes appropriate?
11. Were the methods consistently implemented across participants? (*May use different measures at different ages if necessary; allow for dropouts*).
12. Were the main measures that were used accurate (valid and reliable) and appropriate for answering the stated research question? Reliability >.8
13. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? (*Controls for at least on of the following: Gender, SES, baseline language/communication, NVIQ (VR), age intensity of intervention, Autism severity/outcome, ethnicity*).
14. Was the interpretation of the data appropriate and did it follow clearly from the analysis?

15. Is the research design appropriate for answering the stated research question(s)?
16. If a control or comparison group was used, was matching or other acceptable technique utilized to ensure appropriate group construction?
(*Matched on age, gender*)

.

11 Appendix B: Quality assessment item scores

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q10	Q16	Q18	Q19	Q20	Q25	Q28	Q30	Q31	Total
Droucker et al 2013	1	1	0	1	0	1	1	1	1	1	1	1	0	1	1	0	12
Elsabbagh et al 2014	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	14
Paul et al 2007	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	15
Watson et al 2010	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16
Young et al 2009	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	15
Campbell et al 2014	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16
Curtin & Vouloumanos 2013	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	15
Charman et al 2005	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	1	14
Charman 2003 and Charman et al 2003	1	1	0	1	0	1	1	0	1	1	1	1	1	1	1	1	13

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q10	Q16	Q18	Q19	Q20	Q25	Q28	Q30	Q31	Total
Gillespie-Lynch et al 2015	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	15
Malesa et al 2013	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16
Adamson et al 2009	1	1	0	0	0	1	0	1	1	1	1	0	1	1	1	0	10
Talbott et al 2015	1	1	1	1	1	1	1	0	1	1	1	0	0	1	1	1	13
LeBarton & Iverson 2013	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	15
Leonard et al 2015	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	15
Young et al 2011	1	1	1	1	0	0	1	0	1	1	1	1	0	1	1	1	12
Stone et al 1997	1	1	1	1	1	1	0	0	1	1	1	1	0	1	1	1	13
Bhat et al 2012	1	1	1	1	0	1	0	1	1	1	1	1	0	1	1	0	12
Ference & Curtin 2013	1	1	0	1	1	1	1	0	1	1	1	1	0	1	1	1	13

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q10	Q16	Q18	Q19	Q20	Q25	Q28	Q30	Q31	Total
Ference & Curtin 2015	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	15
McDuffie et al 2005	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	15
Lombardo et al 2015	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16
Seery et al 2014	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	15
Kuhl et al 2013	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	15
Ben-Sasson & Gill et al 2014	1	1	0	1	0	1	0	1	1	1	1	1	0	1	1	1	12
Hellendoorn et al 2015	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	15
Luyster et al 2007	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	13
Thurm et al 2007	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	14
Yoder et al 2015	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	15
Anderson et al 2007	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	14

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q10	Q16	Q18	Q19	Q20	Q25	Q28	Q30	Q31	Total
Stone & Yoder 2001	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	15
Paul et al 2008	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	14
Yoder 2006	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16
Plumb & Wetherby 2013	1	1	0	1	0	1	1	0	1	1	1	0	1	1	1	1	12
Yirmiya et al 2006	1	1	1	0	1	1	1	0	1	0	1	1	1	1	1	1	13
Weatherby et al 2007	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	15
Bedford 2015	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	14

Empirical Research Project

An investigation of language and communication, from infancy to middle-childhood, in children at high familial risk for Autism Spectrum Disorder (ASD)

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4 Abstract

Language difficulties are a common feature of autism spectrum disorder (ASD). Studying the longitudinal development of infants at high familial risk of developing ASD, by virtue of having an older siblings with the disorder, can elucidate the aetiological mechanisms that give rise to the behavioural characteristics and related features of ASD. Thirty-nine high-risk (HR) and thirty-four low-risk (LR) siblings, who completed assessments in infancy and toddlerhood and were subsequently followed up to seven years of age, took part in the current study. Language outcomes at seven years of age were assessed and two potential infant predictors of language outcomes were examined; (1) attention to the eyes relative to the mouth as measured by the eye-mouth index (EMI) and (2) gaze following and attentional engagement to a referent object. The results suggested that the HR siblings with a diagnosis of ASD at 7 years of age (HR-ASD siblings) had intact structural language but had difficulty with the everyday use of language for communicative purposes. HR infants without a diagnosis of ASD did not differ from LR controls on language outcome measures at seven years of age. Negative EMI - greater attention to the mouth - at seven months was associated with better structural expressive language (EL) at seven years regardless of risk status or clinical outcome. In contrast, more attention to the mouth, as measured by the EMI, was associated with more severe parent reported ASD symptoms at 7 years of age in both groups. This suggests that attention to the mouth at 7 months is important for language development whereas attention to the eyes facilitates better social understanding, and less restricted patterns of behaviour. There was no strong evidence to support the role of gaze-following/attentional engagement as a longitudinal predictor of language outcome but the results suggested that greater attentional engagement was associated with fewer ASD symptoms, as measured by parent report and direct assessment of ASD symptoms at seven years of age, in both HR and LR groups. These results suggest that different aetiological mechanisms may give rise to language difficulties on the one hand, and ASD traits on the other, in infants at HR of developing ASD, as well as in typically developing controls.

5 Background

5.1 Autism spectrum disorder (ASD)

Autism spectrum disorder (ASD) is a pervasive developmental disorder defined by impairments in reciprocal social interaction and communication, as well as the presence of stereotyped behaviour and repetitive interests (American Psychiatric Association, 2013). Whereas the core deficits were previously regarded as a triad of impairments, in terms of social interaction, communication and behaviour, more recent conceptualisations have emphasised two core features; social communication and repetitive behaviour, as reflected by changes to the DSM-5 criteria for ASD and supported by validation studies (American Psychiatric Association, 2013; Frazier et al., 2012; Guthrie, Swineford, Wetherby, & Lord, 2013; Mandy, Charman, & Skuse, 2012).

Estimates of ASD prevalence in the United States indicate that ASD affects approximately 1 in 68 individuals, representing 1.47% of the population with estimates increasing by 30% between 2012 and 2014 (Centers for Disease Control and Prevention, 2014). UK estimates range from 1% to 1.5% (Baird et al., 2006; Simon Baron-Cohen et al., 2009; Brugha et al., 2012). ASD is approximately five times more common among males than females (Centers for Disease Control and Prevention, 2014), though the reason for this gender difference is not well understood. In addition, approximately half of those with a diagnosis of ASD have a co-occurring intellectual disability (Charman et al., 2011) and approximately 10% do not develop functional language skills (Hus et al., 2007).

Both genetic and environmental factors confer risk to the development of ASD though the relative contribution of genes and environment is debated (Hallmayer et al., 2011; Tick et al., 2015). Epigenetic factors are likely to further contribute to the aetiology of ASD (Grafodatskaya et al., 2010). However, as of yet, little is known about the causal mechanisms or the process by which symptoms emerge (Elsabbagh & Johnson, 2010b). Understanding how ASD and co-occurring impairments unfold is critical for improving understanding of developmental

mechanisms, identifying children who require intervention and indicating targets for early intervention (Jones, Gliga, Bedford, Charman, & Johnson, 2014).

5.2 Prospective studies of high-risk infant siblings

Until recently, research examining early markers and developmental mechanisms in ASD relied upon retrospective data (Palomo et al., 2006). Investigators have now begun to prospectively study younger siblings of children already diagnosed with ASD. These 'infant siblings' are at increased risk of developing ASD due to the high heritability of the disorder (Tick et al., 2015), with estimates suggesting that approximately 20% reach a diagnosis of ASD by their third birthday (Ozonoff et al., 2011). A further 10-20% of these infants develop sub-clinical ASD symptoms or other developmental disabilities (Messinger et al., 2013).

High-risk sibling designs have the potential to uncover early markers of ASD, as well as related developmental difficulties. In addition these studies can provide important information on the broader autism phenotype (BAP), which constitutes the behavioural and brain characteristics associated with ASD which are found both in affected individuals and their relatives (Bolton et al., 1994; Pickles et al., 2000; Piven, Palmer, Jacobi, Childress, & Arndt, 1997). Better understanding of the broader phenotype can help to identify 'intermediate' phenotypes – dimensional measures of quantitative traits associated with ASD (Elsabbagh & Johnson, 2010b) – for relating genotype to phenotype in both affected individuals and their families. These designs also have the potential to highlight possible compensatory mechanisms and/or protective factors among those at familial/genetic risk who do not show atypical outcomes.

HR sibling designs have primarily sought to identify early signs of ASD and have identified markers across several developmental domains. The evidence suggests that HR infants who are diagnosed with ASD at two or three years of age do not differ from controls in terms of measures of social interaction and communication, motor control or language development in the first year of life but that markers for ASD may emerge in the second year (Ozonoff et al., 2010; Rozga et al., 2011; Young

et al., 2009). In a study of developmental trajectories among HR siblings, those who reached diagnostic criteria for ASD did not differ from controls in terms of measures of social communication, language, visual perception or motor control at 6 months but differences emerged at 12-18 months. Examination of growth trajectories indicated that ASD siblings showed declining trajectories in terms of social communication between 6 and 36 months and slower development of language, motor and visual perception skills (Ozonoff et al., 2010).

Whilst some of the reported impairments are specific to those who later develop ASD, others are present in high risk siblings regardless of later diagnosis. For example, difficulties with face recognition have been reported among HR infants regardless of later diagnosis (de Klerk, Gliga, Charman, Johnson, & The BASIS team, 2014) and poor motor skills among HR siblings in infancy are associated with motor difficulties at 5-7 years among HR infants who do not reach diagnostic criteria (Hayley C. Leonard, Elsabbagh, & Hill, 2014). Impairments which persist in those at HR who do not go on to reach diagnostic criteria for ASD may be a feature of the BAP. Certain early difficulties that are characteristic of high risk siblings 'normalise' in a subgroup of individuals, but persist in others. For example, Hudry et al. (2014) reported that high risk infants showed reduced receptive vocabulary, relative to expressive vocabulary at 14 months, but that only those with ASD or sub-clinical signs of ASD, showed this outcome at 24 months.

5.3 Language in ASD and those at familial risk

Communication impairments in individuals with ASD can range from severe language delay, with an estimated 10% of people with ASD never develop functional language skills (Hus et al., 2007), to relatively intact language (Kjelgaard & Tager-Flusberg, 2001) with more subtle problems with the pragmatic use of language (Bauminger-Zviely, Karin, Kimhi, & Agam-Ben-Artzi, 2014). Among those who develop language, delay is common, with first words produced at an average age of 38 months among those with high functioning ASD, as opposed to 12-14 months in TD (Howlin, 2003). Many severely language delayed children attain phrase speech after four years of age, and this has been associated with their non-verbal and social

abilities (Wodka, Mathy, & Kalb, 2013). Developmental heterogeneity has been reported between 2 and 19 years of age, although expressive (EL) and receptive language (RL) develop largely in tandem (Pickles, Anderson, & Lord, 2014). Atypical acquisition of expressive skills compared to receptive skills – which counters the typical profile whereby receptive language skills exceed expressive language – has been reported (Ellis Weismer, Lord, & Esler, 2010; Luyster et al., 2007). In addition, difficulties with grammar (Eigsti & Bennetto, 2009; Eigsti, Bennetto, & Dadlani, 2007), articulation (Cleland, Gibbon, Peppé, O’Hare, & Rutherford, 2010) and the pragmatic use of language (Bauminger-Zviely, Karin, Kimhi, & Agam-Ben-Artzi, 2014) have been reported in children with high functioning ASD.

Atypical RL and EL development has been reported among high-risk infant siblings aged between 12 and 24 months (Curtin & Vouloumanos, 2013; Droucker et al., 2013; Ference & Curtin, 2015; Hudry et al., 2014; Mitchell et al., 2006; Seery et al., 2014; Young et al., 2009) - regardless of later diagnosis - suggesting that atypical language profiles may also be a feature of the broader phenotype. However, non-significant differences on EL and RL have also been reported at 18 months and at five years of age (Malesa et al., 2013; Talbott et al., 2015). Differences between HR siblings who go on to develop a diagnosis of ASD (HR ASD) and those who do not (HR non ASD) have also been reported, with HR ASD infants and toddlers showing more global and persistent deficits in EL and RL between 12 and 24 months (Mitchell et al., 2006). HR siblings have also been shown to have a reduced RL over EL advantage at 14 months. However, as mentioned above, this was only present in HR infants with ASD or an atypical developmental profile at 24 months (Hudry et al., 2014).

At seven years of age, 40% of high-risk siblings have language, cognitive or academic difficulties, compared to 16% of low-risk controls (Gamliel et al., 2009). Pilowsky and colleagues (Pilowsky et al., 2003) reported that HR siblings were not impaired as a group when compared to siblings of children with general and developmental language delays, at nine years of age. However, there was no TD group, limiting the conclusions that can be drawn from this study. At five years of age, no differences were reported on a composite measure of EL and RL, or parent reported

communicative language, in HR siblings without ASD when compared to controls (Warren et al., 2012). Drumm, Bryson, Zwaigenbaum, & Brian (2015) reported that HR siblings without ASD showed average or above average expressive, receptive and pragmatic language abilities at 8-11 years, though their pragmatic language was poorer than their structural language, and they had difficulties with the phonological aspects of language. Difficulties with structural and pragmatic language were reported in HR siblings with ASD, and not those without ASD, when compared to LR controls (Gillespie-Lynch et al., 2015). Subtle difficulties with pragmatic language have been reported in a subgroup of high-risk siblings aged between nine and twelve years, whereas school achievement and reading abilities appeared to be intact (Ben-Yizhak et al., 2011). Similarly, HR siblings with clinical concerns were reported to have impaired EL and RL compared to HR TD siblings and LR siblings, whereas HR TD siblings did not differ from LR infants (Miller et al., 2015). Therefore the evidence suggests that language difficulties occur among HR siblings in early childhood and may persist to school age among certain subgroups.

5.4 Theories of language development in ASD

Social learning theory proposes that social interaction plays an important role in language learning (Bruner, 1983). More recently, the 'social gating hypothesis' (Kuhl, 2007) has suggested that social information guides language learning mechanisms by ensuring that learning focuses on the speech in the child's environment. These theories have been supported by evidence from typically developing infants, showing that social interaction facilitates language learning (Goldstein, King, & West, 2003; Kuhl, Tsao, & Liu, 2003).

In terms of theories of language development in ASD, theories of social attention and interaction propose that an initial impairment in the ability to attend to social and affective cues give rise to a cascade of impairments in terms of social interaction, joint engagement and language development (Dawson et al., 2004). It has been suggested that social orienting deficits may be a consequence of impairments in social information processing, specifically the processing of biological motion (Allison et al., 2000; Kaiser et al., 2012). Impaired ability to

process biological motion could impact on gaze perception which is thought to be a precursor of joint attention (JA) (Butterworth & Jarrett, 1991; Elsabbagh et al., 2012). JA, the ability to share attention to a referred object, with someone else (Carpenter et al., 1998), is thought to play a key role in social and linguistic development (Tomasello & Farrar, 1986; Tomasello, Carpenter, Call, Behne, & Moll, 2005). Specifically, it is thought to facilitate language learning by creating a shared referential framework within which the child grounds the language used by adults (Carpenter et al., 1998). Indeed, numerous studies have documented associations between JA and language outcomes in TD, ASD and HR populations (Adamson, Bakeman, Deckner, & Ronski, 2009; Charman et al., 2003; Gillespie-Lynch et al., 2015; Malesa et al., 2013; Morales et al., 2000; Thurm, Lord, Lee, & Newschaffer, 2007; Yoder, Watson, & Lambert, 2015). These theories posit that the same aetiological mechanisms give rise to the social and linguistic difficulties that characterise ASD.

It has also been proposed that difficulties with multisensory integration may give rise to ASD symptoms as well as the language difficulties that characterise the disorder (Iarocci & McDonald, 2006; Stevenson et al., 2014). Speech perception involves visual attention to the mouth, as well as attention to auditory information. Congruent visual information enhances speech perception in noisy environments (Sumby & Pollack, 1954) whereas incongruent information alters speech perception (McGurk & Macdonald, 1976). Atypical attention to the eyes and mouth have been reported in ASD (Chawarska, Macari, & Shic, 2013; Jones, Carr, & Klin, 2008; Neumann, Spezio, Piven, & Adolphs, 2006; Spezio, Adolphs, Hurley, & Piven, 2007) and atypical multisensory integration has also been reported (Irwin, Tornatore, Brancizio, & Whalen, 2011; Woynaroski et al., 2013), therefore it may be that children with ASD have difficulty using visual information to facilitate language learning.

5.5 Social attention and language outcomes in HR sibling studies

A number of studies have begun to examine potential precursors to language and communication difficulties in high risk siblings. Early social (Elsabbagh et al., 2014; Young et al., 2009) and joint joint attention (Gillespie-Lynch et al., 2015; Malesa et al., 2013) have been associated with later language outcomes across both HR and LR groups.

Two studies have examined social attention using the eye-mouth index (EMI), which quantifies attention to the eyes relative to the mouth. Results indicated that HR infants did not differ from LR controls in terms of EMI at six and seven months but that negative EMI (greater attention to the mouth) predicted better EL at two and three years, across groups, regardless of risk status or clinical outcome (Elsabbagh et al., 2014; Young et al., 2009). Interestingly, EMI at seven but not 14 months was associated with language outcomes, suggesting that this may be a particularly sensitive period for infants' language development (Elsabbagh et al., 2014). In addition, EMI was not associated with symptom severity or clinical outcome (Elsabbagh et al., 2014; Young et al., 2009) suggesting that it may index specific language learning mechanisms.

Elsabbagh et al. (2014) propose that individual differences in attentional control may account for the relationship between EMI and EL. They examined EMI during complex social scenes that require endogenous attentional control – the ability to exert control over one's own looking behaviour regardless of competing demands for attention from the environment (Johnson, 1990) – and during simple social scenes, where attention is driven by external factors, which relies upon exogenous control mechanisms. EMI during complex social scenes was associated with EL when controlling for EMI during simple social scenes, supporting this conjecture.

As mentioned above, numerous studies have reported associations between JA in infancy and toddlerhood and subsequent language outcomes, in terms of EL and RL, as well as measures of structural language and verbal ability (Adamson, Bakeman,

Deckner, & Ronski, 2009; Charman et al., 2003; Gillespie-Lynch et al., 2015; Malesa et al., 2013; Morales et al., 2000; Thurm, Lord, Lee, & Newschaffer, 2007; Yoder, Watson, & Lambert, 2015). JA requires that an infant shifts attention between the referred to object and the person (Carpenter et al., 1998) and therefore requires not only the ability to follow gaze direction but also look at the referred object and shift attention between the object and the person. Gaze following is thought to be a rudimentary social orienting process, which underlies the later development of JA (Butterworth & Jarrett, 1991). Gaze-following behaviour at 10-11 months, together with vocalisation, has been associated with subsequent RL at 14 and 18 months in TD infants (Brooks & Meltzoff, 2005). The authors suggest that gaze following with vocalisation reflects 'psychological sharing' by the infant. Looking time (attentional engagement) to the referred object is thought to index referential understanding in addition to orienting (Bedford et al., 2012). Unpublished results from the cohort used in the present study, indicated that attentional engagement to the referred object at 14 months was associated with receptive vocabulary at 24 months when HR and LR groups were examined together (Bedford, 2012). Therefore in both of these studies, early measures of gaze following that involved an additional level of social understanding, were associated with later RL. In addition, HR infants with later social communication difficulties (both ASD and non ASD) showed reduced attentional engagement, and overall attentional engagement was associated with the severity of ASD symptoms in the HR infants (Bedford et al., 2012), suggesting that attentional engagement predicts ASD traits as well as language ability.

5.6 Rational and aims

Emerging evidence suggests that language abilities may be an important area of difficulty in high risk siblings of children with ASD. Studies of high risk siblings in infancy and early childhood, indicate a number of potential early markers of later language and communicative difficulties amongst these siblings. However, few studies have reported findings from longitudinal studies of children beyond infancy, therefore little is known about how language develops within these siblings during later childhood. Furthermore little is known about how early infancy markers relate

to developmental outcomes later in childhood. It is therefore important to examine whether the early markers described above predict language ability in later childhood. In addition, it is important to examine whether these markers predict later functioning over and above other neurocognitive signs and symptoms of ASD that have previously been associated with language outcomes including initial language (Luyster et al., 2007; Paul, Chawarska, Cicchetti, & Volkmar, 2008; Thurm et al., 2007), non-verbal ability (Anderson et al., 2007; Thurm, Manwaring, Swineford, & Farmer, 2015) and autistic symptoms (Moricke, Swinkels, Beuker, & Buitelaar, 2010; Thurm et al., 2015), as well as gender, which is associated with language ability in the general population (Voyer & Voyer, 2014). Finally, it is important to understand how these potential early markers of language, operate in the context of ASD symptoms. This will inform theoretical accounts of language development in ASD, help to identify targets for early intervention, as well as potentially identifying intermediate phenotypes that can aid investigation of genotype – phenotype associations.

5.7 Research Questions

1. Do HR siblings without ASD differ from controls in terms of their language ability at 7 years of age?
2. Is there a relationship between attentional engagement and EL?
3. Do individual differences in social attention better predict language than other factors associated with language outcomes in HR and LR infants, including initial language ability, non-verbal ability, and autistic symptoms?
4. Will EMI at 7 and 14 months be associated with the severity of ASD symptoms?

5.8 Hypotheses

1. (i) H_0 : HR siblings will not differ from controls on tests of language ability at seven years of age.

H_1 : HR siblings will have significantly poorer outcomes on tests of language ability at seven years of age than LR controls.

(ii) H_0 : HR siblings with a diagnosis of ASD will not differ from controls on tests of language ability at seven years of age.

H_1 : HR siblings with a diagnosis of ASD will have significantly poorer outcomes on tests of language ability at seven years of age than LR controls.

2. H_0 : EMI during complex social scenes at 7 months will not be associated with EL at 7 years in both HR and LR groups

H_1 : EMI during complex social scenes at 7 months will be associated with EL at 7 years in both HR and LR groups.

3. (i) H_0 : Looking time/attentional engagement will not be associated with RL in HR and LR siblings at 7 years of age.

H_1 : Looking time/attentional engagement will be associated with RL in HR and LR siblings at 7 years of age.

4. H_0 : Attentional engagement at 14 months will not be associated with the severity of ASD symptoms.

H_1 : Attentional engagement at 14 months will be associated with the severity of ASD symptoms.

6 Method

6.1 A priori power calculations

A priori power calculations were carried based on vocabulary differences in this cohort at three years of age (Hudry et al., 2014). It was estimated that 45 participants per group would be retained to seven years of age. A sample size of 45 per group (HR and LR) would afford 89% power to detect group differences with an effect size of $d = 0.62$ in receptive vocabulary ability and 86% power to detect group differences in expressive vocabulary with an effect size of $d=0.58$. As the final retained sample size was smaller than expected, the power calculation was repeated. There was adequate power to detect differences in receptive vocabulary (83.5% power) but tests of difference in expressive vocabulary were slightly underpowered (78.9% power). For the HR-ASD and LR group comparisons, the difference score for EL and RL was used as raw scores for each measure were not reported by subgroup. Apriori calculations assuming sample sizes of 15 for the HR-ASD and 45 for the LR group, indicated that there would be 93% power to detect group differences with an effect size of $d=0.95$. As the sample size was slightly smaller for the LR group, this calculation was repeated and adequate power was retained (91%).

6.2 Participants

Data from 104 children taking part in a prospective longitudinal study of infant siblings at high- (HR sibling; $N = 54$) and low- familial risk for ASD (LR siblings; $N = 50$), recruited as part of the British Autism Study of Infant Siblings (BASIS; www.basisnetwork.org), were used in the current study. Siblings were assessed five time points; at approximately 7 and 14 months of age, and at two, three and seven years of age. Forty-four HR and 37 LR siblings (78% of the original sample) took part in the 7 year assessments. Data from 39 HR and 34 LR siblings who completed language assessments at 7 years of age, and for whom diagnostic information was available, were included in the current study.

HR siblings had an older sibling with a community clinical ASD diagnosis, confirmed using information from the Development and Well-Being Assessment (Goodman, Ford, Richards, Gatward, & Meltzer, 2000) and the Social Communication Questionnaire (Rutter, Bailey, & Lord, 2003) by expert clinicians (TC, PB) ¹. None of the probands or extended family members had medical conditions which met criteria for exclusion (e.g., Fragile X syndrome, tuberous sclerosis). LR controls were full-term infants, with an older sibling, recruited from a volunteer database at the Birkbeck Centre for Brain and Cognitive Development, none of whom had a first-degree relative with diagnosis of ASD. The SCQ confirmed the absence of ASD in these older siblings, with no child scoring above cut-off (≥ 15 ; $n = 1$ missing data). Ethical approval was obtained from the NHS National Research Ethics Service (NHS RES London REC 14/LO/0170) and parents provided written informed consent, in accordance with the Declaration of Helsinki (see Appendix A). Children provided written informed assent wherever possible given developmental level.

Diagnostic assessments were carried out at 7 years of age by four experienced researchers (ES, BM, GP, TC)² based on ASD symptomatology (ADOS-2, ADI-R (HR only), SCQ), adaptive functioning (Vineland- II), and IQ (WASI-II) for each HR and LR child in accordance with DSM-5 criteria (American Psychiatric Association, 2013). None of the 37 LR children had a community clinical ASD diagnosis or met DSM-5 criteria for ASD. Fifteen of the HR group met criteria for ASD (HR-ASD) and 24 did not (HR-No-ASD).

Group characteristics in infancy and at 7 years of age are displayed for HR and LR groups in tables 1 and 2 respectively. HR and LR groups did not differ in terms of gender ($\chi^2(1) = .858$, $p = .354$) or age at the 7 month visit ($t(71) = -.887$, $p = .378$) or 14 month visit ($t(68) = .616$; $p = .906$). The HR group had lower developmental level (Mullen ELC) at 7 months ($t(71) = 2.47$, $p = .016$) and at 14 months ($t(68) = 2.47$, $p = .016$). The HR group had higher scores on the AOSI at 7 months ($t(62.57) = -235$, $p = .022$) but not 14 months ($t(69) = -1.59$, $p = .110$). Groups did not differ in age at the

¹ Tony Charman, Patrick Bolton

² Elizabeth Shephard, Bosiljka Milosavljevic, Greg Pasco, Tony Charman

7 year visit ($t(70) = -1.134, p = .260$). The HR group had significantly lower VIQ ($t(70) = 2.49, p = .015$) and lower WASII FSIQ $t(70) = 2.49, p = .015$) but there were no differences in NVIQ ($t(70) = 1.38, p = .172$) at 7 years. The HR group also had higher scores on the ADOS subscales [ADOS SA: ($t(65.08) = -4.25, p < .001$); RRB ($t(42.64) = -.5993, p < .001$); total ($t(52.93) = -4.98, p < .001$) and SRS scales [SRS SC: ($t(38.04) = -4.47, p < .0001$); RRB ($t(34.04) = -3.68, p < .001$); total ($t(36.36) = -4.263, p < .0001$)].

Table 1 Group characteristics at infancy time points. Means and standard deviations (SD) presented by risk group.

	LR (N=34)		HR (N=39)	
	Mean	SD	Mean	SD
<i>Male: Female</i>	14:20		12:27	
<i>7m age(months)</i>	7.29	1.17	7.46	1.25
<i>14m age (months)</i>	13.70	1.24	13.76	1.64
<i>7m Mullen NVT^a</i>	55.34	7.57	52.71	8.69
<i>14m Mullen NVT</i>	59.79	7.68	54.22	8.61
<i>7m Mullen ELC^b</i>	102.91	11.12	95.67	13.55
<i>14m Mullen ELC</i>	108.91	15.28	100.08	14.59
<i>7m AOSI^c</i>	6.41	3.52	9.0	6.02
<i>14m AOSI</i>	3.36	3.71	4.97	4.66

^a Mullen Non-Verbal T score; ^b Mullen Early Learning Composite standard score; ^c Autism observation schedule for infants (AOSI) total score.

Table 2 Group characteristics at 7 years. Means and SD are presented by risk status and ASD outcome group.

	LR		HR		HR no ASD		HR ASD	
	(N =34)		(N = 39)		(N = 24)		(N = 15)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<i>Male: Female</i>	14:20		12:27		5:19		7:8	
<i>Age (months)</i>	89.34	4.80			91.42	6.28	89.13	6.53

<i>WASI II VCI</i> ^a	120.06	14.03	110.58	19.34	113.87	19.02	110.14	25.87
<i>WASI II PRI</i>	110.06	12.11	105.24	13.79	103.46	11.85	109.57	18.26
<i>WASI II FSIQ</i>	117.06	11.78	108.63	16.19	107.96	12.76	109.79	21.36
<i>ADOS SA</i> ^b	2.13	1.69	4.36	2.69	2.96	1.601	6.60	2.57
<i>ADOS RRB</i>	1.13	.707	4.23	3.14	3.04	2.836	6.13	2.69
<i>ADOS total</i>	1.66	1.18	3.95	2.83	2.46	1.41	6.33	2.92
<i>ADI Social</i> ^c	-	-	7.39	6.79	4.04	5.48	13.14	4.69
<i>ADI Com.</i>	-	-	6.53	5.48	4.25	4.67	10.43	4.59
<i>ADI RRB</i>	-	-	1.68	2.12	0.58	1.41	3.57	1.74
<i>SRS SC</i>	46.60	5.86	60.69	17.27	53.05	10.34	71.86	19.55
<i>SRS RRB</i>	44.37	4.46	57.75	20.09	48.26	11.63	71.62	22.10
<i>SRS total</i>	45.66	5.96	61.50	20.16	52.37	11.74	74.85	22.76

^aWechsler Abbreviated Scales of Intelligence (WASI) Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI) and Full-Scale IQ (FSIQ); ^bAutism Diagnostic Observation Schedule (ADOS) Social Affect (SA), Restricted Interests and Repetitive Behaviours (RRB) and total calibrated severity, score; ^cAutism Diagnostic Interview-Revised (ADI) social, communication (com.) and restricted interests and repetitive behaviour scales (RRB). ^d Social Responsiveness Scale (SRS) average Social Communication scales (SC), Restricted Interests and Repetitive Behaviours (RRB) and total score.

6.3 Measures

The *Autism Observation Scale for Infants* (AOSI; Brian et al., 2008; Bryson et al., 2007) is a semi-structured observational assessment of ASD-related behaviours in infancy. Data were collected at 7 and 14 months and the total score was used as a measure of severity of ASD symptoms.

The *Autism Diagnostic Observation Schedule – Second Edition* (ADOS-2; Lord et al., 2012), a semi-structured observational assessment of ASD related behaviours, was used at 7 years of age. The Calibrated Severity Scores for Social Affect, Restricted and Repetitive Behaviours (RRB) and Overall Total were computed (Gotham et al., 2009; Hus, Gotham, & Lord, 2014) which provide standardised measures of autism severity accounting for differences in age and verbal ability.

The *Autism Diagnostic Interview – Revised* (ADI-R; Le Couteur, Lord, & Rutter, 2003), a structured parent interview, was completed with parents of HR children at 7 years of age. Standard algorithm scores were computed for Reciprocal Social Interaction,

Communication, and Restricted, Repetitive and Stereotyped Behaviours and Interests (RRB).

The *Social Responsiveness Scale – Second Edition (SRS-2; Constantino, 2012)* is a parent-report measure of social impairment. Age-normed total SRS T-scores (mean=50; SD = 10), RRB T scores and average T scores from the social communication scales (social awareness, social cognition, social communication and social motivation) were used in the analysis.

The *Mullen Scales of Early Learning (MSEL, Mullen, 1995)* is a standardised measure (mean 100; SD 15) of motor and cognitive development from 0-68 months. The assessment includes five subscales: gross motor (GM), visual reception (VR), fine motor (FM), receptive language (RL) and expressive language (EL). An Early Learning Composite standard score (ELC) is calculated based on all scales apart from GM. An estimate of non-verbal developmental ability (NVT-score) was computed by averaging the T scores for Visual Reception and Fine Motor subscales. This was completed at visits 1-4.

The *Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI; Wechsler, 2011)* is a standardised (mean 100; SD 15). measure of cognitive ability. The four subtest version was used to estimate verbal (Verbal Comprehension Index, VCI), performance IQ (Perceptual Reasoning Index, PRI)) and full-scale IQ (FSIQ) at 7 years of age

The *Vineland-II (Sparrow et al., 2005)* is a semi-structured interview in which parents rate their child's current level of adaptive functioning in the domains of Communication, Daily Living and Socialization. Age-normed V-scale scores (mean 15; SD 3) of EL and RL, from the Communication domain of the Vineland-II, were used to assess language ability. The Vineland-II was collected at visits 1-5.

The *Clinical Evaluation of Language Fundamentals – Fourth Edition UK (CELF-4; Semel et al., 2006)* is a standardised measure of language ability. Standard scores (mean 10; SD 3) from the Recalling Sentences and the Concepts and Following Directions subtests were used as outcome measures of EL and RL, respectively. The

CELF-4 was completed with children at 7 years of age. Six HR and 10 LR children did not complete the assessment due to time constraints or insufficient language (2 HR-ASD).

6.4 Experimental tasks

Infants were administered eye-tracking tasks during the first and second visits; at 7 and 14 months.

Eye tracking and calculation of the eye-mouth index (EMI)

Details of this task have previously been published in Elsabbagh et al. (2014). Following a baseline condition to orient their attention to the screen, infants were presented with videos of female faces showing four different communicative signals; (i) the eyes displayed gaze shifts towards or away from the infant while no other face part was moving, (ii) the mouth displayed vowel articulation movements while no other face part was moving, (iii) the hands placed next to the face displayed upward to downward motion, while no other part of the face was moving and (iv) the eyes, mouth and hands moved displaying a 'peek-a-boo' sequence. Each sequence lasted approximately 16 s and was presented in a pseudorandom order, with a maximum of eight total trials of each sequence per infant.

During the task, the infant was seated on the parent's lap, at 50cm from the screen, with height and distance of the screen adjusted to ensure good eye tracking. Eye tracking data were collected with a 17-inch flat-screen Tobii eye tracker, which measured gaze direction of each eye separately to evaluate where on the screen the infant was looking. This was achieved using an infrared light source and a camera to record corneal reflection data. A five-point calibration sequence was run. Recording and presentation of the stimuli started when at least four calibration points were marked as properly attuned to each eye. Gaze data were recorded at 50 Hz and fixations were defined using temporal (100 ms) and spatial (35 pixels) filters.

Clearview software was used for gaze data extraction. Areas of interest (AOIs) were defined around the eye, mouth and hands. These were contrasted with another AOI

covering all other areas of the face. Trials were excluded if there was <1s of looking time data. Infants were excluded from the analysis if they did not complete any valid trials. The majority of infants included in the analysis completed the maximum number of trials (average trial count = 7.5) and accumulated between 8–11 s of valid looking time data in each trial.

Looking time to the eyes relative to the mouth was measured across the four conditions, by calculating an eye–mouth index (EMI; looking time towards the eyes - looking time towards the mouth)/ total looking time to any area of the screen). The measure was scaled by total looking time to account for any unusual looking behaviour.

Gaze Following and attentional engagement

Details of the gaze following task have previously been reported in Bedford et al. (2012) and Senju & Csibra (2008). The infants' attention was directed to the screen using small animations at the beginning of each trial. Each sequence was comprised of three parts. Firstly, the infant saw two objects on a table and a female model 'looking down' (3 s), she then looked up, 'direct gaze' (2 s) and she then turned her head to look at one of the objects, 'shift' (6 s). The congruent object was the object looked at by the model during 'shift' phase. The other, non-gazed at object was the incongruent object. Each infant viewed 12 trials. In different trials the same object was once the congruent object and once the incongruent object. The direction of the female's gaze shift was fixed in a pseudo-random order (RLLRLRRLRLR).

Infants sat on their parent's lap 50 cm away from the screen. Their looking behaviour was recorded using a Tobii eye-tracker mounted below a 17-inch flat screen monitor. The distance and height of the screen were adjusted for each infant to ensure good tracking of their eyes. A five-point calibration sequence was run. The eye-tracking task was started when at least 4 points were marked as correctly calibrated for each eye. Gaze data were recorded at 50 Hz with a spatial resolution of 1° after calibration.

For each trial, three AOIs were defined around the face, congruent object and incongruent object. Trials were excluded if infants did not look to the face during 'direct gaze' or if they looked away from the computer screen for the entire 'shift' phase. Data from the 'shift' phase was used to calculate gaze following (proportion of first looks to the congruent relative to the incongruent object), and attentional engagement (looking time to congruent object for all trials in which the first look was correct).

6.5 Analysis

Group differences were examined using *t*-tests (HR,LR) and ANOVAs (HR-ASD, HR-non-ASD, LR), with adjustments made to account for inequality of variance between groups. Planned contrasts were used to examine group differences between HR-ASD and LR groups, HR non-ASD and LR groups, and HR non-ASD and HR ASD groups. The association between infancy measures and language outcomes was examined in the HR and LR groups. They were not examined by clinical outcome as this would have resulted in small sample sizes in each group. Pearson's correlations were used to examine the relationship between infant's performance on experimental tasks in infancy and language outcomes (CELF EL, RL; Vineland EL, RL) at 7 years of age.

Bonferroni correction was applied to all significant results from group comparisons and correlational analyses, to correct for the number of outcome measures used. Analyses were repeated, covarying for NVIQ at outcome and gender [by creating a "dummy code" (males =0; females =1) for gender], as gender is associated with language ability in the general population (Voyer & Voyer, 2014) and NVIQ has been associated with language outcomes in ASD (Anderson et al., 2007). The normality of the distribution of variables was examined by visually inspecting histograms, as well as the skew, kurtosis Kolmogorov-Smirnov test results (see table 7, appendix B for test results). As there was evidence that data were not normally distributed for the Vineland EL and RL in controls, CELF EL controls, CELF RL both groups, SRS scales, ADOS scales and gaze-time data) significant results from *t*-tests, ANOVAs and

correlations were followed up using non-parametric tests (Mann-Whitney U and Kruskal Wallis tests and Spearman's correlations).

Significant correlations between experimental tasks and language outcomes were followed up with multiple regression analysis in order to examine whether social attention in infancy, or initial non-verbal ability (Mullen NVT), initial language (Mullen EL) or emergent ASD symptoms (AOSI), best predicted language outcome. Experimental measures were entered into the first step as these were the main predictor variables. All other measures were entered into the second step. Regression analyses were only performed where there was a significant correlation between performance on experimental tasks and language outcome in both groups in order to prevent over fitting of the model. The relevant assumptions for regression were checked, for multicollinearity, multivariate outliers, and the assumptions of normality, linearity and homoscedasticity. These assumptions were not violated.

Finally, analyses were conducted between performance on experimental tasks and ASD symptoms at 7 years of age. These were conducted using ADOS-2 SA, RRB and total severity scores, as well as SRS total scores, RRB scores and average scores from the social communication scales. Non-parametric Spearman's rho correlations were used as the data were not normally distributed (see table 7, appendix B). Significant results were corrected for multiple comparisons using bonferroni correction for the number of outcome measures used and followed up with partial correlations to covary for NVIQ and gender ("dummy" coded, see above).

7 Results

7.1 Group differences in language outcomes at 7 years of age

7.1.1 Comparison of HR and LR groups

Descriptive statistics for the language outcome measures for HR and LR groups are provided in table 3. The HR group had significantly lower Vineland EL and RL scores at 7 years of age but did not differ from LR controls on the CELF EL or RL scales (see table 3). Differences on the Vineland EL but not the RL scale remained significant after correcting for multiple comparisons (bonferroni correction ($p(.05/4) = .0125$). Differences were significant on the Vineland EL scale ($F(1,67)=7.97$; $p=.006$) and were significant at trend level on the Vineland RL scale ($F(1,67)=3.84$; $p=.054$) when covarying for NVIQ and gender. Differences on the Vineland RL represented a small to medium effect ($r=.294$) and differences on the EL scale represented a medium effect ($r=.381$). Mann-Whitney U tests indicated significant group differences on the Vineland EL, with differences at trend level for the RL scale ($p=.005$; $p=.070$, respectively). As fewer participants completed the CELF than the Vineland, analysis was repeated using only those who also completed the CELF in order to ensure that the differential pattern of findings, using the two instruments, was not due to power issues. Group differences remained significant on the Vineland EL scale ($t(52) = 2.586$; $p=.013$) and there was a trend for group differences in RL ($t(50.88)=1.72$; $p = .072$).

Table 3 Group means (SD) and group comparisons presented by risk status for 7 year outcome measures.

	LR (N = 34)		HR (N = 39)		Group Comparisons
	Mean	SD	Mean	SD	
CELF RL ^a	12.74	2.24	11.47	3.162	$t(53)=1.65$; $p=.105$
CELF EL	12.65	2.99	11.74	2.408	$t(52)= 1.24$; $p=.221$

<i>Vineland RL</i> ^b	16.70	1.89	15.23	3.099	t(64.14)=2.460; p=.017
<i>Vineland EL</i>	17.24	1.95	15.62	2.797	t(70)=2.81 p=.006

^aClinical Evaluation of Language Fundamentals (CELF) scaled scores for receptive and expressive language (RL, EL); ^b Vineland Adaptive Behaviour Scales scaled scores for expressive and receptive language (EL,RL).

7.1.2 Comparison of HR-ASD, HR-non-ASD and LR groups

Descriptive statistics for HR-ASD, HR non-ASD and LR groups on language outcome measures at 7 years of age are provided in table 4. There were significant group differences on the Vineland EL and RL scales (see table 4). These differences remained significant when covarying for NVIQ and gender [EL: ($F(2,66) = 4.56$; $p = .014$); and RL ($F(2,68) = 4.09$; $p = .021$)]. Planned contrasts indicated significant differences between HR-ASD and LR groups, with the LR group scoring significantly higher than the HR-ASD group on both RL and EL scales ($t(17.95)=2.77$; $p=.013$; $t(69)=3.34$; $p<.001$), representing a small ($r=1.34$) and medium effect respectively ($r=.373$). These differences remained significant after correcting for multiple comparisons (bonferroni correction ($p(.05/4)= .0125$)). There was a trend for difference between HR-ASD and HR non ASD for the Vineland RL scale ($t(24.41)=1.81$; $p=.083$), with the HR non ASD group scoring higher than the HR ASD group. Kruskal-Wallis ANOVA indicated significant group differences on the Vineland EL and RL scales ($p=.006$; $p=.045$ respectively) and follow up Mann Whitney U tests indicated that group differences between HR-ASD and LR groups were significant [(EL: $p= .004$) (RL: $p=.013$)]. There were no differences between HR ASD and HR non-ASD groups. Analysis was repeated using only the participants who also completed the CELF. Group differences remained significant on the Vineland EL scale ($F(1,52)= 6.668$; $p=.013$) and there was a trend for group differences in RL ($F(1,52)= 2.957$; $p=.091$).

Table 4 Group means (SD) and group comparisons presented by risk status and clinical outcome for 7 year outcome measures.

LR (N = 34)	HR-non ASD (N=24)	HR ASD (N = 15)
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	Mean	SD	Mean	SD	Mean	SD	Group Comparisons
<i>CELF RL</i>	12.74	2.24	11.85	3.05	10.83	3.38	F(2,52)= 1.85; p=.168
<i>CELF EL</i>	12.65	2.99	11.30	2.13	12.55	2.77	F(2,52)= 1.85; p=.221
<i>Vineland RL</i>	16.70	1.89	15.96	2.68	14.07	3.45	F(2,69)= 5.52; p=.006
<i>Vineland EL</i>	17.24	1.95	16.21	2.06	14.67	3.56	F(2,69)= 6.01; p=.004

^aClinical Evaluation of Language Fundamentals (CELF) scaled scores for receptive and expressive language (RL, EL); ^b Vineland Adaptive Behaviour Scales V-scale scores for expressive and receptive language (EL,RL).

7.2 Infancy measures and language outcomes.

7.2.1 Group differences in infancy measures

Descriptive statistics and group comparisons for experimental tasks in infancy are displayed in table 5. There were no significant differences between HR and LR groups in terms of EMI, gaze following (GF) or attentional engagement (AE) at 7 or 14 months, though there was a trend towards a significant difference in attentional engagement, with the HR group showing reduced attentional engagement.

Table 5 Descriptive statistics and group differences for infancy measures.

	LR (N = 34)		HR (N = 39)		Group Comparison
	Mean	SD	Mean	SD	
<i>7m EMI^a</i>	.265	.446	.215	.4385	t (62)=.452; p=.653
<i>14m EMI</i>	.245	.499	.241	.432	t (62)=.031; p=.976
<i>7m GF^b</i>	.090	.291	.099	.208	t(52)=.141; p=.129
<i>14m GF</i>	.315	.291	.222	.318	t(52)=1.123; p=.259
<i>7m AE^c</i>	.273	.184	.314	.228	t(49)=-.716; p=.478
<i>14m AE</i>	.334	.158	.264	.104	t(49)=1.84; p=.071

^a7 and 14 month eye-mouth index (EMI); ^b 7 and 14 month gaze following; ^c 7 and 14 month attention engagement.

7.2.2 Eye-mouth index and language outcomes

Seven month EMI was associated with 7 year CELF EL in both groups together ($r(45) = -.505, p < .0001$) and in each group separately [HR ($r(22) = -.489; p = .015$); LR ($r(21) = -.571; p = .004$)], representing a large effect size, with 7 month EMI explaining 25.5% of the variance in CELF EL at 7 years. The relationship between EMI and 7 year EL on the CELF withstood correction for multiple comparisons (bonferroni correction ($p(.05/4) = .025$)). In order to replicate previous findings (Elsabbagh et al., 2014), analysis was repeated covarying for EMI in the single feature conditions (eye, mouth and hand), RL (CELF) and non-verbal IQ (WASI-II) at outcome, and diagnosis at outcome. Gender was added as an additional covariate. Results remained significant ($r(36) = -.323; p = .048$). Seven month EMI was not associated with 7 year EL on the Vineland [both groups ($r(61) = -.079; p = .540$); HR ($r(29) = .036; p = .848$); LR ($r(20) = .042; p = .853$)]. The correlation between 7 month EMI and CELF EL was significant in both groups using a Spearman's rho [HR ($r_s(22) = -.505; p = .014$); LR ($r_s(21) = -.432; p = .035$)].

In order to ascertain the specificity of the relationship between 7 month EMI and EL, analyses were conducted to examine the relationship between 7 month EMI and RL at 7 years, and 14 month EMI and EL and RL at 7 years. There was a trend towards a significant association between seven month EMI and CELF RL at 7 years ($r(46) = -.278; p = .056$) when both of the groups were examined together. There were no other significant associations (see table 8, Appendix B for full correlation tables).

Hierarchical multiple regression analysis was conducted to examine whether EMI or other infancy measures previously associated with language outcomes best predicts EL at 7. EMI was entered in the first step of the analysis and all other variables were entered into the second step. Model 1 and model 2 were both significant [$F(1,45) = 15.39, p < .0001$; $F(4,42) = 5.29, p = .002$]. EMI explained 25.5% of the variance, introducing the other variables to the model explained an additional 8% of the variance in EL. However, R^2 change was not significant for step 2 ($\Delta R^2 = .08; F(3,42) =$

1.69, $p = .183$). Only EMI and initial EL were associated with EL at outcome in model 2.

Table 6 Results of regression of 7 month EMI, ASD symptoms, EL and non-verbal ability on 7 year EL

	B	SE B	β	t	P
1 (Constant)	12.88	.408		31.54	$p < .0001$
7m EMI	-3.13	.798	-.505	-3.92	$p < .0001$
2 (Constant)	9.39	2.89		3.25	.002
7m EMI ^a	-3.49	.796	-.562	-4.38	$p < .0001$
7m Mullen NVT ^b	-.026	.045	-.076	-.570	.571
7m AOSI ^c	.054	.065	.109	.836	.408
7m Mullen EL ^d	.098	.044	.302	2.21	.032

^a7 month eye-mouth index (EMI), ^b7 month Mullen Non-Verbal T score; ^c7 month Autism observation score for infants scale total score (AOSI); ^d7 month Mullen expressive language standard score (EL)

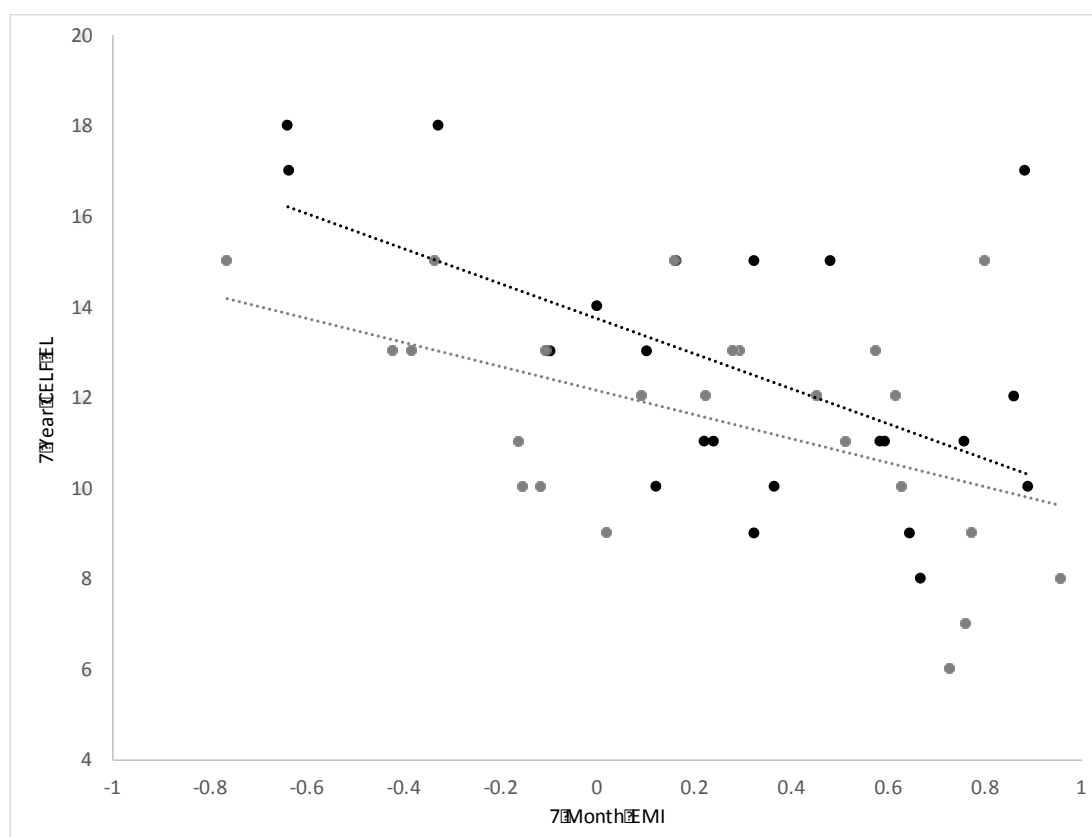


Figure 1 Relationship between 7 month EMI and 7 year EL on the CELF. The HR group are shown in grey, the LR group are shown in black.

7.2.3 Gaze following, attentional engagement and language outcomes

There were no associations between gaze following and language outcomes (table 9, Appendix B) or attentional engagement at 7 or 14 months and RL at 7 years of age, in the group overall or in either group when examined separately (table 9, appendix B). There was a significant positive correlation between attentional engagement at 7 months and Vineland EL at 7 years in the HR group ($r(22) = .448$; $p = .028$) but this did not withstand correction for multiple comparisons (bonferroni correction ($p(.05/4) = .0125$). An examination of the scatterplot suggested that one case may be influencing the results. When this case was removed the correlation was no longer significant ($r(21) = .123$; $p = .575$; see figure 2, Appendix B), suggesting that this individual may be driving the results. However, given the limited sample size and the fact that the outlier was less than three standard deviations from the mean, it may be best to replace it by a value one point above the highest non-outlier score (.73; see Tabachnick & Fidell, 2012). This procedure suggested that the trend remained the same ($r(22) = .356$; $p = .088$). The correlation was not significant using Spearman rho ($r_s(22) = .306$; $p = .146$). There were no associations between gaze following and language outcomes (see table 9, Appendix B, for full correlation tables).

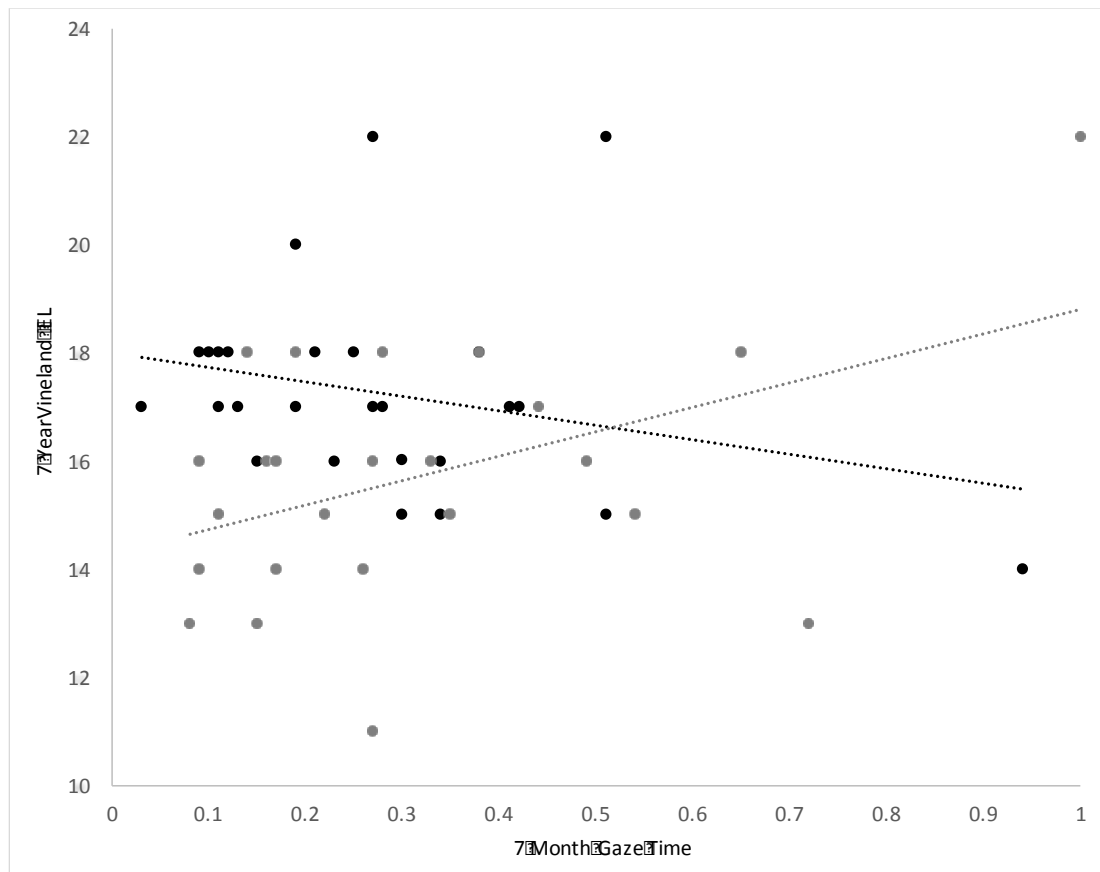


Figure 2 Relationship between 7 month gaze time and 7 year EL on the Vineland. The HR group are shown in grey, the LR group are shown in black.

7.3 Infancy measures and ASD symptoms at 7 years

7.3.1 Eye-mouth index and ASD symptoms

EMI at 7 months was negatively associated with SRS total and social communication scores in both groups ($R_s(57) = -.289$; $p = .027$; $R_s(57) = -.277$; $p = .033$), representing small effect sizes. Greater attention to the eyes was associated with fewer ASD symptoms. In the HR group, EMI was negatively associated with SRS total, RRB and social communication scores ($R_s(26) = -.408$; $p = .031$; $R_s(26) = -.454$; $p = .015$; $R_s(26) = -.392$; $p = .039$), representing moderate effect sizes. Only the correlation between EMI and RRB in the HR group withstood correction for multiple comparisons (bonferroni correction ($p(.05/3) = .016$)). Analyses were repeated, covarying for NVIQ and gender, correlations remained significant between EMI and SRS social communication and total scores ($R(54) = -.381$; $p = .004$; $R(54) = -.392$; $p = .003$) and

for SRS total, RRB and social communication scores ($R(23) = -.480$; $p = .015$; $R(23) = -.502$; $p = .011$; $R(23) = -.466$; $p = .019$) in the HR group. EMI was not associated with scores on the ADOS. (see tables 11 and 12, Appendix B, for full correlation tables).

7.3.2 Gaze following, attentional engagement and ASD symptoms

7 month gaze following was negatively associated SRS SC scores in the HR group ($R_s(21) = -.418$; $p = .047$; moderate effect size), such that better gaze following was associated with fewer ASD symptoms. This did not withstand correction for multiple comparisons (bonferroni correction ($p(.05/3) = .016$). There was a trend in the same direction covarying for NIQ and gender ($R(18) = -.411$; $p = .072$). Attentional engagement (gaze time) at 14 months was negatively associated with ADOS-SA ($R_s(47) = -.434$; $p = .002$), ADOS-RRB ($R_s(47) = -.303$ $p = .034$), and ADOS total severity ($R_s(47) = -.428$; $p = .002$; small to moderate effect sizes) in both groups, such that greater attentional engagement was associated with less severe symptoms. In the HR group, 14 month attentional engagement was associated with ADOS-SA and total severity [ADOS-SA ($R_s(22) = -.417$; $p = .042$); ADOS total severity ($R_s(22) = -.412$; $p = .045$; moderate effect sizes)]. (Full correlation tables are presented in tables 11 and 12, Appendix B).

Correlations between attentional engagement and ADOS SA and total severity withstood correlation for multiple comparisons when examined across both groups, but were not significant in the HR group alone (bonferroni correction ($p(.05/3) = .016$). Correlations between attentional engagement and ADOS-SA ($R_s(45) = -.376$; $p = .009$), ADOS-RRB ($R(45) = -.293$ $p = .046$). and ADOS total severity ($R(45) = -.$; $p = .011$) were significant in both groups when covarying for NVIQ and gender. Correlations between attentional engagement and ADOS scores were not significant in the HR group when covariates were included [ADOS-SA ($R(20) = -.342$; $p = .120$); ADOS total severity ($R(20) = -.368$; $p = .092$).

8 Discussion

8.1 Group differences in language outcomes at 7 years of age

The results of the current study indicated that HR infants with a diagnosis of ASD had difficulty with the communicative use of EL and RL language, when compared with LR controls at seven years of age. This is in keeping with previous studies showing impaired language ability in children with ASD and HR children who meet diagnostic criteria for ASD. (Kjelgaard & Tager-Flusberg, 2001; Luyster et al., 2007; Mitchell et al., 2006; Thurm et al., 2007). HR infants without a diagnosis of ASD did not differ significantly from either of the other two groups, though there was a trend towards a significant difference between HR ASD and HR non-ASD groups for the Vineland RL scale, with the HR non-ASD group scoring higher than the HR ASD group. This suggests that the HR non-ASD group shows a language profile that is more similar to LR controls than to HR-ASD siblings. These results are in keeping with those of previous studies indicating that by middle childhood as whole HR infants without a diagnosis of ASD do not differ from controls in terms of structural and pragmatic language outcomes (Drumm et al., 2015; Gillespie-Lynch et al., 2015; Warren et al., 2012).

Overall the HR group had reduced EL and RL on a measure of everyday use of language, compared to LR controls, with group differences in EL remaining significant after covarying for NVIQ. This is in keeping with previous studies indicating language impairments in HR siblings in early childhood, when outcomes are not examined in relation to diagnostic outcome (Curtin & Vouloumanos, 2013; Droucker et al., 2013; FERENCE & Curtin, 2015; Hudry et al., 2014; Mitchell et al., 2006; Seery et al., 2014; Young et al., 2009). As discussed above, group differences between HR and LR children are likely to have been driven by group differences associated with clinical outcome. Nonetheless, previous studies of language abilities in middle childhood have suggested that some HR siblings without a diagnosis of ASD have difficulty with EL and RL, as well as the pragmatic use of language (Ben-

Yizhak et al., 2011; Miller et al., 2015), therefore there are potential subgroups of HR children without ASD who have language difficulties.

Group differences at 7 years of age emerged on the Vineland but not the CELF EL and RL scales. The CELF is a structured, examiner administered assessment of language ability, which has been used in previous studies of HR infants in middle childhood (Miller et al., 2015; Pilowsky et al., 2003), whereas the Vineland is a parental report measure of language use in everyday life. This suggests that high-functioning children with ASD can complete structured language assessments but have difficulty with the everyday use of language for communicative purposes. Indeed, epidemiological findings indicate that adaptive functioning is significantly lower than IQ, and is impaired in children of average intelligence, in ASD (Charman et al., 2011). Group differences in language outcome were stronger for EL than RL for both HR, LR comparisons and HR ASD, HR-non-ASD and LR comparisons. This counters previously reported findings indicating that HR siblings and children with ASD do not show the typical RL to EL advantage (Hudry et al., 2014; Luyster et al., 2007). Stronger group differences on the EL scale may have been due to the measurement of EL and RL on the Vineland. It may be that comprehension is more difficult to assess than language expression, especially on parent report measures, where parents may find it difficult to know how much their child understands.

8.2 Infancy predictors of language outcomes at age 7

As predicted, EMI during complex social scenes at 7 months was negatively associated with EL at 7 years in HR and LR groups. This extends upon previous findings indicating that EMI was associated with EL in early childhood (Elsabbagh et al., 2014; Young et al., 2009). The relationship between EMI and EL held, when accounting for EMI during simple social scenes, NVIQ and RL at 7 years as well as gender and clinical outcome. In addition, EMI at 7 months was a better predictor of 7 year EL than other markers previously associated with language outcomes - including initial language ability (Luyster et al., 2007; Paul, Chawarska, Cicchetti, & Volkmar, 2008; Thurm et al., 2007), non-verbal ability (Anderson et al., 2007; Thurm, Manwaring, Swineford, & Farmer, 2015) and autistic symptoms (Moricke,

Swinkels, Beuker, & Buitelaar, 2010; Thurm et al., 2015). The only other marker which predicted EL at 7 years was initial EL. As such, the results of this study indicate that EMI is an important longitudinal predictor of language – regardless of risk group or clinical status and that it predicts language outcomes over and above the other markers examined.

As has been previously suggested, greater attention to the mouth relative to the eyes in infancy may reflect endogenous attentional control mechanisms (Elsabbagh et al., 2014). This in turn may lead to better EL development by facilitating attention to the mouth during speech perception. As in previous studies, EMI at 7 months, but not 14 months, was associated with later EL. Evidence from typically developing infants indicates that between approximately four and eight months of age, infants shift attention from the eyes to the mouth of a speaker (Hillairet de Boisferon, Tift, Minar, & Lewkowicz, 2016; Lewkowicz & Hansen-Tift, 2012). This time period corresponds approximately with the canonical babbling stage and is thought to facilitate native language acquisition by providing redundant and highly salient speech cues. From approximately 12 months, infants shift attention back to the eyes when listening to native speech. Attention to the eyes is thought to facilitate access to social cues, once native language expertise has begun to emerge (Lewkowicz & Hansen-Tift, 2012).

The results of the current study and of previous research suggest that the association between EMI and later language may be specific to EL. Young et al. (2009) reported that EMI was negatively associated with growth in EL between 6 and 24 months, as well as EL at 24 months, whereas EMI was only associated with RL at 24 months. Additionally, Young et al. (2009) reported that whereas EMI was associated with EL on both the MSEL and the Vineland, it was only associated with RL on the MSEL. This reflects findings from the current study which indicated that 7 month EMI was only associated with RL at trend level at 7 years when HR and LR groups were examined together. It is therefore likely that the association between EMI and RL is explained by the association between EL and RL.

The results of this study indicated that EMI predicted language outcomes on the CELF but not on the Vineland. Indeed this is in keeping with the results of previous studies that have reported associations between EMI and performance on the MSEL (Elsabbagh et al., 2014; Young et al., 2009), which like the CELF is a structured, examiner administered measure of language ability. Although Young et al., (2009) also reported associations with the Vineland, the association with EL was only significant for EL at 24 months and not with EL growth. In addition, in a study of toddlers with ASD, those with lower EMI (more attention to the mouth) had higher formal language (verbal developmental quotient) compared to their functional language as measured by the Vineland (Campbell et al., 2014). It may be that EMI predicts language outcome on structured assessments due to underlying attentional control mechanisms that also underlies performance on structured tests of language ability.

Contrary to expectations, attentional engagement was not associated with RL at 7 years of age. This runs contrary to previous research indicating associations between both gaze following with vocalisation and attentional engagement, and RL in TD infants, HR and LR toddlers (Bedford, 2012; Brooks & Meltzoff, 2005). It may be that this measure predicts language outcome in early childhood but not later childhood. However, the results from the current study suggest that 7 month attentional engagement may be associated with later EL, which is in line with previous research has indicated associations between joint attention and EL (Charman et al., 2003; Charman, 2003; McDuffie & Yoder, 2010; Yoder et al., 2015).

It may that differences in task demands between the EMI and gaze following tasks explain the differential relationships with seven year outcome. The gaze following task is a relatively simple task whereby the infant follows cues provided by the examiner and therefore may reflect more exogenous attentional control mechanisms whereas the EMI task requires more endogenous attentional control. It may be that these endogenous control mechanisms are particularly important for language learning. On the other hand, it may be that the EMI task is a better predictor of language outcome than the gaze following task because it specifically examines attention the mouth relative to the eyes, which is thought to be play a key

role in native language acquisition (Hillaiet de Boisferon et al., 2016; Lewkowicz & Hansen-Tift, 2012).

8.3 Infancy predictors and ASD symptoms

EMI was associated with ASD symptoms on the SRS. EMI was not associated with ASD symptoms in previous studies, however Young et al. (2009) reported that EMI was negatively associated with socialisation on the Vineland (but that this was accounted for by the relationship with EL). In a study of toddlers with ASD EMI was not associated with socialisation on the Vineland (Campbell et al., 2014). The direction of the effect in the current study was such that more attention to the mouth relative to the eyes at 7 months was associated with increased parent-reported social communicative and total ASD traits at 7 years and more attention to the eyes, relative to the mouth was associated with fewer traits in both groups. EMI was also associated with repetitive behaviours in the HR group. These results may be interpreted in the context of developmental changes in attention to the eyes relative to the mouth in infancy. From birth to 6 months infants pay more attention to the eyes than the mouth (Cassia, Turati, & Simion, 2004; Haith, Bergman, & Moore, 1977), with a shift towards attention to the mouth emerging at approximately six months, at the same time as endogenous attention mechanisms emerge (Colombo, 2001; Richards, Reynolds, & Courage, 2010). Attention to the eyes is thought to be important for social and cognitive development (Langton, Watt, & Bruce, 2000) but it may be that at this critical period for language acquisition, endogenous control mechanisms are required to direct attention to language cues during speech perception and that attention to the eyes detracts from important linguistic information.

Seven month gaze following was negatively associated parent reported social communication such that better gaze following was associated with fewer ASD traits in the HR group, however this did not withstand correction for multiple comparisons. Attentional engagement at 14 months was negatively associated with direct assessments of social-communicative, repetitive behaviours and total symptoms in both groups, such that greater attentional engagement was associated

with less severe symptoms. The association between attentional engagement and social and total symptoms was also significant in the HR group. This is in keeping with previous findings in this cohort, indicating that looking time was associated with total ASD symptoms on the ADOS at two and three years of age and that the effect was largely driven by the HR group (Bedford et al., 2012). Therefore it may be that gaze following is a better predictor of long term ASD symptoms than language ability.

It is worth noting that both EMI and attentional engagement were associated with restricted and repetitive behaviours as well as social communication abilities. This suggests that ASD symptoms may have a common aetiology, which runs contrary to the proposal that the aetiology of ASD traits is distinguishable at the genetic, neural and cognitive level (Happé & Ronald, 2008).

8.4 Theoretical implications

The results of the current study indicated that HR infants with ASD showed difficulties with language use at seven years of age but that those without ASD did not show significant difficulty. This is in keeping with results of previous studies (Drumm et al., 2015; Gillespie-Lynch et al., 2015; Warren et al., 2012) and suggests that language impairments may not form part of the BAP in later childhood.

The association between seven month EMI and EL at seven years in both HR and LR groups, has implications for theories of social processing and language development (Bruner, 1983; Patricia K. Kuhl, 2007) and theories of social attention in ASD, which suggest that initial difficulties with social orienting lead to social-communicative and language difficulties in ASD (Dawson et al., 2004). The results suggest that the modulation social attention is important for language development across typical and atypical development and that the same aetiological mechanisms underlie language development in HR and LR groups, regardless of clinical outcome. Interestingly, EMI was also associated with parent reported ASD traits at seven years of age but the association was such that attention to the mouth was associated with more ASD traits. On the other hand, attentional engagement was

associated with less severe symptoms as measured by a direct assessment of the child. This suggests that different mechanisms underlie language development on the one hand, which is facilitated by attention to the mouth, and the development of ASD symptoms on the other, for which attention to the eyes and engagement with an object of reference predicts fewer ASD traits and symptoms. Importantly, EMI at 7 but not 14 months was associated with later EL suggesting that this is a critical period for language acquisition.

Although the EMI task did not examine multisensory integration specifically, the results suggest that attention to social information in the visual domain is important for language learning, and difficulties with the use of visual information to enhance auditory perception may give rise to language learning difficulties in ASD. Atypical processing of faces (see Golarai, Grill-Spector, & Reiss, 2006, for review) and attention to the eyes and mouth have been reported in ASD (Chawarska, Macari, & Shic, 2013; Jones, Carr, & Klin, 2008; Neumann, Spezio, Piven, & Adolphs, 2006; Spezio, Adolphs, Hurley, & Piven, 2007). Therefore atypical visual attention to faces and/or multisensory integration (Iarocci & McDonald, 2006; Stevenson et al., 2014) of visual and auditory information may influence speech perception in ASD, impacting upon language development. Indeed previous research has suggested that HR infants and children with ASD may not use the visual information to facilitate speech perception (Guiraud et al., 2012; Woynaroski et al., 2013).

Finally, there is a large body of research supporting the role of joint attention in language learning (Adamson, Bakeman, Deckner, & Ronski, 2009; Charman et al., 2003; Gillespie-Lynch et al., 2015; Malesa et al., 2013; Morales et al., 2000; Thurm, Lord, Lee, & Newschaffer, 2007; Yoder, Watson, & Lambert, 2015). Although JA may play an important role in language development during toddlerhood, the results of this study did not provide strong evidence that the precursors of JA (gaze-following/attentional engagement) play an important role in language acquisition.

8.5 Strengths and Limitations

An important strength of the current study is the use of the HR infant design. This allowed us to examine potential precursors to language development in HR and LR infants prospectively using both direct assessment of infants behaviour and parent report measures. Although the majority of the participants were retained to seven years of age, the loss of some participants, together with the fact that diagnostic information were not available for all participants resulted in a reduced sample size at seven years of age. Importantly, the retained sample did not differ from the non-retained sample on measures of ASD symptoms, developmental level or adaptive functioning (Shepard et al, *submitted*), suggesting that the sample retained to 7 years was unbiased. Not all participants were able to complete the CELF, due to time constraints and language difficulties (in one case). A potential limitation of the HR infant design is that samples tend to be self-selecting and higher functioning than clinically ascertained samples. As such, the results may not generalise to the wider ASD population. Nonetheless, given the rarity of these longitudinal data, these results make an important contribution to the literature, which may be followed up in future studies.

8.6 Directions for future research

The results of the current study raise a number of questions that may be addressed by future research. As has been discussed, HR infants without ASD did not differ from LR infants in terms of structural language outcomes at 7 years of age. However, certain individuals who do not have a diagnosis of ASD may have difficulties with language development that persist in later childhood. Future studies, with larger samples could examine subgroups of HR infants with language difficulties who do not meet diagnostic criteria for ASD in order to better understand whether the same aetiological mechanisms give rise to language difficulties in these children.

It will be important that future studies examine mechanisms that underlie performance on the EMI task, as well as the mechanisms that underlie the

association between EMI and EL (and the potential specificity of this relationship), on the one hand, and EMI and ASD traits, on the other. Future studies should examine the role of non-social endogenous attentional control mechanisms, in order to ascertain the specificity of this association with social attention. The results of the current study suggested that EMI may be a better predictor of EL than initial EL, non-verbal ability and ASD symptoms. As the focus of this study was on the role of EMI and gaze-following/attentional engagement in predicting later language, the role of other potential predictors was not examined in their own right. It will be important that future studies examine the role of other potential predictors, including child-focused (e.g. initial verbal ability and ASD symptoms), transactional (e.g. parent-child interaction) and environmental (e.g. socio-economic status) factors, and how these interact with EMI, in order to better understand causal pathways to language development. Finally, these results suggest that EMI may be a useful endophenotype for use in future genotype-phenotype studies. This could enable future research to go back along the developmental pathway to uncover the origin of language and communication difficulties among certain individuals.

8.7 Practical implications

In terms of the implications for services and public policy, the results of this study indicate that HR siblings may not require intervention aimed at improving their language abilities and resources would best be focused on identified areas of difficulty such as increased ASD symptoms (Charman, *in press*). In addition, the results of this study suggest that different mechanisms may underlie the development of language and ASD symptoms. As such, interventions that target ASD symptoms may not improve language outcomes. Indeed early intervention studies have yielded mixed results in relation to language outcomes. For example, an RCT of a parent-mediated communication-focused intervention for young children with ASD, indicated significant reductions in ASD symptoms and improvements in parent reported but not examiner assessed language outcomes (Green et al., 2010). Results from a positive parenting program for HR infants indicated positive gains on all outcome measures including infant attentiveness and

adaptive function, with the exception of language outcomes where nil to negative effects were reported (Green et al., 2015). Taken together with the present findings, these results suggest that separate interventions that target early markers of language development may be better suited to improve language outcomes. The results of this study indicate that interventions which facilitate attention to specific aspects of the face (i.e. the mouth) during speech perception in early infancy could improve language outcomes for those who are at risk of language difficulties.

8.8 Conclusions

Children with ASD had significant difficulties with the communicative use of language at 7 years of age whereas HR infants without ASD were unimpaired relative to controls. This suggests that language difficulties may not form part of the BAP in middle childhood. EMI - attention to the mouth relative to the eyes - during complex social scenes, in early infancy, predicted language outcome in later childhood regardless of risk status or clinical outcome. This measure may be a better predictor than other variables previously associated with language outcomes, such as initial language ability. Attention to the mouth was associated with more ASD traits at 7 years. There was not strong evidence to support the role of attentional engagement during gaze following in language development, though the results suggested that attentional engagement was associated with less severe ASD symptoms at seven years of age. This mirrors findings from clinically referred ASD samples indicating small associations between social and language abilities over time (Bennett et al., 2015). Taken together this implies that different developmental mechanisms give rise to language difficulties and ASD symptoms in children at HR of ASD and in typical development.

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10 Appendix A: Ethical approval, participant information sheets, assent and consent forms.


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13 May 2014

Prof Tony Charman
Chair in Clinical Child Psychology
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Dear Prof Charman

Study title:	The British Autism Study of Infant Siblings: 7-Year Follow-up of children at high- and low- familial risk for autism (BASIS-7)
REC reference:	14/LO/0170
Protocol number:	CSA/14/001
IRAS project ID:	143744

Thank you for your letter of 06 February 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and Vice-Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Shehnaz Ishaq, nrescommittee.london-central@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).



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Participant Identification Number:

CONSENT FORM

Title of Project: British Autism Study of Infant Siblings – 7-year Follow-up (BASIS-7)

Name of Researchers: Tony Charman, Mark Johnson, Francesca Happé, Lizzie Shephard, Bosiljka Milosavljevic

REC reference: 14/LO/0170

I confirm I have read and understand the Information Sheet YES/NO

I have had the opportunity to consider the information and ask questions that have been answered satisfactorily. YES/NO

I understand that my child's participation is voluntary and that we are free to withdraw at any time, without giving any reason, without our medical care or legal rights being affected. YES/NO

I understand that relevant parts of my child's data collected during the study may be looked at by responsible regulatory authorities where it is relevant to our taking part in this research. I give permission for these individuals to have access to such information. YES/NO

I understand that this research may involve video-recordings which may be shared with other responsible research groups within the UK and internationally. These recordings will be given a code and stored securely. YES/NO

I understand the data collected in this study will be entered into a research database and shared with other responsible research groups within the UK and internationally. Data will be coded to maintain confidentiality. YES/NO

I understand that the data collected in this study may be used in future ethically approved research. YES/NO

**BASIS-7: British Autism Study of Infant Siblings 7-year follow-up
Consent/Assent form Version 1.0 13/01/2014**

I agree to my personal information (information that can identify me or my child) being securely shared with the EU-AIMS ALS study team to help my participation in both studies.
YES/NO

I AGREE THAT MY CHILD MAY TAKE PART IN THIS STUDY. YES/NO

FOR CHILD: I AGREE TO TAKE PART IN THIS STUDY. YES/NO

Name of Parent Date Signature

Name of Child Date Signature

Name of Person taking consent Date Signature

One copy for Researcher

One copy for Participant to keep for own records

11 Appendix B: Supplementary material

Tests of normality rests are provided in table 7. Correlation tables for EMI, gaze following and attentional engagement and language outcomes (tables 8, 9 and 10), as well as infancy predictors and ASD severity scores (table 11). Significant correlations are marked with an asterisk and highlighted in bold. Graph of the correlation between gaze time (attentional engagement) and vineland EL with outlier removed (figure 3).

Table 7 Tests of Normality of distribution of variables

Kolmogorov-Smirnov Test						
Measure	Group	Statistic	df	Sig.	Skew	Kurtosis
Gaze Following (7 months)	Control	.156	19	.200	.806	-.318
	HR sibling	.148	15	.200	-.299	-.508
Gaze Following (14 months)	Control	.102	19	.200	-.152	-.841
	HR sibling	.115	15	.200	.631	-.087
Gaze time (7 months)	Control	.167	19	.169	1.80	4.22
	HR sibling	.137	15	.200	.983	.749
Gaze time (14 months)	Control	.158	19	.200	1.64	3.58
	HR sibling	.170	15	.200	1.16	1.72
EMI (7 months)	Control	.136	19	.200	-.602	-.273
	HR sibling	.131	15	.200	.031	-1.43
EMI (14 months)	Control	.171	19	.145	-.817	-.133
	HR sibling	.115	15	.200	-.447	-.355
CELF RL ^a	Control	.212	19	.024	-.724	-.526
	HR sibling	.272	15	.004	-1.42	.580
CELF EL	Control	.168	19	.166	.512	.524
	HR sibling	.187	15	.165	-.356	.580
	Control	.176	19	.123	-.436	.542

VABS RL ^b	HR sibling	.140	15	.200	-.388	.580
VABS EL	Control	.261	19	.001	.723	.524
	HR sibling	.167	15	.200	.941	.580
SRS RRB ^c	Control	.229	19	.010	1.81	2.99
	HR sibling	.230	15	.032	1.326	.580
SRS Social. Com.	Control	.117	19	.200	.822	1.76
	HR sibling	.214	15	.064	.870	.234
SRS Total Score	Control	.188	19	.075	1.34	.524
	HR sibling	.254	15	.010	.964	.142
ADOS-2 SA CSS ^d	Control	.284	19	.000	2.07	5.67
	HR sibling	.237	15	.023	1.05	.134
ADOS-2 RRB CSS	Control	.538	19	.000	4.36	19.00
	HR sibling	.265	15	.006	-.052	-1.81
ADOS-2 Total CSS	Control	.321	19	.000	3.28	12.33
	HR sibling	.351	15	.000	1.33	.960

^aClinical Evaluation of Language Fundamentals (CELF) scaled scores for receptive and expressive language (RL, EL); ^bVineland Adaptive Behaviour Scales scaled scores for expressive and receptive language (EL,RL); ^cSocial responsiveness scale (SRS) restricted interests and repetitive behaviours (RRB) social communication and total scores. Autism Diagnostic Observation Schedule (ADOS)^d Social Affect (SA), Restricted Interests and Repetitive Behaviours (RRB) and total calibrated severity scores.

Table 8 Correlations between EMI and 7 year old language outcomes

		CELF RL ^a	CELF EL	Vine- land RL	Vine- land EL	CELF RL	CELF EL	Vine- land RL	Vine- land EL
		7m EMI				14m EMI			
Both groups	<i>R</i>	-.278	-.505**	.010	.079	-.107	-.081	.075	.107
	<i>P</i>	.056	.000	.936	.540	.471	.586	.557	.405
	<i>Df</i>	46	45	61	61	46	45	61	61
HR	<i>R</i>	-.332	-.489*	-.005	.036	-.017	-.129	.149	.032

LR	<i>P</i>	.105	.015	.978	.848	.933	.539	.414	.861
	<i>Df</i>	23	22	29	29	24	23	30	30
	<i>R</i>	-.268	-.571**	.002	.118	-.329	-.073	-.039	.205
	<i>P</i>	.216	.004	.992	.522	.135	.747	.833	.268
	<i>Df</i>	21	21	30	30	20	20	29	29

^aClinical Evaluation of Language Fundamentals (CELF) scaled scores for receptive and expressive language (RL, EL); ^b Vineland Adaptive Behaviour Scales scaled scores for expressive and receptive language (EL,RL).

Table 9 Correlations between gaze following and 7 year old language outcomes

		CELF RL ^a	CELF EL	Vine- land RL	Vine- land EL	CELF RL	CELF EL	Vine- land RL	Vine- land EL
		7m GF				14 m			
Both groups	<i>R</i>	-.266	-.245	-.099	.006	.068	.160	.228	.071
	<i>P</i>	.142	.177	.521	.967	.710	.380	.137	.646
	<i>Df</i>	30	30	42	42	30	30	42	42
HR	<i>R</i>	-.298	-.055	.119	.215	.059	.317	.250	.237
	<i>P</i>	.203	.822	.563	.290	.804	.186	.218	.244
	<i>df</i>	18	17	24	24	18	17	24	24
LR	<i>R</i>	.045	-.111	-.400	-.129	-.295	-.008	.124	-.168
	<i>P</i>	.869	.683	.065	.566	.268	.977	.582	.455
	<i>df</i>	14	14	20	20	14	14	20	20

^aClinical Evaluation of Language Fundamentals (CELF) scaled scores for receptive and expressive language (RL, EL); ^b Vineland Adaptive Behaviour Scales scaled scores for expressive and receptive language (EL,RL).

Table 10 Correlations between attention engagement and language outcomes at 7 years of age

		CELF RL ^a	CELF EL	Vine- land RL	Vine- land EL	CELF RL	CELF EL	Vine- land RL	Vine- land EL
		7m GF				14 m GF			
Both groups	<i>R</i>	-.097	-.022	-.003	.139	.260	.101	-.003	.221
	<i>P</i>	.597	.907	.984	.369	.151	.583	.986	.150
	<i>df</i>	30	30	42	42	30	30	42	42
HR	<i>R</i>	-.022	-.057	.087	.448*	.282	.076	.076	.154
	<i>P</i>	.929	.823	.687	.028	.242	.766	.723	.473
	<i>df</i>	17	16	22	22	17	16	22	22
LR	<i>R</i>	-.079	.009	.038	-.182	.148	.067	-.304	.132
	<i>P</i>	.770	.972	.865	.418	.584	.805	.169	.559
	<i>df</i>	14	14	20	20	14	14	20	20

^aClinical Evaluation of Language Fundamentals (CELF) scaled scores for receptive and expressive language (RL, EL); ^b Vineland Adaptive Behaviour Scales scaled scores for expressive and receptive language (EL,RL).

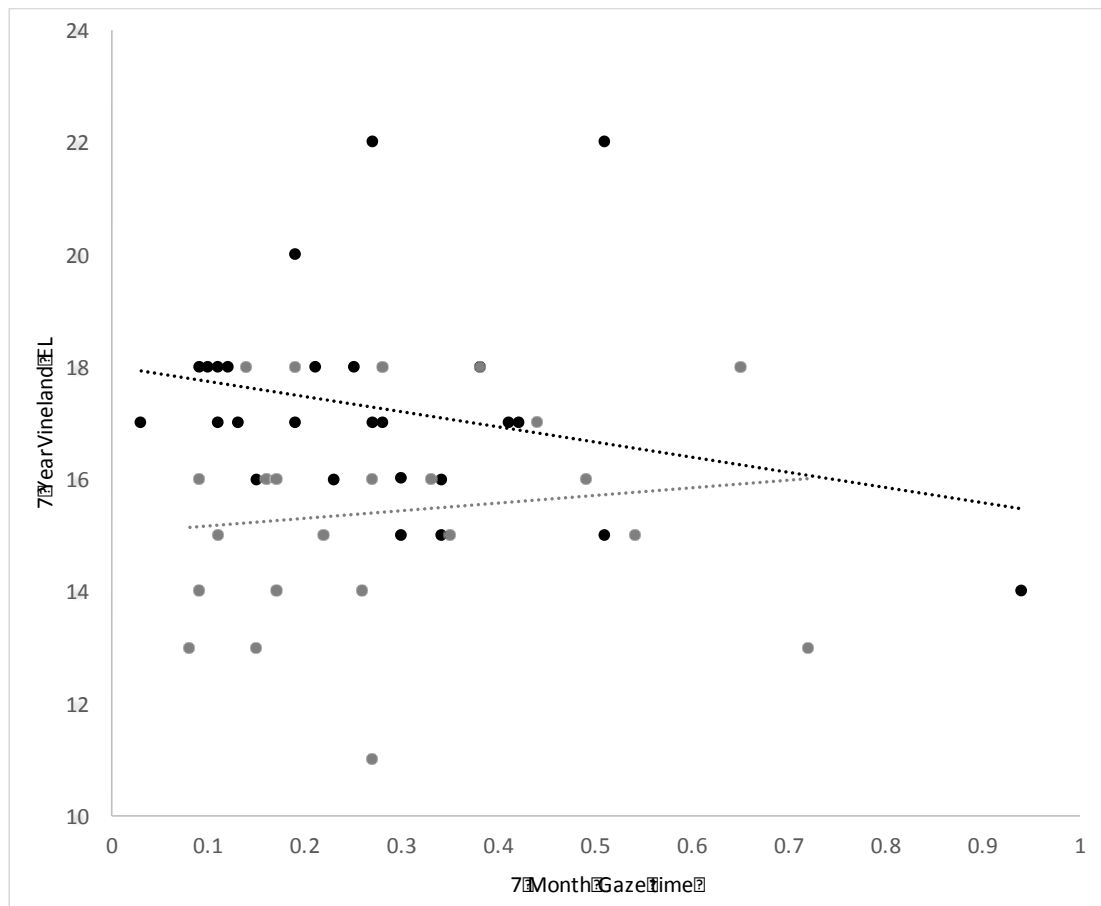


Figure 3 Relationship between 7 month gaze time and 7 year Vineland EL with outlier case removed.

Table 11 Correlations between infancy measures and ADOS scores at 7 years of age

		ADOS-2 SA ^a	ADOS-2 RRB ^b	ADOS-2 Total ^c
Both groups				
<i>7 month EMI</i>	R_s	-.085	-.007	-.041
	p	.512	.960	.752
	df	60	60	60
<i>14 month EMI</i>	R_s	.054	-.106	.005
	p	.678	.412	.969
	df	60	60	60
<i>7 month gaze following</i>	R_s	.265	.126	.221
	p	.057	.375	.116
	df	50	50	50

<i>14 month gaze following</i>	R_s	-.126	-.053	-.090
	p	.375	.710	.528
	df	50	50	50
<i>7 month gaze time</i>	R_s	-.039	.008	-.045
	p	.790	.955	.759
	df	47	47	47
<i>14 month gaze time</i>	R_s	-.434**	-.303*	-.428**
	p	.002	.034	.002
	df	47	47	47
<i>LR</i>				
<i>7 month EMI</i>	R_s	-.170	-.184	-.095
	p	.362	.323	.613
	df	29	29	29
<i>14 month EMI</i>	R_s	.255	.032	.251
	p	.175	.866	.182
	df	28	28	28
<i>7 month gaze following</i>	R_s	.221	.040	.169
	p	.279	.846	.410
	df	24	24	24
<i>14 month gaze following</i>	R_s	-.039	.334	.033
	p	.850	.096	.875
	df	24	24	24
<i>7 month gaze time</i>	R_s	.202	-.142	.074
	p	.333	.500	.725
	df	23	23	23
<i>14 month gaze time</i>	R_s	-.324	-.311	-.329
	p	.114	.130	.109
	df	23	23	23
<i>HR</i>				
<i>7 month EMI</i>	R_s	.034	.174	.087
	p	.858	.348	.640
	df	29	29	29
<i>14 month EMI</i>	R_s	-.001	-.114	-.095
	p	.998	.533	.604
	df	30	30	30

<i>7 month gaze following</i>	<i>R_s</i>	.365	.179	.308
	<i>p</i>	.066	.382	.126
	<i>df</i>	24	24	24
<i>14 month gaze following</i>	<i>R_s</i>	-.123	-.103	-.146
	<i>p</i>	.550	.618	.475
	<i>df</i>	24	24	24
<i>7 month gaze time</i>	<i>R_s</i>	-.264	.051	-.120
	<i>p</i>	.212	.815	.576
	<i>df</i>	22	22	22
<i>14 month gaze time</i>	<i>R_s</i>	-.417*	-.203	-.412*
	<i>p</i>	.042	.342	.045
	<i>df</i>	22	22	22

Autism Diagnostic Observation Schedule (ADOS) Social Affect (SA)^a, Restricted Interests and Repetitive Behaviours (RRB)^b and total^c calibrated severity score.

Table 12 Correlations between infancy measures and SRS scores at 7 years of age

		SRS Total ^a	SRS RRB	SRS SC
Both groups				
<i>7 month EMI</i>	<i>R_s</i>	-.289*	-.255	-.277*
	<i>p</i>	.027	.052	.033
	<i>df</i>	57	57	57
<i>14 month EMI</i>	<i>R_s</i>	-.048	-.027	-.034
	<i>p</i>	.720	.840	.802
	<i>df</i>	55	55	57
<i>7 month gaze following</i>	<i>R_s</i>	-.042	.088	-.091
	<i>p</i>	.775	.547	.535
	<i>df</i>	47	47	47
<i>14 month gaze following</i>	<i>R_s</i>	-.251	-.130	-.256
	<i>p</i>	.082	.371	.075
	<i>df</i>	47	47	47
<i>7 month gaze time</i>	<i>R_s</i>	.138	.271	.095
	<i>p</i>	.356	.065	.525
	<i>df</i>	45	45	45
	<i>R_s</i>	.070	.127	.060

<i>14 month gaze time</i>	p	.641	.395	.690
	df	45	45	45
LR				
<i>7 month EMI</i>	R _s	-.150	-.026	-.141
	p	.421	.891	.448
	df	29	29	29
<i>14 month EMI</i>	R _s	.081	-.085	.101
	p	.671	.655	.595
	df	28	28	28
<i>7 month gaze following</i>	R _s	.205	.219	.147
	p	.316	.283	.474
	df	24	24	24
<i>14 month gaze following</i>	R _s	-.046	-.142	-.019
	p	.822	.488	.927
	df	24	24	24
<i>7 month gaze time</i>	R _s	.063	.123	.043
	p	.760	.550	.836
	df	24	24	24
<i>14 month gaze time</i>	R _s	.338	.230	.284
	p	.092	.258	.159
	df	24	24	24
HR				
<i>7 month EMI</i>	R _s	-.408*	-.454*	-.392*
	p	.031	.015	.039
	df	26	26	26
<i>14 month EMI</i>	R _s	-.129	-.022	-.111
	p	.520	.912	.583
	df	25	25	25
<i>7 month gaze following</i>	R _s	-.371	-.140	-.418*
	p	.081	.524	.047
	df	21	21	21
<i>14 month gaze following</i>	R _s	-.186	.018	-.221
	p	.395	.935	.311
	df	21	21	21

<i>7 month gaze time</i>	R_s	.243	.382	.169
	p	.289	.087	.464
	df	19	19	19
<i>14 month gaze time</i>	R_s	.181	.290	.186
	p	.433	.201	.420
	df	19	19	19

^aSocial responsiveness scale (SRS) restricted interests and repetitive behaviours (RRB) social communication and total scores

Service Related Project

Exploring clinician's views on a lack of treatment response in a sub-group of young people being treated for Obsessive Compulsive Disorders (OCD) at the National Specialist (NS) OCD and Related Disorders Service.

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3 Abstract

Obsessive Compulsive Disorder (OCD) is characterised by recurrent unwanted thoughts, images or urges (obsessions) and repetitive behaviours or mental acts (compulsions) and is a common disorder among children and adolescents. Though it is associated with significant distress and impairment if left untreated, the majority of young people respond well to the first line treatment; Cognitive Behaviour Therapy (CBT) with Exposure and Response Prevention (ERP) (Mataix-Cols et al., 2014; Pediatric OCD Treatment Study (POTS) Team, 2004; T. I. Williams et al., 2010). The National and Specialist (NS) OCD and Related Disorders Service provides CBT packages for children with OCD. Despite best attempts to deliver therapy, there is a sub-group of young people do not respond to treatment. Though previous research has examined factors associated with treatment outcome, little is known about why some young people do not show a significant improvement in symptoms during and after treatment. Therefore the purpose of the current study was to explore clinician's views of poor treatment response amongst a sub-group of young people who attended the National and Specialist OCD service, to facilitate understanding of the factors that contribute to poor treatment outcome in these cases, so that service provision can be improved. Therapists' views were obtained via semi-structured questionnaires. Interestingly, responses to the questionnaire indicated that these young people did not receive the standard protocol of treatment. Several themes emerged when considering clinicians' experiences of working with cases who did not respond to treatment and why the treatment protocol was not followed. Results are discussed in relation to implications for service provision and directions for future research.

4 Introduction

4.1 Obsessive Compulsive Disorder (OCD)

Obsessive Compulsive Disorder (OCD) is characterised by obsessions or compulsions, or both obsessions and compulsions (American Psychiatric Association, 2013). Obsessions are intrusive, unwanted, recurrent and persistent thoughts, images or urges that cause marked anxiety and distress. The person attempts to suppress, ignore or neutralise these with other thoughts or actions. The most common themes are contamination, sexual, aggressive and religious obsessions and fear of harm coming to others (Chung & Heyman, 2008). Compulsions are repetitive behaviours or mental acts performed in response to an obsession or according to rigidly applied rules. Compulsions are carried out with the aim of reducing distress or preventing a dreaded outcome. The most common rituals are washing, checking, repeating, reassurance seeking and ordering (Chung & Heyman, 2008). These symptoms cause significant functional impairment and/or distress.

4.2 Paediatric OCD

OCD was once thought to be rare among children and adolescents. However it is now recognised that OCD is relatively common amongst young people, affecting between 1-2% of children and adolescents (NICE, 2005). OCD amongst children and young people presents similarly to adults, though there are some developmental differences, for example more fear of death of a parent for young children and more sexual and religious obsessions among adolescents (Kalra & Swedo, 2009). Additionally, early onset OCD (less than 20 years of age) is associated with more severe symptoms than late onset OCD (Anholt et al., 2014).

The majority of young people who have OCD meet diagnostic criteria for an additional psychiatric or neurodevelopmental disorder (Pediatric OCD Treatment Study (POTS) Team, 2004). Tics and Tourette Syndrome, Autism Spectrum Disorder (ASD), Eating Disorders, Depression, Attention Deficit Hyperactivity Disorder

(ADHD), Oppositional Defiant Disorder (ODD) and Conduct Disorder are amongst the commonly diagnosed comorbidities (Krebs & Heyman, 2010).

4.3 Treatment recommendations for paediatric OCD

Cognitive Behaviour Therapy (CBT) with Exposure and Response Prevention (ERP) is the first line treatment for young people with OCD as recommended by NICE (2005). Evidence from Randomised Controlled Trials (RCTs) (e.g. Bolton & Perrin, 2008; De Haan, Hoodguin, Buitelaar, & Keijsers, 1998; Pediatric OCD Treatment Study (POTS) Team, 2004; Storch et al., 2007; Williams et al., 2010) supports the use of CBT for treating OCD in young people, with the results of these studies indicating that 40-88% achieve remission.

ERP has been found to be the active element in CBT for OCD (Foa, Steketee, Grayson, Turner, & Latimer, 1984). ERP is based on Behaviour Theory (Rachman, 1971), according to which obsessions are neutral stimuli that become associated with anxiety. The person develops avoidance and escape responses that terminate exposure to the feared stimulus. These behaviours are negatively reinforced, making them more likely to re-occur. The termination of exposure prevents the extinction of anxiety. Therefore the person becomes trapped in a vicious cycle whereby the compulsion (behaviour) provides temporary relief from the anxiety associated with the obsession (stimulus) and maintains the obsession. Treatment therefore involves breaking this cycle by exposing the person to the feared stimulus without them engaging in escape behaviours.

NICE (2005) recommend a stepped care model whereby CBT with ERP is the first line of treatment for young people with OCD, with the addition of a Selective Serotonin Reuptake Inhibitor (SSRI) for those who do not respond to therapy. In an RCT comparing CBT with sertraline, the Paediatric OCD Treatment Study Team (POTS, 2004) reported that combined CBT with SSRI was superior to CBT alone and sertraline alone. There was no significant difference between the use of CBT alone and sertraline alone, however, the effect size for CBT was larger for that of the sertraline alone (Hedge $g = 0.97$ and 0.67 respectively) and more patients achieved

remission in the CBT alone group (39.3%, as opposed to 21.4%). Similarly, in a recent meta-analysis of RCTs comparing CBT with SSRI treatment for children and adults with OCD it was reported that behaviour therapy is more effective than Serotonin Reuptake Inhibitors (SRIs) alone but not selective SRIs (Romanelli, Wu, Gamba, Mojtabai, & Segal, 2014). The combination of behaviour therapy with an SRI was more effective than an SRI alone but no different from behaviour therapy alone. These results highlight the importance of providing effective psychological therapy for paediatric OCD. Indeed, NICE (2005) recommend that children and adolescents who are offered SRIs should also be receiving CBT.

4.4 Standard Treatment Protocol used at the NS OCD Service

There are a number of manualised CBT protocols that can be used for treating paediatric OCD. These include manuals for treating anxiety disorders in general in young people, such as the 'Coping Cat' (Kendall, 1994) and those that have been developed specifically for treating Paediatric OCD (March, Mulle, & Herbel, 1994).

The NS OCD service has developed its own treatment protocol (Turner, 2008). Treatment involves fourteen sessions of CBT, which are carried out over a maximum of 17 weeks. The first two sessions involve psychoeducation about OCD and anxiety. The young person learns to recognise their anxiety 'symptoms' and develops a rating scale to measure their anxiety independent of OCD. The young person learns that anxiety is an everyday emotion and that it habituates over time. He or she then develops a hierarchy of compulsions and learns about the vicious cycle of OCD (formulation). Sessions three to 12 involve carrying out ERP in sessions and at home and cognitive strategies are added to ERP where appropriate. The last two sessions involve relapse prevention.

A recent RCT using the clinic protocol showed that 80% responded to treatment (defined as $\geq 35\%$ reduction on the Children's Yale Brown Obsessive Compulsive Inventory (CY-BOCS; Scahill et al., 1997)) and gains were maintained at 12 month follow-up (Mataix-Cols et al., 2014). The protocol has been adapted for use with

young people with Autism Spectrum Disorder (ASD), with the addition of six treatment sessions and more time spent on psychoeducation. Preliminary evidence using this enhanced protocol suggests adolescents and adults with ASD respond to CBT for OCD (Russell et al., 2013).

4.5 Factors Affecting Treatment Efficacy

Though CBT is an effective treatment for paediatric OCD in the majority of cases, approximately 30% of young people do not respond to CBT for OCD (Pediatric OCD Treatment Study (POTS) Team, 2004; Piacentini, Bergman, Jacobs, McCracken, & Kretchman, 2002). In seeking to explain why some people do not respond to treatment, Rachman (1983) distinguished between 'technical treatment failures', where a patient has not received adequate treatment, and 'serious treatment failures,' where the patient does not improve despite adequate treatment.

The evidence suggests that technical treatment failures may account for a lack of treatment response in a large proportion of cases. In a study of adults attending a national specialist service, or who were members of a national charity for OCD services, it was reported that 60% of patients classified as 'treatment refractory' had not received 'adequate' CBT (Stobie, Taylor, Quigley, Ewing, & Salkovskis, 2007). 'Adequate' CBT was defined according to strict criteria which included the patient having six or more sessions of at least 40 minutes, with both exposure and homework being integral to treatment. 51% of patients had not done in-session exposure, 78% did not have therapist assisted exposure, 22% did not have homework and 25% talked freely whilst the therapist was silent. Similarly, it was reported that though the majority of clinicians reported using CBT in the treatment of paediatric OCD, only a third reported regular use of exposure techniques in sessions (Valderhaug, Gunnar Götestam, & Larsson, 2004). Research carried out within the NS OCD clinic indicated that of 15 young people with 'treatment resistant' OCD, 21/22 previous courses of CBT were not in line with evidence based protocols, with the main reason being insufficient ERP in sessions (Krebs et al., 2014).

A number of therapist factors are likely to impact on outcome by leading to technical treatment failures in certain cases. Therapist practices including not completing ERP tasks and not encouraging patients to go far enough in ERP, choosing the wrong form of exposure (i.e. using imaginal *exposure where in-vivo* would be appropriate and visa-versa), encouraging distraction during exposure, providing reassurance, treating peripheral factors and not the core fear, ineffectively handling mental compulsions and difficulty working with significant others on factors such as reassurance giving and accommodation of compulsions, have been highlighted as common pitfalls in treatment (Gillihan, Williams, Malcoun, Yadin, & Foa, 2012). Interestingly, therapist experience may not be important in predicting outcome as long as adequate training and supervision is provided (van Oppen et al., 2010). However, the therapeutic alliance is an important predictor of outcome. It has been reported that child-rated, parent-rated, and therapist-rated therapeutic alliance is predictive of better treatment outcome and positive early alliance shifts, as rated by the child, is also predictive of better treatment outcome (Keeley, Geffken, Ricketts, McNamara, & Storch, 2011).

In addition to the technical treatment failures described above, a number of factors relating to the young person's characteristics and the family environment have emerged as important in predicting outcome. These may lead to 'serious' treatment failures if adequate CBT is provided, or may interfere with the treatment process such that adequate CBT may not be provided. The evidence suggests that gender, age, and duration of illness are not associated with treatment response (Ginsburg, Kingery, Drake, & Grados, 2008). Severity of symptoms, symptom presentation, number of obsessions and compulsions, comorbidity, greater levels of internalizing symptoms, poor insight, cognitive deficits, greater functional impairment, family accommodation of symptoms, higher parental stress related to accommodation, and the family environment including family dysfunction, negative family interactions and high levels of expressed emotion have all been associated with poorer response to therapy (Amir, Freshman, & Foa, 2000; Ginsburg et al., 2008; Krebs & Heyman, 2010; Peris et al., 2012; Przeworski et al., 2012; Storch et al., 2008a, 2010). However, provided that the core component of treatment is

maintained (i.e. ERP), modifications to protocolled treatment according to the individual's needs, can help to overcome these barriers to treatment (Storch et al., 2010).

Qualitative research exploring factors that may contribute to treatment outcome is limited. Clinical experience and anecdotal evidence suggest that ERP is stressful and can be too aversive for certain clients (Foa et al., 1983; Lee & Rees, 2011). In a qualitative study of CBT for OCD, clients described being afraid of how 'harsh' it is, but also experienced CBT as being purposeful and helpful in developing life satisfaction in the individual (Murphy & Perera-Delcourt, 2014). Patients described ERP as 'distressing' and 'emotionally and physically exhausting' but that it was also a 'life changing' experience (Lee & Rees, 2011). These studies suggest that the experience of ERP is likely to be an important factor in predicting outcome.

4.6 Previous research at the NS OCD service examining factors affecting treatment efficacy

Previous research carried out at the NS OCD service has indicated that age at onset, age at assessment, duration of illness, chronicity of OCD and gender do not predict outcome, but that pre-treatment severity as measured by the CY-BOCS, as well as the use of SSRI's predict more severe symptoms post-treatment (Nakatani, Mataix-Cols, Micali, Turner, & Heyman, 2009). The presence of sexual obsessions (Fernández de la Cruz et al., 2013), temper outbursts (Krebs et al., 2013), depressive symptoms (Brown, Lester, Jassi, Heyman, & Krebs, 2014) and family accommodation (unpublished findings) have not been associated with outcome within the clinic.

5 Rationale

The evidence indicates that the majority of young people respond well to CBT for OCD in the NS OCD Service, but that approximately 20-30% do not show a significant response to treatment (Mataix-Cols et al., 2014). It is important to try to

understand the factors that contribute to poor treatment outcome in certain cases in order to improve service provision.

Previous research carried out within the NS OCD service has examined factors that predict treatment outcome, using quantitative measures and methods of analysis. However, a number of factors hypothesised to predict treatment outcome have not been associated with post-treatment symptoms (see section 4.6) and it is therefore still unclear why some young people within the service do not respond to treatment. All of the measures routinely used to assess outcomes have been examined within the clinic, and with the exception of the CY-BOCS, these measures are parent and child rated. A novel approach to the question of why some young people do not respond to treatment was taken in this study, by developing a questionnaire to examine clinician's views of why some young people do not respond to treatment. Furthermore, given that the clinician's within the NS OCD service are well aware of the technical treatment failures that can occur, and therefore are in a position to manage these within the service, it may be that other factors account for poor outcomes in a sub-group of clients and that clinician's views can provide insight into these additional factors.

A qualitative approach may provide additional insight into the factors that account for poor treatment response for individual cases by allowing an in-depth analysis of the unique factors that contribute to a lack of treatment response for each individual (Hayes, 2000). Qualitative methods allow for the analysis of complex and contradictory information regarding the similarities and differences between people within a real life context and therefore may be able to capture information that has been over-looked or obscured by quantitative methods which emphasise reliability over ecological validity (Hayes, 2000).

The purpose of this study is to evaluate therapy undertaken in the NS OCD CAMHS service where a lack treatment response has been found from the perspective of the clinicians who treated these individuals. It is anticipated that this will allow key themes or ideas to be highlighted that might clarify why clinicians think a particular sub-group of young people have not responded to treatment. This might allow the

clinic to begin to measure or monitor other factors more formally as part of treatment and do further quantitative research in the future to establish different factors relating to patient outcomes when having CBT treatment for OCD.

6 Aims

The aims of this study are to:

1. Explore clinician's perspectives of why a sub-group of young people within the NS OCD service do not respond to treatment.
2. To examine whether technical treatment failures have occurred and if so, to ask clinicians what factors might account for non-adherence to the treatment protocol.
3. To examine whether factors previously hypothesised to influence treatment outcome in the literature appear in clinician's accounts of poor treatment response for certain individuals.
4. To use findings to inform future service research and provision within the NS OCD team.

7 Method

7.1 Setting

This study was carried out at the NS OCD service for Children and Young People at the Maudsley Hospital's Children Department in the Michael Rutter Centre. It is a tier four specialist CAMHS service forming part of the Child and Adolescent Mental Health Clinical Academic Group within King's Health Partners (comprising the South London and Maudsley (SLAM), Guy's and St. Thomas's and King's College NHS Trusts). The service provides assessment and treatment for young people aged between 5 and 18, who have a suspected primary diagnosis of OCD or a related disorder. The majority of young people accepted to the service for assessment have received some input from other services for their OCD. As such, clients tend to be chronic and severe, or cases where previous treatments have been deemed unsuccessful. Approval for this project was granted by the CAMHS CAG clinical audit and service evaluation ethics committee on the 10.02.2014.

7.2 Participants

Data from 290 clients who attended the NS OCD service between 2009 and 2013 was examined in order to select those who had both pre and post treatment measures recorded electronically. Pre and post treatment measures were available for seventy-two young people. The sample included 40 females and 32 males, who had an average age of 13.93 years (range = 8-18; standard deviation (SD) = 2.358).

7.3 Procedure

All of the young people who attend the NS OCD service are assessed using the CY-BOCS, a clinician rated interview which yields a reliable, valid measure of obsessive-compulsive symptom severity in children and adolescents with OCD (Scahill et al., 1997). Cases where there was a less than 25% reduction on the CY-BOCS were selected for this study. A reduction of at least 25% in the severity of symptoms is

considered a treatment response (Simpson, Huppert, Petkova, Foa, & Liebowitz, 2006).

A questionnaire was designed for completion by clinicians in order to explore their views on what may have impacted on response to CBT for OCD. The first question was an open ended question to explore clinician's views of factors impacting upon treatment. The second question examined if non-response to treatment was due to a technical treatment failure. Clinicians were asked if treatment had adhered to the protocol used by the NS OCD team. If not, they were asked the impact of this upon treatment, the reasons why treatment did not adhere to protocol and what changes were made. An open ended question was then asked to examine why the protocol was not adhered to in those cases. Where treatment did adhere to protocol clinicians were asked to comment on other factors that might have accounted for treatment outcome. Clinicians were also asked if, in their opinion, other adaptations to treatment could potentially have improved outcome. The third part of the questionnaire posed specific questions about the potential influence of factors hypothesised to impact on treatment outcome based on previous literature (see section 4.5) and clinical experience. These factors included the OCD presentation, the therapeutic rapport, experience and supervision, the young person's presentation and family environment. Finally clinicians were asked another open ended question about any other factors that may have contributed to the outcome.

Clinicians who had treated the clients who did not respond to treatment were identified by checking the young person's record on the SLAM Electronic Journey Patient System (EPJs). Clinicians who were still employed at the NS OCD service were given a hard copy of the questionnaire and those working abroad were sent an electronic copy to complete and return via email.

Quantitative data were analysed using PASW statistics version 18. Qualitative data were analysed using Content Analysis (CA) which is appropriate for analysing written information (Miles & Huberman, 1994). Stemler (2001) suggests CA is applicable to examining pieces of written communication in order to find trends and the focus of group attention. Categories were derived from the data using

'emerging' coding and are exclusive; the frequency of each instance of the category within the text is recorded in order to produce a quantitative measure of the information provided within the text. Once categories were developed, two independent researchers rated the number of individuals referring to a category and the frequency of references to each category. Reliability analysis, was calculated using the intra-class correlation coefficient ((ICC; Shrout & Fleiss, 1979) in PASW statistics.

7.4 Service User Involvement

Three young people receiving treatment for OCD at NS OCD service at the MRC in January 2014, as well as their parents, contributed to the development of the questionnaire which was given to clinicians. The rationale for the study was explained to them and they were asked to read a draft of the questionnaire and to give feedback. The questionnaire was modified according to their comments and suggestions.

8 Results

8.1 Sample Characteristics

Twelve young people, out of the 72 clients on the database, were identified as non-responders to treatment. This represented 16.67% of the clients on the database who had pre and post treatment measures. This indicates a treatment response rate of 83.33% which is in line with the previously reported response rate for the clinic (Mataix-Cols et al., 2014). However, of these, two received intensive treatment over three days, rather than the standard treatment package and therefore were not included in subsequent analyses.

Ten questionnaires were completed by five of the treating clinicians. Of the ten young people included in the final analysis six were female and four were male. The average age at assessment was 13.7 years of age (range 11-17 years; standard deviation (SD) = 2.058) and the average age at onset of OCD was 10.2 years (range 4-15 years; SD = 3.19).

The average CY-BOCS score at baseline was 29.10 (range = 24-37; SD = 4.606), which is in the moderate-severe range, and the average CY-BOCS score at the end of treatment was 25.6 (range = 21-37; SD = 5.082), which remains in the moderate-severe range. Six of the young people had previously received CBT for OCD and three were taking an SSRI at the time of assessment, with the remainder not taking any medication at assessment. Unfortunately, information about changes to medication during treatment was not available.

In terms of the mode of treatment, one of the young people was receiving treatment as part of a telephone CBT (TCBT) trial and two were part of the d-cycloserine (DCS) trial. One young person had a hospital admission for OCD.

Seven of the young people had no other psychiatric disorder, two had a diagnosis of autism and one had a diagnosis of Asperger's syndrome. One participant had a diagnosis of learning disability. One of the young people had a first degree relative

with OCD and four of the young people had a first degree relative with an anxiety or affective Disorder.

8.2 Qualitative and Quantitative Results

The results of the study are outlined in the following sections. Questions are highlighted in italics. Descriptive quantitative results are presented and qualitative results are summarised in tables 1-11 with category labels, the number of clinicians who referred to the category and the frequency of references to the category indicated. Full category descriptions and examples can be found in the appendices.

8.2.1 Responses to Question One

Please consider this previous case you worked with. Thinking back over the case with hindsight, are there any factors which you consider may have played a role in the outcome of this case? These might be factors to do with yourself, other professionals or the family and patient.

Four categories emerged from responses to question 1 (see table 1).

Table 1 Categories developed from open ended question exploring factors that may have contributed to outcome.

Categories	No of individuals who made reference to it	Frequency of references
1. Young Person Presentation	8	30
2. Family and Social Factors	8	25
3. Professional Issues	3	7
4. Treatment Specific Factors	3	6

8.2.2 Responses to Question Two

Thinking over this case, did you manage to stick to the treatment protocol used at the NS OCD service, accounting for any comorbidities such as ASD?

- Yes 10%
- No 90%

If no, please elaborate, what part of the protocol would you say was not followed?

- 70% did not complete homework tasks
- 60% did not complete ERP every sessions
- 20% did not complete 14/20 sessions within 17/21 weeks
- 20% did not fully address family accommodation
- 0% family were not involved in sessions

How much do you think not sticking to protocol impacted on the treatment outcome for this case? (0 represents 'no impact,' '5' a moderate impact and '10,' a 'strong impact').

- Median = 8 (interquartile range = 4)
- Mean = 6.71 (standard deviation = 2.75)

If treatment did not stick to protocol, do you know why this was the case and what changes were made to treatment?

Four reasons were given for treatment not sticking to the protocol (table 2).

Table 2 Reasons given for not delivering treatment protocol.

Categories	No of individuals who made reference to it	Frequency of references
1. Young person characteristics	7	19
2. Family Factors	3	6
3. Change to treatment goals	3	5
4. Dropout	1	1

If treatment did stick to protocol, are there any other factors which you feel could account for the treatment outcome?

Two reasons were given for other factors that may have accounted for treatment outcome (table 3).

Table 3 Factors other than protocol adherence that may have impacted on treatment.

Categories	No of individuals who made reference to it	Frequency of references
1. Treatment Specific Factors	1	1
2. Family Factors	1	1

Do you think that additional or further adaption of treatment to individual client needs (for example, using additional cognitive strategies) could have improved outcome?

Two categories were developed from answers to the question asking clinicians if adaptations to treatment may have helped (table 4).

Table 4 Categories associated with adaptation to client needs.

Categories	No of individuals who made reference to it	Frequency of references
1. No/Did all that could be done	4	6
2. Use of additional treatment strategies	4	5

8.2.3 Responses to Question Three

8.2.3.1 Question 3A

Did some aspect of the OCD presentation interfere with treatment (e.g. severity or type of OCD, beliefs about obsessions preventing the young person from talking openly, overt rituals being replaced by covert mental rituals)?

- Yes 70%
- No 30%

To what extent did this impact on the outcome? (0 represents 'no impact,' '5' a moderate impact and '10,' a 'strong impact').

- Median = 8 (interquartile range = 4.75)
- Mean = 7.17 (standard deviation = 2.64)

Please provide additional information:

Four categories were developed from the question asking if aspects of the OCD presentation may have impacted on outcome (table 5).

Table 5 Aspects of OCD presentation and treatment outcome

Categories	No of individuals who made reference to it	Frequency of references
1. Characteristics of beliefs and rituals	5	7
2. Severity of symptoms and level of distress	3	4
3. Comorbidities and other difficulties	2	3
4. Insight	2	2

8.2.3.2 Question 3B

Did you have difficulty establishing a therapeutic rapport with this client?

- Yes 50%
- No 50%

To what extent did this impact on the outcome? (0 represents 'no impact,' '5' a moderate impact and '10,' a 'strong impact').

- Median = 4.5 (interquartile range = 4)
- Mean = 5.5 (standard deviation = 2.38)

Please provide additional information:

Two categories were developed from answers to questions asking about the therapeutic alliance (table 6).

Table 6 Categories associated with therapeutic alliance

Categories	No of individuals who made reference to it	Frequency of references
1. Young person presentation	2	5
2. Ability and motivation to engage in treatment	2	5

8.2.3.3 Question 3C

Do you think your experience / supervision or skills had any influence on the outcome of this case?

- Yes 50%
- No 50%

To what extent did this impact on the outcome? (0 represents 'no impact,' '5' a moderate impact and '10,' a 'strong impact').

- Median = 5 (interquartile range = 4)
- Mean = 4.2 (standard deviation = 2.17)

Please provide additional information:

Two categories were developed from the question examining experience, supervision and skills (table 7).

Table 7 Categories associated with experience, supervision and skills.

Categories	No of individuals who made reference to it	Frequency of references
1. Working with complex cases/families	3	6
2. Selection of appropriate treatment	1	3
3. Need for additional support and supervision	1	3

8.2.3.4 Question 3D

Did the young person present with any difficulties that may have impeded their response to treatment (e.g. issues relating to anxiety, motivation or readiness to change)?

- Yes 90%
- No 10%

To what extent did this impact on the outcome? (0 represents 'no impact,' '5' a moderate impact and '10,' a 'strong impact').

- Median = 8 (interquartile range = 1)
- Mean = 8.38 (standard deviation = .916)

Please provide additional information:

Three factors were developed from responses related to the young person's presentation (table 8).

Table 8 Factors associated with the young person's presentation.

Categories	No of individuals who made reference to it	Frequency of references
1. Comorbidities	6	12
2. Insight	6	9
3. Motivation/readiness for change	3	3

8.2.3.5 Question 3E

Were there any family factors (e.g. difficulty engaging the young person's carers/parents, other family members also having OCD, anxiety or other mental health problems, high levels of expressed emotion, criticism, or over-involvement)?

- Yes 80%
- No 20%

To what extent did this impact on the outcome? (0 represents 'no impact,' '5' a moderate impact and '10,' a 'strong impact').

- Median = 8 (interquartile range = 1)
- Mean = 8.38 (standard deviation = .916)

Please provide additional information:

Three categories were developed from clinician's responses to the question about family factors (table 9).

Table 9 Categories associated with family factors.

Categories	No of individuals who made reference to it	Frequency of references
1. Family unable to support young person	7	17
2. Family mental health and learning difficulties	4	6
3. Family Circumstances	3	4

8.2.3.6 Question 3F

Did any stressful events occur to the young person during treatment that may have affected outcome?

- Yes 40%
- No 60%

To what extent did this impact on the outcome? (0 represents 'no impact,' '5' a moderate impact and '10,' a 'strong impact').

- Median = 5 (interquartile range = 4.75)
- Mean = 4.75 (standard deviation = 2.63)

Please provide additional information:

Two categories were developed from clinician's responses to the question about stressful life events that may have impacted on outcome (table 10).

Table 10 Categories associated with stressful life events.

Categories	No of individuals who made reference to it	Frequency of references
1. Parental stress and separation	3	3
2. Loss and illness in the family	2	2

8.2.3.7 Question 3G

Were there any other factors that may have contributed to treatment outcome?

- Yes 20%
- No 80%

To what extent did this impact on the outcome? (0 represents 'no impact,' '5' a moderate impact and '10,' a 'strong impact').

- Median = 6.5 (interquartile range = 0.5)
- Mean = 6.5 (standard deviation = .707)

Please provide additional information:

Two categories were developed from clinician's responses to the question asking if any other factors may have impacted on outcome (table 11).

Table 11 Other factors associated with outcome.

Categories	No of individuals who made reference to it	Frequency of references
1. Professional Issues	1	4
2. Young Person Comorbidities	1	2

8.3 Reliability Analysis

The results of the reliability analysis indicated adequate reliability for both the number of individuals making reference to the category and the frequency of references to each category [single measure ICC (absolute agreement) =.851 for the number of individuals making reference to the category; single measure ICC (absolute agreement) =.789 for the frequency of references to each category (Landis & Koch, 1977)].

9 Discussion and Service Implications

In the present study, clinicians were asked their opinion of the factors that contributed to non-response to treatment in the young person with whom they were working. The results indicated that in the majority (90%) of cases, treatment did not stick to protocol. As such, lack of treatment response in these cases can be seen as technical treatment failures (Krebs et al., 2014). The interesting question is why clinicians thought technical treatment failures occurred; clinicians attributed this to the young person's characteristics and to other factors such as the family and therapist. In the following sections clinician's views of how issues with treatment, the young person's and family's characteristics, and therapist factors, contributed to treatment outcome shall be discussed. The results shall then be discussed in terms of service provision and future research.

9.1 Treatment specific factors

The results of this study highlighted that for those cases who do not respond to treatment within the NS OCD service, the majority (90%) did not receive 'adequate' treatment within the service (Stobie et al., 2007). There were a number of ways in which the protocol was not followed, with poor homework completion being the most frequently reported, followed by ERP not being completed in every session. In a small number of cases treatment was not completed within the allocated time frame and/or family accommodation was not fully addressed. However, in all cases families were involved in sessions. Clinician's ratings suggest they felt that not adhering to the protocol had a moderate to strong impact on outcome. Clinician's attributed non-adherence to the protocol to the young person's characteristics, family factors, change of treatment goals and dropping out (in one case). Clinician's responses suggest that they regarded the young person's characteristics as the most important of these factors, followed by family factors.

Previous research indicates that over half of patients who are classified as 'treatment refractory' have not received adequate treatment (Krebs et al., 2014; Stobie et al., 2007). The results of the present study suggest that technical

treatment failures occurred in the majority (90%) of cases. These results indicate that even within a national specialist service, where therapists are highly aware of the importance of ensuring that evidence-based treatment is provided, technical treatment failures can occur, and may account for poor treatment response.

9.2 Young Person Presentation

The characteristics of the young person emerged as an important factor in explaining non-adherence to the treatment protocol, according to clinicians. Seventy percent of the clinicians regarded that the OCD presentation impacted on outcome and overall they rated the extent of this impact in the moderate to strong range. Characteristics of the beliefs and rituals emerged as an important aspect of the OCD presentation impacting on treatment; for example, fear of the consequences of 'disobeying OCD' and the impact of beliefs and rituals on self-care (e.g. preventing normal eating). Restricted eating in OCD may be driven by a feared consequence of eating that is unrelated to weight-gain in certain cases, or by a comorbid eating disorder. In both cases, restricted eating is likely to impact on CBT due to the cognitive dysfunction associated with extreme weight loss (Brown et al., 2014; Jassi, Patel, Lang, Heyman, & Krebs, Submitted; Krebs & Heyman, 2010).

Clinician's responses also indicated that they thought that comorbidities, such as ASD, Attention Deficit Hyperactivity Disorder (ADHD), anxiety, difficulties with mood, conduct and behavioural problems, as well as risk and deliberate self-harm (DSH) impacted on the outcome of these cases. This reflects the complexity and severity of these cases and is in line with previous research indicating that the presence of certain comorbidities may be associated with poorer outcome in CBT for OCD (Krebs & Heyman, 2010). For example, comorbid anxiety disorders have not been associated with poorer outcome (Storch et al., 2008b) whereas contradictory results have been reported for externalising disorders such as temper outbursts as well as depression (Brown et al., 2014; Krebs et al., 2013; Storch et al., 2008a).

It has been suggested that people with poorer insight into the excessiveness and irrationality of their obsessions and compulsions are less likely to seek help and are

less willing to challenge their obsessive-compulsive symptoms (Krebs & Heyman, 2010). Indeed, the evidence suggests that young people who are treatment-resistant have poorer insight into their symptoms than those who respond to treatment (Storch et al., 2008b). In the current study, clinicians regarded both insight and motivation to change and engage in treatment as important factors contributing poor treatment response. For example, patients who did not have the motivation to overcome OCD were described as 'being overwhelmed by OCD' and being unable 'to imagine life without OCD.' Ability and motivation to engage in treatment was also an important factor and included the ability to attend sessions and perform ERP tasks (e.g. a patient was described as being 'bed-ridden').

9.3 Family factors

Clinician's responses indicated that they considered family factors to have contributed to poor treatment outcome in 80% of cases. Clinician's rated the impact of family factors in the moderate to severe range. Their responses suggest that complicated family circumstances, the family being unable to support the young person, and mental health and learning difficulties within the family, impacted upon outcome in these cases. Stressful life events occurred during treatment in 40% of cases. In all of these cases, stressful events occurred within the family, including parental stress and separation and loss and illness in the family. These findings are in line with previous research indicating that the family environment including family dysfunction, negative family interactions and high levels of expressed emotion are associated with poorer outcome (Ginsburg et al., 2008; Peris et al., 2012; Przeworski et al., 2012).

Interestingly family accommodation of symptoms was not highlighted as an important factor contributing to outcome. Previous research suggests that family accommodation is associated with treatment outcome among adolescents and adults with OCD (Amir et al., 2000; Russell et al., 2013). Russell et al reported that increased family accommodation of OCD symptoms was associated with poorer outcomes in people with OCD and comorbid ASD (Russell et al., 2013). This suggests that the impact of family accommodation of symptoms may depend on the

population being studied. Future studies examining family accommodation in children and adolescents may clarify the role of family accommodation of symptoms in predicting treatment outcome in specific age groups.

9.4 Therapist factors

When clinicians were asked openly about factors impacting on treatment, they referred mainly to the characteristics of the young person and their families. Treatment specific factors and professional issues were also mentioned. Clinicians regarded non-adherence to evidence based protocols as being due to the characteristics of the young person, their family or to a change in treatment goals or dropout. However, therapist factors potentially contributed to the outcome of these cases and to non-adherence to the treatment protocol. ‘Therapist drift,’ whereby clinicians fail to undertake the core tasks of evidence-based psychological therapies for reasons that are more about the clinician than the client’s needs (Kosmerly, Waller, & Robinson, 2014; Waller, 2009), may also have contributed to the outcome of these cases.

In addition, when clinicians were asked specific questions about the potential impact of their experience, supervision and the therapeutic relationship, 50% responded that these factors were likely to have impacted on treatment outcome. Both experience and supervision, and the therapeutic relationship were regarded as having a moderate impact on treatment outcome by clinicians. This contrasts with previous research suggests that therapist experience does not predict outcome in CBT for OCD (van Oppen et al., 2010). However, the therapeutic alliance has been shown to be an important factor in predicting outcome in CBT for paediatric OCD (Keeley et al., 2011).

9.5 Implications for treatment at the NS OCD Service

The results of this study indicate potential areas in which the NS OCD service could invest future research, to continue to improve treatment response for young people with OCD. In addition, discussion of these results with the team highlighted several practical steps that may address some of the common themes. Firstly, involving

local teams in the treatment of these complex cases could help to overcome some of the barriers to treatment discussed above, such as addressing and managing comorbidities and difficult family circumstances. In addition, within the OCD team, it may be that additional treatment strategies could be used in certain cases. For example motivational interviewing (Merlo et al., 2010) and multifamily therapy (Van Noppen, Steketee, McCorkle, & Pato, 1997) may help to overcome some of the difficulties engaging young people in treatment and in addressing complex family circumstances. Finally, it is noteworthy that medication management was not highlighted as an important factor in predicting outcome by the clinicians. CBT with the addition of an SSRI has been associated with superior outcomes (POTS, 2004) and is recommended for cases that do not respond to CBT alone (NICE, 2005). Medication management is an important part of the service provided by the NS OCD team. It was not possible to collect detailed information on medication changes during treatment for these cases. There may be a need for more multidisciplinary consultation between the team and local consultant psychiatrists when treating young people who are not responding to CBT for OCD.

Following discussion of the results with the team several service changes have taken place. A 'waiting list manager role' has been assigned to a clinician in order to monitor the waiting list and ensure that recommendations are carried out. These recommendations are in keeping with factors that may affect outcome, for example, weight gain if weight is below <85% height for weight, ensuring that the young person is at the therapeutic dose of medication, and ensuring that the young person is under-taking treatment for other issues and comorbidities, in parallel or before treatment at the NS OCD service. At the mid-treatment review (session 7), if treatment is not adhering to protocol, treatment is reviewed and discontinued temporarily if necessary in order to address interfering factors. 'Insight' into OCD symptoms is now examined routinely so that it can be addressed in preparation for treatment of OCD.

9.6 Implications for future research

This evaluation also forms part of larger ongoing evaluation of treatment within the clinic. Future evaluations may seek to gain the patients' own perspectives of why treatment may have not been as successful as hoped, in order to build a comprehensive picture of what influences treatment outcomes from both the perspective of the client and their families, as well as the therapist.

The results of this study raise a number of important questions for future research. For example, the results suggest that the young person's presentation (e.g. comorbidities) plays an important role in the outcome of these cases. An important question for future research shall be to establish if CBT for OCD should be carried out in conjunction with treatment for comorbidities or whether it is best to treat one disorder at a time. Clinicians also regarded the family environment as important factor in the outcome of these cases. Future research may wish to examine whether family interventions can improve outcomes. Finally, it is important that future research examine the role of therapist practices in the outcome of these cases.

9.7 Limitations

The results of this study should be interpreted in the light of a number of important limitations. Firstly, only patients who had electronic records of both pre and post CY-BOCS scores were included in the analysis. Secondly, there was no record of medication at the time of treatment and therefore this information cannot be reported. Two of the young people were partaking in the DCS trials and it is possible that this impacted on treatment. We did not ask clinicians a specific question about medication at the time of treatment and clinician's responses suggest that they did not regard medication as an important factor impacting on outcome. Thirdly, we only asked the perspective of clinicians, and therefore the results only represent their perspective on why some young people did not respond to treatment. Finally, the result of this piece of work, being qualitative in nature, reflect the experiences

of clinicians working within the context of the NS OCD service and may not generalise to other contexts.

10 Dissemination

The results of this study were presented at the OCD team research meeting on the 14th of August 2014. This led to a discussion with team members of why technical treatment failures were occurring and what changes could be made to the service. This has led to changes within the service as detailed above. In addition, we discussed ideas for further research as outlined in the previous sections. In addition, this report will be kept with the team as a reference document.

11 Leadership

I developed a number of leadership skills in carrying out this study. Firstly, I developed a questionnaire with two of the clinicians on the team, in order to address the question of why some young people do not respond to treatment. I also took the lead in involving service users in the development of this questionnaire. I then contacted clinicians, several of whom were no longer working within the service and had moved abroad, in order to achieve a 100% response rate to the questionnaires. Finally, I presented the results to the team and led a discussion of practical ways in which the team could begin to address the issues raised in the current study, to minimise the occurrence of technical treatment failures and improve service provision for those who may not respond to treatment.

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13 Appendices

13.1 Category Descriptions

For each question, every occurrence of a phrase within a factor is considered as a separate reference to that factor.

13.1.1 Question 1

Four categories were developed from responses to question 1, 'Please consider this previous case you worked with. Thinking back over the case with hindsight, are there any factors which you consider may have played a role in the outcome of this case? These might be factors to do with yourself, other professionals or the family and patient.

1. Treatment Specific Factors:

This category included any reference to the process and content of treatment including the therapeutic relationship (e.g. openness/honesty in relation to doing rituals during ERP, the modality of treatment (e.g. telephone CBT, inpatient) and the duration /intensity of treatment.

Example: "Our therapeutic relationship wasn't great – she was not open with me (e.g. about rituals she did during ERP)."

2. Professional Issues:

This category included any mention of professional issues, including family/client dissatisfaction with treatment/trial condition, diagnostic issues (e.g. disagreement and lack of clarity in relation to diagnosis), therapist support and supervision and therapist experience in working with the client group or with severe presentations (e.g. in inpatient settings).

Example: "Patient was allocated to the TCBT trial and parents were not happy with condition allocated to."

3. Young Person Presentation:

This category included description of the young person's presentation including the severity and type of OCD (e.g. mental rituals), the client's degree of insight into his/her OCD, his/her motivation to overcome OCD and willingness to engage in treatment, compliance with and/or tolerance of ERP (including homework), degree of functional impairment, ability to tolerate distress, understanding of the treatment model, the complexity of presentation, and other difficulties and comorbidities such as communication difficulties, attention problems, impulsivity, rigidity, social disinhibition, 'temper outbursts', risk issues (e.g. deliberate self-harm (DSH)) and developmental issues including social, emotional, cognitive development.

Example: "Patient's development arrested by years of chronic OCD – socially and emotionally more like an 11 year old".

4. Contextual Factors: Family and Social Environment:

This category included descriptions of the family and social context including parental capacity to support the young person through treatment, parents confidence in managing their child, parental relationship problems, mental health problems, learning difficulties and developmental disorders among family members, family organisation and circumstances (e.g. single parent households), social/ demographic circumstances (e.g. deprivation), family accommodation of OCD and parent's ability to tolerate distress in order to support their child in practicing ERP tasks.

Example: "v. caring and loving family who could not bear to see X upset so huge accommodation for years"

13.1.2 Question 2:

The qualitative section of Question 2 had four parts (A, B, C, D).

13.1.2.1 Parts A and B

Part A asked people to elaborate on their answers if they did not stick to protocol and part B asked people directly to consider why they did not stick to protocol, if that was the case. As the majority of respondents answered one or other of these questions a decision was taken to collapse these two questions and analyse the results together. Where respondents stated that they did stick to protocol but gave an answer to part A or B, this was not coded as the questions were posed to examine reasons why protocol was not adhered to in certain cases. Answers were not double coded where responders gave answers to both parts A and B (in which case part A was coded). Four categories were developed from responses to these questions

1. Young person characteristics:

This category included descriptions of the young person including his/her ability and willingness to engage in treatment, compliance and/or ability to do ERP and/or homework, dislike of attending the clinic sessions (specific mention of dislike of trial components that were not part of the usual OCD protocol were not coded as additional instances), and comorbidities, including low mood, communication difficulties, anxiety and risk/DSH.

Example “couldn’t see the ERP through, was too anxious”.

2. Change to treatment goals:

This category included any description of a change to treatment goals, for example in treating and managing comorbid problems and risk.

Example: “often came to sessions with low mood or deliberate self-harm – became focus of the session rather than ERP”

3. Family factors

This category included any description of family factors such as family accommodation of rituals and parental confidence in supporting ERP/homework.

4. Dropout

This category included any mention of a client dropping out of treatment.

Example: "She dropped out at session 8."

13.1.2.2 Part C.

Two categories were developed from part C of question 2. Responses to the question 'If treatment did stick to protocol, are there any other factors which you feel could account for the treatment outcome?'

1. Treatment Specific Factors:

This category included any reference to the process and content of treatment including treatment condition in a trial.

Example: "disappointment with trial condition."

2. Family Factors:

This category included and mention of family factors including parental separation.

Example: "parental separation."

13.1.2.3 Part D

Two categories were developed from part D of question 2. Responses to the question 'Do you think that additional or further adaption of treatment to individual client needs (for example, using additional cognitive strategies) could have improved outcome?'

1. Use of additional treatment strategies

This category included any description of additional treatment strategies that could have been helpful, including psychoeducation, motivational interviewing, adaptation of treatment for comorbidities, and home based treatment or hospital admission.

Example: “With hindsight, if she hadn’t been in trial I would have treated her phobia of buses first – she was motivated to work on this & it could have engaged her in the CBT model”.

2. No/Did all that could be done

This category included responses that indicated that no additional treatment strategies would have improved outcome.

Example: “No – she received intensive support & two teams – Snowsfield and OCD clinic – we did as much as we could do.”

13.1.3 Question 3.

13.1.3.1 Part A

Two categories were developed from part A. Responses to the question ‘Did some aspect of the OCD presentation interfere with treatment (e.g. severity or type of OCD, beliefs about obsessions preventing the young person from talking openly, overt rituals being replaced by covert mental rituals)?’

1. Severity of symptoms and level of distress.

This category included any description of severity or pervasiveness of symptoms, as well as degree of distress.

Example: “Low impairment vs high distress.”

2. Characteristics of beliefs and rituals

This category included any description of unusual beliefs (e.g. fear of consequences of disobeying OCD), willingness or ability to discuss symptoms and the impact of beliefs and rituals on self-care (e.g. not eating).

Example: "OCD impacted on consumption of food – perhaps impacted on ability to make most of sessions."

3. Insight

This category included any mention of insight into OCD.

4. Comorbidities and other difficulties

This category included any description of comorbidities (e.g. ASD, anxiety) and other difficulties including ability to comply with treatment.

Example; "Very anxious which meant we had to take very small steps. High anxiety may have been due to lack of understanding (?ASD)".

13.1.3.2 Part B

Two categories were developed from responses part B, 'Did you have difficulty establishing a therapeutic rapport with this client?'

1. Young person presentation

This category included any description of the young person including behavioural issues, attachment difficulties, risk/DSH and distress.

Example: "Attachment issues, e.g. one week I was away and she hit her hand with hammer as was distressed by no session"

2. Ability and motivation to engage in treatment

This category included any description of the young person's ability and motivation to engage in treatment, including ability to attend sessions (e.g. ability to get out of bed) and perform ERP tasks, as well as treatment dropout.

Example; " Did not engage - didn't leave bed on ward sometimes."

13.1.3.3 Part C

Three categories were developed from part C. Responses to the question ‘Do you think your experience / supervision or skills had any influence on the outcome of this case?’

1. Working with complex cases/families

This category included any description of the therapist’s experience of working with children who are difficult to engage in or resist treatment, communication difficulties and engaging parents and working with families.

Example: “I could have managed mum and Dad better. We did try to get them parenting support (they didn’t engage) and finally told them that without that and their own treatment we couldn’t offer them anything more.”

2. Selection of appropriate treatment

This category included any description of the therapist’s selection of appropriate treatment including decisions about the appropriate use of intensive treatment, how best to work with family accommodation and the appropriateness of using approaches other than those in the treatment protocol.

Example: “I think that if I were to work with X again I would have offered intensive straight away and would do more work with parents re. accommodation.”

3. Need for additional support and supervision

This category included any reference to the therapist’s need for additional support and supervision.

Example: “More support and supervision was needed.”

13.1.3.4 Part D

Three categories were developed from part D. Responses to the question ‘Did the young person present with any difficulties that may have impeded their response to treatment (e.g. issues relating to anxiety, motivation or readiness to change)?’

1. Comorbidities

This category included any description of comorbidities including ASD, ADHD, conduct problems, anxiety, mood, behavioural problems and risk/DSH.

Example: “autistic features”

2. Motivation/readiness for change

This category included any description of motivation and readiness for change (e.g. being overwhelmed by OCD, ability to imagine life without OCD).

Example: “X was overwhelmed by the drive to obey OCD – had it for so many years he could not see life without it.”

3. Insight

This category included any mention of insight into OCD.

Example: “Poor insight so did not see the point in treatment/changing.”

13.1.3.5 Part E

Three categories were developed from part E. Responses to the question ‘Were there any family factors (e.g. difficulty engaging the young person’s carers/parents, other family members also having OCD, anxiety or other mental health problems, high levels of expressed emotion, criticism, or over-involvement)?’

1. Family Circumstances

This category included any description of family setup including parental relationship problems, separation, single parent families and family organisation.

Example: “Parents separating meant that they appeared to have less emotional resources themselves to deal with X’s difficulties.”

2. Family unable to support the young person

This category included any description of the family’s ability to support the young person’s treatment (e.g. ability to tolerate distress, support ERP, address

accommodation, manage the young person's behaviour, manage fear and aggression, understand the symptoms and treatment, provide adequate emotional support, reach agreement about treatment and show the appropriate involvement with their child's care).

Example: "Mum was highly accommodating ... split in approach between Mum and Dad."

3. Family mental health and learning difficulties

This category included any mention of mental health difficulties, learning disabilities and developmental disorders within the family.

Example: "Mum's mental health (depr) and I think Dad may have had some anxiety difficulties."

13.1.3.6 Part F

Two categories were developed from part F. Responses to the question 'Did any stressful events occur to the young person during treatment that may have affected outcome?'

1. Parental stress and separation

This category included any description of parental stress or separation.

Example: "Parental separation."

2. Loss and illness in the family

This category included any mention of loss or illness in the family (e.g. brother going into army/ grandfather's illness).

Example: "Brother left home for army. Had an effect on parents more."

13.1.3.7 Part G

Two categories were developed from part G. Responses to the question 'Were there any other factors that may have contributed to treatment outcome?'

1. Professional Issues

This category included any description of professional issues including disagreement over diagnosis and treatment, and inconsistent care.

Example; "Professional tension between our team and snowfields on diagnosis on treatment plan may have led to inconsistent approach form someone with ASD – could have been counterproductive.

2. Young Person Comorbidities

This category included any description comorbidities including mental health problems and developmental disorders.

Example: "additional mental health problems (low mood, ASD)

